Victoria Tepe
Charles M. Peterson
Editors

Full Stride

Advancing the State of the Art in Lower Extremity Gait Systems

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Editors
Victoria Tepe, PhD
Senior Scientist/Program Manager
The Geneva Foundation
Tacoma, WA, USA

Charles M. Peterson, MD, MBA, FACP
Research Associate Professor of Chemistry
Syracuse University
Syracuse, NY, USA

President
MarquiSci
Potomac, MD, USA

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Foreword

After visiting injured soldiers at Walter Reed Army Medical Center, President George W. Bush directed the Department of Defense (DoD) to review policies on medical standards for retention on active duty. In 2003, he remarked that "the medical care is so good and the recovery process is so technologically advanced, that people are no longer forced out of the military" and that "Today, if wounded service members want to remain in uniform and can do the job, the military tries to help them stay." This marked a turning point in military policy, and since then, dozens of soldiers with limb amputations have returned to lead or serve with their units in combat zones. Others have returned to civilian life with much improved functionality at least in part because of the advances made through biomedical research by the US Army and Department of Veterans Affairs. Surgical treatment, neurorehabilitation, and environmentally hardened prosthetics have continued to evolve and provide continuous improvements in the return of normal functionality to amputees.

The Military Amputee Research Program (MARP) initiative began in 2004 as part of a previous role of the Telemedicine and Advanced Technology Research Center (TATRC) as an innovation incubator. TATRC specialized in supporting important new ideas that were not part of the planned DoD research and development program. This biomedical technology incubator function was made possible only through congressional special interest funding which, by 2010, had reached an annual funding total of nearly one half billion dollars. Advances in amputee treatment, rehabilitation, and prosthetics and other TATRC-supported efforts in pain management, sensory rehabilitation medicine, and regenerative medicine matured and then transitioned to a completely new DoD program focused on rehabilitation and care of seriously injured active duty service members. This Clinical and Rehabilitative Medicine (CRM) research program now leads research and development for active duty soldiers in close cooperation with the efforts of the Department of Veterans Affairs.

New bioengineering advances that are intended to solve one problem often provide or inspire solutions to other related problems. Advanced prosthetics designed to restore functionality to lower-limb amputees offer such opportu-

nities to enhance biomechanical capabilities for every soldier. Current exoskeleton concepts do not provide the smooth and agile locomotion that current prosthetics have been able to provide many amputees and will undoubtedly benefit from the current bioengineering and neuroplasticity research. The sacrifices made by military amputees, and the research investments made to help them, have laid the foundation for continuing technological enhancement of soldier performance more generally.

This book describes advances that have occurred during the iterative development of the volume itself. Contributing authors have been able to summarize the significance of their collective efforts at a high level and share their ideas on the key problems that remain to be solved. As such, this book provides a research roadmap for interested readers and researchers, providing a trajectory for future research based on a clear summary of what has been tried and what has been accomplished.

Before my retirement from Army active duty, I observed Troy Turner as he worked to develop the concept for the Lower Extremity Gait System (LEGS) project and this book. He deserves much credit for what has been accomplished here. This volume offers readers a spectacular panoramic view of the history and contemporary development of advanced lower-limb prosthetics and an opportunity to share the authors' own enthusiasm for developments that are now within the reach of science and technology to improve man-machine connection, including neural and feedback control systems.

Karl E. Friedl, PhD, COL (US Army retired)
29 March 2017

Preface

"The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable man".

George Bernard Shaw

In 2010, the US Army Telemedicine and Advanced Technology Research Center (TATRC) initiated a project known as Lower Extremity Gait Systems (LEGS) within its programmatic portfolio in advanced prosthetics. TATRC's Advanced Prosthetics and Neural Engineering Research Portfolio Manager was Mr. Troy Turner, who first developed the project's objectives and priorities "as a tangle of lines and a jumble of words on a whiteboard" (Fig. 1) and then depicted its landscape of concerns as a conceptual component map (Fig. 2). His goal was to envision and describe a lower-limb prosthetic system comprised of scalable, manufacturer-agnostic, interoperable devices capable of sharing operational data, sensor data, and power. As an essential theme to inspire development of such a system by researchers and engineers, the LEGS project would also champion an adaptive, user-centric approach to design.

The LEGS project exemplified TATRC's commitment to technology-inspired change and its dedication to "cultivate great ideas, providing freedom to explore new concepts and harbor the zealots to champion them past institutional barriers to change" in military medicine (Grundfest et al. 2012). TATRC often executed its organizational mission with an emphasis on interdisciplinary collaboration, bringing together diverse experts and bold thinkers to target specific problems of military medical importance. Applying this same approach over a 2-year period from 2010 to 2012, TATRC sponsored a series of three LEGS technical meetings to address objectives that were defined and overseen by strategic planning committee experts from the Department of Defense (DoD), National Institutes of Health (NIH), US Department of Veterans Affairs (VA), and academic research labs. These meetings yielded a clearer understanding of knowledge and capability gaps, technology limitations, and other obstacles that must yet be overcome to progress toward the vision originally depicted as a "tangle of lines and a

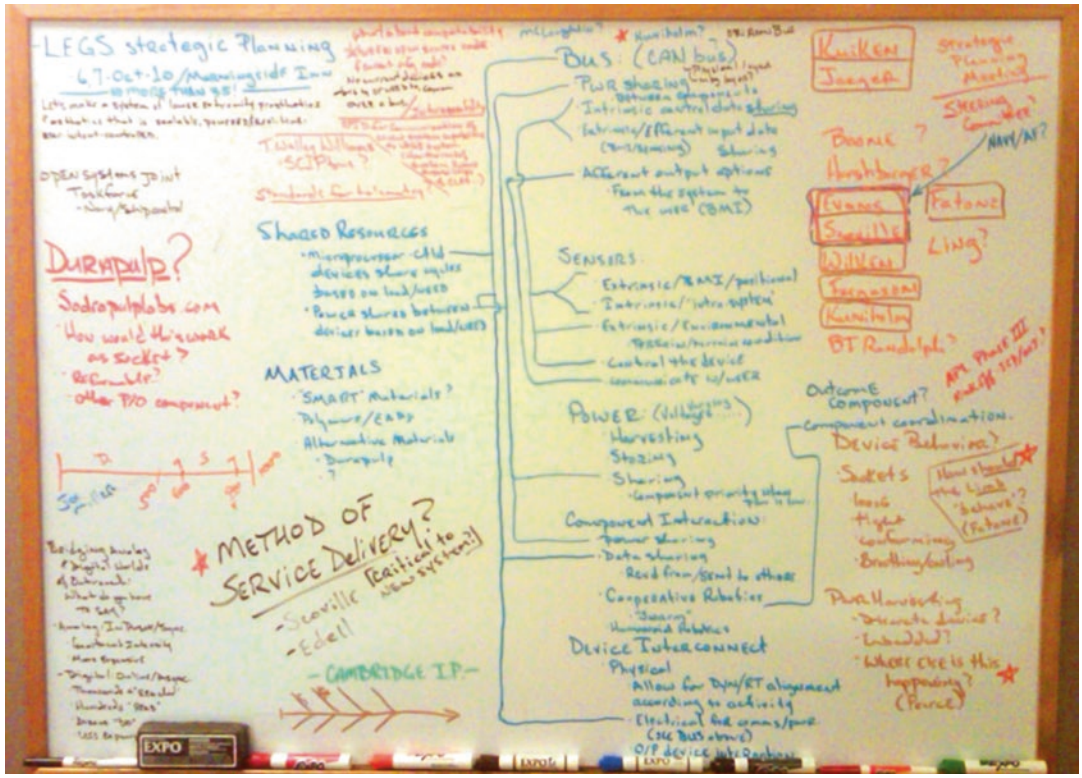

Fig. 1 The original LEGS project white board and concept component map, was documented by Mr. Troy Turner, TATRC's Advanced Prosthetics and Neural Engineering Research Portfolio Manager

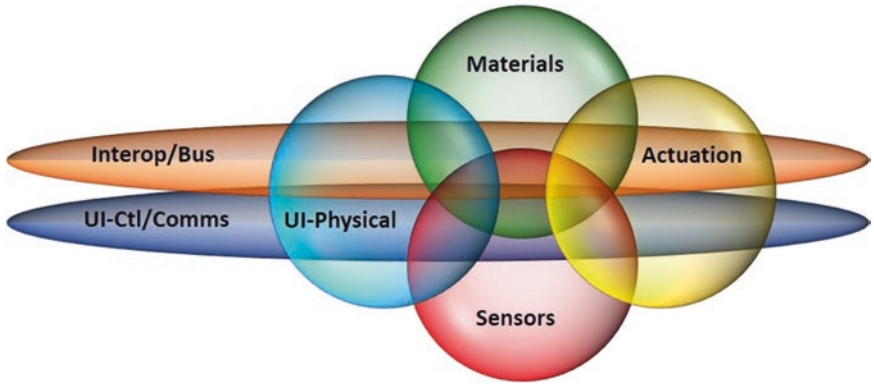

Fig. 2 The original LEGS concept component map emphasized taking advantage of "intersectional advancements" made possible by the integration of readily available ideas and technologies in diverse fields (*UI-Ctl/Comms* user interface/control and communication, *UI-Physical* user interface/physical attachment, *Interop/Bus* interoperability/physical connections/data/power bus)

jumble of words" on Troy Turner's office white board. Specific meeting discussions included challenges related to prosthetic device and system interoperability, user-device control/interfaces, device and system hardware, and device regulatory concerns for researchers. Experts from industry, academe, clinical practice, government agencies, and non-government nonprofit organizations were invited to work collaboratively to consider the present state of the art in advanced lower-limb prosthetics, identify pressing challenges and obstacles, and explore the state of the possible in prosthetic concepts, design, and technology. A final meeting was then held to assimilate the findings and observations of the three previous meetings and to consider remaining knowledge and capability gaps.

Early during the LEGS meeting series and related technical analyses, it became clear that too few published resources were available to address the broad landscape of achievements, objectives, and challenges associated with advanced prosthetic research and development. The current volume was then conceived as a complementary effort to capture insights from the LEGS project itself and further to explore the most advanced and creatively imagined solutions currently available in prosthetic science, componentry, and technical and medical development. Its chapters explore numerous specific achievements, challenges, and opportunities in the advanced development of prosthetic componentry, materials, power and control technology, bioengineering, and medical science.

The first section of this volume begins with an introductory overview of LEGS project concerns and observations, as context for the reader to consider topics and challenges detailed in later chapters. Next are chapters that explore relevant military and civilian needs and an essential historical context of the capabilities and shortcomings of contemporary prosthetics. The section concludes with an overview of essential components used in passive and active lower-limb prosthetics, including sockets, foot, ankle, and knee systems, as well as emerging bionic systems. A second section considers research and development in orthotics, synthetic and biological materials, volitional control, and wearable robotics (also known as exoskeletons). Finally, authors explore advanced science and emerging medical perspectives in research related to limb salvage, osseointegration, limb transplantation, and tissue engineering.

As citizens of western civilization in the twenty-first century, we take for granted the interoperability of components and systems essential to numerous technologies that now play seemingly indispensable roles in our daily lives such as computers, smart phones, home appliances, and automobiles. However, similar advances in prosthetic system design and development have been hampered in part by proprietary interests and by cost reimbursement paradigms that limit component compatibility and device interoperability. In slowing the development of integrated and adaptive systems, these factors force amputees – many of whom have been injured in service to their coun-

try – to accept limitations and delays in progress. We hope the challenges and possibilities presented in this book will lend a greater sense of urgency to overcome industrial, political, economic, and regulatory obstacles and to advance the development of integrated and adaptive prosthetic systems that are increasingly within reach of scientific and technical solution.

The LEGS project was one of many innovative endeavors that have been undertaken by TATRC. We want first to thank US Army Colonel (retired) Dr. Karl Friedl, under whose extraordinary leadership and executive direction we were fortunate to serve this and other TATRC projects and initiatives. The LEGS project was conceived and managed by Mr. Troy Turner, who served as TATRC's Advanced Prosthetics and Neural Engineering Research Portfolio Manager; Troy's ongoing dedication to the design and development of advanced prosthetic solutions continues today through his service to the US Army Medical Research and Materiel Command (MRMC) Congressionally Directed Medical Research Programs (CDMRP). We also acknowledge and thank those who brought essential contract support to the LEGS project through the Survivability and Vulnerability Information Analysis Center (SURVIAC) and in particular the uniquely talented professionals who were engaged to support this work as members of the Biomedical Research and Innovative Neuroscience (BRAIN) team led by Dr. Tepe. Among these first and foremost, we recognize and appreciate the excellent work and tireless commitment of Ms. Stephanie Salas-Snyder, who collaborated closely with government leaders and civilian subject matter experts to craft LEGS technical meeting objectives, information development strategy, technical analyses, and reports. Dr. Jeremy Nelson and Mr. Michael Smith conducted site visits and interviews at military and civilian labs to survey challenges faced by military amputees, methodologies by which state-of-the-art prosthetic and orthotic technologies are developed, and advanced technology and design focus areas of emerging interest to researchers. Ms. Janet Malone's thoughtful and energetic meeting planning skills played a critical role in the success of this and many other TATRC-sponsored projects supported by the SURVIAC. Dr. Suzanne Garcia led the development of the first outline for this volume and built an initial collection of first draft materials.

Finally, we wish to acknowledge and thank an elite group of civilian and military subject matter experts who shared their time and knowledge as project **steering committee advisors** and/or through their direct participation as consultants in LEGS project meetings. These individuals shared detailed discussions, expert insights, and diverse perspectives that were essential to the LEGS project and inspiring to our development of this volume:

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Disclaimer: The views expressed here are the authors' own and do not necessarily reflect the views, policies, or positions of the Department of Defense, the US Government, or employers.

Syracuse, NY, USA — Charles M. Peterson
Tacoma, WA, USA — Victoria Tepe

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Contributors

Elisa S. Arch, PhD Department of Kinesiology & Applied Physiology, Department of Biomedical Engineering, Biomechanics and Movement Science Interdisciplinary Program, University of Delaware, Newark, DE, USA

Kent N. Bachus, PhD Departments of Orthopaedics, Bioengineering, University of Utah Orthopaedic Center, Salt Lake City, UT, USA

Christopher E. Beck, MS, BS Oceaneering Space Systems, Robotics and Automation Program, Houston, TX, USA

James Peter Beck, MD DVA SLC HCS, Department of Orthopedics, Salt Lake City, UT, USA

Roy D. Bloebaum, PhD VA Salt Lake City Health Care System, Bone & Joint Research Lab, Salt Lake City, UT, USA

Michael J. Bosse, MD Othopedic Surgery, Carolinas Medical Center, Charlotte, NC, USA

Warren C. Breidenbach, MD, FRCS (C) Division of Reconstructive and Plastic Surgery, University of Arizona, Tucson, AZ, USA

Shuo-Hsiu Chang, PhD, PT Department of Physical Medicine and Rehabilitation, UTHealth McGovern Medical School at Houston, The NeuroRecovery Research Center at TIRR Memorial Hermann, Houston, TX, USA

Robert J. Christy, PhD Extremity Trauma Research and Regenerative Medicine, US Army Institute of Surgical Research, Combat Trauma and Burn Injury, TX, USA

Sheila M. Clemens, PT, MPT Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, FL, USA

Rory A. Cooper, PhD Human Engineering Research Laboratories, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

Michael Corcoran, BA CPO, Medical Center Orthotics and Prosthetics, Silver Spring, MD, USA

Michael R. Davis, MD, FACS United States Army Institute for Surgical Research, San Antonio Military Medical Center, San Antonio, TX, USA

Alex J. Drew, BSME University of Utah Orthopaedic Center, Department of Orthopaedics, Salt Lake City, UT, USA

Cheta G. Emba, BA Center for the Rehabilitation Sciences Research, Henry M. Jackson Foundation for the Advancement of Military Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Kevin B. Fite, PhD Clarkson University, Mechanical and Aeronautical Engineering, Potsdam, NY, USA

Gerard E. Francisco, MD Department of Physical Medicine and Rehabilitation, UTHealth McGovern Medical School at Houston, The NeuroRecovery Research Center at TIRR Memorial Hermann, Houston, TX, USA

Robert S. Gailey, PhD, PT University of Miami, Coral Gables, FL, USA

Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, FL, USA

Vijay S. Gorantla, MD, PhD, FRCS Reconstructive Transplantation Program, Department of Plastic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Levi Hargrove, PhD Shirley Ryan AbilityLab, Center for Bionic Medicine, Chicago, IL, USA

Sujee Jeyapalina, MD DVA SLC HCS, Department of Bioengineering, University of Utah, Salt Lake City, UT, USA

Eva Lai, PhD Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

Ellen J. MacKenzie, PhD Johns Hopkins Blomberg School of Public Health, Health Policy and Management, Baltimore, MD, USA

Matthew E. Miller, MD Department of Physical Medicine & Rehabilitation, School of Medicine, Uniformed Services University of the Health Sciences; Department of Rehabilitation, Walter Reed National Military Medical Center, Bethesda, MD, USA

Jon E. Mogford, PhD The Texas A&M University System, College Station, TX, USA

Ken Muneoka, PhD Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA

Serdar Nasir, MD Department of Plastic, Reconstructive and Aesthetic Surgery, Hacettepe University, Ankara, Turkey

Paul F. Pasquina, MD Department of Physical Medicine & Rehabilitation, School of Medicine, Uniformed Services University of the Health Sciences; Department of Rehabilitation, Walter Reed National Military Medical Center, Bethesda, MD, USA

Charles M. Peterson, MD, MBA, FACP Research Associate Professor of Chemistry, Syracuse University, Syracuse, NY, USA

MarquiSci, Potomac, MD, USA

Roger N. Rovekamp, Jr., BS, MS Cincinnati Automation & Mechatronics (CAM), Beavercreek, Ohio, TX, USA

Stephanie Salas-Snyder, BS, MS Intel Corporation, Hillsboro, OR, USA

Mohsen Shahinpoor, BSc, MSc, PhD Biomedical Engineering Laboratory, Department of Mechanical Engineering, University of Maine, Orono, ME, USA

Steven J. Stanhope, PhD Department of Kinesiology and Applied Physiology, Department of Mechanical Engineering, Department of Biomedical Engineering, Biomechanics and Movement Science Interdisciplinary Program, University of Delaware, Newark, DE, USA

Victoria Tepe, PhD Senior Scientist/Program Manager, The Geneva Foundation, Tacoma, WA, USA

Troy A. Turner, MBA CDMRP, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, USA

Joseph B. Webster, MD Hunter Holmes McGuire VA Medical Center, PM&R, Polytrauma Transitional Center, Richmond, VA, USA

Fatih Zor, MD Department of Plastic, Reconstructive and Aesthetic Surgery, Gulhane Military Medical Academy, Ankara, Turkey

Part I

Past and Present

The History and Future of LEGS

1

Victoria Tepe, Stephanie Salas-Snyder,
and Charles M. Peterson

Introduction

Military conflicts in Iraq and Afghanistan exposed US service members to the widespread use of improvised explosive devices (IEDs) by enemy combatants and thus to potentially devastating blast-related injuries. Thanks to modern protective military equipment and advanced medical solutions and technologies, many service members have survived these and other injuries that in previous wars would have been lethal. Unfortunately, many survivors have sustained significant limb injuries or losses that require reconstruction or amputation (see MacKenzie and Bosse [35] in this volume) and subsequent orthotic or prosthetic intervention to restore function (see also Pasquina et al. [48] in this volume). Dealing with the number, complexity, and long-term sequelae of limb trauma and amputations has become a top priority for military medical researchers and caregivers, whose work ultimate extends to benefit the treatment and recovery of civilians who suffer similar injuries.

To promote advanced military medical solutions for lower limb amputees, the US Army Medical Research and Materiel Command's (MRMC) Telemedicine and Advanced Technology Research Center (TATRC) sponsored a series of meetings to identify the state of the art and to advance the state of the possible in lower limb prosthetic concept, technology, and design. Participants and contributors were drawn from industry, academe, clinical practice, nonprofit, and government sectors. Government-level subject matter experts were included from the National Aeronautics and Space Administration (NASA), Food and Drug Administration (FDA), Department of Defense (DoD), and Walter Reed National Military Medical Center (WRNMMC). The goal of their

V. Tepe, PhD (✉)
Senior Scientist/Program Manager, The Geneva Foundation, Tacoma, WA, USA
e-mail: vtepe@genevausa.org

S. Salas-Snyder
Intel Corporation, Hillsboro, OR, USA
e-mail: Stephanie.salas.snyder@gmail.com

C.M. Peterson, MD, MBA, FACP
Research Associate Professor of Chemistry, Syracuse University, Syracuse, NY, USA

MarquiSci, Potomac, MD, USA
e-mail: cmarquispeterson@gmail.com

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collaboration with TATRC was to envision and identify requirements for a manufacturer-agnostic lower extremity gait system (LEGS)[1] that would consist of customizable, interchangeable, and interoperable components to restore ambulatory function. The envisioned system would exemplify an easy-to-maintain human-centric design that is adaptively responsive and volitionally controlled by the user and configured to maximize component compatibility through the use of open standards.

The insights and findings drawn from the LEGS meeting series inspired development of this book, with chapters developed and organized to capture the broad scope and multiple domains and disciplines of scientific medical inquiry, componentry, and technical development necessary to foster the design and development of advanced prosthetics in general and of LEGS in particular. Through literature search, site visits, and extensive discussion and collaboration, LEGS project workers and participants identified specific challenges, gaps, needs, and barriers that must be overcome to advance numerous involved component capabilities (see also Fite [7] in this volume) and to bridge the divide between current device capabilities and the ideal future system envisioned as LEGS. Their deliberations targeted essential design features and componentry, including control, sockets, bus, power, algorithms, and the need for open source and open standards to support meaningful and efficient scientific and technical collaboration. Critical knowledge gaps, capability gaps, component limitations, and nontechnical considerations (e.g., limited training, lack of standardization) were identified, pointing to the need for additional research and development to achieve the vision of an advanced system such as LEGS. Here, we summarize the primary concerns and considerations that were addressed as research and development objectives through the LEGS initiative.

Sockets and Sensors

Specific gaps identified included the need for more durable socket technologies, advanced materials, and liners to preserve patient health and comfort while maintaining residual limb homeostasis and management of external forces. Although socket design has advanced over more than a century of prosthetic design and development history (see also Gailey et al. [8] in this volume), today's prosthetic users all too commonly experience residual limb skin problems related to residual limb volume, moisture accumulation, shear force, and external stressors associated with walking and running [4, 29, 39]. Although not yet a viable alternative, researchers are working to develop osseointegration procedures that could eliminate the need for socket-based suspension by allowing direct attachment of a prosthetic limb to the bone (see Webster et al. [61] in this volume). As a near-term requirement for LEGS, project participants identified the need for improved socket and liner materials that enable heat dissipation, user-controlled adjustment, and adaptability to ambulatory function without the need for user input. They considered that these objectives could be addressed initially by determining the minimum biomechanical surface necessary to allow a lighter, more comfortable interface while preserving security and function.

[1]Although it is arguably more common to describe the lost leg as a lost "limb" (vs. "extremity") – the term "limb" distinguishes the leg in whole or part from its extreme appendages (toes) – prosthetic devices designed to replace the lost lower limb are often described as "lower extremity prostheses" (e.g., see http://www.aopanet.org/legislative-regulatory/study-higher-standard-of-care-for-patients-with-limb-loss-or-spinal-injuries-saves-medicare-money-in-most-cases/). Thus, when we refer to the "lower extremity gait system" described by the LEGS project, we use the term "extremity" to describe the envisioned prosthetic system, rather than the limb it supposes to replace.

Socket liner materials have been widely explored, for example, to include thermoplastic materials such as copolymer (TPE), polyurethane (PUR), and silicone. Some difficulties might be mitigated by the incorporation of newer materials, composites, and designs that can exploit the properties of advanced alternative materials such as nickel titanium, ceramic (porous, thread, matrix for composite), shape memory, and thermo-conductive polymers. Unfortunately, the influence of liner materials on prosthetic user performance is not well understood. Little research has been done to inform prescription practice as to how liner material selection might affect individual residual limb and patient health [28]. As a result, clinicians must rely primarily upon their own professional experience. In addition to improved materials research, development, and testing, there is a need for improved socket measurement and fitting processes. Although measurement and fit have improved greatly through the use of computer-aided design (CAD) and other advanced tools, these techniques are not error-free. Practitioners need evidence-based guidance and training to better meet the specific needs of their individual patients.

Socket design and function would be improved by the incorporation of durable, rugged, miniaturized sensors that can be used to provide device and biological feedback to the system and its user. Sensors can be used to detect changes in temperature, pressure, moisture, volume, shear, impedance, kinetics and kinematics, blood flow, and other biological and environmental variables. For example, movement can be "sensed" by measuring linear acceleration via an accelerometer and angular rate via a gyroscope [17]. Sensors can be embedded in wearable items such as socks, but prosthetic applications present unique challenges with respect to sensor size and durability. To fit comfortably, and to function reliably within a prosthetic device socket, the sensor must be miniaturized, flexible, and ruggedized to perform effectively in hot, humid, or desert-like environments and at close proximity to human tissue. Advanced computer capability is also needed to support the integration of multiple sensors as a functional suite with actuator output.

The ideal LEGS would include a responsive homeostatic device that could dynamically manage force, circulation, moisture, volume, and other socket environment variables without requiring direct user input. By feeding proprioceptive and exteroceptive sensor feedback to prosthetic device control, it may be possible to support more natural motion. To this end, it would be helpful to determine what type and how much feedback is most effective, for example, to improve user gait without requiring unnatural or extraordinary effort by the user. Research is needed to test and compare various types of feedback (e.g., tactile vs. auditory) and evaluate their relative effectiveness and impact on user performance. Relatedly, researchers should consider that it may be helpful to prioritize performance-critical feedback and to filter out potentially distracting feedback that might interrupt or hinder performance. The ultimate objective is to translate meaningful information about prosthetic performance and socket environment into effective user control, via adaptive algorithms and control loops that are as analogous as possible to native motor control and reflexive systems.

In order for an advanced prosthesis to "learn" its user's intent, the system will require advanced pattern recognition, time series analysis, and learning algorithms to monitor, analyze, and respond to user performance and outcome data (e.g., correct event detections, responses, adjustments, and falls). One candidate approach is a wireless body sensory network (BSN; [13]), which could be used to monitor physical demands that are placed on the user while mobile (e.g., ground reaction forces during heal-toe strike), supply information directly to the user, and ulti-

mately inform researchers working to improve prosthetic design. Autonomous patient control could further be enhanced through the additional use of electroencephalography (EEG), targeted muscle reinnervation (TMR), and implantable myoelectric sensors (IMES). These volitional control technologies are considered in more detail later in this chapter.

Power and Control

Among the challenges to achieving a fully integrated LEGS system is the need for standardized power and data buses that can communicate effectively and reliably with one another. Currently, separate prosthetic devices (e.g., knee and ankle prostheses) are forced by design to operate independently, never communicating with one another concerning their respective operations, power, or performance. Where a prosthetic configuration includes multiple devices, the user should have the option to exploit fully integrated control and linkage, for example, via a personal computer bus that allows each device to draw power from the other as needed, download updated software for each device, or adjust performance of one device to accommodate the known capabilities or limitations of another. This proposal is achievable in principle but is not yet possible in practice. Integrated device control is well within the capabilities of currently available systems and technologies, but linkage requires willingness on the part of prosthetic manufacturers to employ shared standards.

The "muscle" or driver of the prosthetic is its actuator. Historically, actuator technologies have been heavy, bulky, inefficient, difficult to control, and capable of high force but ineffective for fine movements or adjustments. Direct current motor technology improves actuator power density but at torques and speeds that are not well matched to the needs of prosthetic ankle and knee systems. The speed and force of conventional actuators cannot replicate what is achieved by human musculature that supports native lower limb gait and function. Notable advances have occurred in the development and demonstration of back-drivable and series-elastic actuators that can be more precisely controlled [18, 37, 58]. The application of pneumatic muscle actuators (pMAs) to wearable exoskeleton legs also demonstrates the potential for "soft" actuation, at least in the rehabilitative setting ([3]; Rovekamp et al. [52] in this volume). New designs emphasize force and torque control to support more precise user-system interaction. Additional efforts to achieve biomimetic actuation include explorations using electroactive and conducting polymers [17, 26] and artificial and animal-derived muscle [19, Shahinpoor [56] in this volume]. Among the advantages of these solutions would be more quiet and adaptive function of the sort envisioned through the LEGS initiative [18, 20]. "Soft" technologies and conforming biomimetic structures can also serve to reduce system weight and improve portability and efficiency.

Advanced developments in the field of lower extremity prosthetics are moving increasingly toward actively powered designs that require independent power sources. Here again, the need for open standards and standardization presents a nontechnical but significant challenge. Interoperability among multiple devices is necessary to an integrated system. The ideal power supply/battery would be a single small, centralized, lightweight, rugged, long-duration supply that is quickly and easily rechargeable using standardized connectors and chargers. Additional beneficial capabilities might include central logic data processing, energy harvesting, and stand-by power management.

Prosthetics users desire control that is responsive to their intent. A key design challenge is to provide an effectively balanced combination of conscious and automated control features. The goal is to enable the user to execute behavioral

choices (e.g., position, motion, speed, and trajectory) in real time, unburdened by excessive requirements to monitor or adjust variables that are critical to comfort, safety, or device attributes such as power management. To address the latter concern, a number of advanced prosthetic devices have already demonstrated the benefits of microprocessor-supported control, including improved knee flexion, enhanced energy management, better knee resistance, improved smoothness, and symmetry of gait [25, 27, 53, 55]. As to the need for conscious user control, one key objective of the LEGS project was to consider state-of-the-possible solutions for intent-responsive control.

Volitional Control

Researchers have explored and continue to explore various methods of voluntary control via signals recorded from muscular and neural sources (see Hargrove [14] in this volume). Potential applications have been demonstrated using invasive and noninvasive brain machine interfaces (BMIs), myoelectric sensors (MES), electromyography (EMG), and targeted muscle reinnervation (TMR) [6, 15, 16, 47]. In each case, technical challenges concern signal recording quality, transmission, and signal processing algorithms, additional power requirements, human tissue fragility, and the installation of permanent electrode arrays. Noninvasive BMIs avoid the need for surgical implantation but are relatively more vulnerable to recording artifact. Noninvasive BMI users must learn to control specific derivative signal indices such as brain-evoked potentials, specific rhythms, or firing rates.

Brain-Based Control

Intracranial BMIs have been demonstrated using implanted electrode arrays in animal as well as human subjects, to achieve real-time control of robotic devices via the recording of motor commands from ensemble neuronal activity in the motor cortex [2, 21, 45]. Potential applications include restoration of motor behavior in patients who have suffered loss of function due to brain or spinal disease or injury, including amputation. Though certainly promising, there are numerous biomedical engineering challenges associated with the design and implementation of BMI-based prosthetics. For example, because it is difficult to obtain electrically stable recordings with appropriate fidelity from large populations of neurons in multiple brain areas, implantable amplifiers and signal processors must be resistant to electrical noise and artifact [49]. Computationally sophisticated but efficient algorithms are necessary to translate neuronal activity into command signals that can control prosthetic or robotic actuators with multiple degrees of freedom. It remains to be seen how or if the brain's own plasticity can be exploited effectively to incorporate a prosthetic device into the human body's full neural representation and if the human brain can adapt and respond to accept, integrate, and directly control an artificial limb. Lebedev and colleagues [33, 34] provide thoughtful discussion of numerous bioengineering problems that have yet to be addressed. In addition, there are questions surrounding the biocompatibility, longevity, and sustainability of chronic brain implants. Brain inflammatory responses can cause recording failure, and, to ensure stable recording, it is necessary to prevent movement or migration of an electrode array relative to the underlying cortex [51, 54].

A number of clinical trials are underway or recently completed to study the use of implanted brain-recording devices to achieve "thought" control of external assistive devices such as computers, robotics, and virtual reality environments by individuals who have suffered spinal cord injuries, stroke, or neurodegenerative disease (see ClinicalTrials.gov identifiers NCT00912041,

NCT01393444, NCT01958086, NCT01849822, NCT01964261, NCT01364480). Where the ultimate goal is to control a prosthetic limb, a significant technical question is how best to provide proprioceptive feedback to a user whose ability to control the prosthetic may otherwise depend almost entirely upon constant visual attention to the prosthetic [50, 60].

EEG-based control technologies employ scalp surface electrodes to record spontaneous changes in voltage generated by large populations of underlying neurons. EEG can be used to detect changes that correspond to specific medical conditions (e.g., seizures, coma) and can be derived (averaged) as evoked or event-related potential waveforms to identify responses to specific sensory stimuli, changes in attention, or recognition. EEG signal recording allows high temporal resolution (milliseconds) and has been applied in a variety of settings to support mind-based control of fairly simple tasks such as basic cursor control, with potential application to prosthetic control [11, 31, 32, 36, 41]. However, scalp surface-recorded EEG signals are limited by poor cortical spatial resolution. Recorded signals represent electrical activity coming from large and/or multiple underlying brain regions; signal quality is greatly attenuated by the skull. As a result, EEG signal discrimination and processing tend to be slow and imprecise. EEG recordings are also highly susceptible to contamination by electrical artifact from muscle tissue, body movement, recording instruments, eye blinks, and the environment. EEG electrodes can be uncomfortable and are difficult to position on the scalp with repeatable precision. Thus, EEG-based control is not optimal for applications that involve complex sequences, rapid movements, and multiple degrees of freedom. Other noninvasive methods of recording changes in brain activity associated with magnetic field or blood flow, such as magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI), can eliminate much of the signal distortion associated with EEG and provide much better signal spatial resolution. However, MEG and fMRI recording equipment is very large, fragile, vulnerable to motion artifact, and not at all portable as would be necessary for use to control ambulation. Limited to research and clinical settings, MEG and fMRI may nonetheless be useful in research that aims to identify, localize, and characterize motor control signal sources and patterns to inform other BMI applications.

Muscle-Based Control

Surface-recorded EMG contains signal components from multiple muscle sources. Design features and signal processing strategies are needed to challenge the inherent limitations of surface-recorded EMG and to enhance its utility (e.g., [5, 12, 22–24, 44]). To achieve more robust control of lower limb prostheses, researchers are working to develop safe, comfortable implantable myoelectric sensor systems that can provide greater and more precise control via wireless connection to the target device (e.g., [1, 38, 62]). Long-term implantable myoelectric sensors (IMES) allow recording of source EMG signals, which can be transmitted to a controller by wireless telemetry [38, 62]. To date, research in this area has focused primarily on the use of IMES to control prostheses for upper limbs (e.g., [59]).

Targeted muscle reinnervation (TMR) is an advanced surgical procedure involving the transfer of residual nerves to alternative muscle sites. Once the alternative muscle sites are reinnervated, they produce EMG signals that can be recorded and measured at the skin surface and used to control a prosthetic device. In 2012, TMR was applied to enable an above-the-knee, right leg amputee to climb 103 floors of Chicago's Willis Tower (http://www.npr.org/

sections/thetwo-way/2012/11/05/164335844/amputee-climbs-103-floors-of-chicagos-willis-tower-using-bionic-leg). Though TMR-based control is certainly at the leading edge of volitionally controlled ("bionic") prosthetic system development, additional research is needed to provide sensory feedback to the prosthetic limb or to the reinnervated muscle. Additional degrees of freedom (e.g., via nerve splitting) are also needed to provide more independent signals. These advances are necessary to support systems that are responsive to changing terrain and can avoid obstacles. If TMR can ultimately be combined with advanced tissue replacement/regeneration technologies, it may become possible to develop functional, bio-artificial neuromuscular junctions (e.g., man-made muscle attached to titanium bone).

Biomaterials and Tissue Engineering

Some far-future research and technology development objectives could one day revolutionize or even obviate the need for prosthetics as they are currently defined, designed, and envisioned. Advanced medical scientific pursuits in tissue engineering, limb transplantation, and limb regrowth may eventually allow surgeons to replace lost or damaged original limbs with fully functional, biomaterial substitutes. Various such endeavors are explored in detail elsewhere in this volume (see chapters by Gorantla et al. [9] Shahinpoor [56]; Muneoka et al. [42]).

Explorations in stem cell research are especially relevant to bioengineering objectives. For example, embryonic, induced pluripotent (iPS) and mesenchymal stem cells are under investigation to restore various types lost or diseased tissue, including limb tissues such as the skin, bone, and tendon [40, 42, 46, 63]. Embryonic stem cells are especially flexible for use in bioengineering applications; they are easy to expand in culture and can be differentiated to any cell type [30]. However, it is a challenge to direct and sustain stem cell differentiation, and it can be difficult to predict how stem cells will behave after they are transplanted. Undifferentiated stem cells can give rise to malignant transformation, which must be suppressed. Much additional research is needed to specify signaling proteins, matrix chemicals, and molecules needed to overcome various difficulties. Although similar technical challenges are raised by the use of iPS cells, this approach is less controversial because the cells are derived from adult body tissues rather than human embryos. In principle, iPS cells can be harvested directly from the patient. In an original demonstration that connective tissue cells could be differentiated into other tissue types in three dimensions, Sommar et al. [57] successfully cultured connective tissue cells from human skin in vitro to create cartilage, bone, and vascular endothelium.

Other Requirements

Additional challenges to achieving the envisioned LEGS system do not require new or improved technology itself but rather the pressing need for improved access to existing technology. Chief among these requirements is the need for interchangeable component configurations and platforms that provide open source, innovative, standardized communication with one another via sensors and actuators. Open source innovations are not entirely incompatible with proprietary interests. For example, open application programming interfaces (APIs) can be exposed without revealing their underlying code, to allow programming for component communication without violating proprietary protections. However, a current lack of shared standards in the prosthetics industry slows progress

toward the development of fully integrated systems with interchangeable componentry. The Open Prosthetics Project (openprosthetics.org) attempts to overcome this challenge by supporting open source collaboration among users, designers, and research funders. The objective is to accelerate innovation and promote free sharing of new designs.

The need for open source standards was raised repeatedly by LEGS project participants, who recognized generally that progress on this point is limited only by the willingness of the prosthetic development and manufacturing community itself. When proprietary objections are resolved, it will be possible to overcome current barriers to the system-of-systems approach that is crucial to achieve and advance fully integrated and advanced prosthetic systems. Open standards are needed for power, data, physical, and network component connections.

As a starting point, the prosthetic device community could develop and demonstrate an open source system simply for the purpose of gathering aggregate outcome data (e.g., usage, event detection, long-term monitoring) from various individual prosthetic systems, sensors, and component technologies. A centralized data repository would also be needed to provide access to the collected data and to enable outcome-based research aimed at improving system safety, reliability, and faster regulatory review to the benefit of all concerned. This would also help meet the need for data and information exchange between experts in medicine, industry, academe, and the military.

Participants in the LEGS project meetings also identified the need for more and improved training and awareness to benefit practitioners as well as their patients. As advanced solutions and capabilities develop rapidly, even those who work and are served in dedicated facilities may be unaware of emerging technologies. More proactive efforts are needed to provide continuing education and outreach to those who provide prosthetic services and to patients who need the best available, most advanced and emerging solutions. LEGS project participants suggested holding annual training events, for example, to align with annual professional meetings (e.g., American Academy of Orthotists and Prosthetists/AAOP), as well as centralized training at major military medical centers (e.g., Walter Reed National Military Medical Center/WRNNMC).

Although regulatory processes are certainly necessary to ensure safety, liability, and fiscal responsibility, they sometimes have unintended, unanticipated, and discouraging effects on research and development. Participants in the LEGS meetings considered that best outcomes are rarely driven by policies and practices defined in isolation by a single organization or interest. Rather, policy better supports and represents all relevant objectives, concerns, and perspectives when it is developed as a coordinated effort involving all relevant stakeholders. Where the goal is to create an affordable, capable, safe, and effective prosthetic system such as that envisioned by LEGS, policy development should allow participation of relevant government entities, researchers, industry representatives, clinicians, insurers, and – arguably most important – prosthetics users who can by their own experience speak directly to the health concerns, practical needs, and functional priorities of those who rely on advanced prosthetic technologies.

One regulatory response to these concerns has been the FDA's recent revision of its Investigational Device Exemptions (IDE) guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm). The provisions of the FDA's IDE regulation assign responsibilities to all participants in clinical investigation and exempt consumer preference testing of a modification or of a combination of devices.

When combined with Early Feasibility Studies (usually involving 15 or fewer subjects) and the FDA's Expedited Access Pathway (EAP) program (FDA involvement through the collaborative creation of a "Data Development Plan"), the FDA hopes to "facilitate timely access to medical devices by expediting their development, assessment, and review, while preserving our statutory standards for safety and effectiveness and protecting patients" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393978.pdf).

Conclusion

In May of 2016, two veterans wounded by roadside bombs in Iraq and Afghanistan made history and inspired fellow wounded warriors as they made their way into thin air toward the 29,029-ft summit of Mount Everest. Former Marine Staff Sergeant Thomas Charles "Charlie" Linville and former Army reservist Chad Jukes (Fig. 1.1) both wore lower limb prostheses and took the route less traveled, along the northern, Chinese side of the mountain. Although the two combat amputees belonged to different expedition teams sponsored by different veterans' organizations, they met during the climb. Linville and Jukes had to avoid all of the same dangers that threaten other climbers, while taking care to mitigate potentially more severe consequences. For example, reduced blood flow to an amputee's stump introduces an increased risk for frostbite. But for wounded warriors Linville and Jukes, it is not enough to overcome the challenges of daily life as an amputee. They challenged themselves to extreme adverse conditions, including raging winds and the "death zone" above 26,000 ft.

The many ordinary and extraordinary accomplishments of wounded warriors bring into sharp focus the original vision of the LEGS project as part of TATRC's commitment to "cultivate great ideas" and the exploration of new concepts [10]. This volume was developed not simply to capture the current state of the art but to inspire continued development toward the state of the possible as

Fig. 1.1 Chad Jukes is pictured climbing ice at advanced basecamp (6,400 m) on Mount Everest. Photograph courtesy of Dr. David Ohlson (daveohlson.com)

envisioned by LEGS. For those who will engage prosthetic technology challenges yet to be overcome, this book provides a benchmark for today's state of the science and identifies current gaps in knowledge, materials, technology, and access. The "great idea" envisioned by LEGS was and is a human-centric adaptive and assistive powered system design that is customizable and interchangeable, with interoperable components to restore volitionally controlled ambulatory function. Driven by great ideas, science, engineering, and development of advanced technology are, by necessity, iterative processes that require investment, intellectual freedom, and dogged determination to continue climbing, sometimes against all odds through the thin air of institutional and proprietary barriers.

Originally wounded in 2011, Charlie Linville reached the summit of Mount Everest just 5 years later on May 19, 2016. Chad Jukes, wounded in 2005, arrived at the Mount Everest summit on May 24, 2016. Both climbers have expressed that they want their efforts to benefit veterans and promote physical and psychological healing of the wounds of war. Though humbled by their achievements, we share their desire. We imagine, for example, how future mountain climbers might benefit by the development of LEGS-inspired prosthetics with assistive power, better agility, just-in-time on-the-spot adjustment and correction, and unlimited volitional control. We hope this book provides essential knowledge, perspective, and a creative blueprint that will inspire medical scientists and bioengineers to progress toward such a vision and toward ever more advanced prosthetic solutions.

Disclaimer The views expressed here are the authors' own and do not necessarily reflect the views, policies, or positions of the Department of Defense, the US Government, or employers.

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Lower Limb Disability: Present Military and Civilian Needs

2

Paul F. Pasquina, Cheta G. Emba, Michael Corcoran, Matthew E. Miller, and Rory A. Cooper

Introduction

This chapter provides a brief overview of some of the more common causes of lower limb dysfunction, emphasizing trauma-related injuries seen in both military and civilian populations. We focus primarily on those conditions which impair mobility and we provide an overview of some of the treatment strategies and assistive devices that are currently available to mitigate these effects.

P.F. Pasquina, MD (✉) • M.E. Miller, MD
Department of Physical Medicine & Rehabilitation, School of Medicine, Uniformed Services University of the Health Sciences; Department of Rehabilitation, Walter Reed National Military Medical Center, Bethesda, MD, USA
e-mail: Paul.pasquina@usuhs.edu; matthew.e.miller78.mil@mail.mil

C.G. Emba, BA
Center for the Rehabilitation Sciences Research, Henry M. Jackson Foundation for the Advancement of Military Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
e-mail: chetagrace@gmail.com

M. Corcoran, BA, CPO
Medical Center Orthotics and Prosthetics, Silver Spring, MD, USA
e-mail: Mzelot@aol.com

R.A. Cooper, PhD
Human Engineering Research Laboratories, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA
e-mail: rcooper@pitt.edu

The term "mobility" is often used interchangeably with the term "ambulation." However, mobility can be defined more extensively to include such activities as transferring to and from a bed, chair, or commode; moving through doorways or fire exits; negotiating stairs, ramps, curbs, or obstacles; operating a motor vehicle; or even accessing public transportation. In addition, one must also consider the speed, efficiency, and safety of performing any of these activities in the context of living independently. Successful mobility not only allows the performance of basic living skills, including dressing, feeding, bathing and hygiene, but also promotes more complex activities such as seeking and achieving meaningful employment, community participation, socialization, and the pursuit of recreational or sports activities – all of which may have a significant impact on one's quality of life.

Reestablishing effective mobility for individuals with lower limb dysfunction due to trauma or disease is often a complex challenge and frequently involves the interdisciplinary efforts of many medical, surgical, and rehabilitative specialists. This is especially so when injuries are sustained by exposure to violent physical trauma such as blast force. Surgical intervention often

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requires fixation of fractures, reconstruction of muscle or skin defects, and repair of peripheral vasculature and peripheral nerves. When limb preservation is not possible, amputation may be necessary. Amputation of the lower limb requires extensive presurgical planning to decide what would be the optimal length of the remaining limb depending on the viability of the residual limb bone and soft tissues and what length would best accommodate the most functional prosthesis. For the lower limb, all effort should be made to preserve the hip and knee joints if possible, to reduce the consequential difficulty and energy required for ambulation [1]. In addition, it is important for the surgical team to achieve adequate soft tissue coverage, appropriate muscle balance through myodesis and myoplasty, and effective peripheral nerve management to help diminish problems with symptomatic neuroma formation. Rehabilitative interventions typically involve vigilant observation and protection from secondary complications, such as venous thrombosis or skin ulceration, aggressive pain management, restoring limb range of motion and strength, progressive weight bearing, and when possible gait training with or without an assistive device. Examples of assistive devices include single point canes; walkers or rollators; powered, hybrid, or manual wheelchairs; hand cycles or recumbent cycles; static or dynamic orthotics; and technologically advanced customized prosthetics. Rehabilitation is generally conducted in an interdisciplinary fashion by a team of experts, including physicians, therapists, nurses, social workers, behavioral health experts, prosthetists, and orthotists. Therapeutic interventions are conducted on an individualized basis to best accommodate or assist the unique problems of the individual patient.

Over the past decade, the Department of Defense (DoD) and Department of Veterans Affairs (VA) have cared for over 50,000 combat casualties of the wars in Iraq (Operation Iraqi Freedom) and Afghanistan (Operation Enduring Freedom). Some of the most devastating injuries have been characterized as "Dismounted Complex Blast Injuries" (DCBI), which are often associated with severe bilateral lower limb amputation and/or dysfunction [2]. As a result, the DoD and VA have spent considerable resources to prevent such injuries and to mitigate their negative consequences on human function and performance. Numerous advances in surgical resuscitative techniques, medical evacuation, rehabilitative strategies, and assistive technology have been made to enhance the quality of care available for both military and civilian trauma casualties. In addition, because of the high visibility that injured US service members have received in the media and in local communities, there is a growing public awareness of many of the challenges faced by all individuals with disabilities. Despite these advances, more work is still needed, as thousands of individuals across the globe continue to suffer from conditions causing lower limb dysfunction, such as paraplegia, tetraplegia, hemiparesis, and limb loss. Fortunately, new discoveries in regenerative medicine, cellular therapy, robotics, and neuro-prosthetics offer hope and promise to revolutionize the care and treatment of individuals with disabilities, particularly those with lower limb dysfunction.

Lower Extremity Injury Related to Military Operations

Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have been the largest US armed conflicts since the Vietnam War [3]. Nonetheless, survivability from battlefield injuries is at a historical high as compared with Vietnam and WWII [4]. Advances in body armor design, technologies for countering various types of assault, and improvements in military medicine have dramatically improved service members' ability to survive combat events that likely would

have been fatal just a few decades ago. However, many of those who survive return with significant injuries. Contemporary warfare tactics and new equipment such as sensors, precision-guided munitions, and robotic weapons have rendered opposing military forces increasingly vulnerable. In response, they seek mobility and deadly effect through the use of improvised explosive devices (IEDs), roadside bombs, and suicide bombers. Between 2001 and 2011, 75% of casualties were associated with explosive fragmentation (blast trauma) and gunshot wounds [4]. Previous military conflicts involved small unit fire, maneuver, large set-piece artillery, or other methods, which produced an increasing predictable pattern of injuries over time. The introduction of blast trauma as a mechanism of injury has taken military medicine into unchartered territory.

A case study of the 2010 Afghanistan counter-insurgency military operations revealed that most casualties or injuries could be attributed to service members injured by explosive devices while completing dismounted foot patrols. These dismounted complex blast injuries were characterized by multiple amputations, especially of lower extremities. More generally, 54% of overall casualties during OIF/OEF were due to extremity injury [5]. To address these challenges, military medicine seeks not only to bolster injury prevention efforts but also to address the pain management and functional needs of wounded soldiers returning from combat.

Although lower extremity injuries are more common in combat than upper extremity injuries, both can have significant impact on functionality [6]. Because of the frequent high severity of extremity trauma sustained by combat casualties, often extensive surgical interventions are needed to preserve or salvage a limb. Despite significant advances in medical care, enhanced reconstructive techniques, and careful patient consideration, limb salvage is not always possible and amputation becomes necessary [7]. A recent study by Doukas et al. suggests that service members who undergo extensive limb salvage procedures may have even worse functional outcomes than those who receive amputation [8]. Combat-related injuries, particularly those occurring from a blast, are also likely to affect multiple organ systems. Therefore, it is not uncommon for a service member with limb loss or limb salvage to have other significant coexisting injuries, such as hearing or vision impairment, vestibular disorder, chronic pain, paralysis, traumatic brain injury (TBI), and/or behavioral health disorders such as posttraumatic stress disorder (PTSD). These comorbid injuries present considerable additional challenges for patients undergoing rehabilitation, including those learning to use assistive devices to assist with mobility [9]. Lastly, the most important influence on overall functional outcome may be psychosocial factors such as family support.

The effects of war often also involve civilian populations, whether through direct or indirect fire. Suicide bombs, vehicle bombs, and mortars are particularly lethal to civilians [10]. The dangers of warfare may persist for years after military conflict has ended, through exposure to unexploded ordnance such as landmines [11, 12].

Lower Extremity Dysfunction and Injury in Civilian and Military Populations

Motor vehicle accidents, falls, sporting-related incidences, and other trauma (including repetitive overuse injuries) represent the majority of injuries leading to lower limb dysfunction in both civilian and military populations. Disease-related conditions such as arthritis, peripheral vascular disease, cancer, and peripheral nerve injuries also account for a significant number of disabilities, especially in developed countries. While a comprehensive discussion of each of these conditions is beyond the scope of this chapter, the reader is

reminded that when caring for individuals with lower limb dysfunction, the first priority is to diagnose the underlying cause of the dysfunction in order to either correct the problem or mitigate its potential future complications. In the civilian setting, violent trauma remains a cause of lower limb injury. Similarly to combat-related trauma, violent trauma in civilian settings may also result in severe lower limb damage or even limb amputation. Although data suggests that functional outcomes for civilians with limb salvage are comparable to those for civilians who undergo amputation, overall functional outcomes for both patient categories need improvement [13, 14].

With respect to lower limb injury in civilian settings, lower limb amputation is far more likely to occur as the result of disease rather than trauma in more developed countries. For instance, it has been reported that up to 82% of lower limb amputations in certain regions of the United States are from vascular disease [15]. Furthermore, secondary problems such as diabetes, peripheral neuropathy, and foot ulceration significantly increase the risk of a contralateral limb amputation within 5 years of the initial limb loss, despite steady improvements in the treatment of peripheral vascular disease and diabetes [16, 17].

A comprehensive statistical analysis of the US population during the period from 1988 to 1996 noted that approximately 1,285,000 individuals were living with major limb loss. Dysvascular disease contributed to 46.2 cases per 100,000 persons while 5.86/100,000 had limb loss secondary to trauma and 0.35/100,000 secondary to malignancy of a bone or joint. About 25.64/100,000 of live births resulted in congenital limb deficiency. The prevalence rate for limb loss was highest among individuals over the age of 64. Peripheral vascular diseases and diabetes causing lower limb ulceration and/or infection contributed to 66% of all lower limb amputations. Trauma resulting from crush injuries and/or severing of a limb accounted for 26% of lower extremity amputations based on the same study. Only 5% of lower limb amputation was due to cancer (primarily osteosarcoma), and only 3% of limb loss was attributed to congenital deformities. While the incidence of congenital limb loss remained the same, the incidence of limb loss due to trauma and cancer declined. However, the incidence of dysvascular amputations increased during this study period. More recently, with early disease recognition and management, recent reports have noted decreasing incidence of amputation due to diabetes (study period 2000–2004) and peripheral arterial disease (study period 2000–2008) [18, 19].

The number of those living with limb loss in the United States is expected to double from 1.6 million to 3.6 million in 2050 based on current trends [20]. Currently, two-thirds of all amputations are performed on diabetic patients [21]. Research also shows that nearly half of the individuals who have an amputation due to vascular disease will die within 5 years [22]. Because diabetes is frequently linked with vascular disease, aggressive preventative treatment is needed. Based on current trends, Ziegler-Graham et al. found that the prevalence of diabetes is projected to nearly double by the year 2030, if no action is taken. Furthermore, with an increasing prevalence of obesity in the United States and the recognized connection between obesity and diabetes, the number of amputations secondary to dysvascular disease remains at risk to increase [21].

Considering the major role of vascular disease in lower extremity amputations, it is necessary to recognize the importance of prevention, early recognition, and treatment. Primary prevention is ideal, but early recognition and intervention are also beneficial. Foot ulceration is a frequent complication of arterial and venous vascular disease. The most costly and feared consequence of a foot ulcer is limb amputation, which occurs 10–30 times more often in diabetic persons than in the general population. In fact,

approximately 80% of all non-traumatic amputations occur in individuals with diabetes. Mortality following amputation is also high, ranging from 13% to 40% at 1 year, 35% to 65% at 3 years, and 39% to 80% at 5 years [23]. If foot ulcers can be prevented or treated effectively when they occur, limb amputation might be avoided. More frequent visits to the doctor's office, foot screening programs, and self-management education are secondary steps to support greater awareness and prevention [24].

The national disparity among racial and ethnic groups in terms of limb loss is likely related to poverty and differences in access to primary care and preventative services. Nonetheless, at both the national and international levels, efforts must be made to increase education and provide resources to underserved populations. Economic and social/psychological barriers must be overcome to have a lasting impact [19, 25, 26].

The causes of lower limb dysfunction and particularly amputation in developing countries contrast significantly from those seen in developed countries. Developing countries report higher incidences of trauma and disease due to causes such as landmines, violence, infectious disease, and natural disasters [27, 28]. In developed countries, dysvascular disease accounts for nearly 90% of amputations; other causes, such as cancer and congenital deformities, represent less than 10% [29].

Paresis and Paralysis Causing Lower Limb Dysfunction

Various forms of paresis (weakness) or paralysis (complete loss of motor activity) may significantly impair lower limb function. According to a study conducted by the Christopher & Dana Reeve Foundation, nearly one in 50 people within the United States are living with paralysis. Among 67,000 respondents, the leading cause for paralysis was stroke (29%), followed by spinal cord injury (23%). Just 7% reported acquiring paralysis while serving in the military. Other causes of paralysis included a number of diseases, TBI, and unspecified birth defects. African-Americans and Native Americans were disproportionately represented in the overall number of paralysis cases [30].

More than 40% of new spinal cord injuries (SCI) each year are caused by automobile and motorcycle accidents. After the age of 65, SCI is most often due to falls, and this accounts for more than one-fourth of SCI overall [31]. Attention and care for the elderly should extend the utmost concern for prevention of falls. Sports and recreational injuries, acts of violence, and alcohol are also contributing factors. In the public sphere, better regulation of traffic laws and proper protective equipment are important preventive measures. More stringent restrictions with regard to speeding, helmet use, and penalties for risky behavior might encourage better adherence and reduce the number of injuries [31].

Lower limb paralysis or dysfunction may also be from injury to the brain, whether traumatic or non-traumatic. Perhaps the most common cause of non-traumatic brain injury is a cerebral vascular accident (CVA) or "stroke." A CVA occurs when there is a loss of blood circulation to the brain either from an arterial occlusion or bleed. The resultant lack of oxygen (ischemia) leads to brain cell death [32]. If the damaged nerve cells are within the area of the brain responsible for motor function (motor cortex) of the lower limb, it may cause hemiparesis (weakness on one side of the body) or hemiplegia (paralysis on one side of the body). This is also typically accompanied by spasticity or increased muscle tone on that side of the body, impairing muscle function and range of motion. Preventing the incidence of CVA requires increased education and proactivity on the part of patients and healthcare provid-

ers. Improved recognition of warning signs that suggest not enough oxygen is reaching the brain allows patients to receive medical attention in a timelier manner and ultimately improves their chance of survival. Attention to risk factors by physicians and patients can also prove helpful. Increased age, family history of stroke, gender, and race are factors for stroke that cannot be controlled. Other risk factors, such as hypertension, cigarette smoking, heart disease, diabetes, high cholesterol, physical inactivity, and obesity, are risk factors that can be modified. Identifying stroke risks and treating them accordingly is the best prevention.

Although nearly eradicated in developed countries, poliomyelitis outbreaks continue to occur in some developing countries. Poliomyelitis or polio is a viral infection that affects the spinal cord, particularly the cell body of the motor neuron. One in 200 infections leads to irreversible paralysis, and 5–10% of paralysis cases lead to death. Globally, polio cases have decreased by over 99% since 1988. Yet, a number of developing countries still struggle to eradicate the disease despite advances in immunization systems. In 2005, the Dominican Republic and Haiti experienced an outbreak, and, currently, Afghanistan, Nigeria, and Pakistan remain polio pandemic [33]. According to the World Health Organization, "as long as one child remains infected, children in all countries are at risk of contracting polio." Studies showed that recent outbreaks in Northern Nigeria resulted from rumors that the immunization would cause sterility among the immunized boys. Fighting against cultural stigma and fallacies might be just as crucial to eradicating polio as providing the immunization and medical treatments. Immunizations have no effect on individuals who have already had the disease, so special attention to treatment goals for those adult patients is important as well. Shared literature and outreach from medical professionals in developed countries could assist with this goal [33, 34].

Rehabilitation

Considering the increasing prevalence of individuals (civilian and military) with lower limb injury, dysfunction, and/or amputation, it has become increasingly imperative that the medical community devises new strategies to prevent and effectively treat these conditions. Moreover, increased awareness is needed to help prevent and/or mitigate other health and wellness issues that are commonly experienced by individuals who age with a disability. Problems such as cardiovascular disease, posttraumatic arthritis, overuse injuries, obesity, diabetes, depression, and chronic pain unfortunately remain highly prevalent in patients with lower limb dysfunction. This may be attributable to decreased mobility and exercise but may also be secondary to other physiological factors (neuroendocrine, metabolic, biomechanical, etc.) yet to be fully defined. Therefore, programs to help positively influence modifiable risk factors such as decreasing alcohol and tobacco use, preventing obesity, improving nutrition, and promoting active lifestyles activity are important to incorporate into a comprehensive rehabilitative treatment plan. Equally important is the development of effective assistive technologies such as orthotics, prosthetics, and wheelchairs. These factors with programs that include rehabilitative counseling, adapted sports and recreation, vocational rehabilitation, and driving rehabilitation can help to ensure that individuals with lower extremity dysfunction are able to achieve the highest level of independence and return to active community participation.

Whether treating civilians or military service members with lower extremity dysfunction, the rehabilitative principles of patient education; restoring range of motion, strength, and mobility; maximizing functional independence; and enhancing community participation and quality of life remain consistent. There are, however, unique considerations when caring for the combat

casualty. Military casualties, particularly those who have sustained blast injuries, are more likely to have a higher rate of comorbid conditions that need be accounted for in the development of individualized rehabilitative treatment plans. For example, coexisting TBI with resultant behavioral, emotional, and/or cognitive deficits may significantly challenge teaching a patient how to successfully perform activities such as donning and doffing a prosthesis, sequencing activities of daily living (ADL), or performing vigilant skin surveillance to prevent the development of pressure ulcers. Similarly, with the high rate of psychological health conditions such as depression, anxiety, and PTSD commonly associated with combat injury, it is imperative to insure that the behavioral health treatment plans are fully integrated into the entire rehabilitative program. This also includes carefully managing pharmacological interventions, especially avoiding any potentially adverse drug vs. drug interactions. Lastly, other factors such as the individual's premorbid functional level, desire to remain on active duty, separation from his/her military unit, and geographic barriers between the location of their medical care and their extended social support network all present additional challenges when caring for the combat casualty with lower extremity dysfunction.

Independent of the cause of limb dysfunction, a comprehensive rehabilitation program should always incorporate the patient's short- and long-term goals. Examples of initial short-term goals might include activities such as being able to stand independently or transfer to a wheelchair, while the long-term goal may be returning to running or sports participation. The entire rehabilitation team as well as the patient and patient's family should be involved in setting goals to ensure alignment of objectives among all parties. Equally important is the development of goals that are achievable. Trying to advance goals too quickly may create significant frustration and pressure on the patient, which can in turn reduce motivation and participation. Professionals such as rehabilitative counselors, vocational rehabilitation specialists, behavioral health specialists, recreational therapists, social workers, and coaches can all play a significant role in developing and executing an effective rehabilitative program. Despite the best planning efforts, patients should be told that setbacks such as infections, skin breakdown, difficulty with learning assistive technology, and emotional challenges (e.g., grief, guilt, anger, depression, irritability, hopelessness) are to be expected and that the rehabilitative team is positioned and skilled to help the patient address all of these issues throughout the recovery and reintegration process. For military service members who are interested in remaining on active duty, direct communication between the rehabilitative team and the service member's military unit can help to manage expectations and plan appropriate treatment interventions.

Historically, people suffering from lower limb paralysis had few options for treatment and were generally quite limited in terms of their independence and functional ability. Today in the United States, approximately 3.6 million people use wheelchairs and 11.6 million use canes, crutches, or walkers to assist with mobility [35]. Rather than focusing solely on the need to accommodate lower limb dysfunction with assistive technology, rehabilitation programs now employ therapies that target functional restoration [36]. While many individuals with lower limb paralysis still require the use of a wheelchair for mobility, healthcare professionals apply new programs and technologies that assist leg movement to promote muscle conditioning, bone health, and reduction of secondary complications attributed to disuse. One such system is the functional electrical stimulation (FES) cycle, which can be used at home or in therapy. In addition, more sophisticated systems, including exoskeleton ambulatory systems, are currently available but are generally limited to use

in rehabilitation centers [37, 38]. For patients with paralysis, evidence suggests that intense activity-based therapy may help to restore function [39]. Therefore, several treatment interventions are currently in development to promote neuromuscular recovery and even regeneration. Patients who have little to no voluntary leg movement are able to practice neuromuscular retraining through simulated walking on a treadmill, using an overhead harness support. This "locomotor training" can be facilitated with the aid of therapists to manually advance each leg or with the simultaneous application of FES. These therapies may also improve bone density, cardiovascular, pulmonary, and bladder function, as well as overall quality of life. Currently, lower limb exoskeletons are also being researched (Fig. 2.1). Complete external systems allow patients with paralysis and other causes of lower limb dysfunction to take part in gait training. Significant additional research is needed to evaluate the efficacy of these treatment regimens and to define optimal treatment intensity, frequency, and duration. In addition to their potential to enhance rehabilitation, exoskeleton systems may offer advanced means of mobility for individuals with lower limb dysfunction, including those with paraplegia (Figs. 2.2 and 2.3).

Fig. 2.2 AeroR Ocean Blue, ultralight wheelchair (Photograph Courtesy of TiLite, http://www.tilite.com/)

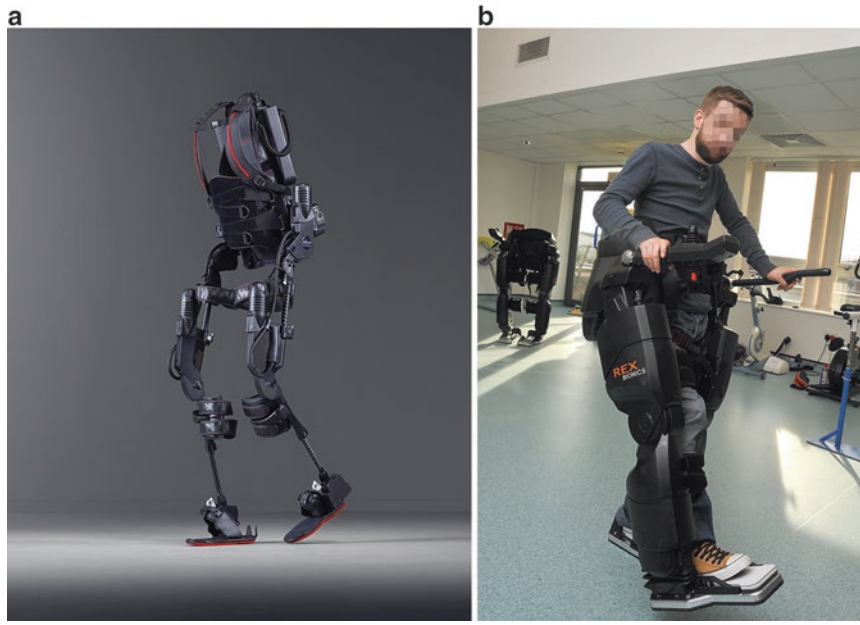

Fig. 2.1 (**a**) Ekso™ Bionics Exoskeleton (Ekso Bionics, Richmond, CA) (Photograph Courtesy of Ekso Bionics, www.eksobionics.com). (**b**) REX™ hands-free robotic mobility device for rehabilitation (Photograph Courtesy of REX Bionics, http://www.rexbionics.com/)

Fig. 2.3 The Mobility Enhanced Robotic Wheelchair (MEbot) is an advanced wheeled mobility platform designed to provide exceptional indoor and outdoor mobility for people with impaired lower and upper extremity function. The MEbot provides such seating and accessibility features as fore/aft tilt, lateral tilt, recline, and elevation within a small footprint for indoor mobility and activities of daily living. In addition, it provides remarkable outdoor mobility to include curb climbing, self-leveling over uneven terrain, and crawling (Courtesy of Human Engineering Research Laboratories (HERL), http://www.herl.pitt.edu/)

Wheelchairs

Advances in wheelchair design, materials, and technologies can now accommodate most patients with even the most complex lower limb dysfunction [40, 41]. Wheelchairs are generally categorized by three types: manual, electric, and hybrid. Manual chairs are propelled by the user, whereas electrical chairs are battery powered and typically controlled through a joystick mounted on the armrest. Hybrid wheelchairs resemble manual wheelchairs, but when the user applies a light torque on the wheel, a motor is activated to aide in propulsion (pushrim-activated power-assist). Selection of the proper wheelchair system requires consideration of multiple factors. The type of wheelchair prescribed should maximize the user's potential and also meet the user's needs, abilities, and desires. Consideration should also be made regarding the frequency of intended use, type of terrain (indoor or outdoor), and transportation needs. Similar to orthotics and prosthetics, wheelchairs should be configured in a customized fashion to best meet the size and dimensions of the user. Proper seat selection, including the type of cushion and dimensions of the chair height, depth, and width, will have a significant impact on the user's risk of developing secondary complications such as pressure ulcers or upper limb overuse injuries as may occur due to excess biomechanical strain (to achieve propulsion) or effective transfer in and out of the chair. Ultralight and lightweight manual wheelchairs may offer ease in transportation and reduce the amount of torque needed to propel the chair; when combined with proper propulsion techniques, a lighter-weight chair may mitigate upper limb overuse.

Manual wheelchair frames may be folding or rigid. Collapsible/folding chairs are easier to transport and store but are often heavier and less responsive to handling and performance. Therefore, the majority of wheelchairs utilized for sports activities have rigid frames. The width, length, and axle position of the chair, its wheels, and casters significantly affect stability. Experienced users often prefer a relatively less stable wheelchair configuration that allows better maneuverability, particularly when required to negotiate obstacles, perform wheelies, or navigate through narrow doorways or other architectural barriers. However, less experienced wheelchair users may require a longer wheelchair with anti-tip bars to provide for greater stability. Wheel camber (the angle that the wheel tilts in or out in the vertical plane) can also

be adjusted. A larger camber creates more side-to-side stability, quicker turning, and protection of the hands as the wider bottom of the wheel protects the user from striking obstacles such as doorways.

Essentially every component of a wheelchair can now be customized. Pneumatic tires are available for a more cushioned ride and, when treaded, can be used to effectively navigate over soft, sandy, or rough terrain. Semi-pneumatic solid wheels made of cast metal alloy and cast plastic are often sturdier and require less maintenance. Hand rims are located on the wheels to allow users to steer the wheelchair independently. Vinyl-coated rings and various projections are available to users with different grip strength. The choice of various foot and armrest configurations can accommodate other injuries or devices such as lower or upper limb fracture, prosthetics, or orthotics. Depending on the individual user's upper limb mobility and/or dexterity, the location and configuration of the chair's wheel locks may also have a significant impact on functional performance. Individuals with hemiplegia or unilateral lower limb amputation can utilize a foot-drive wheelchair, which has a slightly lower seat and a front rigging system that is adapted to permit efficient use of the leg.

Individuals with more severe disability may require a power chair. Power chairs are commonly characterized by three types: indoor, indoor/outdoor, or active indoor/outdoor. Indoor power chairs are typically smaller, lighter weight, and require less power. Their design offers better maneuverability, particularly when negotiating tight indoor spaces. Power wheelchairs that are used for indoor/outdoor spaces or "active" indoor/outdoor use offer wider base tires, enhanced suspension systems, greater power and speed, and tire treads appropriate for use in inclement weather. Power chairs typically have reclining seats, which provide enhanced comfort as well as accommodation for pressure reliefs. For individuals with poor upper body and trunk control, a "tilt-in-space system" configuration may be used wherein the backrest, seat, and leg rests tilt together as a unit without changing in relative configuration to each other. This type of system supports effective pressure reliefs and may also reduce spasticity, enhance posture and seating tolerance, and improve venous blood return by allowing the user to adjust body position throughout the day. Despite the sophistication of many modern wheelchairs, significant expertise is needed to prescribe and fit an optimal system for each individual patient. Similarly, wheelchair training is a very important part of rehabilitation to ensure the user is able to operate the wheelchair safely and effectively. This should include instruction on proper propulsion techniques, obstacle negotiation, and falls prevention and recovery.

Orthotics and Prosthetics

Despite advances in wheeled mobility, ambulation remains a primary goal for individuals with lower limb dysfunction and is therefore a significant focus of rehabilitation. In addition to restoring lower limb strength and range of motion through therapeutic exercise, prosthetics and/or orthotics may also be needed to enhance mobility. A lower limb orthosis is a device or brace worn to support or correct a lower extremity deformity or dysfunction. Lower limb orthotics may be "off the shelf" such as a knee or ankle brace to improve joint stability and protection after an injury. Alternatively, an orthotic may be customized, such as a sophisticated Ankle Foot Orthosis (AFO). AFOs may be used to unload biomechanical forces within the injured ankle or foot. They may also be used to accommodate lower limb paresis or paralysis below the knee by assisting toe clearance or preventing ankle collapse during ambulation. More recently, advanced orthoses have been developed for individuals

who have undergone limb salvage procedures. When combined with aggressive physical therapy, orthotics can be helpful to support a return to high-level activities, including running, and may even help to prevent the need for lower limb amputation [42].

