Lecture Notes in Bioengineering

Franco Simini
Pedro Bertemes-Filho *Editors*

Medicine-Based Informatics and Engineering

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Lecture Notes in Bioengineering

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Medicine-Based Informatics and Engineering

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Preface

Medicine-Based Informatics and Engineering is now available after a major regional Congress (Fig. 1) one week prior to the outbreak of COVID-19 pandemics in Latin America. The plenary and semi-plenary speakers of the 700 strong SABI2020 Regional Meeting were invited to write a chapter while preparing their presentations and their—sometimes canceled—trip to Piriápolis, Uruguay. The SABI2020 Biomedical Engineering and Medical Informatics Congress was a special occasion

Fig. 1 SABI2020 Congress held in Piriápolis, Uruguay March 4–6, 2020, one week before the COVID-19 pandemic reached the Country. Plenary and semi-plenary speakers at SABI2020 were invited to contribute a chapter for this book

to discuss new devices and software to foster medical care and patient–physician relationship, as well as interdisciplinary approaches or social motivations.

Technology has evolved to such a multiplicity of possibilities, and the software can perform so many different functions, that only meaningful applications should be considered for development and clinical use. The mere fact that a physiological parameter can be measured or a function can be performed is not by itself a reason for engineering to suggest a clinical device. To fulfill such adherence of development efforts to clinical needs, interdisciplinary work is necessary to put forward combinations of medical and technological knowledge to feed the Biomedical Engineering research agenda. This line of thought was the first motivation for the authors to contribute chapters for this book.

Within modern technology, information and communication (ICT) are increasingly associated and sometimes included in specific hardware technical solutions. Therefore, the classical distinction between "systems engineering" or "software engineering/computer science" on one side and classical engineering (mechanical, electrical, materials, etc.) on the other side is no longer valid.

Throughout the book, two concepts are present: (i) Medicine should drive the development of Biomedical Engineering (BME) and Medical Informatics (MI) from available and new technology. Since the limitations of technology are reduced, technology "per se" is no longer the privileged starting point of research. Today, the development of biomedical devices, software and systems can almost freely stem from clinical wish lists and desiderata. (ii) The second idea treated implicitly in the book is that BME and MI should merge into a single body of knowledge to better follow the demanding clinical challenges of modern medicine. Having mastered the problems to be solved for survival, physiological compensation, repair and pain reduction, BME+MI are now asked to start from bedside or living milieu to develop ever more sophisticated tools for increasing cohorts of aging populations to contribute to their quality of life: should we call it "Medical Engineering" to include BME+MI?

Within this framework, the book includes chapters addressing these ideas from each author own point of view and expertise. The range of fields in the book is wide enough to give the reader an overview of what to expect in the coming decades in Medical Engineering, concerning new medical software systems, pervasive medicine, wearable devices, prosthesis, intelligent follow-up and anticipatory medicine, as well as the impact of instrument-connected electronic clinical record (ECR) with knowledge derived from the use of artificial intelligence (AI) data analysis.

Chapter "Medicine Based Engineering and Informatics to Foster Patient Physician Relationship" by Franco Simini describes interdisciplinary work within a University Hospital, with details of lessons learned with the development of new devices and of innovative Medical Informatics, such as clinical record systems and chronic condition patient follow-up applications. The translation of software systems from other activities into medicine is described as the possible cause of delayed adoption of ECR when patient–physician relationship is valued and respected. Part of the chapter mentions Technology Transfer to allow a timely dissemination of BME+MI benefits within health care systems, involving licensing to industrial and commercial companies.

Chapter "Statistical Gait Analysis Based on Surface Electromyography" by Valentina Agostini and coworkers is on Statistical Gait Analysis, a contribution to a new way to study gait—a basic human motor task—from an Electromyography (EMG) perspective. By processing surface EMG, this chapter introduces Inertial measurements (IMU—inertial measuring unit) to detect muscle activation gait phases in a simple way, robust to repetitions. The follow-up of entire cohorts of patients in the future will depend on the methods and devices derived from this research, optimizing health care system resources.

Chapter "Brain-Computer Interfaces with Functional Electrical Stimulation for Motor Neurorehabilitation: From Research to Clinical Practice" by Carolina Tabernig and coworkers deals with brain-computer interfaces and specific rehabilitation applications, as developed from clinical practice and described in an interdisciplinary approach. Clinical needs clearly drive this research field.

Chapter "Biopotential Acquisition Systems" by Enrique Spinelli and coworker is an electrical engineering breakthrough contribution to the design of electronic circuits for biopotential amplification. It includes next generation configurations and state of the art designs to obtain the best possible signal to noise ratio in human signal capture for all kinds of biomedical devices.

Chapter "Wearable Bioimpedance Measuring Devices" by Pedro Bertemes-Filho describes a very special kind of signal derived from biological tissues: bioimpedance as used for wearable devices. There is an immense potential behind the availability of non invasive time series to monitor (and therefore the opportunity to act upon) diverse physiological parameters, in intensive care, rehabilitation and assistive devices. Bioimpedance is the modern low cost "general purpose" technology to tackle unsolved problems from a medical perspective with simple non invasive clinical applications.

Chapter "Predictive Cardiovascular Engineering: Transforming Data into Future Insights on Cardiovascular Disease" by Ricardo Armentano leaves behind decades of cardiology and associated palliative pharmaceutical approach to introduce arterial biomechanics to keep us in good health. This is a tremendous "back to the basics" of Medicine made possible by Biomedical Engineering interdisciplinary development stemmed from a profound understanding of cardiovascular physiology. It is a new approach to arterial biomechanics which allows to act with preventive medicine before any symptoms appear later in age.

In Chapter "Engineering Special Medical Devices for Vulnerable Groups", Martha Ortiz and coworker bridge the gap toward vulnerable groups. Biomedical Engineering and Medical Informatics hold the key to develop special medical devices for all, following WHO recommendations.

Chapter "Serious Games and Virtual Reality for Rehabilitation and Follow up of Wheelchaired Persons" by Marta Bez and coworkers describe the development of serious games with virtual reality for rehabilitation and follow-up of wheel-chaired persons, opening the way for interdisciplinary work by clinicians and engineers.

Chapter "Society 5.0 and a Human Centred Health Care" by Violeta Bulc and coworkers is a bold introduction to think health and technology in a new way, with cooperation from industry, politics, business and scientific research to foster better medical devices and software applications. This synergy empowers individuals, firms and government to a yet to be reached level of connection between clinical needs, societal potential and health care system.

Chapter "Clinical Practice, Patient-Physician Relationship and Computers" by Alvaro Díaz Berenguer is a warning to avoid deteriorating the patient–physician relationship with misuses of information and communication technology. Computer technology does not always respect the delicate empathy necessary to fulfill the basic medical functions. Medical Engineering and Medical Informatics can add considerable efficiency, error reduction, follow-up capacity, but should neither hinder nor replace the human species intrinsic patient–physician relationship.

Chapter "Interdisciplinary Collaboration Within Medicine-Based Informatics and Engineering for Societal Impact" by Bianca Vienni and Franco Simini considers Medical Engineering and Medical Informatics from an epistemological point of view. Intrinsically interdisciplinary, the subject matter of the book is analyzed in this chapter from the point of view of "Science, Technology and Society." It is argued that engineering and medicine are also part of the STEMM conglomerate along with mathematics. Reading this chapter will allow the reader to see the links to societal change, as a consequence of ever more sophisticated devices, better (and longer) life spans and closer communications. Medicine and clinical knowledge cannot evolve unconnected to engineering development of devices and software systems.

This book is a contribution to an up-to-date approach to Biomedical Engineering and Medical Informatics from an interdisciplinary point of view, to help the reader put forward new ideas and goals. Within this book, diverse clinical applications, technologies and approaches will help the reader adopt criteria to tackle projects starting from clinical problems and using all available technology.

We wish the reader a pleasant and exciting experience in direct contact with the authors, through their carefully written texts, all meant to foster Medical Engineering!

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Editors, Contributors and Co-authors

The authors of the chapters of this book are the group of invited speakers at SABI2020 Biomedical Engineering and Medical Informatics Congress held in Piriápolis, Uruguay. The careful selection of plenary and semi-plenary SABI2020 speakers was a good opportunity to gather their valuable academic contributions in a book. A few speakers declined writing a chapter, while others were specially invited to contribute with topics within the scope of the book: Medicine-based Engineering and Informatics. The variety of experiences and points of view will help the reader understand how engineering can be part of medicine, provided the goal and starting point of engineering design is based on clinical needs. In order of appearance of the chapters, the following are the authors of this book:

About the Editors

Franco Simini is a professor at the Universidad de la República, Uruguay, PAHO/WHO National Professional (1990–2008), founding member of Espacio Interdisciplinario (2008–2013), pioneering Biomedical Engineering research from Núcleo de Ingeniería Biomédica since 1985 after his Electronics Engineering degree from Universitá degli Studi di Pisa, Italy (1977). He designed telecommunications and medical equipment 1978–1989 in Uruguay. As CLABIO2015 and SABI2020 organizer, he is active in university government and technology transfer. His research spans from biomedical equipment design to medical reasoning modeling in Medical Informatics.

Pedro Bertemes-Filho is a professor of Electrical Engineering, Universidade do Estado de Santa Catarina (UDESC), Brazil, and done Ph.D. in Medical Physics by the University of Sheffield, UK (2002). He is a leader of the Biomedical Engineering Group since 2006, a Fulbright researcher at Dartmouth College (USA), a member of the Brazilian Society of Biomedical Engineering and IEEE Senior Member, a secretary of the International Society of Electrical Bioimpedance and a member of the International Committee for Promotion of Research in Bio-Impedance (ICPRBI). His areas of research are electrical impedance spectroscopy, biomedical instrumentation, devices and sensors.

Contributors

Valentina Agostini, Ph.D. is an associate professor in Biomedical Engineering at Politecnico di Torino, Italy, where she leads a gait analysis laboratory. Distinguished with the Best Methodological Paper Award by Siamoc-Elsevier 2009 and the Best Paper Award at IEEE International Symposium on Medical Measurements and Applications (MeMea) 2014, she is an associate editor of "Frontiers in Sports and Active Living." She authored 85 peer-reviewed publications. She teaches Neuroengineering at Biomedical Engineering M.Sc. program of Politecnico di Torino since 2018, and she is invited to teach courses in Uruguay since 2019.

Ricardo Armentano is a distinguished professor of Biomedical Engineering and a member of the IEEE EMBS Technical Committee on Cardiopulmonary Systems and Physiology-based Engineering. From Argentina and Uruguay, he has acquired international recognition in cardiovascular hemodynamics and arterial hypertension and has extensive experience in Ph.D. supervision and examination. He authored 350+ publications including a book, book chapters and peer-reviewed articles.

Alvaro Díaz Berenguer is a professor of Medicine, Universidad de la República, Uruguay, until 2015, now retired. As Internal Medicine Specialist (1988), a author of articles on Medicine and Society (*Brecha* weekly), he was also "Medicine in Society" Editor of *Archivos de Medicina Interna*. He is a author of several books on medicine and patient–physician relationship and co-authored with his father the book *Medicina y Literatura*. He is a member of the State Hospitals Bioethics Committee, the Patient Safety Honorary Commission and the Bioethics Committee of the Uruguayan National Academy of Medicine.

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Violeta Bulc, M.Sc. is the curator of #Ecocivilisation, former EU Commissioner, former Deputy Prime Minister of Slovenia, an engineer, entrepreneur, innovator, lecturer, author of two books *The Rhythms of Business Evolution* and *The Magic of*

Contribution. She is also an active member within civil society, member of the #EUHealthUnion initiative, connector of global networks, member of the #G100, fostering and co-creating inclusive, open ecosystems toward a thriving world.

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Montevideo, Uruguay — Franco Simini
Joinville, SC, Brazil — Pedro Bertemes-Filho
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Contents

Medicine Based Engineering and Informatics to Foster Patient Physician Relationship

Franco Simini

Abstract Biomedical Engineering and Medical Informatics can improve patient physician relationship by means of new instruments and software applications designed by interdisciplinary teams. Already in the 1980s with the Perinatal Information System, SIP, and now with the Personalized Perinatal Follow-up System, SEPEPE, the first prescription App, biomedical engineering works towards good quality medicine. SIMIC, another personalized prescription App for cardiac failure patients and DINABANG, a torque/velocity measurement device for the sports field are further examples. Synergy with medicine is not found, on the contrary, in clinical records systems based on a naive translation of industrial information systems with no interdisciplinary design. A disruptive innovation, PRAXIS, captures a physician's case mix to assist solve his or her future cases based on medical reasoning sequences. Further examples of technology developed from clinical perspectives are ABDOPRE, a servo controlled vacuum bell to treat intra-abdominal hypertension and NEFROVOL a non invasive measure of polycystic kidney volume. Technology transfer is the desired epilogue of research with examples described here: the pulmonary mechanics instrument MECVENT, the hyperbilirrubinaemia reduction lamp BiliLED and the portable lower limb kinetics metre DINABANG. Biomedical Engineering and Medical Informatics converge on a broad interdisciplinary area that could well be identified as Medical Engineering.

Keywords Medicine based engineering · Medical informatics · Biomedical engineering · Interdisciplinarity · Biomedical devices · Follow-up software · Technology transfer

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1 Introduction

Medicine and Biomedical Engineering share the same motivation to reduce suffering, help ill people and contribute to the adoption of preventive behaviours. To do so, they follow different methods and they aim at different partial results. Medicine relies on physiopathology and a profound understanding of human nature, including an important share of empathy (Díaz-Berenguer 2021). Engineering specifies, designs and builds devices for society and is called Biomedical Engineering (BME) or Medical Informatics (MI) when it solves problems and provides solutions for Medicine.

Empathy may be considered the essence of Medicine (Díaz-Berenguer 2021), while material efficiency best defines Engineering and specifically BME or MI. Medicine also includes, in addition to Psychology, Pharmaceutical Chemistry, Nutrition, Nursing among other specialized knowledge, BME and MI as relevant components, as will be treated in this chapter.

Diversity in Technology has increased to such an extent that a great multiplicity of hardware and software solutions can perform many different functions. These functions span all aspects of society, not necessarily addressing any meaningful medical application. But only a few will be useful in medical terms. The mere fact that a parameter can be measured or a function can be performed does not mean—per se—it will have an impact on patient physician relationship or any medical result. Feasibility is not a reason for BME or MI development with no prior interdisciplinary work. This chapter suggests that only combinations of clinical and technological knowledge can meaningfully feed research in BME and MI. We think that BME and MI could be called Medical Engineering to stress the fact that it is the engineering approach adopted must stem from a medical rationale, irrespective of the specific technology used. Modern digital techniques allow MI to solve problems once only tackled by mechanical or electronics engineering.

BME and MI are growing in significance and share within Medicine, as they are responsible for instrumentation, life support, hospital infrastructure and information management. Along with biological and physiological understanding and, paramount, empathy, Medicine also includes BME and MI, which allow it to reach unprecedented efficiency and success. This chapter deals therefore with the dialectic relationship between clinical knowledge on one side and BME and MI on the other.

One message of this chapter is that only Medicine Based designs can have a beneficiary effect in clinical settings. Already in the 1980s clinicians and public health specialists, in order to lower maternal and neonatal mortalities, needed data regarding pregnancy, labour and newborn babies. The problem was tackled by the interdisciplinary design team (Simini 1999) of the Perinatal Information System, SIP, and later, updated in the 2020s as the Personalized Perinatal System, SEPEPE, the first Prescription App. In another medical realm, SIMIC, a personalized cardiac failure patients follow up system, is also a Prescription App, which allowed to further refine the novel concept, derived directly from the need of physicians to be informed about meaningful details of every day life between visits. Yet as a third example, among hardware devices suggested by clinical practice, the need to avoid lower limb lesions during rehabilitation prompted the design of DINABANG as a torque and velocity portable measurement instrument of use in the sports field.

On the contrary, alas, naive translation of industrial information systems to widespread clinical use is showing signs of reluctant adoption. Since the 1950s Electronic Clinical Record Systems oblige physicians to gather data as stock clerks would do, far from any clinical reasoning approach, due to lack of interdisciplinary design from the onset. But fortunately, a disruptive innovation was designed to help physicians take notes with no templates but rather automatic reminders of similar cases, reducing time-to-diagnostic and minimizing errors or oversights. This concept is present in PRAXIS, which captures a physician's case mix to assist solve future cases with the help of physician-derived reasoning sequences, hence the name, *praxis*. No templates are included in PRAXIS for which a careful Medicine Based design produced a technological match of medical reasoning.

The chapter is organized in four parts: the first part is a commented review of three BME and MI devices and applications originally designed starting from unsolved clinical problems. The second part shows that when some technology, unrelated to Medicine, has been applied to clinical use with a non-clinical criterion, then not surprisingly poor consequences follow. Such is the case of the initial resistance to the use of Electronic Clinical Record (ECR) systems based on collection of predefined lists of variables, distant from any medical reasoning. The third part argues that in order to be effective, BME and MI must be directly motivated by clinical needs and led by specific interdisciplinary approaches. This part if therefore an invitation, using examples, to work in an interdisciplinary way including clinicians, engineers and other users. The fourth part of the chapter looks into the interdisciplinary cooperation to conclude, with examples, that the distinction between BME and MI has become obsolete. Heirs to the Hardware and Software separate realms in the XX century, BME and MI are presently but one interdisciplinary research area. BME and MI could possibly merge into a single body of knowledge to better follow the demanding clinical challenges of modern Medicine. Eventually adopting the combined name of "Medical Engineering", BME and MI are in a position now to develop sophisticated tools to tackle the most demanding physiological stress situations and to address the quality of life of large cohorts of the aging XXI century populations.

2 Medical Problems Trigger Development of Original Equipment and Software

For every answer given as a result of research in Physiology or Clinical practice, new questions arise and new instruments are imagined to use the knowledge in large cohorts of patients. General use software or specific Apps are conceived secondary to clinical evidence so as to obtain better medical results. This section describes three instances of clinical staff or public health groups defining an instrument to fulfill a need in the direction of a further step towards better medicine. The lack of information to put in place proper pregnancy follow up and to manage (and audit) maternity hospitals led the way to a successful distributed information system called SIP (Simini 1999) following the Spanish acronym for Perinatal Information System. The need to enhance and give continuity to patient physician relationship during a chronic condition led the way to the design of SIMIC, a patent pending technological breakthrough or "prescription App". Finally this section reports on the example consisting of the need to optimize rehabilitation and training of lower limb muscles with specific biomechanics measurements in the sports field or rehab facility, which led to the design of DINABANG.

2.1 Poor Follow Up, Maternal and Perinatal Mortality: SIP and SEPEPE Developed

From around 2500 BC until the XX Century, infant mortality has been estimated at 25% of all births (Our World in Data 2021), probably half of which in the first week of life. In several Countries of the Americas neonatal mortality estimates as high as 10% were still common in the 1980 decade, which led the governments of Latin America and the Caribbean to start urgent action to lower it (Schwarcz 1983), considering appropriate knowledge was available but not put in practice. Worldwide, as recently as the year 2000 one of the eight WHO Millennium Goals was set to halve the unacceptable death rate under 5 years of age, which includes neonatal mortality as a major proportion (WHO 2021).

To lower infant mortality, several health programs were planned around 1980–1990 in all Countries of the Americas but statistics were not available to monitor pregnancy nor neonatal health. There was no reliable, standard instrument to follow up on the results of the actions planned or taken. PAHO/WHO, at its specialized research center CLAP at the Universidad de la República, Uruguay, considered the problem from an interdisciplinary point of view, realizing that Maternities did not keep consistent records of perinatal care. In addition to this absence of records, the diversity of neonatal death record criteria, which differed from Country to Country, made health action planning and monitoring difficult for PAHO/WHO and for every government in Latin America and the Caribbean.

The driving force for a new development was therefore the need for a standard instrument to collect data on perinatal care. The data had to be limited only to essential data so as to be conveniently collected. Instead of financing a large scale data collection system to feed mainframe computers with yearly emission of statistics, which was the usual procedure in Countries with sufficient financing, a new approach was adopted. The Perinatal Information System, known as SIP (Simini 1999), was conceived, designed and implemented starting 1983 to make use of a new technology. With very little funds, the emerging technology of the

Personal Computer (PC) was adopted. SIP was a new concept stemmed from a fresh approach to MI, at a time when only large computer centers were considered professional enough to collect financial or any important data. The expenses of personnel and infrastructure to collect data the way rich Countries did, were far above any reasonable Latin American or Caribbean health budget. The strictly necessary set of variables and the most reliable but small and cheap computers were adopted. A simple document, both a hand written clinical record and the data entry form (Perinatal Clinical Record PCR, or HCP for its Spanish acronym), was defined as SIP input (Simini et al. 1990). A traveling copy of the PCR was handed to the pregnant women as a Perinatal Passport, eventually "a posteriori" nicknamed "Cardboard Internet" because it was the way SIP insured that relevant clinical information traveled back and forth from hospital to clinics, or ultrasound imaging facilities, all in the hands of an empowered patient. As a prominent and innovative characteristic, SIP also had, in addition to PC data entry, an original software to calculate PAHO/WHO health indicators. This on-site processed complex information was easily available for the first time to manage perinatal care both at Maternity level and Country analysis of SIP merged data. SIP versions have been available since the decade of 1990 in Spanish, Portuguese English and French, the four main languages used in the Americas. Millions of pregnancies and babies are annually recorded since, all using SIP, which is the basis for decision making in obstetric and neonatal care, training, supervision and research. The concept of "*local-data-entry and local-analysis-by-health personnel*" of SIP is either applied as the original software or as its local adaptations. The point is that the interdisciplinary concept is made real because public health and clinical personnel need immediate information (i.e. complex perinatal health indicators filtered by some variables) at the bedside, the maternity hospital management or the ministry of health office.

SIP system makes a point to always highlight missing information as a quality measurement and gives maternity hospital staff access to ready-made statistics for health care management and research. The same SIP software has the capacity to analyze merged data of a Country or several Countries, with the same tools as a single maternity hospital is evaluated, a new feature derived from discussions amongst engineers, clinical and public health staff (Fig. 1).

One problem detected by clinical personnel using SIP is that the continuity of antenatal care rests upon the patient, pregnant woman. Due to lack of motivation, logistic difficulties or other reasons, antenatal care does not respect the specified sequence of office visits, lab results and imaging tests. The SIP passport records data and events but it is a passive tool, albeit a very useful one. Trying to overcome the lack of antenatal follow up quality, an interdisciplinary team specified an active personal device as a patient physician interaction element. Differences between patients led to the concept of a "personalized" tool. The importance of the data recorded and the relevance of the reminders led to the concept of a "prescription-like" application. And the technological vehicle—the portable terminal or cell phone—led to think of a mobile App. SEPEPE (Spanish acronym for Personalized Perinatal Follow-Up) therefore widens the SIP perspective, making

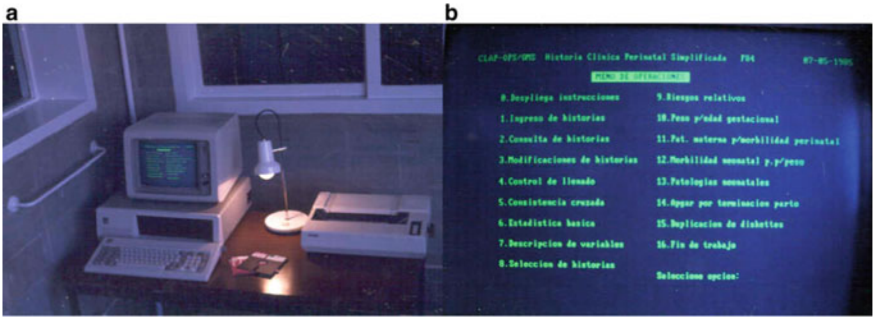

Fig. 1 The perinatal information system (SIP after its Spanish acronym) was a breakthrough in 1985, as a result of interdisciplinary work to solve the problem of lack of health care quality assurance and monitoring. **a** IBM personal computer loaded with SIP in 1985 and **b** close-up view of the SIP "menu" running on DOS operating system

use of the availability of mobile phones among pregnant patients (Rey et al. 2020). Data is collected by the patient at home when prompted by SEPEPE, the patient receives reminders of important facts or behaviours and rare ominous signs can be automatically reported to health care personnel. This may further lower mortality and morbidity, since pregnancy drop-outs to follow up are reduced by timely reminders and messages of concern by the health care team. The quality of perinatal care offered increases as the patient physician relationship is extended during the time between visits. The clinical data entry and analysis of SIP is kept for office and labour room use, but it is now connected to the prescription App SEPEPE. During an enhanced patient physician relationship, the physician prescribes SEPEPE with personalized goals during an informed session. A fresh look at the difficulties of a good perinatal follow up has suggested a remake of SIP, using available technologies at a reasonable cost.

2.2 *Cardiac Failure Patients Lost to Follow Up: SIMIC Developed*

Self-care is of great importance for persons with chronic conditions. Their quality of life, the progression of the disease, and ultimately their survival rate depend upon their lifestyle. Recommendations are part of the patient physician relationship and are periodically adapted, which is the essence of follow-up. Both the patient and the health system are expected to assume responsibility for patient behavioral compliance and medication adherence. The growing number of persons with chronic conditions, as a result of the epidemiological transition, challenges the effectiveness of follow-up practices.

Some systems are available to locate inpatients within a hospital (Decia et al. 2016) and research is active tending towards distance monitoring such as impedance determination of thoracic fluid levels in pacemaker patients (Vollmann et al. 2007). These systems implement one-way communication limited to either to report a patient location or some malfunctioning. What has not been extensively reported is the bidirectional use of information and telecommunication technologies (ICTs) to link patients to the health care institution. Conventional follow-up consists of nurses checking attendance of patients, reminding them of good practices and detecting possible drop-outs before too much time elapses. This follow-up is difficult to put in practice due to the high labour costs.

A new approach was then necessary to avoid losing patients to follow-up and therefore to minimize the consequences of drop-out cases in terms of increased hospitalizations and premature deaths. For cardiac failure (CF) patients, this is specially true, since the reduction of hospitalizations has been associated with low percentages of patient drop-outs (Silvera et al. 2013). In other words, when there is a good follow-up, there are less hospitalizations and the quality of life of patients is better than when drop-outs are frequent. A meaningful and efficient patient physician relationship during follow-up visits depends upon reliable information collected during intervals between visits. Successful treatment for CF patients is linked to the timely adaptation of recommendations along the evolution of the disease. These aspects gave rise to a disruptive concept: ITC is called in to fulfill these "specifications" with a fresh approach, that of developing an App to be prescribed by the physician as an extension of the patient physician relationship. The dynamics of prescription drugs and lifestyle/nutritional recommendations was taken as inspiration for a new Medical Informatics product called SIMIC.

SIMIC (for the Spanish acronym *Sistema Informático de Manejo de la Insuficiencia Cardíaca*) was developed as both an Electronic Clinical Record (ECR) system and an application—to be personalized—installed in the mobile phone of the patient. The personalized follow-up App (Simini et al. 2020) is specified for each CF patient as a set of dialogues, recommended behaviours, data collection and spontaneous note writing from home. During the medical visit, the physician "prescribes" SIMIC, a set of living style recommendations and questions asked periodically. The set of SIMIC automatic messages and data collection is selected from a list of possible "prescriptions" of SIMIC, adapted to the CF stage, just as drug posology is adapted to each patient at every visit. SIMIC is able to detect abnormal behaviors to trigger specific feedback messages to the patient and eventually to alert the healthcare team. Pattern recognition techniques recognize combinations of variables associated to situations to be evaluated seriously (Simini et al. 2020).

In very much the same way as a pharmacy procurement procedure, SIMIC is installed in the mobile phone of the patient at the end of the visit, possibly outside the physician's office. From then on, SIMIC App will be active asking questions and capturing data from the patient, in a respectful way, never becoming intrusive nor insisting unnecessarily. According to the type of follow-up prescribed by the physician, SIMIC will ask questions at random times, on lifestyle, exercise, diet and medication, as well as general mood and family activities. Such prescription is issued only to patients that are able to interact with an App, either alone or with the help of a family member or assistant.

The SIMIC web-based counterpart to the mobile app acts as a backup and clinical record milieu, by which pertinent information—judged as such by the physician at some later personal visit—is recorded in the Electronic Clinical Record (ECR). Just as a wearable device is read in the physician's office after a Holter recording, all information gathered by SIMIC App since the previous visit is available for the physician in subsequent visits. The information recorded by the patient during every day life is displayed and thus contributes to a richly informed conversation, based on recorded facts, body weight variations, exercise and diet data. The physician may decide to include this information, along with his or her notes, in the ECR. The patient physician relationship is thus greatly enhanced by pertinent and timely collected information, which may guide the conversation to efficiently address chronic condition problems.