For individuals with lower limb amputation, a prosthetic is often needed to restore ambulation. Prosthetics are artificial limbs which can vary significantly in their configuration depending on the level of amputation and residual limb function. The size, shape, alignment, and components of lower limb prostheses are custom fit to help restore the most biomechanically efficient gait possible. Important determinants of efficient gait include symmetric or proportionate step length, stance stability, swing clearance, adequate foot position before initial contact, and energy conservation [43, 44]. Despite prosthetic use, individuals with lower limb amputation(s) often demonstrate a number of gait deviations. Some factors that influence deviations from normal gait include poor soft tissue coverage of the residual limb, lower limb contractures, presence of heterotopic ossification, persistent pain, inappropriate alignment or height of the prosthesis, functional impairments of the contralateral limb, and loss of somatosensory feedback or limb position awareness [45]. Many of these factors can be minimized with proper amputation surgery, appropriate prosthetic fitting and alignment, effective clinical interventions, and specialized rehabilitative training. Uncorrected gait deviations may lead to long-term morbidities such as overuse injuries, osteoarthritis, residual limb skin breakdown, and lower back pain. Advances in prosthetic design and rehabilitation interventions attempt to normalize biomechanics, thereby minimizing gait asymmetries that can lead to secondary conditions and impairment [46].

Individuals with lower limb amputation must learn how to appropriately don and doff a prosthetic device and relearn basic mobility skills to successfully achieve independent ambulation. Full ambulatory capabilities enhance the user's ability to carry out independent and free lifestyles. Fundamental to successful lower limb prosthetic fitting is the design and fabrication of the prosthetic socket, which is customized to accommodate the size and shape of the user's residual limb. To accommodate the variability of residual lower limbs, prosthetists are especially skilled at using plaster casting techniques or computer-aided design (CAD)/computer-aided manufacturing (CAM) techniques to meet both static (at rest) and dynamic (in motion) needs of the residual limb. Socket designs often have to be modified multiple times during initial prosthetic fitting to accommodate of residual limb maturation and changes after amputation. Flexible liners may be combined with rigid external sockets to help provide pressure relief to pressure-sensitive areas of the residual limb. Lower limb prosthetics may be suspended to the lower limb by a series of forces and devices, including suction, specialized sleeves, pin locks, and even waist belts.

Prosthetic component choices are different for individuals with above-knee (transfemoral) or below-knee (transtibial) amputations/deficiencies. Transfemoral prosthetic designs focus on adaptations to compensate for the absent knee joint. Prosthetic devices developed for individuals with transtibial amputation are designed to adapt for the missing foot and ankle joints. Because individuals with transfemoral amputation have a higher incidence of gait asymmetry and related complications, research is ongoing to design prosthetic devices that better simulate the anatomical knee and minimize gait deficiencies [47].

A number of updated prosthetics have already been designed for the foot and ankle. The ideal device mimics a proper anatomical foot and can range from simple to complex in its design. When appropriately assigned, the prosthetic foot improves gait efficiency and limits patient gait deviations by stabilizing the knee and supporting the limb overall.

Important aspects of the prosthetic foot include foot-ankle joint simulation which impacts gait, shock absorption to dampen impact on the residual limb, and cosmetic appearance. A dynamic response foot allows the patient to have a lively, responsive feel while walking (Fig. 2.4). The keel changes shape/deforms upon loading, absorbs impact, and returns to its original state (recoils) after the load is removed. Keel thickness can be adjusted based on the patient's weight and activity level. Specialists refer to this type of design as energy storage and return (ESAR) [48]; it allows for self-selected walking velocity, stride length, and decreased compensation necessary on the unilateral amputee's sound limb. When vertical, shock-absorbing pylons are added to dynamic response prosthetic feet and the shock transmitted to the residual limb is decreased even more [49]. Another type of prosthetic foot is the articulated foot, which is multi-axis, permitting patients to take on varying terrains with benefits similar to those of dynamic response feet.

Fig. 2.4 Re-Flex Shock™ prosthetic foot (Ossur Americas, Aliso Viejo, Calif) (Photograph: Courtesy of Ossur Americas, www.ossur.com)

A variety of prosthetic knees are available for individuals with above-knee amputation(s), ranging from simple free swing and locking knees to advanced hydraulic knees, including those with onboard microprocessors that allow variable dampening of knee flexion/extension resistance. Prosthetic knees are often classified as single axis or polycentric. Single-axis knees are typically lightweight and low maintenance. Knee stability is largely determined by alignment of the knee in relation to the socket and foot as well as the control of the patient. These designs can be adapted to include a number of features described below including constant friction, fluid control, and microprocessor or power stride control. Polycentric knees use curved-bearing surfaces or linkages to offer multiple centers of rotation about the knee joint in order to replicate the rocking and gliding motions of the anatomical knee; axis location changes as the knee moves through its range of motion – a phenomenon known as instantaneous center of rotation (ICR) (Fig. 2.5). Polycentric knees may offer more stability than simple single-axis knee designs and improved cosmetic appearance while sitting.

The single-axis prosthetic knee with constant friction is known for its simplicity, durability, and ease of use. Continuous pressure/friction is provided around the knee axis to control the velocity at which the shank and foot can swing to prevent excessive energy use and impact during walking. Resistance is adjustable manually but does not self-adjust as velocity changes. For the majority of people who walk at varying speeds, a more gait-responsive knee is desired. Fluid-controlled knees provide friction that changes with respect to speed. One such type is the pneumatic knee. This knee compresses air while the knee is flexed, storing energy. The energy is returned as the knee extends. Pneumatic knees provide patients with a "springier" feel and pro-

Fig. 2.5 Total Knee® 2100 (Ossur Americas, Aliso Viejo, Calif) (Photograph: Courtesy of Ossur Americas, www.ossur.com)

Fig. 2.6 C-Leg® Genium (Otto Bock, Germany) (Photograph Courtesy of Ottobock, www.ottobock.com)

vide better control than the friction knees. In contrast to pneumatic knees, hydraulic knees utilize hydraulic fluids; hydraulic knees are used more often because they more closely emulate anatomical knee function.

Microprocessor knees are often referred to as "variable dampening knees" (Fig. 2.6). These knees are battery powered and have onboard electronics that sense the user's walking speed (cadence) and in response provide real-time adjustments to knee joint stiffness, offering less resistance and more free swing during faster walking speeds. Variable dampening knees decrease the effort required by the user to control timing and walking motions, leading to a more natural gait and improved gait and balance [50]. These devices are generally more responsive than mechanical knees and can be adjusted throughout the patient rehabilitation period for increased stability and safety.

Powered lower limb prosthetics have recently become commercially available for individuals with lower limb loss (Figs. 2.7, 2.8, and 2.9).

Fig. 2.7 PROPRIO FOOT® (Ossur Americas, Aliso Viejo, Calif) (Photograph: Courtesy of Ossur Americas, www.ossur.com)

Powered prosthetics are engineered and designed to replace the biomechanical forces lost through amputation, such as active knee extension, ankle

Fig. 2.8 emPOWER™ Ankle (Photograph: Courtesy of BionX™ Medical Technologies, www.bionxmed.com)

Fig. 2.9 POWER KNEE™ (Ossur Americas, Aliso Viejo, Calif) (Photograph: Courtesy of Ossur Americas, www.ossur.com)

dorsiflexion, and ankle plantar flexion. As a result, these prosthetic components more closely approximate normal gait kinetics and kinematics, especially at higher walking speeds. In addition, by replacing biomechanical power, it is easier and requires less energy to negotiate inclines, stairways, and transition from sitting to standing. These prosthetic devices have multiple onboard sensors, including strain gages and accelerometers that utilize recognition patterns and algorithms to replace the natural gait.

Despite advances in microprocessor-controlled and powered lower limb prosthetic devices, the majority of individuals with lower limb loss continue to use mechanical knees and manual ankles primarily because of their lightweight, simplicity, reliability, and lower cost. Future research is needed to better understand the role that these technologies have on both the short- and long-term healthcare outcomes of individuals with lower limb loss. In addition, further development of this technology is needed to reduce cost and improve reliability and battery performance to allow more global penetration. While these technologies provide a window to the future of rehabilitative care, significant cost and access barriers persist.

Future Directions

The future of treatment for individuals with lower limb injury and dysfunction should include plans for patients affected by paresis, paralysis, and amputation. Efforts should be made toward restoring function, while at the same time avoiding or at least mitigating the development of secondary long-term health complications for individuals with disabilities. For example, improving the comfort level for wheelchairs and prosthetic devices can avoid development of pressure sores, skin breakdown, and other secondary conditions. Interventions such as direct skeletal attachment (osseointegration) may revolutionize future prosthetic fitting and use [51]. In addition, strategies to improve user interfaces between individuals with disabilities and their assistive technologies (e.g., wheelchairs and prosthetic devices) can be applied to improve responsiveness and adaptability to patient-specific needs. More intuitive control may also allow individuals with impaired cognition or other sensory impairments to independently

operate prosthetic devices more successfully. Lastly, new power sources should be explored to increase availability to patients who may not have constant or reliable access to electricity.

Another integral aspect of rehabilitation includes the role of family members and community, both of which play an important role in supporting the recovery, rehabilitation, and successful reintegration of military as well as civilian patients who sustain lower extremity injuries and dysfunction. Active community participation has a positive influence on quality of life. Therefore, the social context of a physical impairment is important when evaluating overall disability. Individuals with newly acquired disabilities report significant benefit from peer support and mentorship [52]. In the area of physical activity, the use of sport-specific prosthetic devices promotes increased functional ability, participation in group activities, and better quality of life for many users [53]. The community must come together to seek additional ways to be inclusive of individuals with disability and to help improve their community participation. Working together to prevent lower extremity injuries from occurring in the first place, and to improve quality of life for patients who have been injured, will bring us closer to meeting today's military and civilian medical and restorative needs.

Disclaimer The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, the Department of Defense, the Department of Veterans Affairs, or the US Government.

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Sacrifice, Science, and Support: A History of Modern Prosthetics

3

Robert S. Gailey and Sheila M. Clemens

The history of prosthetic care is a history of warfare, disease, medicine, and technology. Humans have engaged in conflict, warfare, and survival of the fittest, often at the expense of life and limb as evidenced by the multitude of military personnel injured in past and present conflicts. Although war and conflict have accounted for a significant share of amputations, other historical factors have also played a role. During the years of industrialization, the United States had an increase in factory accidents resulting in amputation due to unsafe and unregulated working conditions. In addition, disease processes such as vascular disease, diabetes, and tumors are often responsible for limb loss. Frequently the risk factors for limb-consuming illnesses are preventable, and researchers continue to seek avenues of education to improve disease management, prevent industrial and occupational accidents, and decrease the impact of disability. Education, regular clinical care, and early medical interventions have contributed to the reduced incidence of major amputation related to vascular conditions [1, 2]. It has been the life's work of many dedicated researchers, engineers, prosthetists, physicians, and therapists to return amputees to a life without functional limitations. This chapter summarizes the historical advances made toward improving lower limb prosthetic devices and technologies and the motivation behind their development.

From earliest recorded history to the present day, medical engineers have recorded their efforts to develop artificial devices that could take the place of lower limbs lost to disease, injury, and war. Their accounts represent the state of the art and science at different times and places throughout history and reflect humankind's innovative and creative spirit in the face of extreme physical disability. The mythological records tell of gods, goddesses, and mortals whose legs (and arms) of metal and ivory allowed them to carry on through their loss. Early Egyptian (1,500 BC) tombs revealed efforts to replace the eyes, teeth, and legs with devices made of wood, fiber, and

R.S. Gailey, PhD, PT (✉)
University of Miami, Coral Gables, FL, USA

Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, FL, USA
e-mail: rgailey@miami.edu

S.M. Clemens, PT, MPT
Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, FL, USA
e-mail: s.qualls@umiami.edu

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leather. Herodotus (484–425 BC) recorded the story of a Persian prisoner who, in order to free himself from restraints, cut off part of his own foot and later made a wooden toe-filler replacement. The oldest prosthesis unearthed from a tomb in Capua, Italy, was dated about 300 BC. From the pre-Roman era through the Middle Ages, elaborate artificial limbs were made by armorers for the noble class. Though extravagant, the limbs were not especially functional and were typically worn for show or used when riding a horse. Carpenters fashioned the more useful wooden "peg legs" (Fig. 3.1) that served better to support those who survived limb loss and could afford the cost of prosthetic substitution.

Creative fervor during the late Renaissance period and the Age of Enlightenment inspired additional refinements, including the development of artificial limbs equipped with straps, gears, and springs to provide basic levels of articulation. In the early sixteenth century, the French surgeon Ambrose Paré designed complex prosthetic devices, among them an above-knee prosthesis that included a spring and strap-driven knee and ankle. Many question how extensively Paré's prostheses were actually used [3, 4].

Fig. 3.1 Peg leg from 1700s Revolutionary War (Courtesy of Robert Gailey private collection)

War catalyzed progress toward functional prosthetic devices to better the lives of soldier amputees, with improvements in prosthetics eventually extending to civilian amputees. Americans have always supported the notion that military veterans have earned the right to be cared for by their country. Dating back to 1636 and the time of the Pilgrims, it was intended that the battle-injured soldier would be supported by the colony. In 1776, the Continental Congress provided pensions for disabled soldiers. In his 1865 inaugural address, Abraham Lincoln's request to Congress "to care for him who shall have borne the battle and for his widow, and his orphan" [5] has become the Department of Veterans Affairs (VA) motto. These events set the stage for the US government's involvement in caring for those injured through military service and for their families.

The concurrence of wartime conflict with advances in prosthetic design and technology is not a recent development. The unprecedented destructive firepower of the American Civil War, combined with government funding and programs, ushered in a new era in prosthetic devices. Many of today's innovations are based on groundwork laid during the nineteenth century. Improvements in sterile surgical technique, infection control, and advances in first response care in the theater of war were key factors as to why more Civil War soldiers survived devastating injuries that would more likely have resulted in death had they occurred during earlier military conflicts. However, in many cases, survival came at the expense of one or more lost limbs.

At the onset of the American Civil War, soldiers quickly realized they were facing a new foe: advanced firepower. One innovation that made

Fig. 3.2 Minie ball (Courtesy of National Museum of Civil War Medicine, Frederick, Maryland)

the Civil War so deadly was the advent of the Minie ball (Fig. 3.2). Prior to the development of the Minie ball, rifles were difficult to load. The Minie ball was a spin-stabilized rifle bullet that could be loaded quickly and fired accurately. It was designed with a hollow base and two or three grooves, which stabilized its flight for better range and accuracy. It flattened on impact, inflicting larger wounds than were caused by traditional musket balls. The Minie ball shattered and splintered bone, and its grooves carried bacteria, which could eventually lead to gangrene and amputation.

Greater artillery power increased the number of dead and injured soldiers. Amputations comprised 75% of all surgeries performed during the Civil War; 30,000 Union soldiers and 40,000 Confederate soldiers lost limbs [5, 6]. Many survived their initial surgeries only to succumb to infections due to non-sterile techniques in the pre-antibiotic era. The increased ability to maim and kill was not matched by an increase in the physician's ability to heal. The average surgical amputation was performed in fewer than 10 min, with the surgeon likely wiping his surgical tool off on his apron before proceeding, with unwashed hands, to the next injured soldier. Interestingly, it is said that Confederates suffered lower incidence of postsurgical infection when they began to use boiled horsehair to suture wounds. This was done when suture thread was not available. The horsehair was boiled to make it more pliable, with the unknown advantage that boiling also served to sterilize the material [7]. Unsanitary surgical conditions were compounded by surgeons' lack of familiarity with and ineptitude at performing proper amputations. Prior to the war, only 500 of the 11,000 Northern physicians and 27 of 3,000 Southern physicians had performed surgery. Soldiers' residual limbs were often left to heal with protruding bone and tattered tissue edges, causing pain with any attempt to utilize a prosthesis. Surviving Union amputees were provided with prosthetic devices by the federal government, while Confederate soldiers were provided for at the state level [8].

In response to the large number of amputees injured in the Civil War, as well as a growing number of civilians injured in railroad and industrial accidents, the US government established what it called "The Great Civil War Benefaction," which would help to cultivate the burgeoning field of prosthetic device development [5, 6]. The Benefaction was the US government's pledge to provide prostheses to all injured veterans, a forerunner to the federal support given to amputee service members of today. It spawned the movement toward production of prosthetic devices on a much larger scale than had occurred previously. American inventors bent their minds toward developing better prosthetic devices, resulting in new, lighter-weight designs for artificial limbs still composed of wood, metal, and leather. During the 15 years before the war, just 34 patents had been issued for artificial limbs and assistive devices. Subsequently, during the 12 years after the commencement of the Civil War, 133 patents for prostheses were issued, representing an almost 300% increase [6]. Unfortunately, it remained difficult to find quality-made prostheses. Mail order purchasing was common, through catalogues from large companies such as A.A. Marks in New York [5].

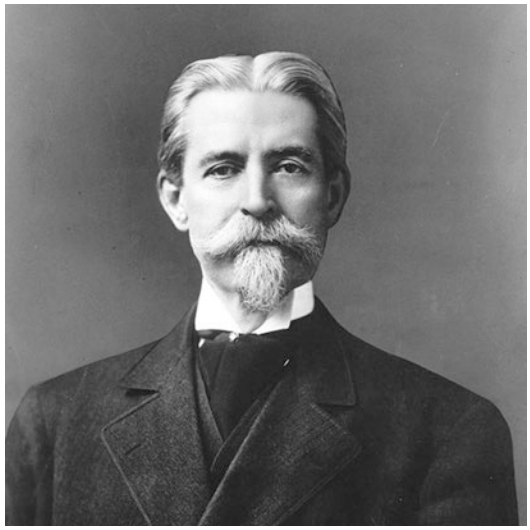

Fig. 3.3 JE Hanger lost his limb above the knee 1861 at the start of the Civil War and went on to patent many prosthetic designs (Courtesy Hanger Clinic)

James Edward Hanger (Fig. 3.3) was a confederate soldier and reputed first amputee of the Civil War (1861) who set forth to improve on the prosthetic devices of the day. Suffering an above-knee amputation even before he had formally enlisted, Hanger decided he would not settle for the wooden peg leg he had been given by the government. At his home in Virginia, he developed the "Hanger limb" by replacing catgut tendons used in the earlier "American Leg" prosthesis with rubber bumpers, to allow for dorsiflexion and plantarflexion (Fig. 3.4). The American Leg was a modified version of James Potts' Anglesey leg, which had been brought to the United States from the United Kingdom in 1839. The American Leg had a series of internal cords that dorsiflexed the ankle when the knee was flexed and plantarflexed the foot when the knee extended [8, 9]. Later, Hanger also developed an articulated rubber foot, a predecessor of the solid ankle cushion heel (SACH) foot, and patented his "Hanger limb" in 1871 (Fig. 3.5) [6].

During the years between the American Civil War and World War I (WWI), limited progress was made in the field of prosthetic devices.

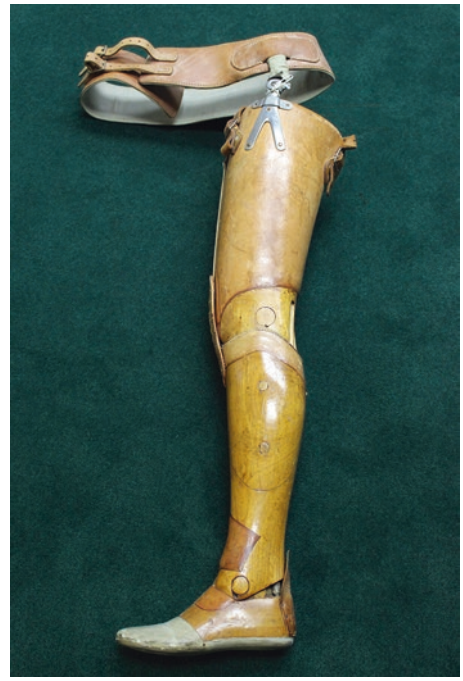

Fig. 3.4 American Leg with cords that dorsiflexed the ankle when the knee bent (Courtesy of Robert Gailey private collection)

Between these periods of conflict, the ability to fabricate artificial limbs belonged to a few highly competitive craftsmen who would quickly patent any saleable mechanisms. However, those who might want to purchase prostheses had no standards to guide them in their selection [10].

Individual states had established homes to care for disabled veterans, but federal programs to assist them were consistently lacking. Soldiers from WWI returned from Europe to find a dearth of available jobs. Without any formal organization to assist them in their return to family and community, many injured service members found themselves unemployed. In 1917, Congress established a new system of veterans' benefits to include compensation, insurance, and vocational rehabilitation.

Concomitantly, the Army Surgeon General summoned those working in the cottage industry of prosthetics, referred to as limb makers, to Washington, D.C., to address the needs of veteran

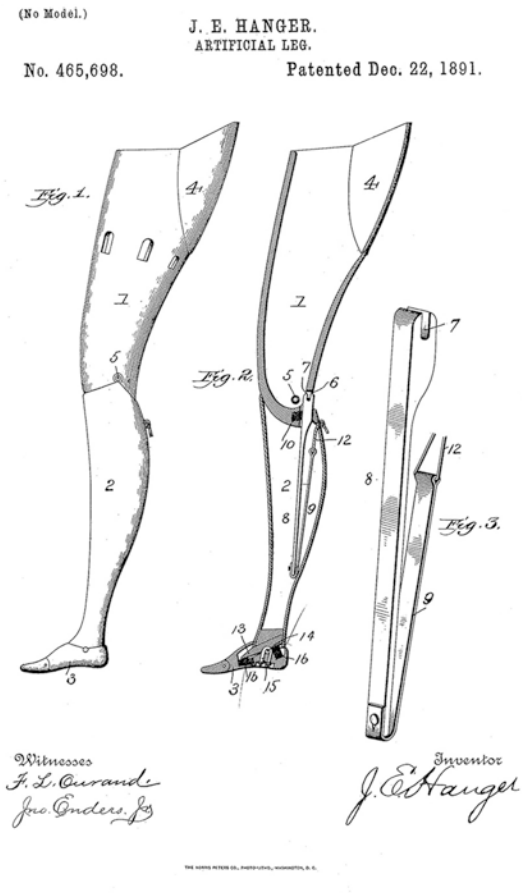

Fig. 3.5 Prosthetic patent filed by JE Hanger in 1891 (Courtesy Hanger Clinic)

amputees. This led to the establishment of the Association of Limb Manufacturers of America, known today as the American Orthotics and Prosthetics Association (AOPA).

By the 1920s, veterans' benefits and compensation were under management of the Veterans Bureau, the Bureau of Pensions of the Interior Department, and the National Home for the Disabled Volunteer Soldiers. In 1930, Congress authorized President Herbert Hoover's request to "consolidate and coordinate government activities affecting war veterans" [11]. The three agencies were subsumed as bureaus within the newly created Veterans Administration. To the present day, the VA is a major funder of prosthetic device research and development worldwide.

Between 1920 and 1945, progress in the advancement of prosthetics in the United States was slowed by pressures of the Great Depression and lack of funding for any programs considered extraneous. If an amputee could afford a prosthetic and could tolerate wearing one, an artificial leg could be fabricated at a local limb shop or mail ordered. Research and development was accelerated in Europe, however, spurred by the needs of a larger World War I amputee population. European researchers advanced rapidly in their study of gait biomechanics, alignment techniques, and methods of fitting above-knee-amputees [12].

The post-WWII era brought about a dramatic shift in thinking with regard to prosthetic devices. During WWII, advances in body armor, aircraft, and radio communications allowed for more offensive operations and troop mobility than had been possible in earlier conflicts. The new nature of combat changed the types of wounds sustained by the troops [6]. Germany's regular use of land mines increased the incidence of lower limb injury. The use of antiseptic technique, antibiotics, and surgical techniques for stabilizing fractures improved survival of limb injuries, as did the use of field medics and modernized vehicles that allowed for faster evacuation of the wounded to aid stations and advanced surgical units. The Surgeon General of the US Army ordered that open amputation with skin traction should be performed exclusively until a revision operation could be developed to reduce the incidence of infection and gangrene and allow for preservation of limb length [13]. Survival improved, but as the result of WWII, a resounding 14,912 US service members suffered amputations (10,620 lower limbs and 870 bilateral lower limbs) [5].

In February 1945, a conference of interested surgeons, engineers, and prosthetists met in Chicago to discuss the challenge of deficient prosthetic research and development. Their goal was to set forth standards for the production of

artificial limbs. At the time, there were no standards for surgical techniques, socket design or fit, prosthetic alignment, or gait biomechanics. To compound the lack of guidance, contracts for prosthetic device development were being awarded by the VA to the lowest bidder. The Surgeon General of the Army, Norman Kirk, responded by establishing the Committee on Prosthetic Devices, later renamed the Prosthetic Research Board, and asked the National Academy of Sciences (NAS) to formulate a prosthetic research and development program.

Later that same year, the voices of American injured service members were heard when they protested the inferior artificial limbs they were being provided by the government. Congress appropriated funds for prosthetic research. The new program would eventually be overseen by the National Academy of Sciences (NAS) through its Committee on Artificial Limbs (CAL). By 1947, the NAS dealt directly with the VA, which administered the program through contracts to several universities and selected manufacturers [14]. The initial concept of the program was to advance prosthetic technology for knee, ankle, and foot designs and to improve upon materials used in fabrication. At the time, there was a significant lack of data to guide improvements in prosthetic design. There was minimal research available to inform gait biomechanics and no formalized data concerning the problem of prosthetic fit. In September 1945 at the University of California, funded by an $18,000 grant, transtibial amputee Howard D. Eberhart[1] and his surgeon Dr. Verne T. Inman[1] began laying the foundation for what is, to this day, the fundamental basis of contemporary prosthetic and orthotic design and development. For the first time, engineers, clinicians, and manufactures came together to employ the systematic approach of applied science whereby the clinical benefits of prosthetic and orthotic appliances were tested clinically (Figs. 3.6 and 3.7). For example, a new prosthetic foot or knee design would have to undergo material testing, motion laboratory assessment, and basic human testing to determine its clinical value, and findings would be published in medical journals.

In 1946, the Surgeon General sent a committee to Europe to investigate the current research and development. A major recommendation by the committee was to initiate introduction of the suction socket to America. Researchers at the University of California were given the task of developing this technology and investigating human locomotion. It was a joint endeavor between the School of Engineering at Berkeley and the Medical School in San Francisco.

In 1948, Massachusetts Congressional Representative Edith Nourse Rogers successfully petitioned Congress to authorize $1,000,000 annually to support development of assistive devices, including prosthetics. The VA established its Research and Development Program to distribute the funds [10]. As a direct result of the new congressionally funded research, knowledge was advanced to improve prosthetic socket design, suspension, human gait mechanics, alignment, knee and foot design, rehabilitation, and dermatological care of residual limbs. A corresponding upper extremity prosthetic device program was developed at the University of California, Los Angeles, under the Advisory Council on Artificial Limbs (ACAL), National Research Council. Concurrently several other grants were administered to fund design and development projects in other laboratories including Northrop Aviation, Vickers Inc., the Army Prosthetics Research Laboratory (APRL), US Naval Hospital at Mare Island (later the Navy Prosthetics Research Laboratory, Oakland Naval Hospital), and Walter Reed Army Medical Center

[1]Eberhart was a well-known engineer and one-time patient of Dr. Verne T. Inman, Chairman of the Department of Orthopedic Surgery at San Francisco.

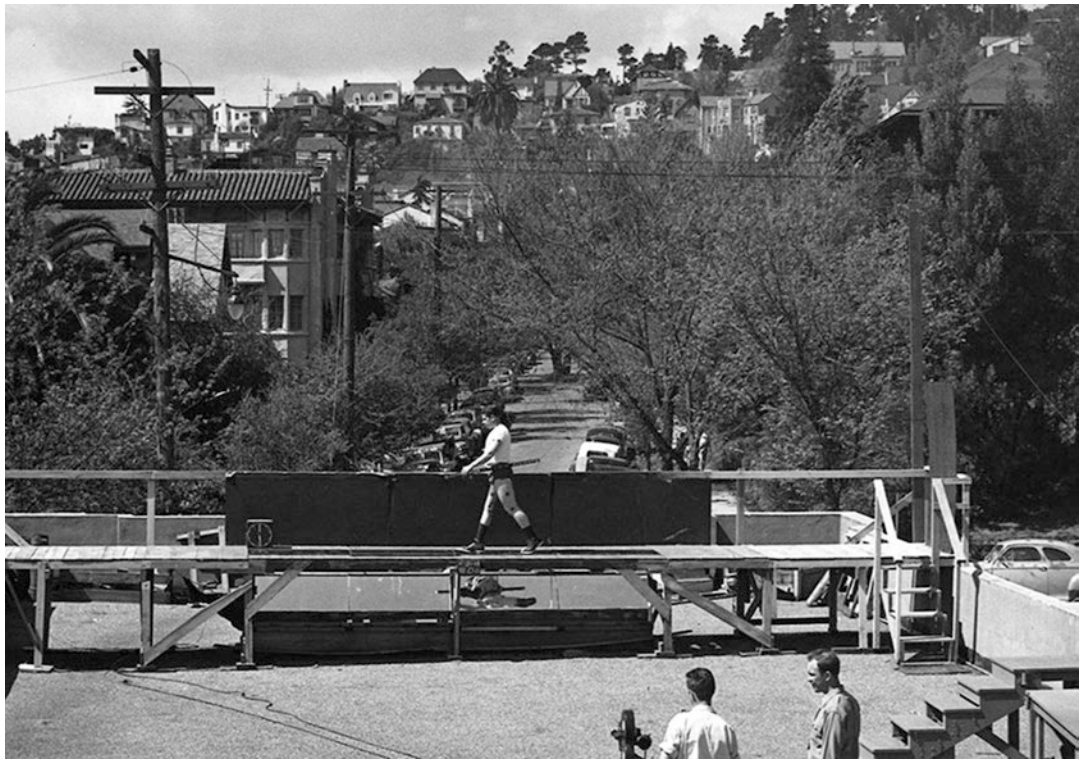

Fig. 3.6 The original rooftop gait laboratory University of California – San Francisco circa 1953 (Courtesy of Robert Gailey private collection)

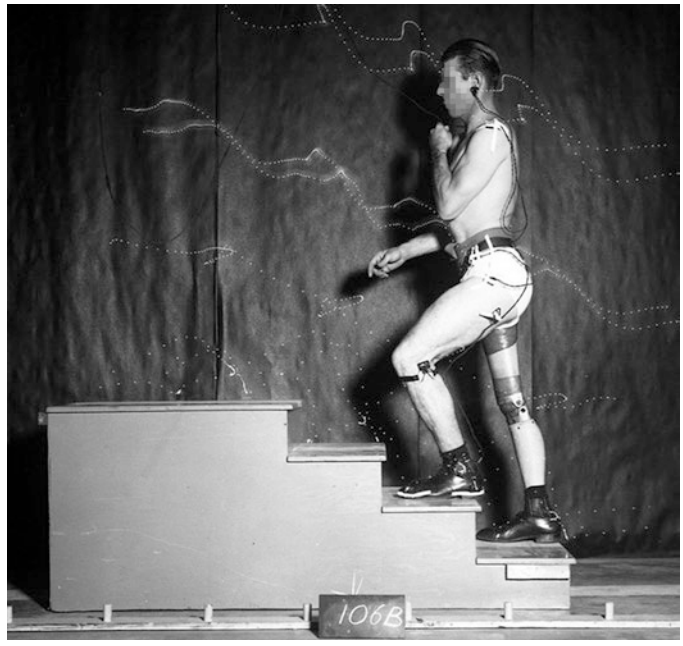

Fig. 3.7 Evaluation of stair ascent biomechanics with a subject with a hip disarticulation prosthesis, gait laboratory University of California – San Francisco circa 1953 (Courtesy of Robert Gailey private collection)

[10, 15]. In 1947, a laboratory was established at New York University to conduct human trials of the prosthetic technology being developed through the ACAL program. During this period, the amount of energy and funding being allocated to prosthetic technology set a new precedent and was instrumental to the emergence of numerous prosthetic technology and design developments between 1945 and 1975.

In the years following WWII, other military conflicts posed additional challenges due to continued advances in military weaponry and combat tactics. Concurrent improvements in first response medical care and evacuation also improved survival. During the Korean War (1950–1953), helicopters were used to transport wounded fighters to Mobile Army Surgical Hospital (MASH) units located less than 10 miles from the front lines, staffed with surgeons, anesthetists, and nurses [12]. The Vietnam War (1961–1975) saw a 70% increase in catastrophic lower limb wounds over the Korean War and a 300% increase compared to WWII [6]. The Viet Cong's use of guerilla warfare, booby traps, land mines, and punji sticks was devastating to the lower limbs of those who encountered them.

More recently, injuries sustained in military conflicts in Iraq (Operation Iraqi Freedom, OIF, 2003–2011) and Afghanistan (Operation Enduring Freedom, OEF, 2001–present) have been characterized by the enemy's use of improvised explosive devices (IEDs). IEDs are designed to maim if not kill, thus assuring that wounded service members and some number of their fellow fighters will be disabled or at least consumed by the urgency to save the lives of their comrades.

Despite the catastrophic devastation of war and the destruction of disease, there is enduring optimism that wounded warriors will return and recover to lead fully functional lives. Researchers, inventors, and scientists in the field of prosthetic devices are among the many who have worked to make this possibility a reality over the last 80 years. The technological advances of modern times have brought many forward-thinking ideas from the past to fruition in the present. The next section of this chapter provides an overview of the development of prosthetics, by component parts, and of the advances made in the rehabilitation of amputees.

Socket Design, Suspension, and Operability

The wearer of a properly designed socket should be able to sense where the prosthetic limb is located in space based on changes in the distribution of pressure on the residual limb. The socket should be comfortable at all times and should pose no irritation to the underlying skin. Pain associated with donning the prosthesis has motivated many efforts to investigate and improve socket materials and technologies. Dermatological issues and the need for sensory feedback are the most common challenges faced by prosthetic manufacturers and users.

Early prosthetic sockets were fabricated from a variety of materials including wood, leather, fiber, and metal. Often seen in below-knee prostheses were leather corsets worn about the thigh with lace up ties and metal sidebars. The residual limb was inserted into a molded leather socket placed into a shank fabricated of wood, metal, or fiber and possibly lined with felt or wax. Above-knee amputees commonly donned a willow wood socket that caused constriction of the proximal third of the residual limb and left the distal end of the limb unsupported; minimal suspension was provided by a woolen sock, belts, and suspenders [16]. These designs often caused problems with edema.

Between the years 1949 and 1955, research led by Charles S. Radcliff at the University of California, Berkeley, produced the total contact

quadrilateral suction socket [17, 18]. This novel, anatomically well-considered approach gave the amputee greater control over the prosthetic limb, more degrees of freedom at the hip, and the ability to engage the remaining leg musculature, without the traditional metal single-axis hip joint and leather waist belt. Nationwide instructional courses were initiated to train prosthetists on fabrication of the new socket design.

The patellar tendon bearing (PTB) total contact below-knee socket applied similar biomechanical principles. Where earlier "plug-fit" designs included a thigh corset, metal sidebars, and suspenders, the PTB instead employed thermosetting laminate plastic sockets as had previously been used in above-knee sockets to enable total contact design [11]. New materials and the total contact socket designs significantly reduced distal end edema of the residual limb and subsequent verrucous hyperplasia [19, 20] that had plagued amputees who wore open-end carved willow wood sockets and had limited the number of people who could wear prostheses [11].

In 1966, New York University undertook investigations to develop a practical method of fabricating a transparent socket [14]. Transparent sockets involved making a plaster casting of the patient's residual limb to create a negative mold, which in turn was filled with plaster to create a positive mold as an exact image of the patient's residual limb. The positive mold could be modified by the prosthetist before application of polyester casting resins or a rubberized covering. Finally, an acrylic material was heated and a vacuum formed over the positive mold. This transparent socket would be fit to the patient. By 1972, the vacuum forming of a polycarbonate sheet of plastic permitted easier evaluation of test sockets where pressures on the soft tissues could be observed [21]. Techniques of fabricating flexible sockets were revolutionized at Philadelphia's Moss Rehabilitation Hospital in 1975, with the introduction of vacuum-formed polypropylene and polyethylene plastic [22]. The advances in plastic materials enabled the prosthetist to provide prosthetic limbs that were more comfortable, flexible, cosmetic, easier to modify, and considerably lighter weight [23].

Other developments in the early 1970s led to the advent of gel liners and silicone liners for below-knee socket designs [24–26]. Improved polymers and composites also allowed for more flexibility of the above-knee socket over muscular areas, permitting better capture of the muscle bulk and thus improving control and, theoretically, the quality of sensory feedback. Contemporary socket research and development focuses on the need to improve comfort and residual limb health. Researchers are looking for ways to provide prosthetic wearers with sensory input from the environment as well as the ability to monitor the socket environment for changes in temperature, pressure, and moisture [27]. Researchers anticipate that one day soon, prosthetic devices will allow the amputee to gather and receive sensory feedback directly from the prosthetic limb, with the ambitious goal that amputees will be able to "feel" with their prosthetic limbs.

Another major goal is to improve the amputee's ability to control the prosthesis. The need for better control has long been recognized. In 1939, Dr. Henry Kessler introduced the surgical procedure known as cineplasty, which involved the creation of a soft tissue flap under which ran tunnels where remaining musculature was attached to rings. The rings allowed for cable attachment to an upper limb terminal device such that the contraction of the muscle would result in a particular intended movement at the attached hook or artificial hand [28]. While cineplasty techniques have long been abandoned, many ideas that would have been impractical or impossible in the past have since become possible through the development of advanced materials and technologies.

Research on pattern recognition provides insight into the vast possibilities, coupled with multiple limitations, which present themselves to modern investigators. Traditionally, a myoelectric prosthesis is controlled by the two sensors positioned over specified muscle sites, to capture EMG signals from surface recordings. The EMG signal information is then translated into movement at the terminal device, typically with one degree of freedom (DOF). The prosthesis may be designed with several modes to control specific movements, such as opening or closing the whole hand, but only one mode can be activated at a time – the mode must be changed for each desired new type of movement. This is accomplished by some combination of sustained or co-contraction of muscles that may be difficult and unintuitive for the user [28]. Pattern recognition provides an alternate approach that involves multiple surface sensors to control several DOF, allowing for more nuanced and complex movements. The use of multiple sensors provides the opportunity to capture and apply a more complex array of overall muscle activity and integrated movement patterns [29]. Ideally, pattern recognition provides the user with more natural and intuitive control.

Powered prosthetic devices were being developed for upper limb applications as early as 1915 [41]. In the 1940s, extensive research and investigation into different sources of power and DOF began in Europe and continued later in the United States. Between 1946 and 1952, the Alderson-IBM project, in cooperation with the VA, produced electrically powered arm systems that showed promise in initial studies but, after further investigation by researchers at the University of California, Los Angeles, were deemed too labor intensive for the amputee user. Congenital limb deficiencies resulting from the thalidomide tragedy in the 1960s stimulated a renewed interest in the development of gas-powered prosthetics. By the 1960s, the Ottobock Corporation had become a major contributor to the field of powered prosthetic development for upper limbs and supplied component parts for use in research.

The Defense Advanced Research Product Agency's (DARPA) Reliable Neural-Interface Technology (RE-NET) program employs peripheral interfaces that use signals from nerves and/or muscles to directly control the prosthesis and capture sensory feedback. Targeted Muscle Reinnervation (TMR) is being investigated for this purpose. Developed in the early 2000s by a team from Northwestern University, with the cooperation of the Rehabilitation Institute of Chicago, this procedure involves rerouting severed nerves from the residual limb to a new location in an intact, proximal "target" muscle [30]. With extensive training, the amputee is able to contract a portion of the reinnervated muscle; EMG signals are then captured by applied surface sensors and translated to elicit specific movements of the prosthesis. More recently, the TMR approach has been extended to clinical applications that integrate EMG signals with robotic technology to control prosthetic knees and ankles. EMG signals from natively innervated and surgically reinnervated residual thigh muscles are decoded by a pattern recognition algorithm, allowing people with amputations above the knee to intuitively control a robotic leg prosthesis [31, 32]. With little more effort than was needed to control a similar movement pattern prior to amputation, the amputee can seamlessly transition between walking, climbing stairs, and sitting in a chair and expect the prosthesis to respond appropriately. When control is more intuitive, prosthetic training time may be reduced.

An unintended consequence of the initial upper limb targeted innervation procedure was the discovery of recovered sensation within the missing limb. While receiving an alcohol rub over his chest after the surgery, a patient claimed that he was feeling sensations in his absent pinky

finger. The explanation was that because the skin over the target muscle in the chest was essentially denervated with the surgery, sensory fibers from the transferred nerve had reinnervated that skin. Therefore, when his chest skin was stimulated, it provided the patient with sensation over certain areas of his missing arm [33, 34].

Looking to the future, one can envision entirely intuitive control of artificial limbs through the use of brain-machine interfaces (BMIs) that capture and apply the electrical activity generated by ensembles of cortical neurons [35]. Recent demonstrations of people with spinal cord injuries learning to control myoelectric prosthetic arm devices through BMIs have generated interest for the emerging field of neuroprosthetics. While BMIs introduce far-reaching potential, several challenges exist including the development of biocompatible electrodes that are capable of long-term use for stable recording of brain activity and implantable amplifiers and signal processors that are sufficiently resistant to noise and artifact to faithfully transmit recorded signals to the external environment [36].

The implications for improved prosthetic user control are extraordinary, though much progress has yet to be made to resolve current difficulties faced when engineering solutions for human subjects whose injuries, capabilities, needs, and objectives are variable. Advances in prosthetic research and development stem from ingenuity in response to human necessity.

Prosthetic Knees

There is no greater loss of function to a lower limb amputee than the forfeiture of the knee joint. The knee plays a critical role in overall power, agility, function, walking speed, and conservation of metabolic energy expenditure [37, 38]. Designing a comparable replacement has proven to be a difficult challenge. To date, mechanical knee joints have been designed as hinge joints that are subject to force, moments, and mechanical alignment of the prosthesis, all of which can also be affected by joints above and below. Developers have long sought to replicate the musculature that surrounds the anatomical knee and to mimic its basic movements. For the purpose of most activities, contemporary prosthetic knee options are surprisingly proficient. However, the amputee's confidence and ability to maneuver naturally remains limited because prosthetic knee joints do not yet support the combination of subtle motions, power, and speed inherent to the human knee.

Single-axis hinged knees were the design utilized in the United States from the earliest days of J.E. Hanger through WWII. After extensive review of the relatively sparse literature and description of devices available in the late 1940s, Inman, Radcliffe, and Eberhart developed improved prosthetic knee mechanisms. Projects were initiated to develop polycentric knee systems and knee control devices that would mimic the function of the quadriceps and hamstring musculature [12]. By the early 1950s, the US Navy's Variable Cadence Knee was the first knee device designed to allow for increased friction toward the end of the swing phase at different cadences. The knee's materials ultimately did not stand up to wear over time; however, a similar design out of Northwestern University became commercially available [14].

In 1949, the Vickers Corporation in Detroit was awarded funding through the NAS to complete work on a hydraulic above-knee prosthesis that had originally been created in 1941 by inventor Jack Stewart, himself an above-knee amputee [10]. To mimic the knee musculature and deliver coordinated action at the knee and the foot, the system utilized hydraulic principles to lock the knee at heel strike and at 20° of knee flexion provided active dorsiflexion of the foot [39]. The rationale was that dorsiflexion at the ankle

allowed for improved ground clearance during swing and more natural gait during late stance. The system was commercially available as the Stewart-Vickers Hydra-Cadence Knee, but because the hydraulic stance component was expensive, it was not included as a feature of the commercial version. The ability to replicate the quadriceps contribution to stance control had not yet been accomplished.

During "Operation Paperclip," the US government expedited selected travel papers of a group of German wartime scientists for swift and safe travel to the United States. Hans A. Mauch, an expert in technical medicine, hydraulics, and aeronautics, was a "paperclip" German recruited by the US government to work for the Air Force. He arrived in the United States in 1946 to work at Wright Air Force Base in Dayton, Ohio. When he had off time, he was encouraged to continue previous work he had pursued in hydraulics and prosthetic devices. It took Mauch just a matter of months to develop the first prototype for demonstration, but an additional 12 years was needed to perfect the system for commercial release in 1968 [40]. Mauch insisted that the delay was because, "I am just making refinements so it will do everything the amputee wants it to do and nothing he doesn't want it to do" [10]. Mauch's statement reflected his premise that the prosthetic leg should be a true functional extension of the human body, a simple axiom that has helped to guide and motivate the thought processes of other prosthetic pioneers and offers a timeless standard for current and future prosthetic practitioners to emulate. More than half a century after Mauch's prototype, the Mauch S-N-S hydraulic knee is still used and fitted routinely on injured members of the US military. The unit provides stance control, varied cadence from walking to running, a hydraulic locking mechanism, free swing control, and a yielding capacity for descending stairs.

During the 1970s and 1980s, manufacturers offered variations on the previously developed single-axis or polycentric knee joints that incorporated friction, pneumatic, and hydraulic mediums for swing resistance with various locks or design configurations for stance control. By the 1990s, with the advent of smaller computer processor boards and increasingly robust computing capabilities, the concept of computerized and microprocessor knee (MPK) systems had captured the interest of scientists and manufacturers alike. In the United Kingdom, the Blatchford Group (Endolite) introduced the first commercially available MPK in 1990 [42]. By the late 1990s and early 2000s, numerous MPKs had become available, including the C-Leg (Ottobock) and Rheo Knee (Össur) (Fig. 3.8). Computerized knees, equipped with sensors, allow for continuous electronic monitoring of knee forces, joint position, and timing, thus enabling the resistance medium (pneumatic, hydraulic, or magnetorheologic fluid) within the prosthetic knee to vary cadence during swing phase and to provide

Fig. 3.8 The original solid ankle cushioned heel (SACH) foot by H. D. Eberhart, University of California-Berkeley (Courtesy of Robert Gailey private collection)

appropriate stance control during walking, traversing varying terrains, and descending stairs with greater safety [43].

The US Department of Defense (DoD) military treatment facilities (MTFs) quickly adopted MPKs for use in helping wounded warriors with limb loss from service in Iraq and Afghanistan. The accepted use of MPK prosthetic systems, along with an unprecedented increase in clinical research, spawned collaborations between government funding agencies, MTFs, the VA, universities, and manufacturers. As always, the emphasis was on providing returning service members with the best care possible. The Military Amputee Research Program (MARP) funded Ottobock HealthCare to develop "an electronically controlled prosthetic knee joint that meets the specific demands of the military staff in real-world activity" [44]. The code name then for the new MPK was X2; now, it is referred to as the X3 (Fig. 3.9). The knee utilizes a key fob to support a variety of cadence variations. It provides increased stance control over its predecessor, the C-Leg, for stair descent and hills, with training can flex for stair ascent, can be combined with numerous feet from other manufacturers, and is water resistant. Significant research investments by the US military have also benefitted civilian amputees through the creation of a civilian product known as the Genium Bionic Prosthetic System.

MTFs have worked with another manufacturer (Össur) to develop solutions that compensate for the loss of knee musculature. The resulting Power Knee™ (Fig. 3.10) provides for the missing contraction of the quadriceps muscle. It uses servomotors to actively extend the knee. It provides powered knee extension to rise out of a chair, ascend stairs, and negotiate hills. One benefit of powered prosthetic devices is that they decrease reliance on the sound limb by increasing lower limb symmetry of work during walking [45] and other activities. Resulting improvement in gait may help to reduce the problem of degen-

Fig. 3.9 Össur Rheo Knee (Courtesy Össur International, Iceland)

Fig. 3.10 Otto Bock X3 (Courtesy Ottobock, Germany)

erative joint disease that occurs more often in lower limb amputees than in the general population [46, 47].

Prosthetic Feet

An ongoing challenge to prosthetic designers is the need for a prosthetic foot that can better mimic the function of the human foot. The importance of motion at the foot was recognized in the design of early prosthetic devices such as the Anglesey leg and the Hanger leg. Even prior to the Civil War in 1858, Dr. Douglas Bly patented "Dr. Bly's Anatomical Leg" which included an ankle that allowed inversion and eversion by way of a polished ivory ball placed in a socket of vulcanized rubber [48]. After the loss of his own lower limb in 1861, J.E. Hanger developed his single-axis prosthetic foot. Bly and Hanger found themselves in constant competition for contracts and care of amputee soldiers being treated in the war hospitals of Washington, D.C.

From the labs at UC-Berkeley and under the direction of Dr. Eberhart came the development of the SACH foot that would be commercialized in 1957 (Fig. 3.11). The SACH foot was designed to mimic natural motion of the anatomical ankle while also providing shock absorption without an articulated ankle joint [10]. Around the same time, the Naval Prosthetic Research Laboratory created the "Navy ankle," fabricated with a rubber block with variable stiffness to provide motions in three planes as well as some rotation. However, the Navy ankle was not commercially marketable due to the constant maintenance it required.

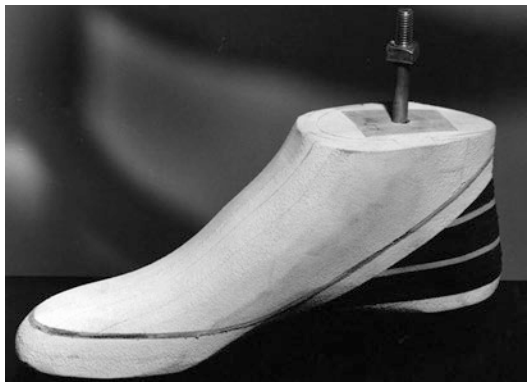

Fig. 3.11 Össur Power Knee (Courtesy Össur International, Iceland)

The SACH foot was not designed to provide rotation at the ankle. From observations made of rotation about the pelvis, femur, and tibia during gait analysis, it was clear that an ankle rotator would be necessary to prevent friction forces from traveling up the prosthetic leg and possibly causing damage to the skin [9]. Several ankle rotator models were designed, and one was applied to the PTB below-knee prosthesis with the SACH foot.

In the late 1970s came the advent of the Stationary Attachment Flexible Endoskeletal (SAFE) foot [49]. The SAFE foot was designed to build upon the simplicity of the SACH foot while mimicking the anatomical structures of the human foot. It imitated the long plantar ligaments with nylon cords and used a bolt block design to create the three planar motions of the subtalar joint. Likewise, multiple manufacturers commercialized other designs such as mechanical single-axis and multiple-axis foot/ankle systems.

In 1984, under the auspices of the newly established and VA-funded Prosthetic Research Study (PRS), researchers at the University of Washington created the Seattle foot. Known as the first "energy storing" foot, the Delrin™ elastic keel stores mechanical energy during the stance phase that is subsequently released immediately prior to toe-off, creating a dynamic response or "springboard" effect [14]. The concept of dynamic response motivated manufacturers to work rapidly to develop various types of "energy storing" or "dynamic response" prosthetic feet.

In 1980, Blatchford Inc. unveiled the world's first carbon fiber prosthetic system using materi-

als first developed for the aircraft industry. The light, high-strength carbon fiber set the course for further development of flexible feet components that would allow for energy return while walking or running [41]. The use of carbon fiber in prosthetics accelerated with the development of the Össur Flex-Foot "J-shape" design that introduced three significant design concepts. The first was the storage of mechanical energy throughout the pylon where the "J-shape" mimics the tibial advancement observed in the human leg. Second, the heel-toe footplate runs the length of the foot to provide greater stability. Third, the use of carbon fiber throughout the device provides the dynamic properties that generate high energy return [50, 51].

Prosthetic feet have since become increasingly more sophisticated with many designs using a combination of carbon fiber for its dynamic properties, elastomer or other composites for ankle mobility, and some form of shock absorption. During the last decade, researchers at Northwestern University introduced the concept of the "roll-over shape," which models the movement behavior of a prosthetic foot by that of the natural foot, a principle now incorporated into many modern foot designs [52].

The combination of advanced materials and innovative design supports development of prosthetic feet that are more responsive to the user and permit people with limb loss to return to sports or other high-level activities. The Össur Proprio Foot™ was the first commercially available foot of this type. Attached to a carbon fiber footplate, the ankle contains accelerometers and angle sensors that sample motion more than 1,000 times per second. As motion is continually monitored, the system is able to detect if the wearer is on level or uneven terrain. The data are then analyzed by patented artificial intelligence, and the ankle adjusts to perform the most appropriate movement required in the moment. Movements are generated by a lightweight motor designed to mimic the muscles of the lower leg. The Proprio Foot™ provides active dorsiflexion during swing and can accommodate ankle angles for ascending and descending stairs and ramps [53].

Until recently, no prosthetic foot had the ability to plantarflex during stance. This changed with the BiOM Foot, funded in part by DARPA and the VA. The BiOM is a powered ankle fastened to a carbon fiber footplate. It exhibits the biomimetic behavior of ankle stiffness at heel strike, which translates the tibia forward, and active plantar flexion at toe-off. The functional value of this type of technology for walking improved negotiation of stairs and uneven terrains, and potential decreased energy cost during gait has yet to be determined [54–57].

A new generation of intelligent prosthetic systems is now in development, through collaborative work underway at DARPA, MARP, the VA, and universities including Vanderbilt University, Northwestern University, and the Massachusetts Institute of Technology. These new systems will combine and coordinate functions of the knee and ankle. Instead of cords and hydraulic cylinders linking the ankle and knee, computer electronics will synchronize the joints. Moving ahead, additional sophistication may be possible through the integration of prosthetics with BMIs, peripheral nerve interfaces, and/or targeted reinnervation. The goal is for future systems to be less reactive (to forces from the ground or from previous steps) and more anticipatory such that signals from the brain or peripheral nerves will immediately elicit desired motion.

Alignment

In early twentieth-century Germany, the concept of the plumb line was devised as a line of reference for prosthetists to apply as they arranged and aligned the component parts of lower limb prostheses [58]. With the development of the

quadrilateral suction socket came the realization that it was imperative to align the entire leg so the hip, knee, and ankle were in a posture that permitted the amputee to functionally use their available musculature, maintain balance, and ensure stability at the knee. Today every prosthetic hip, knee, and foot component has a set of recommended alignment specifications from the manufacture to promote optimal performance with maximum safety.

The 1950s experimental alignment jig device allowed for the adjustment of multiple variables, but its usefulness was limited by the difficulty of translating alignment of a stationary prosthesis to the dynamic condition of walking. In response, researchers developed an adjustable artificial leg and an alignment duplication jig [9]. The new jig was a set of clamps to hold the alignment of the temporary prosthetic in place, while the temporary knee was removed and replaced with wood, metal, or plastic structures and joints [58]. While treating Vietnam veterans, prosthetist Ivan Long built on this work and introduced alignment principles, still used today, seeking to minimize displacement of the body's center of mass by controlling movement of the femur within the socket [59].

For any knee or foot system to function properly, alignment is a critical component, owing to the passive nature of prosthetic knee systems and to the fact that moments are dictated by where forces pass the joint. Despite progress in methods of prosthetic alignment, including computerized alignment systems, no method is foolproof or absolute. Alignment requires a combination of experience, knowledge of biomechanical principles, a discerning eye, and concern for the amputee's individual needs.

Rehabilitation

After the Civil War, the US government set up homes to care for wounded soldiers. Taking a cue from the United Kingdom, rehabilitation programs were established to train teachers and aides to assist in rehabilitating wounded service members. These caretakers were called "reconstruction aides" [6]. Society was realizing the importance of a return to occupation and normal life for the injured soldier.

After WWII, Dr. Howard Rusk, Chairman of the Institute of Physical Medicine and Rehabilitation at New York University, sought to promote President Eisenhower's idea of good will and international peace by providing prosthetics to underdeveloped countries. The President's initiative encouraged the idea that a nation benefits from the income and taxes of its working population [10]. By 1967, new methods were being explored to rehabilitate the amputee as a total person, focusing on his or her return to a functional life. The World Health Organization (WHO) further defined this concept with the support of the International Classification of Function (ICF) model, in which the issues related to rehabilitation are classified at three levels: impairment, activity, and participation. The WHO set the clinical goal that people with limb loss should receive rehabilitative care that can transition them to the "participation" level and thus return to living as productive members of society.

Over the past two decades, amputee rehabilitation has developed into a highly specialized field of care. Hospitals and treatment facilities within DoD and VA are known as leaders in the care of people with limb loss. Increases in federal funding and changes in policy have enabled the VA and DoD to offer exceptional comprehensive care to service members and veterans. At MTFs throughout the DoD, the goal of treatment is based on the philosophy adopted in 2001, which is that at the time of discharge from rehabilitation, the service member should be afforded the choice to retire from service or return to active duty. To meet this goal, the DoD has worked in collaboration with the VA, universities, manufacturers, and noted experts to identify and/or

develop the most effective interventions possible. They work to provide every service member with all necessary medical, surgical, mental health, therapeutic, and prosthetic care, as well as other specialty services when required. The DoD has adopted the sports medicine rehabilitation model, employing more aggressive treatments and higher outcome goals [60]. Every wounded warrior is considered a "tactical athlete," and, as is common in the military culture, wounded warriors work together with each other as a team and with rehabilitation professionals to achieve the best outcome possible.

Technology is the fabric of everyday life in the military. Thanks to advanced protective armor and battlefield emergent care, warfighters injured in combat now have a much better chance to survive serious and multiple injuries. Advanced care after returning from deployment includes the sophisticated rehabilitative techniques and technologies such as virtual reality environments that employ computerized video analysis and visual and auditory feedback to rehabilitate gait and movement patterning. Ultrasound and functional electrical stimulation (FES) are used to strengthen and reinforce movement. Interactive computerized weapons training (Firearms Training Simulation/FATS) is available to prepare service members for return to active duty [61].

Sophisticated as modern technology may be, its role is to augment applied therapeutic care administered by human caregivers. The development of an evidenced-based, four-phase rehabilitation model progresses wounded warriors through the stages of (1) initial management, (2) pre-prosthetic, (3) prosthetic/ambulation, and (4) progressive activities/return to duty. This model is based, with only slight modification, on the ICF model as it applies to military, veteran, and civilian amputees [62]. The integration of rehabilitative technology with hands-on therapeutic intervention has produced measurable positive results. Rehabilitation programs at the MTFs have been so successful that new outcome measures were established [63]. For example, the Comprehensive High-Level Activity Mobility Predictor (CHAMP) has been applied to reveal that many service members with limb loss are capable of achieving speed and agility scores similar to those of noninjured service members [64].

To achieve an optimal outcome after limb loss requires coordinated engagement by a specialized team of individuals who work with the patient and his or her family. While traditional team members (physicians, therapists, prosthetists, and other allied healthcare providers) justifiably receive the majority of credit for successful restitution of function, silent partners in this success are the inventors and clinical researchers who create innovative products and interventions and who work hard sometimes for many years to demonstrate their clinical effectiveness.

Today, service members with limb loss can aspire to achieve functional capabilities comparable to those of their noninjured peers. This is, first and foremost, a testament to the fortitude of each individual wounded warrior who is determined to heal and be whole again and to recover capabilities necessary for return to duty, to family, and to society. The advances that save service members' lives and restore their physical capabilities cannot be attributed solely to advances made in recent decades, many of which are informed and inspired by challenges faced and solutions designed centuries earlier. If it can be said that any good comes of war, it is perhaps that cutting-edge medical solutions are often driven specifically by the need to save and care for injured combatants. Service members' experiences and sacrifice motivate improved medical and rehabilitative care, the benefits of which extend to civilians who sustain similar injuries outside the context of military service.

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Overview of the Components Used in Active and Passive Lower-Limb Prosthetic Devices

4

Kevin B. Fite

Abbreviations

CESR	Controlled energy storage and return
DC	Direct current
IC	Ischial containment
ICEROSS	Icelandic roll-on silicone socket
KBM	Kondylen Bein Muenster
PTB	Patellar-tendon-bearing
PTS	Patellar-tendon-supracondylar
SACH	Solid ankle cushion heel
TSB	Total surface bearing

Introduction

Over recent decades, many advances have been made to restore function lost due to lower-limb amputation, leveraging novel mechanical design, dynamic energy exchange (passive and active), and intelligent control to approximate insofar as possible the function of the human leg. The purpose of this chapter is to review the components currently used in active and passive lower-limb prosthetic devices. This overview spans socket systems for above- and below-knee amputees and the components available to restore function at the foot, ankle, and knee. Considerations include conventional componentry, design solutions, and emerging technologies currently being advanced to expand the performance capability of lower-limb prosthetic devices and improve overall quality of life for those with lower-limb amputations.

The Socket Interface

The fundamental component of lower-limb prosthetic devices is the socket. Serving as the interface between the amputee as user and the prosthesis as device, the socket is responsible for both load transmission to the amputee during weight-bearing support and suspension of the prosthesis when ground forces are absent (e.g., during the swing phase of gait). The specific configuration for the socket depends upon a number of factors including the level of amputation, the anatomy of the residual limb, and the activity level of the amputee. Here we will begin with an overview of socket technology currently used in clinical practice. Due to differences in functional

K.B. Fite, PhD (✉)
Clarkson University, Mechanical and Aeronautical Engineering, Potsdam, NY, USA
e-mail: kfite@clarkson.edu

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requirements dependent upon amputation level, socket technologies for below-knee and above-knee prosthetic devices will be addressed separately. This will be followed by a presentation of some of the advanced research and commercial technologies currently under investigation to improve the fit of the prosthetic device and the comfort and health of the amputee's residual limb.

Below-Knee Socket Systems

Sockets for transtibial amputees can be categorized based on the mechanisms for weight bearing and suspension. Generally there are two approaches for load transmission during weight-bearing support. The first is to concentrate loading at specific weight-bearing surfaces on the residual limb. In this case, the most common example is the patellar-tendon-bearing (PTB) socket [1]. As the name implies, the PTB socket transmits weight-bearing loads to the patellar tendon of the amputee using a bar or protrusion in the socket wall at the middle of the tendon. It should be noted that other anatomical features contribute to the load bearing of the PTB socket. In particular, the tibial condyles and surrounding tissue serve as important weight-bearing structures and, in conjunction with the posterior surface of the socket, help to stabilize the residual limb against the posteriorly directed loads of the patellar tendon bar. The medial and lateral regions of the socket serve to contain the soft tissue of the residual limb and help to prevent the prosthesis from rotating about the residual limb.

The second approach for load transmission is uniform loading over the entire surface area of the residuum. For example, total surface bearing (TSB) socket designs distribute weight-bearing loads uniformly over the residual limb [2, 3]. TSB sockets are custom shaped to contain the residual limb in its nominal volume, leveraging hydrostatic principles to transfer loads uniformly to the surface of the residual limb. Note that TSB sockets typically incorporate a flexible liner between the rigid outer socket and residual limb to stabilize the volume of the residual limb under loading and thereby facilitate uniform distribution of the transmitted loads. The load-bearing functions of both TSB and PTB sockets are typically realized using thermoplastics or carbon composites (infused or pre-impregnated) molded into a rigid structure that fully encloses the relevant residual-limb anatomy.

There are several approaches to suspend the transtibial prosthesis on the residual limb. Mechanical means for suspending the prosthesis include a waist-belt suspension, a thigh-corset suspension, and a knee cuff strapped around the distal thigh, all of which entail additional componentry attached to the proximal end of the socket that is then anchored to anatomical features proximal to the residual limb. Alternative approaches integrate limb suspension directly within the socket. The patellar-tendon-supracondylar (PTS) method extends the medial, lateral, and anterior walls of the socket to completely enclose the patellar tendon and femoral condyles [4]. The PTS method enables additional suspension of the socket at the quadriceps tendon, but with the potential for increased discomfort when kneeling (due to complete enclosure of the patella). Similar to the PTS suspension, the Kondylen Bein Muenster (KBM) suspension technique fully encloses the knee joint through extension of the medial and lateral walls of the socket [5]. However, the anterior wall of the socket is left low, which keeps the patella exposed. The KBM suspension improves ease of kneeling at the expense of somewhat degraded suspension due to the absence of suspension at the quadriceps tendon.

Elastic sleeves that fit over the amputee's thigh and encapsulate the proximal outer socket wall provide additional suspension options. The elastic sleeve achieves suspension through a combi-

nation of negative pressure created in the sealed volume during swing and the tensile elasticity of the sleeve under axial loads. Such sleeves can be used as the sole means of suspension or as an auxiliary suspension when combined with one of the supracondylar suspensions. Drawbacks to elastic sleeve suspension include the possibility of sleeve rupture and perspiration-induced hygiene and skin-irritation issues.

The flexible sleeves commonly used in the TSB socket also support suspension of the prosthetic limb. The concept was first realized in the form of the Icelandic roll-on silicone socket (ICEROSS) [2, 3]. During the donning process, a silicone sleeve is turned inside out and then rolled over the residual limb from the distal end. The sleeve is then secured to a rigid outer socket using a shuttle-lock pin (Fig. 4.1) or hypobaric sealing membrane (consisting of a single ring or series of concentric rings that provide a seal between the silicone and rigid sockets). The stretched liner radially constricts the residual limb and displaces the residual-limb tissue in the distal direction. The resulting interface provides enhanced bidirectional resistance to axial displacement of the residual limb. The silicone acts as a suction socket when suspending the prosthesis and serves to minimize pistoning of the residual limb within the socket when cycling between weight-bearing support and prosthetic-limb suspension. Note that although their use originated in the process of developing TSB sockets, flexible sleeve socket suspensions can also be used in combination with PTB designs. These liners are available in a range of sizes and materials (including silicone, polyurethane, thermoplastic elastomers, and elastomer gels).

Fig. 4.1 The Alpha Hybrid transtibial socket liner (Image courtesy of WillowWood)

A number of clinical studies have assessed the functional outcomes of different transtibial socket designs. With PTB sockets, weight-bearing loads are concentrated at specific locations on the residual limb. Thus, without sufficient pre-stretching of soft tissue at the weight-bearing surfaces when donning the prosthesis, PTB sockets may allow significant tibial movement [6]. While TSB sockets address such issues to some extent, difficulties with donning the socket and the increased potential for hygiene-related issues (due to the requisite liner) are among the potential drawbacks [7, 8]. Comparative studies of PTB and TSB sockets have produced mixed results. A comparison of TSB sockets with ICEROSS suspension systems, and PTB sockets with knee cuff suspensions, found that the TSB socket provided improved suspension and tibial stability [9]. Another comparative study showed the TSB socket enhanced suspension and improved amputee balance [10]. More recently, a comparison of silicone-lined TSB and PTB sockets revealed no significant differences for user satisfaction, performance in gait, and other mobility-related functions [11]. As is evident from clinical evaluations, no single solution is appropriate for all below-knee amputees. Reaching a satisfactory solution requires careful consideration of weight bearing and prosthesis suspension in the context of the state of the individual's unique residual-limb presentation.

Above-Knee Socket Systems

Analogous to below-knee sockets, design considerations for above-knee socket systems revolve around weight bearing and prosthesis suspension. With regard to weight-bearing load transmission, the two common approaches used in above-knee sockets are the quadrilateral and ischial containment socket designs. The origins of the quadrilateral socket date back to the 1950s [12]; the design derives its name from the anterior/posterior and medial/lateral walls evident in a transverse cross-section of the socket. In general, these sockets have narrow anterior-posterior dimensions and wide medial-lateral dimensions. The quadrilateral socket imposes weight-bearing loads on the ischial tuberosity and gluteal musculature that rest on top of the posterior wall of the socket. The anterior wall of the socket provides counter-support to stabilize the ischium and gluteal muscle tissue on the proximal wall. The lateral wall provides adduction and lateral support of the femur during stance, with the medial wall containing the remainder of the residual limb but with little to no weight-bearing function.

The primary alternative approach to the quadrilateral socket is ischial containment [13]. Ischial containment (IC) sockets enclose, to varying extents, the ischial tuberosity and ischial ramus (medially and posteriorly); IC sockets were developed in part to address the tendency for abduction of the prosthetic-side limb during stance when using quadrilateral socket designs [14]. In contrast to quadrilateral sockets, where medial loads are borne by adductor musculature and surrounding soft tissue, IC sockets additionally recruit the skeletal structure of the ischial ramus to augment the load-bearing function provided by the more distal soft tissue. The resulting oblique slope of the medial brim of the IC socket biases the ischial ramus toward lateral and downward displacements within the socket, necessitating a tighter fit on the lateral side of the socket for adequate ramus stabilization. Somewhat analogous to the TSB below-knee sockets, the IC socket seeks to distribute loads uniformly along the length of the femur. However, the degree to which this objective is realized remains largely uncharacterized. As is the case with quadrilateral sockets, vertical loads in IC sockets are borne primarily by the ischial tuberosity augmented by gluteal musculature. Thus, the primary differences between quadrilateral and IC sockets stem from the IC socket's recruitment of the ischial ramus for load bearing in the medial direction (and the changes in socket shape at other locations to accommodate the ischial containment). These sockets are typically fabricated with resin-hardened carbon fiber; they either fully contain the residual limb or, when used in combination with a flexible inner socket, are designed as open-section frames. The benefits of the composite frame and flexible inner socket shown in Fig. 4.2 include the reduced constraints on hip motion (due to the inherent flexibility of the inner socket brim) and accommodation of muscle expansion

Fig. 4.2 ComfortFlex™ Socket System (Image courtesy of Hanger Inc.)

and contraction during ambulation (due to select removal of regions of the outer socket wall).

Suspension options for above-knee socket designs include direct suction on the tissue of the residual limb (silicone suspension socket as previously discussed) or mechanical suspension via auxiliary components strapped to anatomy proximal to the amputated limb. Socket designs that incorporate direct suction on the residual limb achieve limb suspension through a combination of negative pressure, surface tension, and contractile activity of the residual-limb musculature. Such designs typically incorporate a one-way expulsion valve in the distal socket wall to facilitate donning and maintain a seal with the residual limb. Direct suction eliminates mechanical losses between the residual limb and prosthesis, enhancing proprioception through the socket interface. Suction sockets are best suited to users with moderate to long residual limbs that are free of significant volume fluctuations, excess scarring, and redundant tissue.

Silicone suspension sockets extend the benefits of suction sockets to amputees with residual limbs otherwise unsuitable for suspension that requires direct suction. Silicone sockets contain an inner socket that attaches to a rigid outer socket using a pin and shuttle lock or hypobaric seal. Like their transtibial counterparts, silicone liners for transfemoral amputees are available in standard sizes or can be custom molded. Relative to direct suction alternatives, silicone suspension sockets are more tolerant of fluctuations in residual-limb volume; they allow the use of socks and gel pads to compensate for moderate amounts of residual-limb volume loss.

Options for mechanical suspension of the limb include a Silesian belt, a hip joint and pelvic belt, and a total elastic suspension. These designs generally incorporate some form of waste belt that provides for suspension of the socket at anatomical features proximal to the residual limb. Belt systems can be used as the primary suspension mechanism or as an auxiliary suspension option when combined with the suction or silicone suspension systems (during high activity levels or when fitting short residual limbs). Mechanical suspensions can provide enhanced rotational and mediolateral stability and control but require increased componentry that may introduce additional bulk and discomfort.

Socket Augmentation Componentry and Advanced Socket Solutions

A number of commercial systems are available for enhancing suction on the residual limb via vacuum-assisted suction suspension systems, and these systems are available in both passive and microprocessor-controlled varieties. The Harmony® Vacuum Management System (Ottobock Healthcare), shown in Fig. 4.3a, offers mechanical and microprocessor-controlled variations. The mechanical system uses a mechanical pump actuated with each step to provide additional negative pressure to enhance limb suspension. The electronic option expands this functionality, offering four preset vacuum levels with integrated sensing for active regulation of the vacuum pressure. The LimbLogic system (Ohio Willow Wood) shown in Fig. 4.3b provides similar active vacuum regulation with a user-selectable desired vacuum level. In a study involving transtibial amputees, the presence of regulated vacuum pressure during walking resulted in an increase in residual-limb volume, versus volume loss in the absence of the vacuum [15]. A subsequent investigation found that vacuum-assisted sockets reduce positive pressure on the residual limb during stance and increase negative pressure during swing [16]. Shifting of the residual-limb pressure in the negative direction is thought to reduce fluid loss during stance and increase fluid gain during swing, resulting in an overall reduction in volume loss or even volume gain in the residual

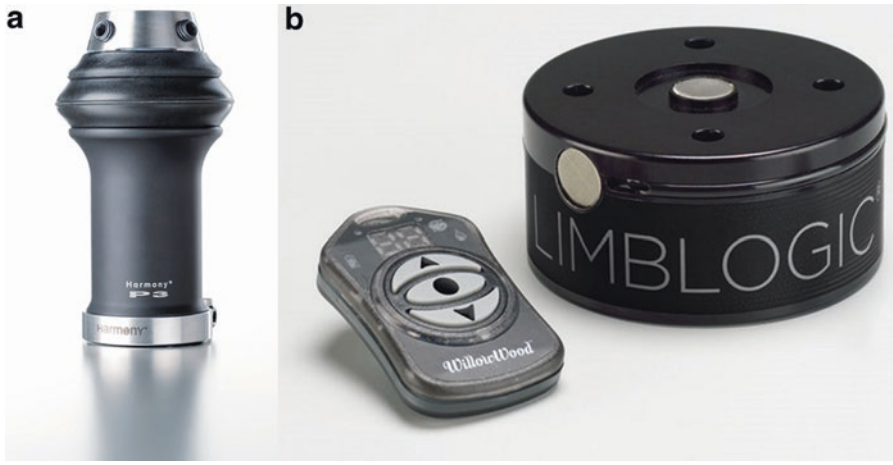

Fig. 4.3 Vacuum-assisted suspension system: (**a**) the Harmony® P3 pump (Image courtesy of Ottobock Healthcare) and (**b**) the LimbLogic system (Image courtesy of WillowWood)

limb. A more recent study based on bioimpedance measurements on the residual limb found similar benefits of vacuum-assisted systems but noted that a number of other factors (e.g., subject health, size and shape of the residual limb, time of day for data collection) also contribute to the observed volume fluctuations [17].

Fluctuations in the volume and shape of the residual limb can significantly affect the fit and comfort of the socket. Common approaches to the accommodation of volume fluctuation include the insertion of socks of uniform thickness and pads within the socket. These strategies offer discrete levels of accommodation best suited for longer time-scale volume fluctuations. Less common alternative options include the use of pneumatic (air-filled) or hydraulic (fluid-filled) inserts within the inner socket to vary the shape and volume of the inner socket in response to fluctuations in residual-limb volume. Pneumatic systems available in the commercial market include the Air Contact System (Ottobock Healthcare, Duderstadt, Germany), the Pneu-Fit™ (Little Rock Prosthetics, Inc., Little Rock, AR), and the Pump It Up!™ socket (Amputee Treatment Center, Batavia, NY). While providing a means to alter volume within the socket, the inherent compliance of the inserts coupled with the relatively high pressures needed to support the residual limb result in large bladder thicknesses, which in turn cause localized high pressures that may cause discomfort or even damage to the underlying tissue [18].

Fig. 4.4 The Active Contact System™ volume accommodation socket (Image courtesy of Simbex LLC)

In lieu of using a compressible fluid, the Active Contact System™ (Simbex LLC, Lebanon, NH) uses fluid inserts to accommodate volume fluctuations of the residual limb (Fig. 4.4) [19]. This system leverages the natural pumping action between the residual limb and a suction socket to draw fluid from

a reservoir into the bladder system (during the suction loads of swing) and distribute it among the bladders (during the compressive loads of stance). Fluid control is accomplished with a purely mechanical fluid-control circuit comprising check valves, pressure regulators, and a flow resistor. The hydraulic system offers the ability to modulate pressures and shear stresses within the socket interface, but the clinical significance of such capability to prosthetic outcomes remains unclear [20]. Current research efforts include the development of an actively controlled bladder system that adjusts bladder pressures in real time with the objective of minimizing high-pressure loading of the residual limb and improving the overall fit and comfort of the socket [21].

In contrast to efforts focused on adaptively containing the soft tissue of the residual limb, osseointegration offers the potential to anchor the prosthetic limb directly to the skeletal system, thereby avoiding many of the difficulties associated with the fit and comfort of standard socket systems [22]. Osseointegration involves a two-part surgical procedure in which (1) a titanium fixture is implanted in the distal end of the residual bone and (2) a transcutaneous abutment protruding from the distal end of the residual limb is affixed to the implanted fixture. The prosthetic limb is then attached directly to the titanium abutment as shown for the transfemoral prosthesis in Fig. 4.5, eliminating altogether the need for traditional socket containment of the residual limb. Benefits include reduced risk of skin irritation or breakdown, improved range of motion, improved sitting comfort, stable suspension of the prosthesis, improved proprioception, and fewer alignment issues. Despite these benefits, limb attachment based on the principles of osseointegration does raise some issues. The surgical procedure requires a lengthy recovery and rehabilitation period as the implant stabilizes prior to realizing its full weight-bearing function. Furthermore, patients face the risk of infection at both the skin-implant interface and the implant-bone interface. Such infections are primarily staph infections of the superficial and deep tissue surrounding the implant [23]. Osseointegrated implants may also suffer mechanical failure between the residual limb and prostheses (necessitating abutment replacement) or loosening within the residual bone (necessitating implant removal and replacement). Nonetheless, provided an appropriate rehabilitation protocol is followed in preparation for unrestricted limb use [22], the principles of osseointegration offer a potentially viable alternative to conventional socket systems.

Fig. 4.5 Osseointegrated transfemoral prosthesis (Image courtesy of Sahlgrenska I.C.)

Despite the current state of the art in lower-limb socket technology and ongoing advances, solutions are still needed to manage temperature and moisture within the socket interface, accommodation of daily and longer-term volume fluctuations of the residual limb, and enhancement of load transmission between the amputee and prosthetic limb. Increased functionality provided by emerging technology introduces increased component weight that, in turn, must be adequately supported through the socket suspension. Additionally, the increased functionality of the prosthesis will likely result in increased levels of moderate and high activity and increased load transmission at the socket interface. Continued socket advancement will be needed to sustain greater loads while maintaining the comfort and health of the residual limb.

Passive Components in Foot-Ankle Systems

Components distal to the socket provide varying degrees of capacity to restore function. While recent developments have resulted in the emergence of externally powered anthropomorphic lower-limb systems with greatly expanded capability, the component landscape in lower-limb prostheses remains largely dominated by passive systems optimized for specific functionalities. Beginning with foot-ankle components relevant to above-knee and below-knee prosthetic limbs, this discussion focuses first on mechanical and microprocessor-controlled passive systems. Following a similar examination of passive knee systems, we consider a number of advanced bionic designs that demonstrate further narrowing of the performance gap between lower-extremity prosthetic limbs and their physiologic counterparts.

The SACH Foot and Single-Axis Foot

The most basic prosthetic foot available is the solid ankle cushion heel (SACH) foot with a solid keel (composed of wood or aluminum) and a cushioned heel wedge, all contained within a molded external cosmesis. The SACH foot is a non-articulating design that provides no significant movement about the ankle either in plantarflexion/dorsiflexion or inversion/eversion. In the absence of ankle plantarflexion at heel strike, the SACH foot instead uses the cushioned heel wedge to dissipate energy in early stance. Forefoot dorsiflexion is approximated with flexible toes positioned distal to the rigid keel. The flexible toes are molded into the cosmesis, providing compliance in the forefoot when transitioning from stance to swing. The SACH foot has no moving parts and provides good shock absorption for up to moderate activity levels. Heel wedges are available in different heights and densities, allowing limited ability to customize the foot to a user's specific needs. Drawbacks to the design include the potential for deterioration of the heel wedge over time and subsequent degradation in performance. Additionally, the rigid keel provides no shock absorption functionality that would otherwise be beneficial during high activity levels.

Fig. 4.6 Basic single-axis foot (Image courtesy of WillowWood)

The single-axis foot shown in Fig. 4.6 expands upon SACH foot functionality with allowance for limited plantarflexion and dorsiflexion of the ankle about its neutral position. Single-axis designs typically incorporate anterior and posterior rubber bumpers of varying durometers to control the ankle's resistance to plantarflexor and dorsiflexor loads. The forefoot compliance of the SACH foot cosmesis is preserved in single-axis feet, but shock absorption at heel contact is realized via ankle plantarflexion into the posterior bumper in lieu of heel cushioning. Single-axis feet enable users to reach foot flat quicker than SACH feet, providing enhanced stability in stance. Though of limited utility for transtibial amputees [24], the stabilizing functions of the single-axis foot make it well suited to low-mobility transfemoral amputees who may benefit from enhanced weight-bearing stability [25].

Energy Return Foot-Ankle Systems

In contrast to the basic SACH and single-axis feet, foot-ankle systems with energy return are designed to absorb and return energy to the user during various segments of the stance phase of locomotion for improved gait efficiency. The VA Seattle Foot, which combines a cushioned heel with a monolithic cantilevered keel composed of an acetal homopolymer (Delrin®), was one of the early pioneering examples of energy-storage foot design and development [26]. Its cantilevered keel progressively stores energy as the foot is loaded through mid-stance and then releases that stored energy as the foot is unloaded in the transition to toe-off. More contemporary designs expand upon the VA Seattle Foot's cantilevered spring configuration by integrating carbon fiber composites to enable tuned compliance in both the keel and heel. Deformation at the heel provides energy absorption at heel strike, which is then released in the transition to mid-stance, augmenting the energy-storage functions of the keel from mid-stance to toe-off.

Additional variations in energy-return foot-ankle systems include designs that offer inversion/eversion compliance and/or vertical compliance. Split-toe keel designs, such as the Esprit foot from Endolite USA, provide multi-axis flexibility with the addition of inversion and eversion compliance to the foot-ankle complex. Multi-axis flexibility offers improved adaptability to uneven and time-varying terrains. Vertical compliance is realized using either compliance of the composite structure or axial spring systems integrated at the proximal termination of the ankle. A feature of the axial spring system is its ability to achieve vertical compression and axial rotation, which modulates the vertical forces and axial moments transmitted to the residual limb. Specialized energy-return foot-ankle systems such as Freedom Innovations' Catapult (Fig. 4.7) designed for medium and high impact recreational and sporting activities are also available on the commercial market. Compliance in such designs is optimized to maximize energy storage and return for jogging, running, and/or sprinting gaits.

Fig. 4.7 The Catapult ™ running foot (Image courtesy of Freedom Innovations, LLC)

The main benefits on walking gait can largely be attributed to flexibility in the keel [27]. Compliance in the foot results in increased step length of the sound-side limb, decreased impact force at sound-side heel strike, and reduced gait asymmetry (for unilateral transtibial amputees). Additional reported benefits of energy-return feet include increased self-selected walking speed, cadence, and prosthetic-side propulsive force. While these improvements often lack strong statistical significance, the trends combined with users' subjective perceptions suggest that energy-return foot-ankle systems do offer benefits of clinical significance for certain users and activities.

Hydraulic Foot-Ankle Systems

Hydraulic foot-ankle systems expand upon composite energy-return designs with the addition of hydraulic componentry to enable tuning of ankle resistance in plantarflexion and dorsiflexion. Higher resistance promotes increased loading and energy return from the heel and keel, whereas lower resistance enables increased ankle movement and improved terrain adaptation. Plantarflexion resistance controls damping and the amount of ankle plantarflexion at heel strike, with dorsiflexion resistance controlling the speed at which the user advances over the foot in transition to swing. Designs such as Endolite's echelon foot and Freedom Innovations' Kinterra™ foot (Fig. 4.8) combine a hydraulic ankle with carbon composite foot springs and allow independent control of plantarflexion and dorsiflexion resistance at the ankle. The hydraulic ankle smoothly adapts to varying terrains and provides more comfortable ankle positions when sitting. The Kinterra™ also incorporates a mechanical spring to provide dorsiflexion assistance during swing for improved toe clearance. Relative to standard energy-return designs, the echelon foot has been shown to provide decreased peak internal stresses and rates of loading on the residual limb as well as improved protection of the distal residual-limb tissue [28]. Additionally, a study of transtibial and transfemoral amputees found the echelon foot provided enhanced user satisfaction and self-reported improvement in gait, indicative of the user-perceived benefits of hydraulic ankles [29].

Fig. 4.8 The Kinterra™ hydraulic foot/ankle (Image courtesy of Freedom Innovations, LLC)

Microprocessor Foot-Ankle Systems

Microprocessor control offers further capability in expanding the performance of passive foot-ankle systems; this has been successfully leveraged in research and commercial foot-ankle systems. Intelligent control of features such as ankle position, plantarflexion/dorsiflexion resistance, and energy storage/release enables the microprocessor-controlled ankle to be optimized to the individual's specific gait and allows it to adapt in real time to variations in gait and terrain. The Össur PROPRIO FOOT® (Fig. 4.9a) is the earliest commercial microprocessor foot-ankle system; it combines a carbon composite foot with a stepper-motor actuated ankle joint. The system does not provide power assist but is instead used to adapt ankle angle to the underlying terrain and to increase swing-phase dorsiflexion for improved ground clearance. The PROPRIO FOOT® incorporates instrumentation for real-time sensing of acceleration and ankle angle and determines appropriate ankle settings depending upon the sensed terrain or activity level. Clinical evaluations of the PROPRIO FOOT® with unilateral transtibial amputees for stair and incline walking yielded socket interface pressures that were closer to those of level walking [30]. Furthermore, increased dorsiflexion during ramp ascent resulted in more physiologic kinetics and kinematics in the prosthetic-side and contralateral limb [31]. While similar results were not realized during ramp descent, users subjectively reported the perception of improved safety in the slope-

adapted configuration (i.e., increased plantarflexion relative to neutral).

More recent commercial systems such as the Endolite élan foot, the Hosmer Raize™ Ankle/Foot System, and the Ottobock Triton smart ankle combine carbon composite feet with microprocessor-controlled hydraulic ankles. The élan foot expands upon the hydraulic design of the echelon foot by including microprocessor control of hydraulic resistance for enhanced response to changes in gait speed and terrain. During incline ascent, the élan foot exhibits large plantarflexion resistance for improved energy return at the heel while reducing dorsiflexion resistance to foster rollover progression. In descent, the microprocessor-controlled ankle resistance decreases in plantarflexion (for improved stability) and increases in dorsiflexion (for improved late-stance weight support). The Raize™ (Fig. 4.9b) provides user-adjustable plantar/dorsiflexion range of motion, heel height, and ankle resistance. It offers terrain accommodation modes for improved stability on slopes and a remote ankle lock for activities such as driving or donning shoes and socks. The Triton smart ankle also uses a microprocessor-controlled hydraulic ankle to enable gait and terrain adaptation. The Triton incorporates proximally located sensing technology to measure forces and moments transmitted to the residual limb at the socket interface. The ankle is dynamically controlled, in part to improve the socket reaction loads during gait. An additional feature of the Triton is mobile app-based connectivity, which facilitates clinician interaction for assessing device performance and user interaction for custom configuration of the device.

As an alternative to energy storage and return via a carbon composite foot, the controlled energy storage and return (CESR) foot (Intelligent Prosthetic Systems, LLC) uses microprocessor-controlled release of energy stored in mechanical springs [32]. The CESR foot incorporates two low-power motors; one actuates a one-way clutch to release the mechanical spring, while the other is used to reset the device following toe-off. Energy captured in the mechanical spring at heel contact is stored until sufficient load is detected in the forefoot, at which point the spring is released to return energy as the forefoot is unloaded prior to toe-off. Clinical evaluations of the CESR foot in transtibial amputees showed increased energy storage in early stance, increased prosthetic-side peak push-off power and work, and decreased sound-side collision work relative to a conventional energy-storage foot and the user's prescribed daily-use foot [33]. However, despite the energetic benefits, the study

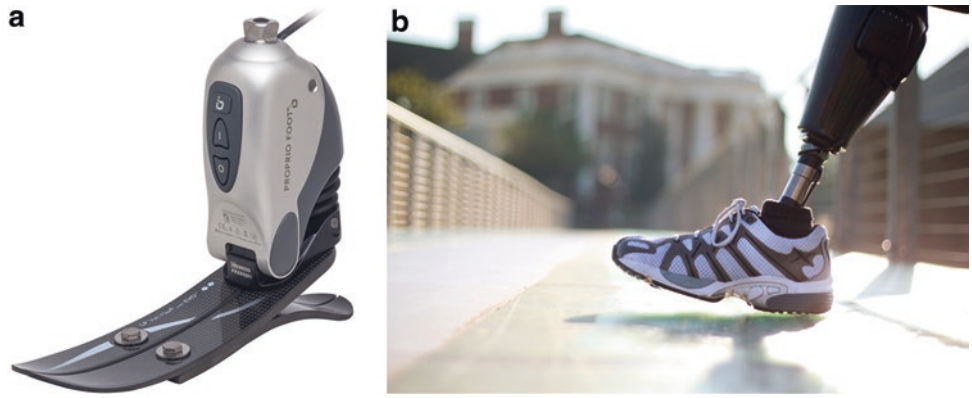

Fig. 4.9 Microprocessor foot-ankle systems: (**a**) the motor-actuated PROPRIO FOOT® (Image courtesy of Össur, Inc.) and (**b**) the hydraulic-based Raize™ Ankle/Foot System (Image courtesy of Hosmer Dorrance Corp.)

found no net change in metabolic cost when compared with the conventional foot and increased metabolic cost when compared with the prescribed foot. While a number of factors other than the CESR likely contribute to the measured metabolic expenditures, the rate of energy release from the CESR foot and the need for increased muscle activity to handle its increased energy release may have adversely affected the metabolic cost of its use.

Passive Components in Knee Systems

The functional requirements of prosthetic knees alter the approaches taken in their design as compared with passive foot-ankle systems. Rather than focus on energy storage and release, the primary design objectives of passive prosthetic knees are stance-phase stability and swing-phase control. As with foot-ankle systems, passive prosthetic knees range from simple mechanical designs to complex microprocessor-controlled variants. Passive prosthetic knees can be divided into three classes: mechanical single axis, polycentric, and microprocessor, each of which is considered here in the context of mechanisms for stance-phase stability and swing-phase control.

Single-Axis Knee Systems

Single-axis knees represent the most basic prosthetic knee design and consist of a single revolute joint at the knee center. Stability is maintained during stance with a combination of prosthetic alignment and user voluntary muscle contractions. By aligning the prosthesis such that the user's center of mass in stance lies anterior to the knee center, knee stability is passively achieved with little voluntary control. This passive or involuntary stability is augmented with voluntary muscle contractions (e.g., hip extensors) that provide additional extensor moments about the knee. The basic single-axis knee provides free or unrestrained motion in swing, limited by the friction in the knee joint. The benefits of single-axis knees include their ease of maintenance and functional simplicity, attained at the cost of reduced mechanical stability in stance. Variations of the nominal design for improved stability include a manual lock to enable a locked-knee configuration, a weight-activated friction brake that is engaged during weight-bearing support (Fig. 4.10), and hydraulic stance assistance. For swing-phase assistance, additional components are available such as hydraulic damping for resistance control in swing, mechanical spring-based swing assist (Fig. 4.10), and pneumatic swing assist.

Fig. 4.10 The 3R90 single-axis knee with weight-activated friction brake and mechanical spring swing assistance (Image courtesy of Ottobock Healthcare)

Polycentric Knee Systems

Polycentric knee designs incorporate a multi-bar linkage rather than a single revolute joint. This design aspect offers features beneficial to both stance-phase and swing-phase performance. The inclusion of a multi-bar linkage results in a changing instant center of rotation as the knee moves through its range of motion. The variation in instant center of rotation enables variable knee stability throughout the gait cycle; small changes in linkage geometry significantly affect the evolution of the instantaneous center as the knee flexes [34]. To provide enhanced weight-bearing stability during stance, the instantaneous center of rotation is located anterior to the vertical component of the ground reaction force. As the knee flexes, the changing instantaneous center of rotation can then be used to foster knee flexion at the transition to swing or, in the case of users who need enhanced stability, to maintain a locked-knee configuration throughout stance. An additional benefit is enhanced ground clearance during swing [35]. As the knee flexes, the change in instantaneous center of rotation effectively shortens the limb during swing, as measured by the distance from hip to toe. Thus, relative to single-axis designs, polycentric knees provide increased toe clearance at smaller knee flexion angles. When the user is sitting, the effective shortening of the limb in flexion also lends itself to improved cosmetic appearance and requires less hip flexion with the prosthetic knee fully flexed [36]. The enhanced stability of polycentric knee designs makes them well suited for transfemoral amputees with short residual limbs due. Additionally, due to the effective shortening of the shank with increased knee flexion, polycentric knees are also well suited for knee-disarticulation amputees or transfemoral amputees with long residual limbs. Options beyond the basic linkage design include pneumatic swing control, hydraulic swing and stance control, and friction-based swing control. An example of a linkage design with pneumatic swing control is shown in Fig. 4.11.

Fig. 4.11 The 3R106 Modular Knee Joint with pneumatic swing-phase control (Image courtesy of Ottobock Healthcare)

Microprocessor Knee Systems

The most advanced passive knee systems also incorporate microprocessor control for enhanced performance and stability. Though technically single-axis systems, microprocessor knees are addressed separately here due to the expanded capability achieved by intelligent microprocessor control. Like their foot-ankle counterparts, microprocessor knees actively control resistance in the knee for improved functionality. They can provide weight-bearing support in fully extended and flexed-knee positions, expanding the range of configurations for which the prosthesis provides stable load-bearing functionality.

Furthermore, the swing-phase resistances can actively adapt to changes in gait and/or terrain for improved comfort and performance.

The RHEO KNEE® (Össur, Inc.) incorporates a damper based on magnetorheological fluid, the viscosity of which varies as a function of an applied electromagnetic field. The RHEO KNEE® controls damping in the knee based on measured knee angle, sensed axial force, and sagittal-plane torque exerted on the frame, providing controlled support in stance and controlled transition into swing. Alternatively, designs such as the Freedom Innovations Plié 2.0 (Fig. 4.12a) and the Ottobock C-leg leverage microprocessor control of a closed hydraulic system to modulate knee dissipation. The C-Leg and Plié 2.0 merge hydraulic swing and stance control with controlled stumble recovery, based on sensed knee angle and axial loads. The Orion2 knee (Endolite USA) pictured in Fig. 4.12b is a hybrid microprocessor knee, combining hydraulic stance control with pneumatic swing control.

Though components and control designs vary from one device to another, they all share the common objectives of enhanced multifunction stance-phase stability and adaptive variable-cadence swing-phase control. While some studies show decreased metabolic energy consumption when using microprocessor knees [37, 38], such findings are not universal [39]. The benefits of microprocessor knees may instead be more attributable to their ability to accommodate multiple terrains and gait speeds with increased user comfort and security [40]. Intelligent microprocessor control of knee resistance relieves the user of cognitive burden related to maintaining stability and limb control, providing enhanced safety [41] and the potential for increased levels of physical activity [39].

The Ottobock Genium knee (Fig. 4.13) expands the performance capability of microprocessor knees through complex sensing and intel-

Fig. 4.12 Microprocessor knees: (**a**) Plié 2.0 (Image courtesy of Freedom Innovations, LLC) and (**b**) Orion2 knee (Image courtesy of Endolite USA)

Fig. 4.13 The Genium microprocessor knee (Image courtesy of Ottobock HealthCare)

ligent mode switching, providing enhanced flexed-knee support that can be used to ascend stairs step over step and better traverse obstacles [42]. Enhanced multifunction control of joint resistance is implemented based on feedback from a gyroscope, accelerometer, and sensors that measure knee and ankle moment, knee angle, and axial load. The Genium is not capable of active power generation, but its ability to prevent knee flexion under load enables the user to utilize extension of the residual limb, e.g., to raise the body's center of mass without also needing to stabilize the knee from collapse. The resulting gait provides a good approximation to the stair-ascent movement patterns of able-bodied subjects, though without any net power generation from the prosthesis. Subjective evaluations comparing the Genium and C-Leg show the Genium improves perception of stability and perceived difficulty, particularly in social and mobility-related activities [43]. Building upon the Genium's performance capabilities, the Ottobock X3 knee additionally provides the ability to detect walk-to-run transitions, at which point swing flexion angles automatically increase. The X3 comes in a ruggedized and fully waterproofed package designed in collaboration with the US military for the express purpose of returning above-knee amputee service members to normal activity levels and, if desired, to active duty. It represents the current state of the art in microprocessor-controlled passive knee systems.

Active Components in Lower-Limb Prosthetic Devices

Mechanical and microprocessor-controlled passive components provide a host of functional capabilities that enable significant restoration of lower-limb function. Despite these capabilities, the ultimate functionality of energetically passive solutions is constrained by the absence of net-positive power generation at the knee and ankle. While energy storage and return at the ankle assists forward progression, the inability to generate net power prevents passive foot-ankle systems from restoring the full functionality of the human ankle. Likewise, the similar absence of net power generation in passive knee systems limits their ability to replicate fully the function of the human knee. Increased metabolic energy expenditures are required for many locomotor functions that are at best approximations. To address functional gaps in performance, a number of recent advances have been made in the design of active, externally powered knee, ankle, and knee-ankle systems to expand the energetic performance of lower-limb prosthetic systems. Such advances primarily build upon electromechanical actuation powered by lithium-polymer battery packs.

Active Ankle Systems

A powered foot-ankle prosthesis developed at the Massachusetts Institute of Technology [44] and commercialized as the BiOM® Ankle System (Fig. 4.14a) provides programmable ankle stiffness control and power assist. The device leverages a series-elastic actuator, consisting of a direct current (DC) motor and ballscrew transmission in series with a mechanical spring, augmented with a unidirectional parallel spring. This feature enables ankle impedance modulation and the output of human-scale torque and power. Feedback control is effected based on joint torque (measured with position sensing integrated in the series-elastic actuator), ankle position (measured with an integrated encoder), and state of foot contact (measured with capacitive transducers integrated at the heel and toe). The combination of impedance control with powered propulsion at the ankle provides decreased metabolic consumption (rel-

Fig. 4.14 Actively powered foot-ankle systems: (**a**) the BiOM® Ankle System (Image courtesy of BiOM) and (**b**) the Odyssey ankle (Image courtesy of SpringActive, Inc.)

ative to conventional energy-return foot-ankle systems) in unilateral transtibial amputees walking at self-selected speed, an achievement made despite the increased weight of the powered foot-ankle [44]. Additional benefits of the powered foot-ankle in level walking include reduced loading in the unaffected limb, which may reduce the risk of comorbidities such as knee osteoarthritis in the unaffected limb [45]. The metabolic energy costs, self-selected walking speeds, and gait patterns enabled by the BiOM® Ankle System are comparable to normative measures in individuals without amputation [46].

Another powered foot-ankle prosthesis developed at Arizona State University [47] is now being commercialized as the Odyssey (Fig. 4.14b) through a partnership between SpringActive, Inc. and Össur. The device uses a spring ankle comprising a DC motor, leadscrew transmission, and helical spring. The helical spring stores stance-phase kinetic energy supplemented with additional motor energy that is then released during toe-off to provide powered plantarflexion of the foot-ankle assembly. Incorporation of the helical spring serves to reduce the overall power requirements of the DC motor. The resulting motor-actuated spring ankle provides power and kinematics comparable to those seen in the gait of non-amputees. Building upon the successes of the Odyssey, a revised design that incorporates dual-motor actuation, dual springs, and component reinforcement is currently under development as a running prosthesis for transtibial amputees [48]. Preliminary results with a single subject with unilateral transtibial amputation demonstrate sustained running at 3.6 m/s (8 mph) from the dual-motor actuation system. Future efforts are focused on reduction of system weight and inertial properties.

Active Above-Knee Systems

The emergence of energetically active solutions for above-knee prosthetic systems began with the Össur POWER KNEE™ (Fig. 4.15a), a motor-driven single-axis knee capable of producing physiologic torque and power outputs. The

POWER KNEE™ incorporates accelerometers, gyroscopes, a torque sensor, and a load cell to monitor the position and orientation of the knee and the external loads being applied to it. These measurements are used to determine the activity and intent of the user and the appropriate knee response. The POWER KNEE™ provides active control of dissipation for activities such as ramp and stair descent. It also provides stance-flexion cushioning at heel contact and propulsive power outputs during level walking and ascent of ramps and stairs. Though clinical evaluations of the effectiveness of the POWER KNEE™ have been limited, a case study involving a single subject performing stand-to-sit transitions showed increased symmetry in hip moment (relative to the C-Leg) between the prosthetic-side and unaffected limbs [49]. More recently, the POWER KNEE™ was shown to provide increased power, increased symmetry of power, and reduced peak ground reaction forces on the unaffected limb (relative to the C-Leg) for sit-to-stand tasks [50]. It should be noted, however, that the study found no significant reduction in power generation of the intact knee, indicative of the users' continued reliance on power generation at the unaffected limb.

A two-degree-of-actuation above-knee prosthesis (Fig. 4.15b) originally developed at Vanderbilt University and currently being commercialized by Freedom Innovations, LLC combines actively powered knee and ankle joints within a single, self-contained design [51]. Each joint is actuated with a brushless DC motor, and the prosthesis is designed to provide physiologic torque and power generation at both the knee and ankle. The current limb prototype includes an axial load sensor in the shank, angle sensors in both the knee and ankle joints, and a 6-axis inertial measurement unit. Experimental evaluations of the limb with a single subject with unilateral transfemoral amputation demonstrate the ability to provide gait kinematics similar to that of nonamputee subjects for level walking [51], incline ascent [52], and stair ascent/descent [53]. The actively powered knee and ankle prosthesis offers the ability to realize powered knee extension, powered ankle plantarflexion, and knee flexion at heel strike, the combination of which is other-

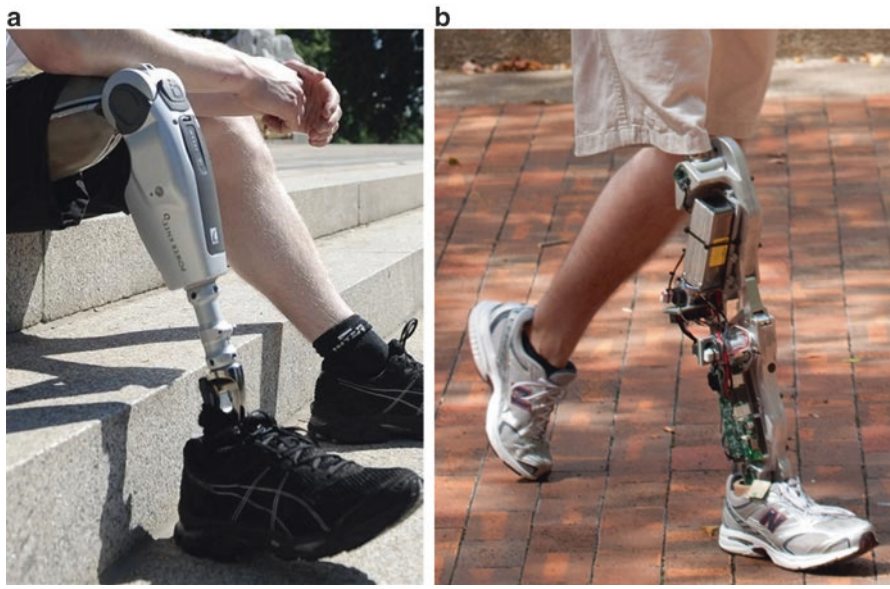

Fig. 4.15 Actively powered above-knee prosthetic systems: (**a**) the POWER KNEE™ (Image courtesy of Össur, Inc.) and (**b**) the Vanderbilt Leg (Image courtesy of the Center for Intelligent Mechatronics, Vanderbilt University)

wise not possible in above-knee prosthetic-limb systems.

Despite the functionality already demonstrated by the emerging bionic limb technology, continued development is still needed. DC motor technology offers improvements in actuator power density but at torques and speeds mismatched to the needs of ankle and knee systems. As such, the development of compact and efficient transmissions persists as a need in lower-extremity prosthetic limbs. Additionally, while lithium-polymer batteries provide power sources of reasonable energy density, efficient exploitation of energy generation and exchange remains a critical requirement for expanding the operation longevity in active limb systems. Related to the issues of power and energy density are the overall weight and build height of actively powered prosthetic devices. For such solutions to be universally applicable, reductions in size and weight must be made for the limbs to fit an expanded range of residual-limb anatomies. Furthermore, the increased functionality afforded by such actively powered designs places increased burden on the weight-bearing and suspension functions of the socket interface. This necessitates continued advances in socket interface technology. The foundations have been laid for general accessibility to advanced lower-limb prosthetic systems, but a number of hurdles still exist with respect to how the enhanced functional capabilities of our most advanced technologies can be made useful and effective for those who will wear them.

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Wearable Robotic Approaches to Lower Extremity Gait Systems

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Roger N. Rovekamp Jr., Gerard E. Francisco, Shuo-Hsiu Chang, and Christopher E. Beck

Introduction

Once confined to science fiction, wearable robots have become reality, with implications for medical and nonmedical applications alike. They promise to augment human strength, increase human endurance, expand human capabilities, and provide patients and doctors with new tools they can use to improve quality of life. It is reasonable now to question many of our human physical limitations, to imagine instead what may be possible by augmentation of our innate capabilities, and to think differently about what it means to be "disabled" by injury or limited by disease. Patients recovering from amputation, or learning to live with paralysis, can find new hope in advanced rehabilitative technologies that may help to restore strength, balance, functional mobility, and independence. Advanced prosthetics controlled by user volition are now possible, raising additional possibilities for freedom of mobility through wearable robotics. Although wearable robotics are not yet widely accessible or affordable to the consumer, researchers and developers continue their work to create systems that can one day be used safely and effectively in home settings.

This chapter provides an overview of wearable robotics, especially lower extremity powered orthoses such as lower extremity exoskeletons, and the role these systems can play in present and future lower extremity prosthetics. First, we consider factors driving the latest surge in wearable robotics research, including increased interest in the area of human-robot interaction and the related necessary technologies. We define the terms "robot" and "wearable robot," and consider what sets wearable robotic systems apart from other lower extremity orthotic and prosthetic systems. We then provide an engineering perspective and review the fundamental elements and classifications of wearable robots, providing

R.N. Rovekamp, Jr., BS, MS
Cincinnati Automation & Mechatronics (CAM), Beavercreek, Ohio, TX, USA
e-mail: roger.rovekamp@cam-revolution.com

G.E. Francisco, MD (✉)
S.-H. Chang, PhD, PT (✉)
Department of Physical Medicine and Rehabilitation, UTHealth McGovern Medical School at Houston, The NeuroRecovery Research Center at TIRR Memorial Hermann, Houston, TX, USA
e-mail: Gerard.E.Francisco@uth.tmc.edu; Shuo-Hsiu.Chang@uth.tmc.edu

C.E. Beck, MS, BS
Oceaneering Space Systems, Robotics and Automation Program, Houston, TX, USA
e-mail: CBeck@oceaneering.com

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some examples of lower extremity wearable robots. We also discuss the various aspects of these devices from the clinical perspective, considering new pilot studies of leading lower extremity exoskeletons performed at the Center for Wearable Exoskeletons at The Institute for Rehabilitation Research (TIRR) Memorial Hermann Hospital. Finally, we briefly address how wearable robotics can be applied to nonmedical industrial and military domains.

Wearable Robotics Revolution: A Long-Awaited Step in Robotics

Wearable robots, including exoskeletons and powered orthotics, have seen rapid progress in recent decades fueled primarily by advancements in the larger field of robotics generally. Unpowered orthotics and prosthetics (O&P) have long been the forebears of these more advanced wearable robotic systems. The challenges that have historically faced orthotists and prosthetists are much like those faced by wearable roboticists today. Specifically, it is a significant challenge to attach the human body to a device (a donned structure) in a manner that minimizes injury and discomfort, creates a kinematic structure of rigid and soft mechanical elements which maps to the anatomical structures of the human body, and absorbs and directs loads to improve the function and mobility of the wearer.

Figure 5.1 provides various examples of wearable technology. The device pictured in Fig. 5.1a is a transfemoral prosthetic socket developed by Martin Bionics for use with a transfemoral leg prosthetic called the Socket-less Socket™. Figure 5.1b shows a lower extremity mobility exoskeleton, the MinaV0, developed by the Florida Institute for Human and Machine Cognition. The attachment of such a device presents challenges similar to attachment of a prosthetic socket, as mentioned above, and introduces new challenges related to the control of human-robotic systems. We will elaborate on this additional challenge in more detail later in this chapter. Figure 5.1c shows the RoboKnee, developed by Dr. Jerry Pratt and designed to amplify power and assist a healthy user with load carriage; the RoboKnee could also be applied to assist a disabled or elderly individual with stair climbing. Figure 5.1d shows the Indego™ produced by Parker Hannifin. Indego's lightweight, compact, and modular design makes it very practical for both clinical and nonclinical use.

The historical evolution of robots and wearable robots is closely linked. Robots, and especially biologically inspired robots (also referred to as biomimetic robots), have advanced from simplistic mechanical machines such as Leonardo da Vinci's mechanical knight (Fig. 5.2a) to complex contemporary systems, such as NASA's R5 (aka Valkyrie) and Robonaut 2 (Fig. 5.2b, c). These systems are designed to appear humanlike in form, replicate human motion and function, and operate as capable assistants to human operators [1]. During the 1960s and 1970s, General Electric carried out one of the first significant efforts to develop an exoskeleton [18]. Funded by the US military, the experimental prototype system known as Hardiman (Fig. 5.2d) illuminated the technology limitations of its time. It was large, heavy, unstable, and difficult to power. The Hardiman system was actually more like two exoskeletons in one. It was built on the premise of "following" rather than interacting closely with the user. In the decades of technology advancement since Hardiman, research has achieved a tighter interaction between human operator and robot. These developments helped set the stage for the more recent surge in wearable robotics research.

There are a number of driving factors behind the recent developments in wearable robotics. Not the least of these is our ever-increasing comfort with a closer interaction between humans

Fig. 5.1 (**a**) Socketless socket for a transfemoral prosthetic (Courtesy of Martin Bionics) (**b**) MinaV0 exoskeleton (Courtesy of Florida Institute for Human Machine Cognition) (**c**) RoboKnee (Courtesy of Dr. Jerry Pratt) (**d**) Indego (Courtesy of Parker Hannifin, USA)

and robots. According to Pons [21], "Originally, robots were only intended for industrial environments to replace humans in tedious and repetitive tasks and tasks requiring precision, but the current scenario is one of transition towards increasing interaction with the human operator…. It is in this context that the concept of *Wearable Robots* (WRs) has emerged." Human-robot interaction, or HRI, has been an active field of research for many years. Today, HRI is finding applications in the automotive, medical, and manufacturing industries, among others. Steady advancement of this field has supported development of robotic devices that can be worn safely by human beings.

No better evidence of the state of HRI can be found than in the relatively recent burst of wearable robot concepts and related advances in the areas of power, actuation, and sensing. Several such systems are depicted in Figs. 5.1 and 5.2, and additional examples will be discussed later in this chapter. Orthotics have evolved, and continue to evolve, from what were once no more than simple mechanical braces into what now serve as full-fledged robots that can sense, "think," and act in concert with the human wearer to achieve more natural or better-than-natural human gait. The potential benefits of robotic orthotics now reach beyond the medical restorative arena to include enhanced human perfor-

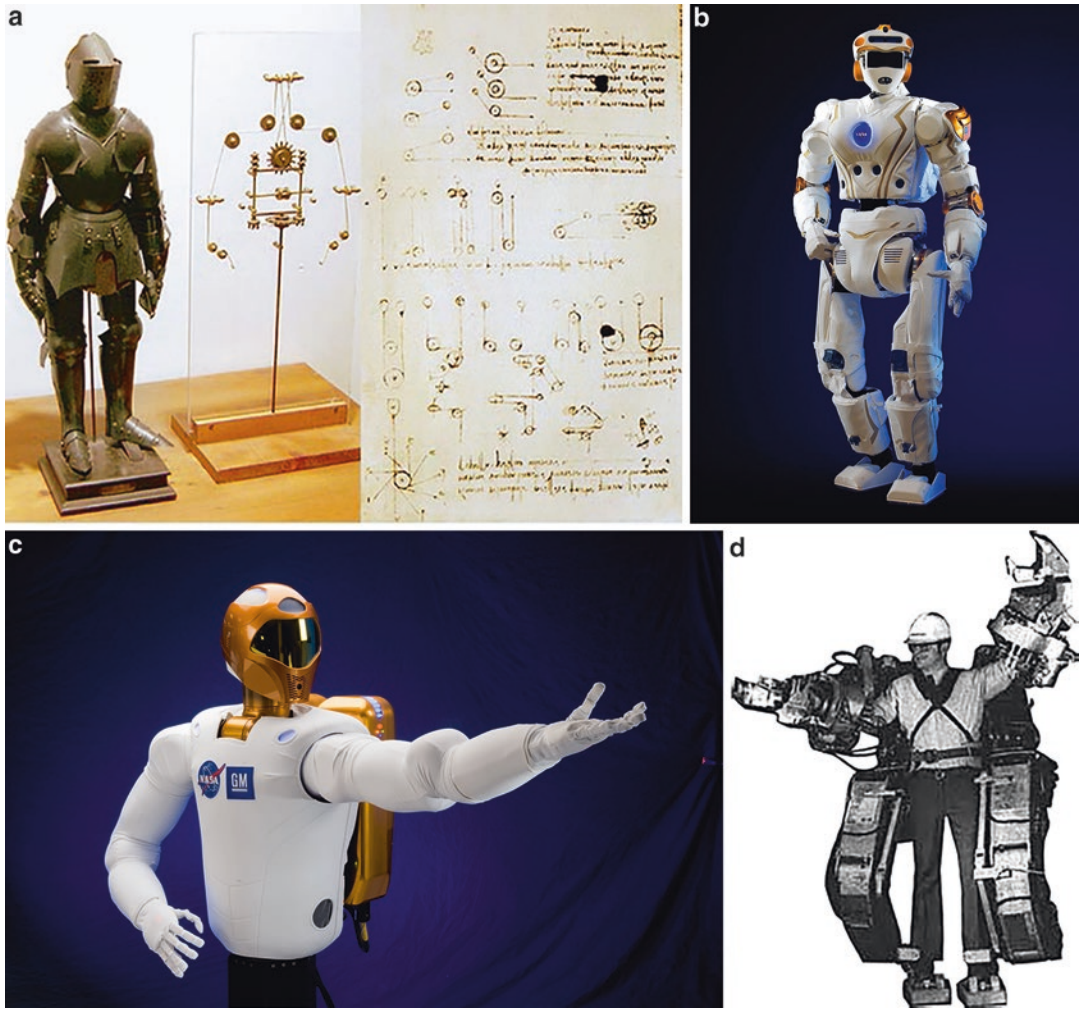

Fig. 5.2 (**a**) Robots began as simple mechanical machines. (**b**) Walking humanoids have begun to mimic human form and function. (Courtesy of NASA) (**c**) Robonaut 2 was developed to work in close proximity to astronauts in space. (Courtesy of NASA) (**d**) Hardiman, developed by GE, helped to illuminate the challenges of wearable technology of the time

mance applications in military, aerospace, and industrial domains.

Behind the wearable robotics revolution are engineers, scientists, physicians, and innovators from a variety of disciplines working to design and develop wearable robotic systems previously out of reach due to limitations in technology. Indeed, this endeavor has captured the interest and imagination of many of the brightest minds in robotics. Knowledge and expertise from various fields inherent to traditional robotics make it possible for roboticists to tackle challenges associated with wearable robotics sensing, software and firmware design, electronics, actuators, and controls. Advances and applications in these fields are necessary but not sufficient. Additional knowledge in the areas of physical human-robot interaction (pHRI), cognitive human-robot interaction (cHRI), and human biology is also essential. A new interdisciplinary field of applied

science known as biomechatronics has developed to address these needs in an integrated fashion. Wearable robotics have the potential to restore function and quality of life to individuals who suffer from neurological and musculoskeletal pathologies of the lower limbs. Lower limb applications have long been the driving force behind wearable robotics development. Through their interest in advanced prosthetic solutions, medical practitioners are bringing greater visibility to wearable robotics as potential interventions for patients in need of assisted mobility and rehabilitation. Wearable robotic devices offer many potential benefits in rehabilitation, for example, as tools with which physical therapists can provide repeatable treatments. These devices also provide a method of modified assistance for scenarios beyond rehabilitation.

Wearable Robotics: An Engineering Perspective

It is useful to describe wearable robots in the broader context of robotics generally. Here, we first define any robot as a machine that senses, "thinks," and acts. More precisely, a robot is a machine that uses sensors (encoders, accelerometers, transducers, cameras, etc.) to sense and perceive the world around it, processors to interpret sensory information and make decisions, and actuators to behave (by the application of forces or torques) based on its processor-based decisions. A robot can also use data that is stored onboard or remotely to inform its decisions and improve its understanding of the world in which it behaves. Robots may be extremely simple, relying upon a single sensor and deciding/acting within a single degree of freedom, or extremely complex, containing dozens of sensors, several processors, and scores of actuators. By extension, we define a wearable robot as a system that senses and "thinks" in conjunction with a human being in order to extend, complement, substitute, or enhance human function.

Within the field of wearable robotics, there are many possible devices that fall into a number of classifications that can be described with the key elements that are a part of every wearable robot. The remainder of this section will examine these key elements in detail and discuss the classifications in which today's wearable robots can be placed. At the end of this section, specific examples of wearable robots are discussed, identifying their key elements and classifications.

Key Elements of Wearable Robots

Human-Robot Interface

A wearable robot includes all of the same elements that comprise a typical robot: actuation, sensing, software, and control. An element unique to the wearable robot is the physical human-robot interface, which includes physical attachment and information exchange. The human-robot interface represents a physical and virtual medium between the human and robot, across which both physical and cognitive information is exchanged in both directions. This information may include interaction forces and pressures, biometric measures of temperature, electromyography (EMG) and electroencephalography (EEG), and information representing sensory modalities of vision, sound, and touch. The physical attachment is a significant challenge due most notably to the wide variability in users' size and shape and the inherent differences in material and stiffness between a robotic device and a human body.

The desire for more sophisticated control of wearable robotics is increasing the emphasis of the advancement of the physical human-robot interface. While the link between precise control and user comfort may not be immediately obvi-

ous, the effect on one needs to be considered when development of the other is the goal. This is one of the most difficult challenges currently facing wearable roboticists. Unmodeled or otherwise unpredicted relative motion between the human and robot (also called interface migration) can make it difficult to control the human limb along a desired path. Traditional rigid, non-wearable robots contain metal components that are bolted or welded together to minimize any undesired relative motion. With wearable robotic devices, bolting to human bone is not an option, and designers must minimize the relative motion through creative choices of materials, shapes, and locations of the interface. With the goal of precise control of the limb, designers must reduce the relative motion while still providing a physical human-robot interface that can be worn comfortably by eliminating pressure points, localized forces, and constriction of circulation, as well as providing a breathable, nonirritating layer closest to the skin.

Structure

The structure of a wearable robotic device can serve several functions depending on the application of the device. It can define the load path and kinematic layout of the joints and can house and protect other sensitive device elements. Early wearable robotic structures were mostly rigid in nature. Recent efforts to reduce unnecessary structure and weight have produced lighter rigid and even softer archetypes that conform better to the human body and human joints, are more portable, and ultimately more biomimetic in nature. This trend toward more conformal devices also affords designs that are less obtrusive and ultimately less visible to an observer, addressing a psychological concern in terms of societal reintegration and user satisfaction.

Sensing

Sensing used in wearable robots includes that of other robots but with the key addition of biological sensors such as EEG and EMG. There also exists the challenge of creating sensors that map to human anatomy, which includes many contours, variations, and degrees of stiffness in contrast to the much more defined consistency and repeatable anatomy of a robot.

Typical robots, such as robotic manipulators, use a variety of analog and digital sensors to determine the state of the robot and the degree to which it interacts with its surrounding environment. In the case of a wearable robot, interaction also occurs between the robot and its user. Position, velocity, and joint acceleration are measured using linear and rotary incremental and absolute encoders available in a variety of shapes and sizes. For measuring force and torque, strain gauge-based sensors are most common, but other techniques that use position sensors combined with elastic elements (springs) are also used (such as with series elastic actuators).

Wearable robotic designs must overcome the additional challenge of sensing the motion of human joints, which are more complex than the joints of typical robots. Moreover, the sensing of the human joint can be highly dependent on the relative motion and alignment of the interface and the human user, thus requiring more advanced sensing techniques.

Recent advances in wearable body networks have increased the amount of data, such as biomarkers and motion data, which can be collected, retained, and analyzed by engineers and clinicians. For the engineers, these additional data provide an opportunity to refine a system design and anticipate its potential failures. For the clinician, additional data support improved prescription, more accurate and effective interventions, and better tracking of patient progress during

recovery. Data-driven applications further increase the demand for sensing capabilities in non-wearable and wearable robots alike.

Actuation

Actuation provides the muscle for all robots. Typical actuation topologies include electric motors (with or without transmissions), hydraulics and pneumatics, and shape memory alloys. High torque and power density (amount of power per unit volume), packaging, and safety are priorities for wearable actuators. Whereas early wearable robots relied mostly on position control, more recent applications focus on force and torque control that enable precise interaction between the user and the robot.

In recent decades, the development of force-controllable and torque-controllable actuation has been a key enabler of increased human-robot interaction in all types of robots. In wearable robotics, the ability to control position and force is especially useful in prescribing compensatory forces and torques in applications of rehabilitation and mobility assistance. Moreover, the ability to apply a known force enables admittance and impedance control strategies that define the interaction of a robot with its environment or, in the case of a wearable robot, its interaction with the human user.

Due to the close interaction of human and robot in wearable robotic systems, safety is a paramount concern. A design goal of many wearable robots is to reduce undesired forces on the user. Such forces can be unsafe or may adversely affect the intended performance of the human-robot system. Actuation topologies that achieve force reduction by using mechanical solutions are desirable. One such design is the Series Elastic Actuator (SEA) (depicted in Fig. 5.3), which limits effective impedance (ability of robot to resist motion of user) by means of an elastic element such as spring. While performance of an SEA is limited at higher frequencies due to inherent compliance, the benefit is added safety and effective filtering of undesirable and unsafe forces between robot and user [16]. Moreover, the relatively low frequency of human motion when compared to, say, an industrial robotics arm makes SEAs even more favorable to wearable robotics applications.

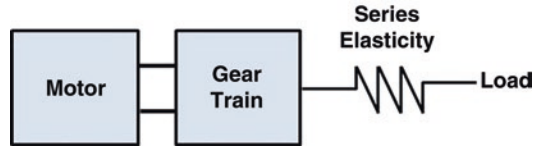

Fig. 5.3 Schematic of a Series Elastic Actuator (SEA)

More recently, soft actuation topologies have received much attention in wearable robotics. Soft actuation is biomimetic in that its behavior is similar to that of human muscles and tendons and thus well suited for wearable systems. Soft pneumatic actuators such as the McKibben actuator have been a topic of research for some time. More recently, tendon actuators have grown in popularity; these offer packaging options not possible with more rigid, collocated direct drive actuators. One drawback of tendon actuator systems is that they can pull but not push, so they must typically be used in antagonistic pairs to produce bidirectional rotary motion. Yet many other advantages remain, making tendon actuators a good candidate for wearable robots.

One clear advantage tendon actuators offer is the ability to locate the actuator mass apart from the joint of actuation. By implementing a Bowden cable transmission, by which the actuation tendon runs through stationary conduit, designers can place the heavy components more proximally on the body, rather than on the limbs. Placement of mass is a concern in wearable robotic device design, especially when considering patients who may already find it difficult to move their limbs. Additionally, since only a thin tendon crosses the

joint center, a much more natural human joint motion can be achieved. One drawback of rigid collocated actuation is that it makes it difficult to replicate natural movement: the systems are sensitive to misalignment, human joints with more than one DOF are often unnaturally constrained, and many external linkages may be necessary since the actuator obviously cannot be placed inside the human joint. Tendon-based actuation systems avoid these issues by eliminating the need for rigid and bulky mass positioned around and across the joint.

Control

Wearable robots are often controlled through a distributed architecture, using a combination of high-level and low-level control. Low-level control is achieved on a motor controller at each actuator, using a basic feedback control loop(s). This is illustrated in Fig. 5.4a, where the controller represents the low-level feedback controller (Fig. 5.4b), the system model or "plant" represents the actuator and interface between the controller and limb, and feedback sensors might include motor encoders, EMG signals, or other sensory feedback. Low-level control is most often achieved with proportional–integral–derivative (PID) control, but other, more sophisticated approaches are also available. The objective of the low-level controller is straightforward: maintain the value of actuator position, force, torque, or velocity commanded by the high-level controller at all times. In this manner, the low-level controller can operate without any information about the state of the rest of the system.

High-level control is typically responsible for performing kinematics calculations, executing gait or exercise algorithms, and generating force, torque, position, or velocity commands for each low-level controller. In lower extremity prosthetic systems, the high-level controller assists or controls gait. This could be as simple as maintaining a prerecorded walking gait or as complex as providing "assist-as-needed" control based on sensor feedback and determination of user intent. Two common control methods are torque (or force) and impedance control. Torque control allows for variable levels of assistance or resistance torques based on real-time, high-rate state information derived from data captured by low-level controllers. Impedance control allows the system to act on position or velocity errors by calculating the corresponding force or torque commands (with sensitivities often tunable by the end user) and sending them to low-level controllers. The low-level controllers then act on the force or torque commands and thereby maintain the robotic joints close to their intended positions. In this way, assist-as-needed control can be achieved by providing variable torque to the user,

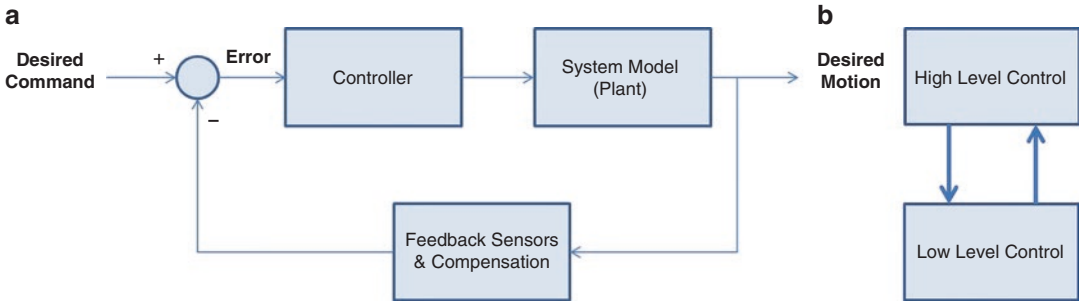

Fig. 5.4 Functional block diagram of (**a**) low-level feedback controller and (**b**) the relationship between high-level and low-level control system

in relation to how well the user is following the prescribed motion. Examples of assist-as-needed controllers have shown promise and have been implemented on lower extremity exoskeletons such as the H2 [5] and LOPES [19].

The above description of assist-as-needed control illuminates the concept of "shared control." That is, while the system maintains low-level control (e.g., of the joint), the user can control high-level operation, for example, taking a step or providing resistance in knee extension. User interfaces such as joysticks, computer displays, and pushbuttons are simple to implement but limited in capability. More complex intent-recognition systems are understandably easier to use – for example, when the user leans forward, the device recognizes user intent to take another step. Systems that assist as needed must share high-level operation with the user; they must be able to seamlessly, cooperatively control high-level operations only as much as required by the user. Regardless of complexity, distributed control paradigms make shared control possible. While the user might have some, all, or no control over high-level operational commands, low-level operations are controlled by the device; there is no need for the user to be aware of or attend to low-level operations, thereby offloading cognitive burden.

Energy Storage

A key enabling technology for wearable robotic systems is portable energy storage, specifically batteries. Advances in battery chemistries, such as lithium-ion batteries, offer increased capacity in smaller packages as are needed to make wearable robots feasible for a variety of applications. While the use of batteries increases the need for proper battery monitoring, current-limiting circuitry, and fail-safe designs, the advantages of portability and an untethered system outweigh the cost and requirements for additional infrastructure, safety, and fault protections.

Safety System

Wearable robots must include well-developed safety strategies that will enter the system into a safe state when it encounters an unsafe condition. Unsafe conditions might include, but are not limited to, hardware or software malfunction; joint overextension; excessive force, torque, speed, or temperature; and electric shock as may result from exposed wiring. In addition, adequate safety measures must be taken to prevent falls. Although the risk of falling cannot be altogether eliminated, strategies to minimize risk should be adopted by user training and/or system design.

Biomechanical Modeling and Simulation

Although modeling and simulation (M&S) tools do not play a key role in every wearable robot design, they do hold potential for advancing research and speeding development. Validated models can be used to improve design effectiveness early in the design process, allowing the designer to experiment with different parameters prior to costly hardware fabrication and with less risk than that involved in testing the impact of changes on human subjects. Human musculoskeletal models can be used to improve system design and to better understand human-robot coupling. Models can also be used in control system design.

Through motion capture, subject measurement, and force data recording, sufficient information can be gathered to inform a biomechanical M&S tool. Such tools typically allow automatic and manual scaling of human musculoskeletal models to more closely match the individual subject being evaluated. Once reserved for athletic

researchers and exercise scientists, motion capture has become a relatively mainstream process, as systems have become more affordable and easier to use. Some systems employ infrared signals to detect markers placed at specific points on the human subject, while other systems have advanced algorithms to detect the location of each human joint through the use of RGB cameras and depth sensors. Force data can typically be gathered through a force plate or via load cell instrumentation.

Once obtained, these Cartesian data are fed into an M&S tool to determine a time history of joint angles through inverse kinematics. In combination with joint angle calculations, force information can be used with the inverse dynamics application of the M&S tool to calculate a time history of human joint torques. Once the torques are known, the tool begins to yield its practical benefit. Virtual actuators can be integrated to determine the best wearable robotic device design. Analyzing the sensitivity of the human joint torques to parameters such as actuator location and level of assistance can be applied to inform the design. These results generally push hardware designers in the best possible direction for initial design before they invest time and money to build prototypes for testing. An optimization routine can also be performed to determine muscle forces, given acceptable assumptions about order of muscle recruitment and maximum forces.

Biomechanical M&S tools can help to inform system design by allowing the designer to adjust musculoskeletal models to target specific research or design objectives. Limb dimensions, user weight, muscle maximum force capability, and other parameters can be tailored to fit the user's individual needs. Biomechanical M&S tools can also perform forward dynamics; in this way, a given time history of joint torques and actuator assistance can be used to predict time history of subject joint angles.

Classifications of Wearable Robots

The combination of key elements and context of application yield a number of different wearable robotic system classifications that represent the most salient features of systems developed to date. These classifications evolve as new technologies and applications enter the design space. In his comprehensive text, *Wearable Robotics: Biomechatronic Exoskeletons*, Pons [21] identifies three primary classifications of wearable robots as described below.

Empowering robotic exoskeletons. These were originally referred to as extenders [15] and defined as a class of robots that extend the strength of the human hand beyond its natural ability while under the control of the human wearer. A specific and singular aspect of an extender is that its exoskeleton structure maps to the human operator's anatomy. Where the objective is to extend the human operator's upper limb reach capability, master-slave robot configurations are typical (e.g., in teleoperation scenarios).

Orthotic robots. An orthotic is a mechanical structure designed and fitted to the body. Its purpose is to restore function that may have been lost or diminished by injury or disease.

Prosthetic robots. A prosthesis is an electromechanical device that substitutes for a body part such as a limb lost to amputation. Prosthetic robots take the form of wearable electromechanical limbs that function as closely as possible to the original native limb. This is achieved by intelligent use of robotic technologies, human-robot interactive technologies (sensing and control), and actuation.

Within these three classifications, there are many subordinate classifications, several of which involve design distinctions relevant to the content of this chapter:

Kinematic alignment. Some wearable robots are designed such that they are kinematically mapped to a human joint, which means that the axis of rotation of the human joint is aligned approximately to the axis of rotation of the robot. This is challenging because unlike the precision rotary bearings that typically make up the joints of the wearable robot, human joints do not have constant centers of rotation. Misalignment is a common issue that can cause undesirable migration (relative motion between the interface and the human) of the wearable robot from its intended placement with respect to the user. Correct kinematic alignment is important to avoid unwanted forces that can cause discomfort or injury as may occur with non-kinematically aligned (e.g., endpoint aligned) devices.

Load path. Wearable robots can be external load path or internal load path systems based on how force that is applied from the environment (e.g., by a weight) passes around (external to) or through (internal to) the user's own skeleton. External load path wearable robots pass load from the environment around the user to a ground; these systems are typically rigid in their construction. External load path systems are often utilized specifically to offload weight from the user's skeleton and joints. By contrast, internal load path systems aim to provide additional torque without offloading weight; these will instead use the human wearer's own skeleton as the load path and thus better reflect how the human musculoskeletal system works in its natural condition.

Figure 5.5 depicts the difference between these external and internal load path systems. The system on the left supports its own weight via a footplate that passes around the user's ankle to the ground. By contrast, the system on the right passes its weight to the human user via multiple interface attachment points.

Rigidity. Historically, wearable robots have been highly rigid systems designed as external skeletons analogous to the human skeleton. More recently, interest in soft wearable robots is driving research into the development of flexible actuators, flexible sensors, and soft structural topologies that are highly conformal to the human anatomy. This objective is driven by the desire to reduce the weight and bulk of the system itself, reduce the user's metabolic expenditure, and better assist users with neuromuscular deficiencies. Softer archetypes conform better to the human body and joints, are more portable, and ultimately are more biomimetic in their form and function (e.g., Fig. 5.6). The trend toward softer systems also affords designs that are less obtrusive and less visible, which is a desirable psychological advantage. However, significant challenges are associated with the control of soft systems. Control bandwidth (loosely defined as the speed at which a system adequately responds to a command) tends to be inversely proportional to physical compliance: interfaces between soft materials and flesh compress and stretch during motion, creating an undesired deadband (essentially a neutral zone of zero output for a nonzero input) in the control system. Additionally, if not properly addressed, migration of the interface with respect to the user yields imprecise joint angle information and Cartesian positions of more distal points on the limb. Software modeling of compliance and migration can help, but it is difficult to develop models that are accurate and repeatable across multiple users.

Portability and wearability. A wearable robot implies a close interaction between human and machine (robot), usually supported by attachment using straps, harness, or some other methods of interface. A robot can also be wearable if it is grounded to a structure such as a cart or overhead support structure or if it is car-

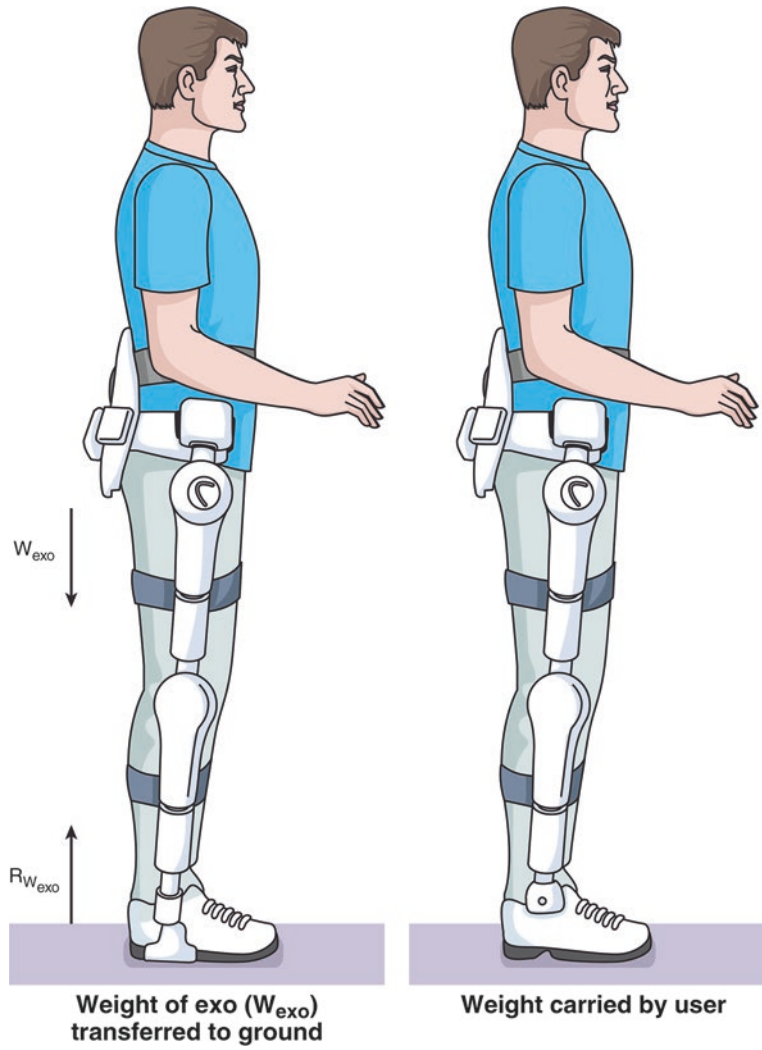

Fig. 5.5 External load path (*left*) and internal load path (*right*) wearable robotic systems. For the system on the left, the weight of the exoskeleton (W_{exo}) is passed to the ground (R_{Wexo}). For the system on the right, the weight of the device is carried by the user

ried by the user. A wearable robot is portable if it can be transported by the user or with the user under its own power. Wearable robot portability has advanced dramatically in recent years, with the objective to move wearable robots beyond laboratory and clinic settings.

Use Case: A Lower Extremity Exoskeleton for Mobility Assistance

The MinaV0 is a lower extremity robotic gait orthosis designed and built by researchers at the Institute for Human and Machine Cognition (IHMC) (Fig. 5.7). It is an example of a rigid, kinematically aligned, external load path exoskeleton. The physical human-robot interface is designed to support users with lower extremity weakness or paralysis.

The MinaV0 has four actuators to provide two actuated degrees of freedom (DOF) per leg, hip flexion/extension, and knee flexion/extension. MinaV0 does not provide any hip ab-/adduction or internal/external rotation of the leg. The torso section consists of a rigid back plate, which has a curvature, to match that of the human spine. MinaV0 is designed to accommodate a range of body sizes. By using nested aluminum tubing as

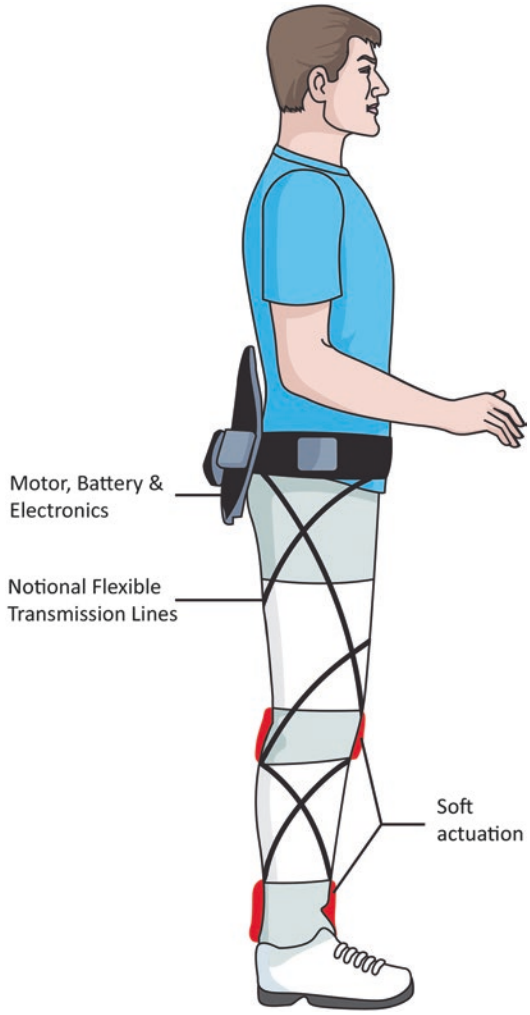

Fig. 5.6 Notional soft wearable robot for the lower limb

structural links, adjustments are made to fit the user. The device attaches to the user at the torso and at the thigh, shank, and foot. At the torso are two shoulder straps and a pelvis strap, which secure the user's torso to the rigid back plate. A tether provides MinaV0 with power for its computer and motors, as well as Ethernet communication. While untethered operation is the eventual goal, currently a fixed power source facilitates testing. Many of the advancements made with the MinaV0 were improved upon in the development of the NASA X1 exoskeleton, a collaborative effort between NASA and IHMC.

Use Case: NASA X1 as a Multipurpose Lower Extremity Exoskeleton

A use case of the continuum model for recovery (explained in more detail later in this chapter) is the X1 exoskeleton, designed with a range of applications in mind (Fig. 5.8). The X1 exoskeleton was developed in the Dexterous Robotics Lab (DRL) at the NASA Johnson Space Center in Houston, TX, in partnership with IHMC in Pensacola, FL. X1 is a technology spinoff from the Robonaut 2 (R2) Project, a humanoid robot currently operating aboard the International Space Station (ISS) [18]. Much of the X1 base architecture was leveraged from R2, including safety systems, basic actuator design, communication scheme, and embedded motor drive controls, all of which have been tested and vetted on the ground and aboard the ISS.

Although developed by NASA, the X1 exoskeleton was designed for applications here on Earth such as zero-assistance control, gait rehabilitation, and assisted walking. The system currently has four active DOF at the hips and the knees, with powered movement constrained to the sagittal plane. It also has six passive DOF for hip abduction and adduction, internal and external hip rotation, and dorsiflexion and plantarflexion. Any of these passive DOF may be left free to move or locked out to intentionally constrain movement. Future improvements currently in development include exchanging the passive ankle for a powered ankle, to allow for additional dynamometry evaluations and countermeasure exercises.

Worn around the legs with a set of cuffs, and around the torso with a backpack and hip belt, the tethered X1 weighs 57 lbs. It also has multiple adjustment points at the thighs, shins, and hips to accommodate a range of users spanning from the 5th to 95th percentile. Each active joint is driven with a series elastic rotary actuator and custom-designed embedded motor controller.

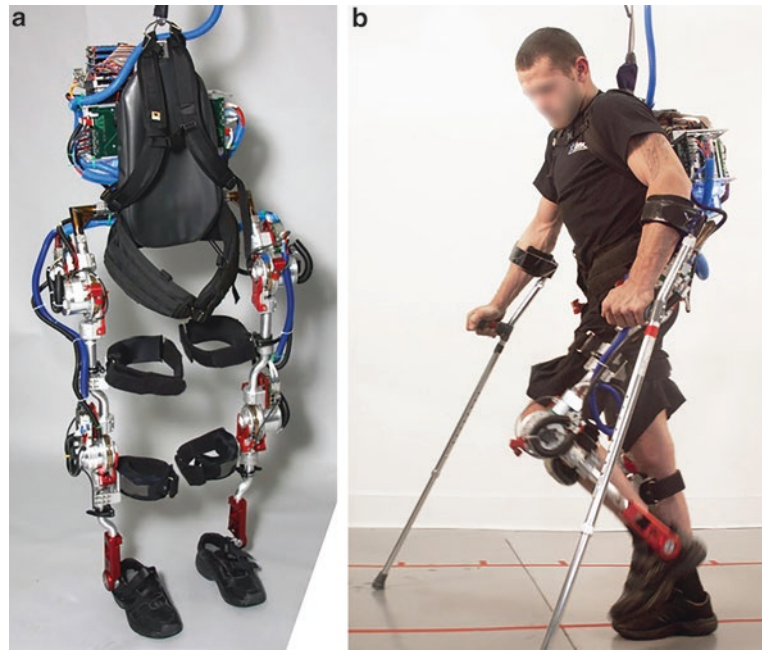

Fig. 5.7 (**a**, **b**) MinaV0 Exoskeleton for Mobility Assistance (Courtesy of Florida Institute for Human Machine Cognition)

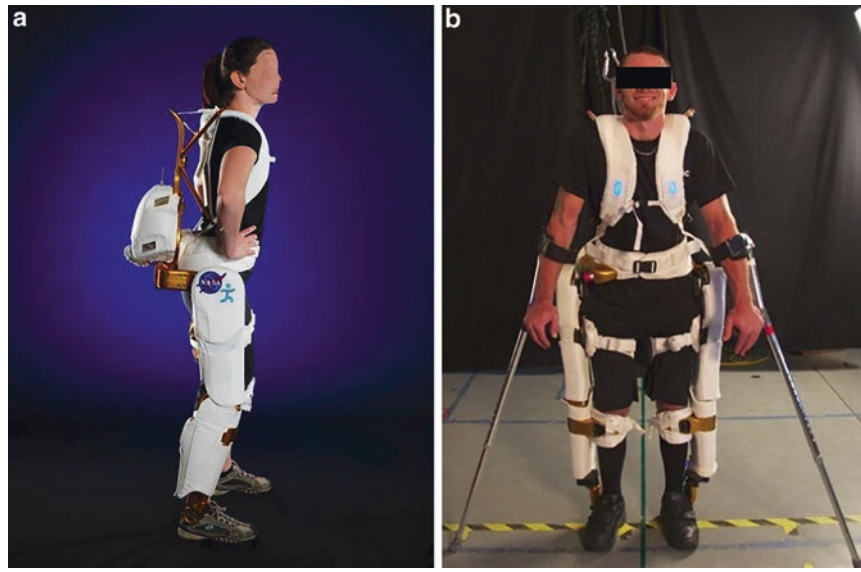

Fig. 5.8 (**a**, **b**) X1 Exoskeleton (Courtesy of NASA)

Series elastic actuators are an ideal choice for actuation because they offer high-fidelity impedance control. Each actuator can be controlled in a number of different states such as impedance, position, and torque control. Additional nested loops allow for safety and control limits including torque, velocity, and current. Other safety considerations include motion-stop controllers and integrated hard stops at each joint to prevent hyperextension or hyperflexion of the knees or hips. This combination of actuator and software design allows the X1 to safely achieve significant

torque loads at each joint as necessary for countermeasures and dynamometry.