By ensuring a continuous communication in both directions (patient at home and health personnel) unwanted situations may be detected in time to prevent them from doing irreversible harm. SIMIC may contribute to more efficient public health management and to lower the cost of good quality medicine. Thanks to a new approach, ICTs as used in SIMIC may allow to deliver the same good quality medicine only possible when a dedicated personal physician cares for only one patient, and extend it to large cohorts of patients, thanks to personalized replicas of the App. SIMIC helps to deliver personalized care for large populations, using a combination of ICT and health personnel. Health personnel may then devote their professional time to personal interviews during visits, and not worry about patients follow-up or drop-out, since SIMIC helps by taking care of the reminder routines. By using SIMIC, if patients show good follow-up behavior, visits may be less frequent, an additional contribution to intelligent personal healthcare.

The main goal of communication with the patient (Simini et al. 1990) is to improve the patient's health and self care, and this communication can be improved in terms of the rhythm of interaction with a canned "intelligence" such as SIMIC. Professional and empathetic conversations between physicians and patients lead to diagnosis, initiate therapy and strengthen a caring relationship. The degree to which these activities are successful depends, in large part, on interpersonal skills of the physician (Duffy et al. 2004) but also on reliable information. Before prescribing the device, the physician must evaluate the patient's ability to learn and to perform what SIMIC asks for. Lack of familiarity with electronic devices or rejection by the patient can hinder the decision to prescribe SIMIC, such as for older patients who may decide to resist the use of cell phones, or refuse to handle ICTs. In these cases, SIMIC can be installed in the mobile terminal of a relative or caregiver (Fig. 2).

SIMIC is a second example, after SEPEPE, of a mixture of BME and MI based on a clinical demand to lower hospitalization of CF patients and improve their quality of life: Medicine Based Engineering.

Fig. 2 Prescription app for cardiac failure patients, SIMIC (*Sistema Informático de Manejo de la Insuficiencia Cardíaca*). Personalized reminders, questions and alerts for the patient, canned in an app, in bidirectional communication with the electronic clinical record updated at each visit. Alerts to the health system may limit patient drop outs and thus are a contribution to better health care quality

2.3 Risk of Lower Limb Lesions During Rehabilitation: DINABANG Developed

Hamstring muscle injuries account for one sixth of all sports lesions reported by athletes, with a high proportion (22–34%) of re-injury (Liu et al. 2012). Current hamstring rehabilitation practices include—during the last phases—exercises involving high levels of force and elevated muscular contraction velocity (Opar et al. 2012). These exercises are routinely performed in clinical settings with no objective control of force deployed, and are solely driven by subjective criteria. Force used is only limited by self perception and dosage by the athlete or real time Physiotherapist's oral instructions. This lack of precision derives in either a second lesion—should the force be too intense—or inefficient exercise—should the strength involved be too weak. The unavailability of precise measurements during physical exercises in the sports field or the therapist's lab puts lower limb rehabilitation at risk of either re-injury or inefficient movements.

As an original contribution, a new instrument called DINABANG was developed as a small footprint portable device to quantify force and velocity (Santos et al. 2017). DINABANG is capable of measuring lower limb velocity and force in a simple way in the sports field, which cannot be done with traditional isokinetic equipment found in well equipped sports laboratories. DINABANG includes alerts of excess or lack of force, based on normal values (Santos et al. 2019).

Fig. 3 DINABANG is a portable instrument to measure force and speed (hence power) involved in lower limb rehabilitation or training. Either excess or lack of effort may lead to lesions or ineffective training or rehabilitation. DINABANG fulfills the need to quantify effort during exercise, in the sports field

Two functions have been included in the design of this new instrument: a quantification of the elastic-resistance rubber band stretching force and the real time determination of acceleration of the ankle (Santos et al. forthcoming). Wireless communication and a special software display measurements on the screen of any portable instrument such as a mobile phone, tablet or laptop computer as shown in Fig. 3.

DINABANG is thus a third example of BME and MI based on specific clinical needs.

3 Technology Introduced in Medicine for the Sake of Technology

When technology by itself produces devices or software for medical use with little or no link to a medical problem or point of view, the results are seldom of value to clinical work. The shelves of Engineering Schools are often occupied by prototypes designed supposedly for medical use and yet never even tried nor accepted by physicians. A new technology adopted by the naive criterion of engineers is bound to land an instrument or a data processing routine on a ground of no use. The mere availability of a technology is not enough for it to be used in medicine. The paradigmatic example is the introduction of the first generations of computer systems to capture clinical records, with serious consequences to this day.

3.1 Enter Computer Science

At the origin of medical informatics often authors did not distinguish what was processed (medical information) from the way it was processed (computers). Collen recalls (Collen 1986) that “medical computer science” was an equivalent expression for “medical information science”, as if what was processed, i.e. information, was the same as how it was processed, i.e. by a computer. And since the method to manipulate data was so important, little attention was paid to the mental way information was actually processed from a clinical perspective. Therefore, a straightforward extrapolation was done by “computer” technicians from other fields of “data capture and processing” to Medicine. Medical doctors were instructed to “enter data” in very much the same way an accounting clerk was shown how to “enter data”, the difference being that the former was dealing with a very complex clinical notes-taking procedure heading to a diagnostic and the latter with a list of expenses. This oversimplification did not take into account the elaborate and variable mental task the clinician performs when dealing with a patient. When the physician considers a case, he or she manages information, either asked to the patient or obtained as clinical evidence. Every piece of data and reasoning is treated in a very special way, (Rosenbloom et al. 2011) which was omitted by the first medical data entry systems. Consider that in the first medical entry systems, a simple factual element is recorded in exactly the same way as a probable diagnostic, subject to subsequent differential appraisal or confirmation. Actually, this mismatch persists to this day. In addition, medical information has special characteristics, such as probabilities associated to given variable values. Despite the complexity of medical information, MI still works very much in the same way as any stock application, and constitutes an example of technology imposed by non medical designers onto physician’s notes-taking routine, omitting crucial patient-physician relationship aspects as well as the mental process associated to the millennia old diagnostic reasoning (Díaz-Berenguer 2021).

3.2 Medical Reasoning is Not Stock Management

Taking notes, writing medical records and reaching a diagnostic or a therapeutic decision along with following clinical guidelines are intrinsic parts of Medicine. It is a complex information processing framework, completely entwined with special ways of reasoning and deduction, sometimes partial, sometimes interim until more evidence is available. Informatics has not always been able to adapt to the essence of medical activity (Simini et al. 2020). Transferring data processing concepts from other fields of life such as commerce or industry, informatics has ignored some of the most specific approaches of medical mental tasks. Medical reasoning can be considered as sequences of pattern recognition instances, rejection of hypotheses, confirmation of previously supposed patterns and refinements suggested by memory-stored previous cases.

Informatics has taken onto itself the assistance to the medical profession and to health in general by offering simple pre-designed opportunities to enter data into computers, often distorting the patient-physician relationship (Díaz-Berenguer 2021). No medical reasoning, no incipient pattern recognition and little variations of data sequence are included in the design of most electronic medical record (EMR) systems, to this day.

Current medical record products are based upon a template of variables established by the MI designer during interviews with a medical specialist, oftentimes named "the client" excluding him or her from the more suitable position of "co-author". The meaningful variables are usually defined with maximum and minimum values, units and labels. Data collection is then specified in an orderly fashion, item by item, in the order the specialist or a textbook suggests. Data is then processed as a multivariate data collection, according to a more or less complex Entity Relation Model (ERM) describing visits, patients, physicians, prescriptions, procedures and all related variables. Normalized nomenclatures, thesaurus and lexicon allow to code data in a way other systems can interpret them, tending towards interoperability (Lee et al. 2021). And yet, the complex task of establishing a medical record in a patient physician relationship has been reduced to an "a priori" list of variables. This list of variables to be filled in, is far from the mental dynamics of a physicians taking notes, which follows one of several lines of thought according to his or her medical schooling, the way the patient refers to a complaint—either singular or multiple—and several other circumstances. Moreover, by unifying data capture, MI ignores the reality that no two physicians practice medicine in the same way. Each physician has an individualized way of reaching a diagnostic and of treating patients, in addition to the fact that the cases seen follow some prevalence mix, very much associated with the particular office or health care center and the personality or the specialization of the physician. MI has nevertheless the potential and capacity to overcome this "template" limitation as will be described in Sect. 4.2.

4 Technology Used from a Medical Perspective

The following are three stories of the development of new BME devices or informatics tools to fulfill specific medical problems. These designs could not have been addressed outside an interdisciplinary team. The projects include clinical as well as engineering staff, sharing responsibilities and tasks, according to personal experience.

4.1 Intra-Abdominal Hypertension Reduction Device ABDOPRE

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are frequently diagnosed in intensive care patients (Pracca et al. 2011). Clinicians need to monitor and control these conditions as both (IAH and ASC) have severe pathophysiological implications. IAH is defined as a sustained increase in intra-abdominal pressure (IAP) above 12 mmHg while ACS is the same sustained increase in IAP above 20 mmHg with associated organ dysfunction. Both IAH and ASC may cause a multi-organ failure and therefore increase the patient's mortality. The usual practice for reducing IAP, when other non-surgical methods fail, is decompression laparotomy (Kirkpatrick et al. 2013). But this is an invasive procedure and therefore the clinicians looked at BME for less traumatic methods to reduce IAP that would avert any potential surgical complications.

An interdisciplinary team was set up to suggest solutions of the minimally invasive type or even non invasive if it were possible. ABDOPRE was eventually developed in response to this need (Schandy et al. 2020): the application of a negative external pressure above the patient's abdomen reduces IAP in a controlled and non-invasive way (Fig. 4).

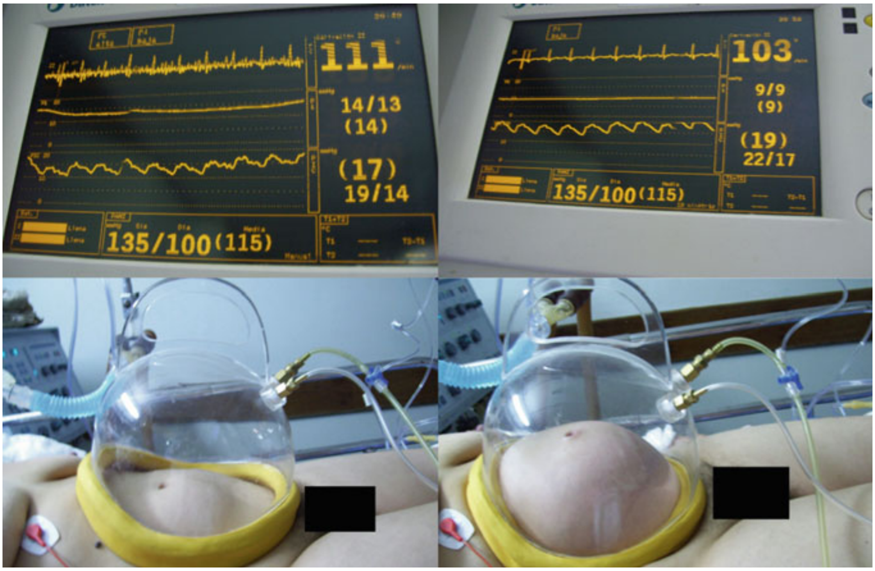

Fig. 4 Non invasive abdominal de-compression using ABDOPRE applied to an intensive care patient. The patient's abdomen distends when an external negative pressure is applied. In the picture on the left the patient has an IAP of 14 mmHg while in the picture on the right ABDOPRE has lowered IAP to 9 mmHg. After Schandy et al. (2020)

4.2 *Medical Informatics to Follow Medical Reasoning: PRAXIS*

To start a visit, the physician usually relies upon the memory of a previous case. Doctors look for matches of fragmented (and sometimes hidden) information. As the consultation progresses, the physician modifies in his or her mind the whole set of values initially obtained or processed, and by doing so records information about the new case. This procedure is not possible with present day MI because the software requires the physician to enter the same information for all patients, in the same order, until bifurcations occur and the tree of possibilities eventually grows. The data structure belongs to the computer designer, and does not mimic nor increase the physician's reasoning capacity. Actually, present day MI applications to record ECR are an obstacle for the physician because the mental process that follows the patient consultation may be completely different from the "a priori" rigid list of variables included in the template, however diversified it may be. Current MI systems do not allow to start—just as the physician usually does—with a supposed type of patient in mind and to refine the questioning and lab results according to intermediate questions until a decision is made. This supposed case type is oftentimes a provisional decision until new evidence is available. Mental pathways during consultation consist in modifying a similar case, even jumping from a possible type of patient to another, until the physician eventually creates a new case, sufficiently confirmed to set the basis for counseling, prescription or treatment. Incidentally this new case will be one of the possible types which may be used for other future consultations. A software product that would mimic the mental process of the physician, with no prior "list of variables" to fill in, would be a rare exception (Low 2015), because current ECR systems follow pre-defined templates.

Informatics can help medicine by strengthening clinical reasoning and decision making. But to accomplish this, the medical software design must start from Medicine and not perform a translation of "data entry/data processing" originally successful in other areas of human activity (Fig. 5).

PRAXIS is a clinical notes-taking software with capability to remember past cases and suggest them to the physician, in a free text context, close to the mental path typical of the medical profession. No lists of variables are to be filled in, and after a first "case type" choice which comes with several "conceptual elements" (Galnares et al. 2021), the physician either dismisses or accepts them. By doing so,


<<Patient.FirstName>> presents with a [significant|moderate|severe] sore throat for [3 days] duration, [significant|moderate|severe] dysphagia and general malaise ~~<<C.CC.Reason.B>> <<C.HPI.Location.B>> <<C.HPI.Quality.B>> <<C.HPI.Duration.B>>. Headache, denies fever or chills. Denies odynophagia.~~

Fig. 5 Notes suggestions offered to PRAXIS user based on a "case type". The physician accepts or dismisses possible findings by clicking on "conceptual elements". PRAXIS is a trademark of InforMed Inc. (2015)

PRAXIS, guides the sequence of thought respecting the sequence followed by the specific physician on a similar patient, applied provisionally to the present patient being considered. At the same time PRAXIS uses the case to build up consolidated evidence of existing or new "case types". This line of research is very promising as it would represent a change of paradigm in computer based notes-taking for physicians, returning to their free reasoning sequences, but with a strong "reminder help" tailored to Medical thought (Simini et al. 2020).

4.3 Polycystic Kidney Volume Measurement: NEFROVOL

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a life threatening disorder characterized by cyst formation and kidney enlargement occurring in one out of 500–1000 births (Pei and Watnick 2010; Alves et al. 2015; Tobal and Noboa 2014). It is caused by mutations which produce renal function decline following its enlargement, making kidney and cyst volume a strong predictor of disease evolution. A study involving 57 adult patients followed up by annual renal ultrasound for a mean duration of 9.9 years detected an average annual increase in cyst diameter of 1.4 mm, an annual growth rate of 3.2% (Terada et al. 2008). Higher rates of kidney enlargement lead to a more rapid decline in renal function (Tobal and Noboa 2014). Only imaging evidence is available to assess the progression of disease for decision making, but neither conventional Ultrasound (US) measurements (ellipsoid volume formula not applicable due to the irregular ADPKD renal shape). Neither gadolinium-based contrast agent MRI and even less, any CT scan contrast agent, which delivers ionizing radiation and is toxic to the kidneys, can routinely be used. This was the original motivation to address the clinical problem of non invasive polycystic kidney volume measurement (Chagot et al. 2018; Simini et al. 2015, 2018), which we called NEFROVOL.

NEFROVOL includes a skin guide for the US transducer and a software to record transverse kidney sections (Fig. 6) and later combines them into an estimated volumetric representation. This 3D reconstructed object represents the kidney volume. All US equipment that can produce a series of DICOM images of kidney sections can feed NEFROVOL, a medical equipment which describes the volume change as a time graph for each kidney (Arrua et al. 2014), in the patient's ECR in Clinical Document Architecture (CDA) format (Simini et al. 2017).

In this section we have shown three examples of diverse BME and MI achievements stemmed from genuine interdisciplinary research, all involving engineering and medicine from the start. The trend of the share of BME and MI will be visited in the next section.

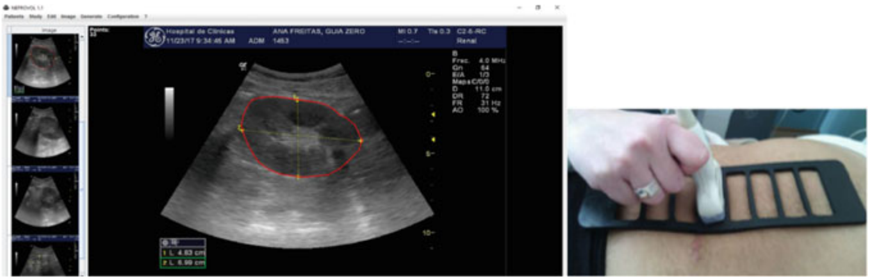

Fig. 6 NEFROVOL software screen. Note the contour drawn by the user on the image being processed and the series of US kidney sections on the left. A mostly regular in shape phantom is shown here. Transducer template on the right. From Chagot et al. (2018)

5 Biomedical Engineering and Medical Informatics

Fulfilling clinicians' suggestions and requests, seventy projects were performed by staff and students at the Núcleo de Ingeniería Biomédica (NIB), all with a prototype or a software product available for clinical appraisal. The projects are the result of theses developed towards an Engineering advanced degree or a Master's thesis, very few as a PhD thesis (NIB 2021). All projects were specified, authored and tested by an interdisciplinary team including both clinical and engineering background staff. On the engineering side, the main discipline was (i) software engineering or (ii) either electrical engineering or in a few occasions mechanical engineering. In a number of cases the projects included both BME (i.e. a hardware prototype) and MI (i.e. software product). An analysis of the mix of expertise developed in the projects follows.

The 70 projects were divided in five years periods of time from 1988 to 2022, considering the ending year of the project. In each period an average of nine projects were finished, belonging to three categories: BME, MI and mixed BME/MI. The share of mixed BME/MI projects over the total number of projects of each quinquennial is shown in Fig. 7. Since the estimation of mixed BME/MI projects every five years is based on an average of about nine projects, a technological tendency can be estimated based on a reasonable number of different kinds of clinical concerns from the same clinical setting, the University hospital. Under the assumption that groups of nine projects can absorb exceptions, the figure shows an increase of the mixed projects from roughly one third to almost one half. This numeric evidence suggests that BME projects increasingly include complex MI aspects and therefore are mixed BME/MI in nature. The informatics is either Artificial Intelligence, Electronic Clinical Record, DICOM image processing or other technologies traditionally excluded from core hardware BME approaches.

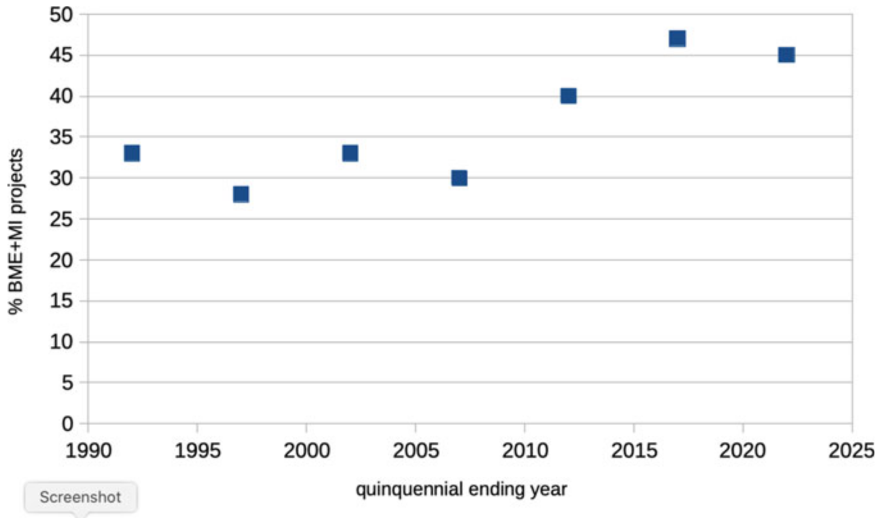

Fig. 7 Evolution of 70 NIB projects developed in five years intervals (mean 8.8 projects every 5 years): share of mixed "Biomedical Engineering and Medical Informatics" projects out of the total number of projects in the same period. Remaining projects are either all software (Medical Informatics) or all hardware (Biomedical Engineering)

6 Technology Transfer

Technology Transfer (TT) or commercialization can be considered the successful "epilogue" of research. It may be seen as a check for appropriate research since an effort is made to enlarge the scope of use of the newly developed instrument or software product beyond the original interdisciplinary group. The following is a brief description of selected events along the path towards TT of BME and MI products. The description of three typical sets of circumstances may help establish a set of lessons learned in the struggle to address TT for the benefit of Society, Medicine, staff and students involved.

MECVENT was developed as a D.O.S. based neonatal ventilatory mechanics instrument to measure airway resistance and pulmonary compliance using a pneumotachographic method (NIB 2021). From 1988 to 1993 five units were build on an individual basis by the original developers and former students. No support from State agencies was available, no investment made and little timetable commitment of former students involved brought as a consequence that no TT was verified beyond the five units sold and used clinically at the University Hospital and private medical offices in Montevideo. This case and others (VARFRE, PESOPAC among others) suggest, as a lesson learned, that personal commitment and State support are necessary for any TT attempt to stand a chance of TT success (Simini 2013, 2015).

BiliLED was designed to solve the problem of costly, high heat lamps to favor bilirubin reduction in new-born babies. It was designed using a novel and spatially uniform optic distribution system of 470 nm wavelength LEDs (bandwidth 35 nm) blue light. A mature product was reached after four successive prototypes were developed and tried over a period of 18 months (2004–2006). A specific grant was then obtained for TT. A licensing agreement was reached with a firm with no biomedical experience, but a solid engineering reputation in elevator control circuits, by which a NIB member of staff worked in the firm to help adopt the prototype and start production in 2007. The grant allowed NIB to buy the first four production BiliLED units to donate to Hospitals. The agreement established that if yearly sales were above 25, 7% royalties on sales was to be paid to the University: the company declared having sold in Uruguay 23 units (proportionally equivalent to about 2500 yearly units in markets such as USA or EU) sold in 2009 until all neonatal units in the Country had purchased one. The global market was ready to buy BiliLED provided an international certification such as CE was secured. Nevertheless, the decision of the licensed firm not to seek further certification had as a consequence that BiliLED was soon discontinued and later the blue LED technology was adopted by most incubator manufacturers. The second lesson learned is that TT is limited to domestic scope unless certification is promptly secured.

DINABANG was initially developed in 2017 as a lower limb portable torque and angular velocity measurement instrument conceived by physiotherapists to avoid strains or inefficient muscle force training. The idea had no competition worldwide since similar results could only be obtained using expensive isokinetic equipment weighting hundreds of kilograms. After local and global patents were filed, a licensing agreement was signed by the University and an academically sponsored spin-off company (MOVI Technology for Life 2021) was incubated in a State incubator. Support was available in different fields such as marketing, public relations and accounting. Within a year of the formal agreement, MOVI ltd had shipped a dozen DINABANG units and several distributors are being contacted in Latin America, all happy with the certification markings underway. The lesson learned is that all aspects are essential and none can be left unattended, from (i) the principals' full time jobs, (ii) a solid State plus (iii) University support and (iv) an original research products matching real clinical needs.

TT efforts are essential in a BME and MI research group, because they confirm the pertinence of developments and keep the "clutch" (Video 2021) in a transmission between the research "engine" and the "wheels of the economy", for the benefit of the Country, the research group and ultimately the patient-physician relationship. Other projects are on their way towards TT such as PARKIBIP (Pasker et al. 2021) to help extend the rehabilitation time and efficiency of persons with Parkinson, IMPETOM (Santos and Simini 2012) to detect fluid occupation of the lungs by bioimpedance or the other products described in this chapter: ABDOPRE, SIMIC/SEPEPE or NEFROVOL.

7 Conclusion

We have presented a selection of BME and MI projects developed by interdisciplinary teams at our Núcleo de Ingeniería Biomédica to extract useful insight for future definitions and strategies. We have mentioned the historical physician's reluctance to use MI applications—such as clinical data entry—to suggest that specifications of new technological projects must start from a medical point of view and not merely translating paper methods to computer monitors. The growing share of MI within BME projects and the increasing coexistence of MI and BME approaches suggest that the distinction between them may soon disappear and a new name may be adopted, such as Medical Engineering. The scope of such a wide term is large and includes areas of research as diverse as tissue engineering, logical diagnostic help, life support equipment, measurement instrumentation, interactive follow up and clinical records. New tools or enhancements of medical functions, such as our latest contribution, the patent pending "prescription App" will also be part of the scope of Medical Engineering. Only implemented so far as SIMIC for cardiac failure and SEPEPE for pregnancy follow up, innovative Apps used as extensions of patient physician relationship will become usual in medical care.

Provided projects stem from a genuine clinical problem, they will include all necessary interdisciplinary contributions to fulfill the goal of BME and MI, or Medical Engineering, which is to create adapted technological solutions to foster patient physician relationship allowing high quality Medicine to be available for all.

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Statistical Gait Analysis Based on Surface Electromyography

Valentina Agostini, Marco Ghislieri, Samanta Rosati, Gabriella Balestra, Gregorio Dotti, and Marco Knaflitz

Abstract To help neurologists, physicians, and physical therapists in the management of patients with altered locomotion patterns, it is of the uttermost importance relying on accurate measurements of gait. Gait analysis becomes even more informative if the electrical activity of muscles is recorded, non-invasively, during the dynamic task of walking, through surface electromyography (sEMG) probes. However, sEMG signals must be processed through advanced techniques to obtain reliable results, easily interpretable by healthcare practitioners. Indeed, the study of how muscles are activated during natural walking (in unconstrained environments) is complex for several reasons, including a high stride-to-stride variability, even more pronounced in pathological subjects. On the other hand, it is crucial to provide clinicians with aggregated information relying on validated parameters and easily usable representations that can be effectively included in clinical reports. This chapter is aimed at introducing: (1) Statistical Gait Analysis (SGA) to automatically analyze hundreds of gait cycles collected during a physiological or pathological walk lasting several minutes, (2) the extraction of principal and secondary muscle activations to obtain consistent clinical indexes, (3) the extraction of "muscle

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synergies" to quantitatively study motor control strategies. Each of these techniques are based on state-of-the-art processing algorithms of the sEMG signal. A brief review of the recent literature published in this field will be presented and discussed.

Keywords EMG · Gait analysis · Locomotion · Muscle activation patterns · Muscle synergies

1 Introduction

The objective and quantitative study of human movement can be fundamental to support clinicians in the diagnosis and evaluation of rehabilitation outcomes of neurologic and orthopedic patients showing altered gait motor patterns and postural balance instabilities. Instrumented gait analysis provides comprehensive data on normal and pathological gait, producing information about spatio-temporal parameters (cadence, step length and duration, percentage of single- and double-support), and joint kinematics (angle of flexion–extension of ankle, knee, and hip) (Perry 1992). In addition, dynamic electromyography (EMG) allows for obtaining the action of muscles and their timing, contributing to outline the patient's walking pattern and an empirical basis for identifying the functional cause of a gait abnormality (Frigo and Crenna 2009; Cimolin and Galli 2014). Similarly, instrumented posturographic analysis provides objective data on the postural sway in upright stance, through the study of the Center-Of-Pressure (COP) signal (Agostini et al. 2011, 2013, 2016; Sbrollini et al. 2020).

In the past, the gold standard to perform gait analysis were stereophotogrammetric systems, i.e., 3D optical motion-capture systems. However, these systems are expensive, require a dedicated gait analysis laboratory and technical personnel, their sample volume is intrinsically limited to a few cube-meters, and they are complex to use, necessitating highly trained experts (typically biomedical engineers) to manage the system calibration and acquisition procedures. Hence, they proved to be unsuitable for clinical gait analysis. Force platforms were frequently used in conjunction to stereophotogrammetric systems to detect gait events, or as a standalone device to carry out posturographic analysis.

Systems based on Inertial Measurement Units (IMUs), integrating accelerometers, gyroscopes, and magnetometers into wearable sensors, are de facto completely replacing stereophotogrammetric systems and force platforms, offering valid low-cost alternatives to perform motion capture (MOCAP) (Agostini et al. 2015a; De Leonardis et al. 2018; Panero et al. 2018). Recently, this has caused considerable interest within the scientific community in the attempt to validate wearable systems in the clinical analysis of gait (Tao et al. 2012; Agostini et al. 2017) and posture (Ghislieri et al. 2019b; Agostini et al. 2019).