Using custom controllers, the X1 can assist or resist a user's movements simply by altering parameters at the high-level interface. This interface allows the user to control position, torque (resistance), or velocity. Flexible control also allows countermeasure specialists to write custom-designed exercise routines.

Wearable Robotics: A Clinical Perspective

Wearable robots have recently become popular in healthcare as a way to augment therapies. As the technology becomes more available, utilizing wearable robotics in healthcare could prove to be a cost-effective and reliable strategy to enhance outcomes for patients. To date, there are not many clinical trials to investigate the effectiveness and efficacy of wearable robot-assisted training. Therefore, in this section, we will discuss the current clinical applications and challenges in wearable robot-assisted training from pilot studies and present a continuum of care that utilizes wearable robotics.

Clinical Role of Wearable Robotics: Past and Present

Over the last two decades, technology-assisted therapies have been integrated into more traditional, hands-on physical rehabilitation programs. Many rehabilitation facilities now offer a variety of devices, including robot-assisted therapies, for clinical and research use. Among these are functional orthoses triggered by electrical stimulation (NESS H200®, NESS L300®, NESS L300® Plus; Bioness, Inc.) or by computers (C-Brace®; Ottobock); robotic rehabilitation systems such as Armeo® (Hocoma) and the treadmill-based robotic gait trainer, Lokomat® (Hocoma); virtual reality systems, and neuroprostheses such as the Cyberglove (CyberGlove Systems, Inc.). These devices and systems are utilized not to replace therapist-driven programs but rather to augment therapy through assisted strengthening, motor relearning, and functional retraining. They offer many potential advantages, helping to meet the requirements of training and therapy through activities that are task specific, goal oriented, appropriately intense (in terms of both resistance and repetition), and novel. Typically, they are designed to deliver specific training paradigms at optional and varying degrees of difficulty. Because technology and robot-assisted therapy systems do not fatigue, they can provide repetitions in a consistent manner over longer durations than human therapists can support. Many such technologies incorporate haptic or visual feedback which, along with their inherent novelty, help to keep the user engaged throughout the training process.

More recently introduced are lower limb wearable exoskeletons, although their optimal role in the rehabilitation process has yet to be fully defined. It is not yet clear if wearable exoskeletons are best applied as mobility aids or if they can also serve as exercise devices for gait retraining, endurance building, and aerobic conditioning. In addition to augmenting rehabilitation, wearable robots can support assisted exercise in pre-rehabilitation and post-rehabilitation settings. Most wearable robots have control systems that can provide resistance, which can be applied in exercise regimens, to promote muscle strengthening, coordination, and improved cardiovascular and musculoskeletal fitness.

Currently, the most readily available wearable robotic devices are those that employ predefined gait trajectory control strategies such as ReWalk™ (ReWalk Robotics, Inc.), Ekso™ (EksoBionics), and Indego™ (Parker Hannifin Corp.). A predefined gait trajectory allows users with lower limb paralysis to walk without active

neuromuscular control. Findings from several feasibility studies [22, 10, 21] indicate that wearable robots of this type are safe to use as assistive devices in the clinical setting. In these studies, researchers have also observed that users benefit therapeutically after short-term use (over weeks or months). Among other benefits, users reported that they experienced less limb spasticity, better sleep quality, and reduced incidence of urinary tract infections. For users who mainly depend upon wheelchairs for daily personal transportation, such health benefits could significantly improve overall health and quality of life. As exoskeletons become more widely available for use in home and community settings, it is reasonable to expect that users will enjoy more significant, lasting, and even permanent improvement in physiological function, cognitive performance, and community integration.

Ongoing Challenges in Clinical Applications

The clinical application of wearable robotics is hampered by some unresolved issues and practical challenges. First, it is not yet clear what patient populations will benefit most directly. Current exoskeleton system designs have limited utility for persons with significant physical impairments, and inappropriate alignment between human anatomical joints and robotic actuators can cause discomfort and tissue damage. Most lower extremity wearable robotic devices require trunk control to stabilize the torso and hand dexterity to operate. Additional challenges include the size and weight of wearable robotic devices and the variable need for devices to support body weight. Last but not least, currently the practical matters of cost and availability unfortunately limit deployment of exoskeletons to a wide clinical arena.

Table 5.1 Ideal characteristics and capabilities of exoskeleton devices for clinical use

Safe: includes built-in redundancies, motion stops, and prevents against joint overextension
Adjustable: flexible fit for a broad patient population, including the elderly and severely neurologically impaired
Biomimetic: analogous to the human body
Affordable and cost-effective: within allowable treatment cost, provides treatment outcomes sufficient to justify cost
Portable: inherently travels with the wearer or easily moved by a single therapist
Durable: capable of supporting several sessions without significant downtime
Modular: allows for addition and removal of device elements over the course of treatment
Flexible: adaptable to changing medical or rehabilitative conditions
Interoperable: open system to allow interface with other clinical devices
Engaging: encourages shared control between the user and the device

To address these challenges, there are a number of ideal characteristics and capabilities (Table 5.1) that would improve the efficacy, utility, practicality, and availability of wearable robotic devices. While some of these (e.g., affordability) will tend to evolve as wearable robotics are more widely used, others present significant design and engineering hurdles.

Pilot Studies

Several pilot studies have been conducted at the Center for Wearable Exoskeletons (TIRR Memorial Hermann) to investigate the clinical application of wearable exoskeletons for various purposes and in various patient populations. Here, we provide an overview of studies performed using wearable exoskeletons for assisted walking and assisted gait training.

Exoskeleton-Assisted Walking

For patients with neurological disorders such as spinal cord injury (SCI), stroke, and multiple sclerosis (MS), the most challenging goal may be to stand and walk. To restore capability for locomotion in a short period of time, compensatory strategies are usually applied to compensate for lost abilities, e.g., through the use of braces or assistive devices. Based on this compensatory clinical approach, wearable exoskeletons are used as assistive devices to enable people with paralyzed or weak lower extremities to stand upright, walk, climb stairs, or even play sports.

In an ongoing pilot study at the Center for Wearable Exoskeletons, patients with paraplegia due to SCI ($N = 2$), hemiplegia due to stroke ($N = 2$), and lower limb weakness due to MS ($N = 3$) participated in a 3-week, 15-session training regimen involving wearable exoskeleton-assisted walking with the Ekso™ device (EksoBionics). The purpose of the study is to determine the prerequisites, such as injury severity or physical functionality, for a user to walk with an exoskeleton. In each session, the participant performs weight shifting while trying to maintain balance and overground walking in the exoskeleton, with the assistance of a trainer. Preliminary results suggest that after five or six sessions of training, most participants can achieve approximately 1,800–2,600 steps during a 1-h session with Ekso. Similar findings were reported in a study of persons with paraplegia and tetraplegia following SCI [12].

In another pilot study, the metabolic cost of walking with an exoskeleton was investigated (Fig. 5.9). Oxygen consumption (VO2 max) and lower limb muscle activation levels (as measured by EMG) during both exoskeleton-assisted walking and unassisted (no exoskeleton) walking were measured in four participants with MS who had some walking capability but who required an assistive device to ambulate long distances (Kurtzke Expanded Disability Status Scale/EDSS 6–7.5). With similar walking distance in 6 min (i.e., fixed walking speed), exoskeleton-assisted walking was associated with a 14.0–26.4% reduction in net maximal oxygen consumption (VO2 max) and a 16.7–22.5% reduction in muscle activation level when compared to the

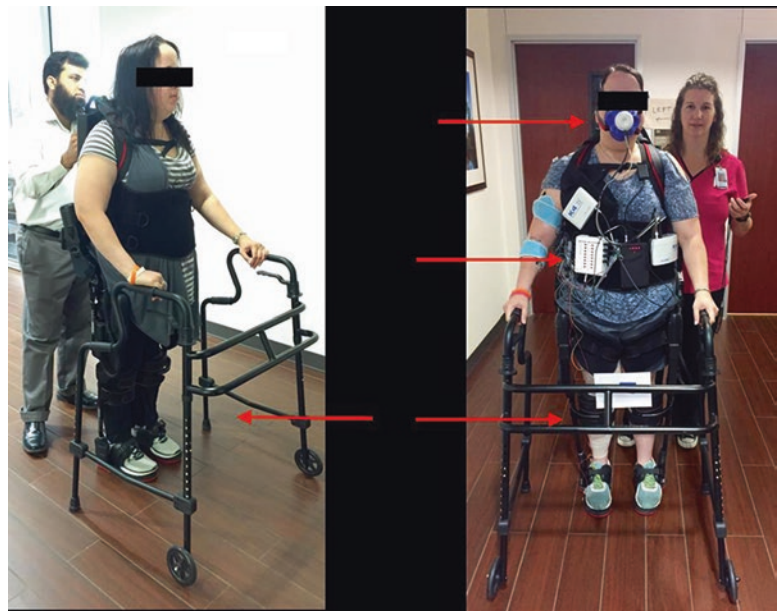

Fig. 5.9 Experimental setup for metabolic and electromyography data collection during exoskeleton-assisted walking (Courtesy of TIRR)

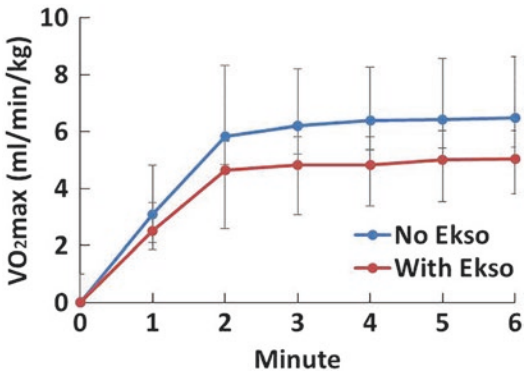

Fig. 5.10 VO2 max during 6-min walk with and without exoskeleton assistance

unassisted case (see Fig. 5.10) [2, 6]. These data suggest that patients who have some level of preserved walking function can also walk with exoskeleton assistance and with reduced energy costs, which may in turn prevent or delay fatigue and enhance walking efficiency.

Unlike predefined gait trajectory, exoskeletons that are designed for mobility, self-standing wearable systems such as the REX® (Rex Bionics) provide a different level and format of assistance for clinical rehabilitation. This device is operated by an external controller (joystick) that requires minimal hand function (see Fig. 5.11); the maximum walking speed of the device is intentionally set to a slow value by the manufacturer. These features allow the REX to serve individuals who have more profound injuries such as high-level spinal cord and severe brain injuries. Clinical trials are currently underway to investigate the use of REX for rehabilitation of these types of impairments (ClinicalTrials.gov identifier NCT02417532). Self-supporting exoskeletons such as REX also raise the possibility of integrating brain machine interfaces that may allow users to perform specific functional activities and therapeutic exercises without the use of manual (joystick) control.

Exoskeleton-Assisted Gait Training

Another common clinical application with wearable exoskeletons is assisted gait training. The emphasis of this approach is to induce plasticity in the neuromuscular and musculoskeletal systems

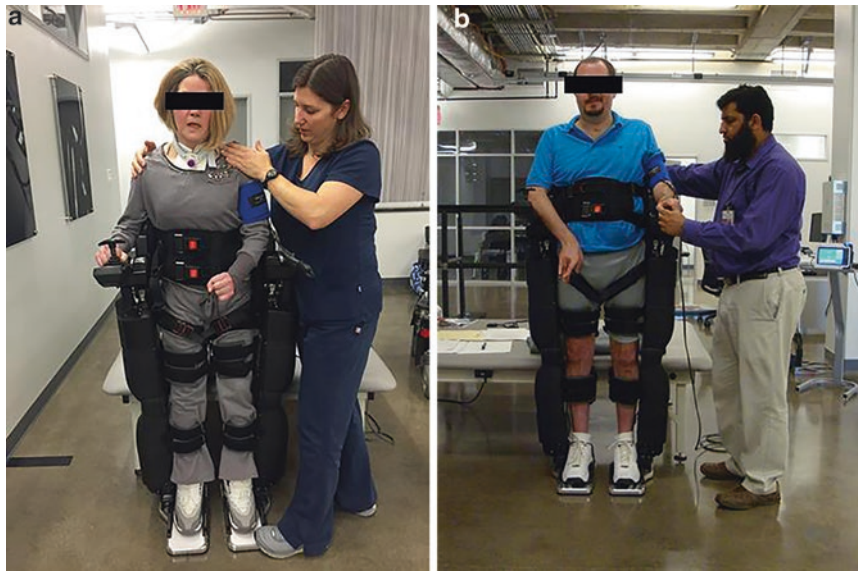

Fig. 5.11 (**a**, **b**) Patients with SCI (Level C1-4) and brain injury (Fugl-Meyer Assessment Lower Extremity = 22) are able to stand in REX with minimal to moderate assistance from a trainer. (Courtesy of TIRR)

by repetitive task performance (e.g., walking), following a task specificity principle of training to facilitate functional recovery. In this framework, a wearable exoskeleton with predefined gait trajectory can be an effective and efficient training tool, supporting hundreds or thousands of tightly defined, consistent repetitions. This enables task-specific training based on mass practice principles that may serve to induce neuroplastic changes in spinal and cortical centers that are critical to walking function [4, 8, 13, 19].

Few studies have yet investigated the effectiveness of exoskeletons to assist in gait training [3, 10, 14]. However, the potential benefit is clear. To better determine the efficacy of exoskeleton-assisted gait training, randomized and double-blinded trials with larger patient cohorts are needed.

In the Center for Wearable Exoskeletons, the authors conducted a pilot randomized study to investigate the feasibility of exoskeleton-assisted gait training in seven patients with SCI (American Spinal Injury Association Impairment Scale (AIS)/AIS C or D, above T12 level of injury). Participants were randomly assigned to receive either 3 weeks of exoskeleton (Ekso)-assisted gait training (Fig. 5.12) or 3 weeks of conventional physical therapy (PT); in each case, participants attended five 1-h sessions per week. During each session, participants in the exoskeleton group donned the Ekso exoskeleton and participated in individualized treatment with Ekso in sit-to-stand, static, and dynamic standing balance, weight shifting, walking, turning, and stand-to-sit exercises. Participants in the conventional PT group performed exercises designed to facilitate gait recovery, including stretching, strengthening, balance training, standing, and gait training. As expected, participants in the exoskeleton treatment group spent a higher percentage of session time (minutes) in an upright position and walking (67.7% ± 0.1% of session time for the exoskeleton group vs. 38.6% ± 0.1% of session time for the PT group). After training, the results showed that the stride length (cm) (i.e., left step length plus right step length) increased significantly from pre- to post-training in the exoskeleton group as compared to a less significant increase from pre- to post-training in the PT group (left step length (cm) increase: exoskeleton = 10.2% ± 1.2%, PT = 2.0% ± 4.1%; right step length (cm) increase: exoskeleton = 8.5% ± 1.3%, PT = 3.9% ± 4.9%). Relative to the PT group, the exoskeleton group also showed more improvement in their walking speed (m/s) (exoskeleton: 26.4% ± 19.6%, PT: 6.18% ± 15.7%) and walking distance (m) in 6 min (exoskeleton: 43.4% ± 32%, PT: 4.7% ± 4.0%). These results suggested that exoskeleton-assisted gait training is safe and can be used to improve gait function, but future studies should include larger sample sizes and higher training intensity.

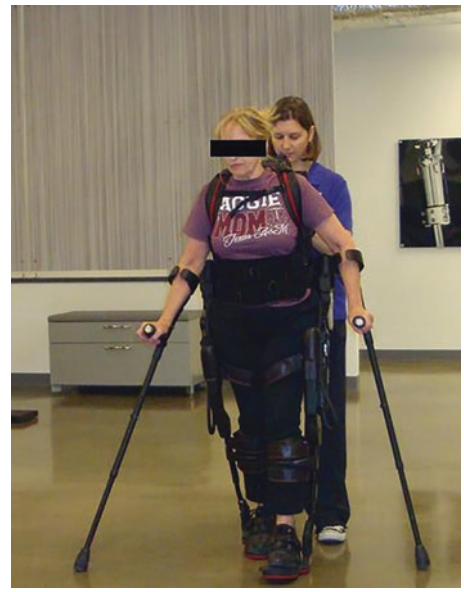

Fig. 5.12 A patient with SCI receiving exoskeleton-assisted gait training (Courtesy of TIRR)

A separate study by Bortole and colleagues [5] investigated the feasibility of gait training with the H2 exoskeleton in patients with stroke (Fig. 5.13). Stroke patients (N = 3) received 12

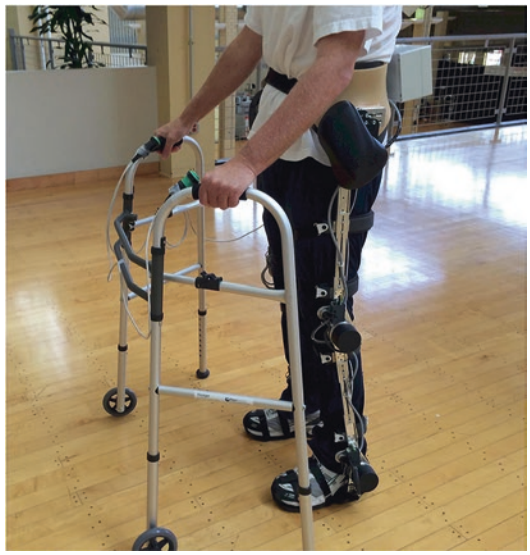

Fig. 5.13 Stroke patient using H2 exoskeleton at the beginning of one training session (Courtesy of Journal of Neuroengineering and Rehabilitation)

sessions of exoskeleton-assisted gait training over a period of approximately 4 weeks; two patients showed improvement in walking distance in a 6-min walk test (5.8% and 76.9%), while the third patient showed no improvement. These results indicated that the H2 exoskeleton could potentially be used as a training device for poststroke gait rehabilitation.

Users' Feedback about Exoskeletons

To explore and evaluate user experience, feedback from the patients ($N = 7$, two persons with stroke, two with SCI, and three with MS) was collected regarding their experience after training with wearable exoskeletons (Ekso and REX) in ongoing trials at the Center for Wearable Exoskeletons. The purpose was to explore and investigate user feedback for each individual device, not to generate comparison between devices; therefore, ID numbers were used to represent each exoskeleton. In the first question, subjects were asked how likely it was they would use a wearable exoskeleton if it were available (Table 5.2). Of the seven respondents, four indicated that they would be likely or very likely to use one of the exoskeletons at home or in the community, while three subjects said they would be unlikely or very unlikely to use such a device.

Table 5.2 Users' feedback: if available, how likely would you be to use a WRE at home and in the community?

	WRE #1	WRE #2
At home		
Very likely	3	3
Likely	1	–
Somewhat likely	2	–
Unlikely	–	2
Very unlikely	1	2
In the community		
Very likely	3	4
Likely	1	–
Somewhat likely	–	1
Unlikely	1	–
Very unlikely	2	2

To further understand the users' responses, we asked them what they liked and disliked about each wearable exoskeleton (Table 5.3). In general, subjects liked the potential benefits such as helping them with balance, posture, muscle strength, physical function, and gait but did not like the design aspects of the exoskeletons (i.e., mechanical noise, restriction in fitting, rigidity, weight) and limited functionality and feasibility (i.e., walking speed, assistance needed to don and doff).

The feedback reported here was very subjective, and our sample size was small. However, it pointed to several challenges that should and can be addressed with respect to device design and ease of use. There are more than 50 institutes and companies currently engaged in developing wearable exoskeletons of various designs, with a variety of control mechanisms and interfaces. Individual preferences may pose new challenges

Table 5.3 Users' feedback to questions

	WRE #1	WRE #2
What did you like about the wearable exoskeletons?	Manipulation of muscles and joints	It allowed me to use my leg muscles while giving a boost when needed
	Improved my walking	Very light and portable
	Strengthens my core for better balance and strengthens my leg muscles	Improved walking, strength, and endurance
	It helped with balance and muscle strength	Helps with balance
	Like how it put you in good position	Help with ease of walking
	Help with posture	It lifted up my foot while walking, so it cleared the ground
What did you dislike about the wearable exoskeletons?	Noise, overheating, bulk	Hard for one person to manage regarding settings, not stable without assistance
	Device is narrow	Bulky
	Too slow	Nothing; would like to go faster
	Ability to stand and walk	Too constricting
	Size and speed	A little heavy
	More speed would be exciting	I could not balance myself in it

for clinicians tasked to select the most appropriate device for individual patient requirements, characteristics, capabilities, objectives, symptoms, and limitations, including operation costs. To achieve optimal efficacy, closer collaboration between users (patients and clinicians) and engineers will be necessary, with attention to user feedback (i.e., patient-centered approach).

Potential Continuum of Devices for Recovery

The studies and devices described above illustrate how the integration of wearable robotics to aid the treatment of neuromuscular maladies can be envisioned along a continuum of recovery (e.g., gait training) and reintegration (assisted walking in daily life). Along this continuum, target opportunities for integration are best defined by user capabilities and objectives as milestones for the introduction or removal of wearable robotics. Although studies with larger sample sizes are needed to better demonstrate safety and efficacy, pilot studies to date show real promise that wearable robotic devices can be used to augment rehabilitation and support independence.

Additional Application Domains

While medical applications have long inspired development of wearable robotics, applications for military, industrial, and personal use have also gained attention and funding. Interest in military and performance enhancement applications has increased steadily through the Defense Advanced Research Projects Agency (DARPA). Programs include the Exoskeletons for Human Performance Augmentation (EHPA), which most notably produced the Berkley lower extremity exoskeleton (BLEEX) [23], and the more recent Warrior Web program, which focused on minimizing the weight and size of wearable robots by emphasizing soft, biomimetic wearable robot designs and reduction in energy expenditure. The Warrior Web program (www.darpa.mil/program/warrior-web) [9] also emphasized compatibility

of designs with current warfighter uniforms, so as to further reduce unnecessary size and weight. The more recent Special Operations Command (SOCOM) Tactical Assault Light Operator Suit (TALOS) program further demonstrates growing military interest in wearable robotics technology. The goal of TALOS is to develop an armored suit to protect SOCOM operators in the field.

Interest in wearable robotics is not limited to the military and medical domains. Powered or unpowered robotic augmentation of human strength and/or endurance may also help to reduce fatigue and injury in industries that rely on extended manual labor and/or load carriage by human workers. Systems that increase the amount of weight a worker can lift have potential value for labor performed in numerous settings such as factories, shipyards, disaster sites, and hospitals.

Conclusion

There is undeniable momentum in the field of wearable robotics design and development, supported by emerging synergy between engineering and clinical domains. Although the potential clinical benefits of wearable robotics are not yet fully established, they are easily envisioned and supported by studies to date. There is an obvious surge in investment, commitment, testing, and development to advance the state of the science and transition its rewards to applications in medical, military, industrial, and exploratory endeavors. The foreseeable outcome is convergence toward solutions that are both beneficial and technically achievable. This will be guided by leveraging HRI knowledge gained through development of advanced prosthetics and orthotics and in the advancement of technologies such as computing power, sensing capabilities, batteries, and motors. The wearable robotics revolution is now poised to lead the way to the future of lower extremity rehabilitation and recovery.

Traditional prosthetics and orthotics have helped patients with rehabilitation and independent living for many decades and will certainly continue to do so well into the future. Wearable robotics promise to further facilitate the goals of daily living. Already, doctors, physical therapists, and clinicians have demonstrated the unique ability of wearable robotic solutions to address specific challenges along the continuum of patient capability and recovery. Wearable robotic technologies described in this chapter can be applied to assist patients in need of acute post-injury support, augmented rehabilitation, or modified independence solutions. At their best, wearable robotics can be configured to meet specific patient capability needs and limitations, arming medical professionals with options and flexibility to address individual needs.

Progress in the field of wearable robotics has coincided naturally with the evolution toward closer interactions between humans and robots, which stems from advances in key enabling technologies (actuation, processing, power, and sensing). Challenges remain. Technical obstacles are magnified by additional hurdles such as cost, insurance coverage, and sociocultural acceptance of robotic technologies. Roboticists, medical professionals, administrators, and engineers are certainly up to the task. Incentive for success lies in the vision of renewed independence for those burdened by injury, disorder, or disease – a vision that will be realized through wearable robotics.

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Orthotic Device Research

6

Elisa S. Arch and Steven J. Stanhope

Abbreviations

AFOs	Ankle-foot orthoses
BRUCE	Biarticular Reciprocating Universal Compliance Estimator
CAD	Computer-aided design
CAM	Computer-aided manufacturing
IDEO	Intrepid Dynamic Exoskeletal Orthosis
FOs	Foot orthoses
KAFOS	Knee-ankle-foot orthoses
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom

E.S. Arch, PhD (✉)
Department of Kinesiology & Apply Physiology,
Department of Biomedical Engineering,
Biomechanics and Movement Science
Interdisciplinary Program, University of Delaware,
Newark, DE, USA
e-mail: schranke@udel.edu

S.J. Stanhope, PhD
Department of Kinesiology and Applied Physiology,
Department of Mechanical Engineering,
Department of Biomedical Engineering,
Biomechanics and Movement Science
Interdisciplinary Program, University of Delaware,
Newark, DE, USA
e-mail: stanhope@udel.edu

Introduction

Orthoses are assistive devices that support joints through alignment, stabilization, or assisting weakened musculature. While prosthetic devices serve to replace a lost limb, the goal of an extremity orthosis is to restore the lost function of an impaired limb [1]. For the lower extremity, the three primary types of orthoses are foot orthoses (FOs), ankle-foot orthoses (AFOs), and knee-ankle-foot orthoses (KAFOs). There are orthoses that also span the hip and pelvis. Orthoses can be further categorized based on a variety of features including their power source (passive, semi-active, or active) and their design (solid or hinged) [2, 3].

In civilian and military populations, there are high rates of extremity and orthopedic injuries that result in limb impairments, which are often treated with orthotic interventions. According to the 2005 Americans with Disabilities report, approximately 27 million people over the age of 15 had a walking-related disability [4]. In the military population, 54% of combat wounds sustained in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) from 2001 to 2005 were extremity injuries [5]. These injuries and associated disabilities limit function, often impeding the ability to work, perform activ-

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ities of daily living, and return to active duty [6]. Orthopedic injuries are the leading cause of soldiers being deemed unfit for duty. Conditions of the foot, ankle, and lower extremity are three of the five most common orthopedic conditions leading to soldier disability in both peacetime and war [6]. Extremity injuries sustained during OIF and OEF accounted for 64% of service members determined to be unfit for duty [7]. The cost associated with orthotic treatment is substantial, and demand is outpacing supply. Disability costs associated with military extremity injuries are projected to be $170 million for a studied cohort of 1,566 injured subjects [7]. In 2010 alone, Medicare expenditures for prosthetic- and orthotic-related charges exceeded $580M [8]. By 2020, the Department of Education estimated that prosthetists and orthotists will be able to serve just 61% of the patients who need personalized rehabilitation devices [9].

Evidence suggests that many orthoses do not provide optimal benefit and value to those who wear them [10]. Characteristics related to fit (orthosis size or shape) and function (mechanical aspects) both influence comfort and performance. Fit and function must be customized to the individual patient to achieve optimal performance outcomes [1, 3]. Routinely, practitioners who prescribe orthoses apply subjective and sometimes contradictory approaches that have little evidence of efficacy [1, 11–13]. As a result, many patients experience suboptimal functional outcomes. Although orthoses appear to be relatively simple devices, the process of designing and objectively prescribing the fit and functional characteristics of an orthosis is remarkably complex. This complexity is reflected in the International Organization of Standardization (ISO) standards that have been developed to define orthotic terminology. These standards define terms relating to patient description, orthosis functional requirements, orthosis design, orthosis mechanical properties, and manufacturing (Fig. 6.1) [3]. They also indicate the importance of engaging an array of clinical, biomechanical, and engineering concepts in order to design and prescribe orthoses with ideal fit and function to promote optimal performance.

This chapter identifies contemporary methods, existing gaps, and promising approaches that may provide enhanced benefit and value to the orthotic user. Improved fabrication of orthoses would help to reduce costs associated with health care and disability claims. We consider the state of traditional patient care practices as well as cutting-edge research, technologies, and approaches primarily associated with ankle-foot orthoses. These advances have the potential for positive impact on patient outcomes and cost of care and, ultimately, the potential to transform the orthotic field.

Traditional Standards of Practice

Standards of practice for prescribing orthoses focus on three main categories: fit, function, and fabrication. These factors are considered when prescribing either a prefabricated or a customized orthosis. Prefabricated or off-the-shelf orthoses typically are available in a range of standard sizes and often include a footplate that is designed to be trimmed down to the individual user's foot size [14–16]. Sometimes there is also the option to select functional characteristics such as the general strut or footplate stiffness, with options such as flexible, normal, or stiff [16].

Alternatively, the orthosis can be custom-made for the user. To make a customized orthosis, the orthotist traditionally begins by manually aligning the patient's joint(s) based on knowledge of the relevant anatomy and then makes a cast of the patient's limb in its corrected alignment [17]. This negative mold helps characterize the shape of the limb and serves as a guideline for fit customization of the orthosis. Plaster is poured into the negative mold to create a positive mold, and the orthotist forms plastic around the positive mold to

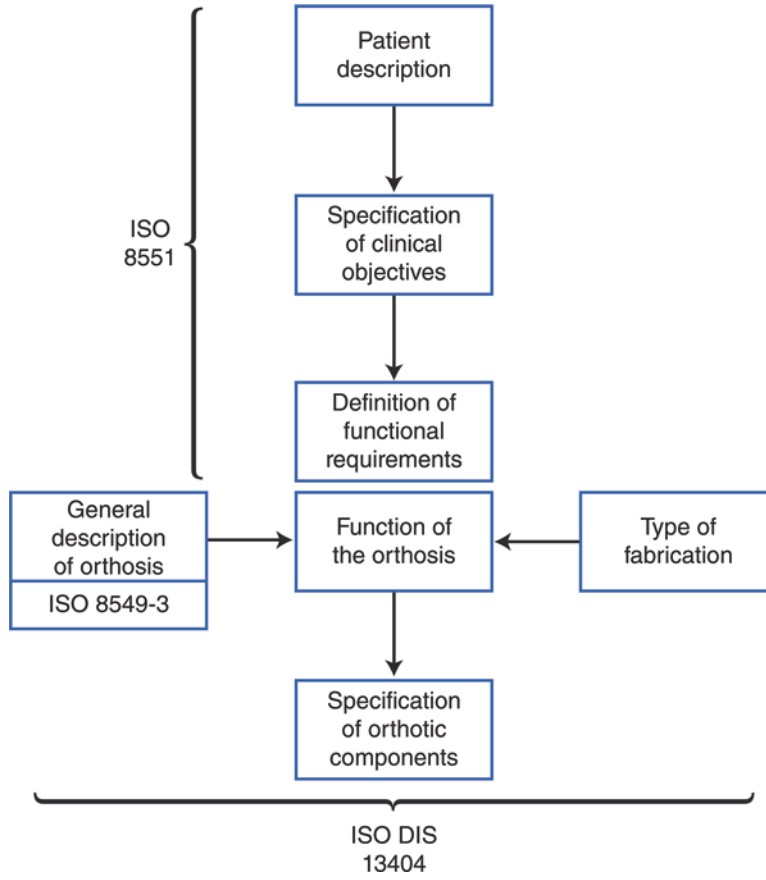

Fig. 6.1 Established ISO standards for orthotic terminology. These standards, which define orthotic-related terms, range from patient assessment to orthosis characteristics to fabrication methods. (Figure originally published in Condie [3])

craft the orthosis [17]. The orthotist then subjectively manipulates trimlines (material thickness) and shape to adjust the orthosis' fit and function.

To customize orthosis function, the traditional prescription process typically begins with a patient assessment. This involves a combination of a physical evaluation, including manually tested strength and range-of-motion measurements, and a visual gait analysis in which the clinician watches the patient walk in real-time or by video recording [18]. Based on the findings of the assessment, the orthotist and physician prescribe the orthosis design and features appropriate to the patient [3]. Although effective treatment with orthoses requires an understanding of normal gait biomechanics, assessment of the patient's biomechanical and functional abilities, and appropriate mechanical function [18], in a traditional clinical setting, these factors are typically considered qualitatively. Orthotists rely on their own judgment developed over years of professional experience and on qualitative descriptions provided by the orthotic manufacturer to represent how different orthosis designs are thought to affect gait biomechanics [19–21]. The functional characteristics of orthoses are rarely, if ever, quantified in a clinical setting. Thus it is difficult to objectively relate orthotic functional design characteristics to patient functional outcomes [1, 11–13].

Even when modern technologies are applied as part of the process, the current clinical standard of practice for fabricating custom orthoses remains highly subjective. As an alternative to the traditional method of limb shape characterization via casting and positive molding, some practitioners capture the size and shape of a patient's limb using

digital scanning techniques [22]. By this method, the positive limb mold is created with the help of a computer-aided design (CAD) program and then modified by digitally extruding or carving the 3D scan image as deemed necessary by the orthotist or technician. However, after the initial digital design phase, the plastic orthosis is still formed manually over physical molds, which have been carved via computer-aided manufacturing (CAM) systems based on the digital positive mold [22].

While some practitioners have in-house orthotic fabricating capabilities for traditional and/or CAD-/CAM-based approaches, others have begun to outsource manufacturing to central fabricators. It is often cost-prohibitive to establish and maintain in-house fabrication systems; rapid treatment can be achieved by overnight shipping [22]. Despite these benefits, it was recently estimated that only 24% of prosthetists and orthotists use central fabricators [23]. The hesitancy to outsource fabrication may be due to the subjective nature of the manufacturing process itself, which can lead to wide variations in product quality [23]. However fabrication is approached, the process remains heavily qualitative and subjective, with the orthotist relying on experience and intuition to prescribe and fabricate the orthosis rather than measuring and quantitatively fine-tuning orthosis characteristics [3].

Orthosis Prescription Research

The prescription of customized orthoses can be divided into features that pertain to orthosis fit and features that pertain to orthosis function. In order to readily customize orthosis characteristics, objective prescription guidelines that relate patient assessment to orthosis fit and function must be established. Research is underway to develop this understanding and to establish methods for guideline implementation.

Characteristics of Fit

In order to customize the fit of an orthosis, the detailed shape of the individual's limb must be recorded and replicated. Traditionally, this is done by the casting process previously described. Upon completion, customized fit is achieved by manually forming plastic around the limb cast [17]. While this approach is effective, it is also time-consuming, messy, and produces substantial material waste [17]. Furthermore, the subjective and manual nature of the process can introduce unwanted variability in fit and effectiveness [24].

As described briefly above, researchers are now working to develop 3D scanning technologies to capture a digital surface image of the limb [25–27]. The digitally captured surface image is then manually refined in a virtual environment, typically using smoothing and extruding functions. These modifications smooth the image to eliminate any gaps or inconsistencies from the scanning process and allow the practitioner to stretch and extrude specific areas of the image to relieve pressure or make room for padding introduced by the orthosis. These 3D scanning technologies have been implemented in some clinical service models to incrementally advance the field through central manufacture of physical limb models without the use of plaster [22].

In current research paradigms, the scanned surface model is used as the basis for creating a 3D CAD model of the orthosis [26, 28–30], which can then be fabricated by a variety of methods to be considered later in this chapter. In combination with advanced manufacturing approaches, the 3D scanning approach reduces the time needed for customization of the orthosis and eliminates the waste associated with traditional casting and manual fabrication processes [25]. Despite these benefits, 3D scanning techniques do not eliminate subjectivity or resulting variability [25, 27].

Some novel, objective approaches to the fit customization process have been proposed. As a concept to quantitatively fit-customize devices, Smith and Burgess described a "by the numbers approach" to the fitting of prosthetic sockets; this technique employs a standardized set of measurements (of the residual limb) to specify the size and shape of a prosthetic socket [22]. To our knowledge, this is the first introduction to the published literature of a quantitative method to customize the fit of a rehabilitation device.

We have proposed a novel approach to customizing the fit of AFOs. Rather than capturing the shape of a patient's limb, we propose a biomechanically linked "shape conformance" process by which a fully parameterized AFO CAD model automatically conforms to the size and general shape of the limb [31]. The process employs discrete 3D measurements of a minimal set ($n = 44$) of biomechanically and anatomically relevant limb surface landmark locations. The discrete 3D measures are expected as input parameters in the fully parameterized CAD model, which automatically adapts its size and shape to conform to the patient's limb when the values of the discrete 3D measures are updated [31, 32]. This unique process automatically conforms an AFO model to the patient's limb, obviating the need to capture and reproduce limb size and shape and simultaneously eliminating the need for manual or subjective manipulation of the CAD model. By linking discrete landmarks directly to the CAD model via parameterization, this approach provides a quantifiable and repeatable method by which parameters of the orthosis CAD model are adjusted to digitally customize the virtual orthosis prior to function customization and fabrication. By linking the CAD model to joint centers and biomechanically based limb coordinate systems, this process also supports parameterized adjustments to important additional fit characteristics. For example, ankle joint alignment and AFO-surfaces-to-skin offset distances can be adjusted to accommodate various padding thicknesses [32].

Characteristics of Function

It is widely believed that in order to help patients achieve their highest functional potential, the functional characteristics of orthoses should be customized to meet each individual's unique needs. However, there are no objective prescription guidelines available yet to support this goal. There are several obstacles to the development of such guidelines. First, the traditional manual approach to orthosis fabrication introduces substantial variability in function [33]. Because the functional characteristics of "crafted" braces are rarely quantified, there is a lack of evidence to support efficacy [1, 11–13]. Second, the majority of clinical studies do not report outcomes of patient assessments (e.g., muscle weakness) to quantify a patient's capability or fail to report orthosis design information [34]. Deriving the relationship between patient assessment (capability), activity level (task demand), and orthosis function (level of device assistance) involves complex biomechanics and gait analysis [1, 18, 20]. Relevant factors involve the influence of the orthosis on the joint(s) it spans as well as interactions between limb segments and the foot's interaction with the ground during activities of daily living [3, 35]. Lacking quantitative detail and evidence of efficacy, it is difficult to link patient capability and activity level to orthosis design and function, which in turn constrains development of an objective model for orthosis prescription. Years have been spent developing the technology necessary for advanced orthotic design, fit, and function, but the need persists for systematic research to quantify device and patient characteristics as well as their interaction during functional activity.

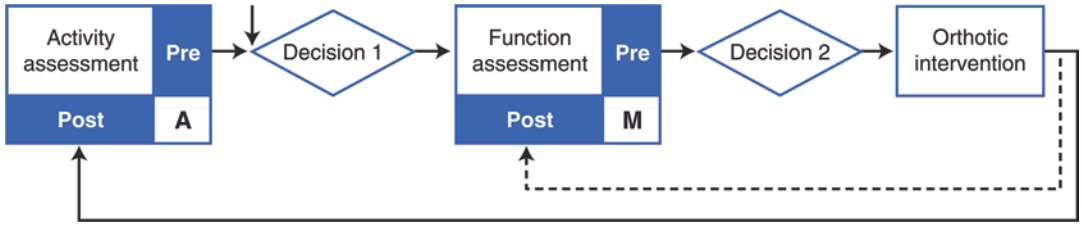

Fig. 6.2 A proposed conceptual prescription model for ankle-foot orthoses. This prescription model highlights two important factors in customizing and prescribing ankle-foot orthoses. (Figure originally published in Harlaar et al. [1])

Harlaar and colleagues proposed that objective, evidence-based prescription guidelines should be based on (a) assessment of a patient's activity level and gait function and (b) specification of the mechanical characteristics of the orthosis [1]. Prescription guidelines must apply these factors to match the orthosis specifically to the patient's individual needs [1] (Fig. 6.2). Additionally, Brehm and colleagues proposed quantitative performance measures of patient activity to evaluate the efficacy of orthoses [11]. To develop evidence-based prescription guidelines in combination with these measurements, they proposed a core set of outcome parameters, which include measures of joint, bone, and muscle [11].

Bending stiffness, or the resistance to bending of a passive-dynamic orthosis, is one of the primary functional characteristics that many research and practitioners believe should be customized for individuals to achieve optimal function [1, 10, 36, 37]. To adjust orthosis stiffness, orthotists usually modify material thickness or trimlines. Numerous approaches have been proposed to measure orthosis bending resistance [38], but these methods are seldom employed in a clinical setting. Thus, no objective criteria exist for selecting or prescribing orthosis stiffness.

Researchers are using experimental and computational techniques in the effort to develop prescription guidelines for orthosis stiffness, primarily for AFOs. AFOs can provide dorsiflexor assistance by providing plantar flexion resistance or plantar flexor assistance by providing dorsiflexion resistance. AFOs that assist the dorsiflexors are commonly prescribed for individuals with foot drop. While it is fairly straightforward to create an AFO that can hold the ankle in a neutral position during swing, it is important not to make the orthosis so stiff that it restricts ankle motion during stance [10]. Kobayashi and colleagues employed an experimental AFO with quantifiable and adjustable stiffness to investigate the influence of AFO stiffness on gait [39]. Their findings demonstrate that too much plantar flexion resistance can induce undesired knee flexion in early stance, thereby emphasizing the need to customize AFO stiffness to provide the proper amount of assistance required [40]. However, comprehensive patient assessment measures were not reported, thus limiting the ability to relate AFO stiffness to patient functional outcome. Although it seems clear that stiffness should be related to the patient's individual strength and functional ability, specific guidelines have yet to be determined.

For individuals with weakened plantar flexors, AFOs should provide dorsiflexion resistance to supplement weakened ankle plantar flexion activity to control shank progression during the stance phase of gait [41]. Restoring ankle moments to normal levels may be critical to restoring functional gait. This was demonstrated in a controlled perturbation study which showed that healthy individuals maintained invariant ankle moments during gait when an ankle exoskeleton provided supplemental plantar flexion torque [42], and similar findings have been documented in other studies [43]. It has been shown that in patients with plantar flexor weakness, AFOs

can provide supplemental plantar flexion moments [44–46] as well as additional benefits including tibial advancement control, supplemental ankle power, and longer strides. However, only one of those studies, which was a pilot study, reported AFO bending stiffness [46]. The magnitude of the AFO stiffness is important, as is the timing energy returned by the AFO [47] and the AFO's work about the ankle [48].

The studies referenced above demonstrate the benefits of resistive plantar flexion and dorsiflexion AFO stiffness and suggest important parameters that can be targeted to improve gait. Still missing, however, is a method by which to determine optimal device stiffness in relationship to patient weakness, functional ability, and outcomes. Recent efforts to quantifiably customize the stiffness of AFOs have used finite element analysis to establish the bending stiffness of virtual orthoses [49, 50]. In these studies, finite element analysis of orthosis computer models was used to predict strains under a given load to estimate stiffness. Orthosis shape characteristics could then be adjusted to tune the bending stiffness of the AFO. Thus, finite element analysis enables the stiffness of an orthosis to be predicted and adjusted (tuned) prior to manufacturing.

Although not yet used in clinical practice, many researchers have developed other techniques to experimentally quantify the stiffness of already manufactured AFOs [38]. Notably, one group has developed a novel, clinically applicable device to test the stiffness and neutral angle of AFOs [51]. The Biarticular Reciprocating Universal Compliance Estimator (BRUCE) measures stiffness of an AFO and/or AFO-shoe combination about the ankle and metatarsal joints across a functional sagittal plane ankle range of motion. It accommodates a wide range of AFO sizes and shapes because it measures angles and moments in the same manner as a traditional gait analysis and applies boundary conditions that mimic conditions during AFO use. BRUCE can also be operated in a clinical setting (Fig. 6.3). Other techniques have been tested to measure AFO stiffness, but many do not apply appropriate boundary conditions. This is potentially problematic because AFOs are very sensitive to loading conditions [52].

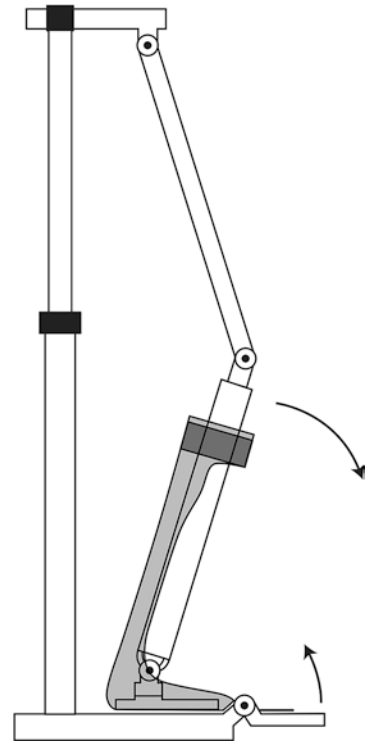

Fig. 6.3 Design of an ankle-foot orthosis stiffness testing device. The novel Biarticular Reciprocating Universal Compliance Estimator (BRUCE) design provides an excellent example of a clinically viable device that provides valuable quantifications of orthosis bending stiffness. (Figure originally published in Bregman et al. [51])

In addition to stiffness, other important characteristics have been identified as necessary for customized orthoses. For example, footplate design and orthosis joint alignment are two components that can be customized to improve gait function by facilitating foot-to-floor motion and controlling kinematics of the entire lower extremity. A footplate creates a lever arm for the rest of the orthosis to rotate, so it is important for at least a portion of the footplate to be rigid [1]. Additionally, it has been noted that footplate length should be

prescribed either to limit or to preserve joint motion, depending on the patient's impairment profile, with the overall goal to facilitate functional gait and stability [12]. As an addition or alternative to customizing footplate length, rocker bottom shoes or rockers built into the footplate may reduce plantar pressures and pain [53]. Finally, footplate design can influence the dynamics of the entire lower extremity. For example, a case study with a patient with hemiplegia demonstrated that tuning the AFO in combination with footwear improved knee kinematics [54].

In conjunction with footplate design, orthosis joint alignment should be customized by considering the alignment of all lower-extremity joints. For example, in a rigid AFO, the unloaded AFO ankle joint angle influences the position of the tibia and therefore of knee and hip net joint moments. All of these parameters should be taken into account when prescribing the AFO ankle joint alignment [1]. Limb segment kinematics must also be considered [35]. Malas noted that the prescription and design of AFOs must consider the shank angle to the floor, which is influenced by AFO design and by the interaction between the AFO and footwear [12]. It has been suggested that the AFO shank-to-floor angle should stabilize the proximal lower-extremity joints and properly align the patient's posture. Depending on the patient's impairment profile, orthoses were found to be set with a shank-to-floor angle anywhere between 7° and 15°, although 10–12° is most common [12].

Encompassing all of these concepts, Elaine Owen proposes a prescription algorithm prescribing a combined orthosis-footwear system based on shank kinematics in a clinical gait assessment [35] (Fig. 6.4). Nonetheless, there is still a lack of quantitative evidence to identify the net influence of these parameters on patient kinematics and kinetics. As a result, orthotists are left with a clinical decision tree by which to select and customize AFO and other footwear characteristics [55].

Devices in Development with Customizable Function

To meet the increasingly important need to provide highly customized functional aspects of orthoses, researchers are exploring various orthotic design approaches ranging from passive dynamic (springlike) to active dynamic (powered) [2, 31]. Passive orthoses use material properties or mechanical elements such as springs to generate mechanical characteristics. They can control joint motion and provide torque assistance; however, they have a limited capability to adapt their function for different tasks (e.g., walking, running, stair ascending) or even within a single task (e.g., stance vs. swing of gait). Power-harvesting passive orthoses contain elements that harvest power through motion, such as oil dampers or pneumatic components. Semi-active orthoses use a variety of technologies that store and release energy; these devices often include some type of control scheme but cannot feed energy into the system. Active orthoses contain a power source that puts energy into the system and actuators that run by a control scheme. Active orthoses have a greater capability for dynamic adaptability but see limited use in the traditional clinical setting due to their costs and complexities (weight, size, power sources, and control schemes) [2].

Incorporating many of the fit and function customization concepts into its design and prescription, the Intrepid Dynamic Exoskeletal Orthosis (IDEO) is a customized carbon fiber passive-dynamic orthosis that has helped limb-salvage wounded warriors achieve high levels of function [56, 57] (Fig. 6.5). This novel design provides dramatic improvements in functional gains over other orthoses currently available. However, the IDEO still relies on traditional fabrication methods for customization of fit and function. The footplate and cuff are handcrafted using traditional limb shape replication methods, and a trial-and-error method is used to converge

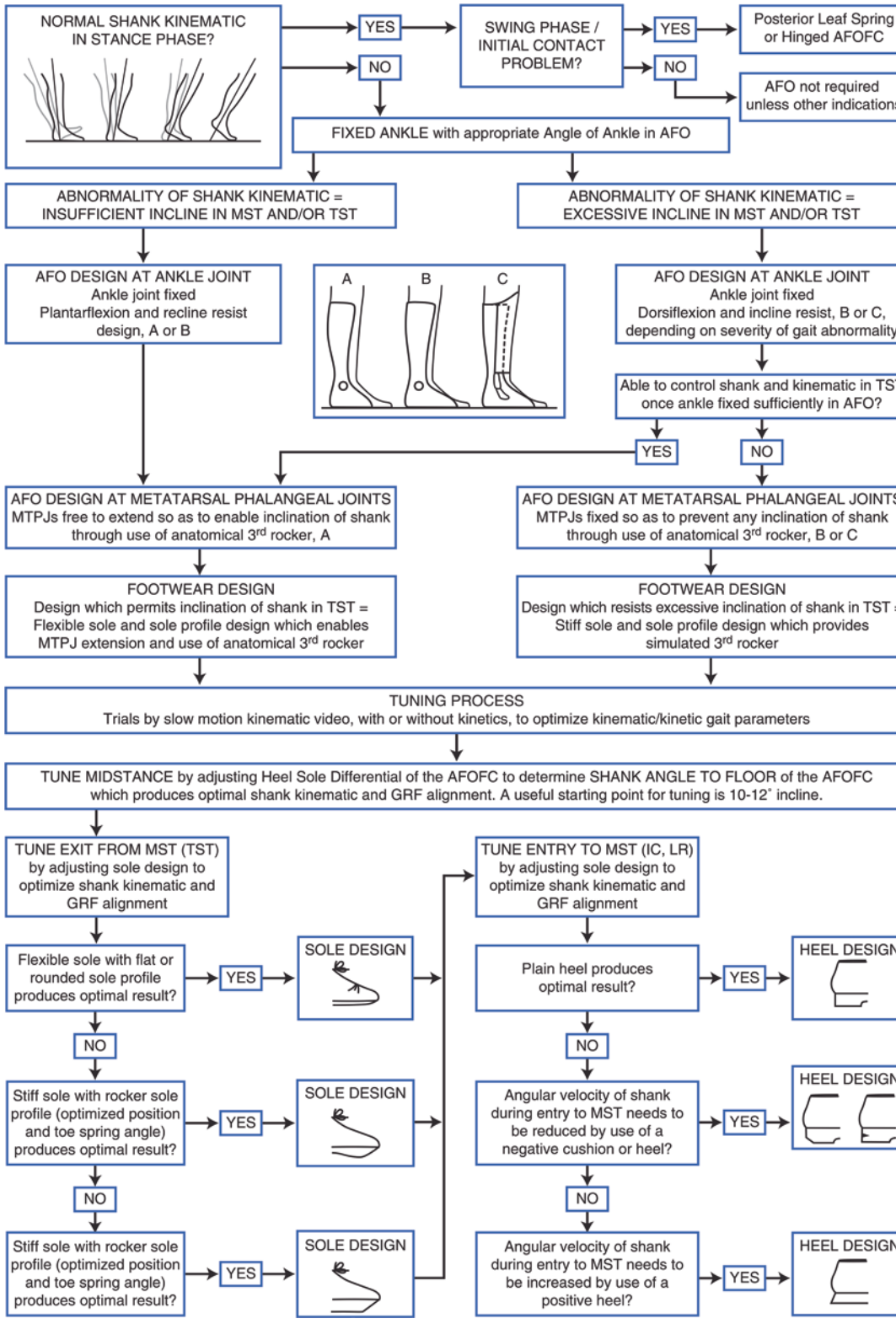

Fig. 6.4 A clinical decision tree for selecting and customizing ankle-foot orthosis and footwear characteristics. This clinical prescription model serves as an excellent basis for developing and implementing objective prescription models for customizing orthosis characteristics. (Figure originally published in Owen [5])

Fig. 6.5 Novel fit- and function-customized passive-dynamic ankle-foot orthosis design. The Intrepid Dynamic Exoskeletal Orthosis (IDEO) demonstrates the importance of fit and function customization and can be used as a basis to establish a powerful, objective design and prescription method for orthoses. (Figure originally published in Patzkowski [57])

on the proper off-the-shelf strut stiffness; there is limited ability to objectively prescribe the IDEO's bending stiffness.

To improve the customization of stiffness, orthotic joints have been developed with variable impedance for use in both ankle [58, 59] and knee [60] applications. These efforts aim to enable regulation of joint stiffness throughout the gait cycle. If successful, such joints could provide resistance to control segment or joint motion when necessary and reduce resistance to allow for greater range of motion when needed.

Alternatively, pneumatically powered, myoelectrically controlled AFOs and KAFOs are being developed to provide assistive torques about a joint [61, 62]. These orthoses have the potential to promote more natural gait [45], although to date use of these orthoses has been limited to the research laboratory. Finally, harnessing passive-dynamic properties, Ingimundarson and colleagues have designed a footplate with varying and tunable stiffness throughout its length to facilitate functional foot-to-floor motion and promote natural segment kinematics [63].

Devices have also been developed to address joint and segment alignment and kinematics. The primary feature of such devices is their ability to selectively lock or unlock the orthosis joint throughout the gait cycle, based on the phase of gait. The locking mechanism may be controlled by feedback from weight or pressure sensors [64], a pneumatic circuit connected to a pump embedded in the sole of the shoe [65], or an actuator with active control [66], in each case allowing it to integrate with passive or active devices. Customizing the alignment of the orthosis joint is important to customize its function. Pallari and colleagues have designed a pivot joint with customizable axis and a framework for integrating the joint into a customized subject-specific orthosis [67]. The pivot joint allows the axis of rotation to be customized to better mimic the rotation of an individual's natural joint.

Takemura and colleagues are working to develop an AFO to control and measure ankle motion [68]. Their "Stewart Platform-Type" device has an adjustable rotation axis to better mimic natural ankle dynamics. While not yet translated to clinical practice, this orthosis design focuses on an important concept: the dynamic nature of joints. Joints naturally and automatically adjust their characteristics, such as location and orientation rotation axis, during a single activity (e.g., throughout the gait cycle) and between activities (e.g., walking vs. running). However, the dynamic nature of human joints is rarely captured in prosthetic and orthotic devices. Thus, the wide range of settings and adaptability of the Stewart Platform-Type orthosis in development

holds great potential for enabling users to achieve high levels of function across a range of activities.

Orthoses Fabrication

Efforts to advance orthosis fabrication techniques focus on frameworks capable of rapid and cost-effective manufacturing. Because each prescribed device is unique – it is also important to improve key aspects of customized fit and function – the emphasis in the majority of these frameworks has been utilization of additive manufacturing.

Additive manufacturing, also referred to as 3D printing, uses a layer-by-layer approach by which material is additively joined to create a 3D component [69]. An array of additive manufacturing methods and materials are available. Recently, advancements in additive manufacturing now enable parts to be manufactured directly from CAD models and used in functional applications, not merely as prototypes [70, 71]. This new capability holds great promise for the manufacture of objectively customized orthotic devices and may simultaneously reduce time and cost associated with current methods. Additive manufacturing technology can be used to manufacture individual fit-customized components that are connected, via passive or active mechanical parts, to complete the function customization of the orthosis. An alternative is to use additive manufacturingto create fully fit- and function-customized passive-dynamic single-part orthoses [28–31].

Additive manufacturing requires the development of a CAD model of the customized orthosis. Traditional size and shape data are obtained to define the limb and are applied to drive the fit of a custom, patient-specific CAD model. These data first must be captured by the clinician through 3D scanning or 3D digitizing techniques, discussed previously in this chapter. Once developed, the geometry of the CAD model can be manually adjusted to customize its function. Often, finite element analysis is used to predict the mechanical properties of the device, and the CAD model geometry is then modified, iteratively or through an optimization scheme, until targeted mechanical properties are achieved [49, 50].

Researchers have demonstrated the feasibility of using additive manufacturing – in particular, selective laser sintering or fused deposition modeling – for foot and ankle-foot orthoses [28–30, 50, 72]. These studies created orthoses with targeted mechanical properties that mimicked commercially available devices [29] and foot orthoses with a range of stiffness values that had sufficient differences in mechanical properties to induce changes in subjects' lower-extremity dynamics [72]. Others report work to characterize the properties of parts manufactured by selective laser sintering to derive accurate material properties for use in finite element modeling and thus to better predict and tune the functional characteristics of ankle-foot orthoses [71].

Despite the promise of additive manufacturing, the orthotic industry has yet to embrace this technology. One reason may be that many believe it is essential to use a hands-on approach to assess patients and align them for casting. Many of the approaches described above attempt to replicate hands-on assessment and alignment in a virtual CAD environment. These frameworks do require the subjective formation and development of a unique CAD model for each orthosis. Outsourcing the CAD modeling may be a cost-effective option [23], but many orthotists may prefer to work the design themselves.

To facilitate the use of CAD tools and rapid manufacturing for non-experts, one group developed a CAD support tool, which defined design constraints based on rapid manufacturing requirements and capabilities [70]. Alternatively, the process introduced by Schrank and Stanhope relies on shape conformance of a single, fully parameterized CAD model. Under this framework, the clinician digitally obtains and inputs a set of numerical

parameters, indicating selections for fit and functional characteristics into a computerized form or spreadsheet. This triggers the CAD model to automatically adapt its size and shape to customize the orthosis [31]. Approaches such as these, which enable clinicians to objectively control orthosis fit and function without CAD expertise, appear promising but require additional substantial technological development. For instance, it is a substantial task to develop a fully parameterized CAD model with the complex geometry of an AFO that can self-adjust (without editing the model) to a wide range of sizes and shapes based on a minimal number of external instructions (parameters).

Orthosis Delivery Frameworks

Recognizing the importance of integrating objective prescription with advanced manufacturing methods, several research groups have proposed system of service frameworks to execute the full customization and fabrication process. Focusing on foot orthotics, Lowe eliminated the need for casting by using sensor pads to capture static and dynamic 3D data about the shape of the patient's foot [73]. The data are then analyzed and quantified to determine specifications for orthosis customization. Use of software for analysis and quantification provides automation capabilities, which expedites the process and minimizes the need for practitioner input that could introduce subjectivity and variability into the process. The customized device design can then be sent directly to a manufacturing terminal.

Providing a firmer link between biomechanical assessment and orthosis design for athletes, Crabtree and colleagues present a system for the design and manufacture of personalized, symptom-specific sport insoles [74]. This framework describes how results from biomechanical assessments, ideally performed using reliable and repeatable methods, should be used to drive prescription (fit and function of the insole). The model is integrated with CAD technology (for customization of design and material) and CAM systems or other manufacturing methods for rapid and objective fabrication (Fig. 6.6). This framework encompasses the important concepts for objective customization and manufacture, including patient assessment, task demand, and device design, and so holds great potential to facilitate high levels of user function.

Several frameworks have also been proposed for the objective customization and rapid fabricate of ankle-foot orthoses [26, 31, 50, 75]. In general, these frameworks focus on methods to (a) capture information pertaining to fit, (b) use computer modeling to design and customize orthosis function, and (c) fabricate the device using additive manufacturing technologies. The method proposed several years ago by Mavroids, Sivak, and colleagues used 3D laser scanning to capture shape characteristics of the patient's ankle-foot complex. The digital data were then manually manipulated to create a customized computer model of the AFO [26, 75]. While effectively eliminating the process of producing a physical model of limb shape, the proposed framework relied on scanning techniques and manual manipulation of the virtual scan to customize the AFO computer model. These subjective steps introduce sources of potential variability in the process and make customizations difficult to repeat with precision.

Described previously in this chapter, the framework developed by Schrank and Stanhope uses a novel approach [31, 32], introducing an automated orthosis design and manufacturing framework (Fig. 6.7) whereby a fully parameterized CAD model automatically customizes its fit and functional characteristics based on prescription parameters and discrete 3D measurements of landmark locations. This eliminates the need for subjective manipulation of the computer model to customize design. Next, a parameterized optimization process and finite element analysis are used

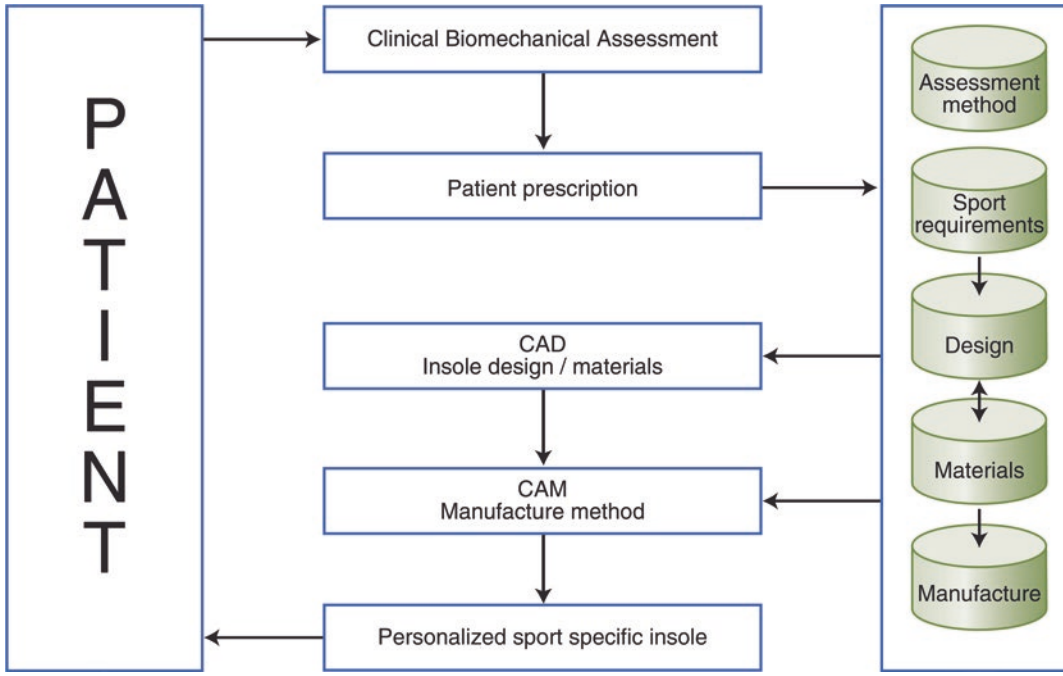

Fig. 6.6 A proposed framework for designing and manufacturing customized foot orthoses. One of the most comprehensive frameworks currently presented in the literature, this framework conceptually links biomechanical patient assessment to orthosis design as well as incorporates a method for designing and objectively manufacturing the customized orthoses. (Figure originally published in Crabtree et al. [74])

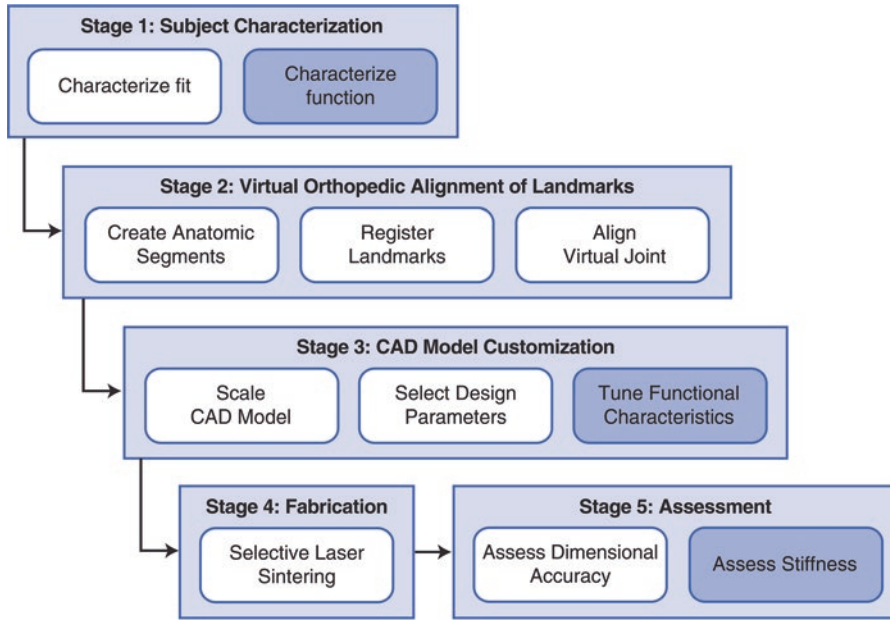

Fig. 6.7 A proposed framework for the automated design and rapid manufacture of orthotic devices. This framework combined with an objective prescription model that links patient assessment to orthosis design characteristic settings holds great potential for establishing a system of service to objectively and rapidly customize and manufacture orthoses that are optimally designed for every individual. (Figure originally published in Schrank and Stanhope [31])

to modify the dimensions of functional components, thereby predicting and adjusting the bending stiffness of the fabricated AFO. This represents a powerful automated design and centralized manufacturing framework capable of objective functional design, but further research is needed to enhance the set of fabrication materials, add additional parameterized customizations, and – as is needed for all frameworks – define a prescription model that can drive orthosis function customization toward optimal functional outcomes.

Summary and Conclusions

Orthoses are traditionally prescribed and fabricated through a subjective process based primarily on qualitative guidelines and orthotist experience. While select clinical groups are making advances toward more objective design, the clinical field remains primarily craft based, relying on the knowledge, skills, and abilities of well-trained and experienced practitioners. The industry as a whole has not yet fully embraced modern technological capabilities for use in customized prescription of orthosis fit, function, and fabrication.

In recent years, the research and manufacturing communities have made great efforts to advance the field of orthotic devices. While the introduction of new technologies into the fitting process has been positive, gains have been incremental with limited integration into traditional clinical settings. Efforts to develop objective prescription guidelines to customize the function of orthoses are also underway but have proved equally challenging. Numerous important functional characteristics have been identified, including orthosis bending stiffness, footplate design, and alignment, and experimental devices have been designed to apply them. However, we have not yet achieved a comprehensive understanding of the interplay among the many factors that determine a patient's level of impairment and those that promote desired functional outcomes. An improved understanding of that interplay is essential to the construction of objective fit and function prescription guidelines. Finally, novel technologies have been developed to manufacture custom orthoses rapidly with precisely tuned fit and functional characteristics, but use of these technologies remains limited by the strength, durability, and cost of available materials.

Frameworks have been proposed for the objective prescription and fabrication of orthoses whose fit and functional characteristics advance functional outcomes, but these have yet to be fully realized in practice. Innovative design and fabrication frameworks hold great potential to rapidly and objectively customize and manufacture orthoses. However, new frameworks need to be refined, tested, and integrated into clinical settings before they can be adopted as service models.

While research efforts are well on the way to establishing significant technological capabilities, the challenge lies in clinical implementation of these technological capabilities. Current reimbursement models, which drive the clinical orthotic field, do not support the use of the most advanced instrumentation in standard clinical settings. The most advanced technological capabilities are costly and not yet supported by adequate data to establish reliably improved outcomes. Quantitative evidence to demonstrate enhanced outcomes may provide the necessary incentive for third-party payers to increase reimbursement. It has been documented that patients who achieve high levels of function are more active, which in turn reduces the incidence of chronic health conditions. This is an important objective not just for those who use orthoses and prostheses but also for the broader population of citizens whose insurance premiums and taxes are applied to cover costs associated with health care generally. According to the Centers for Disease Control, 75% of all healthcare costs in 2009 were due to chronic health conditions [76] and in 2011 amounted to a cost of approximately two trillion dollars [77].

Data are needed to demonstrate improved outcomes, associated long-term health benefits, and potential cost savings. Such an effort would likely require support through a large-scale consortium that links individual care system such as the US Department of Veterans Affairs (VA) and Department of Defense (DoD) medical treatment facilities with industry and academic centers of excellence. Without the constraints of current reimbursement models, the objective would be to access and use advanced instrumentation with relevant clinical populations to demonstrate and document evidence of impact. Within this same consortium model, research can continue in parallel to advance and optimize technologic capabilities, reduce costs, and streamline processes for implementation in the insurance-dependent civilian population. Ideally, results from coordinated basic and clinical research can pave the way to reimbursement for care that allows patients to live happier and healthier lives while also reducing the lifetime cost of health care.

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7 Synthetic and Biological Multifunctional Smart Materials Applications to Lower Extremity Gait Systems

Mohsen Shahinpoor

Abbreviations

C-PAN	Conductive polyacrylonitrile
CP	Conductive polymer
FES	Functional electrical stimulation
Gly-Gly	Glycylglycine
IBPMC	Ionic biopolymer metal composite
IPCC	Ionic polymer conductor composite
IPCNC	Ionic polymer conductor nanocomposite
IPMNC	Ionic polymer metal nanocomposite
NMR	Nuclear magnetic resonance
PAA-PVA	Polyacrylic acid-polyvinyl alcohol
PAAM	Polyacrylic-acid-bis-acrylamide
PAM	Polyacrylamide
PAMPS	Poly(2-acrylamido-2-methyl propane) sulfonic acid
PAN	Polyacrylonitrile
PTFE	Polytetrafluoroethylene
PZT	Lead zirconate titanate
PVDF	Polyvinylidene difluoride
PVDF-TrFE	PVDF trifluoroethylene
RSC	Royal society of chemistry
SMA	Shape memory alloys
SMP	Shape memory polymers

M. Shahinpoor, BSc, MSc, PhD (✉)
Biomedical Engineering Laboratory, Department of Mechanical Engineering, University of Maine, Orono, ME, USA
e-mail: shah@maine.edu

Introduction

This chapter presents a review/survey of a number of multifunctional "smart" materials and artificial muscles that have the potential for application to lower extremity gait devices, orthotics, prostheses, and systems. These materials change shape and deform in response to an external stimulus such as an imposed electric or magnetic field, a change in pH, a change in temperature, or other environmental changes. The shape change and deformation of these materials can be used to perform a function similar to that of mammalian muscle.

Katchalsky [1, 3] and Kuhn [2] were the first to discover a family of materials with physical behavior comparable to that of muscle. The "pH muscles" were the first artificial muscles that contracted and expanded in response to pH changes in their proximal surrounding environment. Charge repulsion of bound carboxylic acid groups drove an extended molecular configuration of gel molecules. Exposure of the carboxylic

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acid groups to protons in the surrounding media converted the gel molecules from their elongated form to a more compact, less electrically charged form. However, the cycles of addition of hydrochloric acid (HCl) and sodium hydroxide (NaOH) resulted in an accumulation of counter ions, with the effect of diminishing the ionic interactions at each cycle, which in turn diminished the muscle-like function of the gel. This raised the need for "local ion feeding" to sustain ionic interactions. In the present chapter, I show that it is possible to have two interpenetrated networks, one elastic and the other electrically conducting, thus creating the necessary ions locally. Ion pumping and redistribution in soft polymers and polymer gels may prove viable as ways to achieve soft, biomimetic artificial muscles.