On the other hand, multichannel systems already proved their usability, accuracy and reliability in clinics (Agostini et al. 2014b, 2015b, d, 2018; Carlone et al. 2016).

These systems are based on fully integrated solutions that include foot-switches (to directly detect gait events), electro-goniometers (to directly record joint kinematics), and surface EMG probes (to identify, non-invasively, muscle activity), all synchronized with a video recording. The multichannel STEP32 system (Medical Technology, Italy), developed at BIOLAB of Politecnico di Torino, was specifically designed for clinical gait analysis to obtain a portable solution, usable out-of-lab, at a reasonable cost (Agostini et al. 2010, 2015a, c; Gastaldi et al. 2016; Panero et al. 2018). Medical personnel can directly handle the system, without the need for demanding training or specific technical skills. However, the most important characteristic of the system are the implementation of the algorithms for Statistical Gait Analysis (Agostini et al. 2010; Agostini and Knaflitz 2011, 2012; Agostini et al. 2014a, 2020). These algorithms allow for the automatic segmentation and classification of hundreds of gait cycles collected during several minutes of overground walking, and for the user-independent processing of the muscle activation intervals, with the extraction of the most frequent muscle activation modalities. This helps a correct handling of the high intra-subject variability characterizing EMG patterns during a "natural" walking task, i.e., overground. Notice that constraining the subject to walk on a treadmill is a technical stratagem frequently used to bypass the stride-to-stride variability characterizing natural gait. The STEP32 system avoids the necessity to constrain the subject to treadmill walking (the use of which is not always advisable in clinics). The system also avoids the necessity of any manual selection of a few representative gait cycles from an overground walk, subjectively chosen by an expert.

New advances in the processing of EMG signals in pseudo-periodic human movements (e.g., walking, cycling, running, and swimming) showed that it might be important to distinguish between principal and secondary muscle activations (Rimini et al. 2017b; Ghislieri et al. 2020a). Principal activations are those muscle activations strictly necessary to perform the motor task under study, i.e., indispensable to obtain the various phases of each cyclic biomechanical output. Secondary activations are auxiliary activations that may be present in some of the movement cycles (and absent in the rest of the cycles): these extemporary actuations of the muscles have the role to adjust motor outputs in presence of internal or external disturbances or increased stabilization needs. Recently, the BIOLAB team developed the CIMAP algorithm (Clustering for Identification of Muscle Activation Patterns) to group the movement cycles sharing similar timing patterns (Rosati et al. 2017a), providing a technical base to extract principal and secondary activations during locomotion. This methodological procedure allows for obtaining robust indexes helpful in clinics, such as the EMG asymmetry index (Castagneri et al. 2018, 2019).

Current trends in literature hypothesize that the Central Nervous System (CNS) controls the muscle-skeletal system through muscle synergies (Tresch et al. 2006; Torres-Oviedo and Ting 2010; Taborri et al. 2018; Ghislieri et al. 2020b, c), sequentially co-activating group of muscles, triggered by neural commands bursting at specific timings of the movement cycle. This is a promising way to study motor control in a quantitative, non-invasive manner. In particular, studying muscle synergies allows obtaining a deeper understanding about the "programme" through which the CNS guides the moving body. Again, this might have important applications in the management of patients affected by neurological disorders altering motor patterns. Furthermore, neurofeedback, neurorehabilitation through human–robot interfaces, and myoelectric control of robotic exoskeletons are among the most important research frontiers that are quickly developing in this field.

This contribution aims to review the main methodologies developed during the last decade, in the field of "Statistical Gait Analysis" and its clinical applications to the management of patients affected by pathologies altering locomotion patterns. It also provides an outline of the body of knowledge developed in the advanced processing of surface EMG signal collected during gait, to help the clinical interpretation of abnormal motor patterns, and the extraction of principal and secondary activations. Furthermore, this chapter introduces how an in-depth study of muscle synergies might provide new insights into the understanding of patients' motor-control strategies.

2 Statistical Gait Analysis

Traditional gait analysis most frequently analyzes only a few gait cycles of a subject's walk. The tested subjects are typically required to hit two force platforms placed at a short distance, one for each foot (the entire sole of the subject's foot must be placed on each platform), while their motion is recorded by a set of stereophotogrammetric video-cameras. However, this procedure frequently does not allow for capturing the natural walk of the subject and its cycle-to-cycle variability, featuring human locomotion.

New trends in gait analysis prescribes to take into account several hundreds of consecutive steps: this allows describing gait from a statistical point of view. In this case, results are highly repeatable and user-independent. This procedure is known as "Statistical Gait Analysis" (SGA) (Agostini et al. 2010) and requires the automatic analysis of gait signals continuously recorded for 3–5 min. This procedure provides accurate measures of time-distance parameters, joint kinematics, and muscle activation patterns. The multichannel system STEP32 was designed to perform SGA in the clinical setting and includes (Fig. 1):

- Foot-switches to measure the foot-floor contact and detect gait phases;
- Electro-goniometers to measure the kinematic angles of the joints (ankle, knee, and hip), during gait;
- Surface EMG probes to acquire the electrical signals from the muscles in a non-invasive manner, during gait.

An example of the signals acquired during a walk is provided on the right panel of Fig. 1.

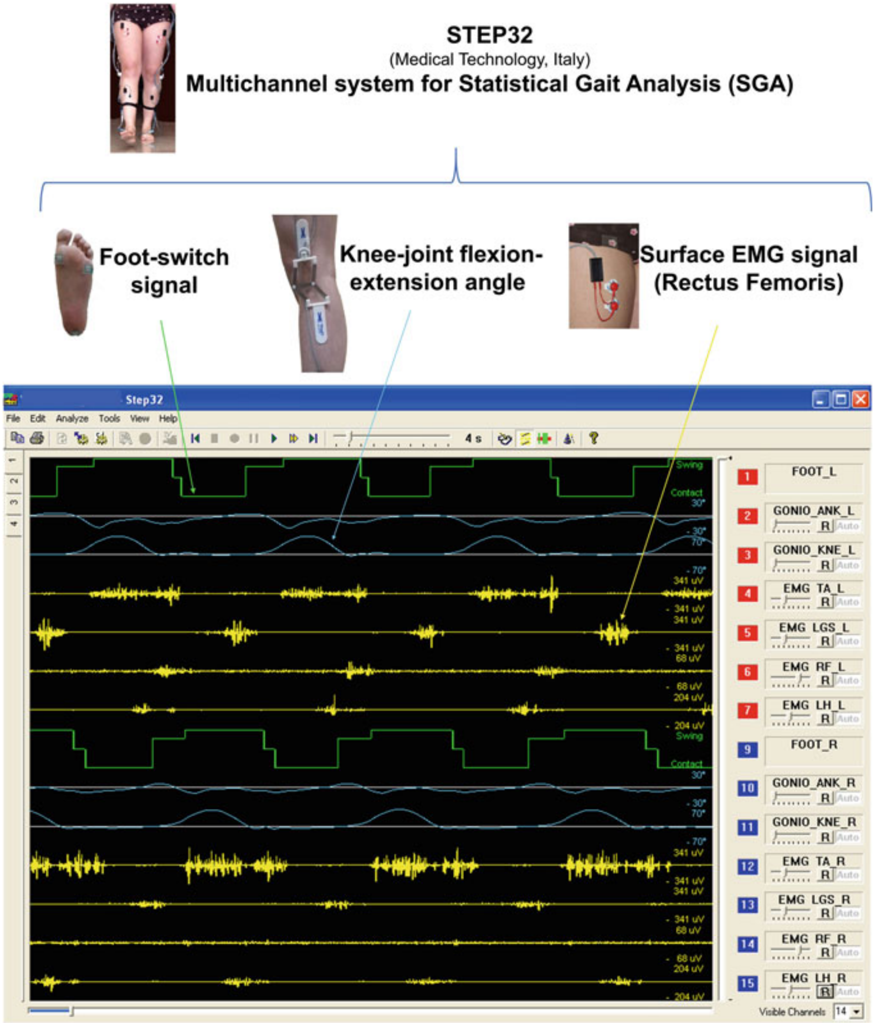

Fig. 1 The multichannel system STEP32 (Medical Technology, Italy) includes foot-switches, electrogoniometers and surface EMG probes to acquire gait signals. In this example, 14 channels are used, 7 for each lower limb: they are highlighted by a red square for the left side, and by a blue square for the right side. For each side, the system has recorded 1 foot-switch or "basographic" signal (displayed in green), 2 joint kinematic signals of the ankle and knee joints in the sagittal plane (displayed in cyan), and 4 surface EMG signals from the main lower-limb muscles, i.e. Tibialis Anterior (TA), Gastrocnemius Lateralis (LGS), Rectus Femoris (RF) and Lateral Hamstrings (LH) (displayed in yellow)

Usually, 3 foot-switches are attached to the sole (beneath the heel, 1st, and 5th metatarsal heads). Since each foot-switch has 2 possible states (open/close), they overall provide $2^3 = 8$ combinations of possible voltage levels (8-level basography). However, it is generally preferred a simplified version in which only 4 levels are considered (4-level basography). These 4 levels correspond to the following gait phases (Fig. 2):

- Heel contact (H) → only the switch under the heel is closed;
- Flat-foot contact (F) → the heel-switch is closed, and at least one of the metatarsal-head switches are also closed;
- Heel-off or Push-off (P) → at least one of the metatarsal-head switches are closed;
- Swing (S) → all foot-switches are open (the foot is raised from floor).

Identifying these 4 levels during locomotion allows for detecting the sequence of foot-floor contact phases and their duration. Furthermore, the 4-level basography provides the base for the automatic segmentation of gait signals into separate gait cycles.

The gait cycle is the sequence of biomechanical events between two consecutive initial supports (or "strikes") of the foot from the same lower limb. The sequence HFPS is the most common gait cycle observed in healthy subjects, and can be considered the "normal" or "typical" gait cycle. However, gait cycles can be composed of other sequences of gait phases, different from the normal one, called "atypical" cycles, which can be prevalent in the pathological gait (Fig. 3). For example, in subjects with equine foot, the cycle usually begins with a forefoot

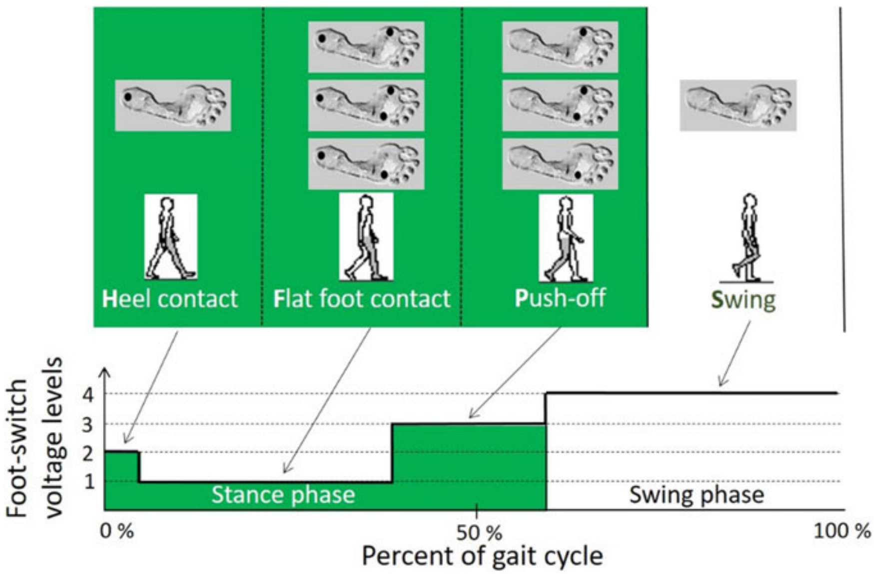

Fig. 2 HFPS is the most common gait cycle observed in healthy subjects. It consists of the following sequence of foot-floor contact sub-phases of stance: heel contact–flat foot contact–push-off (H-F-P), followed by swing (S)

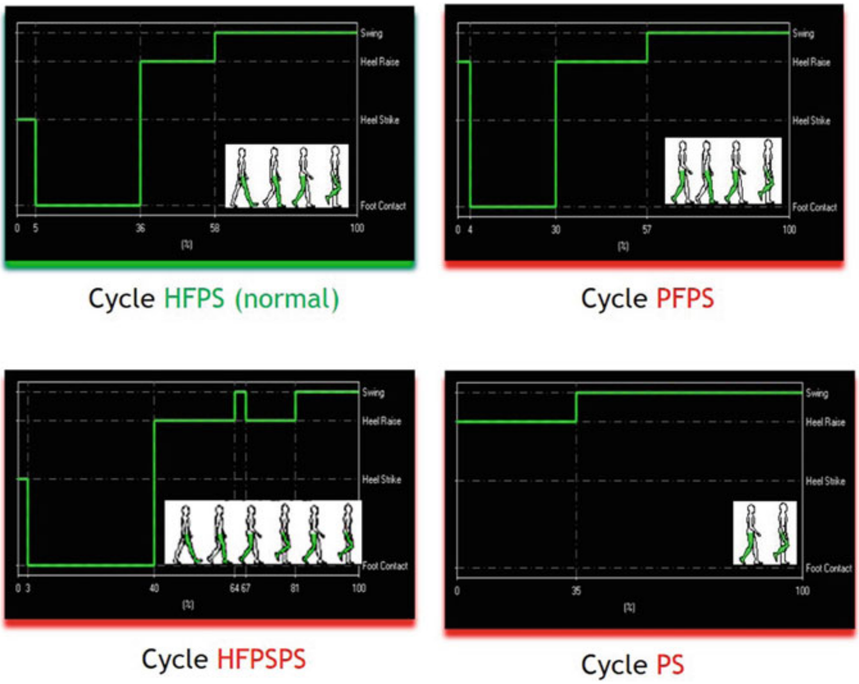

Fig. 3 Different kinds of gait cycles are displayed: the normal gait cycle (HFPS), and some examples of atypical gait cycles (PFPS, PS, HFPSPS). In particular, both PSPS and PS cycles are characterized by a forefoot strike, typical of hemiplegic gait. In HFPSPS cycles, the forefoot drops during the swing phase (indicating insufficient foot clearance)

strike, instead of a heel strike. In many neuro-degenerative diseases (such as cerebral stroke, Parkinson's disease, multiple sclerosis, and muscular dystrophy) patients can display foot-drop during the swing phase. The analysis of "long" walks of at least 100–250 consecutive gait cycles shows that both typical and atypical cycles may be present, both in pathological and healthy subjects. In healthy subjects, it is usual to observe up to 5–10% atypical cycles, especially if direction changes are part of the acquisition. In pathological subjects, depending on the pathology, the occurrence percentage of atypical cycles can significantly increase, up to 100%, in severely compromised subjects. Hence, it is important to segment and classify all the different types of gait cycles, as well as their frequency of occurrence. Indeed, different gait cycles involve different patterns of muscle activation. Therefore, muscle activation patterns must be studied separately for each gait-cycle type. Moreover, in pathological subjects, even in presence of normal cycles, the phases H, F, P, and S, may have altered duration (augmented or shortened) with respect to the corresponding phases of healthy subjects. The precise knowledge of the duration of the sub-phases of stance (H, F, and P) provide additional spatio-temporal parameters, with respect to those usually found in the literature, which can be useful in clinics.

Therefore, the first step towards the statistical analysis of gait is the identification of all the different cycles of a walk. This task can be performed automatically, without user-interaction (Fig. 4). Then, the average joint kinematics and muscle activation patterns are obtained, separately for each specific gait cycle typology.

3 Principal and Secondary Activations

In spite of the above-described efforts to manage EMG variability, this latest remains very high, even when analyzing normal locomotion. For a specific subject's muscle, different activation patterns are usually present during gait, each characterized by a specific frequency of occurrence (Di Nardo et al. 2017). This makes it difficult the interpretation of clinical results. Indeed, the high stride-to-stride variability is one of the key factors that limited the widespread use of EMG in clinical gait analysis (Agostini et al. 2020). To overcome this limitation, the CIMAP algorithm was designed to cluster similar EMG cyclic patterns (Rosati et al. 2017a, b). Afterwards, in post-processing, it is possible to separate principal from secondary activations, i.e., distinguish the essential muscle activations required to perform the motor task from the aleatory adjustments also recorded in the EMG signals. In Fig. 5 it is displayed an example of principal and secondary activations extracted from a series of gait cycles collected during a subject's walk. Extracting principal activations allows for obtaining accurate and repeatable features from EMG gait patterns, both in healthy and pathological subjects. These features are useful to build robust and reliable indexes helping the clinical interpretation of gait data. As an example, this

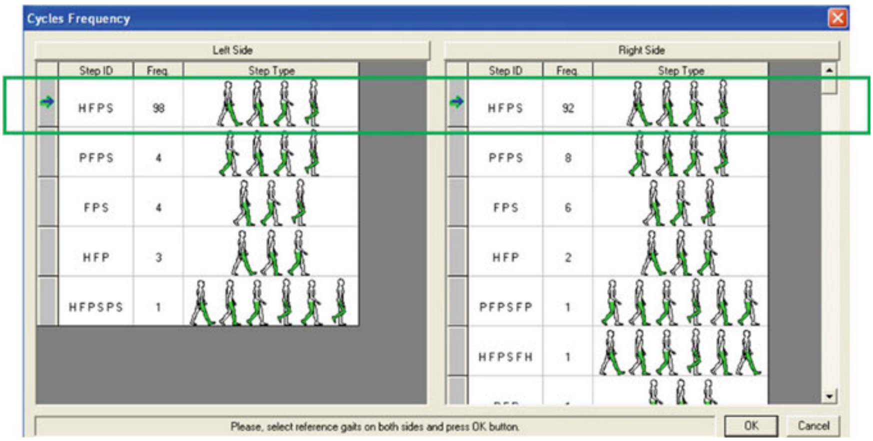

Fig. 4 Example of selection of gait cycles in a healthy subject. An arrow indicates the typical gait cycles observed on the left and on the right side (the most frequent cycles)

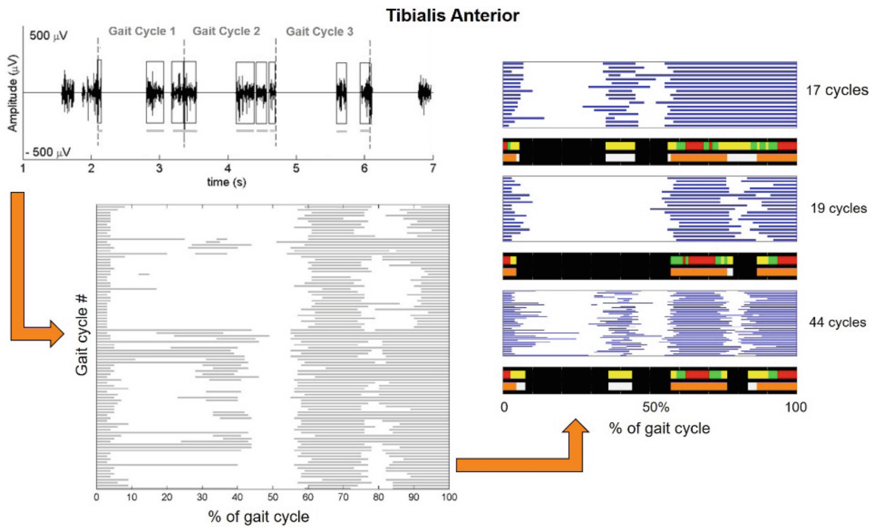

Fig. 5 Example of extraction of principal activations from the EMG signal of a Tibialis Anterior muscle (collected during a walk of a healthy subject). First, the muscle activations are detected for each gait cycle. Second, the activation-interval dataset is prepared, time-normalizing each gait cycle. Third, gait cycles are grouped into clusters sharing similar timing patterns, and the prototype of each cluster is calculated. Then, the principal activations are obtained as the intersection of the clusters' prototypes. Hence, principal activations are the "common intervals" of the prototypes, displayed as orange bars (secondary activations are displayed as white bars)

methodology was used to define an EMG asymmetry index characterizing gait, that was then validated on different cohorts of orthopedic patients (implanted with knee megaprosthesis after bone tumor resection, or implanted with hip or knee prostheses for osteoarthritis treatment), neurological patients (elderly subjects affected by idiopathic normal pressure hydrocephalus and hemiplegic children after cerebral palsy), as well as healthy subjects of different ages (elderly, adults, and children) (Castagneri et al. 2019).

4 Muscle Synergies

Recording EMG signals from a set of 12 muscles of the lower limb and the trunk, and applying a reduction algorithm, typically the Non-Negative Matrix Factorization (NNMF) algorithm (Tresch et al. 2006), locomotion can be described by 5 muscle synergies, each corresponding to a specific and clearly recognizable biomechanical function (Rimini et al. 2017a). In other words, the matrix of EMG signals collected, non-invasively, during gait can be "reverse engineered" to unravel the neural commands issued by the CNS to specific group of muscles, properly weighted (see Fig. 6). Each muscle synergy (or "motor module") comprises:

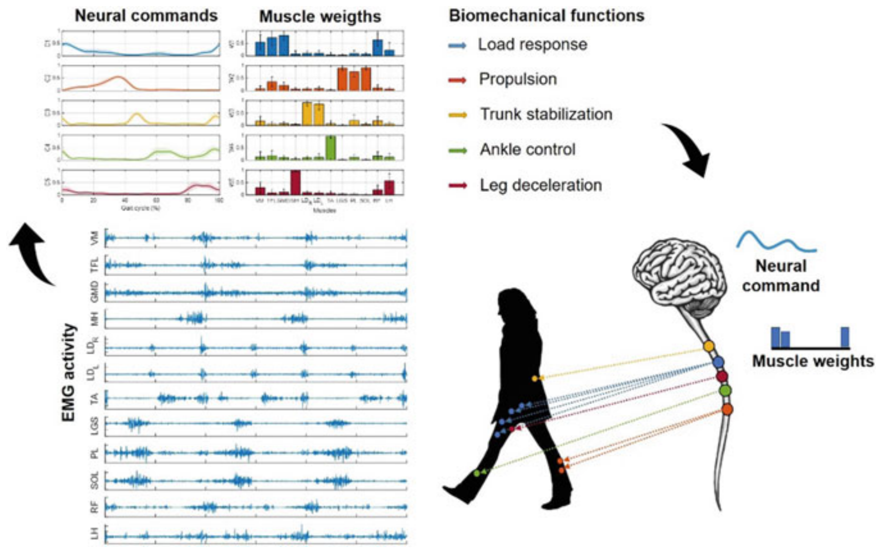

Fig. 6 Reverse engineering of neural commands. From EMG signals recorded during gait, it is possible to extract muscle synergies (neural commands and muscle weights of each motor module)

- Time-dependent activation coefficients ("neural commands"), expressed as a percentage of the gait cycle;
- Time-independent weights (defining which muscles are active in the synergy and quantifying their amount of contribution to the synergy).

Muscle synergies are consistent both within and between subjects, and they are hypothesized to be the building blocks used by the CNS to produce movement.

Also in this framework, the importance of robust EMG pre-processing is essential to obtain reliable results (Ghislieri et al. 2019a), and the splitting of principal and secondary EMG activations before the extraction of muscle synergy can help the interpretation of results (Ghislieri et al. 2020a).

As a final remark on muscle synergies, it should be mentioned that they are revolutionizing not only the neurological assessment in clinics (e.g. in post-stroke subjects), but are becoming a milestone also in robotics (in robot-control design), and in sport science (in the evaluation of athletes' performance and definition of training guidelines) (Taborri et al. 2018).

5 Conclusion

This chapter is a very dense summary of the research activities that was carried out in the last decade in the advanced processing of EMG signals. It can be intended as a basic introduction to Statistical Gait Analysis, to the extraction of principal and secondary muscle activations, and to the quantitative study of motor control strategies through the extraction of muscle synergies. All the techniques and algorithms mentioned herein were published in the reported literature, where the interested reader can found the implementation details.

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Brain-Computer Interfaces with Functional Electrical Stimulation for Motor Neurorehabilitation: From Research to Clinical Practice

L. Carolina Carrere, Carlos H. Ballario, and Carolina B. Tabernig

Abstract People with central nervous system injuries or damage usually present motor sequelae that limit their daily living activities and hence their quality of life; so they need neurorehabilitation therapies to improve their motor function. Functional Electrical Stimulators (FESs) are used to recover the grip and release of objects and/or the foot dorsiflexion during the gait, among others. A FES device produces or assists movements through the application of electrical stimuli to either mixed or sensory nerves. It is commanded by the patient when his/her motor intention is detected. Brain-Computer Interfaces (BCIs) are an emerging technology that has been proposed to facilitate the restoration of the affected motor functions. They record signals of electroencephalography, extract its most relevant features and, through a classifier, detect the patient's intention to control an actuator device, such as a FES. In this chapter, the general structure and operation of BCIs which use surface FES as an actuator device is described. Two therapeutic applications of BCI-FES for motor neurorehabilitation of patients with stroke and multiple sclerosis are also described. In both studies, the patients showed improvement on motor functional outcomes which might have related to changes in their CNS. This encourages further research to elucidate the mechanisms that underlay and drive this motor recovery. These two application are examples of interdisciplinary collaboration between physicians and biomedical engineering researchers for presenting an emerging technological solution to improve patients quality of life. More studies focus on this direction are needed to realize the translation research to clinical practice.

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Keywords Brain computer interface · Functional electrical stimulation · Stroke · Multiple sclerosis · Neurorehabilitation · BCI · FES

1 Introduction

Motor function is usually affected after injuries to the Central Nervous System (CNS), such as stroke (Li and Francisco 2015) or Multiple Sclerosis (MS) (World Health Organization and Others 2008). Faced with the cue of performing a movement, people with stroke or MS squeals either cannot do it or can carry it out with deficiencies. This chapter addresses novel techniques based on technology for detection of motor intention (MI) to restore impaired motor function and describes two examples of their translation from research to clinical practice.

Stroke is a sudden loss of neurological function as a result of the interruption of the blood supply to the brain and causes sequelae of hemiplegia (paralysis of one side of the body) or hemiparesis (weakness in the limbs on one side of the body). It is the leading cause of physical disability and the second cause of death (World Health Organization 2017). MS is a degenerative disease of the CNS that affects approximately 2.3 million people worldwide and has a great impact on the patients' quality of life (World Health Organization 2017). The functional impairment of major clinical relevance for MS patients is gait disturbance, characterized by an asymmetric pattern, muscle weakness and fatigue (Miller et al. 2017; Springer and Khamis 2017; Sternowski and Perone 2017). These motivate the search for new technologies and rehabilitation strategies to assist or restore the lost or impaired motor function; based on the adaptation and learning capacity of the CNS that facilitates its functional reorganization after injury (He et al. 2008). These rehabilitation strategies are usually addressed from the Peripheral Nervous System (bottom-up approach), from the CNS (top-down approach) or by combining both approaches, which is a novel approach that has emerged recently.

Functional Electrical Stimulation (FES) is a bottom-up strategy, which helps to achieve or assists the movement of the affected limb through the application of an electrical stimuli to mixed nerves by direct activation of motor units or sensitive stimulation to evoke the withdrawal reflex. It proposes the voluntary control by the patient of an electrical stimulator with special characteristics for the activation of the affected neuromuscular system (Tabernig and Spaich 2021). In stroke patients, FES is used in upper limbs to grasp and release objects and, in lower limbs, to achieve or assist the dorsiflexion of the foot drop through electrical stimulation of the external popliteal sciatic nerve during the swing phase of gait, among other applications (Cheryl and Popovic 2008; Doucet et al. 2012). In MS patients, FES has been used to assist the cycling motion (Scally et al. 2020) or the gait by assisting the swing phase (Miller et al. 2017; Springer and Khamis 2017; Sternowski and Perone 2017).

To face rehabilitation from a top-down approach, brain-computer interfaces (BCIs) have recently emerged. A BCI is a system that records the activity of the

CNS and turns it into an artificial output that replaces, restores, increases, supplements or improves the natural output of the CNS and therefore changes the interactions between the CNS and its external or internal environment (Brunner et al. 2015). Although a BCI can record CNS activity by different means, the electroencephalography signal (EEG) provides a reliable and relatively low-cost method that makes it suitable for use in the clinical setting by patients and healthcare professionals. In this chapter we will refer to EEG-based BCIs.