The application of artificial materials and biomaterials to orthoses, prostheses, and related systems presents several well-defined challenges. The materials must produce large stresses (1 atm) with a relatively fast response (1 s) but without generating too much heat. Materials must also be chemically, mechanically, electrochemically, and electromechanically robust, user-friendly, and available at a reasonable price.

Biological muscle is a complex actuating system with the capacity to perform diverse functions. The fundamental building blocks are micro-sized contractile units called *sarcomeres*, which contain three filament types: thick, thin, and connecting [4, 5]. Muscle contraction is based upon the sliding interaction of thick and thin filaments [5]. These filaments are polymeric materials that form a highly ordered, gel-like lattice. The myosin subunits of the thick filaments serve as nanomotors (crossbridges), driving thin filament past thick. The mechanism is based upon a chemomechanial nanoscale motion that can ultimately cause biological muscle to contract in a collective manner to achieve macroscaled motions with useful forces. The principle involves many units acting in series and in parallel to achieve strength and speed of contraction, with the macrostructure of skeletal attachment contributing leverage such that a length change of 10% or less in a muscle can produce a dramatic movement of attached skeletal structures. Strength is further scalable by adaptive nerve stimulation such that no more muscle fibers are actuated than necessary for a given load. The system is well supplied with feedback mechanisms to monitor and adjust for speed, length, and force generation. Anatomic arrangement forms groups of muscles that counter one another, often in antagonist pairs, to increase the speed, accuracy, and flexibility of possible movements.

It may take researchers many years to develop artificial muscles that match the complexity and efficiency of mammalian muscles. On the other hand, synthetic muscles may offer a broader scope in the complexity of motions and strength than natural muscles, which are limited by lack of protein stability and by the restriction of metabolic pathways. The following sections will consider various types of multifunctional smart materials and artificial muscles that may be used for orthotic and prosthetic devices and systems.

Chemomechanical Polymers

Chemomechanical polymers are a family of smart multifunctional materials with the potential to be used as artificial muscles. Changes in the chemical environment can trigger large deformations in these materials (contractions and expansions, basically Riemannian growth and shrinkage as defined by change in volume and mass). Chemomechanical polymers therefore serve as both sensors and actuators at the same time. Commonly, these materials respond to changes in pH and are called pH muscles.

However, with pioneering work of Schneider and co-workers [6, 7], it became possible to use

supramolecular recognition sites within these materials, covalently bound to the polymer backbone. This allowed a variety of chemical compounds to be used as actuating molecules to induce shape change, rather than relying on pH. Non-covalent effectors (e.g., metal ions), isomeric organic compounds (e.g., enantiomers), nucleotides, amino acids, and peptides could now drive chemomechanical deformations and shape changes. By increasing the surface-to-volume ratio of polymer particles, the speed of the responses can be significantly increased.

Schneider and co-workers [6, 7] describe the principles and recent development in the field of chemomechanical polymers, with an emphasis on their *function*. They describe the performance of these materials in the presence of different chemical stimuli and, to a lesser degree, discuss their underlying structural and mechanical properties.

Contractile Polyacrylonitrile Artificial Muscles

Fibrous chemomechanical polymers made with polyacrylonitrile (PAN) present a tremendous possibility for contractile artificial muscles (see Shahinpoor and co-workers [8–12]). This section describes the properties of raw PAN fibers, activation of PAN to allow chemical-ionic control, modification to allow electrochemical control (conductive PAN or C-PAN), and finally the implications of electrospun conductive PAN nanofibers (C-PAN-N). Contractile PAN artificial muscles are particularly suitable for replacing mammalian muscles; they produce antagonist muscular action similar to the action of the main leg muscles like the quadriceps (rectus femoris), hamstrings (biceps femoris), calves (gastrocnemius), and tibialis anterior to mobilize the foot as shown in Fig. 7.1.

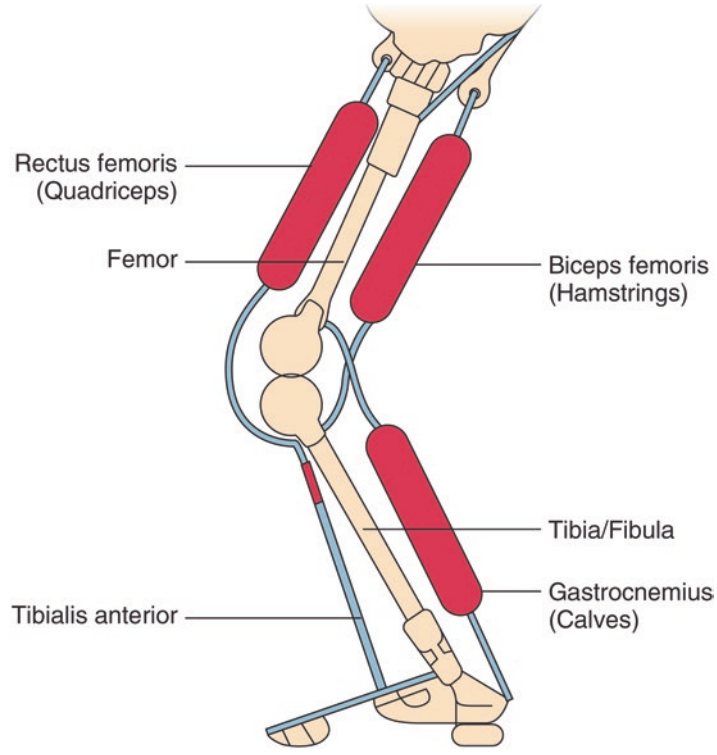

Fig. 7.1 A sketch of main lower extremity gait muscles in the leg

Fibrous PAN, which is commercially known as Orlon® or artificial silk, is an acrylic fiber annealed to cross-link the macromolecules and then hydrolyzed to make them ionic and, ultimately, pH active (Fig. 7.2). Since pH depends on the concentrations of H+ or OH− ions, it is possible to make PAN muscles contract and expand in electrochemical cells by using simple saline solutions in the presence of an electric field which generates H+ and OH− by simple electrolysis of the saline solution.

Figure 7.3 depicts a skeletal structure equipped with fibrous contractile PAN biceps muscles.

Fibrous contractile PAN muscles can be packaged similar to mammalian muscles and, even in antagonist forms, similar to biceps or quadriceps muscles as shown in an assortment of such PAN muscles in Fig. 7.4.

Preparation of Ionically Active Contractile PAN Muscles

Raw PAN fibers are composed of roughly 2,000 individual strands of PAN, each about 10 μm in diameter. The activation of PAN induces cross-linking by the formation of pyridine rings by low-temperature annealing (e.g., 220 °C for 2 h) and subsequently converts nitrile groups to carboxylic

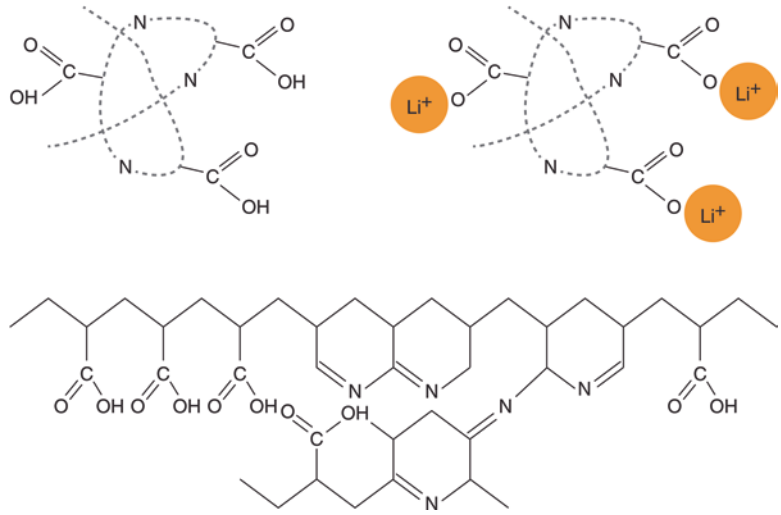

Fig. 7.2 PAN expansion/contraction is explained by osmotic pressure changes. *Top left:* neutral state; *top right*, in alkaline solutions LiOH. When pure water is in contact with alkaline PAN, there will be an osmotic pressure-driven water influx expanding the PAN muscles. The bottom picture shows the PAN molecules after expansion

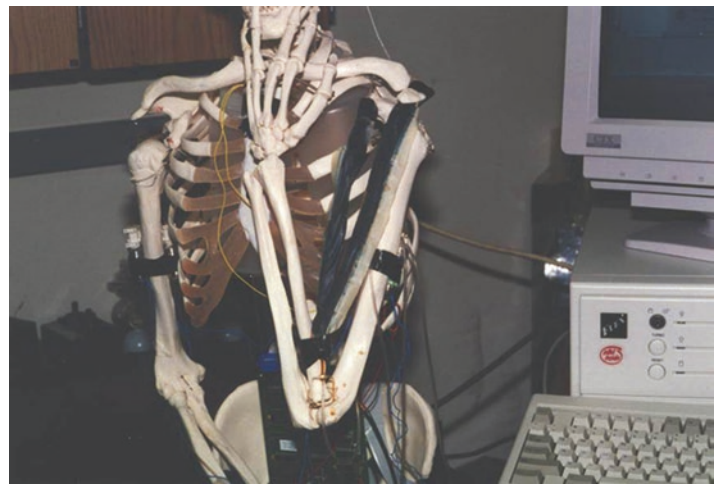

Fig. 7.3 Skeletal structures equipped with contractile PAN biceps muscles

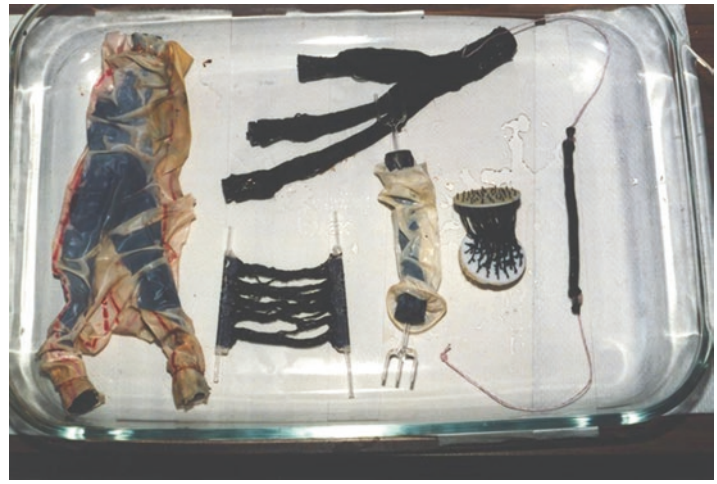

Fig. 7.4 An assortment of PAN artificial muscles in a variety of configurations that may be applicable to lower extremity gait systems

acid groups by saponification with sodium or lithium hydroxide (e.g., boiling in a solution of 1 N LiOH for 30 min). The degree of cross-linking depends on annealing temperature and time, which in turn determines the amount of free nitrile groups left to be converted to carboxylic acids during saponification. Activated PAN fibers become hyperelastic like a rubber band. This ionically active PAN can contract in response to a flood of cations such as H^+, while the presence of hydroxyl ions (OH^-) causes the fibers to elongate.

The term "activated PAN fibers" refers to PAN fibers behaving such that length varies depending upon the ionic concentration of cations in the solution. In our laboratory, it has been observed that acidic pH-contracted PAN fiber bundles of ten fibers can expand more than 200% by alkaline pH activation and yet reversibly contract back to their original length upon acidic pH activation. The use of PAN fibers as artificial muscles is promising since PAN fibers can convert chemical energy to mechanical motion. The change in length for pH-activated fibers is typically greater than 100%; contraction/expansion of PAN microfibers has been observed up to 500% [8–12]. Figure 7.5 depicts typical stress-strain curves for activated PAN muscle fibers. They are comparable in strength to human muscles (~20 Newtons/cm^2) and have the potential to be medically implantable. However, the fact that PAN fibrous muscles must be chemically activated raises the need for potentially complex plumbing systems. Electromechanical activation may be more feasible and appropriate to lower extremity applications, as discussed in the following section.

Electrochemically Controllable Polyacrylonitrile Artificial Muscle

Artificial muscles made from PAN provide greater mechanical strength than do those made from polyelectrolyte gels. The electrochemical contraction and expansion of PAN artificial muscles [12–18] offer great potential for applications to lower extremity prosthetic devices and systems. Electrical activation of contractile ionic polymeric fibers dates back to the works of Hamlen, Kent, and Shafer [19]. In recent years, other investigators have advanced development of electrochemomechanical conductive muscle fibers [20–24].

The idea of using a graphite or gold fiber electrode was motivated by the fact that these materials could produce necessary ions for contraction and elongation, respectively. Another advantage is their chemical/mechanical endurance in chemical

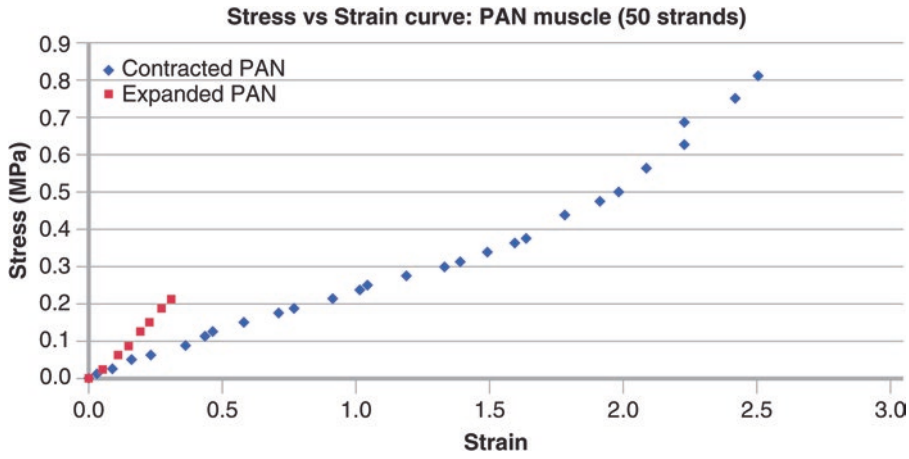

Fig. 7.5 Normal stress-strain relationship for the contracted and the expanded state of PAN muscles

environments during activation and contraction/elongation processes. Figure 7.6 depicts how the graphite fiber is wrapped around a PAN fiber for electrochemical activation as shown in Fig. 7.7.

In an electrochemical cell, electrolysis of water generates hydrogen ions at the anode, while hydroxyl ions are formed at the cathode. Therefore, electrochemical reactions can be used to control the length of a PAN artificial muscle, either by locating a PAN muscle near an electrode where the ions are generated or, if the conductivity of activated PAN can be increased, by having the PAN muscle serve as the electrode. PAN fibers can be activated electrically by providing a conductive medium in contact with or within the PAN fibers. Such electrical activation can be made to have low overvoltage for hydrogen and oxygen evolution. At the anode, oxygen evolves via $2\mathrm{H_2O} \Rightarrow O_2 + 4H^+ + 4_e^-$, and the counter reaction at the cathode is $2\mathrm{H_2O} + 2_e^- \Rightarrow H_2 + 2\mathrm{OH}^-$. Upon being hydrogenated near the PAN anode, the decreased pH causes the PAN fibers to contract by the same effect as chemical activation. If the polarity of the applied electric voltage is reversed, then PAN fibers become elongated. As described before, PAN muscles can be contracted and expanded electrochemically in an electrochemical cell equipped with a dilute saline solution (0.2 mN NaCl). In this case, graphite fibers are intermingled with PAN fibers to make PAN-G fibers and are used either as anode electrode (contraction, H^+ ions) or as cathode electrode (expansion, OH^- ions) in the chemical cell.

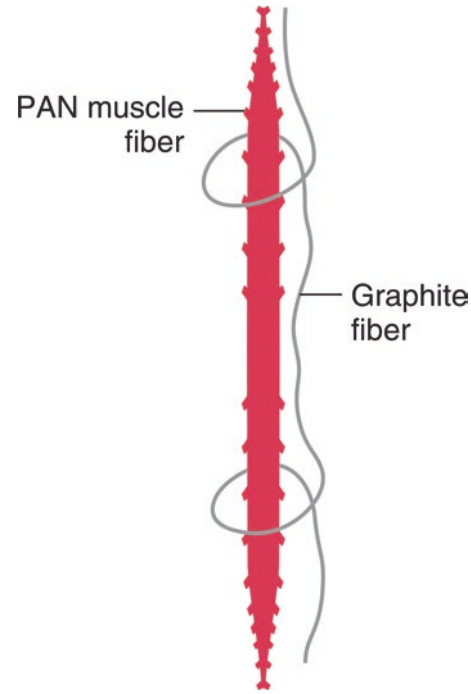

Fig. 7.6 Each fiber has a diameter of 6.4 μm and the configuration of the intermingled graphite fibers and PAN muscle fibers

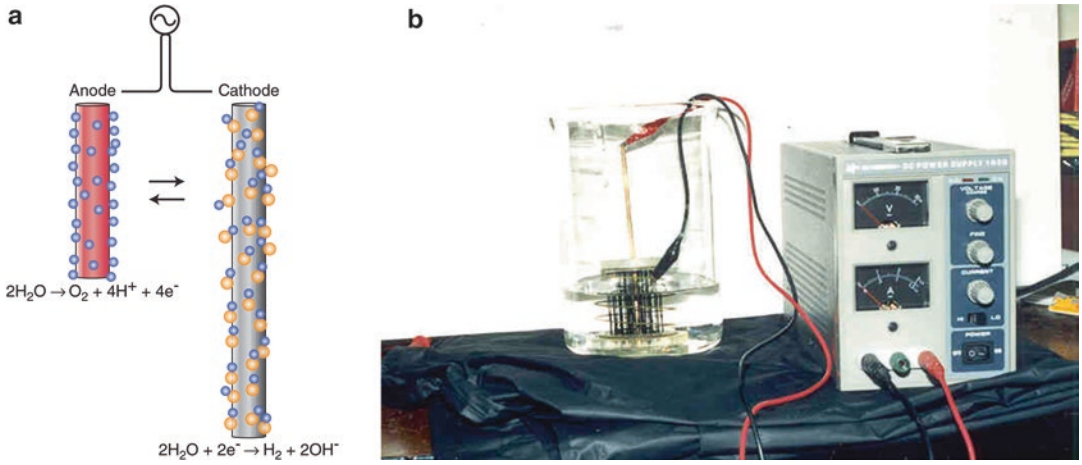

Fig. 7.7 The operating principle of the C-PAN fiber (**a**). Experimental setup for electrical activation of C-PAN artificial fibrous muscles with the anode (*red*) attached to a copper electrode and the cathode (*black*) attached to C-PAN muscle (**b**)

Whereas pH-activated PAN fibers exhibit more than 100% contraction or expansion in a few seconds, electrochemically activated PAN fibers, by contrast, exhibit just 50% change in length within a few seconds. C-PAN is a conductive composite of PAN, achieved by increasing the conductivity of PAN fibers. This can be accomplished by making a composite of them with a conductive medium. Gold, graphite, carbon nanotubes, or conductive polymers (polyaniline or polypyrrole) can be used. When a C-PAN fiber bundle is placed in an electrochemical cell as an electrode, its expansion and contraction can be controlled by varying the applied electric field polarity. Typically, a nearly 50% change in C-PAN muscle length occurs in a few minutes time when it is placed as an electrode in a 10 mM NaCl electrolyte solution connected to a 20-volt power supply. (Described later in this chapter, nanofibrous C-PAN, or C-PAN-N, reduces the response time to just a few seconds.)

Direct Metal Deposition Technique

Conductivity of PAN can be increased by chemical deposition of platinum on PAN fibers to make it conductive PAN or C-PAN. Raw PAN fibers can be immersed in a tetraammineplatinum chloride monohydrate solution. The PAN fibers will then be placed in a reducing solution containing sodium borohydride ($NaBH_4$). The solution is slowly heated to 50–60 °C with agitation and periodic additions of 5% $NaBH_4$ solution to reduce platinum (Pt) metal. This process is repeated several times to seed the PAN fibers with Pt. After platinum deposition, the C-PAN fibers can be activated by the method previously described. The results of electrical contraction and elongation of a C-PAN platinum muscle is shown in Fig. 7.8 [12–18].

The electric activation of C-PAN in our labs produced the approximate mean rate of contraction of $L/L_o \approx 5\,\%/\text{min}$, while the approximate mean rate of elongation was $L/L_o \approx 3\,\%/\text{min}$. The anomaly in both contraction and expansion is believed to be due to the nonuniform electro-osmotic diffusion of H^+ and OH^- in and out of the C-PAN fiber bundle. To address these problems, the electric activation scheme was changed by using thin graphite fibers serving as an effective adjunct electrode circled around, intermingled, and combined with PAN and gold as a counter electrode. This is described further in the next section.

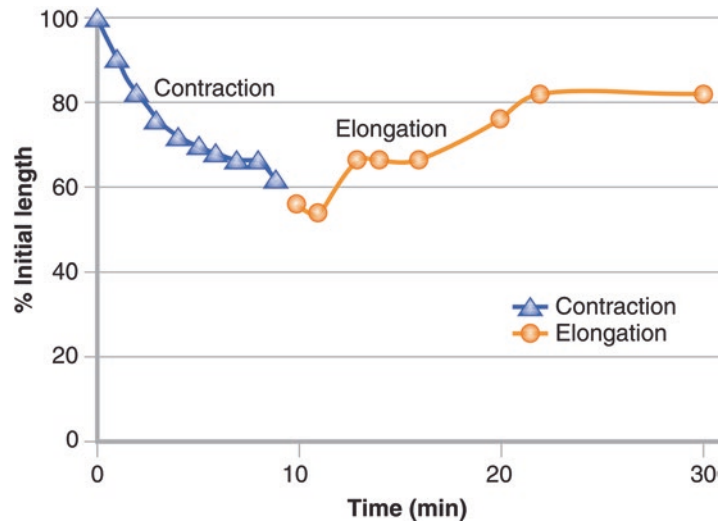

Fig. 7.8 Electrical activation of muscle composed of fiber bundle of 50 C-PAN platinum fibers. Initial muscle length, 5.0 cm; number of fibers, 50; cell voltage, 20 V; current, 120 mA. Polarity of electrodes reversed at $t = 10$ min

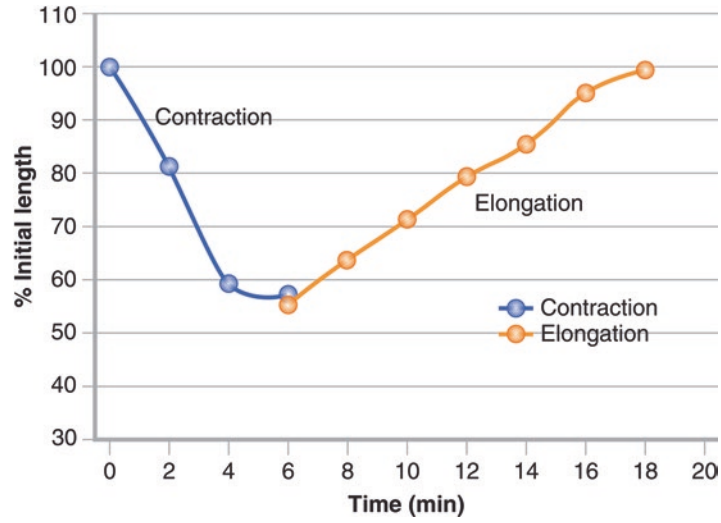

Fig. 7.9 Electrical activation of contracted and expanded C-PAN fiber bundles

Figure 7.9 depicts the electrical activation of C-PAN fiber bundles made with intermingled graphite fibers.

Figure 7.10 depicts the electric activation of C-PAN fiber bundles with intermingled graphite fiber electrodes in an electrochemical cell. Response times are significantly improved relative to the previously reported [11, 12] C-PAN platinum fibers, with contraction and elongation observed as fast as $\delta = L/L_o \approx 10\,\%/\text{min}$.

Efficient production and diffusion of the necessary ions (H^+ and OH^-) and their distribution over the C-PAN fibers is the key to producing fast-reacting fibers. Note that with single PAN fibers composed of 2,000 strands of 10 μm microfibrils diameter PAN microfibers intermingled with graphite fibers (PAN-G), it was observed that the contraction time was reduced by approximately 60% compared to 50-μm C-PAN fiber bundles. The activation of a single strand of 10-μm fiber reduced the contraction time to a few seconds, as shown in Fig. 7.10.

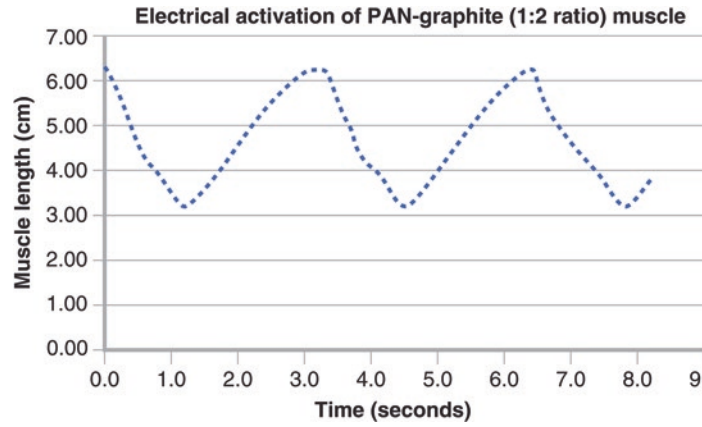

Fig. 7.10 Variation of Length of C-PAN-G strands of 10 μm in diameter with Time (seconds) in a 0.2 mN NaCl cell under a voltage of 20 volts (1PAN-2G ratio in a special helically wound configuration)

Toward Nanoscaled Artificial Muscles and Molecular Motors

Biological muscles are magnificent nano- to micro- to macroscaled actuating and sensing systems. Inspired by the fact that extremely fast-response times can be attained by hierarchically moving toward smaller and smaller diameter fibers, nanofibers of PAN were manufactured using a technique called "electro-spinning" [17]. Furthermore, C-PAN nanofibers have been fabricated by the electro-spinning method [17] and then ionically activated.

Commercially available PAN fibers (Orlon®) are composed of 2,000 strands of microfibrils, each 10 μm in diameter. Known as artificial silk, they are widely used for textile applications. The electro-spinning method typically produces fiber diameters in the 10s or 100s of nanometers and opens up new opportunities in industrial, biomedical, and consumer applications.

PAN nanofibers were suitably annealed, cross-linked, and hydrolyzed in our artificial muscles laboratory to become "active." These results indicate the potential in developing electrically activated C-PAN-N artificial nanomuscles and linear nanoactuators. Furthermore, these results offer great potential for using electroactive fiber bundles of C-PAN nanofibers as artificial muscles for linear actuation. Realizing that the response time of PAN artificial muscle is governed by the diffusional processes of ions/solvents interaction, the use of PAN nanofibers or fibrils is promising for fabricating fast-response PAN artificial muscles. The contraction/elongation behavior explanation is based upon the exchange of counter ions and solvent (in this case, water) in and out of activated PAN. Thus, Donnan equilibrium theory may describe the situation properly because of the charge transport across charged polyelectrolytes. C-PAN nanofibers used in an electrochemical cell for chemomechanical linear contractile transduction are expected to provide contraction response times comparable to biological muscles, i.e., in the range of a 3–5 ms.

In conclusion, electrochemomechanically activated C-PAN artificial muscles can be developed in a manner suitable for industrial and medical applications. By increasing the conductivity of activated PAN, PAN-based linear actuators, arranged as antagonist pairs, can be electrically activated. In a few seconds' time, close to a 50% change in C-PAN fiber length is induced in a weak electrolyte solution at modest voltage. Experimental results so far suggest great potential for developing fast-activating C-PAN-N muscles and linear actuators for use in lower extremity prosthetic devices and systems.

PAN nanofibers used in an electrochemical cell for chemomechanical linear contractile

transduction are expected to provide contraction response times comparable to biological muscles, i.e., in the range of a 5–10 ms.

Mathematical Modeling of Contraction and Elongation of C-PAN Fibers

A possible explanation for the contraction and elongation of PAN muscles is based upon the carboxylic acid groups having the molecular geometry of activated PAN. At low pHs, all carboxylic acid groups on activated PAN are likely to be protonated, thus potentially collapsing the network by polymer-polymer affinity and contracting the polymer chain through neutral charge of the acid groups and hydrogen bonding between neighboring carboxylic acid groups. Based upon the Donnan theory of ionic equilibrium, the important forces arise from (i) the induced osmotic pressure of free ions between activated PAN fibers and their environment, (ii) the ionic interaction of fixed ionic groups, and (iii) the network itself. Among these, the induced osmotic pressure of free ionic groups could be the dominating force.

Electrical activation of PAN fibers is performed in an electrochemical cell such as shown previously in Fig. 7.7. Note that at the anode, oxygen evolves via $2H_2O \Rightarrow O_2 + 2H^+ + 4e^+$, and the counter reaction at the cathode is $2H_2O + 2e_e^- \Rightarrow H_2 + 2OH^-$. Upon being hydrogenated in the vicinity of the PAN anode, the decreased pH causes the PAN fibers to contract by the same effect as chemical activation. Also, reversing the polarity of DC, elongation of PAN fibers is simply obtained.

In the following section, a basic theory is presented for the contraction of PAN fibers in an electric field, based on electrocapillary transport and electroosmotic dynamics.

Electrocapillary Transport Modeling

Consider the gel fiber to be a swollen cylinder with outer radius r_0 and inner radius r_i and assuming an electric field to be aligned with the long axis of these cylindrical macromolecule ionic chains. Further, we assume the polyions are evenly distributed along the macromolecular network at regular distance b. Thus, we employ the conservation laws, namely, conservation of mass and momentum, to arrive at the following governing differential equation for the flow of counterion containing solvent in and out of the gel macromolecular network.

$$\rho \frac{\mathrm{dv}}{\mathrm{dt}} = \rho \ g + \rho^* E + \mu \nabla^2 v - \nabla p \qquad (7.1)$$

where ρ is the density of the liquid solvent which is assumed to be incompressible, v is the 3-D liquid velocity vector and ∇ is the gradient vector operator, ∇^2 is the Laplacian operator, g is the local gravitational acceleration vector, μ is the solvent viscosity, p is a hydrostatic pressure, E is the imposed electric field vector, and ρ^* is the charge density governed by the following Poisson's equation.

$$\rho^* = -D^* \nabla^2 \psi \qquad (7.2)$$

where D^* is the dielectric constant of the liquid phase and ψ is governed by the following Poisson-Boltzmann equation:

$$\nabla^2 \psi = \left(4\pi n\varepsilon / D^*\right) \exp\left[-\varepsilon\psi / \mathrm{kT}\right] \qquad (7.3)$$

where n is the number density of counterions, ε is their average charge, k is the Boltzmann constant, and T is the absolute temperature. The electrostatic potential in polyelectrolyte solutions for fully stretched macromolecules in polyelectrolyte solutions is given by the following equation, which is an exact solution to the Poisson-Boltzmann Eq. (7.8) in cylindrical coordinates.

$$\psi(r,t)=\left[\mathrm{kT}/\varepsilon\right] \ln\left\{\begin{array}{l}\left[r^2/\left(r_0^2-r_i^2\right)\right]\sinh^2 \\ \left[\beta\ln\left(r/r_0\right)-\tan^{-1}\beta\right]\end{array}\right\} \quad (7.4)$$

where β is related to $\lambda=(\alpha\varepsilon^2/4\pi D^*\mathrm{bkT})$, where α is the degree of ionization, i.e., α= n/Z, where n is the number of polyions and Z is the number of ionizable groups and b is the distance between polyions in the network. Furthermore, $n=[\alpha\varepsilon^2/4\pi D^*\mathrm{bkT})]$ and $\beta's$ are found from the following equation:

$$\lambda=\frac{1-\beta^2}{1+\beta\coth\left[\beta\ln\left(r_0/r_i\right)\right]} \quad (7.5)$$

Let us further assume that due to cylindrical symmetry, the velocity vector $v=(v_r,v_\theta,v_z)$ is such that only v_z depends on r and further that $v_\theta = 0$. Thus, the governing equations for v_z = v reduce to:

$$\rho\left(\frac{\partial v}{\partial t}\right)=f\left(r,t\right)+\mu\left(\frac{\partial^2 v}{\partial r^2}+\frac{1}{r}\frac{\partial v}{\partial r}\right)-\frac{\partial p}{\partial r} \quad (7.6)$$

Let us assume a negligible radial pressure gradient and assume the following boundary and initial conditions:

at $t=0, r_i\le r\le r_o$, $v=0$, at $r=r_i, \forall t, v(r_i)=0$, and at $r=r_o, \forall t, \left(\partial v/\partial r\right)_{r=r_o}=0$. Furthermore, the function $f(r,t)$ is given by:

$$f\left(r,t\right)=n\varepsilon E\left(r,t\right) \left\{\begin{array}{l}\left[k^2r^2/2\beta^2\right]\mathrm{Sinh}^2 \\ \left[\beta\ell n\left(r/r_o\right)-\tan^{-1}\beta\right]\end{array}\right\}^{-1} \quad (7.7)$$

where $k^2=(n\varepsilon^2/\mathrm{DkT})$.

An exact solution to the given set of equations can be shown to be:

$$v\left(r,t\right)=\sum_{m=1}^{\infty}e^{-(\mu/\rho)\beta^2\mathrm{mt}} k_0\left(\beta_m r\right)\int_0^t e^{(\mu/\rho)\beta_m^2\xi}A\left(\beta_m,\xi\right)d\xi \quad (7.8)$$

where β_m,s are the positive roots of the following transcendental equations:

$$\frac{J_0\left(\beta\ r_i\right)}{J_0'\left(\beta\ r_o\right)}-\frac{Y_0\left(\beta\ r_i\right)}{Y_0'\left(\beta\ r_0\right)}=0 \quad (7.9)$$

where J_0, Y_0, J_0', Y_0' are the Bessel functions of zero order of first and second kind and their derivatives evaluated at r_0, respectively, and

$$\begin{aligned}&k_0\left(\beta_m,r\right)\\&=N^{-(1/2)}\left\{\frac{J_0\left(\beta r\right)}{\beta_m J_0'\left(\beta r_0\right)}-\frac{Y_0\left(\beta r\right)}{\beta_m Y_0'\left(\beta r_0\right)}\right\}\\&=N^{-(1/2)}R_0\left(\beta_m,r\right)\end{aligned} \quad (7.10)$$

where

$$N=\left(r_0/2\right)R_0^2\left(\beta_m,r_0\right)-\left(r_i^2/2\right)R_0'^2\left(\beta_m,r_i\right), \quad (7.11)$$

$$A\left(\beta_m,\xi\right)=\left(1/\mu\rho\right)\int_{r_i}^{r_0}\varsigma\ k_0\left(\beta_m,\varsigma\right)f\left(\varsigma,\xi\right)d\varsigma. \quad (7.12)$$

Having found an explicit equation for $v(r,t)$, we can now carry out numerical simulations to compare the theoretical dynamic contraction of ionic polymeric gels in an electric field with contractions shown by experiments. In order to compare the experimental results and observations with the proposed dynamic model, a number of assumptions, simplifications, and definitions are first made. Consider the ration $W(t)/W(0)$, where $W(t)$ is the weight of the entire gel at time t and $W_0 = W(0)$ is the weight of the gel at time $t = 0$, just before the electrical activation. Thus,

$$W\left(t\right)=W_0-\int_0^t\int_{r_i}^{r_0}2\pi\rho v\left(r,t\right)r\mathrm{d}r\mathrm{d}t \quad (7.13)$$

which can be simplified to

$$\left[W\left(t\right)/W_0\right]=1-W_0^{-1}\int_0^t\int_{r_i}^{r_0}2\pi\rho v\left(r,t\right)r\mathrm{d}r\mathrm{d}t \quad (7.14)$$

The initial weight of the gel is related to the initial degree of swelling $q = V(0)/V_p$, where $V(0)$ is the volume of the gel sample at $t = 0$ and V_p is the volume of the dry polymer sample. Numerical simulations were carried out based on the

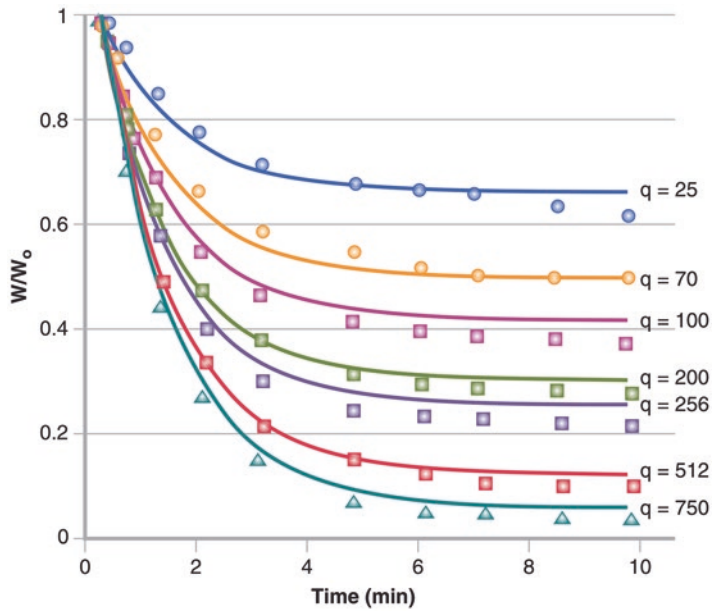

Fig. 7.11 Computer simulation (*solid lines*) and experimental results (scattered points) for the time profiles of relative weight of the PAN for various degrees of swelling q

assumptions that the cross section of the gel remains constant during contraction of the gel sample and

$\varepsilon = e = 1.6 \times 10^{-19}$ Coulombs.

T = 300° K.

$\alpha = 1$, D = 80.

$\mu = 0.8 \times 200910^{-3}$ Pa.sρ = 1,000 Kg/m^3.

$b = 2.55 \times 10^{-10}$ m, k = 1.3807×10^{-23} Joules/°K.

$r_i = 6.08 \times 10^{-10}$ m, $r_o = r_i q^{(1/2)}$.

q = 25, 70, 100, 200, 256, 512, 750.

The initial length and cross section of the sample are, respectively, $l_0 = 1$ cm and $S = 1$ μm^2, and the electric field is $E = 5.7$ volts/cm. The results of numerical simulation are depicted in Fig. 7.11, which shows reasonable agreement with experimental results also shown in Fig. 7.11.

Ionic Biopolymer Metal Nanocomposites (IBPMCs)

In this section, the application of the ionic biopolymer metal composites (IBPMCs) to orthotics, prostheses, and prosthetic systems will be briefly explained. The results, properties, and characteristics of ionic polymer metal composites (IBPMCs) are briefly reported here as biomimetic multifunctional distributed nanosensors, nanoactuators, nanotransducers, and artificial muscles. Fundamental considerations for biomimetic distributed nanosensing and nanoactuation will also be discussed, followed by some recent advances in manufacturing techniques, force optimization, 3-D fabrication of IBPMCs, recent modeling and simulations, sensing and transduction, and product development.

The reader is referred to references [25, 26] for recent findings on the use of ionic polymer metal composites (IPMCs) and ionic polymer metal nanocomposites (IPMNCs) as biomimetic distributed nanosensors, nanoactuators and artificial muscles, and electrically controllable polymeric network structures. Reference [25] describes the methods of fabrication of several electrically and chemically active ionic polymeric gel muscles including polyacrylonitrile (PAN), poly(2-acrylamido-2-methyl-1-propane sulfonic) acid (PAMPS), polyacrylic-acid-bis-acrylamide (PAAM), and a new class of electrically active composite muscle known as ionic polymeric conductor composites (IPCCs) or ionic polymer metal

composites (IBPMCs), made with perfluorinated sulfonic or carboxylic ionic membranes.

Many electrochemical processes and devices utilize poly(perfluorosulfonic acid) ionic polymers. These materials [25, 26] exhibit good chemical stability, remarkable mechanical strength, good thermal stability, and high electrical conductivity. As described in [25], a number of physical models have been developed to understand the mechanisms of water and ion transport in ionic polymers and membranes. Morphological features influence transport of ions in ionic polymers. These features have been studied by a host of experimental techniques including small and wide-angle X-ray scattering, dielectric relaxation, and a number of microscopic and spectroscopic studies.

The emerging picture of the morphology of ionic polymers is that of a two-phase system made up of a polar fluid (water)-containing nonsymmetric dipoles and ion cluster network surrounded by a hydrophobic polytetrafluoroethylene (PTFE) medium. The integrity and structural stability of the membrane is provided by PTFE backbones, and the hydrophilic clusters facilitate the transport of ions and water in the ionic polymer. These nanoclusters have been conceptually described as containing an interfacial region of hydrated, sulfonate-terminated perfluoroether side chains surrounding a central region of polar fluids. Counter ions such as Na+ or Li+ are found close or near to the sulfonates. The length of the side chains has a direct bearing on the separation between ionic domains (where the majority of the polar fluid resides) and the nonpolar (hydrophobic) domains.

High-resolution nuclear magnetic resonance (NMR) of some perfluoroionomers shows an unusual combination of a nonpolar, Teflon-like backbone with polar and ionic side branches. It has also been well established [25, 26] that anions are tethered to the polymer backbone and cations (H^+, Na+, Li+) are mobile and solvated by polar or ionic liquids within the nanoclusters of size 3–5 nm. IBPMCs can be manufactured three-dimensionally using a liquid form of perfluorinated ionic polymers or a raw, melt-processable form of Nafion called XR-resin. By meticulously evaporating the solvent (isopropyl alcohol) out of the solution, recast ionic polymer can be obtained [25].

Electrically Induced Robotic Actuation

In perfluorinated sulfonic acid polymers, there are relatively few fixed ionic groups. They are located at the end of side chains and demonstrate a preferred orientation. Therefore, they can create hydrophilic nano-channels, so-called *cluster networks* [27]. Such configurations are drastically different in other polymers such as styrene/divinylbenzene families that primarily by cross-linking limit the ability of the ionic polymers to expand due to their hydrophilic nature. Cations attract water molecules, causing them to separate from the polymer backbone charged pendant groups, thus expanding the network. Once an electric field is imposed on a network, the conjugated and hydrated cations rearrange to accommodate the local electric field, resulting in network deformation (Fig. 7.12).

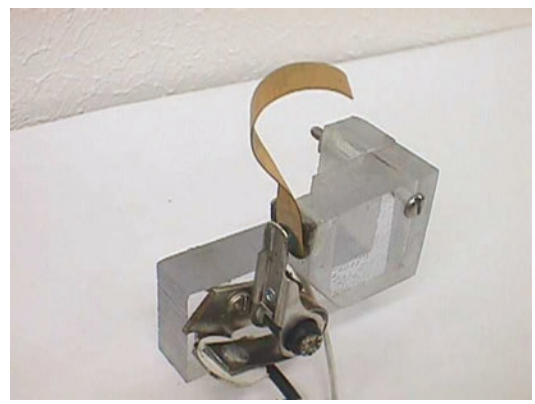

Fig. 7.12 Asymmetric twisting and bending of IBPMC strip (10 × 80 × 0.2 mm)

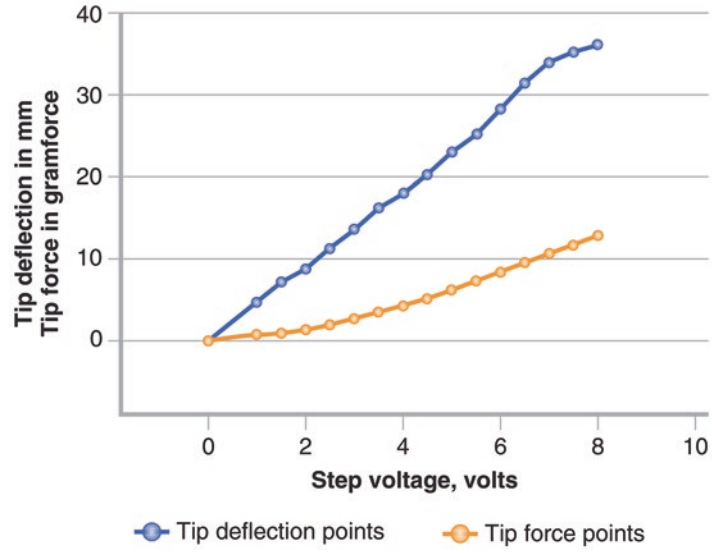

Fig. 7.13 Variation of tip blocking force and the associated deflection if allowed to move versus the applied step voltage for a 1×5×0.3 mm IPMNC Pt-Pd sample in a cantilever configuration

Once an electric field is imposed on an IPMNC cantilever, in the cantilever polymeric network, the hydrated cations migrate to accommodate the local electric field. This creates a pressure gradient across the thickness of the beam; thus the beam undergoes bending deformation. Figure 7.13 depicts typical force and deflection characteristics of cantilever samples of IPMNC artificial muscles.

Distributed Nanosensing and Transduction

Shahinpoor, Kim, and Mojarrad [25] have reported on sensing and transduction properties of ionic polymer conductor composites. Typically, flexing of IBPMC strips in a cantilever form sets them into a damped vibration mode that can generate a similar damped signal in the form of electrical power (voltage or current) as shown in Fig. 7.14.

As far as force generation is concerned, IBPMCs generally have a force density of about 40 [15]. This means that in a cantilever configuration, they lift 40 times their own weight.

Modeling and Simulation of IBPMCs

de Gennes et al. [28] presented the first phenomenological theory for sensing and actuation in ionic polymer metal composites. Asaka and Oguro [29] discussed the bending of polyelectrolyte membrane-platinum composites by electric stimuli and presented a theory on actuation mechanisms in IBPMC by considering the electroosmotic drag term in transport equations.

To summarize the underlying principle of the IBPMC's actuation and sensing capabilities, it can be described by the standard Onsager formulation using linear irreversible thermodynamics. When *static conditions* are imposed, a simple description of *mechanoelectric effect* is possible based upon two forms of transport: *ion transport* (with a current density, $\underset{\sim}{J}$, normal to the material) and *solvent transport* (with a flux, $\underset{\sim}{Q}$, *we can assume that this term is water flux*). The conjugate forces include the electric field, $\underset{\sim}{E}$, and the pressure gradient, $-\underset{\sim}{\nabla} p$. The resulting equation has the concise form of,

$$J(x,y,z,t) = \sigma \underset{\sim}{E}(x,y,z,t) - L_{12} \underset{\sim}{\nabla} p(x,y,z,t) \qquad (7.15)$$

$$\underset{\sim}{Q}(x,y,\mathrm{zt}) = L_{21}\,E(x,y,z,t) - K\nabla\,\underset{\sim}{p}(x,y,z,t) \qquad (7.16)$$

where σ and K are the material electric conductance and the Darcy permeability, respectively. A cross coefficient is usually $L = L_{12} = L_{21}$. The simplicity of the above equations provides a compact view of the underlying principles of actuation, transduction, and sensing of the IPMNCs. The value of the Onsager coefficient L is of the order of 10^{-8} m^2/V-s. Other parameters have been experimentally measured to be $K \sim 10^{-18}$ m^2/CP (centipoise), $\sigma \sim 1$ A/mV or S/m, where S/m is Siemens per meter.

In conclusion, IBPMCs may function as multifunctional smart materials with distributed nanosensing, nanoactuation, and nanotransduction capabilities for possible use in lower extremity prosthetic devices and systems.

Chitosan-Based Biopolymers as Multifunctional Biomaterials

Chitosan is a multifunctional biopolymer derived from exoskeletons of shellfish and marine invertebrates such as shrimp, crabs, and lobsters [30–32]. It shows promise for development into artificial muscles for lower extremity prosthetics.

Chitosan is derived from deacetylation of chitin, the abundant natural polysaccharide found in the exoskeleton of crustaceans. It is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). Figure 7.15 displays the general molecular structure of chitosan.

To manufacture chitosan, chitin is N-deacetylated by treatment with a 45% NaOH solution, followed by purification procedures.

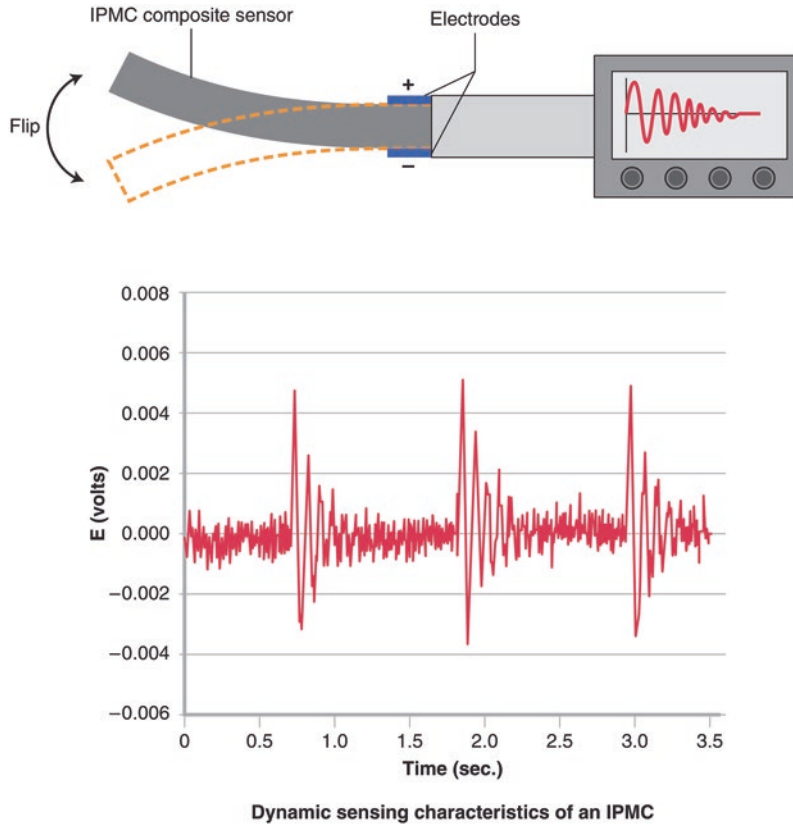

Fig. 7.14 A typical sensing configuration (*top*) and voltage response of an IBPMC strip (10 × 40 × 0.2 mm) under oscillatory mechanical excitations (*bottom*)

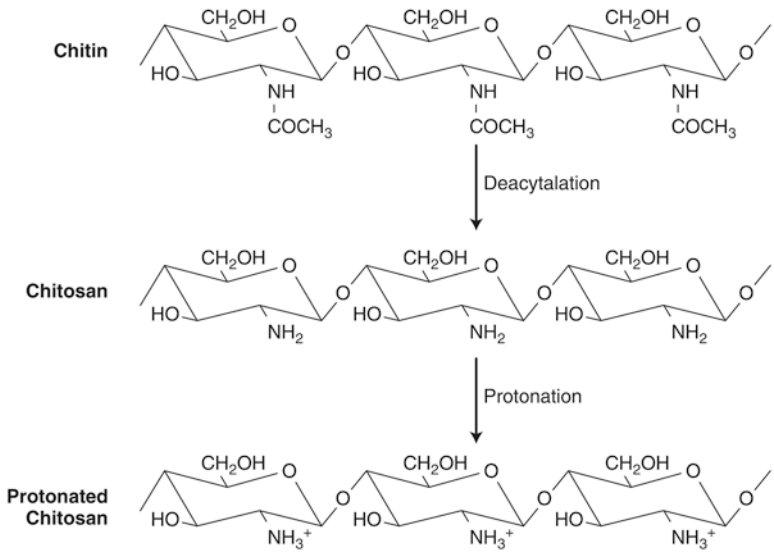

Fig. 7.15 Molecular structures of chitin, chitosan, and protonated chitosan [32]

The protonatable amino groups formed render chitosan a cationic polymer, which can be formed into gels with polyanions. Molecular weight and degree of N-deacetylation are important determinants of chitosan properties. Chitosan molecules have a rodlike or coiled shape at low degrees of deacetylation, due to the low charge density of the acetylated polymer chain, and an extended and flexible chain at high degrees of deacetylation where charge repulsion dominates. Chitosan is an ionic polyelectrolyte; its solution is viscous and electrically conductive, like that of many other biological molecules such as DNA. Polyelectrolyte hydrogels such as chitosan undergo reversible deformation in response to external stimuli such as electricity.

Response rate and concomitant force produced are mainly determined by the structural design of the chitosan polymeric composite. Compared to other polymers such as IBPMCs, conductive polymers, and electrostrictive polymers used in artificial actuators, chitosan-based hydrogels are more similar in their physical constitution to soft tissues, but they exhibit slower response and smaller actuating force. In its favor, chitosan has very good biocompatibility and is non-cytotoxic with antibacterial properties. Although chitosan artificial muscles cannot currently match the real muscle in terms of range of motion, strength-to-weight ratio, and speed of response, there is a potential for applications to lower extremity gait devices and systems in the future as research continues. A recent development to increase the load carrying capacity of chitosan created a composite of chitosan and IBPMCs, as reported by Shahinpoor [30–32]. Based on these new developments, it is anticipated that more chitosan-based intelligent biopolymers will become commercially available for biomedical and industrial applications in the near future.

This chapter concludes with a brief discussion of other possible synthetic multifunctional materials for lower extremity orthotics and prosthetics. The reader is also referred to a number of other intelligent, multifunctional materials not explored here but certainly appropriate as artificial muscles, sensors, and actuators (Shahinpoor and Schneider [33]).

Conclusions

The applications of smart materials, electroactive artificial muscles, and in particular contractile artificial muscles show great promise for lower

extremity prosthetics. Many muscles in the leg such as the hamstring, the quadriceps, the calves, and the tibialis anterior essentially operate by antagonist contractions and thus are contractile. Additional research and development will determine the best approach for the multiplicity of requirements needed to substitute for human muscular function. This chapter considered a number of multifunctional smart biomaterials and artificial muscles that could be considered for use in lower extremity prosthetics, including chemomechanical polymeric contractile artificial muscles, electrochemically controllable polyacrylonitrile (PAN-C and PAN-G) artificial muscles, and ionic biopolymer metal nanocomposites (IBPMCs). Electrical activation of C-PAN artificial muscles is demonstrated by increasing the conductivity of PAN artificial muscles. The conductivity of PAN is increased by either depositing a coat of metal on the fibers or interweaving it with conductive fibers such as graphite fibers (PAN-G). Electrochemical reactions are used to generate hydrogen ions or hydroxyl ions for contraction and elongation. Therefore, by increasing the conductivity of activated PAN, a PAN-based linear actuator can be electrically activated in an antagonistic manner potentially suitable for industrial and medical applications. Increasing the conductivity of PAN fibers by making a composite of them with a conductive medium such as platinum, gold, graphite, carbon nanotubes, grapheme, and conductive polymers such as polyaniline or polypyrrole has been shown to allow for electric activation of PAN fibers when a conductive polyacrylonitrile (C-PAN) fiber bundle is placed in a chemical electrolysis cell as an electrode. Typically, close to 50% change in C-PAN fiber length in a few seconds is observed in a weak electrolyte solution under some 10 s of volts.

In order to decrease the response time of C-PAN, polyacrylonitrile-nanofibers (PAN-N) were also successfully fabricated by the electrospinning method. As expected, the response time of C-PAN is governed by the diffusional processes of ions/solvents interaction. The use of such PAN-N is promising for fabricating fast-response PAN artificial muscles.

Experimental results have demonstrated great potential in developing fast-activating C-PAN-G muscles and linear actuators, as well as integrated pairs of antagonistic muscles and artificial muscle sarcomere and myosin-/actin-like assembly.

Finally, smart chitosan-based biomaterials were evaluated as multifunctional materials. The convergence of scientific disciplines in the area of smart materials for prosthetics provides hope for amputees of all ages and capabilities – soldiers and civilians alike – that limb loss need not mean the loss of crucial capabilities.

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Volitional Control Research

8

Levi Hargrove

Abbreviations

DBN	Dynamic Bayesian network
DOF	Degree of freedom
EMG	Electromyographic
Hz	Hertz
LIFEs	Longitudinal intrafascicular arrays
TMR	Targeted muscle reinnervation

Introduction

The quest for intuitive methods to control upper and lower limb assistive devices is a rich and diverse field of research. To achieve their full capabilities, assistive devices must respond predictably and reliably to the user's intentions. It is not especially difficult to infer the intentions of able-bodied individuals by measuring their movements and interactions with instruments and the environment. However, it is very difficult to predictably and reliably decode the intentions of those with neuromuscular impairments. It is impossible to measure the movement of an amputated limb; instead, we must infer the intentions of an amputee by measuring and decoding neural signals.

The focus of this chapter is volitional control, defined as voluntary control of an assistive device through a seamless combination of neural signals and mechanical interaction with a device. Much of the available literature in this area stems from a decades-long history of research and clinical effort to control upper limb prosthetic devices. More recently, technological advances have expanded the field to include control of computerized leg prostheses and exoskeletons. The chapter provides a brief introduction to upper limb myoelectric control and targeted muscle reinnervation, followed by consideration of myoelectric control of lower limb prosthetics, and finally a review of emerging technologies that may soon have dramatic impacts on the field.

Introduction to Upper Limb Myoelectric Control

Upper limb prostheses fall into three categories: cosmetic, body powered, and externally powered devices. Cosmetic devices mimic the shape and

L. Hargrove, PhD (✉)
Shirley Ryan AbilityLab, Center for Bionic Medicine, Chicago, IL, 60654, USA
e-mail: l-hargrove@northwestern.edu

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appearance of the lost limb and are usually worn for aesthetic reasons; they do not provide much functional capability to interact with objects. Body-powered prostheses are controlled by harness and cable systems that transmit mechanical motion or forces generated by movements of the user's body. Electrically powered devices use battery-powered motors. They can also look very cosmetically appealing, but successful operation of such devices requires an intuitive control method. Most frequently, this is achieved by decoding neural information from electromyographic (EMG) signals.

Conventional Methods to Control Upper Limb Prosthetic Devices

Each time a muscle contracts, even if it is damaged or partially missing due to amputation, ionic currents within the muscle body create electrical potential differences (EMG signals) that can be measured using electrodes [1]. For many decades, it has been possible to control upper limb prostheses using neural information extracted from EMG signals. The conventional method of control is to place electrodes over a pair of agonist/antagonist muscles and use estimates of EMG signal amplitudes to control opposing movements of a prosthesis [2]. Such systems work best, and feel most intuitive, if physiologically appropriate muscles are available; for example, using an EMG signal from the biceps to control elbow flexion and an EMG signal from the triceps to control elbow extension. This type of control requires that the antagonistic muscles contract independently and that the EMG signals are not contaminated by cross-talk (EMG signals from other muscles). Unfortunately, high-level upper limb amputees have very few suitable muscles remaining. Thus, most conventional amplitude-based control methods are limited to a single degree of freedom (DOF).

Overview of Pattern Recognition Myoelectric Control

Pattern recognition-based control is an alternative to conventional control methods. Rather than mapping the EMG signal from a single muscle to the movement of a prosthetic device, pattern recognition technology identifies patterns across a set of EMG signals from several muscles. The identified patterns are then mapped to device movements, allowing for control of more DOFs. As independent muscle contractions are not required, and cross-talk is merely part of the EMG pattern, pattern recognition places fewer restrictions on electrode placement. This is especially applicable to transradial amputees who often have significant remaining musculature on the residual limb [3]. Pattern recognition relies on machine learning algorithms that identify and label patterns from a set of "training" data. It is therefore important that the patient be able to generate consistent EMG signals for reliable prosthesis control [4].

Many decades of research have identified several feature sets and classifiers that provide excellent classification accuracy for many movements. A feature set is some statistical descriptor of the EMG signals, for example, the mean absolute values of the signals over a given time window. A classifier is created using machine learning techniques to assign characteristic features to corresponding specific movements. More recently, studies have focused on quantifying control improvements when using pattern recognition during functional tasks [5] and in the home (vs. controlled laboratory) setting [6]. During these experiments, patients are trained by therapists to use their prosthesis to complete activities of daily living such as opening cupboards or manipulating objects. These activities require significant movement planning and coordination, even with unimpaired body systems, and so are often more difficult than completing more limited tasks and experiments within a laboratory

environment. For example, when pouring water into a glass, a unilateral amputee must control both the prosthesis and the contralateral (intact) limb. Pattern recognition myoelectric control is now commercially available as a clinically viable alternative to conventional control methods.

Introduction to Targeted Muscle Reinnervation

EMG signal measurement is required for either conventional or pattern recognition control. For low-level amputation, (e.g., transradial level), the residual musculature is sufficient to generate EMG signal patterns for a variety of movements. At higher levels of amputation, physiologically appropriate muscles may be missing. This is often referred to as the myoelectric control paradox: the individuals in greatest need of functional improvement also have the fewest remaining muscles to provide control information.

A solution to this problem is through a surgical technique known as targeted muscle reinnervation (TMR) [7]. In the TMR procedure, nerves that originally innervated the amputated limb are transferred to muscles that are rendered biomechanically nonfunctional by the amputation (Fig. 8.1a). Following the procedure, nerves reinnervate these "target" muscles, which then generate EMG signals, amplifying the neural signals carried by the redirected nerves [8]. The technique has been performed successfully in labora-

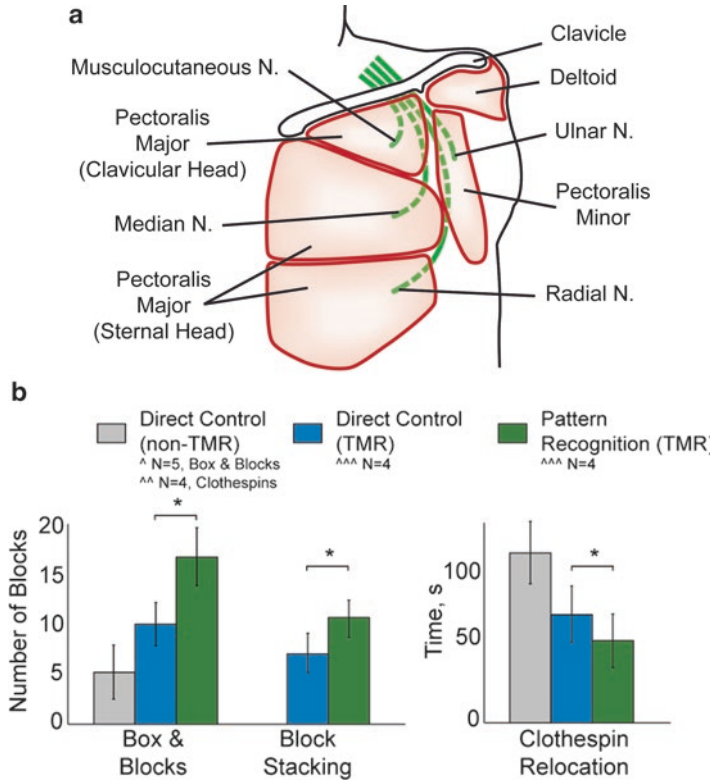

Fig. 8.1 (**a**) Schematic depiction of targeted muscle reinnervation for a shoulder disarticulation amputee. The surgery divides the pectoralis muscle into four segments, which are separately reinnervated by transferred nerves to create independent sites for prosthetic control (Reprinted from Kuiken et al. [55] Copyright (2007) National Academy of Sciences, U.S.A.). (**b**) Targeted muscle reinnervation provides significant and clinically relevant control improvements when used with conventional amplitude control. TMR provides additional improvements when used with pattern recognition (Modified from L. Hargrove et al. [5]. © [2013] IEEE)

tory and clinical settings around the world. A key benefit of TMR is that it creates at least four independent and physiologically appropriate control sites for high-level amputees, who can then be fitted with and operate commercially available arm systems.

A secondary outcome of TMR, through reinnervation of skin over the target muscles by transferred sensory afferents, is restoration of a physiologically and anatomically appropriate sensory pathway that allows subjects to accurately discriminate pressure and temperature [9]. When appropriate locations on the reinnervated skin are stimulated, patients can consistently and reliably map the sensation to specific locations on the missing limb. In theory, this means a sensor can be placed on the prosthesis to control a mechanical actuator, called a tactor, which touches the patient's reinnervated skin and generates sensation that is perceived to come from the prosthesis. Although this technology has been tested successfully in laboratory settings, challenges associated with placement of the tactor within a socket have thus far prevented incorporation of this technology into patients' daily-use prostheses.

TMR is very synergistic with pattern recognition technology. Transferred nerves carry rich neural information, including control information for intrinsic hand muscles, that can be decoded using EMG pattern recognition [8]. More than 16 different movements, including wrist movements and hand-grasp patterns, can be classified with accuracies greater than 95%. More importantly, TMR subjects demonstrate improved functional control when using pattern recognition control vs. conventional control (Fig. 8.1b) [5]. When compared to functional performance prior to TMR surgery [10], the results are very compelling.

To date, TMR has been used primarily with high-level upper limb amputees; however, individuals with transradial amputation may also be well suited for TMR. Transradial amputation often leaves significant residual limb musculature, but control information for intrinsic hand muscles is carried by severed nerves and thus is inaccessible. Restoration of this neural information through TMR may allow for better control of multiple DOF hand prostheses, but selection of the most appropriate target muscles for nerve transfer is challenging.

While TMR offers many benefits, it does not provide an obvious mechanism to restore proprioception. As a result, the user must still rely on visual information to determine where the prosthetic limb is positioned in space. This is in contrast to individuals with intact limbs, who are aware of their limb position even when their eyes are closed. Restoration of proprioceptive feedback in TMR patients will likely require stimulation of the peripheral or central nervous system.

Neural Control of Lower Limb Prostheses

EMG signals are often characterized as having Gaussian or Laplacian-like distributions, in which the variance of the signals is proportional to signal amplitudes [1]. For sustained contractions, the signal may be considered stationary until muscles fatigue, causing signal changes. This property is exploited for both conventional and pattern recognition control of upper limb prostheses. Stationary EMG signals are also appropriate for controlling powered lower limb prostheses in non-weight-bearing situations, e.g., when the user wants to reposition the limb for comfort or to prepare for a difficult transfer. However, during ambulation, EMG signals are non-stationary and quasi-cyclic. Thus, techniques previously developed for controlling upper limb prosthetic devices must be modified to control a powered leg during ambulation. In addition,

recording EMG signals during ambulation requires modification of the user's socket to incorporate electrodes, which remains one of the most challenging aspects of creating a clinically viable volitional control system.

Measuring EMG Signals from the Lower Limb

To obtain high-quality EMG signals, electrodes must maintain good contact with the user's skin. This is accomplished by minimizing the movement of the socket with respect to the patient's skin and underlying residual muscles. It is critical that the EMG signal measurement system neither impair the suspension of the prosthesis nor compromise the skin of the residual limb. In addition, the EMG measurement system should be comfortable when worn for long durations. Clearly, it is a considerable challenge to achieve all of these requirements.

One method to collect EMG signals is to embed stainless steel dome-shaped electrodes into the walls of a well-fitting suction socket [11]. Suitable electrode locations can be identified by palpation, marked on the patient's residual limb using an indelible marker and verified using adhesive electrodes. The patient then dons a transparent diagnostic socket, and the selected locations are marked onto the prosthetic socket. Holes are drilled at these locations and electrode domes are inserted through the socket wall. To maintain suction, it is important to seal the socket around the electrodes using, for example, silicon putty. If the electrodes maintain good skin contact and do not irritate the patient's residual limb during ambulation, a durable permanent socket can then be created (Fig. 8.2a–c).

The EMG measurement system described above has been very successful for transfemoral amputees, who often have a large amount of adipose tissue, resulting in a very compliant socket/

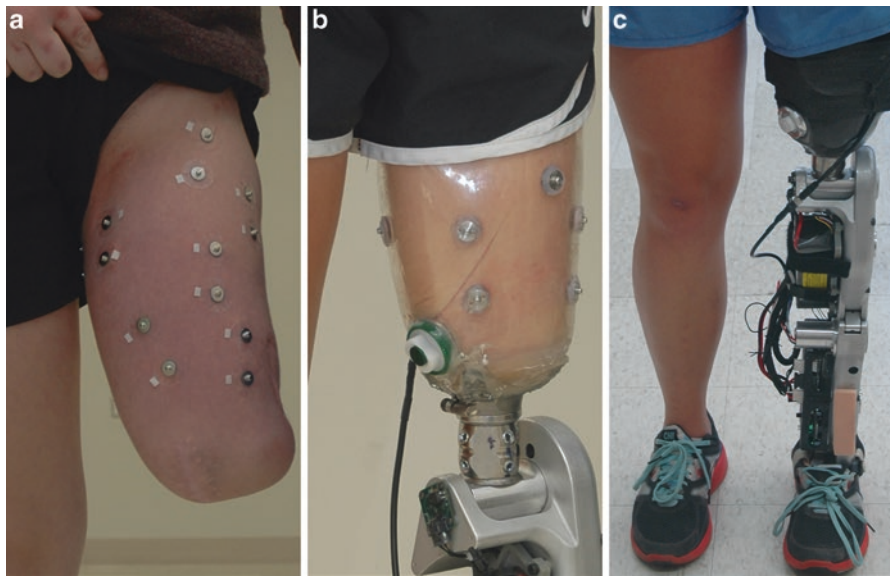

Fig. 8.2 (**a**) Suitable electrode locations are identified by palpation and verified by adhesive electrodes placed on the skin (Reproduced from [22]; © Hargrove et al.; Licensee BioMed Central Ltd. 2013). (**b**) Electrode locations are transferred onto a clear diagnostic socket (Reprinted with permission from Journal of NeuroEngineering and Rehabilitation). (**c**) A permanent EMG socket, with embedded electrodes, being worn by a user

residual limb interface. However, many amputees, especially transtibial amputees who have a much less compliant socket/residual limb interface, choose to wear a gel liner or sock to enhance their comfort. In this case, textile-based electrodes constructed from a silver-coated fabric may be used. This type of electrode is not as rigid as a stainless steel dome and so does not apply as much pressure at the point of contact on the residual limb. If the liner is carefully constructed, it will maintain suction without interfering with the suspension of the socket [12].

Before EMG signals are transferred to the microprocessor that contains the volitional control algorithms, raw signals must be amplified, filtered, and digitized. Surface EMG signal amplitude is usually recorded in millivolts (mV), and it is very common to use a differential amplifier with a gain in the range of 1,000–5,000. Because high accelerations occur at certain moments during ambulation, such as when the leg swings or makes contact with the ground, there may be considerable movement artifact that corrupts the EMG signals. Movement artifact is a major source of electrical noise, whether caused by movement of electrode lead wires or by movement of the skin with respect to the electrode or the underlying muscle. Careful management of the lead wires and a properly fitting socket/liner are usually sufficient to alleviate the first two sources of noise; however, it is very difficult to prevent movement of the underlying muscle with respect to the skin. Additionally, a significant degree (in the order of centimeters) of movement ("pistoning") between the residual limb and socket is known to occur during dynamic activities, even when well-fitting sockets are properly donned [13]. Generally, high-pass filtering is recommended to reduce motion artifact [14]. The corner frequency of the high-pass filter is specific to the muscle and application; for this application, a corner frequency of 30–50 Hz is reasonable. Finally, the signal must be digitized and sent to the microprocessor. An analog-to-digital converter of 12–16 bits is sufficient, provided that the amplifier gain has been properly set; a sample frequency of 1,000 Hz is often employed to capture the useful spectrum of EMG [15]. If the microprocessor is co-located with the EMG acquisition system, then it is relatively straightforward to incorporate the EMG information into the volitional control algorithms. Otherwise, an efficient communication bus with as few wires as possible should be used [16].