EEG-based BCIs identify MI by means of detecting changes in the sensorimotor rhythms (SMR) of the EEG when the user imagines/intends/performs or observes movements (Jeannerod 1995). In particular, event-related desynchronization (ERD) is a phenomenon of the brain activity from the sensorimotor and supplementary motor areas in response to a MI and observed as a decrease in the amplitude of the SMR *mu* (8–12 Hz) and *beta* (13–30 Hz) of the EEG (Pfurtscheller and Lopes da Silva 1999; Neuper and Pfurtscheller 2010). ERD can be described in time and space. In movement preparation, ERD starts about 2 s prior to voluntary movement-onset over the contralateral hemisphere. When the motor task is cue-paced, ERD is time-locked to the movement and topographically restricted to the electrodes overlaying the involved motor area. ERD can be quantified as a percentage of band power decrease with respect to a reference period (ERD%) (Pfurtscheller and Lopes da Silva 2011; Pfurtscheller and Neuper 2003), as it can be observed in Fig. 1.

ERD-based BCI's general structure for MI with FES (BCI-FES) is shown in Fig. 2 and consists of three modules: Sensor and Conditioner, Motor Intention Detector and FES device (Carrere et al. 2020a).

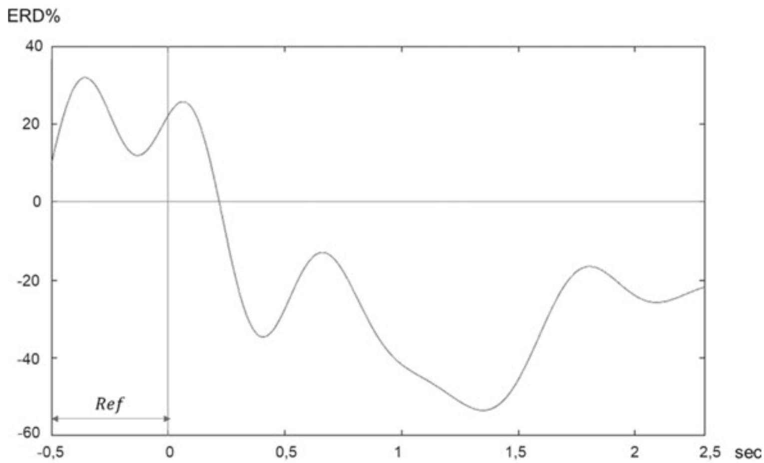


Fig. 1 Average ERD% time course (n = 30 trials) in *mu* rhythm of one healthy subjects during cue-paced foot motor intention recorded at foot cortical position: electrode Cz (horizontal line: level of reference; vertical line: cue; Ref: reference period)

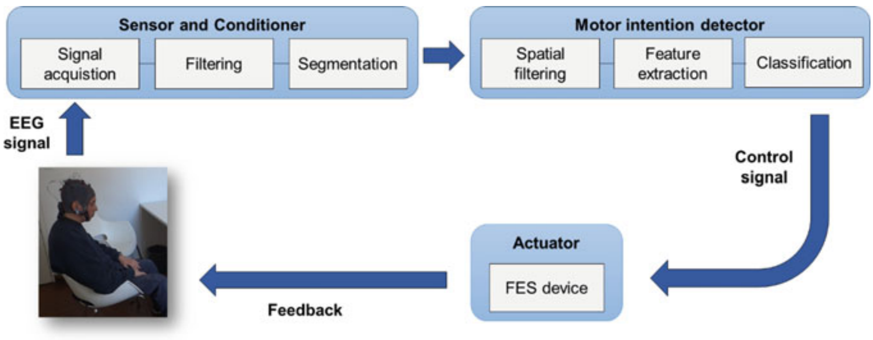


Fig. 2 General structure of an ERD-based BCI with FES. Modified from Carrere et al. (2020a)

The first module comprises the following blocks: Signal acquisition, Filtering and Segmentation. The first two blocks record and filter the EEG signal between 8 and 30 Hz. EEG electrodes are placed on the scalp over the sensorimotor area in accordance with the international 10–20 system. Then, data from each channel are segmented and sent in blocks to the next module. In the Motor intention detector module, spatial filtering is implemented to improve the signal to noise ratio and to enhance the signal from the cortical position of interest; for example from Cz for lower limbs, C3 for the right upper limb or C4 for the left upper limb. The Feature extraction block generates the feature vector that best represents the MI. The Classification block is responsible for translating the features into a control signal, which activates the FES device and provides feedback to the user.

For the design and development of an ERD-based BCI for people with stroke or MS, it is essential to understand the behaviour of ERD in these patients by contrasting it with that of healthy people with whom the developed technology is usually preliminarily evaluated.

2 ERD Characterization in Stroke and Multiple Sclerosis

The ERD time-course during simulated MI of healthy subjects and MI of stroke subjects are shown in Fig. 3, in which time evolutions of mean ERD% can be observed. These ERD time-courses are also analyzed to determine the ERD-onset latency, which is defined as the time at which the ERD% is negative and remains negative up to the end of the MI task (Leocani et al. 2005). Aguilar et al. (2020) reported that the ERD% of the simulated MI from healthy subjects evidences similarities in amplitude when compared with the patients' affected limb MI ERD% but with a shorter latency (healthy: *mu* rhythm 0.8 s, low *beta* rhythm: 0.8 s, high *beta* rhythm: 0.3 s; patients: *mu* rhythm 0.8 s, low *beta*: 1.3 s, high *beta* rhythm: 1.2 s). These findings provided the basis for the simulation of MI by healthy volunteers in the preliminary stages of BCI development.

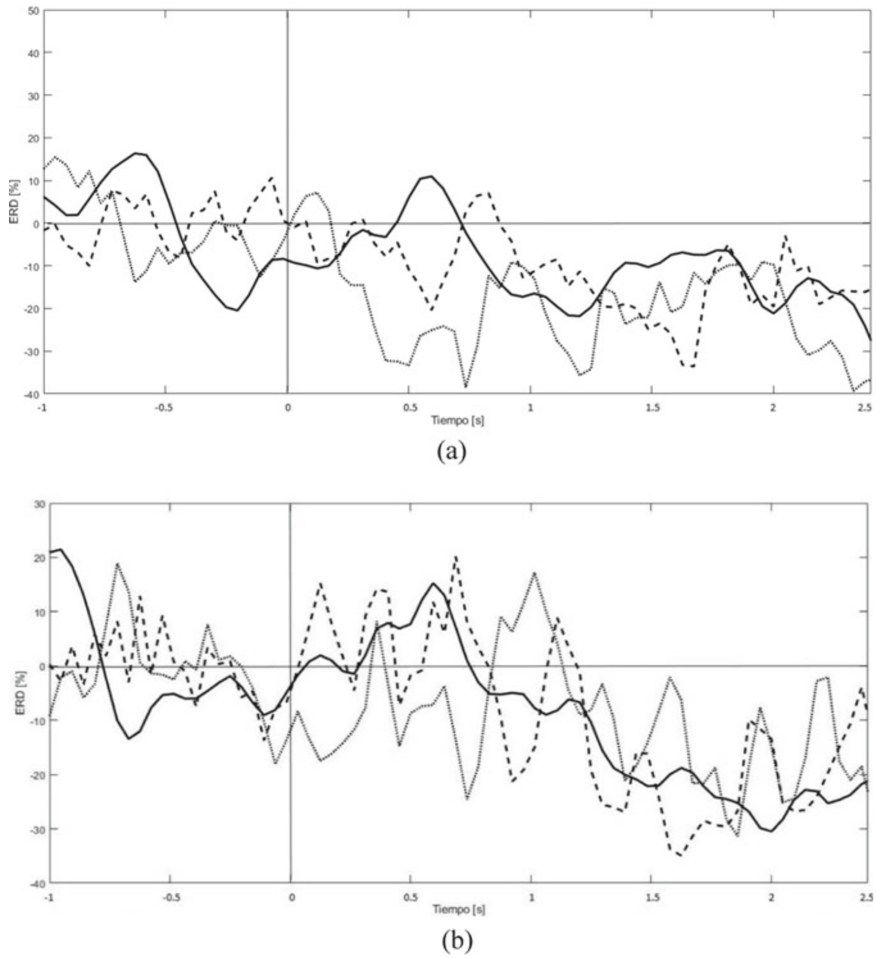


Fig. 3 Averaged ERD% time courses, obtained at Cz channel from the foot MI. *Mu* rhythm (solid line). Low *beta* rhythm (dashed line). High *beta* rhythm (dotted line). Vertical line: cue. **a** Simulated MI from healthy volunteers, **b** MI from stroke subjects. Modified from Aguilar et al. (2020)

ERD can be analyzed as a function of space in topography maps, in which the spatial distribution of the determination coefficient of determination r^2 for a specific frequency is represented. This estimator assumes real values between 0 and 1, and it can be computed from the EEG signal spectra corresponding to the rest and to the MI (Schalk and Mellinger 2010a). Values of r^2 close to 1 indicate a very good discrimination of both conditions, while values of r^2 close to 0 are associated with conditions that can be scarcely distinguished (Aldea and Oana-Diana 2013).

Figure 4 shows the topographic maps [obtained with BCI2000 Offline Analysis (Schalk and Mellinger 2010a)] of eight chronic stroke patients for the EEG frequency

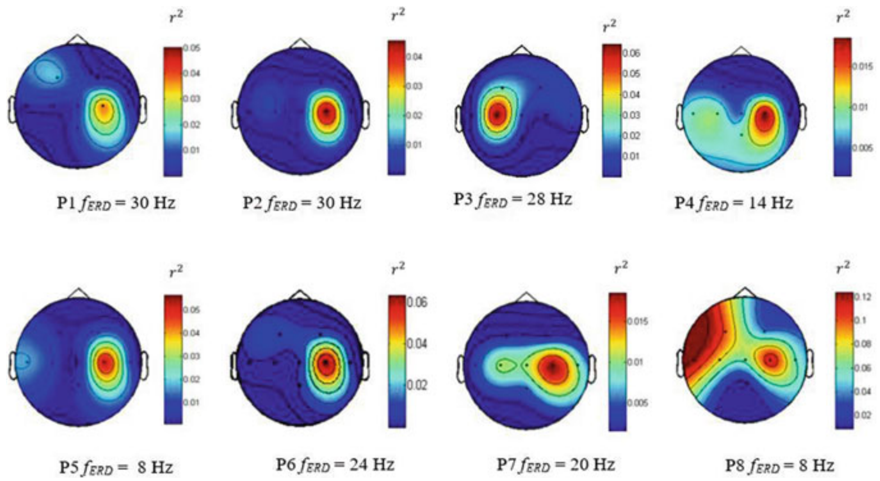
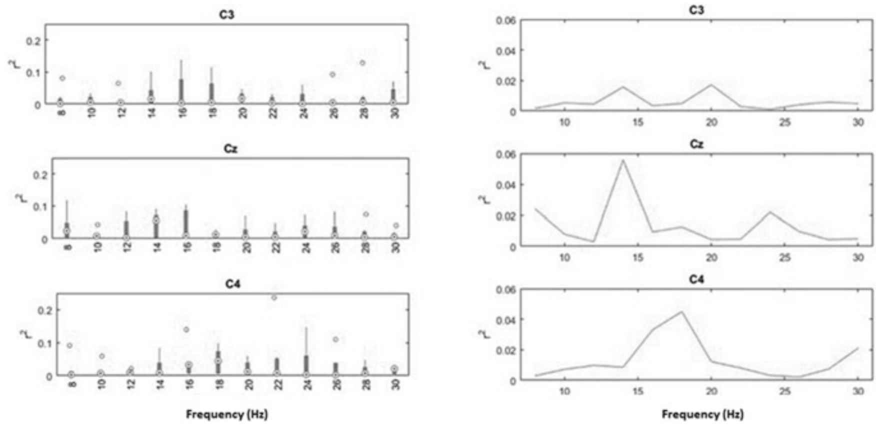


Fig. 4 Topographic maps during MI tasks of the paretic upper limbs for the selected f_{ERD} for each of the eight patients, On the right: color scale of r^2 for each map. Modified from Tabernig et al. (2018)

in which the ERD was maximal (f_{ERD}). Each map is a representation of the cerebral cortex seen from above where the recording channels (in black spots) are identified and the value of the coefficient of determination r^2 in each cortical area is represented (in color-coding). In all the maps, desynchronization in cortical areas associated to upper limb movement are evidenced through a high value of r^2. It is also observed that f_{ERD} could be identified in both sensorimotor rhythms: *mu* and *beta*. ERD is observed during MI of the paretic arm in all patients involved, which provides support for the use of ERD-based BCI with stroke patients. However, the cortical topographic maps were different in each one of them with respect to the spatial location, the value of r^2 and the EEG frequency bands. This reinforces the need for an individual BCI calibration for each patient-user (Tabernig 2018).

The ERD frequency behaviour during MI in post-stroke patients was also assessed by the r^2 (Tabernig et al. 2019). EEG signals from C3, C4 and Cz electrodes were recorded in seven chronic ischemic stroke patients during rest and MI of their affected hands. The r^2 spectra were estimated between 8 and 30 Hz, as it can be observed in Fig. 5. The median of r^2 reached 0.05 during MI of the affected hand; so it is a possible real value to be taken into account in BCI developments for stroke people. It was also observed that stroke survivors have discrimination capacity in the injured hemisphere during the MI of their affected limb.

Regarding the ERD behaviour in MS people, Fig. 6 shows time evolution of ERD% at Cz electrode during dorsiflexion MI of the most affected foot of seven patients with relapsing–remitting and secondary progressive MS. It can be observed that MS people are also able to desynchronize their SMR, but the ERD-onset latency (452 ms) is longer than the mean reported for healthy people from other authors [407 ms (Leocani et al. 2005), 444 ms (Carrere et al. 2021)].



(a) Box plots (b) Medians

Fig. 5 r^2 spectra for the SMR during the MI of the left affected hand for the electrodes C3, Cz and C4. **a** In a circle with a central point, the median; in full bar, the first and third quartile; in an empty circle, the outlier values; and in a thin line, the maximum and minimum values; **b** the medians of the r^2 coefficients. Modified from Tabernig (2018)

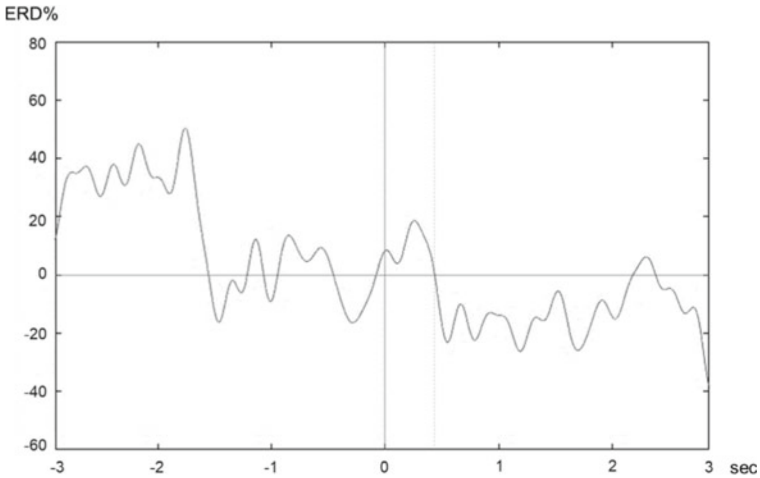


Fig. 6 Grand average ERD% time course (n = 107 trials) in *mu* rhythm of seven multiple sclerosis patients during cue-paced foot motor intention of the most affected limb recorded at foot cortical position: electrode Cz (horizontal line: level of reference; vertical line: cue; dot line: ERD-onset latency)

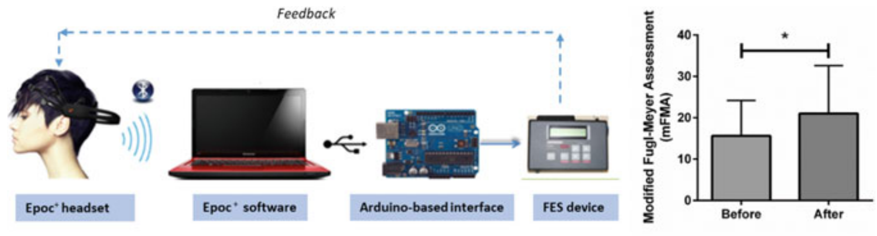
3 BCI-FES for Motor Function Recovery in Stroke

Ictus changes the life of the patient and his/her family, since stroke-associated paralysis is one of the main causes of disability in adults (World Health Organization 2017); hence, it is very important to rehabilitate and restore the affected functions of the post-stroke patient.

Neurorehabilitation therapies intend to generate sensorimotor stimuli through the repetition of movements and their incorporation into activities of daily life (Winstein et al. 2016) facilitating activity-dependent CNS plasticity (Malouin and Richards 2010; O'Dell et al. 2009). It is known that the type, form, and timing of sensory feedback affects this motor re-learning (Levin et al. 2010). Current evidence suggests that the neural correlate that associates MI generated in ipsilesional areas with the activity produced by visual, cutaneous and proprioceptive feedback would be a mechanism of motor learning (Moritz et al. 2008; Legenstein et al. 2010; Tyson et al. 2013). This association between the afferent information with MI can be provided by a BCI, which combines the top-down and bottom-up approaches. This type of combined approach is recently emerging. For the upper limb, a clinical study reported statistically significant improvements in the motor function of the upper limb of stroke patients using an ERD-based BCI with active orthosis prior to physiotherapy sessions (Ramos-Murguialday et al. 2013). Regarding the use of FES as an actuator of an ERD-based BCI and for therapeutic purposes, the first clinical studies have recently been published (Biasiucci et al. 2018). They showed that BCI with FES elicits significant, clinically relevant, and lasting motor recovery in chronic stroke survivors more effectively than sham FES. For more details on the use of BCIs to recover functions, see the review of Cervera et al. (2018).

An exploratory study reported by Tabernig et al. (2018) assessed the possibility of using a BCI with FES to restore the upper limb motor function in stroke people. Eight severe chronic stroke patients were recruited. The therapeutic intervention involved 20 sessions where a FES device was activated when the patient's cerebral activity related to MI was detected. As it can be observed in Fig. 7a, the used BCI consisted of 4 blocks: the Emotiv Epoc$^{+®}$ headset with the electrodes and amplifiers; the Emotiv Epoc$^{+®}$ software; an Arduino-based interface that interconnects the two blocks; and a two channels FES device to provide intrinsic feedback to the patient (Jure et al. 2016). The EEG signal was processed using the CognitivTM Suite provided by EMOTIV Epoc$^{®}$ (Emotiv 2014), whose operation relies on ERD (Lang 2012).

The upper limb motor function was assessed, before and after the intervention, by the modified Fugl-Meyer score (primary outcome). Spasticity, motor activity, range of movement and quality of life were also evaluated (secondary outcomes). A statistically significant and clinically relevant post-treatment improvement ($p < 0.05$) was detected in the primary outcome measure Fig. 7b and in the majority of secondary outcome scores. The authors suggest that the proposed BCI-FES therapy could be beneficial for the neurorehabilitation of stroke individuals.



(a) (b)

Fig. 7 Feasibility study of using ERD-based BCI with FES for upper limb motor recovery of stroke patients **a** The ERD-based BCI with FES used in the study. **b** Modified Fugl-Meyer score before and after intervention. The asterisk * indicates a statistically significant change ($p < 0.05$). Modified from Tabernig et al. (2018)

4 BCI-FES for Gait Recovery in Multiple Sclerosis

It has been reported in the literature that FES (bottom-up approach) has no therapeutic effect on walking speed over short distances for MS patients (Miller et al. 2017). On the other hand, encouraging results related with changes in brain activation patterns after motor rehabilitation treatment have been found in these patients (Bonzano et al. 2019; Prosperini and Di 2019). In this regard, it has been suggested that neural plasticity in MS patients might be induced if the rehabilitation training is task-oriented (Prosperini and Di 2019; Lipp and Tomassini 2015; Tomassini et al. 2012). In this sense, Carrere et al. (2020b) reported a study aimed at evaluating the feasibility of a therapeutic intervention based on BCI-FES to initiate the gait (as a meaningful functional task) when foot dorsiflexion MI is detected, as a new combined approach for gait rehabilitation of MS patients. For this purpose, the therapeutic intervention was evaluated in 9 patients with relapsing–remitting and secondary progressive MS.

The used BCI-FES included three modules: Sensing and Conditioning and Control Signal Generator, an electronic interface and the FES device, as it can be observed in Fig. 8 (Carrere et al. 2020a).

The first module consists of the wireless amplifier and A/D converter g®. Nautilus (Guger Technology) and the BCI2000 platform (Schalk and Mellinger 2010b). The EEG is filtered with a digital band-pass filter between 0.1 and 30 Hz and frequency power line filter at 50 Hz. The data from each channel are segmented and sent in blocks of 8 samples (31.25 ms of duration) to the next module.

In the Control Signal Generator module, a Laplacian spatial filter is implemented to improve the signal to noise ratio and to enhance the signal from the foot cortical position, Cz. Then, in the Feature Extractor block, the amplitude spectrum is computed in 500 ms signal epochs. In the Feature Selector block, the amplitude spectrum at the f_{ERD} is selected. Afterwards, the Classifier block computes the mean of the EEG amplitude in the f_{ERD} that corresponds to the MI task and compares it with a threshold to generate the control signal.

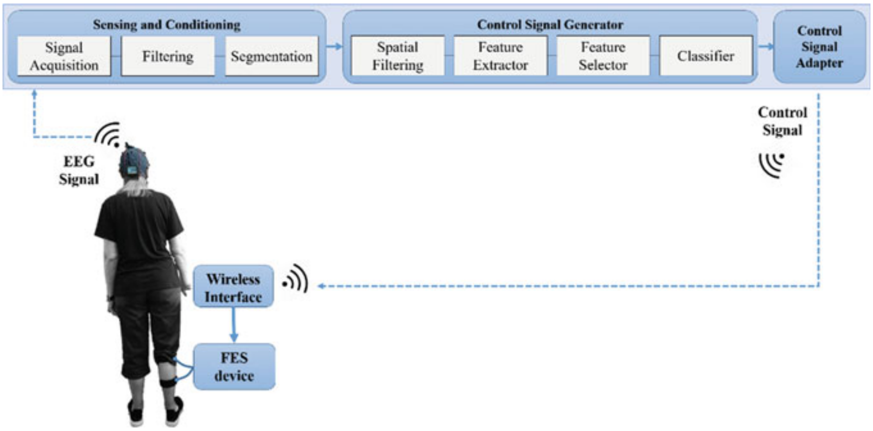


Fig. 8 Structure of BCI-FES for gait rehabilitation of MS patients, with its modules: sensing and conditioning; control signal generator, control signal adapter, wireless interface and FES device (dash arrow: wireless communication, solid arrow: wired communication). Modified form Carrere et al. (2020a)

The Control Signal Adapter module establishes Bluetooth® communication between the computer and the Wireless Interface, which is based on an Arduino Nano Rev3® board. Its output signal activates the FES device. It is a two channel FES stimulator (Flexicar S.A.). The electrical stimulation parameters are set prior to use by the therapist.

The intervention consisted of 24 sessions that were performed 3 times a week. Subjects with relapsing–remitting (no relapse in the last 3 months) and secondary progressive MS were evaluated pre and post therapy by different clinical gait measures and the ERD-onset latency. As it can be observed in Fig. 9, a significant and clinically meaningful post treatment improvement was observed in the Timed 25-Foot Walk (a decrease of 20.6%, $p = 0.018$) and the Multiple Sclerosis Walking Scale-12 items in percent (a decrease of 47%, $p = 0.028$). After the treatment, an earlier ERD-onset latency ($p = 0.021$) was also observed, which could suggest that functional brain connections involved in SMR modulations could have been positively affected.

Despite the fact that more studies with a larger sample size are required to validate the efficacy of this approach, authors suggest that BCI-FES technology could be an effective intervention for MS gait rehabilitation.

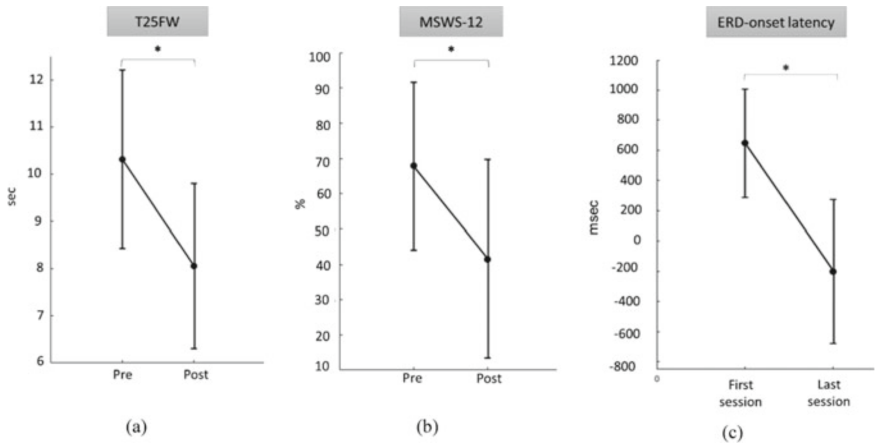


Fig. 9 Results of main outcomes from pre- and post-intervention (n = 9). Bars signify intervals of one median absolute deviation around the median (central point). **a** T25FW: timed 25-foot walk **b** MSWS-12: 12-item multiple sclerosis walking scale **c** ERD-onset latency. Asterisk indicates statistical significant difference. Modified from Carrere et al. (2020b)

5 Conclusion

BCIs are an emerging technology, mainly in their application for functions recovery. BCIs require research, design, development and evaluation, performed usually in a laboratory environment. In this regard, their current major problem is their transfer to the clinical environment where healthy professionals and patients use them to complete the processes of evaluation and validation for, finally, daily use. Facing this challenge, the general structure of ERD-based BCI with FES for motor function recovery was presented. The time and frequency characterization of ERD post-stroke and MS patients have been also introduced. Finally, two BCI-FES applications in neurorehabilitation for these patients were summarized, showing the beginning of a journey towards the use of BCI by its final users.

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Biopotential Acquisition Systems

Federico N. Guerrero and Enrique M. Spinelli

Abstract Biopotential acquisition systems have evolved for more than a century and can be considered a very mature technology in some respects. However, the conditions under which they must operate have also evolved. The most challenging applications see biopotential measurements moving from laboratories and medical offices to non-conditioned environments and providing 24-h monitoring through networked digital data connections. In this chapter, the design of biopotential amplifiers is contextualized within this framework which claims for reliable wearable devices with constraints of cost, portability, usability, and robustness. The main implication for the system is discussed: a trade-off between the dynamic range, frequency range, and power consumption which must be defined considering specific features to be extracted from the biopotential signal. Implementations can take advantage of a wide range of commercial devices from operational amplifiers for the front-end, mixed-signal systems-on-chip for analog to digital conversion, powerful microcontrollers for data processing and user interfacing, and wireless chips benefiting from ubiquitous infrastructures such as Bluetooth, WiFi, or mobile networks for data transmission following a variety of possible paths from the personal area network to a server in the cloud. Of course, an adequate instrumentation stage is key to deliver the functionality that these technologies enable. Therefore, we discuss the non-idealities impacting the performance of the analog front-end, measurement topologies including multiple-electrode configurations, grounding, and common-mode voltage managing strategies, a general approach to power-line interference analysis, and an analysis of motion artifacts and filtering.

Keywords Biopotential instrumentation · Electrocardiography · Electromyography · Electroencephalography · Electromagnetic interference · Driven-right-leg

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1 Introduction

Biopotentials are electrical signals produced by the cells in our bodies. They are made up of tiny ionic movements generated by pumps in the walls of cells, eventually leading to ionic flows in extracellular fluids. The body's inner tissues and fluids constitute a heterogeneous medium for these currents, but it is useful for analysis to approximate them as a homogeneous *volume conductor*, a medium with a given conductivity that allows currents to circulate and produce voltage drops (Plonsey and Barr 2007). Some of these voltage drops are measurable from as far as the outer skin. A great amount of information can be obtained from our biopotentials if we can read them in precise locations on our body's skin, as most have surely witnessed when subjected to an electrocardiogram (ECG) test.

The parameters of biopotential signals have a wide range of variations because the underlying phenomena that produce them can be very variable. We will focus on those signals measurable from the surface of the skin, which is a location generally very far away from the biopotential sources. Hence only the product of coordinated activity from a high number of cells is usually measurable, such as waves produced by vast regions of the cerebral cortex in scalp electroencephalograms (EEG), the combination of many action potentials from a high number of motor units in superficial electromyography (EMG), and of course the potent heartbeat in ECG.