Non-weight-bearing Independent Control

As described above, non-weight-bearing situations are ideally suited for EMG control. For example, the user may wish to reposition the prosthesis while dressing or preparing to transfer into or out of a car, or simply to allow for a more comfortable sitting position. Researchers have proposed using EMG pattern recognition to volitionally control knee movements for a transfemoral prosthesis and noted high classification accuracies for knee flexion and extension [17, 18]. Other signal processing techniques such as Kalman filtering have been proposed to track knee movements using surface EMG signals measured from the thigh muscles [19]. While promising, these early studies were somewhat limited because they used non-amputee subjects and did not consider control of ankle movements. Ha et al. [20] have shown that, within a knee impedance paradigm, EMG signals from the quadriceps and hamstrings could be reliably decoded using pattern recognition-based quadratic discriminant analysis to position an amputee's virtual knee. In this approach, the knee joint was modeled as a virtual spring-damper system to determine how the device responds to forces imparted by the user or the environment. As an analogy, consider a bed

mattress with a foam layer on top. The bed may feel hard or soft depending on what type of springs are used in its construction and the thickness of the foam layer. Using motors, a high-fidelity virtual spring-damper system could change the stiffness (the springiness) and the damping (the thickness of the foam layer) very quickly, so the prosthesis can feel very stiff while walking, or very compliant while lowering the user down a set of stairs. The pattern recognition system generates an estimate of the angular velocity of the intended movement. The spring stiffness and damper values are tuned empirically, and the angular velocity is integrated to estimate the equilibrium position. In this paradigm, a change in equilibrium position creates a torque command that causes movement at the knee joint. Although subjects could accurately track a position command in a virtual environment, this approach was not implemented on a powered prosthesis, and ankle movements were not considered.

Using an approach similar to Ha et al. [20], we have shown that both knee and ankle movements can be accurately decoded using EMG signals measured from the residual muscles of transfemoral amputees [21]. However, in this case, additional above-knee residual limb muscles were used together with a linear discriminant analysis pattern classifier. Once again, an impedance control framework was used, this time to independently control a virtual knee and ankle. This control system was implemented on a powered knee prosthesis with real-time feedback, and subjects showed strong potential for ankle control [22]. Transfemoral amputees could control ankle movements without having had TMR surgery, a somewhat surprising result since the primary muscles used to control the ankle are located below the knee. Our interpretation is that the subjects employed intuitive co-activation strategies that were identified by the pattern recognition control system.

Control During Ambulation

It is likely that improved control during ambulation will provide more substantial benefits than improved non-weight-bearing control. During ambulation, the prosthesis and user must work synergistically. Regardless of activity, the user relies on the prosthesis to bear his or her weight during the stance phase of gait and expects that the foot will clear the ground in swing phase. Improper operation may lead to falls and potentially serious injuries. Consequently, any system that incorporates volitional control must use a method that is very safe, predictable, and robust.

Direct Estimation of Joint Torques EMG signals can also be used to estimate the net torque generated at a joint [23] or the impedance of the joint [24]. This approach has been used with a transfemoral amputee to directly control the impedance of a powered knee prosthesis during level-ground walking and during stair ascent [25]. Despite the absence of proprioceptive feedback, net torque control provided consistent and repeatable performance after a training period. It is unlikely that this approach will be generalized to transfemoral amputees without surgical intervention such as TMR. However, EMG signals from the gastrocnemius have been used to help transtibial amputees control powered plantar flexion [26]. While the required torque could easily be generated using an alternative method, qualitative feedback from users indicates that they experience an enhanced feeling of being in control of the device when using EMG.

For individuals with intact but impaired limbs, such as hemiparetic stroke survivors, direct estimation of torques across multiple joints (i.e., knee and ankle) may be more feasible. The style of volitional control best employed depends on whether the treatment goal is to restore functional movement or to promote rehabilitation. For example, if not challenged appropriately by a robotic orthosis, humans tend to "slack" and rely on the device rather than gener-

ating the natural joint torques required for movement [27]. Direct control of joint torque in proportion to generated EMG signals would encourage wearers to contract their muscles, which in turn would promote positive functional and therapeutic benefits.

Pattern Recognition Ambulation Mode Recognition Rather than directly estimating the torque generated by each joint, it is possible to instead estimate what ambulation activity the user is attempting to perform. For example, by interpreting patterns in the EMG signals, it is possible to determine if a user is walking, navigating stairs, or performing another ambulation activity. To accomplish this, pattern recognition strategies that have been used to control upper limb prostheses must be modified to accommodate non-stationary signals and to take advantage of the cyclic nature of gait.

Huang et al. used a mechanical sensor (a load cell) within a prosthesis to determine when a prosthetic foot hit or was lifted off the ground [28]. An EMG pattern recognition system trained to recognize several ambulation activities at these discrete gait phase points was found to have error rates of approximately 10%. This work was extended by segmenting gait into a number of phases such that EMG signals were continually classified to predict ambulation activities. The information within the EMG signals was found to complement information measured from additional mechanical sensors placed on the prosthesis [29]. Such systems are well suited to accommodate non-stationary signals during ambulation but do not take advantage of the time-history information available in gait.

There are several methods available to incorporate time history into a pattern recognition system. The majority voting (median filter) method employs a buffer of previous pattern recognition decisions kept in memory [30]; the decision that occurs most frequently in the buffer is selected as the predicted ambulation mode. This method is computationally simple and is good for smoothing spurious misclassifications; the drawback is that it tends to cause unacceptably long delays, especially when transitioning from one activity to another. Bayesian statistical methods can also be used to incorporate time-history information. Young et al. [31] tested a Dynamic Bayesian Network (DBN) classification strategy to incorporate prior sensor information, measured over the gait cycle, with current sensor information. When tested in six transfemoral amputees, this computationally efficient method significantly outperformed a system without time history and a system using majority vote (Fig. 8.3).

Use of residual limb EMG significantly reduces ambulation mode misclassifications for transfemoral amputees [32, 33]. Studies have also shown that it is certainly possible, though perhaps unnecessary, to predict activities using EMG signals in transtibial amputees where the intact knee remains under voluntary control [34, 35]. Finally, EMG signals are sensitive to a number of variables such as electrode positioning, skin electrode impedance, and muscle fatigue. These variables change over time; consequently, the performance of the control system may deteriorate [36]. Thus, a method of adapting the control system to accommodate these changes is needed before a viable EMG pattern recognition system can be clinically implemented. This is an ongoing area of research for both upper and lower limb EMG-based control systems.

Targeted Muscle Reinnervation for the Lower Extremity

TMR has been performed on several lower limb amputees as it appears to be an excellent clinical treatment for painful amputation neuromas [37]. Cadaver studies have shown that the sciatic nerve may be easily segmented into the tibial and common peroneal branches and coapted onto avail-

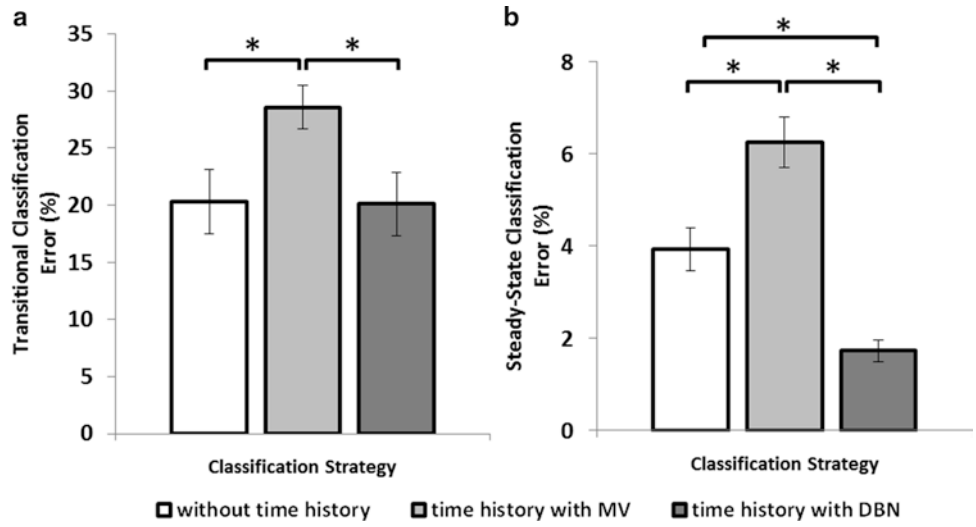

Fig. 8.3 The ambulation mode prediction error rate (**a**) for transitions between ambulation modes and (**b**) during steady-state activity. The delay imposed by majority voting appears to increase error in both cases. The improvement provided by incorporating time history through the DBN provided significant improvements in the steady-state error rate [31]. (Reprinted with permission from Springer)

able donor motor points on the semitendinosus or the long head of the biceps femoris [38].

This surgery was successfully performed on a knee disarticulation amputee (Fig. 8.4). EMG patterns were then evaluated through high-density EMG, and the patient's ability to control a virtual leg prosthesis and a robotic leg prosthesis was determined [39]. The results indicated that the TMR subject had better control than did non-TMR subjects, especially when controlling four DOFs within a virtual environment (Fig. 8.5). Qualitatively, we noted that the TMR subject had much better control over a physical prosthesis than did the non-TMR subjects. The error rate of the DBN-based ambulation mode selection was found to be 1.7% for the TMR patient when ambulating over level ground, up and down slopes, and up and down stairs. This error rate is slightly lower than the error rates achieved by non-TMR subjects using the same type of control system for the same modes [31]. TMR thus may provide some improvement in neural control for lower limb prostheses, but more work is required to determine if this is clinically beneficial. TMR may also allow extension of the method proposed by Hoover et al. [25] to directly control knee and ankle impedances during ambulation or to modulate the amount of plantar flexion power as proposed by Wang et al. [26]. However, these ideas remain to be tested.

Emerging Technologies

Implantable EMG Recording Systems

An earlier section of this chapter highlighted many challenges associated with the efforts to collect surface EMG signals from lower limb amputees. To address these issues, several research groups have proposed implantable EMG recording systems [40, 41], which generally fall into one of two categories. One approach uses addressable, wirelessly powered, self-contained modules that are inserted directly into muscles of interest; EMG data are obtained by telemetry. The second type of system employs a

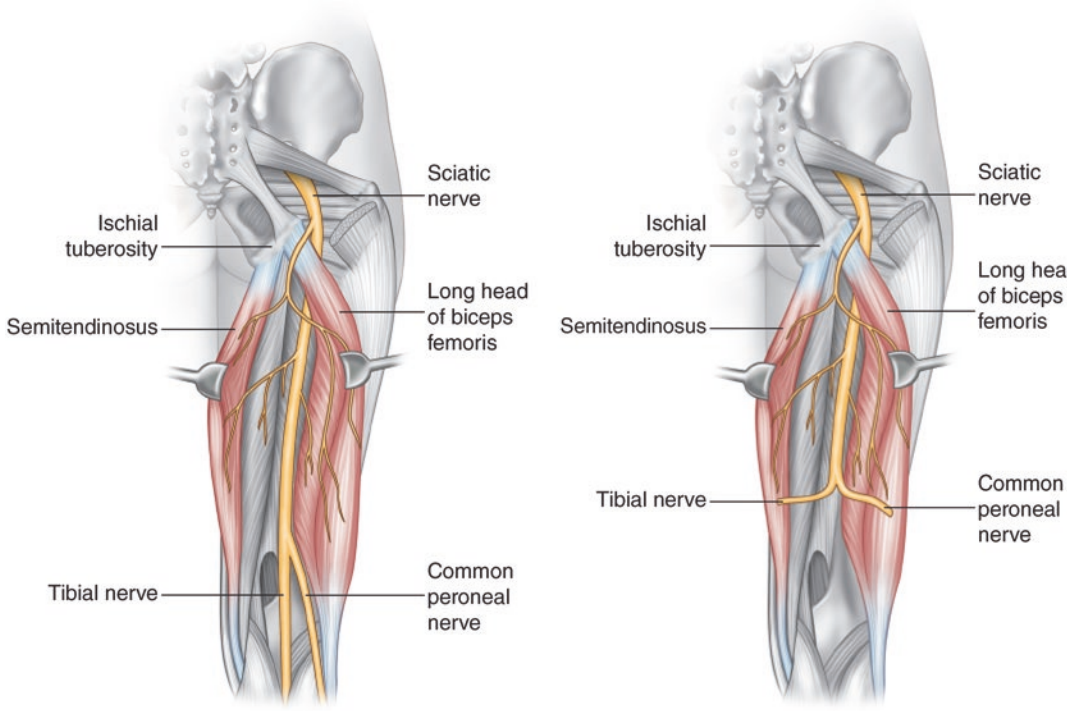

Fig. 8.4 Nerve-transfer surgery performed during a knee disarticulation amputation to restore ankle control information to the hamstrings muscles [39]. Severed branches of the sciatic nerve (*left*) are transferred to residual leg muscles (*right*)

wirelessly powered link to a central receiver that sits under the surface of the skin, from which lead wires are guided into the muscles of interest. Both of types of system would overcome issues associated with maintaining consistent electrode-skin contact. It is expected that a muscle implant will travel with the muscle when it contracts; thus, implantable EMG systems may also alleviate problems associated with movement artifact. Each approach offers benefits and introduces challenges. For example, self-contained modules do not have lead wires, which are often a source of failure in electronic systems; however, it is difficult to provide adequate wireless power to systems buried in deep muscle tissue. Wired systems are much more efficient at power coupling because the central receiver is located close to the skin's surface, but of course wired systems also raise the possibility of lead wire breakage.

An additional advantage is that intramuscular electrodes generally allow for more focal EMG readings with higher signal-to-noise ratios. As a result, the measured signals usually contain little or no muscle cross-talk. This should provide dramatic improvements for systems that attempt to directly control either joint impedances or joint torques.

Peripheral Nerve Recordings

In theory, it is possible to measure neural control signals directly from peripheral nerve fibers (vs. indirectly from EMG signals). However, nerve signals are more difficult to measure because they are an order of magnitude smaller than EMG signals. Consequently, an implantable system is used to measure the signals, with electrodes located within (intraneural) or directly

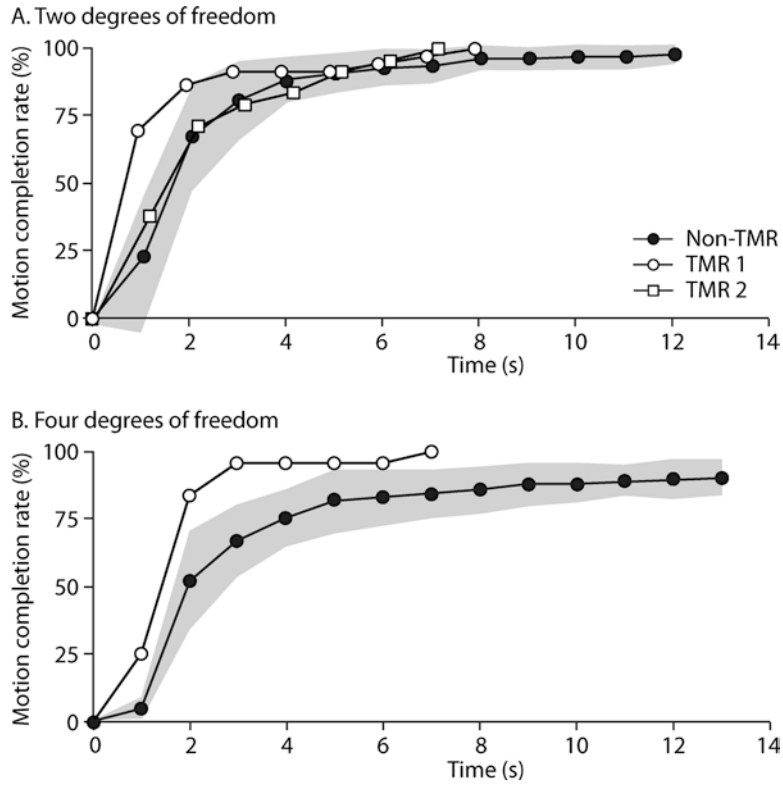

Fig. 8.5 Non-weight-bearing prosthesis control in a virtual environment by a TMR amputee and non-TMR amputee subjects ($n = 4$) (Reprinted with permission from Taylor and Francis Group)

adjacent (extraneural) to the nerve fibers. Extraneural electrodes, such as a nerve cuff electrode, have found chronic use in functional electrical stimulation (FES) systems [42]; however, it can be difficult to record from or to stimulate a single nerve fiber or bundle. In contrast, intraneural electrodes penetrate the nerve and allow for much more selective measurements. Examples of intraneural arrays include longitudinal intrafascicular arrays (LIFEs) and multielectrode arrays [43] (e.g., Utah Slant Array) [44] and sieve arrays [45]. These devices have been studied primarily using animal models, with limited human trials, yet show promise for bidirectional prosthesis control. Perhaps the most exciting aspect of these technologies is their potential to provide robust sensory feedback. Recently, upper extremity amputees have had multiple extraneural [46, 47] or intraneural [48] arrays chronically implanted to measure EMG from, or to stimulate, the median, ulnar, and radial nerves. A variety of stimulation waveforms were explored and resulted in the ability to elicit anatomically appropriate feelings of tapping, light pulsing, and pressure. Over the course of the study period (>250 days), sensory thresholds remained constant, indicating that the recording interface was stable.

Many issues need to be overcome before peripheral nerve recording technology is ready for widespread clinical deployment. When recording from a peripheral nerve proximal to the spinal cord, very selective measurements can be recorded, but it is difficult to identify targeted nerve fibers from the larger nerve bundle. As a result, a very dense multielectrode array with innovative signal processing will likely be needed for prosthetic device applications. The array will have to be compact because large multielectrode arrays introduce the risk of nerve damage by accidental nerve penetration, electrode movement, and annulus fibrosus [49].

Recording from the Brain

Various methods are available to record signals from the brain. These range from highly invasive methods that record signals directly from the primary motor cortex [50] to noninvasive methods that record electroencephalographic (EEG) signals from the surface of the scalp [51]. Because they are noninvasive, EEG signals have become an increasingly popular area of research for volitional control of assistive devices. High-density EEG, processed using independent components analysis, has been recorded from able-bodied control subjects in the gait phase cycle during walking [51]. Isometric and isotonic muscle contractions of the knee and ankle cause distinct EEG activation patterns when high-density measurements are processed using independent components [52]. EEG signals have also been used to control a robotic orthosis. In this work, a system was trained to discriminate between idling (e.g., standing) vs, walking on a treadmill. It was found that the intent recognition system was able to distinguish between these activities correctly with approximately 95% classification accuracy. Although promising, EEG recordings are easily corruptible by artifact and so require signal processing. Even eye blinks can cause detectable changes in EEG signals. Furthermore, though EEG recording systems are noninvasive, they are inconvenient and sometimes uncomfortable to wear. Thus it remains to be seen how well an EEG-based system will be tolerated by users and how well such systems will generalize to uncontrolled laboratory settings.

Perhaps the most impressive demonstration of control via brain recording was observed through processing of neuronal spikes measured directly from the primary motor cortex. In a study by Hochberg et al. [53], two tetraplegic subjects had a 4×4 mm, 96-channel microelectrode (Utah Array manufactured by Blackrock Microsystems) implanted in their dominant M1 hand area. After several practice sessions, a Kalman filter-based neural decoder was constructed to identify user intent from neural spikes recorded by the microelectrode array. The subjects were able to move a robotic arm volitionally and reliably around a workspace and to grasp and release objects. A similar study by Collinger et al. [54] also created a neural decoder from a 96-channel microelectrode array implanted in the primary motor cortex of a subject with tetraplegia. The neural decoder was based on a linear model that related neuronal firing rates to movement velocities and was used to control a robotic limb with seven DOFs. These preliminary results are very exciting; however, additional research is needed to determine the long-term viability and stability of the implanted recording electrodes.

Summary

Volitional control is an active but challenging field of research. Each of the diverse approaches described here has merits, limitations, and drawbacks; it is too early to predict which one, or several, approach will be most successful. Given the complexity of the challenge and the diverse needs and capabilities of the users who require lower limb assistance, a one-approach-fits-all solution is unlikely. However, one thing is certain—there will be enormous growth in this field of research in the upcoming years.

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Part II

Next Steps

Limb Amputation Versus Limb Salvage

9

Ellen J. MacKenzie and Michael J. Bosse

Introduction

High-energy lower extremity trauma is common in the military and civilian settings, the result of war-related trauma in the former and most often the result of high-speed motor vehicle crashes and industrial accidents in the latter [1, 2]. The clinical management of these injuries is fraught with challenges that include complex wound management, infection, bone loss, articular surface involvement, heterotopic ossification, segmental nerve loss, complete muscle tendon unit loss, and compartment syndrome [3–5]. Challenges in the acute phase of treatment are compounded by the needs that present in the post-acute and rehabilitation phases of recovery.

Significant advances made over the past 15–20 years in related medical and surgical subspecialties have drastically altered our ability to reconstruct severely injured lower extremities. Patients whose extremities would have been deemed "non-salvageable" and therefore amputated several decades ago are now routinely entered into lengthy limb reconstruction protocols. Concurrent with the development of limb salvage techniques has been the application of materials technology to the prosthetics industry. Prosthetic function and comfort have been significantly improved through bioengineering advances in below-knee and above-knee prosthetics made of strong, lightweight materials, designed to incorporate energy returning foot and ankle modifications. Now, near normal function is possible for many amputees. These advances in technology, along with reports of less than optimal outcomes following aggressive attempts at limb reconstruction, have created a therapeutic dilemma for the orthopedic surgeon. While now technically feasible in most cases, it has become increasingly apparent that limb salvage is not always advisable.

Since 1987 when Dr. Sigvard Hansen published an urgent plea for the development of treatment guidelines to avoid "… prolonged, costly and fruitless salvage procedures" [6], there have been several investigations to compare outcomes under amputation versus limb salvage sce-

E.J. MacKenzie, PhD (✉)
Johns Hopkins Blomberg School of Public Health, Health Policy and Management, Baltimore, MD, USA
e-mail: emackenz@jhsph.edu

M.J. Bosse, MD
Orthopaedic Surgery, Carolinas Medical Center, Charlotte, NC, USA
e-mail: mbosse@carolinas.org

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narios. Several attempts have also been made to define objective criteria to guide the decision of whether and when to amputate or reconstruct severely injured legs [7–10]. Most of this research is based on experience at civilian level I trauma centers. More recently, investigations in the military setting [11, 12] shed some new light on the results of earlier civilian studies. In this chapter, we review the current literature from civilian as well as military perspectives and discuss the factors that influence outcomes beyond the decision to amputate or reconstruct.

Comparing Limb Salvage and Amputation Outcomes

Several reviews of the civilian literature [7–10] point to limitations in study design due to small sample sizes, lack of generalizability beyond a single medical center, and inadequate control for factors that may influence the decision to amputate or reconstruct a severely damaged limb. Only one large, multicenter, prospective study has yielded level II evidence in the comparison of outcomes following amputation versus limb salvage.

The *Lower Extremity Assessment Project (LEAP)* [13] prospectively identified 545 adults aged 16–69 who were admitted to eight level I trauma centers and treated for a high-energy leg trauma below the distal femur. The study compared outcomes among those who underwent early amputation (n = 161) versus limb reconstruction (n = 384). High-energy limb trauma was defined as encompassing complex fractures (Gustilo Grade IIIB and IIIC fractures, selected Grade IIIA fractures), dysvascular limbs (i.e., knee dislocations, closed tibia fractures, or penetrating wounds with vascular injury), major soft tissue injuries (i.e., de-gloving or severe crush/avulsion injury), and severe foot and ankle injuries. Of the 545 patients enrolled in the study, 90% were followed for 12 months, 84% for 24 months, and 76% for 84 months.

The LEAP study found that after adjusting for differences in patient and injury characteristics, there were no differences in functional outcomes as measured using the Sickness Impact Profile (SIP). The SIP is a well-validated measure of self-reported difficulties across 12 categories of function in physical and psychosocial domains [14]. Outcomes for both groups were found to be poor on average, with little improvement and in some cases worsening of outcomes at 7 years [15]. The mean SIP score at 24 months was 12.0 and 42% of patients had SIP scores greater than 10, a value widely thought to represent significant disability. Further, only 51% of those employed before the injury had returned to work [16]. At 24 months post-injury, 42% screened positive for a likely psychological disorder (as measured by the Brief Symptom Inventory) [17]; 37.6% reported symptoms of depression [18]. Although the LEAP study did not specifically screen for posttraumatic stress disorder (PTSD), 29.4% of patients in the study reported symptoms of generalized anxiety at 2 years post-injury. There was no group (amputation versus reconstruction) difference in the prevalence of psychological symptoms.

A subgroup of LEAP study patients who sustained severe hindfoot or ankle injuries had particularly poor outcomes. Salvage patients requiring a free flap or ankle arthrodesis experienced significantly worse SIP outcomes when compared to patients who underwent transtibial amputation [19]. While the number of patients represented in this subordinate analysis was small (58 amputations and 38 salvage patients), their results are in line with the belief held by many surgeons that for some patients with severe distal tibia and hindfoot injuries, transtibial amputation may provide better long-term functional outcome than limb salvage. More research is needed to determine the injury burden break

point that would allow us to identify individual patients who would fare better with amputation after severe distal tibia, ankle, and/or foot injuries with major soft tissue, bone, or ankle joint articular surface loss.

Although the LEAP study revealed few discernible differences in functional outcomes, patients who underwent reconstruction were more likely (48%) than their amputee counterparts (34%) to be rehospitalized for a major complication within 2 years [20]. Among patients who received limb salvage treatment, only 3.9% went on to have a late amputation. Although rehospitalizations for limb-related complications add significantly to the healthcare costs for patients who undergo reconstruction, total 2-year costs in this study were higher for amputation patients ($91,105) versus limb salvage patients ($81,316) due to the additional costs associated with purchase and maintenance of prosthetic devices [20]. Given the need for ongoing prosthetic care and a new prosthesis every 2 or 3 years, these differences will naturally tend to increase over the course of the amputation patient's lifetime. Total projected lifetime healthcare costs for patients undergoing amputation ($509,275) were more than three times higher than for patients undergoing reconstruction ($163,282).

The findings of the LEAP study add support to the argument that reconstruction of a lower extremity severely injured below the distal femur is a reasonable goal at an experienced level I trauma center and that this approach will reduce lifetime healthcare costs. At the very least, it is clear that direct costs per se should not be used as rationale to deny the opportunity for limb reconstruction. The LEAP study results have been bolstered by a formal cost-utility analysis of amputation versus limb salvage, suggesting that limb salvage is the dominant cost-saving strategy [21].

What is also clear from the civilian literature is that recovery is challenging for amputation and limb salvage patients alike and that outcomes are often more affected by economic, social, and personal factors than by initial surgical treatment or extent of residual impairment [22]. Figure 9.1 provides a framework for summarizing some of these factors and their relationships to patient outcomes. These relationships are complex but it is increasingly clear that long-term functional outcome and quality of life after major limb trauma are adversely affected by early complications and by pain and psychological sequelae such as depression, anxiety, and posttraumatic stress. What we also know, however, is that high self-efficacy, good coping strategies, and robust social support networks can mediate the impact of these secondary conditions. In particular, self-efficacy was found to be one of the strongest determinants of good outcome in the LEAP study. Self-efficacy refers to an individual's confidence in being able to perform specific tasks or activities. Individuals with low self-efficacy tend to expect failure and are more likely to disengage from the coping process [23]. Early (post-acute) psychological screening and intervention to address patients' psychosocial needs may support improved long-term outcomes.

There are several reasons why findings from civilian trauma studies may not extend to military casualties. The mechanisms of military injury are different, with blasts generating 79% of all combat casualties and 19% from gunshots compared to a predominance of blunt mechanisms in civilian trauma [24, 25]. The military medical system of care is also different, involving staged treatment and evacuation from the combat theater. Demographically, military patients will have at least a high school education. In general it is reasonable to expect that members of the military benefit from a relatively robust social support network involving family as well as fellow military unit members. Access to rehabilitation and prosthetic services may also be more consistent in the military. The incidence of posttraumatic stress post-injury, on the other hand, may be

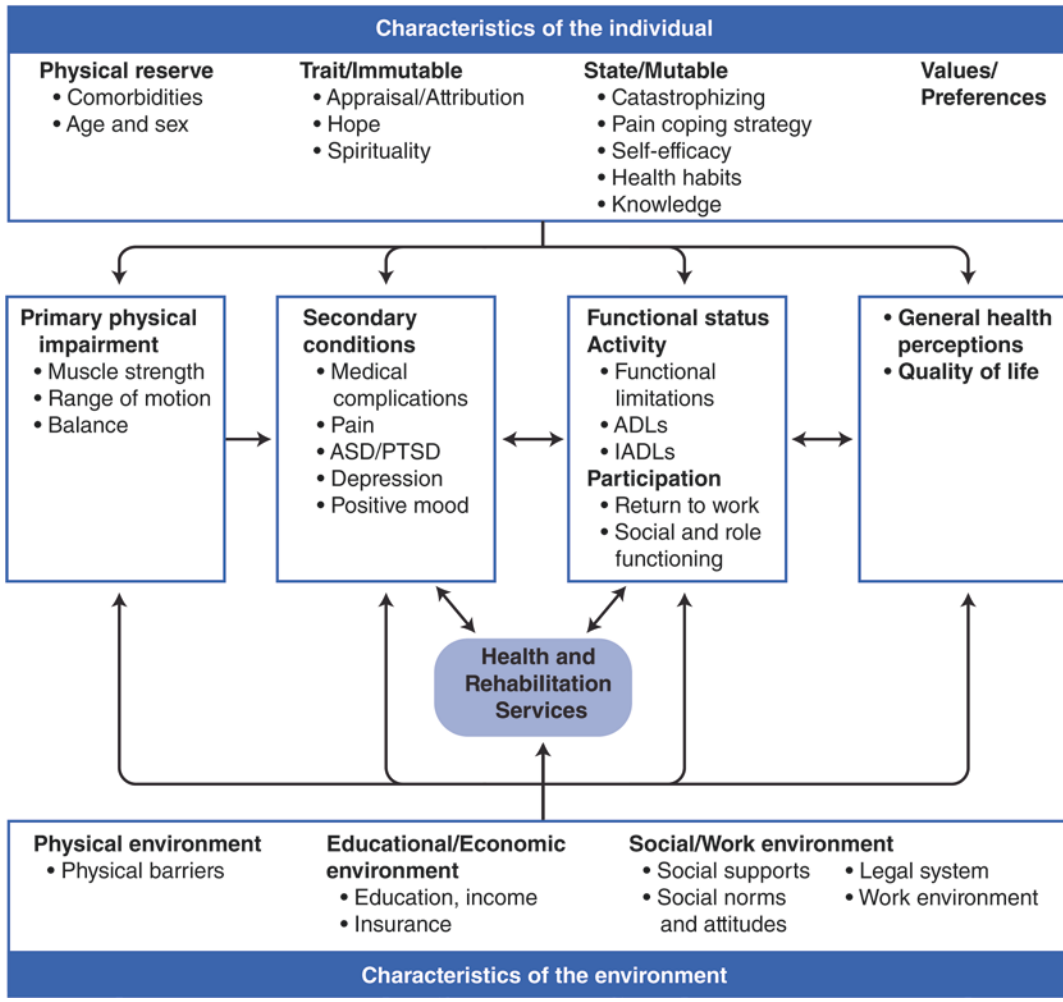

Fig. 9.1 Conceptual framework for assessing outcomes following major limb trauma. *ASD* acute stress disorder, *PTSD* posttraumatic stress disorder, *ADL* activities of daily living, *IADL* instrumental activities of daily living (Modified from MacKenzie and Bosse [22])

higher among military versus civilian trauma patients.

Two studies provide evidence that amputation versus reconstruction outcomes may indeed be different for those who are injured in combat (versus blunt force injuries common in civilian settings) [11, 12]. Both studies represent complex extremity trauma sustained by service members in Iraq and Afghanistan. Melcer and colleagues [12] retrospectively examined medical records of 687 patients who underwent early amputation during the first 90 days post-injury (early amputees) and compared them with 84 patients who had amputations more than 90 days after injury (late amputees) and with 117 patients who were treated for leg-threatening injuries who did not undergo amputation (limb salvage group). Although early amputees and limb salvage patients experienced similar 2-year rates of physical complications, early amputees were less likely to have been diagnosed with PTSD, mood disorder, or substance abuse. Early amputees also received significantly more outpatient care, including physical therapy and follow-up of psy-

chological problems, than their limb salvage counterparts. Late amputees had higher rates of both physical and mental health diagnoses than either early amputees or limb salvage patients.

The Military Extremity Trauma and Amputation/Limb Salvage (METALS) Study [11] was a retrospective cohort study of 324 service members deployed to Afghanistan or Iraq who sustained either a traumatic amputation or one of the following: revascularization, bone graft/bone transport, local/free flap coverage, complete deficit of a major nerve, or complete compartment injury/compartment syndrome. Participants were interviewed (at an average of 38 months post-injury) and their medical records were abstracted. After adjusting for covariates, participants with an amputation scored significantly better on all domains of the Short Musculoskeletal Functional Assessment (SMFA) [26] as compared to those whose limbs had been salvaged. They also had a lower likelihood of PTSD (using the posttraumatic stress disorder (PTSD) checklist – military version) [27] and a higher likelihood of being engaged in vigorous sports as measured using the Paffenbarger Activity Scale [28]. No relationship was found between amputation status and depressive symptomology (using the Center for Epidemiological Studies Depression Scale), [29] pain interference, or work/school status. Overall, 38% of patients in the study screened positive for depressive symptoms and 18% for PTSD. At follow-up, more than one-third (36%) were neither working, on active duty, nor attending school.

These two studies point to similar conclusions and stand in contrast to those of the civilian LEAP study, indicating that service members who undergo amputation have better functional and psychological outcomes than those who undergo limb salvage. One explanation for the difference may be that military members have better access to state-of-the art prosthetic devices and prosthetic care [30–32]. Inadequate insurance coverage often limits the type and number of prostheses available and accessible to civilian amputees. In addition, military amputees may benefit from more focused rehabilitation early in their recovery (compared to both military limb salvage patients and civilian amputees). Clinical and rehabilitation pathways for the treatment of amputees have been well established through the military amputee care programs (ACPs) [33]. Military amputees often spend more than 1 year in rehabilitation in residence where they have ready access to prosthetists and can benefit from targeted reintegration programs. In contrast, very few civilian amputees are hospitalized for rehabilitation (18% in the LEAP study) [20], and many have limited access to outpatient physical therapy services. Military amputees may also benefit from greater access to peer support early on in their recovery, which may in turn support better long-term outcomes. Peer visitation is an integral part of the military ACP and has been shown to be highly valued among service members with combat-related amputations [34]. Treatment pathways for limb salvage patients in the military are less well defined. The study by Melcer and colleagues [12] found that compared to amputees, limb salvage patients received significantly less care at most outpatient clinics. The differences were particularly acute for psychiatric or psychological care. In the first 24 months post-injury, 88% of early amputees made visits to psychiatry clinics (38% to psychology clinics) compared to only 29% of limb salvage patients (22% to psychology clinics).

The Utility of Scoring Systems as an Aid in the Decision to Amputate or Reconstruct

Given the difficulty in making the decision to amputate versus reconstruct, several attempts have been made to develop a scoring system that

can help to guide this important clinical decision early, in the acute phase of treatment [35–42]. These systems are based on information about patient age, boney injury, soft tissue damage, nerve and vascular injury, warm ischemia time, contamination, and presence of systemic shock. The most notable approach is the Mangled Extremity Severity Score (MESS) developed by Johansen and colleagues [35]. The LEAP study evaluated the MESS along with four other scoring systems and found that none had acceptable levels of sensitivity for predicting which patients would eventually require amputation [40]. Other studies in civilian and military settings have confirmed these results [41, 42], and there is now general agreement that these scoring systems are limited in their utility to the surgeon who is weighing the pros and cons of early amputation versus reconstruction. Although lower scores can reinforce the surgeon's decision to reconstruct, higher scores should not be used to determine treatment.

What has been confirmed, however, is that the lack of plantar sensation at initial presentation is *not* a universal indication for amputation. Bosse and the LEAP study team [43] compared the outcomes of 26 insensate plantar feet that were amputated with 29 insensate feet that were salvaged and with 29 matched controls selected from among a larger cohort of salvaged sensate limbs. Disability outcomes at 2 years post-injury were similar. Furthermore, an equal percentage of salvage patients (55%) presenting with and without plantar sensation had normal plantar sensation at 2 years. Only one patient of the 29 with insensate feet at admission had completely absent plantar sensation at 2 years.

Future Directions for Research

Major limb trauma is a significant cause of long-term disability in military and civilian environments. Although meaningful advances have been made in the treatment of these injuries, remaining knowledge gaps challenge our ability to ensure best possible outcomes. The Extremity War Injuries Working Group has identified several priority areas of research [44, 45]. Some of these gaps are highlighted here and in other chapters of this volume.

Acute Treatment and Prevention of Complications Following Limb Salvage

Poor functional outcomes following limb salvage are most often associated with volumetric muscle loss [46] and major nerve injury [47]. Unfortunately, few effective strategies are available to address these problems. Promising new tissue regeneration technologies, including the use of extracellular matrix scaffolds and stem cells, are currently under investigation for the treatment of volumetric muscle loss in animal models [48–50]. To date, no major human work has been presented. Studies to identify potentiating growth factors and to investigate the clinical effect of stem cells or conduits to recover nerve function also hold promise, but these investigations cannot advance without additional basic and translational research investment [47].

Hospital readmission for complications (e.g., infection) emerged as one of the most important predictors of poor outcome for patients in the Lower Extremity Assessment Project (LEAP) study [51]. Surgical site infection and osteomyelitis rates range from 14% to 60.0% in both military and civilian settings [52–58]. Studies are underway to better characterize the wound "bioburden" (i.e., the species and quantity of bacteria present on the wound surface) at the time of definitive wound coverage/closure; these studies could provide a platform to develop and evaluate strategies for reducing surgical site infections [56, 59]. One promising and potentially cost-

effective preventive approach is the application of local antibiotic directly to the site of the wound [60–63].

Posttraumatic osteoarthritis (PTOA) and pain are common secondary conditions after complex lower limb trauma, yet continued refinement of existing treatment methods has failed to decrease the substantial incidence and severity of these potentially disabling conditions. Additional research is needed to better understand the underlying mechanisms of these conditions and find effective strategies for their treatment early in the course of recovery.

There remains controversy regarding optimal procedures for transtibial amputation. Many surgeons advocate for an amputation with a tibia-fibula synostosis technique (Ertl procedure) in young and active patients, observing that this procedure can provide a better prosthetic interface as well as end bearing capacity and soft tissue stability that improve performance and functional outcome. Others strongly advocate for a standard posterior flap (Burgess procedure) without the synostosis, arguing that patients have similar outcomes with fewer complications and lower costs [64–67]. The outcomes of these two approaches have not yet been compared in an appropriately powered prospective and randomized clinical trial.

Advancements in Orthotics and Limb Salvage Rehabilitation

While prosthetic advances and amputee rehabilitation have facilitated high-level function following amputation, few if any such advances have been seen in orthotics and rehabilitation for limb salvage patients. Orthotic options have been limited primarily to plastic posterior leaf spring ankle foot orthosis (AFOs). More recently, however, a team at the Center for the Intrepid and the San Antonio Military Medical Center (SAMMC) has developed a custom energy-storing ankle foot orthosis, the Intrepid Dynamic Exoskeletal Orthosis (IDEO) which when integrated with a rehabilitation program designed specifically for adaptation to the IDEO may significantly improve limb salvage outcomes and reduce the number of delayed amputations [68–71]. The IDEO incorporates a posterior mounted carbon fiber strut with a proximal ground reaction cuff and distal supramalleolar AFO. The proximal ground reaction cuff is a circumferential support fashioned in the style of a patellar tendon bearing prosthetic located at the proximal leg, with a posterior attachment to the proximal end of the carbon fiber strut. The distal supramalleolar AFO spans from the posterior attachment to the distal end of the carbon fiber strut, around the ankle joint, and under the foot to the toes. A cushioned heel allows for shock absorption during the loading response. Inspired by prosthetic running feet, the laminated carbon fiber footplate is rigid, resulting in deformation primarily through the posteriorly positioned carbon fiber strut. The plantar-flexed position of the footplate combined with a gradual roller shape allows for increased deflection and energy storage as the tibia progresses forward from mid to terminal stance. This also allows for forefoot loading during agility and running activities. The modular design allows adjustments to alignment and to strut stiffness based on individual patient strength gains; it also facilitates donning and doffing to accommodate volumetric muscle changes from strength gains or edema.

To maximize their success with the IDEO, patients participate in a high-intensity sports medicine approach to rehabilitation for 4 weeks before receiving the device and for 4 weeks after receiving the device. This multidisciplinary Return to Run (RTR) clinical pathway focuses on strength, agility, and speed with the goal of enabling patients to return to running, sports, and military deployment [68].

In a small study of 18 subjects with unilateral dorsiflexion and/or plantarflexion weakness, the functional performance of the IDEO was compared against no orthosis and two commercially available orthoses: the Allard BlueRocker™ (BR) and a rigid plastic posterior leaf spring (PLS). All participants in this study also completed the RTR clinical pathway. Performance was significantly better with the IDEO on nearly all functional measures compared to all other bracing conditions [69, 70]. Another study of 84 patients found improvements in performance tests and patient-reported outcomes (the SMFA and VR12) 4 weeks after receiving the IDEO and completing the RTR clinical pathway [71]. Among subjects who initially considered amputation, the majority favored limb salvage after this noninvasive intervention.

Further testing of the IDEO device and the RTR clinical pathway is currently underway at both the Center for the Intrepid and at two additional military treatment facilities (Naval Medical Center San Diego and Walter Reed National Military Medical Center Data) [72]. Data are also needed to test whether the IDEO can be fabricated and fitted outside military treatment facilities in a cost-effective way so that civilians with major foot and ankle trauma can also benefit from the technology. If the positive results obtained thus far can be confirmed in a broader population, the IDEO and RTR approach could significantly change the decision to amputate.

Rehabilitation

A major finding of the LEAP study was that early symptoms of anxiety, posttraumatic stress, and depression are important determinants of poor outcome for amputation *and* limb salvage patients. High self-efficacy and strong support systems played a protective role and were associated with better long-term recovery. These findings argue for early screening for risk and protective factors and for the development of interventions that directly address the psychosocial needs of patients. Routine screenings for PTSD and depression have become more common in the military; however, screening is far from standard practice in civilian trauma care [73]. While promising new treatments are being introduced for all victims of trauma, more research is needed to determine which strategies work best and at what cost. Of particular interest are the relative advantages and disadvantages of pharmacotherapy versus cognitive behavioral therapy (CBT) and other psychological approaches to treatment [74, 75].

When clinically diagnosed, anxiety, PTSD, and depression should be managed by appropriate mental health professionals. However, there is an increasing body of evidence to suggest that when provided in the early stages post-injury, interventions such as peer support and self-management can help to optimize recovery by preventing early signs and symptoms from developing into diagnosable conditions [76]. Hospital-based peer visitation programs have become an integral part of the US Armed Forces Amputee Patient Program [33, 34]. An appropriately trained peer visitor can speak with the unique credibility of direct experience and can offer practical suggestions for getting through the day. Self-management programs build from the principle of peer support, providing patients with skills and confidence to take charge of their recovery [77]. Self-management programs incorporate the principles of CBT and emphasize (1) problem solving, (2) setting goals and monitoring progress, and (3) practicing symptom management skills such as reducing negative thoughts. They reduce maladaptive coping responses, increase self-efficacy, and target the

individual's ability to self-manage his or her own medical and psychological problems.

While self-management interventions have gained widespread application in the treatment of diabetes, arthritis, and other chronic conditions [78–80], only recently have they been extended and made available to individuals with major limb trauma and limb loss. The Next Steps Program is one self-management program that has been designed specifically for trauma patients (http://www.amtrauma.org/programs/trauma-survivors-network/next-steps/index.aspx).

Face-to-face and electronic/online versions of the program are available. The online version offers an especially cost-effective means to connect trauma survivors from around the country and to teach them the essential skills of self-management (http://nextstepsonline.org/). A program developed specifically for amputees is also available through the Amputee Coalition of America [81]. More research is needed to establish the cost-effectiveness of these types of programs and to better understand possible barriers to their implementation, especially in civilian trauma center settings.

Measuring Long-Term Outcomes

Current studies of long-term outcome following amputation and limb salvage are limited by reliance on measures that have the potential for ceiling effects. Standard measures of self-reported outcome such as the SIP [14], the Musculoskeletal Function Assessment (MFA) [26], and the Short-From Health Survey (SF-36) [82] may not be sufficiently sensitive to detect differences in the performance of higher-level activities that are important to injured young, active civilians and service members. When using standard batteries to assess functional outcome, it may be helpful to include self-reported measures of participation in vigorous recreational and sports activities [28].

It should be recognized that the administration of multiple batteries will increase respondent burden and may be impractical in large, multi-center studies. To address these and other limitations of traditional self-reported outcome measures, the National Institutes of Health (NIH) invested in the development of the Patient Reported Outcomes Measurement System (PROMIS) [83]. PROMIS makes it relatively more feasible to capture information from across multiple domains by use of computer adaptive testing (CAT) which provides short, precise measures. CAT can also extend the ceiling and floor of individual domains, thereby enhancing responsiveness of the test measures to small differences along the full functional continuum. Studies are now underway to evaluate the utility of CAT and PROMIS for assessing patient outcomes following orthopedic trauma [84].

Standard performance assessments have also been developed and tested to assess function in older adults; typically, this would include activities such as rising from a chair and walking a short distance. These measures are generally appropriate for functional assessment of individuals with significant impairment, but they are often inadequate to assess potential for improvement in more active adults. Wilken and colleagues at the Center for the Intrepid and Brooke Army Medical Center (BAMC) have developed a battery of six performance measures that are increasingly used to measure functional capacity in military outcome studies [85]. The performance battery measures are easy to understand, require little equipment and space, and can be used to assess a range of functional domains including agility, speed, and strength/power. Early work has shown these measures to be reliable, but additional research is needed to establish their predictive validity and sensitivity to treatment differences.

Conclusions

The research literature that compares outcomes after limb salvage and amputation has generally failed to show meaningful differences between the two, with the exception that military amputees may be advantaged by unique access to state-of-the-art prostheses and intensive rehabilitation. What is clear, however, is that regardless of the treatment option selected, long-term functional physical and psychological outcomes are often poor. Factors that predispose individuals to worse functional outcomes and thus lower rates of return to work or military duty include extent of soft tissue injury, major complications, pain, early signs of anxiety, posttraumatic stress, and depression. High self-efficacy and a good social support network can help to buffer psychosocial consequences of traumatic injury. In addition to the need for strategies and techniques to prevent medical complications and manage pain, screening may be desirable to identify risk and protective factors, guide referrals as may be needed to appropriate services or programs, mitigate development of long-term secondary conditions, and thereby benefit overall recovery.

It is encouraging that significant advances are being made in the acute treatment and rehabilitation of both amputation and limb salvage patients. It is important that research investments continue as needed to refine new technologies and improve innovative treatments. Collaboration between the military and civilian trauma communities has been and will be important to further research and to ensure translation of research into practice. In particular, three consortia have been established with funding from the US Department of Defense (DoD) to support this goal. The Armed Forces Institute of Regenerative Medicine (AFIRM) is a multiinstitutional, interdisciplinary network of scientists working to develop advanced treatment options for severely wounded service members [86]. The Major Extremity Trauma Research Consortium (METRC) is a network of military and civilian clinical centers and one data coordinating center that conduct multicenter clinical research studies relevant to the treatment and outcomes of orthopedic trauma sustained in the military [87]. The BADER Consortium ("Bridging Advanced Developments for Exceptional Rehabilitation") advances orthopedic rehabilitation research capabilities at military medical treatment facilities and at Department of Veterans Affairs (VA) clinical centers [88]. Together, these consortia facilitate collaborations between military and civilian scientists dedicated to the discovery and evaluation of treatments that will improve outcomes among service members and civilians who sustain major orthopedic trauma. Throughout history, lessons learned from battle have yielded medical knowledge, insight, and experience fundamental to advancing the care of traumatic injuries that unfortunately also occur in civilian settings. Likewise, it is important to further develop and refine the hard-won lessons of war through research and practice in the civilian domain, to benefit those who may be injured in future conflicts.

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Osseointegration Research

10

Joseph B. Webster, Kent N. Bachus,
James Peter Beck, Sujee Jeyapalina, Alex J. Drew,
and Roy D. Bloebaum

Abbreviations

CFU	Colony-forming units
CT	Computed tomography
DSA	Direct skeletal attachment
EEFP	Endo-exo femur prosthesis
HA	Hydroxyapatite
ILP	Integral-leg prosthesis
ITAP	Intraosseous transcutaneous amputation prosthesis
LEAFS	Lower extremity ambulation feedback system
MAR	Mineral apposition rate
OI	Osseointegration
OPRA	Osseointegrated prostheses for the rehabilitation of amputees
POP	Percutaneous osseointegrated prostheses
Q-TFA	Questionnaire for persons with transfemoral amputation
ROM	Range of motion
RSA	Radioisometric analysis
THA	Total hip arthroplasty
VA	Veterans affairs

Introduction

The amputee needs a secure and comfortable connection between his or her residual limb and the prosthetic limb to which it is attached. Traditionally, this has been accomplished by the use of a socket interface. Despite material

J.B. Webster, MD (✉)
Hunter Holmes McGuire VA Medical Center, PM&R, Polytrauma Transition Center, Richmond, VA, USA
e-mail: joseph.webster@va.gov

K.N. Bachus, PhD
Departments of Orthopaedics, Bioengineering, University of Utah Orthopaedic Center, Salt Lake City, UT, USA
e-mail: kent.bachus@hsc.utah.edu

J.P. Beck, MD
DVA SLC HCS, Department of Orthopedics, Salt Lake City, UT, USA
e-mail: james.beck@hsc.utah.edu

S. Jeyapalina, MD
DVA SLC HCS, Department of Bioengineering, University of Utah, Salt Lake City, UT, USA
e-mail: sujee.jeyapalina@hsc.utah.edu

A.J. Drew, BSME
University of Utah Orthopaedic Center, Department of Orthopaedics, Salt Lake City, UT, USA
e-mail: alex.drew@utah.edu

R.D. Bloebaum, PhD
VA Salt Lake City Health Care System, Bone & Joint Research Lab, Salt Lake City, UT, USA
e-mail: Roy.bloebaum@hsc.uta.edu

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and design advances that have improved prosthetic socket suspension systems, a number of challenges remain that can compromise the amputee's comfort and ability to function. These challenges include loosening of the prosthesis, poor heat transfer, skin breakdown, residual limb pain, range-of-motion (ROM) limitations, and discomfort when sitting. Sockets can also be difficult to don and doff and can impose vascular and neurologic compromise. Compared to currently available socket suspension techniques, direct skeletal attachment (DSA) of a prosthetic limb by osseointegration (OI) offers many advantages including improved mechanical transfer of motion, reduced risk of skin irritation, improved ROM, and enhanced comfort. However, OI also presents potentially serious risks and entails a prolonged period of recovery and rehabilitation. Risks include periprosthetic infection, implant breakage, and the possibility of additional revision surgeries.

To advance the acceptance and success of osseointegration, it will be important to reduce and/or resolve associated risks. In this chapter, we consider related aspects of osseointegration implant design, surgical approach, infection prevention strategies, and rehabilitation. Each concern will be discussed in historical context, with attention to current experience in European countries, available research findings, and future directions.

Endoprosthetic Implant Design

Historical Perspective

The first example of percutaneous skeletal fixation can be traced back to Malgaine, who in 1843 used a tibial fixation screw and traction to stabilize complex fractures of the leg [1]. Not until a century later were attempts made to attach the skeletal limb to an external limb prosthesis. The earliest documented attempt came in 1946, when Drümmer, a surgeon from Pinneberg, Germany, fit four transtibial amputees with intramedullary tibial implants [2]. After observing the high soft tissue revision rate in amputees following World War I, Cutler and Blodgett of Harvard also sought to achieve direct skeletal attachment of prostheses in transtibial amputees. Cutler and Blodgett were the first to use a screw type intramedullary device manufactured from an early cobalt-chromium alloy. Evidence from a test series of 18 dogs suggested that weight-bearing with this device was well tolerated by the animals [1].

Beginning in 1956 and with support from the Orthopaedic Research and Educational Foundation as well as the Veterans Administration, orthopedic surgeon Dr. John Esslinger studied the merits of direct skeletal attachment of prostheses [3]. During his research through the 1960s, Esslinger experimented with an array of different materials for bone ingrowth [3]. Implants were placed in 29 dogs and 1 Capuchin monkey. The animals were observed for up to 6 years post-implantation. Key contributions by Esslinger included early accounts of stress shielding (osteopenia due to shifting of stress to the implant, thereby "shielding" the bone from osteogenic signals) as well as development of the first two-stage surgical placement of a transcutaneous implant [3]. In 1967, Dr. Vert Mooney, an orthopedic surgeon and clinical researcher in California, became the first American to perform direct skeletal attachment of a prosthetic limb in a human subject. Placed in the right humerus, the implant was constructed from a porous ceramic reinforced by a compression-stressed stainless steel intramedullary rod. Eight months later, the implant was removed due to infection [2].

In 1976, medical scientist Dr. Charles William Hall became the first to experiment with a supracortical device that fits over the periosteal surface of the bone. This approach was abandoned after several design iterations [4]. During the mid-

1980s, Hall had greater success with a new titanium porous-coated intramedullary device. He also published a comprehensive set of design criteria for the direct skeletal attachment of prosthetic devices (Table 10.1) [4, 5]. Hall produced this list not only to inform his own decisions but also as a foundation for future investigators and designers to build upon.

Table 10.1 Original Dr. Charles William Hall criteria

1. The device must be a skeletal extension penetrating the skin such that normal loads are transmitted directly to the skeletal system and not through intervening soft tissues
2. These loads must be distributed so as not to damage the prosthesis, the bone to which it is attached, or any interfacial tissue ingrowth
3. Gross and microanatomical limitations must both be considered so that the device neither restricts the circulation nor otherwise impedes tissue healing
4. The skeletal extension must be a functional unit that permits freedom of motion with no pain
5. Although not an absolute necessity, the design should permit minor adjustments to be made externally rather than requiring secondary operative procedures
6. The device must have a surface suitable for tissue adhesion and/or ingrowth at both the bone interface and the skin interface. The skin interface must prohibit the development of a sinus tract and/or inhibit bacterial invasion
7. All materials used in fabrication must be compatible with interfacing tissues, must become functional for the purpose intended, and must not cause adverse systemic reactions
8. The total end product must be readily sterilizable, using routine hospital procedures
9. The device should be designed to permit easy application under standard operating room conditions
10. Ultimately, the design should permit the use of existing skeletal muscles to power external articulating mechanical joints. This, of course, demands development of an artificial tendon that will provide a strong tenacious interface with the musculotendinous portion of the existing skeletal muscles, penetrate the skin without allowing any entrance for bacterial invasion, and transmit the muscle's power to the load in an efficient manner

In 1965, a Swedish physician at the University of Gothenburg, Per-Ingvar Branemark, and his colleagues began to experiment with intraosseous anchorage techniques for dental prostheses using commercially pure titanium [6, 7]. In 1981, this team first coined the term "osseointegration," defined as direct contact between living bone and implant, without intervening fibrous encapsulation [8]. Branemark's work earned him numerous honors and revolutionized the way cementless orthopedic implants are approached [8]; he is considered the father of osseointegrated implant systems [9]. Influenced by the dental and craniofacial reconstruction anchorage systems pioneered by Per-Ingvar Branemark, his son, Dr. Rickard Branemark, led work to achieve long-term osseointegrated fixation of major limb prostheses [10–15]. Although the procedure was first developed in 1990, the rehabilitation process was standardized in 1999 as the "osseointegrated prostheses for the rehabilitation of amputees" (OPRA). Between 1990 and 2011, the OPRA system was implanted in more than 130 amputees of various amputation levels and locations [13, 16]. Contemporaneously, two other European methods of OI were developed, the integral-leg prosthesis (ILP) and the intraosseous transcutaneous amputation prosthesis (ITAP) system [17–20]. Figure 10.1 provides an overview of the OPRA system as compared to ILP and the ITAP systems currently in use in Germany and Sweden.

Current Practices

Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) System

The endoprosthetic stem of the OPRA implant system (Fig. 10.1a) is constructed from a tube of titanium machined along its length to contain self-tapping threads for cortical engagement [11]. Radially placed perforations of this threaded cylinder are intended to allow vascular communica-

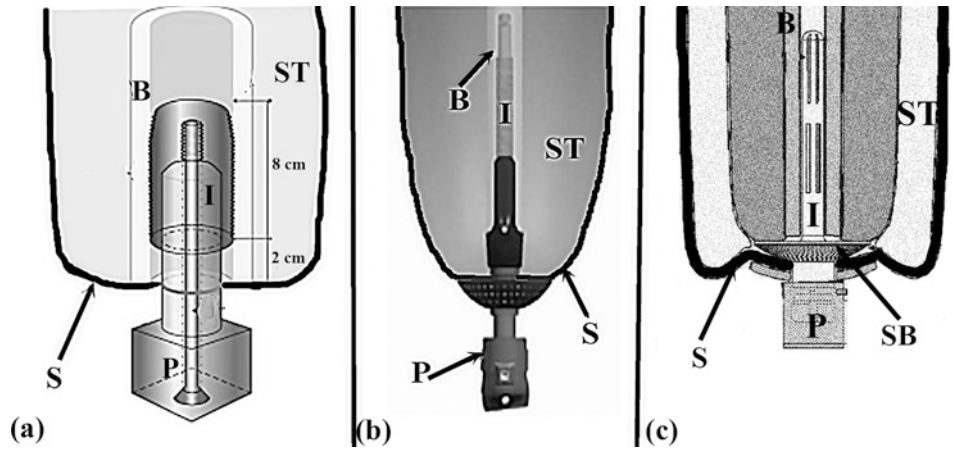

Fig. 10.1 Schematic representation of European OI prosthetic systems: (**a**) OPRA system, (**b**) ILP system, and **c** ITAP. (*B* – host bone tissue, *I* – endoprosthetic implant, *P* – percutaneous post, *S* – skin, *SB* – subdermal barrier)

tion between the endosteal bone surface and the marrow cavity [11]. There is no implant flange to cap the bone end at the resection plane; rather, the device is recessed 8–20 mm proximal to the bone end.

Threading of the stem throughout its entire length is unique to the OPRA implant system. This design results in fixation similar to a fully porous device but can cause stress shielding and distal bone resorption that can lead to increased fracture risk over time [21]. However, while radioisometric analysis (RSA) of individuals with the OPRA implant system showed distal bone remodeling, fixation was not adversely affected in observations made up to 7 years post-implantation [22]. Implant migration, particularly rotational movement about the long axis, was observed in a number of patients. This rotational movement could be attributed to the circular cross section of the endoprosthetic stem, which may not provide inherent torsional stability. A secondary effect of distal bone resorption in the OPRA system, this resorption may destabilize the skin seal achieved by attaching the skin directly to the underlying bone at the time of second surgery. This phenomenon has the potential, over time, for complete dissolution of the interface and may account for the 38–58% rate of later stomal infection and recurrence of infection after antibiotic treatment, reported with the OPRA system [23, 24].

Another key design feature of the OPRA stem is its hollow implant geometry with radially placed holes for vascular communication with the marrow cavity [11]. Studies on the effect of medullary vasculature disruption have shown that periosteal blood flow increases up to sixfold to compensate for the loss of endosteal supply, and limited reaming may even improve the outcome of diaphyseal fractures and tissue necrosis [25, 26]. Other researchers have found that total hip arthroplasty (THA) can reduce femoral perfusion immediately following surgery, but long-term changes were not examined [27]. Given the mixed conclusions in the literature regarding the effect of disruption of the endosteal blood supply, it is worth noting that currently only one THA stem design allows for partial preservation of the marrow canal, making this a unique feature of the OPRA device among skeletal prosthetic docking systems [28].

Integral-Leg Prosthesis (ILP) (Formerly Endo-Exo Femur Prosthesis (EEFP))

The ILP system (Fig. 10.1b) was developed in Lübeck, Germany, under the guidance of Dr.

Horst Aschoff [29, 30]. It has been implanted in patients with transfemoral amputations since 1999 [17–19, 30, 31]. To date, it has undergone three changes in both device design and surgical technique [19]. Design revisions have dealt primarily with the management of the soft tissue barrier, to eliminate the porous tripod structure at the skin-implant interface and at the bone-capping portion of the device. The most recent design iteration replaced the porous tripod structure with a low surface energy titanium-niobium-oxynitride surface [TiNb(ON)] [19]. This surface has low wettability characteristics that promote drainage and exteriorization of tissue fluids and thus improves ease of stomal hygiene. Through all three design revisions, the gross device material has remained a cast cobalt-chrome alloy.

A defining characteristic of the ILP system is its predominantly porous-coated strategy for bone ingrowth into the endoprosthetic stem. Except for small segments of surface near the distal resection plane and the proximal tip of the implant, all surfaces are coated in heavily porous spongiosa metal (Fig. 10.2). While fully porous stems are still widely used in THA, Engh and colleagues recognized a number of advantages to limiting the amount of porous coating on an implant stem [32]. These advantages include less surface area for metal particulate generation due to wear. In addition, the likelihood of distal implant fixation is reduced, which in turn reduces cantilever loading of the stem [33], resulting in fatigue fracture. Limited porous coating also provides for easier revision. Perhaps most importantly, the preservation of force transfer near the implant insertion point serves to maintain bone stock [32]. Subsequent study illustrated that proximal porous coating in hip stems maintained micromotion adjacent to the porous coating, although the motion remained below the threshold for fibrous capsule formation [34]. Further observation of the ILP implant system is needed to determine whether the amount of porous coating can be safely modified in future design revisions.

Intraosseous Transcutaneous Amputation Prostheses (ITAP)

Developed in England under the leadership of biomedical engineer Dr. Gordon Blunn [35], the ITAP system (Fig. 10.1c) is an intramedullary device for exoprosthetic limb attachment. Early iterations of the device were used to restore function in a dog model, in human digits, in extraoral craniofacial defects, and most notably in a transhumeral amputee [20, 36, 37]. Performed in 2007, the transhumeral implant was placed using the single-stage operation developed previously in the dog model. A 2010 follow-up report indicated no fractures or loos-

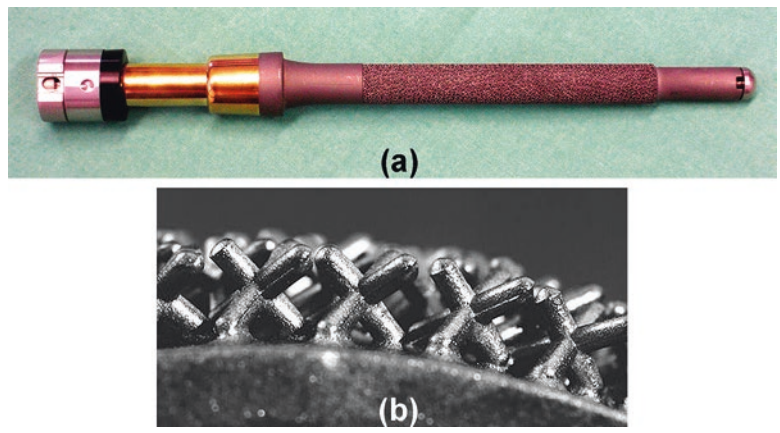

Fig. 10.2 Current (third generation) ILP device design

ening of the endoprosthetic stem [20]. A subsequent presentation reported use of the ITAP system in 18 transfemoral amputees, but implant survival rates have not been reported as of this writing [38].

The device used in the transhumeral case study incorporates a titanium alloy (Ti-6Al-4V) endoprosthetic stem that is circular in cross section and press-fitted into the medullary canal with or without cement. Rotational stability is achieved through a series of six radially positioned self-cutting flutes [20]. Perhaps the most defining characteristic of the ITAP device is the use of a hydroxyapatite (HA) coating for promoting osseointegration of the endoprosthetic stem and to promote soft tissue integration to insure a skin seal at the interface [39, 40].

Since the 1980s, HA coatings have been widely adopted in total hip stems and acetabular cup fixation. Since that time, it has been shown that HA coating can enhance ingrowth and attachment of bone into a porous surface [33, 41, 42]. However, some controversy still exists regarding the durability of HA coatings and their potential for acting as a wear particle generator, possibly inducing osteolysis and component loosening through third-body wear mechanisms [43, 44]. More recent longitudinal studies have found that the use of HA coatings in total hip arthroplasties does not significantly alter the survival rate of the implant systems [45, 46]. The use of HA as an implant coating is a continuing topic for debate as there is no clear evidence for improved clinical outcomes over those of porous titanium alone [45].

Although there have been no reports of HA implants loosening in the transhumeral or transfemoral studies, published radiographs of the ITAP transhumeral implant show poor "fit and fill" (immediate and continuous stability of the bone-implant interface) in the medullary canal [20]. Close geometric implant fit in the medullary canal has long been identified as necessary for achieving good osseointegrated fixation in cementless implants [47]. Clinical and experimental studies have shown that good fit helps maintain strain levels closer to physiologic levels [48] and reduces implant micromotion [49, 50]. Both of these factors could affect the long-term survival rate of the ITAP system.

Design Features of Total Hip Stems and Megaprostheses

While percutaneous skeletal fixation of a prosthetic limb presents its own unique set of challenges, this is not the only situation in which success requires stable implant fixation in the diaphysis of a long bone. Khanuja et al. recently published a review of cementless femoral fixation in total hip arthroplasty (THA). They defined six primary classifications of hip stem design [51], and their cylindrical and fully porous-coated classification most closely resembles the ILP stem used by Dr. Aschoff in Germany. This hip stem design had excellent implant survival rates but was associated with proximal stress shielding and thigh pain. Cutouts to reduce flexural stiffness, and the addition of a polished distal tip in some of these designs, helped to alleviate thigh pain [51]. Current total hip arthroplasty stem designs show a trend toward proximally coated stems that rely on metaphyseal fixation. This allows for increased preservation of physiologic strains across the entire residual bone structure, which reduces bone resorption and simplifies revision.

Current options for megaprostheses, which are often used in reconstructions following massive bone removal due to cancer, show a trend toward distal fixation through the use of porous coatings or screws located near the resection plane [52, 53]. Compress-type implants use an anchor located away from the resection plane to prestress the bone, inducing hypertrophy to reduce stress shielding [54]. In all cases, the phi-

losophy of design can be summarized in the following manner: provide adequate fixation while reducing the effects of stress shielding and improving the ease of revision surgery.

Percutaneous Osseointegrated Prostheses (POP)

Investigators with the Department of Orthopaedics at the University of Utah and the Salt Lake City Veterans Affairs Medical Center have developed an osseointegrated implant with unique features for use in a large animal model. For the implant development, the fused metacarpal third/fourth bones from 20 mature crossbred sheep carcasses were imaged using a computed tomography (CT) scanner. The digital images were then reconstructed to provide anteroposterior and mediolateral dimensions as well as the three-dimensional morphology of the medullary canal at 1 mm increments throughout the length of each bone (Fig. 10.3). From these data, three implant sizes and surgical broaches, corresponding to the 25th, 50th, and 75th percentiles, were fabricated from medical grade titanium alloy (Ti-6Al-4V) (Fig. 10.4). The proximal intramedullary portion of each implant was textured by grit blasting to facilitate bone attachment by ongrowth and to achieve tight bone-implant integration. The subdermal barrier and the most distal portion of the stem were coated with a 500–750 μm thick commercially pure titanium coating (Thortex, Portland, OR) with a porosity of 52% ± 12% [55].

Developed as a single-stage device, much like the ITAP, the percutaneous osseointegrated prostheses (POP) device was validated in a weight-bearing, large animal study involving 86 sheep

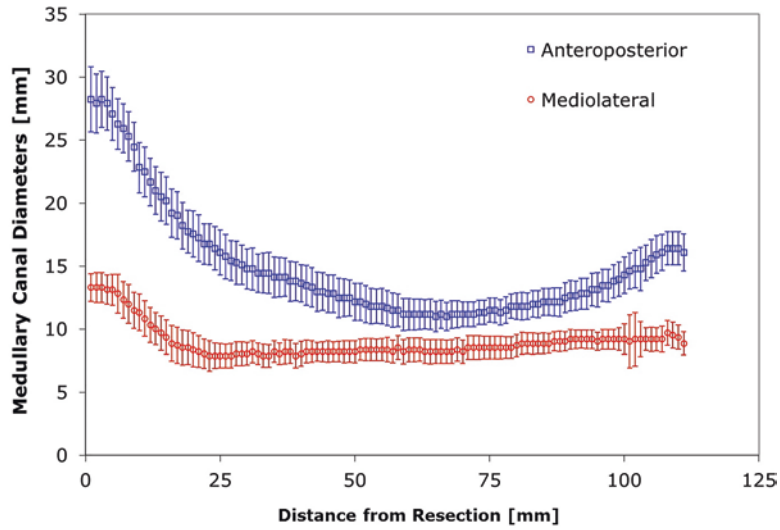

Fig. 10.3 Mean and standard deviation of anteroposterior and mediolateral dimensions of sheep metacarpal 3 bone

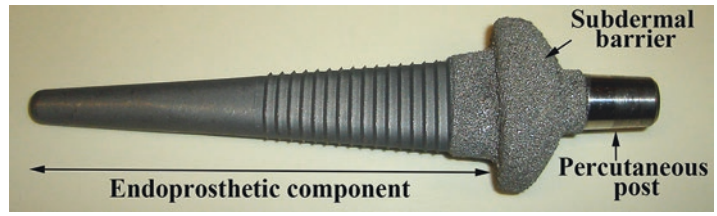

Fig. 10.4 POP sheep implant with attached exoprosthesis

[56]. The implant's geometry is unique when compared to the OPRA, ITAP, and ILP devices in that the cross section of the POP implant is oval to mimic the medullary anatomy and because the anatomic geometry was derived from population data as opposed to individual subject imaging. In addition, limited distal porous coating was utilized for osseointegration in stark contrast to the fully threaded or heavily porous designs previously examined. The results of these unique design decisions and future design modifications for pending human implantation are discussed in the following section.

Future Design Considerations

The use of CT data combined with 2D image processing shows that the POP implant has excellent fit and fill results. Looking forward, a number of emerging technologies in image processing, biomaterials, computational modeling, and prosthetic devices may influence the design of future percutaneous implant attachment systems. New automatic segmentation routines for image processing may reduce the workflow of translating medical images to accurate 3D anatomical representations. Likewise, new computational modeling tools in the emerging field of statistical shape modeling may allow for rapid optimization of intramedullary stem geometries; this would reduce development costs and lower regulatory hurdles associated with the use of custom orthopedic implants [57]. Short- and long-term fracture risks can be analyzed preoperatively using advanced finite element tools, and new materials may allow faster healing and reduced long-term remodeling effects of stress shielding. Perhaps the most exciting development on the horizon is the leveraging of a percutaneous osseointegrated implant for the routing of peripheral nerve signals and neural control of advanced prostheses [58–60]. While some of these technologies are already being tested and others are still in their infancy, it is certain that the already long history of direct skeletal attachment of prostheses will grow richer with time.

Surgical Techniques

Surgical techniques that are used to implant percutaneous osseointegrated endoprosthetic devices must vary to accommodate different system materials and device designs. Surgical methods must also be adapted to the means selected to achieve intramedullary bone-to-device attachment (osseointegration) and to produce a biologically stable skin-to-implant interface (stoma). While certain aspects of the surgical method are necessarily unique to specifics of implant design, other requirements apply across all circumstances. For example, it is always necessary to maintain a continuous and ample blood supply to the device/skin and to the device/medullary bone interfaces.

Patient Selection Processes

In general, human trials of percutaneous osseointegrated DSA systems have applied similar subject selection and exclusion criteria. Exclusion factors typically include risk factors that interfere with bone healing such as dysvascular and atrophic bone conditions, immature bone (age), and suppressed innate or humoral immunity. Patients who require chronic narcotics, immunosuppressive medications, corticosteroids, or chemotherapy and those suffering from neoplastic and chronic liver or renal disease are also excluded. Diabetes mellitus and a high BMI are associated with increased risk for sepsis and poor wound healing. Heavy smoking is also a relative contraindication [11, 17, 19]. Advanced age with poor bone quality precludes

acceptance [17, 19]. The status of the residual limb is another key consideration, including good condition of the skin and freedom from severe osteopenia and underlying metabolic bone disease or infection. The need for at least 12 cm of remaining bone, the absence of a hip flexion contracture, and the absence of significant degenerative arthritic changes in the joint proximal to the device are commonly accepted as important criteria. Neurological and psychosocial conditions should be considered as well.