From the perspective of an engineer, it becomes apparent that there are several hard challenges when measuring biopotentials: the skin can be an electrical isolator when it is dry, and the locations must be precisely chosen to obtain valid information. Furthermore, mechanical movements can alter electrochemical balances in the site of measurement, physical properties of the tissue, modifying its electrical parameters, and even the relative position of the biopotential source to the measurement point. Fortunately, we can rely on trained professionals such as nurses, doctors, and technicians who know how to counteract each and every one of these difficulties: they prepare the skin before placing measurement electrodes, they have learned through study and experience the best locations to place them, how to best lay the wires to avoid motion artifacts or when it is convenient to tape the electrodes to the skin. They can even device solutions to pesky problems such as electrical interference present in the recordings, usually manifested as a 50/60 Hz signal superposed to the biological signal. However, this is also a hindrance to their jobs, and they might not always be able to access the patient in telemedicine or wearable applications.

Biopotential measurement applications have successfully followed the trend towards miniaturization, portability, and digitalization that other devices such as the smartphone have transited, or perhaps, enabled. The measured signals can be stored in digital records to have well-organized clinical information in a doctor's office or throughout a whole hospital or region. But more than this, rich and powerful software and networking ecosystems have enabled long-sought fantasies to become truth: a datum available in one location can be instantly transmitted to any other location in the world and multiplied for any number of receivers. The data can be presented in beautiful real-time graphs embedded with so many design elements and processing aids that it can be understandable for untrained individuals and be used to learn about body processes useful in medicine, sports, or even turned into art (Guerrero et al. 2020).

The wide spectrum of applications that modern digital platforms enable also expands the use-cases of the technology. If biopotentals can be visualized and analyzed in all kinds of platforms everywhere in the world, then it becomes desirable to also acquire them everywhere and whenever: during daily life activities, at a medical center or at home, whether in the company of medical or trained professionals or alone. Hence, it is desired that biopotential acquisition equipment become *wearable*, i.e., unobtrusive devices that can be installed on the body with the ease of a piece of clothing. This has many implications regarding the ability of the equipment to effectively acquire the intended biopotentials. It must remain functional when the electrodes are placed on unprepared, high impedance skin; the proper biopotential signals must be captured without the assistance of professionals to place them in the correct location, and interference and motion artifacts must be avoided. Lowering the cost of the devices can also lower the accessibility barrier. Many of these characteristics can be provided with the help of ergonomics, industrial design, materials engineering, and other disciplines, but an important part must be played by electronic instrumentation.

Analog electronic instrumentation will always be present because of the analog nature of the world, although thankfully more and more functions of the analog portion of the circuitry can be replaced by more easily modifiable digital processing. A block-diagram of a biopotential acquisition device that considered only the "amplifier" would be a poor representation of today's reality: in a wearable, always-connected acquisition platform a full appreciation of the engineering problem is gained through an expression of the complete problem. The biopotential signal is taken from the body to a screen that may be in the user's watch a few centimeters away from the electrode, or in a doctor's office across the continent. Hence our amplifier does not stop in the digital-to-analog converter (ADC) but on a networked platform, and this is relevant to analog design. The digital window into physiological signals is wider than ever and full of potential, can we make the analog window into biopotentials equally wide and robust? It is the job of the instrumentation front-end to avoid limiting these possibilities and enable truly wearable measurements.

2 Fundamentals of Biopotential Measurement Systems

2.1 Basic Elements

Figure 1 displays a simplified representation of a measurement system. At its most basic, the biopotential signal is measured between two points in the body, hence a differential measurement is depicted as a general example. At the chosen

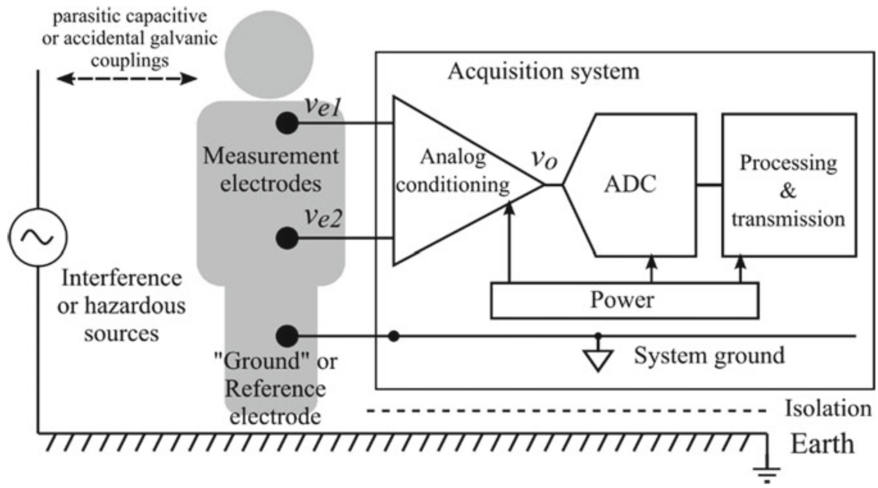

Fig. 1 Schematic depiction of a biopotential acquisition system

measurement sites, some form of biopotential electrodes are applied, either wet, pre-gelled, dry, or non-contact (Searle and Kirkup 2000; Mathewson et al. 2017; Spinelli and Haberman 2010).

The key process allowing to conduct biopotential measurements is the electrochemical transformation of ionic charges into electronic charges happening at the skin–electrode interface. The skin is a formidable protector for our body, not least among its properties that of becoming an electrical isolator. Mother nature had the foresight of protecting us even from phenomena created by our technology; our hearts are delicate electrical clockwork pieces in which very faint currents can wreak havoc. However, our thick skin impedes these currents from establishing when we touch moderately high voltages because of its high electrical impedance. That is, our skin can act as a very good electrical isolator, mostly when it is dry. Of course, it is also porous and can become moist through sweating in which cases it becomes, in fact, quite a good electrical conductor (Grimnes 1983).

The properties of skin, and preeminently the outer, drier, layer, make wet or pre-gelled electrodes preferable as reliable connections to the body because they provide a biocompatible electrolytic solution that lowers the skin impedance and produces a low-noise interface. Their main disadvantage is that they dry out as time goes by, degrading their performance. In some areas such as hairy sites, they are also difficult to apply. Hence, important efforts to achieve high-quality dry electrodes are undertaken.

Because of their characteristics, biopotential electrodes both enable and complicate measuring biopotential signals, making it necessary to design an acquisition system specifically tailored to the task. The biopotential signal as-is suffers from the interposition of the very high and variable electrode impedance. Therefore, a key function of the analog stage is to obtain a low impedance output signal feasible to be connected to any other circuit stage, be it the input circuitry of the ADC or a second analog processing stage. At the same time, the signal must be properly conditioned to fit the voltage range of the ADC's input and its dynamic range. Hence, the required gain and possibly a voltage level shift must be provided. The basic characteristics of biopotential amplifiers, and amplifiers in general, are treated in depth in several works such as by Spinelli and Guerrero (2017) and by Neuman (1998). In Sect. 2.2 we will present a basic scheme to establish terminology and focus on some important fundamentals about the analog stage.

Being able to model the analog stage is one part of the problem, but equally important, in Fig. 1. The connection of the measurement system with the body and the roles of ground and earth are remarked. For simplicity, a so-called "three-electrode" connection or topology is shown. This topic will be tackled with detail in Sect. 2.3.

Finally, the matter of signal acquisition is constrained by the intended processing and transmission. There is a wide range of ADCs available for signal digitalization, suitable for different types of biopotentials and possible end-use of these biopotentials. These options will cascade back to the analog stage design, but they also are strongly dependent on the destination of the signals, hence the topic will be treated in Sect. 3.

2.2 Modeling the Analog Front-End

The analog conditioning stage schematized in Fig. 1 is shown in more detail in Fig. 2. The amplifier has been separated into an "ideal" device and lumped components that produce an equivalent effect to that which would be observed if the real device were used. The case considered represents the instrumentation stage with a differential-input amplifier that also presents a differential output with voltage v_{od}, for which Eq. 1 would be fulfilled.

$$v_{od} = v_{o1} - v_{o2} = G_{dd}(v_{e1} - v_{e2}) = G_{dd}v_d. \tag{1}$$

That is, ideally only a scaled version of the differential input v_d would be present at the output. However, the real output is given by Eq. 2.

$$v_{od} = G_{dd}v_d + G_{dc}\frac{(v_{e1} + v_{e2})}{2} = G_{dd}v_d + G_{dc}v_{cm} \tag{2}$$

where it is shown that the common-mode voltage at the input of the system will also contribute to the differential output through a mode transformation represented by G_{dc}. If this equation is referred to the input instead of the output, we obtain:

$$\frac{v_{od}}{G_{dd}} = v_d + \frac{G_{dc}}{G_{dd}} v_{cm} = v_d + \frac{v_{cm}}{CMRR}. \tag{3}$$

Equation 3 reveals the most "famous" non-ideal amplifier parameter, the common-mode rejection ratio (CMRR). This parameter is relevant because high-amplitude interference signals may be present as common-mode signals that must be rejected by the amplifier. That is the reason why the signal source is presented as a CM-DM decomposition as in Fig. 2: the DM contains the biopotential signal of interest, and the CM contains unwanted interference signals (Huhta and Webster 1973).

In this case, the amplifier has a differential output. There are several options for ADC selection demanding different topology characteristics. Some ADCs have differential inputs; hence the circuit of Fig. 2 can be directly connected. The advantage of retaining a fully differential circuit is that mode transformations are reduced providing an ideally infinite CMRR (Spinelli et al. 2003). Many ADCs, usually general-purpose ones, have a single-ended input, hence a different output stage is preferable, such as depicted in the inset of Fig. 2. The discussion has been centered on voltage-mode devices because they are available off-the-shelve with a good parameter range, however, current-mode devices are used in integrated designs, including a wide array of instrumentation amplifiers (Safari et al. 2019).

The amplifier (or the system represented by this equivalent amplifier) will have other non-ideal parameters as also depicted in Fig. 2. Of utmost importance are the input bias currents i_{b1} and i_{b2}, because (i) they must be lower than the accepted safe DC current that can circulate through the body of 10 μA (IEC 2020), and (ii) the system design must provide a sufficiently low-impedance path for these currents to ground, otherwise they can produce saturation of the input stage. Commercial special-purpose devices can reach ultra-low bias currents below 10 fA where careful design of the circuit board can provide, by parasitic elements, a polarization path (Sun and Yu 2014).

Other important parameters are the input common-mode impedance Z_i which affects interference rejection in high-electrode-impedance systems, and, in high-amplification systems, the offset voltage of intermediate stages can be problematic

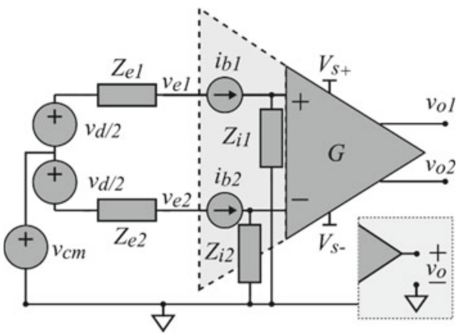

Fig. 2 Detail of a representative analog stage with differential input and output. An alternative single-ended output is shown in the inset

(Spinelli et al. 2001). The offset of the first stage would be superposed with the electrode's DC potential so it is a second-order parameter in the design. These parameters and their impact on EMI will be referenced later in this Chapter (Sect. 4.4).

2.3 Connection to the Body: The Subtleties of "Ground"

Transforming the biopotential signal into a common-mode and differential-mode set is the basis for understanding the connection topologies to the body. But first, there is an even more fundamental issue schematized in Fig. 1. The common node of the measurement system is usually referred to as "ground". Ground is the potential to which all voltages of the measurement system are referred. It is very important to avoid confusion with "Earth" potential, which is marked with a different, three-line connector in the diagram. This is not always the preferred nomenclature, but in the following, we will consider Earth to be the potential of the surroundings of a person and the equipment.

It can be assumed that all electrical sources in the surroundings, most importantly the power line, will be connected to Earth. Any electrical source different from the biopotential activity is a menace for our delicate measurements and possibly a health hazard as well, so it is imperative to avoid the person or our system becoming a return path for currents from these sources to Earth. Therefore, all means must be taken to extricate the measurement system from any circuit including earth: Ground and Earth must be galvanically isolated. As mentioned, wireless, portable devices make this much easier than their desktop counterparts (Metting van Rijn et al. 1991).

Of course, the measurement system operates between voltage limits imposed by its power supplies v_{s+} and v_{s-} (measured against ground), hence a reference to the body is necessary to keep the biopotential signals within this operational range. For this purpose, a reference, ground, or "third" electrode is used to make a connection from ground to the body. Then, the measurement electrodes are applied to the areas where the signal of interest can be measured: above a muscle, on the head near different areas of the brain, or according to standard lead locations for ECG recordings.

There are many variations on the connection topologies in relation both to the reference and measurement electrodes. Some basic alternatives are displayed in Fig. 3. In the first row of the figure, single-channel options are shown. The three-electrode differential option is well-used thanks to a compromise of simplicity and robustness. However, the two-electrode differential version proposed by Thakor and Webster (1980) has gained new utility for wearable devices thanks to its reduced complexity and the reduced coupling capacitances to EMI sources of this kind of equipment (Babusiak et al. 2020). In this case, careful design of the common-mode impedance or active CM control strategy is critical for maintaining the proper input range (Dobrev et al. 2005).

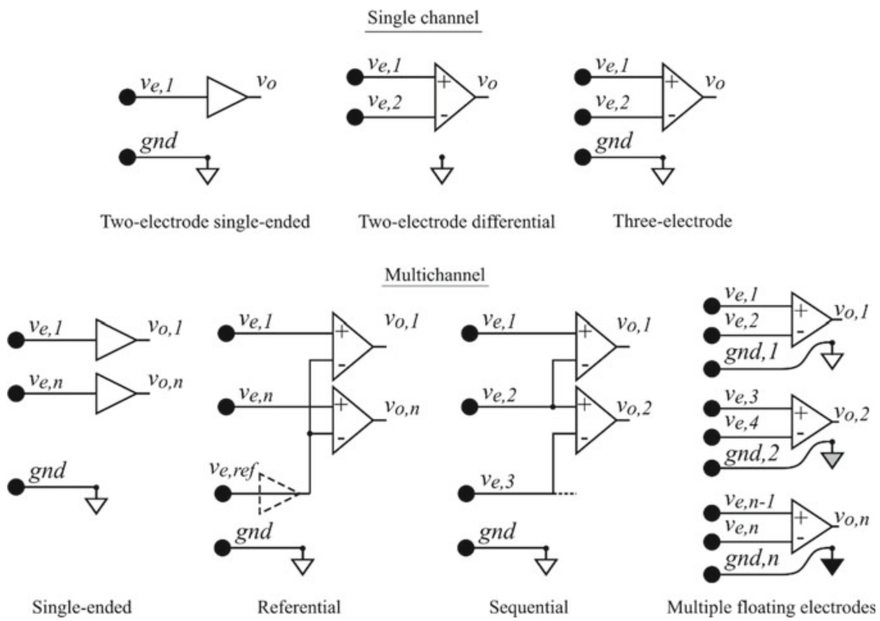

Fig. 3 Example measurement topologies. Each biopotential source may benefit from further specialization

The referential topology is very useful with multichannel measurements since the digitized channels can be used to construct any desired signal by linear combinations. This implies transferring complexity to the digital portion of the system. However, in the digital domain, strategies such as real-time reconfiguration can help improve measurements by eliminating signals affected by noise or artifacts (Alotaiby et al. 2015) or simply obtain different combinations that become of interest during the review stage (Lagerlund 2000).

The referential topology provides CM rejection by making every measurement differential but a careful routing of the signal and considerations about signal buffering must be made to avoid increased EMI due to electrode impedance imbalance. Moreover, the referential configuration adds a very critical point: the reference measurement electrode, which can affect all channels if degraded. Therefore, a single-ended multichannel topology can be superior if coupled with CM reduction techniques. In this case, a reference can also be chosen among the available signals, but the signals are not degraded by the failure of this signal: valid information is retained, and a simple software reconfiguration allows recovering the data. In EEG measurements the same information can be obtained through different montages, although with different signal quality (Pethe et al. 1998). This fact has been well utilized in studies aiming for real-world applications such as Brain-computer interfaces (BCIs) based on steady-state visually evoked potentials (SSVEPs) or even sleep monitoring, where signals from hairless locations were sought (Floriano et al. 2020) as well as measurements from within the ear (Kappel et al. 2019).

Another measurement technique is the use of multiple single-channel sensors which can be applied to different locations on the body, each with its grounding electrode. This is the strategy of superficial EMG sensors which measure localized signals with inter-electrode separation of the order of 1 cm. Solutions for EMG multi-site measurements have migrated towards wireless independent units, each with its own reference electrode but floating relative to each other. The approach of multiple standalone electrodes was successful in EMG commercial wearable solutions (such as Deslys' Trigno platform) and proved attractive as a way of deploying multiple electrodes. However, the multi-lead ECG signal needs sites far apart and a common voltage reference among all of them. Some strategies hence attempt to establish a common reference among separate electrodes on the body (Hsieh et al. 2019).

An important concern for all these topologies is at what potential to set the reference to the body to establish a proper CM voltage, and furthermore, being able to exert a controlling action over the CM voltage to counteract possible fluctuations. As shown by Eq. 2, if v_{CM} contains spurious signals, they can interfere with the biopotential of interest contained in v_d. And because the "ground" connection is made using an electrode, it is not a good low-impedance connection securing a firm CM voltage, hence v_{CM} fluctuations are an expected problem.

Figure 4 shows CM managing strategies, commencing with the mentioned simple "grounding" to the left. For a single-supply system, ground should be replaced by a positive voltage, usually the midpoint of the supply. If the electrode impedance were 0, the grounding scheme would suffice, but it is not so, and interference currents can circulate through it causing a deviation from the desired potential (Huhta and Webster 1973). A very high CMRR at the amplifier could reject part of the CM interference, but it is not always easy or convenient to achieve. Moreover, part of the CM is transformed to DM interference *before* the amplifier (through the "potential divider effect" discussed in Sect. 4.1) hence additional circuitry is very usually employed to *reduce* v_{CM} fluctuations before they cause problems.

There are several options for the CM reduction circuitry. The goal is to establish a reference voltage v_{ref} that v_{CM} should ideally be equal to, then measure the actual v_{CM}, and finally, if it differs from v_{ref}, inject a current through the reference electrode to counteract the difference and drive v_{CM} to the desired reference point. Of course, what has been described is a standard negative feedback control loop.

The most popular CM reduction circuit is the "Driven Right Leg" or DRL, shown in the center of Fig. 4. The DRL obtains a measurement of v_{CM} through averaging two or more channels and uses it to calculate the error against v_{ref}. In contrast with the DRL, the Body Potential Driving (BPD) circuit to the right of Fig. 4 takes a measurement using an individual electrode, and all remaining measurement electrodes are dissociated from the CM managing circuit. This difference can have an impact on system robustness: the fit of the CM measurement to the true

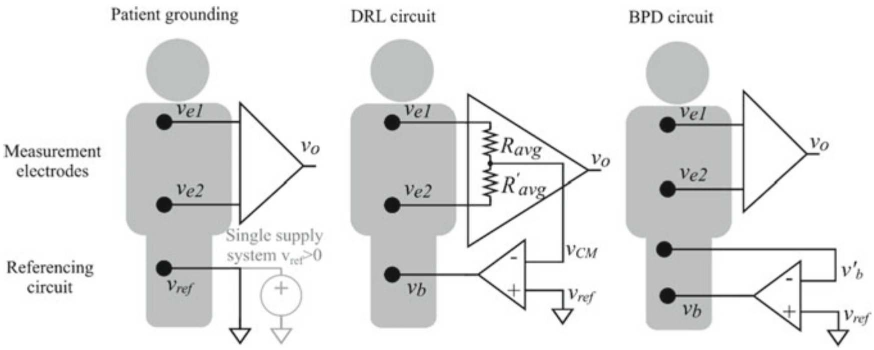

Fig. 4 CM managing strategies. The amplifiers shown in the DRL and BPD circuits usually include additional circuitry to ensure the loop is stable

v_{CM} of the body can be worse in the BPD circuit, but it will still work even if one measurement electrode is detached. In contrast, the whole system will fail if one electrode is detached in a DRL scheme.

An important concern for amplifier designs including CM loops is loop stability. The detailed operation of the DRL and BPD circuits and design considerations for stability can be well-understood consulting works by Levkov (1982), Winter and Webster (1983), and Metting van Rijn et al. (1990). Following the analysis presented in these papers, it can be concluded that a DRL circuit can easily provide, with assured stability, an effective or equivalent improvement of CMRR of 30–40 dB at the most important interference frequencies of 50/60 Hz. With careful design and mindfulness of the operation conditions, as much as 60 dB reductions are obtained by the mentioned authors. Higher CM reduction can be achieved at particular frequencies by digital DRL techniques (Haberman and Spinelli 2010), or increased performance at power-line harmonics by using transconductance amplifiers (Spinelli et al. 1999) or different compensation strategies (Guerrero and Spinelli 2017a). A potentially undesirable effect of the DRL circuit, even with a single-site location, is that it can produce worse EMI in some topologies (Gomez-Clapers et al. 2011). This could be regarded as a second-order effect, generally negligible, but worth considering if a fixed topology is planned.

Some devices apply CM management strategies to several locations simultaneously. A classic example of multiple-site referencing is double ear-grounding in EEG montages. In an active electrode design for a wearable multichannel platform published by Catacora et al. (2020), each electrode has its own DRL circuit, all taking the shared power-supply mid-point as reference. Therefore, the electrodes included global design considerations to avoid violating the total safe current limits in multichannel applications. This would mean decreasing the performance of the DRL because of the strict DC limits, so an AC-coupled DRL was included to conform to higher AC limits.

3 Interconnected Data Management and Biopotential Acquisition

3.1 The Road to and Challenges of New Devices

The first complete biopotential measurement system was, famously, an ECG readout device from Willem Einthoven with an antecedent from Augustus Wallace, achieving an amazing feat for their time: observing millivolt-level signals from the body. An interesting detail about Einthoven's ECG machine is that a few years after its invention, a modification was made so it could transmit the signals up to a mile away through telegraphy wires (Barold 2003). Health telemonitoring was invented practically as fast as electrophysiological health monitoring.

Notwithstanding early developments, ECG signals were first stored by recording traces of light on photographic plaques. Both the acquisition equipment and the data storage medium were large and cumbersome. Then, for a long time, the preferred data storage medium was a trace on paper; storage was local, restricted to the physician's office or the archives of a medical institution. Finally, all systems are being translated to the digital domain, including efforts to digitize existing paper archives (Holkeri et al. 2018), which means also opening the possibilities for mobile access to the data, even real-time monitoring from remote locations.

The "monitoring side" of acquisition technology experienced a great jump in possibilities thanks to the internet, mobile data networks, and powerful portable computing platforms such as notebooks, tablets, and smartphones. Furthermore, the "digital alphabetization" has become enormously extended as everyday life activities for many people include access to video streaming platforms and messaging applications. Recent successful studies of health telemonitoring relied on installation and use by elderly people of a smartphone application and dedicating hospital personnel to aid in monitoring as an integral part of the medical service (Yun et al. 2018; Koole et al. 2019).

This expansion of the monitoring tools has found a partial correlation with the acquisition equipment itself. Wearable biopotential measurements are slowly becoming a reality and enabling many areas of application (Cibis et al. 2017; Ramasamy and Balan 2018). Wearable ambulatory ECG devices have recently achieved success in wireless "patch" single-lead equipment, deploying in clinical use. Evidence suggests usefulness for detection of conditions such as atrial fibrillation and superiority in comfort, compliance, and duration versus the Holter monitor; however, they present insufficient performance when there is a lack of reliable wireless connection, a need to access to raw data without assistance from the parent company, or of integration with clinical electronic records (Fung et al. 2015; Leenen et al. 2020; Cosoli et al. 2021).

Complementarily, the available digital analysis tools make it possible to automatically evaluate vast amounts of information. Therefore, data sent from wearables on large numbers of people have a realistic destination. A good indication of progress again is related to the ECG with the approval of automated arrhythmia detection through an accessory for a commercial smartwatch (Chon and McManus 2018).

EMG measurements are also a field where big leaps have occurred, with comfortable wireless systems allowing measurements in challenging movement scenarios. For example, audiovisual content generated from biopotential signals can be included in artistic performances (Ceriani et al. 2020) as has been broadly covered in the New Interfaces for Musical Expression (NIME) conferences (Erdem et al. 2017; Hattwick and Wanderley 2017). Performances involving dancers present a unique challenge for wearable biopotential measurement systems because they must remain functional under a wide range of movements and varying interference conditions and the output of the device needs to interphase with commonly used multimedia systems. The measurement equipment is usually based on commercial devices such as MYO armband (formerly produced by Thalmic Labs) or g.Sahara (g.tec). The authors have successfully implemented and deployed a multimodal biopotential measurement system capable of acquiring ECG and EMG signals and transmitting the processed features through a wireless link (Guerrero et al. 2020).

The challenges imposed by wearable devices directly interfaced to the internet, sometimes referred to as "Internet of Things" (IoT) devices, are depicted and listed in Fig. 5. The device must keep working under an unreliable connection, for prolonged extensions of time, with limited storage, and with limited presence from trained professionals to detect or correct anomalous situations. Hence, there is an enormous emphasis placed on *reliability*. These conditions pose significant challenges for analog electronics, which will be explored in-depth in Sect. 4. Furthermore, although adhesive-based devices have achieved success as discussed above, they are not ideal because they may cause itch, irritation, or allergies (Trobec et al. 2018). Thus, there is still a need for advancement in electrode material and affixing methodology currently pointing to the use of dry or capacitive electrodes which require high-performance, specialized analog front ends (Chi et al. 2012, Fu et al. 2020).

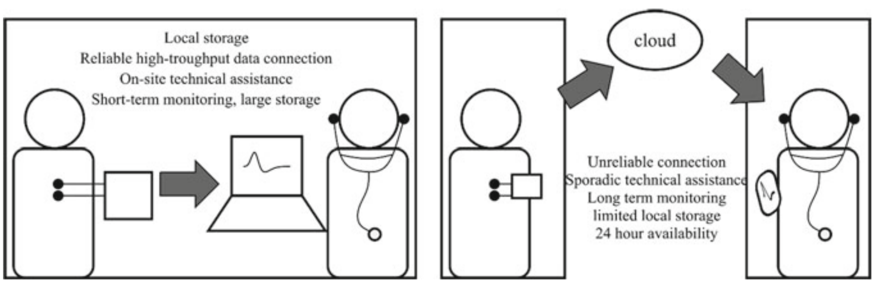

Fig. 5 A comparison of measurement conditions when shifting to an "Internet of Things" health monitoring paradigm

3.2 Characterization of Biopotentials with Application-Oriented Criteria

In order to design appropriate solutions for biopotential acquisition from the analog front-end, including digitalization, to data transmission, we must first characterize the signal source and ponder our goals. If biopotential signals are measured with the goal of clinical analysis, then the system design will be constrained by strict signal quality parameters and standards that allow interpreting biopotential signals in a repeatable way for diagnosis. However, as discussed, for many applications in the consumer market or when specific features are needed, a lower quality may suffice while low power operation or low cost becomes critical.

The frequency and amplitude range should be defined, but they will not result in independent factors because they are linked through ADC selection and data transmission stages. Low resolution and fast ADCs are cheap and readily accessible in most general-purpose microcontrollers. High-resolution ADCs are more expensive and achieve lower rates but are excellently suited for biopotential instrumentation. Similarly, large bulk data transmissions are possible and simple even in real-time applications like video streaming, but they become challenging when a small lag is required.

3.2.1 Dynamic Range

High-resolution analog-to-digital converters are well suited for biopotential measurements because they offer an extremely high Dynamic Range (DR). The DR is the ratio of the highest amplitude that needs to be acquired to the smallest resolution needed. A high DR solves the classic biopotential measurement problem of resolving the very small physiological signals submerged in the large electrode offset.

The highest amplitude of biopotential signals can range from 100 μV to a few mV, depending on signal type and location. However, biopotential measurements will also include the electrodes' DC offset and baseline fluctuations due to motion artifacts, which can both be in the range of 100 mV. A pessimistic bound for the largest DC amplitude in a differential channel can be found in the standards for clinical ECG equipment (ANSI/AAMI/IEC 2016), where it is required to accept a ± 300 mV electrode offset. That is 2 orders of magnitude higher than the highest amplitude of biopotential signals. Hence, there is a very significant difference in DR if the biopotential signal is to be acquired by first eliminating the low-frequency content due to the electrode offset, or if is acquired including it.

On the other end of the DR calculation, i.e. the smallest needed resolution, very detailed and clinically relevant features require the highest resolution present in the standards. The EEG is among the signals requiring the lowest input noise due to the instrumentation given by a spectral density of $10\,\mathrm{nV}/\sqrt{\mathrm{Hz}}$ for superficial measurements (Scheer et al. 2006) or 100 nV_{rms} in a 100 Hz bandwidth. Linnenbank et al. (1995) recommend choosing the amplitude of the least significant bit of the ADC between 1 and 3 times the RMS noise value, hence a lower bound for the DR calculation for the most demanding measurements is 300 nV.

As a result, the measurement DR for the most extreme conditions results in $log_2(600\ \mathrm{mV}/300\ \mathrm{nV}) = 20.9$ bits. Hence, a 21 bits DR is adequate, even under pessimistic considerations, for the most demanding biopotential measurement applications. This is the reason why Sigma-delta ADCs with upwards of 19-bit resolution have been recognized as a particularly good solution for DC-coupled biopotential measurements (Curtin 1994) and included in a very successful acquisition chip family, ADS129x from Texas Instruments. Using these converters, a very simple analog processing stage can be used to acquire even the most demanding signals.

The other option is to apply high pass filtering to the signal, therefore reducing the required DR by almost 60 dB to the range of 12–16 bits. The analog stage will be more complex, but the ADC can be simpler or have a higher data rate. Successful examples of this strategy are high-end INTAN Technologies integrate circuits (ICs), including 64 to 256 14-bit channels. The strength of these ICs is that they include complex and configurable analog processing within the chip, hence simplifying the external analog stage like ADS129x ICs but through a different strategy. Thus, the possibilities for acquisition front ends now range from generic low DR ADCs embedded in general-purpose microcontrollers to highly specialized acquisition chips. Table 1 summarizes applications and technologies for each DR segment.

3.2.2 Frequency Range

Biopotential signals have important content in given frequency regions that must be preserved in order to achieve different goals. The case of ECG is well-determined because the morphology of the wave must be preserved to allow medical doctors to study the health of the organ. The ANSI/AAMI/IEC (2016) standard historically gave precise indications for the filtering characteristics of a biopotential amplifier about the preservation of ECG waveform. Electrocardiography devices used for diagnosis need a 0.67–150 Hz bandwidth, but general-purpose ECG devices used for rhythm interpretation will need to comply with a less restrictive bandwidth of 0.67–40 Hz (Mahdiani et al. 2015; Young 2019).

EMG also has long-standing recommendations (Merletti and Cerone 2020) and the same principle applies. Amplitude and power features could be reliably estimated with a diminished 100 Hz bandwidth typical of wearable armbands (*Myo Armband* from Thalmic Labs), but a full 500 Hz bandwidth was needed to improve detection for more complex features and was critical when applied to the EMG of persons with amputations (Phinyomark et al. 2018). Hence, not only the signal characteristics but also its intended use typical of application-oriented wearable devices inform decisions regarding the acquisition equipment.

Table 1 Necessary dynamic range for different biopotential signal types and characteristics of available technology

Dynamic range	ADC characteristics	Examples of target biopotential signals
10–12 bits	Integrated in general purpose microcontrollers Low cost High channel-count High speed May require oversampling	AC coupled Hearth rate detection EMG envelope with previous analog processing
16 bits	Stand-alone or integrated in analog-oriented microcontrollers Medium cost Low channel count Specialized products	AC coupled signals All biopotentials (loss of integrity during high-amplitude artifacts)
24 bits	Stand-alone or in dedicated AFEs with medium channel count Specialized microcontrollers with low channel count Higher cost	DC coupled All biopotentials

Biopotential signals are on the low-frequency side of electronic design; the design challenges are more often related to successfully achieving a cut-off frequency very close to 0 Hz, or directly DC-coupled measurements. Despite the low frequency predominant for biopotentials, the captured signals are often high-resolution and may be high-channel-count which can lead to the necessity of high data throughput.

Challenging designs also arise with hardware attempting to record some features like spikes, which need a wider high-pass frequency, and especially when combined with a high channel count. Table 2 presents a coarse summary of biopotential signals with their frequency range, not only from a purely theoretical frequency content evaluation but also considering their intended application and hardware characteristics.

3.3 *Connectivity Alternatives*

Connectivity alternatives have an impact on the rest of the device. The end goal of a connected device is to reach a server connected to the web, but there are many paths to do so, according to the data volume, expected environment, and applications (Ray 2018). Figure 6 shows a schematic representation of several alternative pathways based on commercial, general-purpose technology. Presently, there are widely available off-the-shelve wireless solutions, which have experienced a reduction of cost but are still maintaining a strong limit regarding the trade-offs between data volume, transmission distance, and power savings.

Table 2 Frequency characteristics of different biopotential signals and hardware requirements

Frequency characteristic		Examples of target biopotential signals	Hardware requirements
f_L	f_H		
$f_L = 0$		DC-coupled acquisition (all biopotential signals)	24-bit converter
$0 < f_L < 1$ Hz		Clinical ECG Low frequency EEG Electrooculogram (EOG)	DC coupling or specialized AC coupling. Reset
1 Hz $< f_L$		Some features from ECG, EMG, EEG	Simple AC coupling and/or signal processing
10–40 Hz $< f_L$		EMG with artifact suppression filtering	
	$f_H < 40$ Hz	Several EEG bands Non-diagnostic ECG with EMI filtering	Simple to manage in low-end microcontrollers
	$f_H < 100$ Hz	EEG Non-diagnostic ECG Lower feature-count EMG	
	150 Hz $< f_H <$ 1 kHz	Clinical ECG Some features from EMG	Specialized hardware for large multichannel electrode arrays
	450 Hz $< f_H <$ 1 kHz	Diagnostic EMG (no spikes)	
	1 kHz $< f_H <$ 10 kHz	EMG Invasive EEG spikes	

FH: Low-pass cut-off frequency, *FL:* high-pass cut-off frequency

Bluetooth is a very flexible and practical technology, with the advantage of being present in all smartphones and notebooks. It is meant for the personal area network, transmitting date effectively to nearby devices, but struggling with 5–10 m ranges and signal blocking caused by the body (Damis et al. 2018). Improving these limits demands an increased power consumption to boost transmission power or retransmission (Shah et al. 2008). A Bluetooth device can transmit signals or notify events to a smartphone carried by the person or a computer on a desk, where a resident application would relay the data to the web through the available connection.

WiFi gives a greater range and freedom of movement at the cost of an order of magnitude greater consumption. Development of low-cost miniaturized WiFi transmitters is fairly recent, and their consumption makes them unfeasible for multi-day wearables, although the case has been made that total energy can be lower if a single WiFi device is used vs. using a Bluetooth relay to a WiFi connected device (Kolamunna et al. 2017).

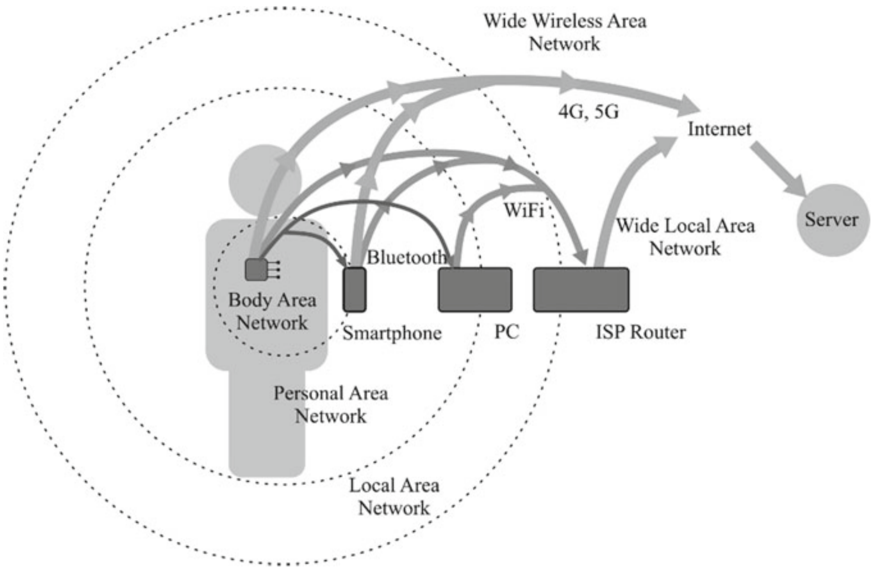

Fig. 6 Representation of the protocol pathways of a wearable device to the Internet using general-purpose, widely available technologies

WiFi has the advantage that its infrastructure is available in many locations. However, credentials exchange may not be straightforward; the "Internet of Things" paradigm is changing the way devices can connect to a network without troubling the user, but solutions are not yet fully streamlined, and a lot of legacy hardware is still in use (Jewell et al. 2015). As a second point of note, the embedded platform should be a higher-end system to be able to handle WiFi protocols. The ongoing replacement of 8-bit microcontrollers with low-cost 32-bit multi-core microcontrollers is helping in this direction. In the case of direct access to the internet through WiFi, the device can talk directly with the server using real-time protocols, with minimal intervention from the user.

Finally, mobile data networks such as 4G can provide a very wide geographical coverage with few signal-loss spots and high bandwidth. The disadvantage of such a solution is the need for an ad-hoc subscription to a mobile carrier with, still, a high cost per data unit, and possible data "caps". Hence, while technologically mobile carrier networks have reached a maturity point where raw, real-time signal transmissions are possible, the issue of cost may be problematic.

Different technologies have different data volume throughput. If a target application is defined, the type of wireless link can be selected to accommodate the necessary data rate. On one end, very low data rates are needed when the bulk of the processing is done on the acquisition equipment, i.e. hearth rate calculation, and thus only a few data points must be transmitted. On the other end, cases such as real-time raw biopotential signal transmissions from high-density arrays represent the largest challenge demanding a very high data rate.

Even when sending the "raw" signal through a wireless link, there are options to decrease the necessary data rate and therefore reduce power consumption. Biopotential signals have particularities that allow implementing compression algorithms that reduce the size of data to be relayed. There are two main types of compression: lossy and lossless (Naït-Ali and Cavaro-Ménard 2010). Lossy compression does not retain the full original data, instead, it relies on signal characteristics, usually tailored to each type of biopotential signal, to avoid sending redundant information at the cost of losing some level of detail or effectively reducing the signal-to-noise ratio, with different methods suited for preserving key characteristics (Němcová et al. 2018). Because of the characteristics of biomedical signals, lossy schemes generally achieve very good compression ratios (CR, the quotient of the original signal size to its compressed size). A lot of these methods are based on achieving a sparse representation in one domain such as time, frequency, or time–frequency. On the other hand, lossless compression achieves significantly lower CRs between 2 and 3.5 for EEG and ECG, and between 1.45 and 4 for EMG (Guerrero and Spinelli 2017b).

When biopotentials are measured with the full DC-coupled dynamic range including electrode offset, it is immediately noticeable that a lot of this DR is wasted most of the time. However, during critical segments containing artifacts, these systems have the ability to preserve signal integrity. Hence, the price of preserving integrity during some moments comes with a heavy disadvantage of large data samples. Lossless compression or encoding algorithms are a good way of preserving all information while minimizing data rate. Channel capacity must be guaranteed, but importantly, power can be saved when the signal is "quieter" (Hussein et al. 2017; Guerrero and Spinelli 2017b).

The question of amplifier power consumption becomes relative because the transmission hardware may consume an order of magnitude more than the acquisition portion of the system. Currently, single-supply low-noise operational amplifiers with consumption in the order of tens of μA are available, although the chips with the best noise performance still tend to be in the 100 μA–1 mA range. The acquisition and even low-grade processing stages can achieve very low power-consumption figures such that energy harvesting becomes an available power source for continuous monitoring, but not if data transmission is included (Richards et al. 2020). A higher data volume in these devices also increases power consumption because more transmission bursts are needed, or a higher data rate must be selected (Ayoub and Eltawil 2020). Integrated systems have made great leaps forward in terms of low consumption, especially for high channel count arrays where power-per-channel becomes critical, and for implantable or in-vivo measurements where power dissipation must be minimal to avoid tissue heating.

4 Challenges to Biopotential Acquisition Circuits

The transition to wearable devices impacts several aspects of the biopotential acquisition system. They must leave offices to operate in a non-conditioned environment, in aggressive interference conditions, placed on moving subjects, and under power consumption restrictions.

4.1 Electromagnetic Interference

The main design requirements for biopotential acquisition systems originate from power-line interference. A typical model is depicted in Fig. 7. The main power-line interference mechanism is the electric field that can interact with the patient leads through capacitive coupling and originate a common-mode voltage v_{CM}. This voltage is produced by the current i_{ISO} flowing through the isolation impedance imposed by C_{ISO} and causing a potential difference between the measurement system ground and the body when it finds a path through the "third electrode" impedance Z_{E3}:

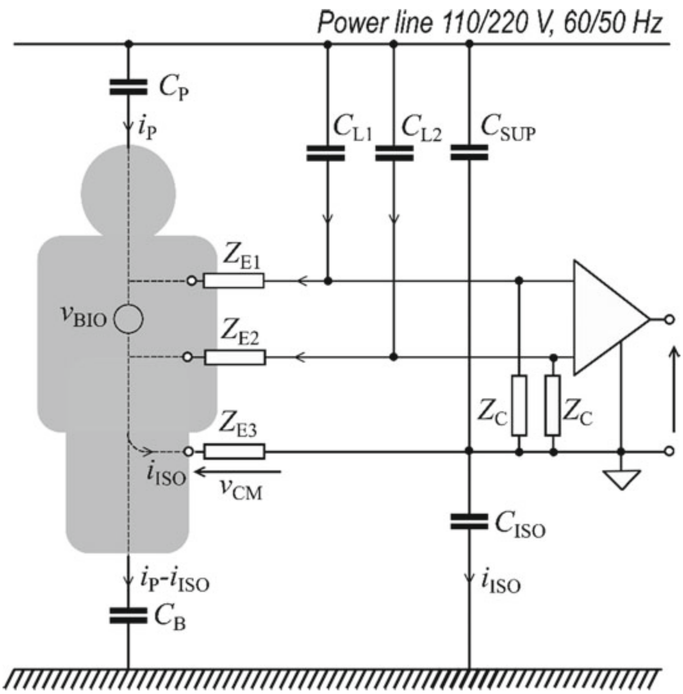

Fig. 7 Power-line interference model for conventional "office" biopotential acquisition systems

$$v_{CM} = i_{ISO} Z_{E3}, \tag{4}$$

The current i_{ISO} can be approximated by:

$$i_{ISO} \approx V_{PL} \omega_{PL} \frac{C_P}{C_B} C_{ISO}, \tag{5}$$

and v_{CM} results:

$$v_{CM} = V_{PL} \omega_{PL} \frac{C_P}{C_B} C_{ISO} Z_{E3}, \tag{6}$$

where Z_{E3} is the impedance of the ground electrode. Due to imbalances between the electrode impedances Z_{E1}, Z_{E2}, part of the common-mode voltage v_{CM} is transformed into a differential mode voltage $v_{iD.EMI}$ that will be amplified as biopotentials are. This mode-transformation because of the *potential divider effect* (Huhta and Webster 1973) is given by:

$$v_{iD.EMI} = v_{CM} \frac{Z_{E1} - Z_{E2}}{Z_C} \tag{7}$$

Capacitive couplings to the patient's leads are not a problem for wearable devices, because the amplifier can be placed close to the patient's body. Also, being battery powered, the coupling capacitance C indicated in Fig. 7 between the ground plane and the power line is negligible. Moreover, wearable devices are small-sized and their isolation capacitances C_{ISO} are very low, typically less than 1 pF (Haberman et al. 2011), and as (6) predicts, reduced common-mode voltages v_{CM} result. Figure 8 shows an interference model for wearable devices, where no couplings from the power line to the patient cables nor to the amplifier ground plane appear, simplifying the analysis for these cases.

4.2 High Common-Mode Impedance

The characteristics presented in Sect. 1 seem to introduce a good outlook for portable devices and EMI but, to be easy to install and remove and remain usable with little professional assistance, they may use dry, textile, or capacitive electrodes or persist during operation with degraded electrodes, which present high impedances Z_{E1}, Z_{E2}, Z_{E3} and also significant imbalances between them.

Therefore, biopotential acquisition using wearable devices implies dealing with high, variable, and unpredictable electrode impedances. This, in turn, demands high common-mode input impedances Z_C to reduce interference voltages according to (7), and a large input voltage range to tolerate high-amplitude motion artifacts.

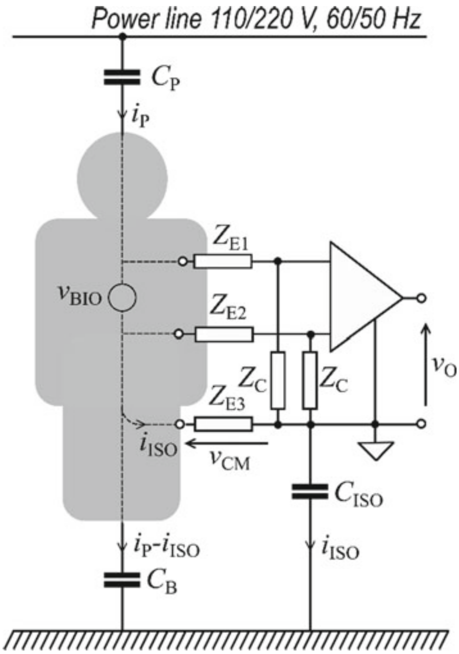

Fig. 8 Power-line interference model for wearable devices

A simple way to achieve high common-mode impedances is by using *active electrodes,* which means including amplifiers in the electrode itself (Hagemann et al. 1985; Nonclercq and Mathys 2004). The maximum Z_C value this technique allows achieving is limited by the OA input capacitance C, which can be a few pF leading to Z_C values around 1 GOhms @50 Hz. This is suitable for dry electrodes, but it is not high enough for capacitive electrodes that demands ultra-high Z_C impedances (Habibzadeh et al. 2020). There are two techniques to increase Z_C above the limit C imposes: compensate the current that flows through C by neutralization circuits (Amatniek 1958; Spinelli and Haberman 2010), or directly eliminate this current by power-supply bootstrapping (Guerrero and Spinelli 2018).

4.3 Motion Artifacts

Biopotential acquisition systems must deal with high amplitude artifacts. These undesired signals arise in the electrode–skin interface when it changes because of motion, pressure, and even dermal and amplifier features. Dry and capacitive electrodes, appropriate and usual for wearable devices, present high electrode–skin impedances and are very susceptible to artifacts (Spinelli and Haberman 2010).

Capacitive electrodes present low-frequency artifacts due to amplifier input bias currents and slow movement such as breathing. In addition, shocks and any change in pressure on the electrodes produce significant artifacts. Figure 9 shows a record obtained by capacitive electrodes (lower trace) and simultaneously by disposable pre-gelled electrodes (upper trace). During the first 15 s, the patient was resting, then they were in apnea until second 12, and breathing normally until around the 20-s mark when soft knocks were applied to the electrodes. As can be seen, wet electrodes present low DC offset voltages and are robust against motion artifacts, but this is not the case with capacitive electrodes. They present high dc potentials, low-frequency drifts and are highly affected by movements and shocks (Spinelli et al. 2012).

Low-frequency artifacts and DC offsets can be removed by ac-coupling, but the cut-off frequency f_C must be carefully set to avoid jeopardizing biomedical signal information. For instance, ECG signals require f_C values lower than 0.05 Hz to fulfill the frequency and transient responses the IEC/AAMI standards impose under some conditions. Figure 10 shows the results of ac-coupling with $f_C = 0.05$ Hz on the signals recorded by wet electrodes (lower trace) and by capacitive ones (3 upmost traces). Note that, in the case of wet electrodes artifacts were almost completely removed, but they persisted for the capacitive electrode record. The effect of the artifacts is reduced by increasing f_C to 1 Hz (trace starting near 1 mV offset) and to 3 Hz (trace starting at 4 mV offset), but the resulting ECG signal loses diagnostic capabilities. It can be used for example for heart-rate measurements, but not to detect ischemia events.

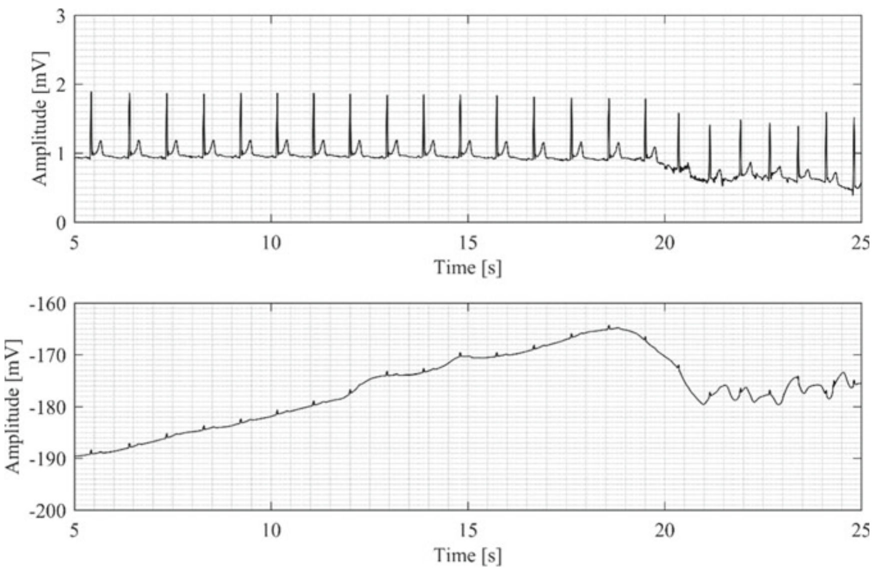

Fig. 9 ECG records. The upper trace was obtained using standard disposable electrodes and the lower trace using capacitive electrodes

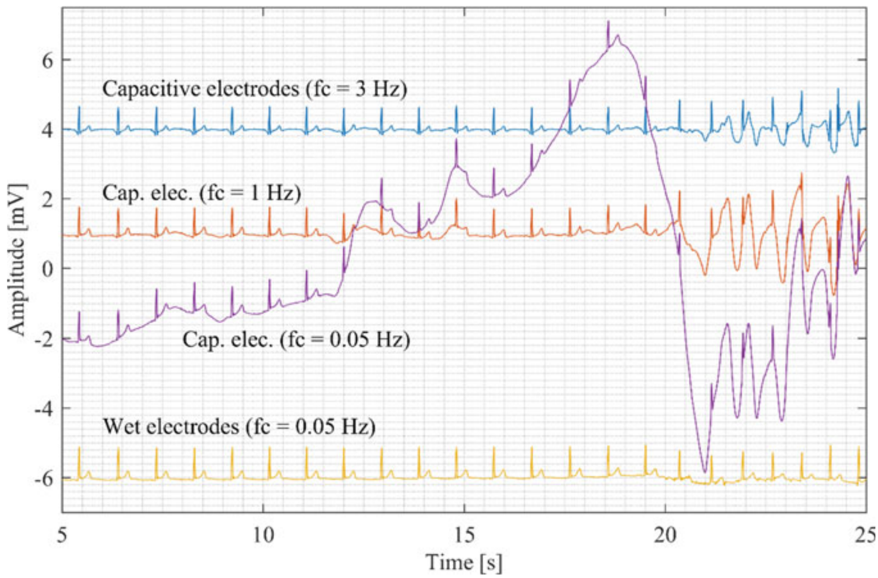

Fig. 10 ECG records acquired using wet electrodes (lower trace) and capacitive electrodes with high-pass filters of different cutoff frequencies applied. Traces were intentionally DC shifted for ease of viewing and identification

As stated, artifacts can be reduced by filtering. This can be done by using analog circuits or by digital processing. In the latter case, the biopotential acquisition system must have an input range large enough to avoid saturation, typically hundreds of mV, with resolutions of μV and even better. This means a Dynamic Range of around 100 dB, which is very high, but also possible with the current available Sigma-Delta ADCs such as present in the ADS1299 IC from Texas Instruments. Digital signal processing provides great flexibility, allowing to easily change the device frequency response. Then, the same front-end can be used for ECG, EMG, or EEG signals, with wet, dry, or capacitive electrodes, just making simple software adjustments.

Movement artifacts are not a serious issue for EMG signals, because they range from a few Hz to 500 Hz, thus allowing to set high cut-off frequencies f_C (typically 5–10 Hz). Figure 11 shows an EMG record picked up with dry electrodes placed on the biceps muscle using a bipolar channel, where the muscle was contracted from second 10 to second 15. The upper trace, which shows significant motion artifacts, corresponds to the signal acquired with a DC-coupled channel, whereas the lower is the result of AC coupling it with $f_C = 10$ Hz, where artifacts were substantially reduced.

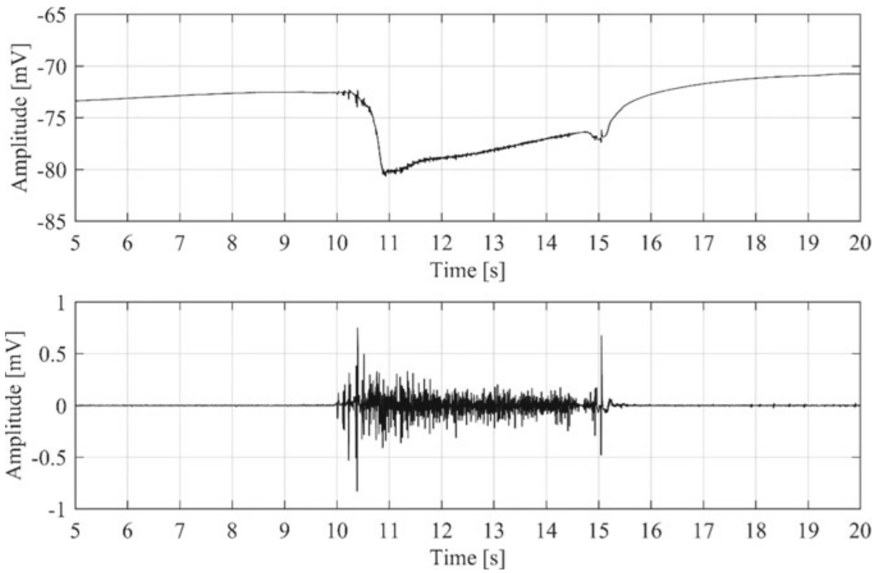

Fig. 11 EMG records measured using dry electrodes. The upper trace corresponds to a DC-coupled measurement, and the lower trace is the same signal with a 10 Hz high-pass filter applied

4.4 About Some Biopotential Amplifiers' Myths

There was (and is) a great interest in achieving biopotential amplifiers with a huge CMRR but, how much CMRR is enough? The common-mode voltage v_{CM} imposed by the power-line distribution network rarely exceeds a few mV (Haberman et al. 2011), and it is much lower in well-isolated systems as wearable devices are. It can be easily reduced by 30 dB and more using a Driven Right Leg circuit (Winter and Webster 1983; Guerrero and Spinelli 2017a), lowering the EMI level to below 0.1 mV. So, an amplifier with a CMRR of 90 dB is enough to reduce v_{CM} effects below the amplifier noise level. Higher CMRR values would not seem to provide significant power-line rejection improvements.

Another concern is the implementation of front-ends or active electrodes with high gain, with the rationale of reducing the overall noise voltage. The purpose of these circuits is to perform an impedance transformation, presenting a high impedance to the measurement electrodes and a low one to the next stage. In order to achieve a high input impedance, CMOS or JFET OAs are used, which present noise spectral densities e_n of 5–10 $\mathrm{nV}/\sqrt{\mathrm{Hz}}$, whereas the amplifier gain can be provided by a second stage implemented by bipolar OAs with e_n as low as 1 $\mathrm{nV}/\sqrt{\mathrm{Hz}}$. Hence, the overall noise is imposed by the front-end independently of its gain, and a simple unity gain buffer is a good option for impedance transformation without introducing gain mismatches.

5 Biopotential Measurement Systems Outlook

As stated in this chapter, many engineering disciplines contribute to biopotential measurement systems, and there have been transformative changes in all of them in recent times. The possibility of creating truly wearable electrophysiological monitoring devices useful in a variety of settings is a reality as demonstrated by both research and commercial equipment that exist today.

From the point of view of electronics, the high level of integration and cost reduction brought about by technology for massive consumer markets has had a great impact. Integrated systems-on-chip provide very high-quality solutions for biomedical acquisition and there is high availability of low-power, high-performance devices at a low cost. A prime example are high dynamic range analog-to-digital converters that have provided a solution to DC-coupled biopotential signal acquisition and are available as application-specific standard products. Ubiquitous wireless infrastructure such as WiFi, Bluetooth, and mobile data networks make possible the development of always-connected devices, although the power consumption of wireless transmission is still some orders of magnitude above the rest of the components of the acquisition system.