The Swedish Experience: OPRA

Preoperative CT is used to determine implant size. Once implant size is determined, surgical implantation is performed in two stages.

Stage 1: Muscles are dissected free from the femur for a distance of 5–10 cm above the bone end. Using a jig that grasps the shaft, an alignment rod is passed into the medullary canal, and the position is checked with C-arm imaging. The canal is bored out with hand reamers that increase in size by 1 mm increments. Cutting the canal is done slowly and with frequent saline irrigation to avoid heating and bone necrosis. The central alignment is checked frequently until the canal is prepared for the implant. The final fixture position is inset 8–20 mm proximal to the bone end and is again verified with radiographic imaging using an intraoperative C-arm image intensifier. The hollow lumen of the fixture is irrigated with saline before placement of the "healing cylinder," a temporary central insert, and its retaining screw. These removable parts seal the lumen against tissue ingrowth and protect the inner abutment threads until the second-stage surgery [11]. The muscles and soft tissues are repositioned, the wound is closed over suction drains, and a compressive dressing is applied.

Stage 2: Approximately 6 months after the first surgery, the initial surgical scar is excised, and full thickness skin and subcutaneous tissue flaps are established. Redundant soft tissue is excised. Myoplasty and myodesis are done by suturing to reciprocal muscles or the distal periosteum but not over the end of the bone or through drill holes, as this has proven to impede healing at the penetration site. The penetration site is marked on the subdermal side of the flap that will cover the bone end. The abutment size and fit is checked, and the abutment is passed through a stab wound, or a core made in the skin with a dermatology biopsy punch, and seated in the hexagonal fitting in the lower end of the fixture. The abutment retaining bolt secures the entire construct and is screwed into the interior threads of the implant to finger tightness. The soft tissue is carefully sutured to hold the prepared fat-free subdermal surface of the skin flap against the flat end of the bone while avoiding any compromise of the skin circulation. Conventional skin closure is done, and suction drainage may be used to prevent accumulation of hematoma. The abutment bolt is tightened with a torque wrench to 12 Nm of torque, and the penetration site is dressed with paraffin gauze and a light pressure bandage. A "dressing cylinder" 10 cm in diameter applies sufficient pressure to hold the undersurface of the skin in intimate contact with the bone end until healing, but not with so much pressure that skin necrosis occurs.

Surgical Hallmarks of the OPRA System

1. Vascularized full thickness skin on vascularized bone. No subcutaneous fat.
2. Immediate tight skin seal at the stoma. Skin becomes firmly attached to the bone in 2–3 weeks.
3. No skin motion at the stoma.
4. The intramedullary portion of the device is immediately stabilized in the bone.
5. The intramedullary portion of the device does not cap the bone end. The stoma is not remote from the bone end. The opening to the outside environment is on the edge of the medullary canal.

6. The subject is not immediately weight-bearing; in fact weight-bearing is delayed 6–18 months. The limb is immediately vertical.
7. Gravity drainage can occur from the stoma although the initial skin seal is tight.
8. The surgical site is isolated for several days with daily dressing changes and cleansing thereafter. Antibiotic dosing is applied as needed.
9. Stomal hygiene is done daily with sterile saline irrigation and sponge debridement.

The British Experience: The ITAP

This device is made of titanium alloy with a shaft incorporating cutting flutes (to prevent rotation in the medullary canal). A large umbrella-shaped flange, coated with hydroxyapatite, directly underlies the skin and overlies the subcutaneous tissue of the amputation stump. This flange is perforated with 0.7-mm holes into which the skin and soft tissues grow, producing a seal between the internal and external environments and a reduction in relative motion of the skin at the exit point [36, 37, 39, 40].

Surgical procedure: Plain X-rays and CT imaging are used to design a custom-built ITAP implant. The ITAP device is driven into the medullary canal with a slap hammer. Titanium mesh is secured around the bone to allow the residual muscle groups to be myodesed to the end of the bone. Stump revision involves excising excess skin and fat to create an asymmetric flap at the end of the stump. A circular area of this flap, equal in size to the distal surface area of the flange, is cleaned of all subcutaneous fat. The majority of the blood supply of this skin comes from the subdermal plexus, and the thinned skin is in intimate contact with the hydroxyapatite-coated porous surface. A stab wound creates an exit point for the attachment shaft for the exoprosthesis, and the thinned flap is sutured to the flange with interrupted sutures. A Poron washer, held in place by a cap that is adjusted daily, holds the skin against the flange, while cutaneous integration occurs [6].

Surgical Hallmarks of the ITAP Device

1. Vascular full thickness skin with no subcutaneous fat on an avascular hydroxyapatite-coated flange.
2. Immediate tight skin seal at the stoma. Skin sutured to the flange becomes adherent to the hydroxyapatite surface over time.
3. Little to no initial skin motion at the stoma. In time there should be no skin motion.
4. The intramedullary portion of the device is immediately stable.
5. The flange and underlying soft tissues partially cap the bone end, and the stoma is remote from the medullary canal.
6. The limb is immediately vertical.
7. Gravity drainage can occur from the stoma although the initial skin seal is tight.
8. The surgical site is isolated for several days. Showering and sterile debridement are allowed.
9. Stomal hygiene is done daily with an application of antibiotic ointment.

The German Experience: The ILP

The Aschoff device was introduced in 1999. Since then, it has evolved through three empirically derived design changes with three distinct modifications of the surgical technique [18, 19]. The current design was introduced in early 2009 (Fig. 10.2). All surgeries are completed in two stages, separated by an interval of 6 weeks.

Surgical technique: The length and diameter of the anticipated intramedullary implant are determined preoperatively from plain radio-

graphs or CT scanning. The C-arm image intensifier is used intraoperatively to confirm central axial reaming and broaching. Approximately 12–15 cm of residual femur is needed to successfully implant the existing device [17]. In one case, this bone length was achieved with distraction osteosynthesis, but this technique is time consuming and difficult. Despite being functionally successful, it has been excluded from current surgical options because of the attendant complication of a controlled draining sinus [19].

Stage 1: Skin flaps are fashioned, and the amputation stump is revised by myodesis and fatty tissue excision to allow a soft tissue depth of 1.5–2.5 cm between the final outside skin and the end of the medullary implant. To establish equal leg lengths and parallel knee axes, the femoral shaft may be shortened to a 12 cm distance above the axis of the intact knee; this accommodates the knee mechanism of the exoprosthetic limb. Periosteum is preserved to assure bone vascularity. The femoral shaft is opened and is power reamed or cold broached under visual control with C-arm imaging. When the appropriate endoprosthesis is selected, the end of the bone is milled flat, 90° to the central axis of the bone, so that the impacted endoprosthesis will bear weight equally around its circumference and lessen stress shielding. The implant is impacted into the femoral canal with a hand mallet and is capped with a threaded filler plug to prevent soft tissue growing into the female Morse taper during the 6-week interval before the second-stage surgery. Final soft tissue work is done, and the wound is closed over drains.

Stage 2: Six weeks after the first-stage surgery, the connecting system for the exoprosthesis is fitted. The central axis of the endoprosthesis is found by probing with a Kirschner wire into the hex screwdriver fitting of the capping plug. A soft tissue channel, which is approximately one third wider than the diameter of the bridging connector, is cored to reach the capping plug, and the tissue cylinder and plug are removed. The exposed female Morse taper is dried with a sponge, and the bridging connector, with male Morse tapers on each end, is inserted and secured with the system modules to attach the exoprosthesis. The smooth polished bridging connecter and the extraosseous portion of the endoprosthesis (implant) are coated with TiNb(ON). This coating prevents adherence of the soft tissue channel of the stoma to the extraosseous portion of the implant and the bridging connector (Fig. 10.2). The connector is fitted with a silicone cover, and a gauze dressing is applied to the stoma. When surgically cleared, patients begin the hygiene protocol of cleaning the stoma twice daily with a handheld shower and mild non-perfumed soap free of antimicrobials.

Surgical Hallmarks of the ILP

1. Vascularized skin and periosteum.
2. No more than 1.5–2.5 cm of subcutaneous fat and muscle between the endoprosthesis and the stomal opening.
3. An open stoma with free gravity-assisted tissue drainage around a TiNb(ON) surfaced bridging connector.
4. Free initial skin motion at the stoma, which becomes reduced with tissue maturation.
5. At the first-stage surgery, the intramedullary portion of the device is immediately stable in the canal. By the time weight-bearing has begun, osseointegration for 6–8 weeks have occurred.
6. The end of the transected femur is capped with the device making the stoma remote from the medullary canal of the bone.
7. Gravity wound drainage occurs, and the stoma is initially open.
8. The surgical site is dressed as needed, and only a single dose of prophylactic antibiotics is given.
9. Stomal hygiene is done once or twice a day daily with water and a mild non-perfumed soap without antimicrobial agents.

The Sheep Amputation Model

It is difficult to approximate the conditions of human patients when using any quadruped experimental model of percutaneous skeletal prosthetic attachment. Because sheep have bone healing and bone deposition rates (mineral apposition rate (MAR)) and secondary osteonal structures quite similar to those of humans, a sheep model has been widely used to study fracture healing and osseointegrated implant designs [61, 62]. However, because the sheep femur does not bear weight in a true axial direction when the knee is in full extension (comparable to the human condition), the ovine model fails when trying to duplicate a transfemoral amputation. The sheep's fused third/fourth metacarpal does however bear axial weight, and this bone has proven to be a reliable indicator of the progressive stages of osseointegration [55, 56, 63, 64] (Fig. 10.5). Unfortunately, the physiology of the skin-implant interface is only partially translatable to that of the human wound-healing conditions. The soft tissues in the region just above the hoof are very dissimilar to those in the human transfemoral residual limb. The fused third/fourth sheep metacarpal is covered only with skin with no muscle or subcutaneous fat and has posterior dewclaws, in addition to the tendons and tendon sheaths.

Surgical Procedure

Skeletally mature 2–3-year-old mixed breed sheep are used for the single-stage amputation and implantation procedure [65, 66] (Fig. 10.6). Preoperative standing radiographs, at a fixed distance with a 3D reference, allow template implant size selection. A transverse skin incision is made just proximal to the hoof and extended proximally in the medial and lateral coronal plane. This circumferential incision is completed with a transverse posterior incision immediately proximal to the dewclaws. The anterior skin flap must be carefully dissected in a proximal direction so that it is devoid of any subcutaneous tissues and fat. In addition, the anterior sagittal vessels are visualized and carefully protected in a saline-soaked gauze sponge. The hoof-metacarpal joint is disarticulated and the hoof removed. The distal condyles of the metacarpal are removed with a bone saw at the greatest dimension of the metaphyseal flare. The saw cut is at 90° to the long axis of the medullary canal of the metacarpal. The

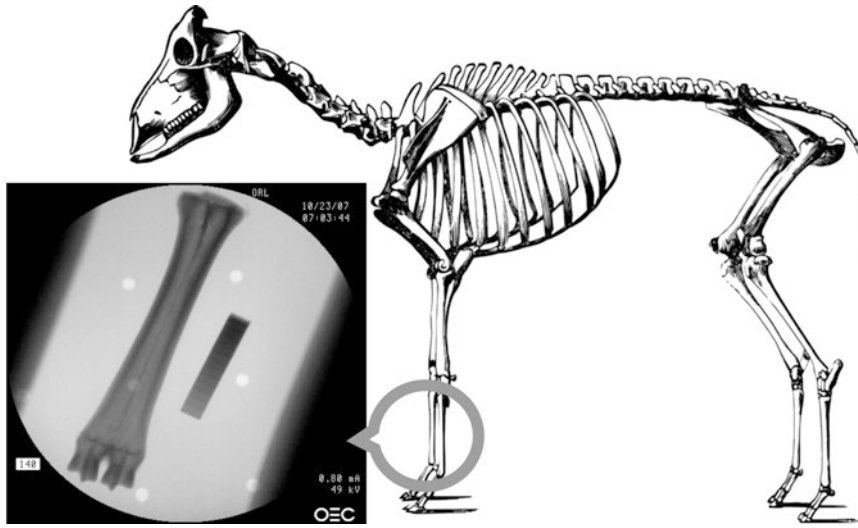

Fig. 10.5 Sheep skeletal system with radiograph showing fused metacarpal 3 and 4 bones

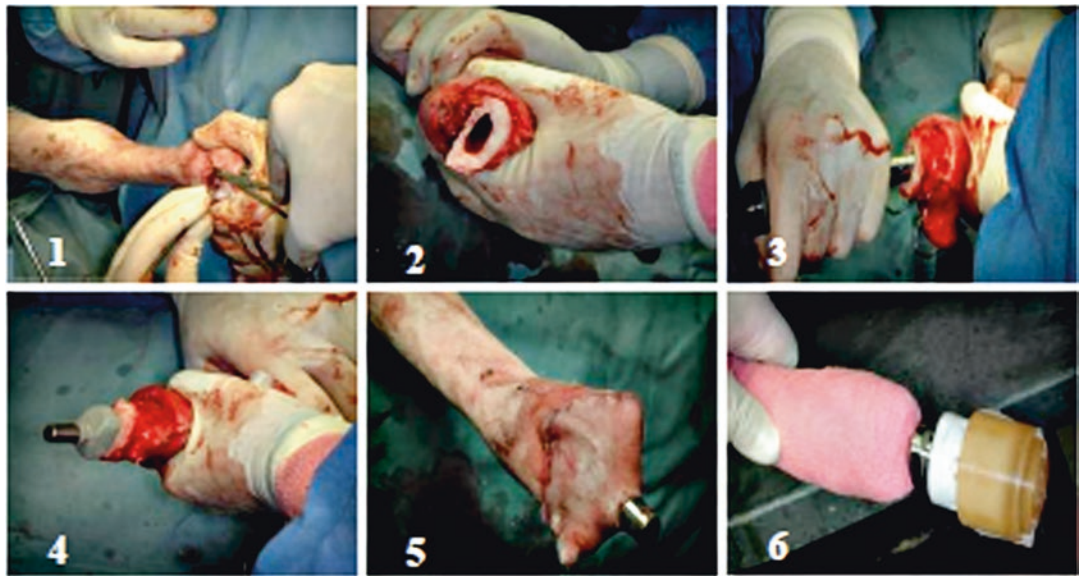

Fig. 10.6 Sheep amputation surgery: (1) dissection of metacarpal skin flap, (2) reamed metacarpal canal, (3) insertion of implant, (4) securely inserted implant in the medullary canal, capping the bone end, (5) implant site showing a Morse taper protruding through the skin, and (6) dressed wound with an attached exoprosthesis

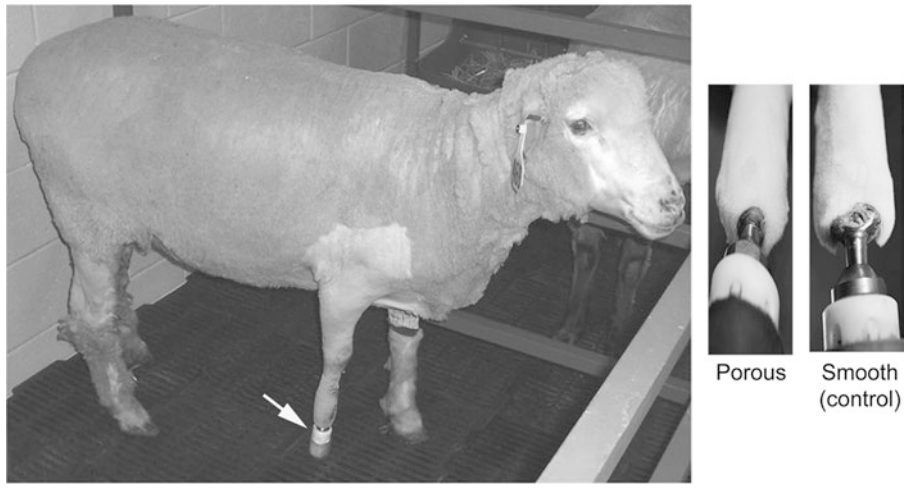

Fig. 10.7 A sheep fitted with a percutaneous osseointegrated prosthesis to the right fore limb; RHS images show skin-implant interface of the implant exit sites

remaining distal cancellous bone surface is drilled to expose the medullary canal. The canal is then reamed and broached to accept the implant. Using a hand mallet, the selected implant is driven tightly into the medullary canal. The skin flap is revised, but any redundant skin flaps are not excised. While carefully visualizing and avoiding the flap vessels, a midline sagittal stab incision is made, smaller than the Morse taper on the implanted device. The skin is stretched over the Morse taper and allowed to adhere to the structured titanium of the exposed shoulders of the implant to rapidly establish skin attachment and seal at the stoma (Fig. 10.7).

Surgical Hallmarks of the Sheep Amputation Model

1. A vascularized full thickness skin flap with no subcutaneous fat on an avascular porous titanium surface.
2. An immediate tight skin seal at the stoma with "Velcro"-like skin attachment to the shoulders of the device.
3. No skin motion at the stoma.
4. The intramedullary shaft of the device is immediately stable in the metacarpal.
5. The end of the transected metacarpal bone is capped by the device; thus the stoma is remote from the medullary canal of the bone.
6. Immediate weight-bearing is allowed, and the limb is immediately vertical.
7. Gravity drainage can occur from the stoma although the initial skin seal is tight.
8. The surgical site is isolated for 2 weeks, and prophylactic antibiotics are maintained for 7 days.
9. Stomal hygiene is done each week with a biocide.

Infection Prevention Strategies

European Osseointegration Experience and Programs

Although DSA provides a robust prosthetic suspension system, the absence of complete skin-to-implant integration and an epithelial seal at the implant exit site creates a portal of opportunity for bacterial invasion of the periprosthetic tissue region. Prolonged absence of this seal can promote superficial infections (erythema at the stoma). If left untreated, this may progress to deep-tissue infection and eventually osteomyelitis. As reported in European clinical trials, such deep-tissue infections occur with a variable incidence rate and can result in the need for implant removal [19, 20, 23, 24, 67–69].

Currently, three unique infection-limiting procedures have been employed in conjunction with OI prosthetic systems. They are (1) limiting the mechanical force by removing the excess soft tissue between the residual bone and the dermis (OPRA design), (2) encouraging the formation of hypergranulation periprosthetic tissue against an ultrasmooth implant surface as a first line of defense against bacteria (ILP design), and (3) obtaining a biological skin seal with the implant by using a perforated subdermal flange coated with hydroxyapatite biomimetic (ITAP design). The OPRA and ILP systems have employed a two-stage surgical approach to establish bone-to-implant integration before penetrating the skin when placing the percutaneous abutment for exoprosthesis attachment [11, 13, 17, 19]. To date, this two-stage surgical approach, which obtains a stable, osseointegrated endoprosthesis before any loading is allowed through the implant construct, has been used in over 300 patients with some success.

Reported infection rates for OPRA [23, 24, 67, 69] and the ILP [19] prosthetic systems vary between surgical centers and techniques. Infection rates range from as low as 0% for the latest design and surgical protocol modification of ILP systems [19] to almost 55–100% for OPRA implant systems [24, 67].

As discussed above, infections at the interface continue to be reported despite some success in limiting skin motion. In a 3-year study, Tillander and his coworkers prospectively followed 39 patients with the OPRA system for approximately 36 months [69]. They employed a semi-quantitative analysis to quantify the colony-forming units (CFU) of bacteria in and around the percutaneous abutment. Their data showed 5% frequency of infection at inclusion and 18% frequency at follow-up. However, the findings are difficult to interpret because 18 (49%) of the patients included in the study had a

history of infection prior to the study [69]. Although various microbes are found at all interfaces, the probable pathogens were limited to *Staphylococcus aureus*, *coagulase-negative staphylococci*, *Enterococcus faecalis*, and *E. coli* species [69]. This study also reported that two patients became severely infected. In one patient, the infection resolved after a short course of antibiotic therapy, while the second patient required implant removal to cure the infection. Within the infected group, this was a 50% failure rate with antibiotic treatment [69]. The inability of conventional antibiotic therapy to control periprosthetic infection may be attributable to the establishment of biofilms on the implant surfaces.

In a study conducted in the United Kingdom with the OPRA system, 2 of 11 patients (18%) became infected and had their abutments removed within 2 years following surgery [68]. Moreover, Bragdon et al. recently reported approximately one infection per every 2 years, indicating a 100% infection rate in the OPRA implant system [67]. More recently, two further OPRA studies had reported infection rates of 38% (5-year study) and 55% (2-year study) in transfemoral cases [23, 24]. Infection data from patients with the OPRA system indicate that immobilization of the skin at the implant-skin interface does not by itself prevent periprosthetic infection.

In the ILP system, a 2 cm soft tissue envelope is maintained between the skin and bone to limit interfacial forces and to permit soft tissue adaptation (hypergranulation tissue formation) to act as a barrier for fighting infection [17–19]. Since granulation tissue is highly adapted to fight bacterial invasion, its presence at the interface is considered beneficial. Some promising infection data were presented in a recent publication by Aschoff and colleagues, who found that the initial high rate of stoma-associated infection and revision rates (70%) seen in their first generation of ILP designs was reduced to 0% in the current design (Generation 3) [19]. In this type of percutaneous system, the study suggested that the best infection prevention strategy is daily cleansing of the skin-implant stoma with water and a mild soap and gentle debridement of tissue and biofilm from the interface using a shaving brush. Microbiological examination of the implant exit site of ILP patients, using only conventional culture techniques, produced findings similar to those in OPRA patients [70–72]. This led the researchers to conclude that (1) bacterial colonization of the stoma is unavoidable, (2) bacterial colonization does not correlate with infection, (3) the pathogenicity and virulence of colonizing bacteria does not correlate with the appearance of infection, and (4) disinfection and antibiotic treatment are counterproductive [71].

In both the ILP and OPRA implant systems, serous drainage persists at the interface in some patients [17, 69]. Clinicians hypothesize that the drainage, together with the smoothness of the implant and the daily cleaning regimen used by the patients, helps to maintain the critical colonization of mutualistic bacterial species at the interface, thus preventing serious infections [19]. The ITAP system uses a biomimetic surface coating for establishing skin seal with the implant surface, preventing entrance of ascending infection from the external environment. In this system, a HA-coated, perforated subdermal barrier is used to promote the integration of implant and soft tissue, thus stabilizing the interface [36, 37, 39, 73]. For example, a single-stage ITAP implant was used in a subject with transhumeral amputation in 2009, and 2 years later no infections were reported [37]. There is an ongoing clinical trial of the ITAP system in 18 transfemoral amputees, but success and infection rates of this system have not yet been reported [38].

With these European systems (OPRA, ILP and ITAP), superficial infections have been treated with short courses of antibiotics or a local topical antibiotic ointment [13, 23, 24, 69]. When early clinical infection occurs, the safest and

most successful approach may be to use the established surgical principles of exteriorizing the infection site by incision and drainage [74]. This was an inspiration from the wound management principles of the famous French surgeon, Dominique-Jean Larrey [75]. In the case of deep infections, device removal may become necessary. Clinical resolution of deep infection in OI prosthetic systems resembles that of the two-stage treatment protocol used in total joint revision surgeries to resolve infection. In these cases, the first-stage treatment is removal of the infected endoprosthetic components, insertion of a temporary spacer with antibiotics, and systemic antibiotic treatment. The second stage involves an operation to insert a new implant system [13, 17].

In summary, three different approaches have been used clinically to prevent periprosthetic infection with OI prosthetic devices. All three surgical procedures have reported some success with preventing the excessive interfacial forces between the periprosthetic tissue and implant, thereby preventing sinus tract formation around the implant. However, infection remains a concern in every case.

Research and Development in the United States

Since 2005, translational animal studies have been carried out by research teams at the University of Utah and at the Salt Lake City VA Health Care System [55, 56, 63–66, 76–78]. Initial studies investigated the use of antimicrobial agents to prevent infections, but this approach was found to be unsuccessful [77, 78]. Currently, the use of porous-coated surfaces has proven to be effective in limiting infections [65, 66, 76, 79] at least in the short term. Porous-coated surfaces promote early bone and soft tissue ingrowth, allow interdigitation with the surrounding host tissue, and, in turn, limit skin motion (shear) at the exit site and encourage attachment. It has been shown that this approach promotes mechanical skin stabilization at the implant-skin interface and limits onset of infection [65, 66, 76, 79].

In a single-stage implantation study, sheep were implanted with endoprosthetic constructs incorporating either a porous-coated subdermal barrier ($n = 14$) or a smooth titanium (Ti) subdermal barrier ($n = 8$) [65]. Clinical, microbiological, and histopathological data showed that the porous Ti barrier prevented superficial and deep-tissue infections in all animals (14/14, 100%) at the 9-month endpoint. In contrast, animals with the smooth Ti implant construct had a 25% (2/8) infection rate. Survival analysis identified a statistically significant difference between the groups (log-rank test, $p = 0.018$) [65]. However, epithelial downgrowth (marsupialization), while slowing on the porous surface, has been shown to persist and continues out to 2 years even dissecting the initially attached fibrous connective tissue from the porous structure.

Bone-to-implant integration analyses indicated that the bone ingrowth into the pores of the endoprosthesis allowed mechanical stabilization of the device within the first 3 months after its implantation. There was a linear relationship between bone ingrowth and pullout force [55]. MAR also increased during the first 6 months following implantation, supporting the ingrowth data [64]. These findings support an early weight-bearing rehabilitation protocol, provided the implant is stabilized within the medullary canal by a secure intramedullary fit that limits micromotion [63].

As mentioned although the data from these studies indicated no infection in the porous-coated group, the investigators noted that with increasing implant time in situ, the skin continued to "downgrow" [66]. Downgrowth – also known as skin regression or marsupialization – refers to the growth of epithelium along the implant in such a way that the external surface of the skin faces the implant. This is a native immune response to rees-

tablish the skin's protective barrier function by attempting to expel the implant [66, 80].

Histological evaluation of the tissue at the skin-implant interface (Fig. 10.8) revealed that the periprosthetic tissue was a granulation tissue wound bed, onto which the epithelial tongue migrates. Immunohistochemical (IHC) analyses of the periprosthetic tissue (fresh frozen) taken at the interface verified the presence of the granulation tissue – a highly vascularized tissue indicated by a high florescent collagen IV signal density (Fig. 10.9) at the interface [66]. Terminal epithelial cells were found to express keratin VI, the keratin type expressed by metabolically

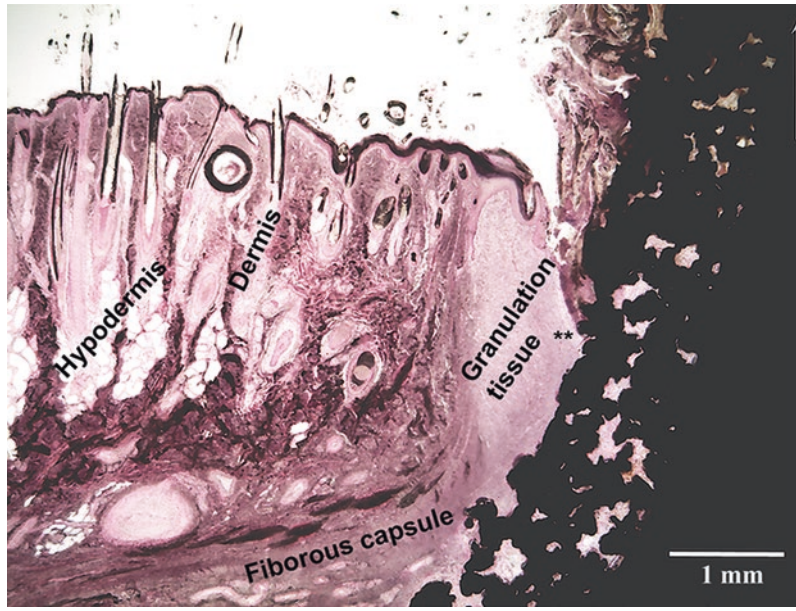

Fig. 10.8 A typical sheep skin-implant interface (H&E stained cross sections) showing interfacial difference in tissue morphology. "**" shows the position of the three-phase junction (point at which skin, implant, and external environment meet). *White arrow* indicates the direction of the implant exit site. Two different tissue morphologies are shown at the periprosthetic region immediately adjacent to implant: (1) hypercellular granulation tissue at the three-phase junction and (2) aligned fibrous capsule between the healthy skin and the implant

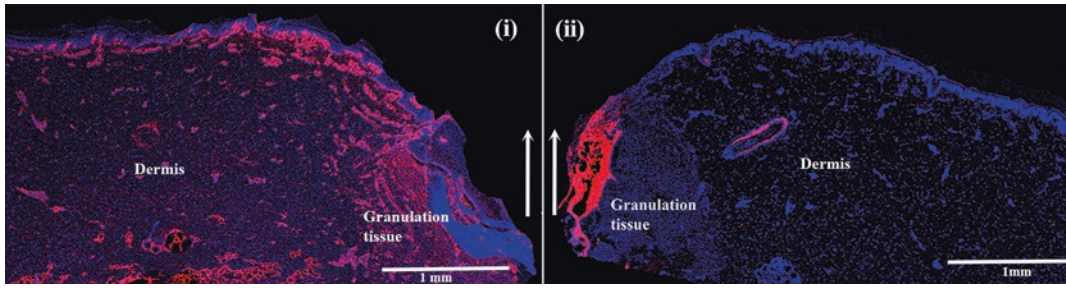

Fig. 10.9 Confocal micrographs of tissue biopsies taken at the interface showing immunofluorescent antibodies against collagen IV (i) and keratin VI (ii). *Blue* = nuclear stain (DAPI). *White arrows* show the relative position of implant post and implant exit site. The epithelial tissue that covers the granulation tissue bed is expressing keratin 6, which indicates wound-healing response (i). The granulation tissue region is highly vascularized indicated by collagen IV (found in endothelial and epithelial basement membranes) signals (ii)

active migrating keratinocytes of the advancing wound edge [80–83]. The IHC validated that the periprosthetic tissue was a highly active tissue and proved the presence of an ongoing wound-healing phenomenon at the interface. "Impaired wound healing" is therefore suggested as the probable mechanism of downgrowth and granulation tissue formation around the implant.

In the human clinical situation, continual proximal skin migration could expose the interconnecting porous coating, which could be deleterious to the long-term, infection-free survival of the implant. A 24-month sheep study has validated this concern as one animal with the porous-coated implant showed clinical signs of infection 15 months after implantation surgery; data from this study will be published shortly. Although the presence of highly vascularized granulation tissue at the interface may be ideal for fighting infection, critical influx of pathogenic bacteria that reside within the exposed pores of the coating (pores which communicate with the external environment as a result of downgrowth) may adversely influence the stability of the interface. This introduces the potential for a rapid shift from healthy to infected state. Additional studies are required to further investigate this potential complication.

A permanent, non-migrating skin seal is the ideal environment to prevent infection. Based upon our studies and the observed evolution of OI implant designs and surgical protocols tested in Europe, it appears that the exposure of the porous coating to the environment provides a potential avenue for bacterial colonization in the human recipient. The porous-coated implant system could be an ideal system for mechanically stabilizing the implant-to-soft tissue interface only if a method of preventing skin marsupialization can be identified. Achievement of a non-migratory skin seal remains a challenge. Using immunohistochemistry techniques, researchers at the University of Utah continue to investigate the mechanism of downgrowth. Permanent solutions will require an improved understanding of the underlying causes of this continuous healing phenomenon around the implants. Studies are being conducted to understand the effects of cell-to-implant matrix attachment and of mechanical forces, with the goal to prevent continuous wound healing at the interface.

Future Considerations

In order to completely prevent infection arising from skin-implant interface, it is necessary to reestablish the skin's native protective function by obtaining and maintaining both the dermal and epidermal integrations with the implant. Although current strategies to prevent infection may not be ideal, new soft tissue management and surgical techniques, together with consistent hygiene, have shown improved results. Additional directed research is needed to develop a permanent, non-migratory skin seal. Specifically, research is needed to elucidate the reaction of periprosthetic tissues to interfacial mechanical forces, to understand wound-healing cascades, and to advance development of biomimetic surfaces that can arrest wound healing. Since all skin-implant interfaces have proven to be colonized by skin bacteria, it is also highly likely that establishing an ideal microbial environment at the stoma, one consisting of mutualistic and commensal bacteria, may serve to protect against the invasion of pathogenic bacterial strains. Although this is a challenging agenda, we believe it will support effective bioengineering solutions to prevent infections that currently originate from the skin-implant interface.

Rehabilitation Considerations

Functional use of a prosthetic limb requires comfortable, secure, and stable suspension of the device on the residual limb. Currently available

socket suspension systems can come loose or completely disconnect from the residual limb. They are frequently also associated with skin breakdown, residual limb pain, and sitting discomfort. Sockets can be difficult to don and doff, limit ROM, and may provoke vascular and neurologic compromise. Sockets typically provide poor heat transfer; this can cause excessive residual limb temperatures and sweating, which contribute to dermatologic complications. Individuals with residual limb volume fluctuations, adherent scar tissue, neuromas, or heterotopic ossification may experience even greater difficulties.

Compared to socket suspension, DSA by osseointegration offers many documented and potential advantages [11, 13–15, 84–86]. Through osseointegration, load bearing is transferred to the bone instead of the residual limb soft tissues. This provides secure and stable suspension as well as improved mechanical transfer of motion [87, 88]. There is a reduced risk of skin irritation and breakdown, improved ROM, and enhanced comfort. Osseointegration may also decrease the time and effort required to don and doff a prosthesis. Individuals who have undergone osseointegration for the DSA of prosthetic limbs have also reported improved proprioception of the prosthesis which has been termed "osseoperception" [15, 89].

European Experience and Rehabilitation Outcomes

As noted previously in this chapter, the application of osseointegration for DSA was pioneered by Dr. Rickard Branemark and his father, Per-Ingvar Branemark. Dr. Rickard Branemark's postsurgical rehabilitation protocol begins partial weight-bearing 6–8 weeks following the stage 2 procedure, with utilization of a short-length training prosthesis [13, 90]. Weight-bearing is performed with gradual, axial, static weight-bearing that begins at 20 kg for 30 min twice a day. The condition of the bone at the time of surgery dictates the weight-bearing progression into a normal or half-speed speed protocol (Table 10.2). The visual analog pain scale (VAS) is used to modify the rate of progression [13].

Table 10.2 Dr. Branemark's rehabilitation protocol progression

Normal speed protocol
Static weight-bearing is increased by 10 kg/week
Visual analog scale (VAS) pain should be maintained <5
Partial weight-bearing with full prosthesis started 3 months after stage 2 surgery
Partial weight-bearing gradually advanced over 3 months
Total protocol – 6 months/total time from stage 1 surgery – 12 months
Half-speed protocol
Weight-bearing increased more slowly
Visual analog scale (VAS) pain should be maintained <3
Partial weight-bearing with full prosthesis started 6 months after stage 2 surgery
Partial weight-bearing more gradually advanced over 4–6 months
Total protocol – 10–12 months/total time from stage 1 surgery – 16–18 months

Dr. Branemark has published general outcomes from the first 100 patients who were treated in his program under the OPRA protocol. The study provides excellent detail on the rehabilitation protocol but does not provide detailed information about functional and gait outcomes [13]. Several other osseointegration programs around the world have adopted the Branemark approach but also report limited information about rehabilitation outcomes [68].

Dr. Branemark's group evaluated 13 patients who had used osseointegrated prostheses for 3–15 years [84]. Participants reported subjective improvements in terms of functional restoration, prosthetic device use, and quality of life. However, the study did not capture complications and experiences of patients whose osseointegration treatments were unsuccessful. More detailed rehabilitation outcomes have been published on

18 patients with osseointegration who had passed the 2-year follow-up period [14]. Outcomes in this group were assessed using two self-report questionnaires: the SF-36 Health Survey (SF-36) and the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA). This study found statistically significant improvements (vs. preoperative measures) for four of the scales of the SF-36 (Physical Functioning, Role Functioning Physical, Bodily Pain, and Physical Component Score) and for all four scores of Q-TFA (Prosthetic Mobility, Walking Habits, Problem Score, and Global Score). The authors concluded that these results demonstrate improved general physical quality of life, increased prosthetic device use, better prosthesis mobility, and fewer prosthesis problems following osseointegration.

Another study also examined specific functional outcomes in 22 subjects undergoing osseointegration. Before and after implantation, subjects were surveyed using several functional outcome measures, including the global score of the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA), prosthesis use, 6-min walk test (6MWT), Timed Up and Go (TUG) test, and oxygen consumption during treadmill walking. All measures were found to be significantly improved when using the osseointegrated prosthesis [91].

In Germany, Dr. Horst Aschoff has adopted a more aggressive weight-bearing and rehabilitation strategy that has evolved along with his implant design [74]. With early generation implant designs, partial weight-bearing began 4–6 weeks following the stage 2 procedure and gradually advanced over a 4–8-week time period, depending on bone structure and pain symptoms. With newer generations of the implant design, patients are allowed to begin partial weight-bearing within the first week after the second surgery and can advance to full weight-bearing without an assistive device as long as pain remains at an acceptable level. Dr. Aschoff's program has not published more specific rehabilitation and prosthetic training protocols or functional outcomes.

Some studies have examined electromyographic and kinematic gait changes following osseointegration. A study of residual limb electromyographic muscle activity in five transfemoral amputees with osseointegrated fixations found that these patients were unable to maintain a maximum voluntary contraction of constant amplitude. This differed from controls without amputations. Based on the varying EMG profiles in amputee subjects, the authors recommended further work to develop optimal muscle anchorage to ensure maximal mechanical performance [92]. Kinematic data were gathered for the lower extremity and pelvis in 19 subjects following osseointegration, to compare pre- and postoperative measurements versus healthy controls. Postoperative data showed values for hip extension and pelvic tilt normalized significantly but did not reach control values. Patients increased hip extension by a median of 7.3° ($p = 0.007$), changing from −2.68 (range −13.4° to 10.7°) to −9.9 (range −29.4° to 5°). Anterior pelvic tilt was reduced by 4.0° ($p = 0.016$), changing from 21.7 (range 11.9–34.8°) to 17.7 (range 5.5–25.7°) [93].

Research and Development in the United States

For amputees presented with the option of osseointegration, a major factor in their decision is the prolonged postoperative course of recovery and rehabilitation associated with the procedure. A study that examined perceptions and acceptance of osseointegration found that improved acceptance would also require addressing infection prevention, the possibility of implant failure, and the long-term risks associated with the procedure [94].

Researchers in the United States have been working to address these issues and postoperative rehabilitation regimens. Objective, clearly defined outcome measures are critical to demonstrate improved rehabilitation and functional outcomes. Researchers at the University of Utah have focused on the development of a rehabilitation strategy that prioritizes safe and timely return to independent ambulation while optimizing the speed and strength of osseointegration at the bone-implant interface. Their work has focused on the development of specific rehabilitation tools for quantitative measurement and monitoring of progressive weight-bearing and implant stability.

In a large animal model study discussed previously, the gait characteristic outcomes of sheep were examined over a 12-month period [56]. This study found no statistically significant differences in stride length or stance time for the osseointegrated limb at any time point. However, differences were noted for weight-bearing by the osseointegrated forelimb versus the contralateral forelimb. The sheep loaded their osseointegrated limb a mean value of approximately 80% of their pre-amputation loading condition at 1 month following surgery; by 12 months, this mean had dropped to approximately 74%. Although statistically significant, the sheep otherwise maintained a symmetric gait pattern and had no functional limitations. The reasons for the decreased weight-bearing on the osseointegrated forelimb are unknown.

Easy-to-use, noninvasive resonance frequency devices have been developed to determine the stability of dental implants. Resonance frequency measurements correlate with stability of implants placed in the mandible [95–97]. Research has also been performed to develop a resonance frequency-based rehabilitation tool that will allow noninvasive monitoring of the strength and stability of an osseointegrated implant for amputees. The goal is to facilitate efficient rehabilitation while protecting the implant from loosening or failure. An in vitro model was used to simulate irregular medullary canal implant contact and osseointegration [98]. In this model, a strong correlation was found between the resonance frequency values and the force required for implant push-out. Mechanical displacement forces also correlated with the distance from the point of fixation to the proximal end of the implant. Additional studies are underway to develop this device for clinical application.

The ability to monitor and regulate weight-bearing during ambulation will also be important to advance effective and efficient rehabilitation while protecting the integrity of an implant [99, 100]. Gait- and weight-bearing monitoring devices currently in development will provide feedback to the subject when weight-bearing on the OI limb exceeds a predetermined threshold. Measurement of weight-bearing in real time during ambulation can facilitate dynamic ambulation activities while preventing implant failure at the bone-implant interface. In a design and validation study, the Lower Extremity Ambulation Feedback System (LEAFS) was able to determine stance time (time during which the limb is in contact with the ground) consistent with a clinical motion analysis laboratory and detected the same stance time asymmetries as the motion laboratory in subjects with unilateral amputation [101–103]. Use of LEAFS has been shown to be feasible in persons with transtibial amputations, and in a small number of subjects, there were considerable improvements in trunk sway and gait symmetry [103]. Another study demonstrated that symmetry based on stance times and stance forces could be predicted using instrumented shoe insoles. The authors also determined that instrumented shoe insoles and real-time feedback could be used for improving patient compliance with weight-bearing regimens or other time- or force-based symmetry analyses outside of the gait laboratory setting [101, 102].

Devices have been developed and proposed to reduce forces on the bone-implant interface and to protect the interface from catastrophic level forces [104–107]. The Rotasafe device used by Dr. Branemark is designed to protect the bone-implant interface from rotational forces [13]. The ideal design of an overload protection device would protect the implant from torsional, axial, and bending overloads, allowing each mode of protection to be independently adjusted. This ideal device would also include a nondestructive, resettable protection mechanism, and size and weight characteristics compatible with transfemoral prosthetic restoration.

Rehabilitation and prosthetic gait training are vital components of successful osseointegration for the DSA of prosthetic limbs. Post-implant rehabilitation techniques and protocols have been developed and implemented outside of the United States, but there is limited evidence yet to support their effectiveness and outcomes. Continued research will support development of these rehabilitation interventions and improve functional outcomes following osseointegration.

Summary

Osseointegration for the DSA of prosthetic limbs has the potential to substantially benefit certain individuals with limb loss. Advanced control systems and newer prosthetic components emphasize the importance of secure suspension to promote optimal performance through full ROM and direct transfer of forces. Osseointegration approaches applied in Europe have been complicated by infection and implant failures and involve prolonged rehabilitation protocols. These concerns are partially resolved by advances in technology and technique. Researchers in the United States are also working to address these issues and to implement human clinical trials. The success of these trials and further research will determine the degree to which osseointegration becomes a reasonable and an accepted alternative to socket suspension techniques for certain individuals with lower extremity amputation.

Disclaimer The views expressed in this presentation are those of the author(s) and do not reflect the official policy or position of the Federal Government of the Department of Veteran Affairs.

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Lower Extremity Transplantation: Concepts, Challenges, and Controversies

11

Vijay S. Gorantla, Fatih Zor, Serdar Nasir, Warren C. Breidenbach, and Michael R. Davis

Abbreviations

ATG	Antithymocyte globulin
BMI	Body mass index
BTFA	Bilateral transfemoral amputations
CD	Cluster of differentiation
CMV	Cytomegalovirus
CNS	Central nervous system
DCBI	Dismounted complex blast injury
EBV	Epstein-Barr virus
GU	Genitourinary
GWOT	Global war on terror
HLA	Human leukocyte antigen
IED	Improvised explosive device
IgG	Immunoglobulin G
IRI	Ischemia reperfusion injury
LET	Lower extremity transplantation
MAST	Military antishock trousers
NMJ	Neuromuscular junction
OEF	Operation enduring freedom
OIF	Operation Iraqi freedom
OPTN	Organ procurement and transplantation network
PASG	Pneumatic antishock garments
PTLD	Posttransplant lymphoproliferative disease
RT	Reconstructive transplantation
TF	Transfemoral
UNOS	United Network for Organ Sharing
VCA	Vascularized composite allotransplantation

V.S. Gorantla, MD, PhD, FRCS (✉)
Reconstructive Transplantation Program, Department of Plastic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: gorantlavs@upmc.ed

F. Zor, MD
Department of Plastic, Reconstructive and Aesthetic Surgery, Gulhane Military Medical Academy, Ankara, Turkey
e-mail: fatihzor@yahoo.com

S. Nasir, MD
Department of Plastic, Reconstructive and Aesthetic Surgery, Hacettepe University, Ankara, Turkey

W.C. Breidenbach, MD, FRCS (C)
Division of Reconstructive and Plastic Surgery, University of Arizona, Tucson, AZ, USA
e-mail: wbreidenbach@surgery.arizona.edu

M.R. Davis, MD, FACS
United States Army Institute for Surgical Research, San Antonio Military Medical Center, San Antonio, TX, USA
e-mail: Michael.r.davis166.mil@mail.mil

Civilian Statistics and Spectrum of Lower Extremity Loss

The most common causes of lower extremity amputations in the USA include vascular, traumatic, neoplastic, and congenital etio-pathologies

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[1, 2]. Approximately 623,000 of the estimated 1.6 million limb amputees (per 2005 data) in the USA suffer from a major amputation of the lower extremity. Diabetes and other peripheral vascular disease etiologies account for more than 80% of these amputations, with only around 16% of cases secondary to trauma [3].

Epidemiologic and population health projections estimate that peripheral vascular disease-related lower extremity amputations will increase exponentially by the year 2050. In fact, in the next three decades, when combined with those suffering with upper or multiple extremity amputations, 1 in 120 individuals will have an extremity amputation [4].

Although trends for traumatic extremity (including lower) amputations have shown a decline since 1980, trauma remains the second most common cause of amputation in the USA. An analysis of the National Trauma Database reveals that in major trauma, bilateral and unilateral lower extremity injuries led to the predominant number of amputations [5]. The average age of the trauma patient was 37 years, with a peak between 20 and 29 years of age. The economic, psychosocial, and public health impact of lifelong physical disability in a population this young is significant when compared to similar challenges in elderly (>70 years old) populations prone to vascular disease-related amputations [6–9].

Combat Wounds and Challenges of Multiple Extremity Trauma

There are few scenarios more challenging than the management and care of combat casualties. Historically, military conflict has always been the significant force for advancing our knowledge of injury management. Practices of far-forward combat casualty evacuation and care originally practiced by military medical personnel in the Korean and Vietnam wars, for example, became foundational practices for modern emergency medicine [10].

Improvised explosive devices (IEDs), blast (high-pressure shock waves), landmines, and shrapnel fragments accounted for the majority of combat injuries sustained among the approximately two million American troops who have served in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and other military operations related to the Global War on Terror (GWOT) since October 2001 [11]. Although Kevlar helmets and other advances in body armor have saved the lives of many service members, these protective devices do not protect against blast and impact injuries to the head, face, and extremities. Thus it is not surprising that injuries and injury patterns sustained by service members during the decade of war between 2001 and 2011 are characterized by extremity, craniofacial, and genitourinary (GU) trauma [12].

One study of major upper and lower extremity amputations over a decade of conflict in OEF and OIF determined that there were 1,631 amputations in 1,221 service members. Of these, lower extremity amputations comprised 76.3% [transtibial amputations (41.8%, 683 cases), transfemoral amputations (34.5%, 564 cases)] compared to 14% upper extremity amputations (228 cases). The remainder (9.7% cases) sustained multiple extremity amputations [13]. The number of service members with multiple limb amputations was found to be higher than in prior conflicts.

Dismounted Complex Blast Injury (DCBI) became the hallmark injury of the Afghanistan Theater of Operation (ATO) [14, 15] where rugged mountainous terrain forced service members to conduct many operations on foot, rather than in armored vehicles as was more common in the Iraq Theater of Operation (ITO) [16]. DCBI was characterized by devastating high-energy improvised explosive device (IED) trauma uniformly involving bilateral lower extremities, upper extremities (mostly nondominant), lower abdomen,

pelvis, and genitourinary systems [17–19]. The number of service members who were evacuated from theater suffering from triple and quadruple amputations secondary to DCBI was double the number of multiple extremity amputations reported over the previous 8 years combined (2001–2009) [20]. Aggressive, advanced, multidisciplinary in-theater management of DCBI has enabled significant improvements in service member survival. However, these devastating, complex, multiple extremity injuries have challenged the best conventional reconstructive or rehabilitative options, such as free vascularized tissue transfers and prosthetic alternatives, resulting in persistent functional and psychosocial impairment [21, 22].

Emergence of Reconstructive Transplantation

Catastrophic but survivable injuries sustained by service members in conflict and by civilian victims of terrorist attacks have tested the mettle and primary tenets of conventional reconstructive surgery [23–26]. Reconstructive transplantation (RT) was a specialty born of the necessity to address these challenges [27]. RT involves the transplantation of vascularized composite allografts (VCA), including but not limited to upper and lower extremity, craniofacial, genitourinary, tracheal, and abdominal tissues [28].

Conventional reconstructive procedures rely on the use of autologous tissues for major tissue loss. Often, such reconstruction requires repeated surgeries, prolonged hospitalization, prolonged morbidity, donor site defects, and often-poor aesthetic and functional repair or outcomes. By allowing transfer of vascularized tissues matched to the recipient defect, RT facilitates like-with-like repair of devastating injuries that challenge the very mettle of the best conventional reconstructive options.

RT is now the new realm of solid organ transplantation. Since VCA grafts are derived from either deceased or (in some cases) living donors, and since they are "primarily vascularized," the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) have recently enacted policy changes to define and designate VCA under "solid organs" for the purposes of donation and transplantation [29].

Worldwide, over the past 15 years, more than 200 VCA procedures have been performed, including more than 100 upper limb and 30 face transplants [30]. Patient/allograft survival and immunologic/functional outcomes have been mixed, ranging from dismal to suboptimal to encouraging. If we consider overall graft survival outcomes alone, results to date have been superior relative to the early outcomes seen with conventional solid organ transplants. However, the clinical potential of these procedures has remained untapped due to the known and unknown lifelong hazards of immunosuppressive drugs. Although the technical, immunologic, and functional feasibility of VCA as an alternative restorative option has been established in indications such as hand and face RT, much remains desired to improve the safety, efficacy, and applicability of this promising reconstructive modality [31].

Although the definition of "success" across different VCA remains a challenge, VCA have the potential to restore the appearance, anatomy, and function of otherwise debilitating or devastating injuries not otherwise conducive to conventional reconstruction [32, 33]. Successful RT procedures can also avoid the need for multiple revisions and can achieve superior functional and/or aesthetic outcomes without the high costs of multiple surgeries and hospitalizations as are associated with conventional reconstruction. The remainder of this chapter is an overview of lower extremity RT, focusing on the concepts, challenges, and controversial aspects with a critical appraisal of success to date.

Conceptual Basis of Lower Extremity Transplantation

Clinical Experience with Lower Extremity Transplantation

According to the most recent OPTN and UNOS data available (as of April 15, 2016), there are 59 approved VCA programs located in 26 centers (including civilian, military, or Veterans Affairs-affiliated institutions) across the USA (Table 11.1). Most of these programs were approved over the last decade (2006–2016). The majority (49/59) are approved for upper extremity, head and neck, and abdominal wall VCA [34]. A minority (10/59) are approved for genitourinary (may include uterus, penile, ovarian, testicular VCA) and lower extremity VCA. As of August 2016, there were only two programs approved for lower extremity transplantation (LET) in the USA, and no lower extremity transplants have yet been performed in the USA. Worldwide, only four programs have performed LET [35]. Experience in LET is therefore limited, but valuable insights are now emerging to inform challenges, opportunities, and future prospects for lower extremity VCA.

Table 11.1 Number and type of OPTN-UNOS-approved VCA programs across 26 transplant centers in the USA (data current as of April 15, 2016)

Type of VCA program	Number of approved programs
Upper extremity	18
Head and neck	17
Abdominal wall	14
Genitourinary transplantation	8
Uterine	3
Penile	2
Genitourinary (not specified)	3
Lower extremity	2
Total approved programs	59

These numbers will grow as additional programs are approved. Specific VCA program identities and information will be released in an upcoming paper, currently in preparation by UNOS. The American Society for Reconstructive Transplantation (ASRT) also makes available a National Directory of VCA Centers in the USA as a resource to provide program and contact information to VCA candidate patients and their families: http://www.a-s-r-t.com/NationalDirectoryofVCACenters.html. (Note: Not all OPTN-UNOS-approved VCA programs are included in the ASRT National Directory)

The pattern of injuries associated with DCBI is characterized by devastating trauma to lower extremities, notably bilateral transfemoral amputations (BTFA) with or without concomitant upper limb loss [14–16, 18, 19, 36, 37]. Similar injuries have also been observed in civilians such as those who were injured in the Boston marathon bombing in 2013 [24, 25]. For patients who suffer such severe injuries, RT teams around the world have been eager to offer VCA as a treatment option in the form of LET.

Four cases of lower extremity VCA have been reported, in the peer literature or lay media, including one pediatric recipient and three adult recipients (one bilateral LET, one unilateral LET [with two upper extremities], and one bilateral LET [quadrimembral with two upper extremities]) (Table 11.2). The combined transplant recipients uniformly succumbed to complications during or after surgery. The bilateral LET recipient developed posttransplant lymphoproliferative disease (PTLD), which necessitated amputation to prevent mortality. These cases are summarized here in brief.

The world's first LET was performed in 2006. The patient was a 3-month-old baby separated from her ischiopagus twin sister who had an inoperable and non-survivable cardiac anomaly [38, 39]. The twins had shared three lower extremities, providing the opportunity to "transplant" one limb from the deceased twin to restore normal symmetric lower limbs in the surviving twin. Although described as an LET, this procedure may not qualify as a true allogeneic transplant because it was a genetically identical twin-twin transfer and did not require immunosuppression. The patient is now over 10 years postsurgery. Sensation to light touch has returned,

Table 11.2 Summary of lower extremity transplantations and multiple extremity (tandem) transplantations across the world

Lower extremity transplantation and multiple extremity transplantation			
Year	Program and team leader	VCA components	Outcomes
2006	Toronto, Canada	Recipient was a 3-month-old baby girl	Six-year follow-up shows motor and sensory return with independent ambulation albeit the use of braces and limb length discrepancy. MRI evidence of cortical integration of limb
	Zuker	Unilateral LET with hip socket	
		No immunosuppression was needed, as donor was a genetically matched ischiopagus twin sister who succumbed after birth	
2011	Valencia, Spain	Bilateral transfemoral LET in 22-year-old male who received limbs from a full HLA mismatched female donor	Active knee extension and plantar flexion were achieved at 12 months with Tinel's sign at malleolar level
	Cavadas		Ambulation possible with assistance
			Patient developed primary central nervous system lymphoma at 15 months, necessitating discontinuation of immunosuppression and explantation of limbs
2012	Antalya, Turkey	Bilateral upper extremity and right LET in 34-year-old male with triple amputation secondary to electrocution injury	LET was lost to perfusion issues 24 h after surgery
	Ozkan		Patient succumbed at 5 months after LET to disseminated aspergillosis with multi-organ failure
2013	Ankara, Turkey	Quadrimembral transplantation (right shoulder level and left mid humeral transplantation; bilateral transfemoral LET)	Patient succumbed to hemodynamic complications on day 4 after surgery
	Nasir	Recipient was a 27-year-old male with quadruple amputation secondary to electrocution injury	

albeit diminished throughout the entire limb. Hip flexion and knee extension/flexion have recovered to levels that allow independent ambulation (with bracing) and engagement in recreational sports activities. Ankle plantar and dorsiflexion and knee extension were poor, requiring semitendinosus and biceps femoris tendon transfers.

The first adult LET was performed in 2011 in a 22-year-old male recipient with a traumatic BTFA sustained 2 years prior to surgery [40]. The donor was female with a full human leukocyte antigen (HLA) mismatch. Both donor and recipient were seronegative for cytomegalovirus (CMV). The donor was negative for Epstein-Barr virus (EBV) IgG, while the recipient was positive for the antibody. The patient failed a trial of prosthetics and refused osseointegration as an alternate option. The transplant levels were in the mid distal femoral shaft, with ischemia times at 3.5 h (right limb) and 5.5 h (left limb). The protocol consisted of alemtuzumab induction (anti-CD52, Campath ®, Millennium Pharmaceuticals) followed by a triple drug regimen (tacrolimus, mycophenolate mofetil, and prednisone taper). Two episodes of Banff Grade 1 acute rejection were noted in the first 12 months along with a quadriceps abscess, all of which were successfully treated. The patient had a left femoral nonunion following plate and screw bone fixation. Function of the lower extremities

steadily improved, with active knee extension (but with bilateral extensor lags), strong foot plantar flexion, and incipient foot dorsiflexion. Sensation and proprioception were not reported, but Tinel's sign (elicited by lightly tapping, manifests as tingling in the distribution of the nerve) advanced to the plantar level. The patient was able to ambulate with partial weight bearing on parallel bars at 15 months. Soon after, he was diagnosed with a primary central nervous system (CNS) lymphoma (PTLD), mandating immediate cessation of immunosuppression and graft explantation [41].

The world's first triple extremity transplant was performed in 2012 in Antalya, Turkey. The cause of limb loss in the 34-year-old male recipient was a childhood electrocution injury. This case was never published in the peer literature. Data from media reports and meeting presentations by team members indicate that the patient underwent amputation of the lower extremity on day one after surgery due to perioperative hemodynamic complications but ultimately succumbed to renal failure secondary to disseminated aspergillosis at 5 months after transplantation [42, 43].

The first quadruple (quadrimembral) extremity transplant was performed in Ankara, Turkey, in 2012. The patient was a 27-year-old male recipient who had also sustained a childhood electrocution injury (Fig. 11.1) [44]. The donor was a fully mismatched 40-year-old male. Given the massive amounts of transplanted tissue and a potassium-rich preservation solution, the patient suffered from cardiac arrest during reperfusion. This necessitated open cardiopulmonary resuscitation and massive transfusions (200 units) with hemodialysis during the intraoperative and perioperative phases. The protocol consisted of antithymocyte globulin (ATG) induction followed by a triple drug regimen (tacrolimus, mycophenolate mofetil, and prednisone). The patient succumbed to complications 4 days after surgery.

Challenges Associated with Lower Extremity Transplantation

Procedural and Patient-Related Considerations

The surgical sequence of LET may differ from upper limb transplantation [45, 46]. Following bone fixation in LET, it is logical to perform hamstring muscle and sciatic nerve repairs prior to vascular anastomoses. This allows all of the remaining procedures to be performed with the patient in supine position and eliminates positional changes during surgery. Temporary shunts can be used to minimize ischemia time between neuromuscular repairs and definitive vascular anastomoses (Fig. 11.2).

Often, the zone of injury associated with lower extremity amputation extends beyond the amputation level. Thus, donor limb retrieval must be planned accordingly to procure donor neurovascular and osteomyocutaneous tissues adequate for reconstruction of the recipient defect. Dissection up to common iliac vessels for transfemoral transplantation and popliteal vessels for transtibial transplantation is preferred. Similarly, a sufficient length of the sciatic nerve must be harvested to provide a tension-free nerve repair following resection of the injured and/or scarred recipient nerve segment.

LET requires careful intraoperative hemodynamic monitoring (pressure, coagulation parameters) as well as high volume resuscitative management. The significant transfusion needs, especially in bilateral LET, mandate availability of blood products (erythrocyte suspensions or fresh frozen plasma) or colloids.

Revascularization after clamp release in LET may also cause extreme blood volume shifts into the intravascular space, leading to drastic hypovolemia, significant reperfusion injury, and electrolyte imbalances, all of which could be life-threatening [47]. The lower limb (especially

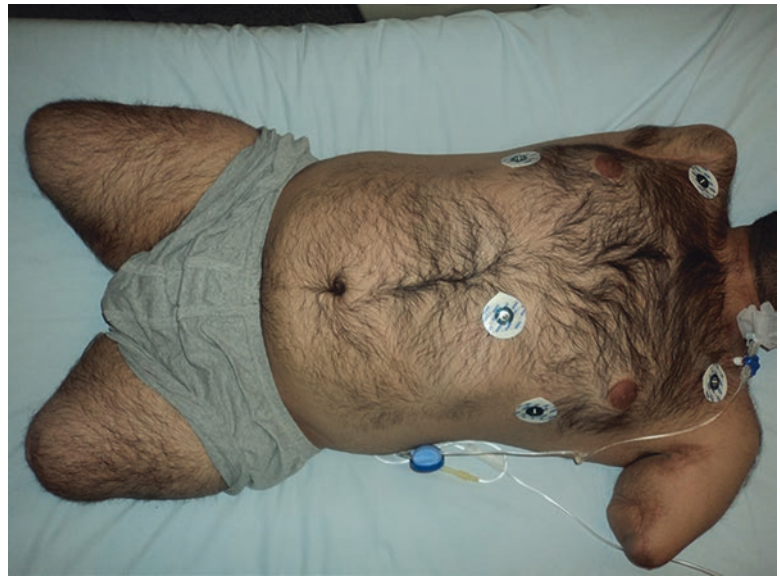

Fig. 11.1 World's first quadrimembral amputee to receive multiple extremity transplantation

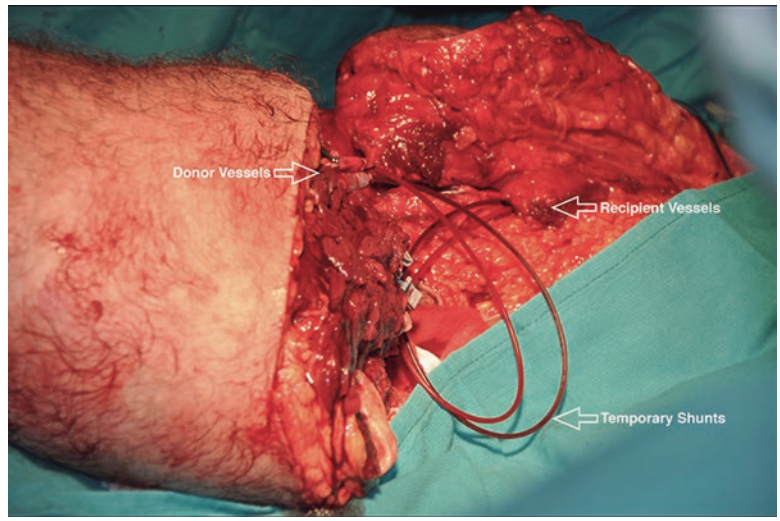

Fig. 11.2 Temporary vascular shunts between donor and recipient vascular beds to minimize ischemia time while accomplishing skeletal fixation and neuromuscular repairs

the thigh) has a large muscular compartment and vascular bed. LET, especially when performed bilaterally, increases body mass nearly twofold. As the allografts are preserved with cold preservation solutions, revascularization may trigger hypothermia. Hypothermia alters the distribution and decreases the metabolism of most drugs, including anesthetic drugs and muscle relaxants, thus prolonging recovery. Postoperative shivering increases metabolic rate and can lead to myocardial ischemia. Coagulopathies, increased incidence of surgical wound infection, and perioperative cardiac morbidity are other potential risk factors.

Prefilling the allograft with warm (37 °C) crystalloids prior to vascular clamp release can prevent catastrophic blood pressure or body temperature drops by inducing a hemodilution effect (compensated in advance with packed red cell transfusion) rather than volume depletion. Additional measures

such as airway heating and humidification and cutaneous warming may be helpful.

The neuromuscular tissue components of the lower limb are sensitive not only to the effects of cold ischemia (from cold preservation) but also to reperfusion injury after revascularization in LET. Ischemia reperfusion injury (IRI) has multipronged physiologic and immunologic effects ranging from hypovolemic shock and hyperkalemia to oxidative stress and innate immune activation with increased risk of acute and chronic rejection [25]. Ex vivo pulsatile machine preservation with normothermic or sub-normothermic perfusion (blood, hemoglobin oxygen carriers) can minimize risk of IRI and associated complications.

IRI can also worsen hypovolemia, leading to hypoperfusion or ischemia of transplanted limb muscles. This causes reactive vasodilatation following reperfusion and further worsens hypotension. For example, following BTFA, subjects undergo a significant change in the body mass index. With time, there are cardiac adaptations (such as changes in cardiac output) that occur to match the new BMI. The degree of such adaptation is directly proportional to the time since amputation. Following LET, the total body mass increases nearly twofold, resulting in inordinate demands on cardiac output and leading to tissue hypoperfusion. Intraoperative use of military antishock trousers (MAST) or pneumatic antishock garments (PASG) must be considered to manage this phenomenon.

Lower limb amputation can lead to limitations in mobility and a resulting propensity for a sedentary lifestyle. Proximal (vs. distal) leg amputation is associated with greater risk of cardiovascular disease, and bilateral (vs. unilateral) amputation introduces greater cardiac risk [48]. Such "deconditioning" can worsen cardiac decompensation in LET patients, increasing their risk of acute hypoperfusion and potentially complicating their rehabilitation.

Nerve Regeneration

Neuroregeneration remains the other major, but understudied, poorly understood, and primary challenge in efforts to advance lower extremity VCA. Functional outcomes after clinical VCA upper extremity and face transplantations have been acceptable in some patients, but in many cases, motor and especially sensory function have been unsatisfactory or dismal. Slow or suboptimal nerve regeneration, delayed muscle reinnervation, or denervation can all predispose to poor recovery. Inadequate or ineffective nerve regeneration can result in loss of graft function, which equates to graft "failure" even in an immunologically viable graft [49, 50]. This is a feature unique to VCA, in contrast to solid organs.

There are significant unknowns yet to be addressed concerning long-distance neuronal regeneration in lower extremity VCA. The lower extremities are inherently distinct in their evolutionary intent and functional complexity as compared to the upper limbs. They are designed primarily to support ambulation, load bearing, balance, posture, gait, and proprioception. Sensation is less precise, and range of motion is less complex in the leg and foot versus a hand capable of complex tactile or prehensile functions with multiple degrees of freedom. Unlike in upper extremity VCA, where the distance of nerve regeneration is much less than in lower extremity, and considering the rate of regeneration compared to upper extremity VCA, LET requires nerve regeneration across longer distances, which may take 1–3 years (at 1 mm/day). Therefore, even if active post-LET rehabilitation can minimize the risk of disuse atrophy in target muscles following nerve repair, denervation atrophy is a major challenge to good motor and sensory outcomes. The key objectives are to maintain or maximize the pro-regenerative capacity of the de-axonized distal nerve, support recipient axonal regeneration to distal sensory/motor targets, and achieve func-

tional cortical neuro-integration. The neurotrophic effects of tacrolimus have been demonstrated in experimental models (mostly small animals) and are widely touted to occur in clinical VCA; its effectiveness remains unknown [51, 52]. Even the best neuroregeneration outcomes may be compromised due to the lack of a viable neuromuscular junction (NMJ) or muscle target leading to poor functional outcomes. In the neurotrauma literature, although regenerative outcomes are more favorable for femoral and tibial nerves, it remains disappointing for the sciatic and common peroneal nerve proximal to or around the knee [53–55]. Repair outcomes vary widely, and no randomized studies exist, making it difficult to compare results of operative versus nonoperative treatments [56]. The time duration, extent, and adequacy of nerve regeneration in LET will determine the strength of reinnervated quadriceps, balance, gait, and locomotion. Similarly, we do not know if or how the effects of cyclic loading and shearing forces on the sole might trigger inflammation and rejection [57] or how the lack of plantar sensation and proprioception could increase the risk of trophic ulceration, rejection, or graft loss.

Ambulatory Rehabilitation

Absent or poor quadriceps function early after transplantation can cause significant knee extensor lag and hamper expeditious ambulation [58]. The lack of compensatory plantar flexion around the ankle joint leaves a gait pattern that relies heavily on reflexes to deal with unexpected perturbations [59]. In LET patients, this phase of recovery can be worsened by lack of sensory or proprioceptive input from target muscle groups.

The Hoffman reflex (H-reflex) is a key compensatory neuromodulatory process [60] that may be impaired after LET in high transfemoral (TF) amputees, especially in the soleus and gastrocnemius muscles. The H-reflex is the central component of the stretch reflex, i.e., the transmission from Ia afferents to α-motoneurons in the spinal cord [61]. The soleus/gastrocnemius H-reflex is strongly modulated during the gait cycle and is upregulated in the stance phase while being suppressed in the swing phase [62]. Zuker et al. provided the first evidence that the spinal reflex arc may be affected in LET as reflexes could not be elicited in the transplanted limb. The possible basis was that the reflex arc (comprised of an afferent sensory segment in the muscle spindle of the donor patellar tendon and an efferent motor segment in the recipient quadriceps) was interrupted during LET and was not reconstituted even at 6 years after surgery [39].

An intact neuronal innervation modulates the H-reflex with a change in body position, such as from prone to standing, supine to standing, and sitting to standing [63]. In LET patients, switching from a sitting, supine, or prone position to a static standing position imposes additional postural demands as the base of support decreases, destabilizing posture and increasing the risk of falls and fracture [64]. LET recipients may benefit from partial body weight supported treadmill training and conventional over ground walking training as can be helpful to spinal cord injury patients. Overall challenges to the recovery and rehabilitation process after LET include changes in balance, lower extremity motor function, and unpredictable return of spatiotemporal gait parameters.

Bone Fixation and Healing

Stable and sturdy bone fixation and healing can be a challenge after LET. In most LET patients, bone fixation has consisted of locking plates and screws, with acceptable short-term (<2 years) results [65]. However, the efficacy of this approach has been questioned given the critical

need to stabilize healing osteotomies while allowing early mobilization and weight bearing [66]. Instead, some have recommended the use of static, large bore intramedullary nailing to overcome the risk of hardware failure or nonunion [67] and to achieve superior weight bearing early after LET [68]. The experience with knee joint VCA provides valuable insights into the role of bone fixation using intramedullary arthrodesis nailing followed by immediate weight bearing. Between 1996 and 2002, six patients were transplanted with total knee joints consisting of proximal femoral shaft and distal tibial elements [69]. All grafts were lost by 56 months to either acute rejection that was refractory to immunosuppression [70] or to chronic rejection. However, in all cases bone healing and osseous integration of the graft were completed within 6 months with no delayed bone healing or nonunion [71]. This correlates with reported results of bone healing in hand transplants [72–74]. Although this data may indicate that immunosuppression is not deleterious to bone healing, but three of the six patients with knee joint transplants sustained fatigue fractures requiring arthrodeses, bone healing outcomes in the pediatric LET recipient have been satisfactory at 6 years of follow-up [39]. Long-term bone healing outcomes in adult LET remain to be established.

Controversies and Debate in Lower Extremity Transplantation

Indications for LET

There are currently no uniformly agreed standards for patient selection or indications for LET. Proponents of LET suggest that subjects with distal (below knee, e.g., distal tibial) amputations should be the first to be offered these transplants and that such a level should be an inclusion criterion [75]. The rationale for such recipient selection seems to be based on lower predicted perioperative risks associated with reduced hemodynamic compromise, third spacing of fluids, and ischemia-reperfusion injury compounded by large antigenic tissue loads. Proponents also have argued for the use of LET as a means to convert high above-knee (e.g., BTFA) amputations to below-knee stumps; the rationale in this case is to provide opportunities for superior prosthetic alternatives and functional return in selected amputees who have failed prosthetic rehabilitation. Both of these indications for LET recipient selection are debatable. Distal amputees have a range of prosthetic choices consistent with excellent ambulatory function, without the need for lifelong immunosuppression and potentially life-threatening risks. On a similar note, LET is a poor surgical option for conversion of an above-knee (transfemoral) to below-knee (transtibial) stump given the increased propensity of possible skin breakdown and/or graft compromise or failure due to rejection in a stump that is exposed to sustained mechanical irritation at the stump-socket interface [76, 77]. As noted previously in this chapter, the first case of LET was performed in a pediatric twin-twin scenario that necessitated no immunosuppression and had the best potential for nerve regeneration given the very young age of the recipient (3 months postnatal). Such a benefit-to-risk justification is not realistic to expect in adult amputees seeking lower extremity VCA. In fact, experience with adult LET thus far has shown that the risks are significant and may indeed be life-threatening. This underscores the need for stringent recipient selection criteria.