There are still technical challenges to be addressed such as optimal electrode affixation mechanisms or battery duration, and avenues that promise better devices still such as capacitive measurement. A new set of problems arise with connected wearable devices such as user-friendliness and ease of integration with existing medical digital infrastructure. However, a significant advancement that can be recollected from studies referenced in this chapter is that wearable devices are commencing their integration into mainstream medicine with successful experiences in hospitals and the consumer market, including long-sought goals such as monitoring patients during everyday life activities at their homes.

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Wearable Bioimpedance Measuring Devices

Pedro Bertemes-Filho and Kaue Felipe Morcelles

Abstract Medical wearable technologies have been growing since the last two decades with the launch of new generation diagnostic devices, due to its mobility and low cost. Electrical Bioimpedance (BIA) technique has been widely used for being considered one of such innovative technologies, contributing for lowing costs and time in the characterization of biological materials. BIA is considered an intelligence support tool in medical and biological applications, such as: detection of cancerous tissues, body composition, blood glucometer, water and bovine milk quality meter. BIA devices have promising advantages, such as simplicity, sensitivity, selectivity, low detection limit, low cost, low power consumption and miniaturization. However, in some cases, the diagnostic feature with impedance measurements requires a mathematical model to reduce possible uncertainty values, as well as an accurate hardware for working wireless at low power supply. Thus, this book chapter focus in a generic wearable bioimpedance, presenting the basic concepts, definition, main measuring circuits and the models for data analysis. It also contains a brief review of some medical wearable applications using BIA, discussing advantages and limitations of these devices.

Keywords Wearable technology · Biomedical sensors · Electrical bioimpedance · Wearable applications

1 Wearable Devices: Basic Concepts

Recent trends in modern medicine are focusing on implementing healthcare outside hospitals and clinics, providing conditions for treatment and rehabilitation to patients at home. This shift in paradigm requires continuous, remote and minimally

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invasive assessment of health parameters, combining multiple sensors and advanced communication protocols. In this context, wearable medical devices stand out, allowing intimate interactions between sensors and body while minimally interfering with the user's lifestyle. Wearable devices can be defined as systems composed of electronic circuits, sensors and actuators capable of being worn by the end-user, which can be integrated into clothing or body accessories. This chapter is focused on wearable sensors for monitoring and diagnostics, therefore wearable actuators are out of the scope. Wearable sensors collect continuous real-time data of different health parameters in a non-invasive or minimally invasive fashion, which may then be stored and accessed locally by the user or sent to a remote processing unit.

Several types of sensors can be implemented in wearable medical devices, depending on the type of measured data and application. Data can be acquired directly by sensing physical parameters of the body substrate and the surrounding environment, such as temperature, acoustic vibrations, bioimpedance, vital biosignals, light-absorption, movement and position. Regardless the sensor type, the device should be easy to wear and to operate by the user, as well as minimally interfering with daily activities. Therefore, wearable devices are usually implemented by small, light and non-invasive sensors. Common wearable sensors for healthcare are:

- *Light Sensors*: typically consists of light-emitting diodes (LEDs) combined with photodiodes, working as emitter and receiver, respectively. They are used for light absorption and scattering measurements and can be applied in photoplethysmography and glucose measurements (Pandey et al. 2017; Tamura et al. 2014). Near-Infrared (NIR) is a typical choice, but other wavelengths can be used, depending on the application. Wearable luminous sensors are designed to be light and small, but the amount of power required may limit the autonomy in some applications.
- *Electrical Sensors*: implemented using contact electrodes made of biocompatible conductive materials, or contactless magnetic/electric coupling, using coils and capacitors (respectively). It can monitor continuously body generated signals, such as ECG and EEG, or measure bioimpedance by applying electrical currents and measuring the resulting voltages (Grimnes and Martinsen 2015). Medical applications include heart-rate monitoring, hydration level measurement, breathing profile characterization and glucose tracking. There is a trade-off between contact area and electrode impedance, which limits the minimum volume of the design. Moreover, artifacts caused by motion and contact are major limitations in accuracy.
- *Temperature Sensors*: Skin temperature is an important health parameter to monitor the presence and evolution of infections, local inflammations, and to improve diagnostics in multi-sensor applications. A variety of sensors can be implemented to measure temperature, such as thermoresistors, thermistors, semiconductors, thermocouples, dilatation mechanical systems, infrared detectors and pyrometric sensors. The electrical based sensors (thermocouples,

thermoresistors, thermistors) are the most suitable for wearables, due to their reduced size and simplicity of the instrumentation.
- *Motion Sensors*: Home healthcare of elderly and people with disabilities requires continuous monitoring of movement and position, in order to monitor the level of activity and to detect and prevent falls. Both parameters are also important in sports applications, to evaluate performance physical condition of athletes. Moreover, it provides context for applications that are sensitive to motion, thus detecting and compensating motion artifacts. Typically, inertial sensors (gyroscopes and accelerometers) are implemented as motion sensors, which can directly detect angular variations and linear acceleration. Angular and linear motion parameters (i.e. acceleration, velocity and position) can be calculated by processing this type of data.

Besides sensor type, body location is an important wearable design parameter. The location of a wearable device is primarily defined by the intended application. Data may be only available, or provide better signal-to-noise ratio, at a specific location of the body (e.g. respiration measurements at the chest). If a parameter can be measured at different locations, the choice of wearable position should optimize ergonomics and convenience. For instance: heart rate can be measured at the chest, neck, legs and wrists, but the wrists provide easy access for controlling the device and reading the data in a real time basis, similar to a smart watch. Therefore, when choosing the location of a wearable one should try to optimize signal integrity, ergonomics, usability and wearability.

Despite using different types of sensors, wearable devices can be decomposed in operational blocks common to most designs. Figure 1 shows a block diagram for the generic wearable sensor system, comprising the sensor array, analog front-end, digital processing (DP) and control unit (CU), data transfer module (DTM) and power supply.

1. *Sensor array*—Comprises all sensors of the design. It can be made of multiple sensors of the same type, to obtain redundancy or spatial information of the data, or different types of sensors, to measure distinct features and provide context to the device. The sensor array is responsible for transducing the biological parameters into electrical information, either in an active or passive form. Active sensors generate voltages and currents from other physical quantities (e.g. chemical reactions, light and temperature) that can be directly sensed by the measuring system. Passive sensors modulate their own electrical properties (resistance, capacitance, inductance) according to the sensing parameter. Passive sensors cannot be read directly, as they need an electrical interrogation stage to generate a voltage or current to pass through the sensor, generating an electrical response to be read by the measuring circuit.
2. *Analog Front-end*—It is the first stage of the measuring circuit. The analog front-end is responsible for the analogue preprocessing, such as signal amplification, filtering, demodulating and digitalization. The amplifying and filtering stages should be accurately designed in order to maximize the signal-to-noise

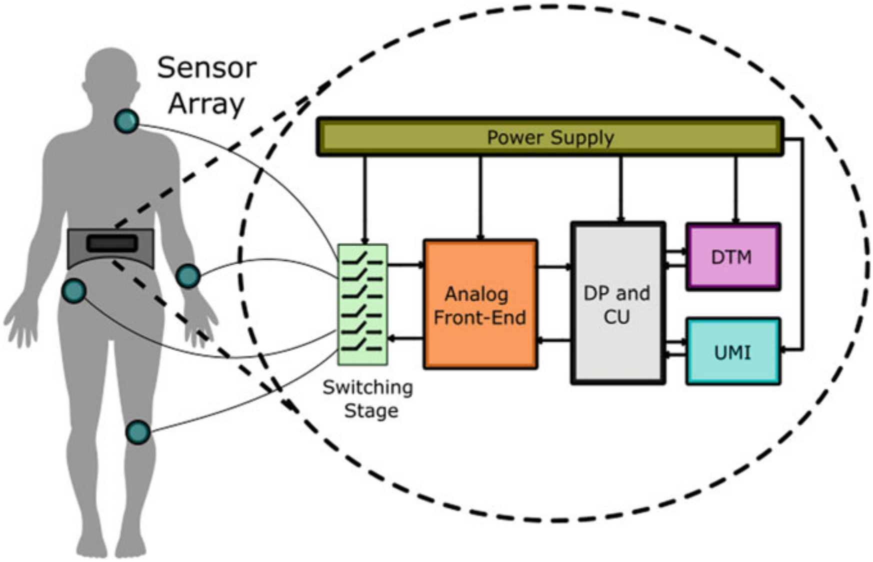

Fig. 1 Diagram for a generic wearable sensor system, showing the main stages: sensor array, analog front-end, digital processing (DP) and control unit (CU), data transfer module (DTM) and power supply

ratio (SNR) of the system and to eliminate unwanted offsets, low frequency drifts and artifacts. Demodulation is needed when the signal of interest is modulated by a carrier wave, which is often the case in bioimpedance and capacitive sensors. Finally, the digitalization stage provides anti-aliasing filtering and level shifting for the analog-to-digital converter (ADC) which, in turns, discretize and codify the signal. By using digital-to-analog converters (DAC) and current/voltage sources, the excitation circuit may also be part of this stage by either providing power for the passive sensors or interrogating the active ones. If multiple sensors are used, one can either implement an analog front-end for each different sensor or design a switching network to commutate between the sensors, which is better suited for sensors of the same type.

3. *Digital Processing and Control Unit*—After digital conversion, the signal must be processed to yield meaningful information to the user. This task is usually performed by microcontrollers, Digital Signal Processors (DSP) or Field-Programmable Gate Arrays (FPGA). DSPs are microprocessors with architecture and instructions optimized for signal processing that requires fast and complex operations, such as the Discrete Fourier Transform (DFT) and digital lock-in demodulation. Generic microcontrollers are better suited for lowcost applications that demand less processing power. FPGAs, on the other hand, are the best choice when high throughput and signal parallelization are required (i.e. simultaneous processing of multiple signals). Besides digital processing, this stage is also responsible for controlling the overall measuring

circuit, which includes switching between sensors, generating excitation signal, selecting the gain and offset of amplifiers, managing the power supply, storing data to be transferred and interpreting commands at the human-computer interaction (i.e. User Interface—UI).

4. *Data Transfer Module*—Data must then be transferred from the processing unit to the User Interface (UI). Similarly, the UI must be able to communicate commands to the processing unit. This process is performed by the data transfer module, responsible for stablishing a communication network between all components of the device. The communication protocol depends of the architecture of the wearable. Simple I2C, UART and SPI protocols can be used if both wearable and UI are electrically connected, usually when the whole system is at the same location (e.g. smart watches). However, if a remote UI is used, wireless transmission is needed, using communication technologies like infrared, Bluetooth, Zigbee, Wi-Fi, and 4G. Wireless communication to a central unit allows the application of Internet of Things (IoT). IoT can be used to connect multiple wearable sensors of one patient to a network infrastructure, enabling doctors to remotely monitor multiple patients at home and hospitals to store patient data at a central server in real-time. The implementation of IoT in medical wearable devices should be designed carefully to provide a safe communication path, avoiding data corruption and malicious invasions using state of the art encryption and error-detecting techniques.
5. *User Interface* (*UI*)—This stage includes every module implemented to provide interaction between the user and wearable, including measured data display and control/configuration mechanisms. It can be divided in two different approaches: local UIs and remote UIs. Local UIs are embedded in the wearable and should be as simple as possible in order to reduce size and weight. It typically consists of an LCD display and few buttons for configuration. It should be located at a convenient part of the body, preferably wrist or arm, allowing easy access to the user. On the other hand, systems using remote UIs transfer data by a wireless link to a central unit away from the body (e.g. a personal computer or a mobile device). In this case, most of the digital processing is made in the central unit, relieving the needed amount of processing at the wearable site. Both hardware and software of an UI should be user-friendly to maintain comfort and wearability.
6. *Power Supply*—There are three main paradigms in wearable power supply: portable energy, energy harvesting and wireless power transfer. Portable energy is the most used power approach in wearables, being performed by simple batteries and voltage regulators. Although simple solutions, batteries are bulky and stiff, and may not be well suited if the application requires small and flexible sensors. Therefore, instead of relying on the stored energy, the device can harvest from the body or the environment, building up enough energy to power the wearable device. This technique is designed for small sensors that require low amount of power. Energy can be harvested from heat, pressure, radio-frequency radiation and light (Park et al. 2019). However, the availability of energy, as well as the efficiency of the harvesting process, are too low for

complex digital processing circuits working continuously over time. Therefore, this technique is limited to very simple sensors and circuits, leaving most of the processing steps to external units. Finally, wireless power transfer can charge a wearable device without direct contact, using electromagnetic coupling between antennas. It is most desirable in case the user does not have access to the device (e.g. implants), and has a great potential for system miniaturization, due to the lack of batteries (Park et al. 2019).

Bioimpedance sensors are devices capable of measuring the electrical impedance of biological tissues. The impedance of a sample is intimately related to the material constituents and its geometry. In medical applications, impedance spectroscopy (i.e. impedance measured over a wide frequency range) yields information about chemical composition, cell health, type, density and organization of the sample under study. Also, continuous impedance measurements can be used to monitor the time evolution of dynamic properties, such as blood flow, respiration and hydration level. Because bioimpedance is measured on the skin site via surface electrodes, these parameters can be assessed non-invasively, and the flexibility of electrode design allows the technique to comply with the requirements of wearable sensors. Therefore, there is an increasing trend in the literature to develop wearable bioimpedance solutions for medical applications, providing non-invasive, continuous and remote measurements of physiological data using the passive electric properties of tissues. A generic example of wearable bioimpedance applied with a smart watch is presented in Fig. 2, including an array of six dry electrodes, wireless communication and context sensors to provide extra information (like temperature, motion and humidity).

Although compatible with wearable devices, bioimpedance sensors introduce new limitations and challenges to the system design, with some of them yet to be solved. The use of electrodes generates errors caused by contact impedance which is, in turn, inversely proportional to the contact area. This generates a trade-off between measurement accuracy and sensor size, which limits the miniaturization of the wearable. Moreover, long term measurements require dry electrodes, which are known to provide high contact impedance due to the *stratum corneum* and poor compliance with the body surface. Contact impedance may be improved by surface treatment of the electrode, using rough surfaces to increase the effective contact area or using minimally invasive spikes to penetrate the layer of dead cells.

Movement artifacts can also easily degrade the signal, especially in slow dynamic measurements, such as impedance cardiography (ICG) and breathing. When the user moves, both contact and relative position of the electrodes varies, as well as the distribution of the internal tissues. Therefore, movement causes unwanted impedance changes that are often several orders of magnitude larger than the signal of interest, easily saturating the measurement. Both contact impedance and movement artifacts can be reduced by using flexible sensors and tight clothing to insure contact with the skin. This approach improves the stability of contact impedance, although not solving the dry stratum corneum issue. However, movement artifacts may still be present, due to displacement of the internal tissue. Thus,

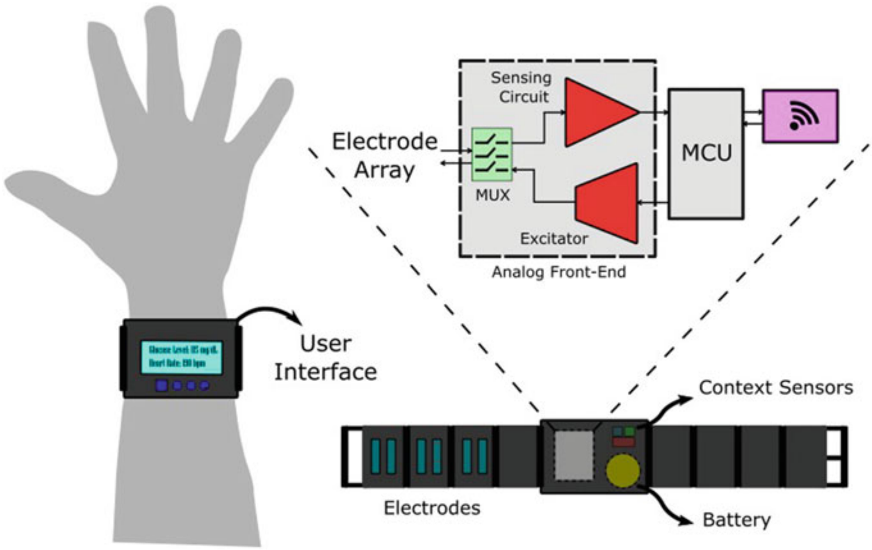

Fig. 2 Example of a bioimpedance-based smart watch. The analog front-end is composed by a sensing circuit, excitator and multiplexer (MUX). The microcontroller (MCU) reads and processes the measured data, sending information to the user interface and the wireless communication interface. Dry electrodes are placed at the interior side of the watchband and can be used to monitor body parameters such as blood flow, sweating and glucose level. Context sensors provide extra information, such as temperature, motion and humidity

motion sensors (accelerometers and gyroscopes) can be integrated to the wearable in order to detect movement (Cavalieri and Bertemes-Filho 2020). A typical approach is to only measure when the user is still, and turn-off bioimpedance when the motion sensor detects movement. Besides movement artifacts, impedance variations caused by changes in temperature, humidity and unwanted physiological processes degrades the sensor accuracy, as the bioimpedance sensor may not be able to differentiate between artifacts and the signal of interest. Context sensors (Fig. 2) are then used to measure the parameters related to the artifacts, providing context to the measurement and compensating errors during signal processing.

2 BIA Technology: Definitions and Concepts

Bioimpedance is the measure of an equivalent resistance which opposes to an electrical current flow within a biological material. It can be obtained by applying a constant amplitude alternate electrical current (I_{input}), measuring the resulting voltage (V_{meas}) and calculating the resultant impedance (Z_{calc}) of the internal biological material constituents.

Most of bioimpedance analysis use tissue samples, which are frequency dependent by presenting both resistive and reactive behavior within the spectra. Tissue can then be characterized in terms of real and imaginary parts of the impedance, so different tissue properties can be distinguished. Complex bioimpedance can be analyzed using Nyquist plots (Fig. 3). Nyquist plots are made using the imaginary (−ZI) and real (Zr) parts of impedance and can be used to identify key parameters of the tissue's frequency behavior, as well as distinctive patterns and shapes in the data. The circuit shown in Fig. 3a can be used to model a single cell behavior upon frequency, where R_{ext} represents the extracellular fluids, R_{int} represents the intracellular components and C_m the membrane equivalent capacitance. Biological tissues are composed of many different cells organized in multiple geometries, thus presenting more than one frequency dispersion. Typically, two dispersions are found in bioimpedance data, as shown in Fig. 3b. It models these dispersions at low and high frequency, where C_d and R_d represent the dispersion capacitance and resistance, respectively.

However, tissue is more less unlikely to be represented by a simple combination of resistors and capacitors since it is a non-homogenous and anisotropic material. Therefore, researches have representing its spectra by fractal polynomial functions, such as the Schwan model (Schwan and Kay 1957) shown in Eq. 1. Studies by Cole and Cole (1941) represented the anisotropy behavior by adding the alpha parameter (α), which is a constant with values from zero to 1, and it depends on tissue type. The non-linearity is modelled by a constant phase element (CPE) represent by Z_W in Fig. 4a.

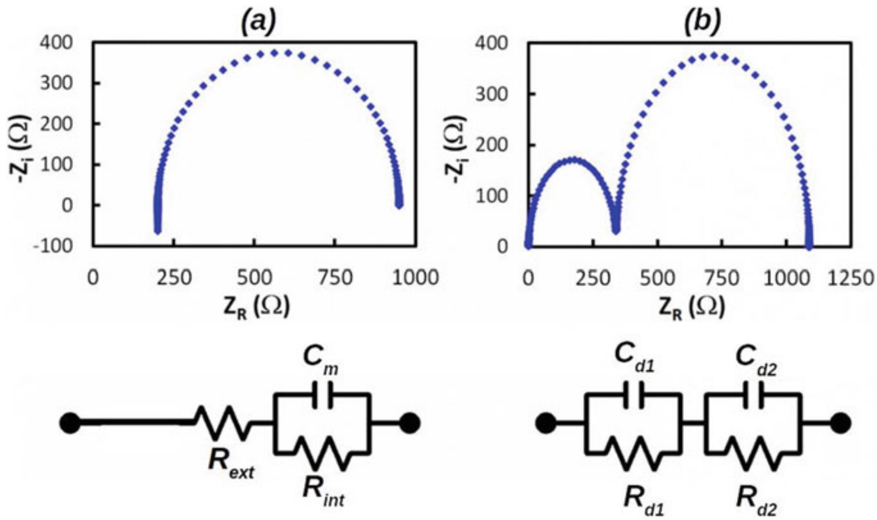

Fig. 3 Example of Nyquist plots for 2 different circuit networks

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + \left(j\frac{\omega}{\omega_c}\right)^\alpha} \tag{1}$$

where ω_c is the angular characteristic-frequency, R_0 is the resistance at zero frequency, i.e. DC, and R_∞ is the resistance at high frequency, i.e. infinity.

Tissue measurements are much more complex than this if we consider the electrode/tissue interface, which plays a great role in the data spectra at low frequencies (see Fig. 4). Interface impedance is mainly defined by the local polarization of charges at the contact region and Faraday currents caused by ion exchange via redox reactions. The choice of electrode is one of the most important issues in this research area, affecting both modulus and phase of the measured bioimpedance, depending on electrode type, size and shape. It is important to notice that the circuit in Fig. 4 can only be applied for AC analysis, as the CPE does not conduct DC currents.

Bioimpedance measurements can also be significantly affected by stray capacitances, which may cause current leakages at the injection and measurement sites. Stray capacitances can be reduced by optimizing the connections between cables and the analog circuitry. Measurements can be done by using 2, 3 and 4 electrodes. The 2-electrode technique is called bipolar, in which both current injection and measuring voltage use the same pair of electrode/cable. Figure 5 shows the main impedances and variables in a bipolar measuring technique, where the measured voltage Z_{meas} can be calculated according to Eq. 2. The impedance is calculated by V_{meas}/I_{input}, where I_{input} is assumed to be constant over the frequency range under study. However, stray capacitances to ground decreases the frequency response of the injecting current and measuring circuit.

$$Z_{meas} = \frac{V_{meas}}{I_{input}} = \frac{V_{Zel1} + V_{Zbio} + V_{Zel2}}{I_{input}} \tag{2}$$

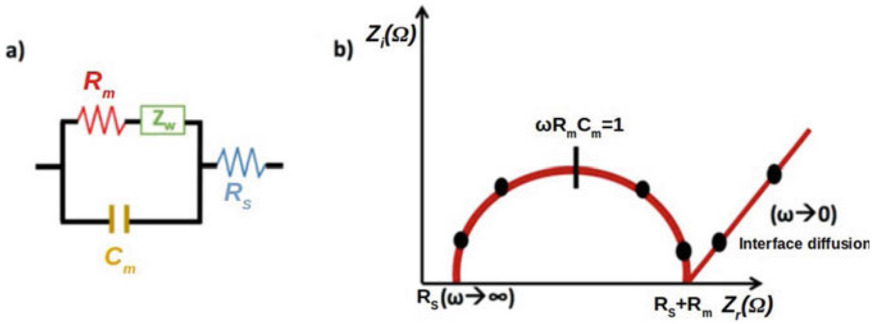

Fig. 4 **a** Equivalent circuit for a biological sample, where R_m represents the intracellular fluids, R_S represents the extracellular fluids, C_m represents the membrane capacitance and Z_W is a constant phase element; **b** Nyquist plot for a circuit biological network

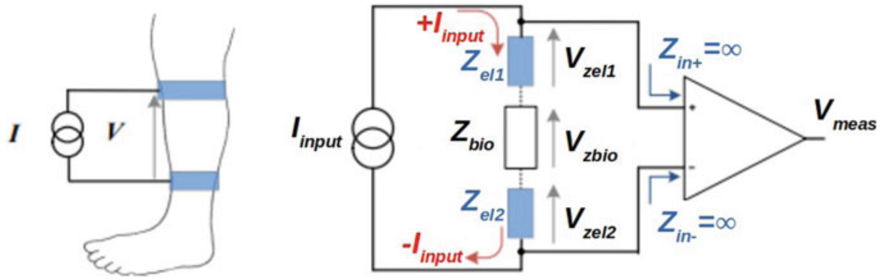

Fig. 5 Equivalent circuit of a bipolar bioimpedance technique, where I_{input} is the injecting current, Z_{el} is the electrode impedance, Z_{bio} is the biological sample, Z_{in} is the input impedance of the measuring amplifier, V_{zel} and V_{zbio} are the voltage across the electrode and biological sample, respectively

If we assume that the input impedance of the measuring amplifier is infinite, then the impedance Z_{meas} under study can be calculated according to Eq. 3. The electrode impedance is high at low frequencies and decreases as increasing frequency, therefore Z_{bio} is less affected by the electrode impedance at higher frequencies.

$$Z_{meas} = \frac{V_{meas}}{I_{input}} = 2Z_{el} + Z_{bio} \tag{3}$$

Most of bioimpedance systems use either 3 or 4 electrodes. By connecting a shunt resistor in series with the biological sample to a third electrode, which is usually connected to ground, the load current can be also measured by a non-inverting amplifier. As a result, both modulus and phase attenuations at the load current due to stray capacitances may be compensated when calculating the resulting impedance of the biological sample. Even using the 3-electrode technique, electrode polarization implies a significant side effect into the measure data, especially at lower frequencies. Besides, given that one of the electrodes is connect in series to a shunt resistor for measuring the load current, there is a loss of safety when measuring in vivo human samples according to the standard IEC 60,601-1. Furthermore, if current measurement is required, then an extra operational amplifier is necessary, as well as a second channel in the analog-to-digital converter. The most effective and accurate type of measurement in bioimpedance uses the 4-wire or 4-electrode method, which is also called by tetrapolar technique. Figure 6 shows the main impedances and variables in a tetrapolar measuring technique. If both current source and instrumentation amplifier are ideal, the impedance of the biological sample is equal to the measured transfer impedance, minimizing the effects of electrode impedance. The transfer impedance can then be converted to the impedivity or conductivity using probe factors.

Neither the current source circuit nor the measuring circuit are ideal devices, as they have a strong dependence on the open loop gain of the operational amplifiers upon frequency, as well as input parasitic impedances and other built-in

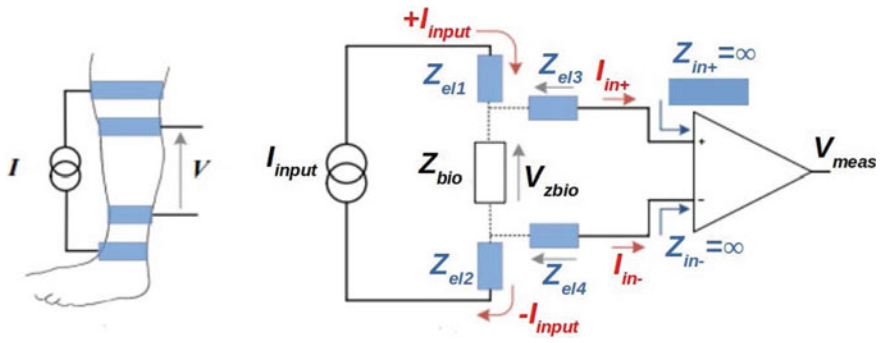

Fig. 6 Equivalent circuit of a tetrapolar bioimpedance technique (modified from Serres 2012), where $\pm I_{input}$ is the injecting current at both side of the current source and $\pm I_{in}$ is the bias current at the both inputs of the instrumentation amplifier

non-idealities. Also, cables and connections introduce significant parasitic impedances to the measurement. The shorter the cables the better, especially at higher frequencies. The use of triaxial cables have been widely applied in bioimpedance systems, where guarding technique (also called active shielding) can be easily implemented. The guarding is used to reduce parasitic leakage currents by isolating a sensitive amplifier input from large voltage gradients across the printed circuit board, which is done by feeding the measured voltage at the electrode to the internal shield of the cable, as shown in Fig. 7.

Besides cables, instrumentation amplifiers and current sources, other electronic blocks are required for bioimpedance measurements. A basic example of such a system is shown in Fig. 8. A control unit is required for changing the amplitude of the voltage being generated, sweeping the frequency and activating the analogue-to-digital converter.