A recent survey-based study evaluated attitudes regarding LET among lower limb amputees [78, 79]. Nearly two-thirds (64.6%) of the 770 lower limb amputees surveyed reported an interest in being evaluated for a potential LET. Enthusiasm for LET did not appear to be influenced by respondent geographic location,

sex, socioeconomic status, cause of amputation, laterality (unilateral or bilateral), or level of amputation. However, respondent interest in LET did vary by age, interval since amputation, and satisfaction with prostheses use. Most of those who expressed an interest in LET indicated that restoration of knee and/or ankle joint function would be the most important criterion for transplant success. Respondents also identified sensation as an important consideration, secondary to restoration of motor function. Although this study sheds preliminary insight into amputees' attitudes toward LET as a treatment option, no objective inclusion or exclusion criteria or appropriate indications for LET have yet been established.

Prosthetic Alternatives Versus Transplantation

As with any innovative VCA, it is the responsibility of providers to thoroughly examine the availability or lack of alternative options in every case. In the context of lower extremity amputations, there are excellent alternative options available in the form of prosthetic devices. Indeed, these systems have enabled many patients to return to fulfilling social, professional, and personal lives. Admittedly, there are challenges associated with prosthetic fitting in above-knee amputees, especially in cases of BTFA, but the pace of technology in this area is fast advancing with the engineering of superior, stronger, biocompatible, and lightweight materials and with the development of biomechanical, microprocessor-controlled systems that enable real-time dynamic gait and ambulation management (e.g., hydraulic mechanical knee [Mauch SNS knee], magnetorheological-based Ossur Rheo prosthesis, and the Ottobock C-leg) [80–82].

Service members with BTFA have accomplished positive outcomes with the use of bilateral microprocessor knees, which are programmable for each patient with advancing progress during rehabilitation [83]. The role of powered prostheses for individuals with bilateral lower limb loss has not yet been determined, but the concept offers great hope for many individuals with mobility challenges and particularly for aging amputees. Powered prosthetic devices such as the Power Knee (Ossur, Foothill Ranch, CA) use sensors that detect muscle signals in the stumps of TF amputees to power knee movement controlled by an electromechanical actuator augmented by accelerometers, gyroscopes, and torque and load sensors [84]. It is the first motorized prosthetic knee available for unilateral or BTFA subjects. The potential merits of microprocessor-controlled lower limb prostheses include: reduced effort during ambulation; improved symmetry and natural gait; increased confidence in the prosthetic recipient during over ground use such as navigating stairs, inclines, and uneven terrain; and reduced risk of falls. More recently, wearable robotic exoskeletons have also been developed to support successful ambulation in individuals with spinal cord injury. These devices (e.g., Ekso Bionics GT, Indego powered exoskeleton, and ReWalk exoskeleton) can help BTFA amputees who are challenged by poor adaptation or failure with other options [85–87]. Osseointegration is a more recent option approved in Europe, involving titanium implants on the stump to anchor the prosthesis and thus eliminating the need for a socket and associated complications. Standardized protocols for this procedure and subsequent rehabilitation have reduced failure rates and improved quality of life for patients [88].

The arguments for the proposed benefits of LET (versus prosthetic or osseointegration solutions) are currently focused on expectations for satisfactory protective sensation at the least, with potential at best for discriminatory, proprioceptive, or reflexive sensory motor recovery and alle-

viation of phantom sensation [89, 90]. Admittedly, if LET could accomplish independent ambulation with return of sensation, it could also circumvent a host of challenges associated with prosthetic solutions, including but not limited to stump and socket issues, power issues, low back pain, and energy consumption. Although the outcomes reported by Zuker et al. in pediatric LET are encouraging in this regard, no similar inferences are yet possible in the adult LET population, which has been uniformly disappointing with two patient deaths early after surgery and one transplant removal due to a neoplastic complication 2 years after surgery.

The role, relevance, and potential impact of LET in subjects with BTFA remain controversial. Some of the sophisticated prosthetic technologies already on the market or under development have enabled independent community ambulation in recipients. Lower extremity prostheses do not (yet) offer tactile or proprioceptive sensation to support normal gait function, but unlike LET they do not require lifelong immunosuppression [91].

Tandem Transplantation (LET with Face or Upper Extremity VCA)

Simultaneous (tandem) complex transplants have been reported involving combination face and upper extremity or upper and lower extremity VCA (bilateral or unilateral). Three of the four of reported tandem transplants have died due to operative or perioperative complications such as overwhelming sepsis or shock [92–94]. One patient survived but had to undergo removal of both transplanted upper extremities only to preserve a face transplant [95]. Uniformly, quadruple VCA and triple VCA procedures have been associated with a very high rate of failure. There are risks associated with the large antigenic burden, overwhelming ischemia-reperfusion injury, large volume resuscitation requirements, extended anesthesia times, and a host of other surgical and technical challenges. Quadrimembral VCA (Fig. 11.3) or even bilateral transfemoral LET involves a massive amount of allogeneic bone marrow, drastic hemodynamic shifts (acute

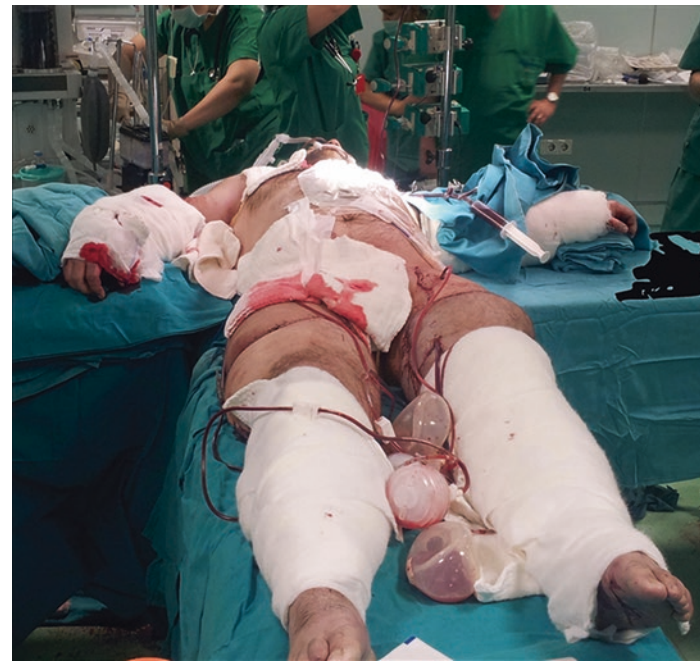

Fig. 11.3 Quadrimembral (tandem upper and lower extremity) transplantation

30% increase in vascular bed) upon transplantation, and electrolyte imbalances (e.g., secondary to K+ overload from preservation solutions) that can lead to cardiac arrest/anesthetic complications. Tandem VCA may be relevant in patients with mixed upper and lower limb loss, for whom prosthetic options present unique challenges (e.g., difficulty donning and doffing devices without caregiver or adaptive support). In such patients, prosthetic rejection is common, and quality of life outcomes are uniformly poor.

Optimal Experimental Models for LET

The literature includes numerous reports of orthotopic limb transplants in quadruped models such as rats, [96, 97] swine, [98, 99] dogs [100, 101], and nonhuman primates [102]. However, the choice of an appropriate animal model for LET remains debatable.

Bipedal locomotion is among the most distinguishing motor behaviors in human beings [103]. Humans evolved from prehistoric quadrupedal ancestors [104]. Thus, human infants start walking quadrupedally before they acquire stable bipedalism with growth [105]. This transition is accompanied by skeletal changes such as increasing lumbar lordosis, sacral kyphosis, and increased hip and knee extension [106]. There is no cortical reorganization in infants with commencement of bipedalism. There is currently no reliable or robust small or large animal experimental model for LET that allows objective assessment of motor, sensory, or proprioceptive function applicable to bipedal locomotion as it develops and manifests in humans [107].

Innately quadrupedal four-legged animals such as rats and nonhuman primates (e.g., apes) can exhibit occasional bipedal behavior. However, their walking posture is significantly different from that of humans, in whom the skeletal system has evolved specifically to support bipedal locomotion, which requires significantly greater energy consumption than quadrupedal locomotion [108, 109].

The use of unilateral hind limb or forelimb transplantation in rats as a preclinical model for LET is problematic because rats are quadrupeds. Although bipedalism can be surgically induced in rats by forelimb and tail amputation within 24 h of birth [110–112], quantitative differences in gait are hard to distinguish between bipedal and quadrupedal rats [113].

Chimpanzees, which share over 99% of human genes, can walk bipedally but without full extension of hip or knee joints. While chimpanzees and other animals use their limbs to support their body weight, maintain body balance, and produce propulsive force, there is a clear difference between the ischium of the chimpanzee and that of the human. The caudal orientation of the ischium in chimpanzee affects the ability of the hamstrings in hip extension, preventing bipedalism in chimpanzees, while the dorsal orientation of the ischium in humans is key for bipedalism [114].

Gait kinematics and electrophysiologic studies in bipedal rats and chimpanzees suggest similarities in neuronal control as has been observed in humans, at least at the level of the spinal cord [110]. This reinforces the inference that observed differences are likely due to skeletal and/or muscular adaptations. Taken together, these limitations constrain the relevance and value of rodent and even nonhuman primates as models for LET studies.

Cortical Reintegration After LET

High-definition MRI has shown promise with neurotractography techniques that can provide intricate detail of anatomy, architecture, and alignment of existing and new nerve fiber pathways in hand transplant grafts [115, 116]. These methods also confirm that neointegration into sensorimotor cortex occurs in upper extremity

RT recipients who are undergoing rehabilitation and allow objective tracking of functional progress after surgery [28]. Similar findings have been reported after pediatric LET [39]. Functional MRI performed at 6 years after surgery, during movement of the transplanted leg, revealed distinct activation in the contralateral motor strip with a significant signal medial to the hand area, confirming a typical cortical representation for leg movement. This finding supports the hypothesis that in a 3-month-old child born without an intact lower limb, the cortex integrated the transplanted extremity and acquired plasticity to achieve its control. This phenomenon has not yet been demonstrated in adult LET recipients. With respect to overall functional neuroregeneration and rehabilitative outcomes in upper or lower extremity VCA, the potential significance of such cortical reintegration remains unproven and controversial.

Future Prospects

Though currently faced with daunting challenges and inordinate risks, the promise of lower extremity or combination complex VCA is alluring. Experience to date, with a limited number of patients, has been associated with unacceptable morbidity (e.g., PTLD) and high mortality. If successful neurofunctional outcomes (protective sensation and community ambulation) can be established, and if the hurdles of reliable long-distance nerve regeneration, chronic immunosuppression, and perioperative complications can be overcome, then LET may be seen as a viable option for carefully selected patients who have failed, rejected, or are otherwise ineligible to use conventional prosthetics. This underscores the need to assess and/or develop strategies to minimize the risks of possible failure secondary to factors such as infection and lack of sensorimotor nerve regeneration, proprioceptive, or reflex neuromodulatory feedback control of balance, nonunion of healing osteotomies or fatigue failure of bone fixation, and catastrophic reperfusion injury, hemodynamic, and other surgical challenges. For broader feasibility of lower extremity VCA, it is imperative that we identify strategies to facilitate rapid and effective nerve regeneration, as well as timely distal target reinnervation. There is a need for objective longitudinal surveillance of peripheral nerve regeneration and cortical neurointegration through noninvasive, high-resolution imaging technology. Although optimistic parallels and inferences can be gleaned from upper extremity replantation and transplantation procedures to inform and justify LET, we must be cautiously cognizant of the different demands, risks, and challenges inherent and unique to these procedures.

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Limb Regrowth and Tissue Engineering Alternatives

12

Ken Muneoka, Eva Lai, Robert J. Christy, and Jon E. Mogford

Introduction

Thanks to investments by the Department of Defense (DoD) and Department of Veterans Affairs (VA) to advance research, development, and clinical rehabilitation programs, the majority of wounded warriors with amputated limbs today lead active lifestyles that just two decades ago may not have been possible. Prior to the global war on terrorism, the majority of service-related amputations occurred mainly as the result of noncombat causes, including disease and vascular disorders, and involved older veterans [91]. Current DoD and VA investments in programs to support amputation research and care came about largely in response to recognizing that the injury patterns of service members wounded in more recent global conflicts against terrorism involved mostly young combat amputees with a desire for active lifestyles [31, 32, 56, 91, 110]. These young combat amputees desire and deserve every opportunity for functional recovery, which for some means returning to the battlefield [20, 54, 91, 123].

Some military medical investments have supported novel approaches to rehabilitating combat amputees at the Walter Reed Army Medical Center (WRAMC) Military Amputee Research Program (MARP), initiated in 2004. The MARP closed in 2011, to be followed by the opening of the Military Advanced Training Center (MATC) at the Walter Reed National Military Medical Center (WRNMMC). These programs have transformed amputee care from its traditional emphasis on healing and retraining basic living skills to a relatively more extensive program whose goal is to help wounded service members reclaim active and mobile lives. Through strategic partnership between MARP and the Telemedicine and Advanced Technology Research Center (TATRC)

K. Muneoka, PhD (✉)
Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA
e-mail: kmuneoka@cvm.tamu.edu

E. Lai, PhD
Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA
e-mail: lai@jhu.edu

R.J. Christy, PhD
Extremity Trauma Research and Regenerative Medicine, Combat Trauma and Burn Injury, US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX, USA
e-mail: robert.j.christy12.civ@mail.mil

J.E. Mogford, PhD
The Texas A&M University System, College Station, TX 77840, USA
e-mail: jmogford@tamus.edu

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Advanced Prosthetics and Neural Engineering Research Portfolio (2004–2014), technological advancements were made possible to include motorized knees and ankles and advanced fitting that allow amputees to climb stairs, walk on uneven terrains, and in some cases even compete as Olympic athletes. Depending on patients' injury severity scores, functional recovery, medical and physical exams, and job positions, combat amputees may also return to active duty. Though the precise numbers are difficult to pin down, a small percentage (13–16%) of combat amputees have returned to active duty, including a smaller number (57 as cited in [20] Washington Post article) have even returned to combat [8, 20, 21, 54, 106, 123].

In 2014, the Defense Advanced Research Projects Agency (DARPA) Revolutionizing Prosthetics Program, first established in 2006, produced an FDA-cleared, advanced neuro-controlled prosthetic arm that allows the user to control the arm by thought, much as if it were a native limb. Other recent significant prosthetic technical advances and improvements include interfaces that allow increased movement, mobility, and somatosensory feedback [112].

Despite dramatic technological advances, most amputees would naturally still prefer not to have lost their own natural limbs. A native limb provides a high degree of proprioception, rapid reflexes, flexible ability to walk on different terrains, energy efficiency when ambulating, dexterity to control fine finger motor movements, freedom from phantom limb pain [3, 53, 98], and the simple joy of touch. The preference to preserve these abilities is reflected in the decisions of upper limb amputees who opt for limb transplantations. Johns Hopkins surgeon Dr. W.P. Andy Lee has performed several upper limb transplants, including for military amputees, and notes that some lower limb amputees have also expressed a desire for lower limb transplants.

Much additional research and development must be explored to achieve the ideal of reestablishing natural limbs with fully preserved capabilities and without the risks currently associated with limb transplantation, which include tissue rejection, infection, and the need for immune-suppressive drugs. The next technological challenge is to accomplish limb regeneration through limb regrowth or tissue engineering. The remainder of this chapter will consider the current state of the art in recreating a lost limb, either through stump regeneration or via reattachment and reinnervation of a tissue-engineered limb.

Limb Regeneration: Past and Current Research

Limb regeneration in salamanders has been studied for centuries, but many consider it a biological exception rather than a phenomenon relevant to human limb regeneration. Newts and salamanders possess extraordinary regenerative capabilities that extend beyond limb regeneration, but these animals are generally small, aquatic or semiaquatic, and evolutionarily distant from mammals. However, the salamander limb is actually anatomically similar to the human arm, and there are large salamander species (e.g., Chinese giant salamanders grow to over 5 ft in length and weigh up to 145 lb) that retain regenerative capabilities. This suggests that the overall size of the limb does not represent an insurmountable obstacle for successful limb regeneration.

Regenerative ability has been thought an evolved trait and therefore phylogenetically specific [37]. This runs counter to a more classical view of limb regeneration as an ancestral property of all vertebrates, lost through evolution [99, 100]. If regenerative capability is an ancestral property, it may be possible to reawaken the trait in humans, as tooth formation was reawakened in birds after 75 million years of repression [16, 45]. The two views are not mutually exclusive, i.e., it is likely that regeneration is a primi-

tive trait that has differentially evolved among specific vertebrate groups. Nevertheless, the ability to regenerate a limb in an adult vertebrate is restricted to certain organisms, so an understanding of the regeneration process can only come from studies on salamanders and newts.

An initial and important consideration is to recognize that limb regeneration is a process, not a single event. Additionally, it is important to dismiss the misconception that the solution for human limb regeneration will be the discovery of a "magic potion" to miraculously stimulate limb regrowth. Limb regeneration involves a series of stages and steps, beginning with limb amputation and traversing through wound healing, dedifferentiation, blastema formation, growth, pattern formation, morphogenesis, and finally redifferentiation (Fig. 12.1).

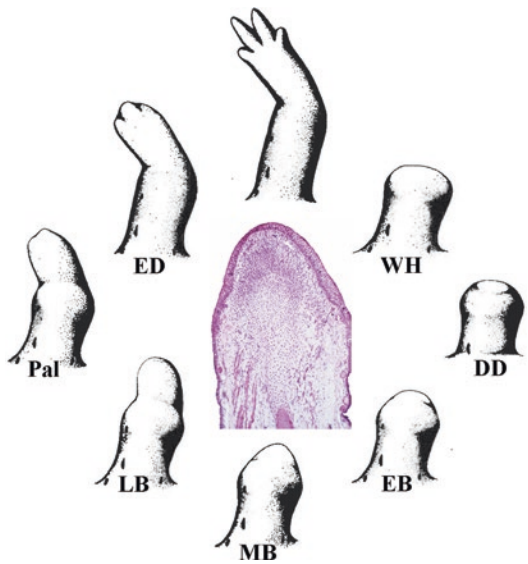

Fig. 12.1 Stages of limb regeneration in salamanders. Outer images represent staged drawings of newt limb regeneration. Stages include wound healing (*WH*), dedifferentiation (*DD*), early bud (*EB*), medium bud (*MB*), late bud (*LB*), palette (*PAL*), and early digit (*ED*) before redifferentiating into a replacement limb. Central image shows a blastema with distal mesenchyme, differentiated proximal tissue, and a gradation of differentiating tissues in between. (Modified from Iten and Bryant [48])

Key to this process is the formation of a transient structure, called a blastema, which is composed of an immature and specialized epidermis encasing a population of proliferating, undifferentiated cells. The blastema has characteristics similar to the limb bud that forms during embryogenesis [79, 80]; however, there are important differences. First, the limb bud emerges from the flank of the embryo and forms the entire limb structure, whereas the blastema forms at the level of limb amputation and only forms the limb structures that have been removed by amputation. This indicates that blastema cells need a mechanism to determine what portion of the limb structure survives the amputation injury, so the appropriate anatomy of the limb can be replaced. This characteristic of blastema cells is called positional information, an as yet poorly understood spatial map of the limb anatomy that is integral to defining what will regenerate and to establishing a functional interface with the mature tissues of the limb stump. The developing limb also needs a system of positional information to specify the various anatomical parts of the limb. Since the limb bud possesses regenerative abilities, evidence suggests a developmental map of positional information that must be amenable to the process of regeneration.

The concept of positional information lies at the heart of understanding regeneration, and the process of intercalation (see Fig. 12.2) is a unifying principle. It is generally accepted that cells must possess positional information that controls the differentiation of anatomically distinct tissues [117]. There is an abundance of indirect evidence implicating fibroblastic cells (of the interstitial tissues) as the cell type that possesses positional information [11, 15, 85, 97]. Since these cells do not differentiate into physiologically distinct parts of the body, they are proposed to act by directing cells such as myoblasts, chondroblasts, and osteoblasts to undergo spatially patterned differentiation responses. In this way, anatomi-

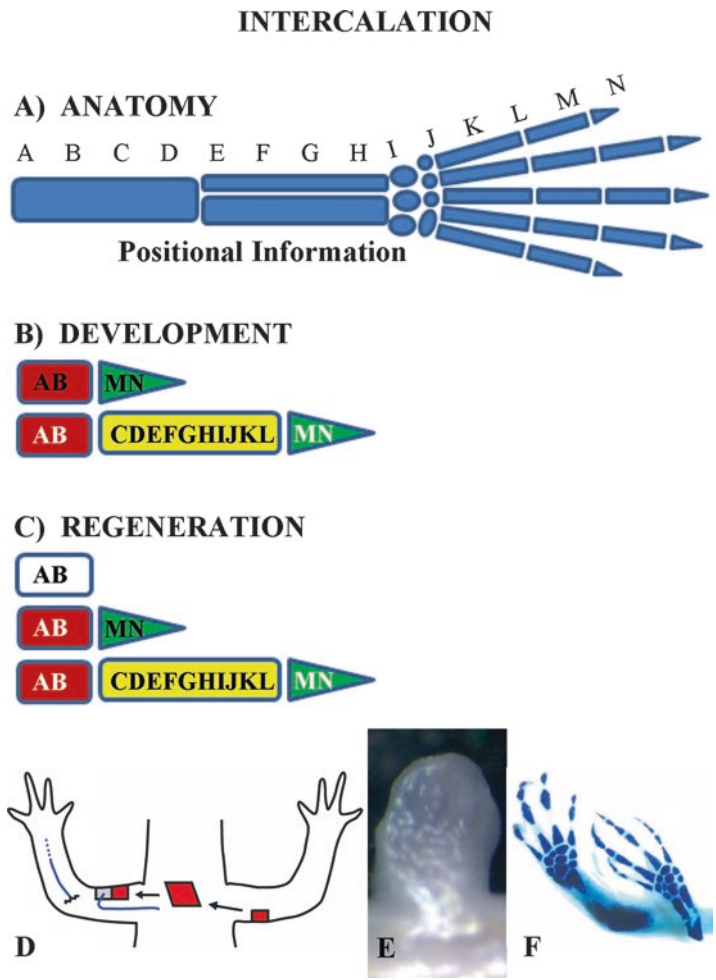

Fig. 12.2 Intercalation. (**a**) Limb cells possess positional information that identifies a cell's position relative to the limb as a whole. Positional information is depicted here as upper arm (*A–D*), forearm (*E–H*), wrist (*I–J*), digits (*K–N*). (**b**) During development, cells first specify the most proximal (*A/B*) and the most distal (*M/N*) information. Intermediate positions are then established by intercalation. **c** During limb regeneration, positional information of the stump (*A/B*) and the most distal tip (*M/N*) are reestablished after amputation; intervening information is then formed by intercalation. (**d**) An accessory limb can be ectopically induced from a simple skin wound; induction requires deviation of a transected nerve to the wound and a graft of skin from the opposite side of the limb. (**e**, **f**) Stages of accessory limb formation. (**d–f** Modified from Endo et al. [28])

cally distinct components with similar physiological function can be established.

As metaphor, it may be helpful to consider the global positional system (GPS) and how we use it to navigate the planet. Targeting positional information to a specific cell type that conveys spatial information to other cell types mimics the GPS, in that positioning is controlled based on interactions with a series of satellites which in turn convey spatial information to specific geographical landmarks. In biological terms, an example to consider is the proximal-distal patterning of the vertebrate limb. The limb initially forms a chondrogenic skeletal pattern that is later replaced by more permanent osteogenic cells. The proximal-distal skeletal pattern includes a single element in

the upper limb (humerus, femur), paired elements in the lower limb (radius/ulna, fibula/tibia), and multiple small elements in the hand/foot region (carpels, tarsals, and phalangeal elements) (Fig. 12.2a). Prior to differentiation, the cells of the limb bud display spatially distinct patterns of gene expression, such that some genes are specifically expressed in cells associated with the distal limb region and other genes are specifically expressed in those cells associated with the proximal limb region [111]. Studies on the mouse limb bud provide evidence that the specification of the proximal and distal limb regions occurs early in development and is followed by the specification of the intervening (intermediate) limb regions [72] (Fig. 12.2b). It has long been hypothesized that positional interactions between limb regions, as exemplified by the mouse limb studies, control cell proliferation and the formation of intervening limb regions by a process called intercalation [34].

Studies on the regenerating salamander limb help to uncover the characteristics of positional information and intercalation. Using these processes, the amount of tissue that regenerates is always linked to the level of amputation, and the pattern of the regenerate is always normal. The mature tissues of the adult salamander limb are quiescent and do not respond to spatial cues required for regeneration [13]. For this reason, it is generally thought that positional information is reacquired as a response to amputation injury and, indeed, genes that are expressed in a position-specific manner during limb development are reexpressed in the blastema during limb regeneration. One critical finding was that very early in the regeneration process, genes associated with the level of limb amputation and genes associated with the distal limb region were reexpressed at the amputation wound [36]. This creates conditions at the amputation wound that are very similar to the early developing limb: both proximal and distal cells are present in the early blastema, and as regeneration proceeds, intervening limb regions between the distal tip and the stump are proposed to regenerate by intercalation (Fig. 12.2c). The process of intercalation is presented here in a simple one-dimensional format using the proximal-distal axis of the limb to help conceptualize limb patterning in both limb development and limb regeneration. Studies using a variety of regenerating models, including insects and planaria, illustrate how universal this concept is for regeneration [1, 7, 34].

A second major difference between limb development and regeneration following amputation injury is that the latter must undergo a healing response. In salamanders, this includes a rapid wound closure response, an inflammatory response, the histolysis of existing tissues around the wound, and the release of cells with stem-like characteristics that are recruited to form the blastema. There is clear evidence that wound closure and inflammatory response are necessary for the regeneration process [39, 102], but it is not yet clear whether the two responses involve independent mechanisms. A number of progenitor cell types that are released from stump tissues and participate in blastema formation are lineage restricted, which is to say they produce in the regenerate the same cell type that they formed in the limb prior to amputation [55]. These include epidermal cells, Schwann cells, and muscle progenitor cells. The involvement of muscle progenitor cells has been the focus of considerable attention and controversy in the limb regeneration field [60]. It is now clear that muscle tissues regenerate by activating stem cells called satellite cells in the newt but that in the axolotl (also called the Mexican salamander), mature myofibers undergo a dedifferentiation response that involves cellularization and fragmentation to generate individual progenitor myoblasts [76, 101]. These differences within the urodeles, an order of amphibians that include salamanders and newts, exemplify how regenerative strategies have

evolved to facilitate a successful regenerative response.

In addition to the variety of lineage restricted progenitor cells that make up the blastema, there is evidence that multipotent fibroblastic cells of the interstitial connective tissue also contribute to the blastema. The connective tissue of the dermis has been studied most extensively. Tissue grafting studies show that cells of the dermis over-contribute to the blastema [83] and that these cells participate in regenerating other limb tissues (e.g., skeletal, tendons) as well as re-forming the dermis [27, 55]. Since there are a number of distinct cell types in dermal connective tissue, e.g., fibroblasts, vascular, and perivascular cells, it remains to be demonstrated which of these cell types are multipotent. The cells of the dermis have also been implicated in controlling the process of intercalation so they represent the best candidate cell type for expressing positional information during regeneration [109]. It is unclear whether there is direct, indirect, or no relationship between dermal over-contribution to the blastema, multipotency of dermal cells, and the role that the dermis plays in regulating positional information.

Unraveling the process of blastema formation is not a simple matter. In animals that regenerate, limb amputation is always followed by blastema formation which leads to growth and morphogenesis of the regenerated limb. Traditional experimental approaches involve modulation to inhibit limb regeneration, for example, denervation of the limb inhibits blastema formation and limb regeneration. This suggests that truncated nerves produce a factor or factors necessary for limb regeneration [105]. Experiments to characterize the "neurotrophic factor" have identified a number of factors that can rescue part or all of the denervation effect [59, 70, 75, 77]. Attempts to enhance the regenerative response of non-regenerating limbs have generally been unsuccessful [33]. The major reason for this is that limb regeneration is a process and not an event, i.e., regeneration requires an ordered series of critical steps to be successful. The clearest example of this is observed by experiments in which regeneration is stimulated not by limb amputation but by modifying a lateral wound on a limb surface to stimulate an ectopic or accessory limb to form in a salamander [28].

Skin wounds on the salamander limb undergo a rapid and perfect healing response, but deviating an intact transected nerve to the wound site stimulates blastema formation. The induced blastema eventually regresses, and the limb is not structurally modified. However, combining nerve deviation with a graft of skin from the opposite side of the limb results in the production of a blastema that undergoes growth and morphogenesis to produce an ectopic limb (Fig. 12.2d–f). One role of the nerve is to stimulate the wound epidermis to transition into a functional apical epithelial cap (AEC), which is required to initiate blastema formation [102]. This represents an important step in the regeneration process; blastema formation alone is insufficient to stimulate limb regeneration. Beyond the transformation of the wound epidermis to the AEC to stimulate blastema formation, limb regeneration requires that the blastema itself must be composed of cells from disparate parts of the limb that presumably use positional information to organize the regeneration response. Thus, a secondary requirement is to introduce cells that are derived from the opposite side of the limb to create the necessary positional disparity. This stepwise model for limb regeneration establishes a foundation for considering how limb regrowth is controlled in regeneration-competent animals [28] and provides important insight into how regeneration can potentially be stimulated in regeneration-incompetent animals such as humans.

A third difference that sets the regenerating limb apart from the developing limb is that the

regenerated structure must reestablish a functional interface with the mature tissues of the limb stump. There is experimental evidence that the process of limb regeneration is autonomous, i.e., explanting a regenerating blastema to an ectopic site results in the formation of an ectopic limb [107]. Indeed, accessory limb studies show very clearly that the induced regenerated limb need not have a skeletal interface with the host limb (Fig. 12.2f). This implies that a critical aspect of regenerating a limb involves an independent integrative process of melding a developing structure with the mature tissues of the injured limb. During limb regeneration, the stump/regenerate interface appears histologically as a graded transition. For example, in the central image in Fig. 12.1, a differentiated skeletal element can be seen at the base, transitioning to the differentiating cartilaginous template of the regenerating proximal skeleton at the base of the blastema to the still undifferentiated blastema of the distal regenerate. This process has been poorly studied but likely involves the activities of matrix-eroding cells, such as osteoclasts, as well as the production of proteolytic enzymes, such as matrix metalloproteinases that are known to be upregulated in association with the regenerative response [114, 119]. This process is also likely to be important for establishing a functional interface between mature tissues and newly regenerated structures using scaffolds and/or stem cells.

Are Humans Capable of Regeneration?

There are several factors that limit the ability of human tissues and organs to respond to injury by regenerating amputated body parts such as arms and legs. Considerable speculation is necessary to address the question of how these limitations might be overcome. One way to think about human regeneration is in developmental terms. The mature human oocyte has developmental potential – i.e., the capacity to form the human body pattern – yet cannot do so in the absence of fertilization. If the oocyte is defective, then its full developmental potential is not realized even if fertilization does occur. We can use a similar analogy to conceptualize limb regeneration. The salamander limb possesses regenerative potential because, upon amputation, a sequence of specific events temporally and spatially coordinates the replacement of amputated structures. The question of whether humans are capable of regeneration can be rephrased to ask whether human cells possess developmental (regenerative) potential. This question is easier to address because we can evaluate amputation injury in the context of regenerative mechanisms and experimentally test if structural replacement can be enhanced. Recent regeneration studies focusing on a rodent digit amputation model provide convincing evidence that the regenerative potential of mammals is quite high and that humans may indeed be capable of regeneration [120, 121].

We start by outlining some conceptual boundaries for how mammalian regeneration studies might proceed. First, recent evolutionary studies suggest that specific molecules such as the cell surface three-finger protein Prod1, which are critical for salamander limb regeneration, are unlikely to be present in mammals [37]. This does not mean the regenerating salamander limb model is not important; it simply raises caution that some of the molecular pathways for regeneration may be unique. Second, since the regeneration process will parallel the developmental process, we can focus on the similarities of the molecular pathways between regeneration and embryonic mammalian development. This is clearly the case for the process of differentiation during tissue turnover or replacement following injury, i.e., myogenesis during muscle repair parallels myogenesis in development [122], and the same is true for osteogenesis during bone healing

[29]. Third, many studies show that relative to mammalian adult tissue, regenerative capability is enhanced in the mammalian embryo, fetus, and neonate; this indicates that developing tissues possess an enhanced regenerative potential. In rodents, embryonic limb amputations in vitro elicit a partial regenerative response [14, 24], and in utero limb or digit amputations in mice result in clear regenerative responses [95, 116]. In humans, experiments have shown that amputated fetal digits initiate a regenerative response when maintained in long-term culture [2], and transverse limb defects in newborns are associated with small digit-like structures called "nubbins" that are hypothesized to represent a regenerative response to in utero injury [35]. Studies of skin in fetal wound healing demonstrate a scarless healing response, which in newborns transitions to scar-forming healing [62]. However, embryonic amputation studies indicate that the ability for scarless wound healing by itself is not sufficient for limb regeneration [116]. These studies point to the use of developmental models as one way to understand regenerative potential [81] and to tissue maturation as a key process that negatively impacts the ability for tissue regeneration. This process has spawned the concept that there are regeneration "barriers" that are progressively established as the limb matures [78].

Fingertip and Digit Tip Regeneration

The regeneration of fingertips in both children and adults is well documented in the clinical literature [25, 47, 65]. More recently, parallels between digit tip regeneration in mice and fingertip regeneration in humans have peaked interest in the feasibility of human limb regeneration [82]. In this regard, mouse digit regeneration has become an important experimental model to explore both the fundamental mechanisms of mammalian regeneration and potential strategies to enhance limb regenerative capabilities. The mouse digit tip regenerates following amputation from early development and through adulthood, although specific details such as regenerative rate do vary with age. Regeneration of fetal digits can also occur in vitro, making this model valuable for cell and molecular biological experimental studies. Genetic studies show that Msx1, a transcriptional repressor important for embryonic cell differentiation and highly expressed in the forming digit tip, is required for successful fetal digit regeneration [43]. Other related transcription factors that are also expressed specifically in the developing digit tip, *Msx2* and *Dlx5*, have been shown not to be required for regeneration [63]. The *Msx1* mutant phenotype can be rescued during digit development in vitro by extrinsic treatment with BMP4, a growth factor in the bone morphogenetic protein family shown to be downstream of Msx1 activity. Both fetal and neonatal digit regeneration are inhibited by treatment with the BMP antagonist Noggin [43, 120], whereas the regeneration of normally non-regenerating digit amputations can be induced by treatment with BMP2 or BMP7 [120, 121]. Based on these studies, there has been considerable attention focused on the role of BMP signaling in both endogenous and induced regeneration (see discussion to follow).

Neonatal and adult digit tip regeneration involves the formation of a blastema [30, 44]. The mouse digit tip is structurally defined by the terminal or third phalangeal element (P3); this bone has the shape of a flattened cone with a basal bone marrow region and a pointed distal tip (Fig. 12.3a, b). The P3 element articulates proximally with the second phalangeal element (P2) forming the P2/P3 joint (Fig. 12.3b). The P3 element is unique because it is encased within the nail organ that has recently been shown to be required for the regenerative response [108]. Surrounding the P3 element and subjacent to the epidermal layer is a thin layer of loose connective

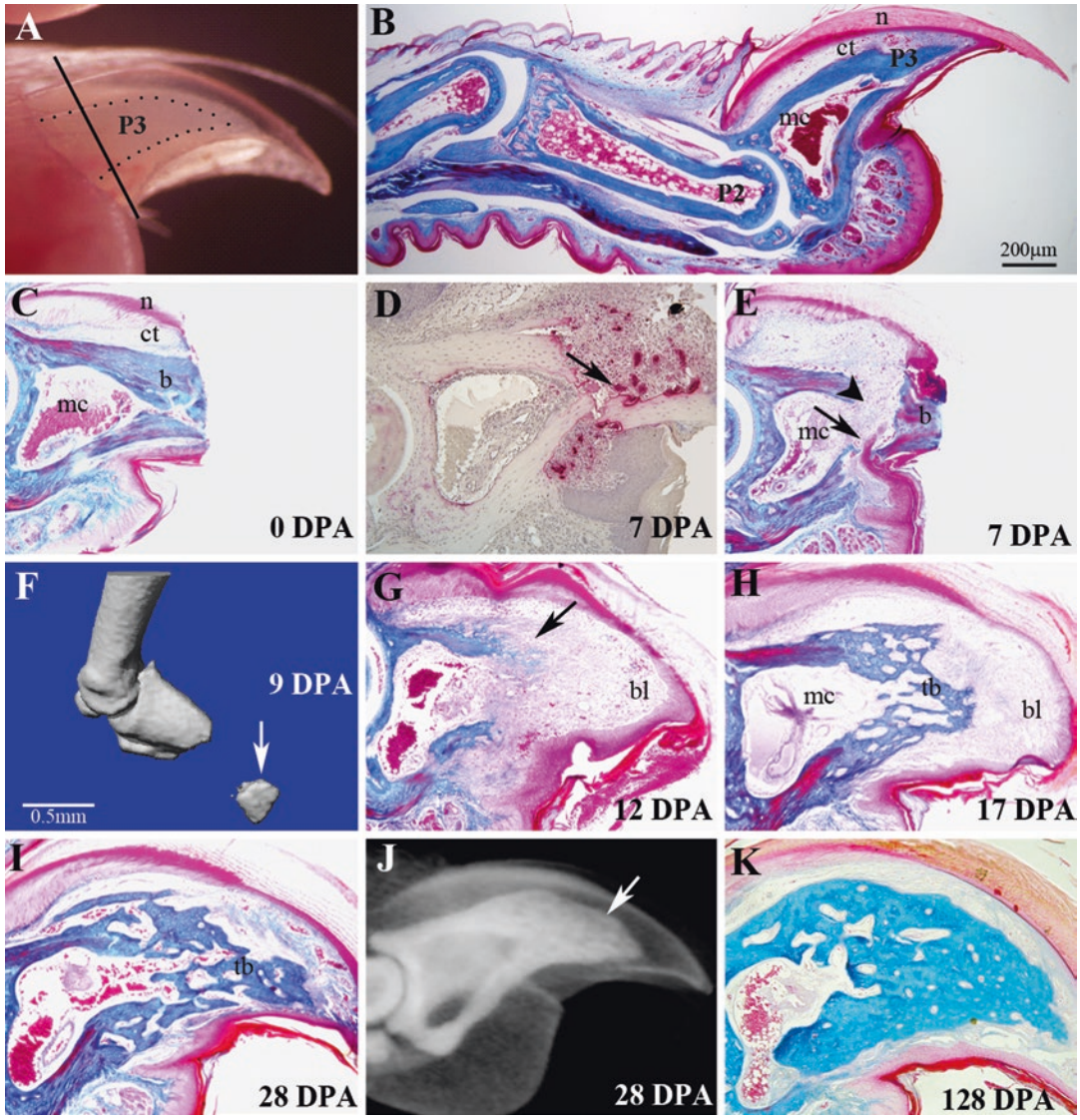

Fig. 12.3 Digit tip regeneration. (**a**) External view of mouse digit tip with P3 skeletal element outlined; solid line indicates amputation plane. (**b**) Section of adult digit showing P3 skeletal element, bone marrow cavity (*mc*), connective tissue (*ct*), and nail organ (*n*). P3 element articulates proximally with P2 skeletal element. (**c**) Section of digit tip immediately after amputation involving bone (*b*), connective tissue (*ct*), and nail (*n*) but not marrow cavity (*mc*). (**d**) TRAP staining identifies osteoclasts (*arrow*) localized to the amputated stump. (**e**) Section of regenerating digit at 7 DPA showing epidermal migration (*arrow*) through eroded stump bone causing re-amputation and sloughing of amputated bone (*b*). (**f**) Micro-CT scan shows a re-amputated distal bone fragment (*arrow*) prior to being sloughed off. (**g**) Distal blastema (*bl*) and initiation of proximal skeletal differentiation (*arrow*) first evident by 12 DPA. (**h**) At 17 DPA, new trabecular bone (*tb*) regenerates proximally, while blastema (*b*) is present distally. (**i**, **j**) At 28 DPA, regenerated trabecular bone (*tb*) is histologically distinct from the stump bone (*I*) but anatomically similar (*arrow*) to the amputated structure (*J*). (**k**) Increased bone density of the regenerate at 128 DPA (**a**, **c**–**k** Modified from Fernando et al. [30])

tissue that consists of fibroblasts and vasculature. Digit tip amputation transects the length of the P3 element without exposing the marrow region; thus the amputation wound includes a central bony region surrounded by loose connective tissue with nail epidermis on the dorsal and lateral aspects and epidermis ventrally (Fig. 12.3c).

Following amputation, the wound healing response is complicated because the wound epidermis does not heal over the amputated P3 element. Instead, there is an upregulation of osteoclasts that gradually erodes the distal bone (Fig. 12.3d), and the wound epidermis closes through the eroded bone (Fig. 12.3e). The timing of wound closure is quite variable, but results in the development of a secondary amputation plane and a distal bone fragment in the process of being discarded are often observed in micro-CT images of the regenerative response (Fig. 12.3f). This secondary amputation opens the bone marrow region to the digit tip amputation wound, and once wound closure is completed (7–10 days post-amputation), the blastema forms (Fig. 12.3g). The blastema is composed of proliferating mesenchymal cells, and cell marking studies show that cells are derived from multiple tissues of the digit stump [66, 96, 118]. Like amphibian limb regeneration, skeletal differentiation initiates in the proximal blastema and progresses distally until the complete digit tip is regenerated (Fig. 12.3h, i). The regenerated digit tip is structurally similar to the original; however, the regenerated bone forms rapidly and is trabecular rather than cortical bone (Fig. 12.3j). With time the regenerated bone becomes denser, but the trabecular nature of the bone is maintained long after the regeneration process is complete (Fig. 12.3k).

Transplantation of labeled hematopoietic stem cells and parabiosis studies show that circulating cells do not contribute to the major structural tissues of the regenerated digit [96]. Cell-specific lineage mapping studies show that a number of mesodermal and endodermal cell types are lineage restricted during digit tip regeneration. In these lineage studies, cell marking involving the induction of a cell type-specific label shows that *Col2*-expressing chondrocytes do not contribute to the regenerate, whereas *Sp7*-expressing osteoblasts and *VE-cadherin*-expressing endothelial cells contribute to the regenerate and are lineage restricted [66, 96]. The use of promoter-specific *Cre* expression to track cell lineage has also been useful in determining whether specific cell types change phenotype during regeneration. Unfortunately, it is impossible to determine whether cells of the regenerate are specifically derived from labeled stump cells or from other labeled cells. Cell labeling studies have excluded *Sox9*-expressing skeletal cells, *Scx*-expressing tendon cells, and *Tie2*-expressing endothelial cells, as cell types that do not undergo transdifferentiation during regeneration [96].

Epidermal cells are lineage restricted and play a critical role in the regeneration response. The major epidermal structure of the digit tip is the nail organ, which is comprised of the proximal nail matrix, the distal nail bed, and the overlying differentiated nail plate. Nail stem cells are localized in the nail matrix and give rise to proximal-distal columns of cells that extend into the nail bed and differentiate into the continuously elongating nail plate. The importance of the nail in regeneration is highlighted in a recent study showing that nail stem cell differentiation is Wnt dependent and that disrupting the canonical Wnt signaling pathway in the epidermis not only inhibits nail growth but also inhibits the skeletal regenerative response [108]. Additionally, gain-of-function studies show that activation of canonical Wnt signaling in the epidermis of proximal (non-regenerating) P3 amputations induces nail and skeletal regeneration. Since the epidermis is well known to be essential

for amphibian limb regeneration, perhaps it is not surprising that mammalian regeneration is also dependent on the epidermis. It does foster confidence that parallel strategies for regeneration have been maintained between evolutionarily diverse species. Together, these cell lineage studies identify the epidermis as essential for a regenerative response and provide evidence that the regeneration blastema is composed of a heterogeneous population of multiple, lineage-restricted progenitor cell types.

BMP signaling has also been identified as a signaling pathway important for digit regeneration [120, 121]. Multiple BMPs and their receptors are prominently expressed during blastema formation, and digit tip regeneration is inhibited by treatment with the BMP antagonist, Noggin. The neonatal mouse digit has been a useful model for studying induced regenerative responses. Amputation through the P2 element is proximal to the nail organ and never elicits a regenerative response, rather always forming a truncated skeletal stump (Fig. 12.4a, b). The application of a microcarrier bead containing BMP2 induces a consistent regenerative response that involves the regrowth of the P2 skeletal element and marrow region (Fig. 12.4c, d). Like the P3 regenerative response, the newly formed bone is trabecular and smoothly integrated with the stump bone. Critical aspects of this induced regenerative response include the placement of a transient BMP2 source, and the timing of the treatment must be coincident with the completion of wound closure. This suggests that the dynamics of wound closure create conditions in which the healing response can transition to a regenerative response by modifying the microenvironment of the amputation wound.

What is the nature of the BMP2 response? The most immediate effect of BMP2 is the transient upregulation of *Msx1* and *Pedf*, two genes that are associated with the endogenous P3 regenerative response. The role of PEDF in regeneration has not been characterized; however it is known to antagonize angiogenesis, and the digit blastema is avascular [30]. In addition, within 24 h of BMP2 treatment, there is enhanced proliferation of cells that are directly responsive to the canonical BMP signaling pathway (Fig. 12.4e). Within 48 h of BMP2 treatment at the amputation site, endothelial cells begin to express the chemokine SDF-1, which acts as a chemoattractant to recruit CXCR4-positive mesenchymal cells to the wound [64] (Fig. 12.4f). By 3 days post-BMP2 treatment, a zone of proliferating mesenchymal cells distinguishes the BMP2-treated amputation from non-regenerating controls (Fig. 12.4g). At this same time, a population of *Col2a1*-expressing chondrocytes initiate differentiation at the distal end of the stump. Hypertrophic chondrocytes are not present at 3 days post-BMP2 treatment. By day 5, however, the *Col2a1*-expressing chondrocytes begin differentiating into *Col10a1*-expressing hypertrophic chondrocytes in the proximal region of the regenerate (Fig. 12.4h, i). By 7 days post-BMP2 treatment, there is a distally localized zone of proliferating chondrocytes and a proximal zone of hypertrophic chondrocytes that establish an interface with the stump bone (Fig. 12.4j). In addition, osteoblasts make their first appearance at 7 days post-BMP2 treatment and initiate osteogenesis within the zone of hypertrophic chondrocytes. This BMP2-induced regenerative response only involves the regeneration of new bone tissue, and there is no evidence for the differentiation of chondrogenic tissues of the P2/P3 joint. What is novel about this response is the de novo formation of an ectopic endochondral ossification center [121]. Endochondral ossification typically occurs between two growing skeletal elements and is the mechanism for bone elongation during maturation. By understanding how to control the formation of new endochondral ossification centers, it may be possible to stimulate patterned bone regeneration from any amputated stump.

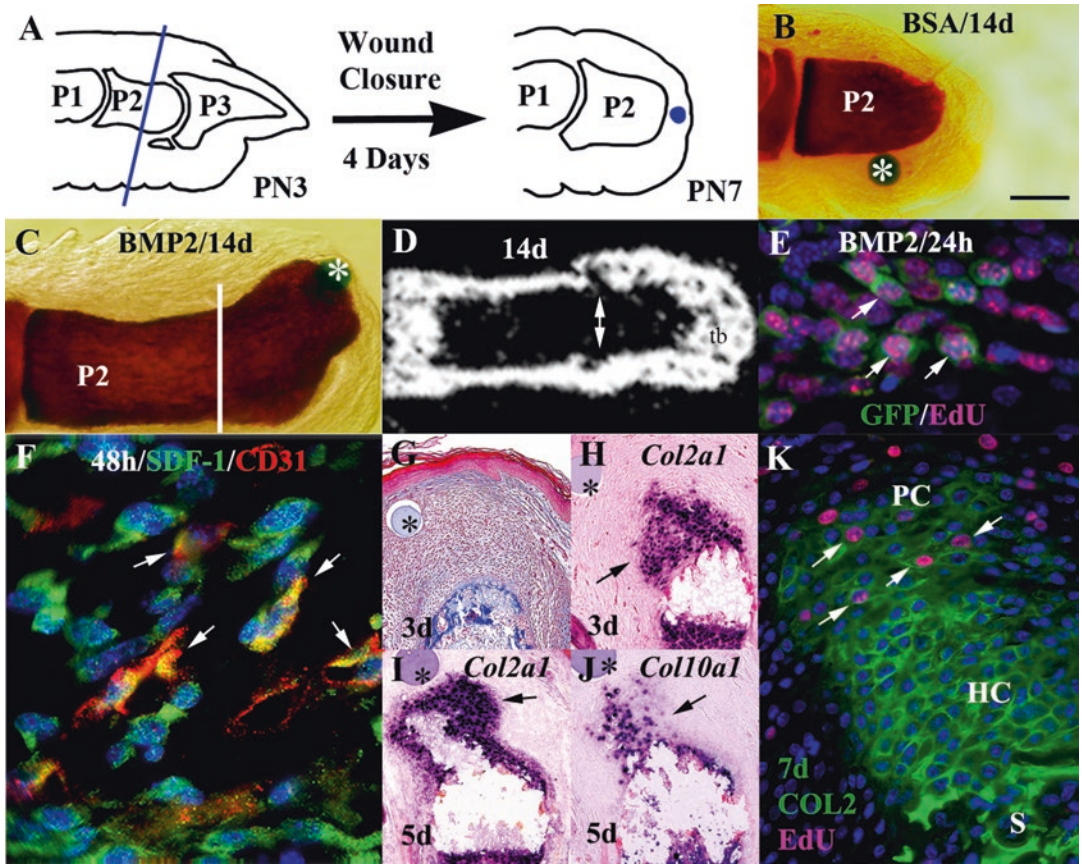

Fig. 12.4 BMP2-induced endochondral ossification center. (**a**) Diagram shows amputation level (*blue line*) and positioning of BMP2 bead when wound closure is complete 4 days after amputation. (**b**) Control digits show no regeneration with treatment with a BSA bead (*). (**c**) Digits treated with a BMP2 bead (*) show skeletal regeneration. (**d**) Radiographic section showing regenerated trabecular bone (*tb*) and skeletal irregularities (*double arrow*) identifying the amputation level. (**e**) EdU incorporation (*arrow*) in the BRE-*Gfp* transgenic reporter mouse shows that BMP2 acts as a mitogen. (**f**) Co-immunostaining shows that BMP2 induces endothelial cell (*red*) expression of the chemoattractant SDF-1α (*green*). (**g**) Section showing mesenchymal cell accumulation following BMP2 treatment (*). (**h–j**) In situ hybridization showing *Col2a1* (*arrow* in **h** and **i**) and *Col10a1* transcripts (*arrow* in **j**) are induced in sequence by BMP2. (**k**) Regenerating endochondral ossification center contains proliferating chondrocytes (*PC*) (*arrows*) apically and a quiescent proximal zone of hypertrophic chondrocytes (*HC*) contiguous with the stump (S). (**a–e**, **g–k** Modified from Yu et al. [121]; **f** Modified from Lee et al. [64])

While BMP signaling is well known to play an important role in bone regrowth, studies using the digit regeneration model indicate that the cells at the amputation wound site respond to BMP2 in a position-specific manner. It is important to remember that limb regeneration requires that cells at the site of injury retain or reacquire spatial information concerning the level of amputation. Since the mammalian regenerative response is restricted to the digit tip, it has been impossible to determine whether a system of positional information is present and required for successful regeneration. BMP2 has been shown to induce a regenerative response from two distinct digit levels, and the anatomy of the responses is also distinct. Detailed analyses of the two responses show

that BMP2 stimulates cells at two amputation levels to regenerate in a position-specific manner (Fig. 12.5). BMP2-induced digit regeneration, whether from a proximal P3 amputation or a mid-P2 amputation, establishes an endochondral ossification center that mediates skeletal regeneration. What is distinct between the two amputations is the proximal-distal polarity of the endochondral ossification centers. The regenerated endochondral ossification center displays an inherent polarity that can be identified based on the relationship of the proliferating and hypertrophic chondrocyte populations.

During development of the distal end of P2 element, proliferating chondrocytes are distal relative to the hypertrophic chondrocytes, whereas the P3 element forms with only a proximal growth plate in which the proliferating chondrocytes are proximal to the hypertrophic chondrocytes (Fig. 12.5e). Thus, the developmental polarity of endochondral differentiation at the P2/P3 articulation is reversed. Similarly, BMP2-induced P3 regeneration forms an endochondral ossification center with proliferating chondrocytes proximal to the hypertrophic chondrocytes (Fig. 12.5a, b), whereas the BMP2 response to P2 level amputations results in an endochondral ossification center with proliferating chondrocytes distal to hypertrophic chondrocytes (Fig. 12.5c, d). These studies show that in response to the same inductive signal, cells of the P2 and P3 amputation wounds respond in a position-dependent manner to regenerate the appropriate skeletal structures. This finding establishes for the first time that a system of positional information is present in the mammalian

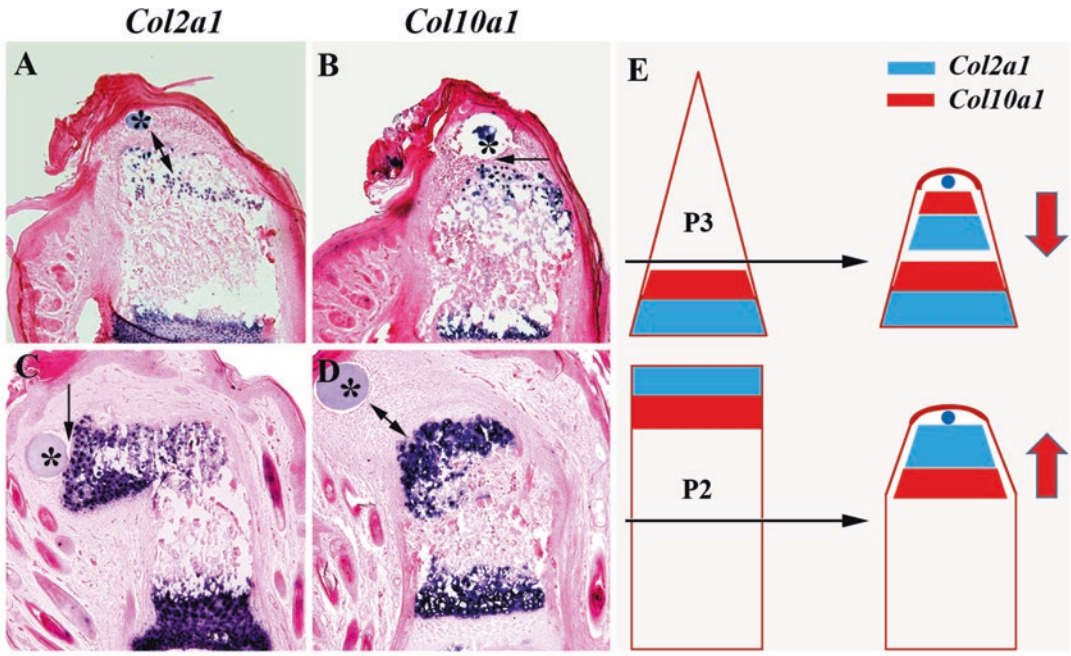

Fig. 12.5 Patterning of BMP2-induced regeneration is level dependent. Distal is toward the *top* in all images. Microcarrrier beads are indicated by *. (**a**–**d**) Section in situ hybridization of induced regeneration from proximal P3 amputation (**a**, **b**) and P2 amputation (**c**, **d**) shows that BMP2 induces endochondral ossification centers of opposite polarity indicated by the expression domains of *Col2a1* (**a**, **c**) and *Co10a1* (**b**, **d**). (**e**) Diagrammatic summary displaying shift in polarity of the endochondral ossification centers induced by BMP2 (*blue bead*) from two different amputation levels (*black arrows*). (Reprinted from in Yu et al. [121])

digit and that this system is used to organize and induce regenerative responses.

The digit represents an excellent model to explore fundamental aspects of mammalian regeneration and to discover ways to enhance the regenerative response. However, by comparison to the limb, the digit is small and far less complex. For example, digits lack muscle tissue, and the amount of regenerated tissues that require reinnervation and revascularization is much smaller. To explore whether BMP2 treatment can enhance regenerative responses in adult limbs, the neonatal digit regeneration studies were used as a guide. Amputation of the hind limb shank at a level proximal to the fusion of the tibula and fibula was selected for studies, so that the distal fusion of these two skeletal elements could be used as a patterning marker for regeneration (Fig. 12.6a). Using a protocol that was appropriately modified for an adult limb amputation (i.e., proportionally enhanced dose, modification of the delivery vehicle, modification of treatment timing, etc.), a single treatment of the limb amputation wound with BMP2 was found to be effective in eliciting a patterned skeletal regenerative response in adult mice [121]. Control amputations treated with the vehicle failed to elicit a regenerative

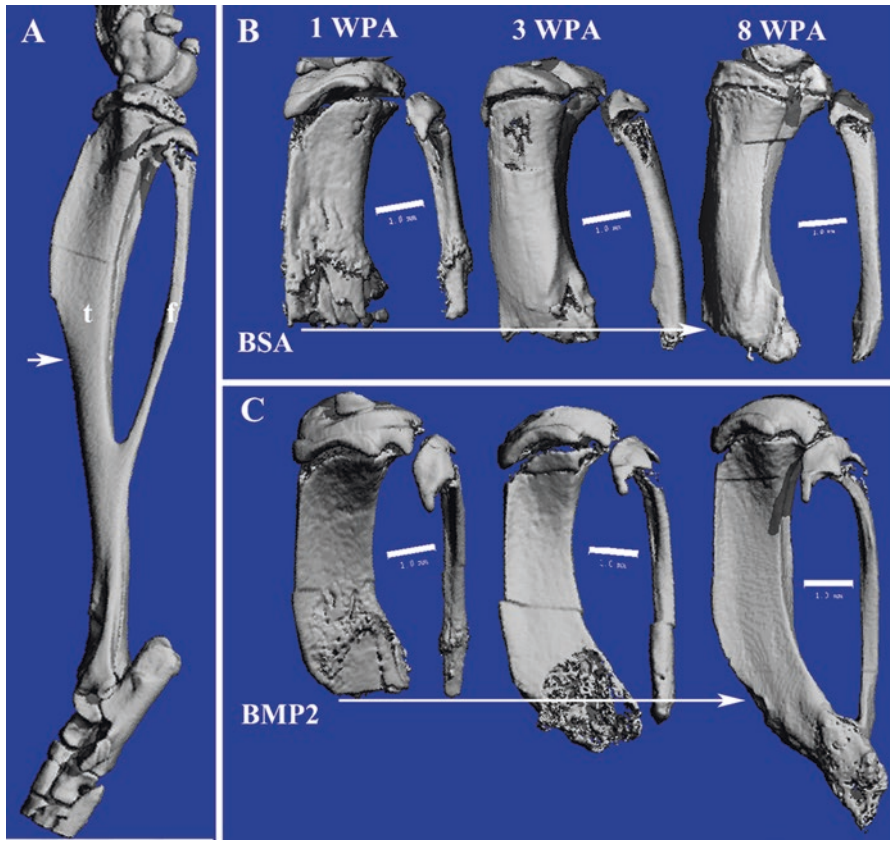

Fig. 12.6 Regeneration response to Bmp2 after adult limb amputation. Distal is toward the *bottom* of all images. (**a**) μCT image showing skeleton of the mouse hind limb shank (consisting of the tibia (*t*) and fibula (*f*) that fuse distally), and the level of amputation (*arrow*). Simple amputation was made through the mid-shaft of the shank to transect both tibia and fibula proximal to the point of fusion. (**b**, **c**) μCT scans of a BSA control (**b**) and a BMP2-treated limb (**c**) at 1, 3, and 8 weeks post-amputation (WPA). BMP2-treated amputations displayed organized distal bone growth resulting in skeletal elongation and distal bone fusion indicative of a properly patterned regenerative response. (Modified from Yu et al. [121])

response. The BMP2- treated amputations regenerated significantly more bone that involved bone lengthening as well as fusion of the tibia and fibula (Fig. 12.6b, c). Like the digit model, this regenerative response only involved the formation of new bone tissue, and the induced response was incomplete. Nevertheless, the data clearly show that adult limb regenerative capacity can be enhanced by the spatiotemporal targeting of BMP2 administration. This offers a proof of concept that the general strategy of tapping into unrealized regenerative potential can provide a path for future therapies in regenerative medicine.

Regeneration and Pathology

With an enhanced understanding of the regenerative potential following traumatic injury, it is instructive to reevaluate pathological conditions involving tissue overgrowth. There is growing concern about the number of modern war zone amputations displaying heterotopic ossification (HO) associated with the healing response. HO refers to the atypical formation of bone in soft tissue, joints, and muscle, which presents a significant obstacle to rehabilitation and the fitting of prosthetic devices. While HO occurs infrequently in civilian amputee populations (11%), the prevalence of HO is approximately 63% in combat-related amputations. This difference has been attributed to modern ballistics designed to maximize gross foreign contamination by the inclusion of nontraditional projectiles that maximize infection by microorganisms [26, 93, 94]. The formation of heterotopic bone is painful, creates problems with prosthetic devices, and can require multiple surgical revisions to remove the excessive bone. HO presents a major obstacle to the rehabilitation of previously healthy soldiers to high levels of activity [92]. Although HO is a significant pathological problem in combat orthopedics [19], the regeneration biologist can be encouraged by the fact that new bone is forming at the amputation wound, albeit in an inappropriate fashion. It suggests that the body is responding to the injury by attempting to regenerate, even if the conditions at the wound do not support a functional response. This represents an opportunity to use our understanding of mammalian regeneration to guide the body's response toward controlled ossification that can be functionally integrated with the bone stump.

Heterotopic bone formation is attributed to a number of distinct healing responses including inflammation, vascularization, and an ectopic BMP signaling source that initiates endochondral ossification [67, 94]. Chondrocytes initially form a chondrogenic template that is subsequently invaded by the vasculature and osteoprogenitor cells that form the new bone. Our understanding of HO is enhanced from research on the genetic disorders fibrodysplasia ossificans progressiva (FOP) [51] and progressive osseous heteroplasia [50], both of which present with heterotopic bone formation. Studies on patient-derived cell lines suggest that overexpression of both BMP4 and BMPR1A, as well as underexpression of BMP antagonists, is required for HO development [23, 103]. There is evidence that a number of different cell types can be recruited and act as progenitors for HO, including adipocytes, mesenchymal stem cells, and perivascular cells [67, 86, 90]. The pathology of HO has clear parallels to the BMP-induced regenerative response described above, with the BMP signaling cascade acting as an initiating center that stimulates proliferation, recruitment, and chondrogenesis to establish an endochondral ossification center. There is also a temporal component to the regenerative response in that BMP2 treatment prior to wound closure or late in the wound healing process induces ectopic bone formation rather than regeneration (Yu and Muneoka unpublished data). Thus, there is a clear relationship between the spatiotemporal positioning of a BMP source and whether or not

a regenerative response is induced. It is significant that the non-regenerative BMP2-induced response is the formation of ectopic bone similar to the pathological condition of heterotopic bone. Obvious parallels between this model of regenerated/ectopic bone and the pathology of HO suggest that one approach to controlling HO is to focus on the BMP signaling pathway during wound healing. Since HO initiates by forming an endochondral ossification center, then one obvious therapeutic approach would be to inhibit this process by modulating the recruitment, proliferation, or differentiation of chondroblast progenitor cells. Alternatively, it may be possible to manipulate the presentation of HO to engineer a functional ossification response and control skeletal regeneration of the amputated bone stump. In this way, broadening our understanding of regenerative potential in mammals and humans in particular has dual benefits. On the one hand, this understanding can be applied to treating specific pathological conditions such as HO. On the other hand, the pathological response to traumatic injury can be instructive for gaining insight into human regenerative potential.

Limb Regeneration Through Tissue Engineering Strategies

In this section, we explore the concept of tissue engineering, including regenerative medicine-based strategies and bioprinting technology currently being explored for the development of replacement tissues and organs (see also [71]). Tissue engineering involves the use of living cells and other materials living and/or nonliving to form a scaffold structure that can support tissue formation. Since tissue engineering was first conceived in 1987, its potential has been advanced by more recent developments and significant achievements in regenerative medicine, including autologous engineered bladder constructs for cystoplasty [4], tissue-engineered cartilage for knee repair [46], and tissue-engineered airway for replacement and transplantation [69]. Some tissue-engineered products have been implanted into patients with favorable outcomes [40, 42, 89]. Given these accomplishments, it seems possible that the same principles of tissue engineering and regenerative medicine could be applied to reconstruct other human body parts such as digits and limbs. Certainly we recognize that the tissues successfully engineered to date are significantly less complex than entire human extremities characterized by multiple tissue types and layers, intricate micro-architectural structures, elaborate microvasculature, and an integrated peripheral nervous system. Formidable challenges must be overcome to make possible in practice what we can, for now, imagine only in principle. Here we provide an overview of potential near-term strategies and applications, with reference to supporting literature. We encourage the interested reader to learn more from other more comprehensive works in the field of tissue engineering (e.g., [61, 115]).

We begin with a focus on the current possibility of using tissue engineering and regenerative medicine strategies to reconstruct functional tissue of the amputated limb itself, as may be useful to improve prosthetic socket fit, regenerate stronger bone and muscle tissues for osseointegration, or implant tissue-engineered constructs to strengthen peripheral nerve interfaces for electromyogram (EMG) control of a prosthetic device. Where there is insufficient tissue mass or functional tissue to don and control a prosthetic device, for example, tissue engineering could be applied to create a larger tissue mass. Direct implantation of an experimental acellular biologic scaffold material that received an investigational device exemption (IDE) from the US Food and Drug Administration (FDA) has been clinically tested for the treatment of volumetric muscle loss in a small number of patients with varying

success to increase strength and function [38, 73, 104]; however, a different research group has tried to duplicate the study in small preclinical animal model but failed to observe notable functional improvements in the treated animals [5]. Also in development is an in vitro tissue-engineered muscle repair construct combined with bladder acellular matrices for treating volumetric muscle loss injury; this approach was evaluated in a small preclinical animal model and shown to improve functional outcome compared to the untreated leg of a control animal [18]. Scaffold-free approaches have also been considered [113]. These strategies could be applied to address lost muscle volume and to strengthen the surrounding muscle tissue of an amputated limb for improving fit and control of the prosthetic device along with a prescriptive rehabilitation program [38].

Recent papers offer comparison of tissue engineering and regenerative medicine strategies for regeneration of volumetric muscle loss and identify key challenges [41, 74]. TATRC has also invested and explored development of tissue-engineered muscle constructs as biomimetic peripheral nerve interfaces to act as a signal amplifier for improving the control of an EMG-based prosthetic device. For upper limb amputees who lack sufficient musculature to control motorized neural prosthetics, this approach could offer an alternative to surgical targeted reinnervation without having to sacrifice healthy tissues [57, 58].

In theory, tissue engineering and regenerative medicine-based strategies could be applied together to engineer tissue constructs for the replacement of a human limb, in whole or in part. A scaffold would first be needed to create the desired tissue architecture. Scaffolds can be engineered to provide geometry, porosity, mechanical compliance, and microstructure similar to the tissues or organs needed. Cells are then placed on the scaffold to form the desired tissues. This can be done using a variety of cell sources and types, including autologous cells, stem cells, or induced pluripotent cells (iPS). Biologically active molecules such as growth factors may be added to encourage neovascularization. Formation of the tissue and its microstructures occurs largely through self-assembly; a combination of forces including diffusion and intramolecular forces drives the placement of cells and biologically active molecules on the scaffold. Uniform cell distribution may not always be achieved; placement and orientation of the cells may not result as desired. Surfaces of the scaffold may need to be engineered to provide directional guidance for the cells to align in desired configuration.

More recently, bioprinting has been explored as a technique to create tissue structures and organs [12, 49, 84]. Bioprinting enables creation of complex, three-dimensional tissue-engineered structures by dispensing live cells (in liquid or gel form) in a specific programmed pattern without the need for a three-dimensional scaffold [87]. Bioprinters work by depositing one or several cells at a time through the nozzle of each print head, in the same way an inkjet printer dispenses ink onto a piece of paper. This cell printing action can generate one layer of cells at a time using one or multiple print heads and cartridges. By printing multiple tissue layers, one over the next, the resulting multiple ultrathin layers of living cells produce a three-dimensional cellular object such as a living tissue. Printing can be programmed and designed to dispense multiple ultrathin layers composed of one or more types of cells and to include other biological factors or biocompatible components (e.g., growth factors and nutrients) in various patterns to create specific micro-architectural details and cell orientations. Thus, placement of cells through bioprinting is more precise than by tissue engineering. When combined with three-dimensional design software (e.g., computer-assisted design, commonly known as CAD) that translates medical images of

an organ or other body part, a personalized tissue structure can be replicated, including the intricate micro-architectural details of replacement tissue or an organ capillary network. Advantages of this approach include greater personalization, improved precision, and the capability to more closely mimic natural tissue structure.

Although bioprinting offers distinct capabilities and flexibilities for design and creation of living tissue structures, this technology also faces the same formidable engineering challenges associated with traditional tissue engineering. These challenges include (1) the need to create a vast, complex microvascular system to transport nutrients through the tissues and to the cells, export cellular debris, and exchange gases to keep engineered tissues viable; (2) technical difficulties associated with culturing neurons, which are required to engineer nerve pathways; and (3) the need to coax innervations from the host system to enable implanted muscle tissue to function. In addition, it is an enormous hurdle to integrate multiple and different tissue types and structures such that when combined, they can function together as a whole to include muscle tissue innervation and neurosensory pathway regeneration. Here we will focus on the essential challenge to engineer a vast microvascular network that is capable of sustaining viable tissue-engineered constructs.

Researchers working in tissue engineering and bioprinting have explored ways to create a microvascular networks. Tissue engineering strategies have evolved beyond the inclusion and controlled delivery of active biological molecules, such as angiogenic growth factors, to activate development of neovascularization networks [88]. Combination approaches now include novel scaffold design with incorporation of a perfusion system [10] and use of protein or cell therapy with endothelial and endothelial progenitor cells [17]. Nonetheless, the ability to engineer a sophisticated microvascular network that can reach every cell and tissue layer remains an elusive achievement [6, 52]. Advances in bioprinting technologies now provide the capability to create a microvascular system that can mimic original tissue through the use of biodegradable hydrogel or biopolymer to create the channel space [9]. Channels are lined by dispensing and printing the appropriate cells [22] to mimic microvascular system properties (e.g., network, flexibility, pathways, diameters, etc.). However, this approach is a slow process. Depending on channel diameter size and network complexity, the bioprinting process could take several days or weeks; it is driven largely by the biology and time scale of cell and tissue development. Delay is problematic because in the absence of a finished and functional microvascular network, earlier layers of printed cells may lose viability. Without a microvascular network in place, nutrient supply is driven mainly by diffusion, which is a slow delivery process that approaches a zero gradient once a critical distance is reached. Thus, the layers of cells and tissues that are located farthest from oxygen and nutrient sources will die. To date, it has not been possible to construct a microvascular system beyond a few millimeters in thickness [68]. This is a significant limiting factor for the engineering of large and complex human organs and tissue structures that are multiple layers of tissues thick. Still, hope remains that a functional engineered limb may one day be realized.

Summary

Humans have an innate ability to heal following traumatic injury, but we have no innate ability to regenerate critical parts of ourselves lost to injury or disease. We have discovered methods to clone complete animals' single adult cells, and we have established the sequence of our entire genome. We can defy aging by reprogramming an adult cell back to its embryonic

state. These are enormous achievements, to be sure. More profound still would be the ability to regenerate lost or injured arms, legs, spinal cords, hearts, jaws, eyes, and other organs and structures. This objective is not yet easily within reach, but it is well within the realm of the possible. It is no longer merely the stuff of science fiction.

Recent success demonstrating induced regenerative responses in adult mammals [121] provides proof of concept to validate a vision of human regenerative potential. Commitment to the vision and additional research will be necessary to advance medical science and technology in support. Tissue engineering and bioprinting strategies may make it possible eventually to engineer, modify, and/or replace lost limbs with functionally equivalent extremities. Artificially regenerated and tissue-engineered limbs are now at least conceivable in theory. In practice, engineering challenges must be overcome through continued advancement of scientific discovery and technology development.

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