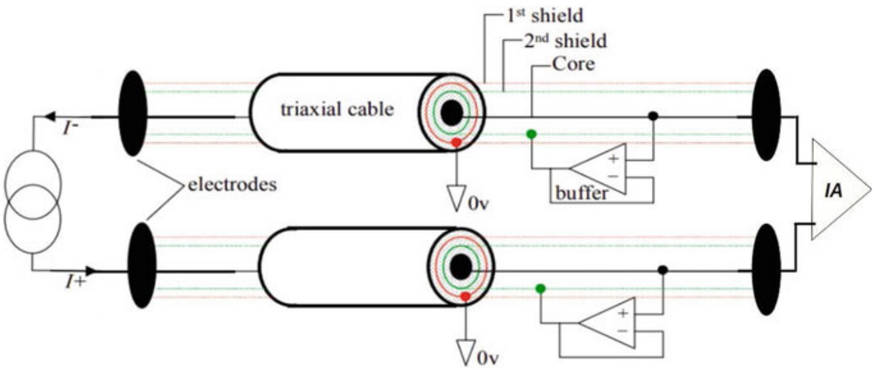

Fig. 7 The application of active electrode technique by using triaxial cables and buffers (Cortesy from Bertemes-Filho 2002)

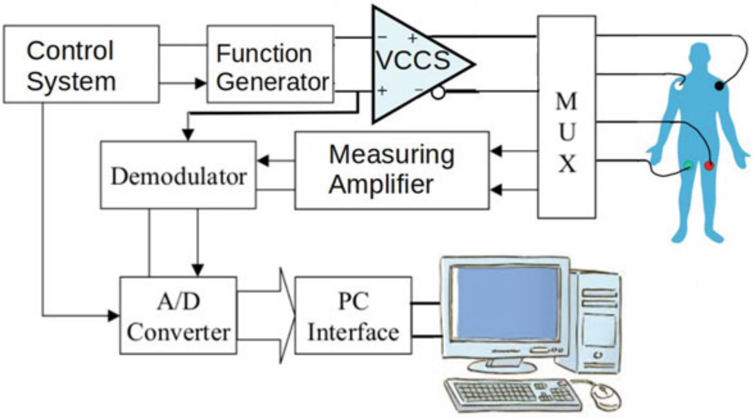

Fig. 8 Basic block diagram for a BIA system, where VCCS is the voltage controlled current source and MUX is the analogue multiplexer

The function generator can be either an analogue or digital one, which depends mainly on the frequency range and type of the signal. Analogue function generation can be easily implemented using oscillators, which uses passive and active elements, such as the Wien Bridge, Phase-Shift, Colpitts Crystal and the Square Wave and Filter oscillator. Most of BIA systems use sinusoidal waves due to its high Signal-to-Noise (SNR) ratio and straightforward digital signal processing. A pulse-based sine wave generator can be implemented to make an approximate sine wave from pulses and filters, which is then smoothen by RC or LC filtering to get a continuous sine-like shape. Integrated devices that automatically generate sine, square and triangle waves, called function generators, can also be implemented. These devices can generate a fixed output frequency defined by external capacitors and resistors, or perform frequency sweeping, such as the integrated circuits (IC) XR-2206 from Exar and MAX038 from Maxim. On the other hand, an interesting way to produce a sine wave is to do it digitally using Direct Digital Synthesis (DDS). The DDS begins with a read-only memory (ROM) that stores a series of binary values that represent values that follow the trigonometry equation for a sine wave. This is a versatile, accurate and robust technique to implement frequency sweep using sine waves.

The output of the current source (i.e., VCCS) can be single end if the load is grounded, otherwise needs to be balanced (drive and sink current) for a floating load. In vivo load should be isolated from ground to comply with the safety specifications regulated by the IEC 60,601 standards. Most BIA systems use instrumentation amplifiers to measure the differential voltage across the load, due to its high rejection rate of noise and common-mode voltages. If more than 4 electrodes are used, an analogue multiplexer (MUX) is recommended, especially for body composition and impedance tomography applications. Special care needs to be taken when multiplexing the measuring circuit, as multiplexers contain on-resistances and significantly high input capacitances, which can degrade the measured voltage, especially at higher frequencies. For applications which require either real-time or parallel operation, demodulation blocks are often necessary, providing direct extraction of the real and imaginary parts of impedance. It is the direct conversion method in which the measured single tone signal is mixed with the source waveform, at the same frequency, so that the magnitude and phase of the measured current (or voltage) can be determined after a low-pass filtering stage. A deeper description of the presented instrumentation approaches used in a BIA system can be found in the chapter book by Bertemes-Filho (2020).

After signals are properly digitalized, both magnitude and phase of the impedance under study can be recovered and further processed to extract the material properties. Modelling is a serious issue in electrical impedance spectroscopy, where the material characterization is required. Figure 4 shows a circuit example for this type of modeling, and Eq. 1 is widely used for extracting tissue properties. For instance, Eq. 1 can be used to differentiate between normal and cancerous tissues by calculating the $\log(R_0/R_\infty)$ of both. Furthermore, the phase angle PA, defined by the ratio between resistance (intracellular and extracellular resistance) and reactance (cell membrane-specific resistance), is one of the most important parameters in BIA. PA is a fundamental indicator of good or poor health, but also of good or worse health. It makes it possible to monitor the progress of a person suffering from a serious illness, to check his improvement or deterioration in his condition and to monitor the physical condition of athletes (Kumar et al. 2012). PA can be calculated according to the formula: $PA(°) = (Z_I/Z_R) \times (180°/\pi)$, where Z_I is the reactance part of the impedance whereas Z_R is the resistive one. It is known that the angular cutoff frequency ω_c will depend on the material's type, therefore it can also be used for characterization using the Nyquist plot (see Fig. 4b). Besides analytical modelling, more complex and sophisticated results can be obtained using artificial intelligence and machine learning, which automatically correlates the whole raw impedance data with the biomedical information about the tissue sample under studied. These techniques can lead to more accurate diagnosis and decision making.

3 Medical Applications

Wearable devices are usually indicated for personal healthcare applications, especially the ones requiring continuous real time monitoring of a biological parameter, such as breath, heart pulse, O_2/CO_2 level and glucose. The possibility of wearing the device promotes a more comfortable experience, better compliance with the irregular surface of the body and minimum interference with the user's lifestyle. This section presents and discuss the five applications of wearable bioimpedance devices proposed in the literature: breathing and cardiac pulse monitoring, glucose measurement, hydration level estimation and knee joint healthcare. Figure 9 shows different regions for electrode placement in these applications.

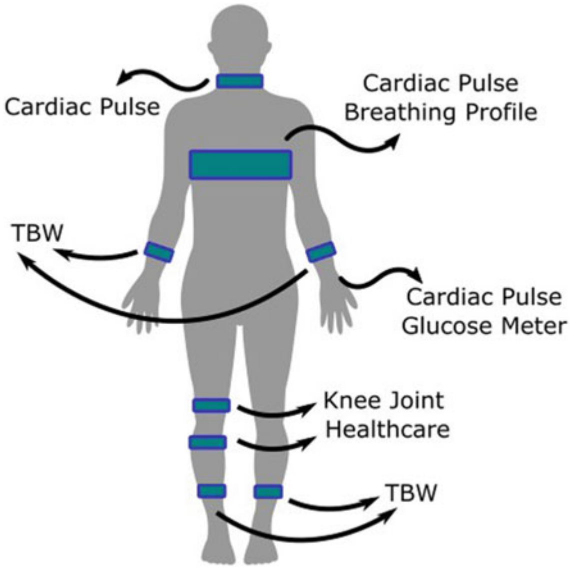

Fig. 9 Body regions for electrode positioning of different wearable bioimpedance devices found in the literature. The applications include monitoring of cardiac pulse and breathing profile, glucose measurements, total body water (TBW) estimation and knee joint healthcare

3.1 Monitoring Breathing Profile

During respiration, the lungs change the whole thoracic impedance dynamically, due to the circulation of air and displacement of tissues. Therefore, bioimpedance can be used to monitor and analyze respiration profiles. The period, amplitude and shape of the impedance wave can be correlated with lung status and activity. For instance, the literature provides evidence that the relationship between air volume and thoracic impedance is linear (Blanco-Almazan et al. 2019). Also, bioimpedance can detect if the lungs are filled with liquid, or if one of the lungs is failing during breathing (Smeets et al. 2020). The long-term monitoring of the respiratory system is of interest for home healthcare and medical rehabilitation. Wearable bioimpedance devices are convenient for continuous assessment of the thorax, due to its easy application, personalization, non-invasiveness and minimal interference during routine and therapeutic activities. These devices can be used, for instance, to monitor physical conditions of athletes during training, or to monitor elderly and homecare patient's health status in the daily basis.

The thoracic region is the best place to monitor such signals, thus bioimpedance is usually measured between electrodes located on the opposite surfaces of the chest, such as the laterals. Several wearable devices for lung monitoring are presented in the literature. Metshein and Parve (2015) proposed large and flexible capacitive electrodes for wearable bioimpedance to monitor vital signals, specifically breathing and heartbeat. The electrodes were arranged on a *t-shirt* structure, covering the whole back, shoulders and laterals of the body. Bipolar measurements were able to clearly visualize breathing rates. Blanco-Almazan et al. (2020)

proposed a wearable device based on bioimpedance and myographic signals to quantify airflow limitations in patients with Chronic Obstructive Pulmonary Disease (COPD) in real-time and non-invasively, providing an alternative to the conventional approach based on spirometry. Using a single frequency of 80 kHz, the system was able to measure the dynamic impedance of different respiratory loads in an incremental threshold inspiratory loading protocol.

Bioimpedance measurements of the thorax can also track the liquid content of lungs, as blood and water are significantly more conductive than air and solid tissue. Cuba-Gyllensten et al. (2014, 2016) designed a wearable to monitor pulmonary congestion in patients with acutely decompensated heart failure. The device implemented four textile electrodes integrated on a belt, injecting 16 frequencies between 10 and 1000 kHz. The impedance curves were fitted to a Cole model. The wearability of the device, combined with the dry textile electrodes and easy utilization, provides a personal setup that can be used at home and is able to be accessed remotely by the patient's caregiver. A similar study was conducted by Smeets et al. (2020), using the resistance at 80 kHz as a fluid correlated parameter to evaluate the congestion level. The bioimpedance was also well-correlated with fluid status. Patients that obtained an increase of the thoracic impedance at 80 kHz presented better outcomes after follow-up, which showed the potential of the technique to predict the evolution of patients after decongestion therapy. The study concluded that bioimpedance can be a promising technique to measure how effective the decongestion therapy is.

3.2 Cardiac Pulse Monitoring and Characterization

While the heart pumps bloods through the circulatory system, a periodic displacement of liquid occurs in every segment of the body. Because the blood conductivity is several times higher than most tissues, changes in the local impedance can be sensed. The analysis of the impedance wave caused by blood flow is called impedance cardiography (ICG). The sensitivity of these measurements depends on several factors, but the proximity to large vessels is the most obvious one. Thus, the measurement regions are usually the chest, waist and neck. Important cardiac parameters can be extracted from ICG, such as heart rate, hemodynamics, status of patients with heart transplants and detection of heart diseases (Marquez et al. 2013).

The location of the measured signal is important. Although the thorax presents larger impedance variations, the wrist is more convenient for wearables (Kõiv et al. 2018). Moreover, the thorax impedance change is highly dominated by breathing (Kõiv et al. 2018; Metshein and Parve 2015). Several wrist-wearable bioimpedance prototypes for blood flow monitoring were presented in the literature, in the form of electrode bracelets (Cho et al. 2009; He et al. 2016; Jivet 2014; Kõiv et al. 2018; Krivoshei et al. 2013a, b; Schneider et al. 2017). He et al. (2016) proposed the use of bipolar flexible rubber electrodes to measure the blood pumping at the wrist. The device was able to measure ICG, but, as in many other wearables, motion and contact artifacts were significant, thus measurements were stable only when the user was still. Dry and flexible electrodes were also proposed by Marquez et al. (2013), although having similar limitations.

Aortic pressure can also be sensed via bioimpedance. Krivoshei et al. (2013a, b) applied a wearable unit to measure radial blood pressure non-invasively, as an alternative to the tonometry method. The device implemented was the Circmon BT101, which is a tetrapolar ICG system integrated into a bracelet, using electrodes made of a silver compound to measure the impedance of the wrist at 125 kHz. The wrist placement allowed movement, but artifacts were largely present. Kõiv et al. (2018) proposed real-time multifrequency bioimpedance to reduce influence of contact impedance and motion. Frequencies between 1 and 200 kHz were applied via binary signal. Theoretical flexible gold electrodes, including active guard rings to avoid surface current leakage, were presented as possible solutions to further reduce errors (Kõiv et al. 2018).

3.3 Glucose Measurement

Not only blood flow can be measured via bioimpedance, but also its contents. The density of cells, proteins, carbohydrates and other substances can be correlated with the impedance magnitude and phase, especially in multifrequency applications. One of the most important substances to be monitored in the blood stream is the glucose: real time monitoring of blood glucose is essential for controlling diabetes. It is known that both blood and skin tissue changes with the level of glucose (Abdalla et al. 2010; Gao and Tang 2011; Satish et al. 2017). Commercial glucose meters collect the users blood using a small needle to pinch the tip of the finger. This assessment is invasive, not in real-time and not user-friendly. Therefore, there is a need for a reliable device capable of monitoring glucose automatically, continuously and without harming the user.

One of the main design issues is the electrode configuration. Glucose can be monitored through skin by using capacitive or direct contact electrodes, and both can be easily integrated into a wearable. Caduff et al. (2018) integrated dielectric measurement units into a wearable multisensor device capable of tracking glucose trends. Capacitive electrode arrays with different penetration depths were also proposed by Mueller et al. (2011). Different penetration depths are of interest to compensate the influence of artifacts that impact different layers of the skin, such as sweat and temperature, but motion and contact artifacts are still a major problem. The use of flexible sensors can help to stabilize the capacitance in the case of skin irregularities and motion, reducing variations in the air gap (Persad et al. 2015). Interdigital electrodes were investigated by Pockevicius et al. (2013), and also showed potential of measuring blood glucose, with errors within 10%.

Although the clear correlation between impedance and glucose, in situ bioimpedance is also influenced by several unwanted factors, such as motion, temperature, applied pressure, pH and sweating. Therefore, to improve the reliability of glucose predictions, hybrid techniques are more likely to succeed in wearable devices. Optical methods, such as Near Infrared (NIR) and Raman scattering, have also been used. NIR can detect the blood glucose level using the absorption rate at a particular wavelength but is limited in the penetration depth and glucose specificity (Haxha and Jhoja 2016; Huang et al. 2020; Pandey et al. 2017). Methods combining NIR and bioimpedance spectroscopy were proposed by some authors, collecting impedance from the wrist and NIR measurements from the fingertips or arms (Andersen et al. 2019; Guevara and González 2010; Pathirage et al. 2019; Tronstad et al. 2019; Santos 2017). Another multisensor wearable was proposed by Caduff et al. (2018). It measured dielectric and optical parameters, temperature, sweat, humidity and movement (Zanon et al. 2018). Besides multiple glucose measurements, multisensor devices can be used to measure parameters not related to glucose, such as sweat, temperature and body movement (Caduff et al. 2018). This extra information can help compensating patient dependent variations and the effects of unwanted artifacts (Huang et al. 2020).

Glucose monitoring was presented here as application for impedance measurement. However, despite of many attempts and some promising calibration with spiked media, a real glucose monitoring using impedance measurement through the skin is still lacking towards a reliable commercial device.

3.4 Hydration Level Estimation

Body water is full of free electrolytes, presenting higher conductivity than cells at low frequency. Therefore, the hydration level of the body can be monitored using bioimpedance. The measurement of the whole-body and segmental bioimpedance can provide estimations of the total body water (TBW) (Hännikäinen et al. 2007). Integrating TBW sensors in wearable devices has several biomedical applications, for instance in accessing the hydration levels of athletes during exercises, or real-time monitoring of infants and elderly people (Agcayazi et al. 2017; Dutt et al. 2020; Hännikäinen et al. 2007).

Hännikäinen et al. (2007) proposed a wearable to measure TBW in athletes, in order to avoid dehydration. The system implemented the inverse relationship between water content and the parallel resistance of the body (Grimnes and Martinsen 2015). Textile electrodes, electronic system and user interface were integrated into a sports jacket, measuring impedance between wrists and ankles. The authors were able to track impedance variation caused by water body decrease, but measurements were susceptible to movement artifacts. Segmental measurements may improve reliability (Hännikäinen et al. 2007). Leonov et al. (2019) proposed a wearable to measure water between the forearms, proving the device capability to measure real-time variation trends in hydration using the resistance level. However, care should still be taken to compensate variations due to food intake, body shape, motion, electrode position and sweating (Leonov et al. 2019).

Agcayazi et al. (2017) proposed a device to measure real time hydration monitoring in infants. The proof-of-concept implemented the AD5933 impedance analyzer with Bluetooth module for wireless communication, using bipolar electrodes at 50 kHz. The prototype was integrated into a leg wearable, placing electrodes between the anterior and posterior calf (Agcayazi et al. 2017). In adult tests, the device was able to detect hydration trends. However, it was not able to measure absolute TBW, which is already expected from bioimpedance based methods.

3.5 Knee Joint Healthcare

Acute knee injuries, particularly the ones associated with the joints, are often difficult to treat and require long rehabilitation after the incident or surgery. During treatment, and for some time after recovery, knee healthy status should be accessed to inform about injury evolution. Also, for recovered athletes, real time monitoring of the knee is important to prevent overloading. Edema is often present in acute knee injuries. Therefore, local accumulation of liquid is found around the affected region. Because the body fluids have higher conductivity than the surrounding tissue, resistance decreases. Furthermore, the capacitive reactance associated with cell mass reduces, due to the structural damage. Therefore, bioimpedance can be used to quantify the issue and monitor the evolution during rehabilitation (Hersek et al. 2016).

Hersek et al. (2016) proposed a wearable to quantify the knee joint status during injury and recovery. The device implemented tetrapolar measurements between the thigh and calf, applying currents at 50 kHz to measure changes associated with structural evolution of the injury and dynamic blood flow. Dry electrodes were integrated into knee braces. Motion artifacts were eliminated by taking the measurements in a still position. Results showed that the healthy knee presents higher resistance and lower reactance than the injured one, as expected (Hersek et al. 2016). More importantly, the difference between healthy and injured knee impedances decreased with rehabilitation, showing the potential of the technique to track the effectiveness of the treatment. To avoid errors due to posture and movement, a position detection routine was implemented using an accelerometer on the shank, which identifies if the user is in the correct position (Hersek et al. 2016).

Teague et al. (2020) proposed a multimodal wearable device for knee healthy monitoring, combining bioimpedance measurements for edema estimation with acoustic, temperature and inertial sensors, providing a full set of information about knee structure, edema and kinematics. The sensors were housed and integrated into polylactic acid (PLA) braces, fixed to the leg via Velcro straps. The inertial and temperature sensors detected the presence of motion artifacts and environmental changes, providing context to the electrical and acoustic measurements. The bioimpedance stage of the system was based on the AD5933, using a four-electrode configuration with a frequency range between 5 and 100 kHz (Teague et al. 2020). Long term use of the device was limited by the battery and the gel electrodes. Also, the structure of the device is still bulky and not user-friendly, which may reduce user compliance for domestic applications.

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Predictive Cardiovascular Engineering: Transforming Data into Future Insights on Cardiovascular Disease

Ricardo Armentano

Abstract Cardiovascular Engineering presents a wide spectrum from basic to translational research, in all aspects of cardiovascular physiology and medical treatment. This research that utilizes engineering principles and methods to advance fundamental knowledge and technological solutions related to the cardiovascular system. Coverage ranges from wearable medical devices; hemodynamics and tissue biomechanics; tissue engineering and regenerative medicine; machine learning, predictive analytics and IOT. This framework plays an important role in the research, development and management of medical technologies under a new paradigms that tend to accomplish with the "Bench to Bedside" term used to describe the process by which the results of research done in the laboratory are directly used to develop new ways to treat patients. The personalized risk estimation and cardiovascular diagnosis provided allows designing and implementing individualized strategies of prevention and treatment. The multiparametric approach improves risk estimation and vascular diagnosis since the dissimilar distribution, impact or manifestation of vascular changes associated with cardiometabolic risk and cardiovascular disease are considered.

Keywords Cardiovascular engineering · Predictive · Preventive · Bench-to-Bedside · Risk estimation

1 Introduction

After the age of 20, when the individual has completed their growth process, the elastic fibers which provide most of the elasticity to the human body (they are present throughout it) stop renewing or they do so to a limited extent. What is less

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known is that these fibers are vital for a variety of functions, such as breathing and nutrition. For this reason, the "elastic capital" available starts deteriorating, more or less rapidly, according to our lifestyle. Under this premise, current worldwide research is focused on developing solutions to study, protect, stimulate or even replace elastic fibers or the viscoelastic components in the body. As a result of this, the elastic properties of tissues and organs, involved in many pathologies, are emerging as a new and promising field of research in biology and medicine. If the skin instantaneously returns to its original shape after it is pinched, this shows youth. If it takes longer, a mature age has probably been attained. Since elastic fibers (continuously subjected to stress by many organs) do not renew in adult age, aging constitutes a risk factor, although this is not the only agent responsible for the presence of pathologies.

As Nicholo Macchiavello stated in the sixteenth century: "At first, an illness is easy to cure, but difficult to diagnose; but as time goes by and it has not been identified or treated, it becomes easy to diagnose and difficult to cure." Today, without the intervention of invasive techniques, it is possible to determine the general state of a patient's artery network and thus their vascular age. As Sydenham said in 1928: "A man is as old as his arteries". Since 2007, the European guidelines for the management of Arterial Hypertension include "arterial Pulse Wave Velocity" and "Carotid Intima-Media Thickness" (or the presence of atheromatous plaques in the carotid arteries) as markers of target organ damage to be evaluated in the hypertensive population. Additionally, there are already collagen fiber substitutes available in the market, which are generally used as "biological stents", a kind of metallic spring which is slid inside an artery in order to expand it in the event of an atheromatous occlusion.

In order to replace tissues with elastic failure in humans, the use of biomaterials is usually considered. Currently, biomimetic biomaterials, that is, those which imitate nature and are inspired by their shapes and materials, are being studied and implemented. In the specific case of the human elastin substitution by in vitro cells previously mentioned, tests are being carried out to integrate it into biomaterials so as to increase their elastic behavior. An interesting application in this area is the development of elastic biological inks for 3D printing (which are usually too rigid to be used in the biomimetic field), in which polymers imitating nose cartilage are already "being printed" in order to improve the structure of the prostheses used in rhinoplasty. In addition, progress has been made in relation to the injection of this synthetic elastic protein in zebrafish arteries. In this regard, its adequate diffusion and attachment to vascular walls has been demonstrated and its effect on the enhancement of blood vessel elasticity is trying to be characterized.

Considering that changes in the elasticity of biological tissues are often related to pathologies, their evaluation using high resolution devices helps to provide an early diagnosis. There are still many efforts to be made in order to gain a better understanding of elasticity and remediate its associated pathologies. The key lies in deeply understanding its mechanisms related to subtle physico-chemical bonds, both at the intramolecular and the inter-molecular levels. Indeed, the problem is to define which of the study scales is the most appropriate one to characterize such properties. This approach could be addressed by implementing mathematical models at different scales. Numerical modeling has been intensively developed in all the areas where it is possible to represent phenomena using differential equations, creating knowledge models. Building a model is a special process: a theoretical framework must be chosen, as well as a formalism to describe a study object, and everything should adapt to the question that is posed about that object. It also involves considering, from the very beginning, the means to validate this model: it must be possible to demonstrate that it adequately responds to the question posed. It must undergo simulation, consisting of its computational implementation through algorithms with calculation schemas, together with the use of a processing architecture adapted to the calculations to be performed, which might be associated to specific processors (such as graphics processors) or computer clusters that might be decentralized. The principle of simulation is to vary the constitutive parameters of the model in order to evaluate its evolution. The enhancement of the computing power available and the improvement of algorithms to accelerate calculation has facilitated access to this simulation-modeling cycle (Sommer 2016).

2 Modeling Arterial Biomechanics

The development of a representative model of arterial wall behavior requires, first of all, the appropriate identification of the parameters governing its functioning. In the analysis of vascular mechanical response, arterial pressure constitutes the phenomenon responsible for the excitation of the model, while the variation in arterial diameter is its associated response (Milnor 1989). The classic approach suggests using elementary components which have a dominant characteristic, so that their combined response provides an estimation of the behavior observed. The analysis of the trajectory of the arterial wall stress-deformation loop reveals the presence of purely elastic (ideal springs), purely inertial (ideal masses) and purely viscous (ideal dashpots) components. Their combined action will represent the stress exerted by the wall to oppose the stretching or mechanic demand applied to it (Milnor 1989).

Ideal springs are characterized by its elastic constant E, according to Hooke's law. This law assumes a linear relation between the stress applied (σ) and the longitudinal deformation experienced (ε). In the case of ideal dashpots, the damping constant (η) is the relation existing between σ and the rate of change of σ respect to time. The elastic components react to the magnitude of the deformation, while the viscous components react to the velocity at which such deformation occurs. As a result, the inertial components (M) react to the rate of change in velocity with respect to time in velocity. The latter are usually neglected due to its scarce contribution (Milnor 1989). The mission of the elastic component is to absorb the impacts produced by the typical pulsatility of the arterial pressure wave. The elastic component accumulates kinetic energy during systole, which will be returned during diastole if no stimulus is present. The objective of the viscous dashpot is to control the intensity in the return of such energy, protecting the elastic element from abrupt reactions which cause the wall to enter a permanent oscillation regime as it impacts against the fluid. In summary, the function of the dashpot is to dissipate part of the energy delivered by the elastic element in the form of heat (Armentano et al. 1979; Cymberknop et al. 2013).

The model adopted to represent the behavior of the arterial wall takes into account its ability to actively regulate its damping effect. The constitutive equation developed in our laboratory makes it possible to perform a mathematical biopsy of the vascular wall characterizing the individual elastic response of the elastin, collagen and smooth muscle fibers, as well as the viscous and inertial components of the wall associated to the hypertrophy and hyperplasia processes of muscle cells (Barra et al. 1993; Armentano et al. 1995, 1979). The vascular tissue behaves as a smart material, with the ability to adjust the values corresponding to the elastic and viscous components in order to optimally adapt to the various pulsatility and oscillation conditions either in the short, medium or long term (Barra et al. 1993).

2.1 Muscle Arrangements of Smart Springs-Dashpots

High frequency vibrations tend to produce mechanical injuries in every physical system. In an article which had a high impact in the biomedical and engineering fields (Armentano et al. 1979), we demonstrated that muscle cells function as an arrangement of smart springs-dashpots, having a protective effect against high frequency stretching, adjusting energy dissipation as is in fact the case with arterial hypertension, where the typical hyperpulsatility of the disease produces high vibrational energy like an earthquake would produce on civil structures such as buildings, bridges or any concrete structures.

In this article, we showed the in vitro and in vivo analysis of common human carotid arteries using adaptive modeling techniques to calculate mechanical impedance, fluency and stress relaxation. From these data, we demonstrated that smooth muscle cells act as smart springs-dashpots by dissipating high frequency components which might be eventually responsible for harmful effects causing mechanical fatigue on the arterial wall. In hypertensive patients, energy dissipation is strongly increased, protecting the arterial wall itself, but producing an extra load on ventricular ejection, which leads to the conclusion that smooth muscle cells modulate their degree of activation and the remodeling of the arterial wall, thus preventing the high frequency vibrations that damage the components of the arterial wall (Armentano et al. 2007).

2.2 Viscoelastic Mapping of the Arterial Wall and *in Silico* Models

One of the most robust points of our contribution in the characterization of the viscoelastic behavior of veins and arteries was obtained by mapping different regions of the vascular tree and evaluating vessels of different compositions and dimensions (Zócalo et al. 2006, 2007, 2008). In vitro studies measured vascular pressure and diameter in 4 different veins and in 11 different arteries using the in vitro system previously described. For a complete characterization, the viscoelastic response was modeled with an arterial pressure-diameter transfer function from which the viscous, elastic and inertial properties can be calculated heartbeat to heartbeat, along with the energy dissipated by the parietal damping as well as the damping function of each segment. A viscoelastic mapping of the regional differences of ovine blood vessels with the energy dissipation of each segment was performed. Veins and arteries show a mechanical behavior corresponding to the biomechanical function they perform for its structure, location and geometry. The arteries selected for mapping were (Valdez-Jasso et al. 2009): carotid, brachiocephalic trunk, ascending aorta, proximal, medial and distal aorta and the femoral artery. The in vitro circulation system was used to impose pressure waveforms, which were internally evaluated using solid state microtransducers inserted in each artery through a small incision. The sonomicrometry technique previously mentioned was used to obtain the waveforms of the external diameter. In this work, we demonstrated how a simple viscoelastic model such as Kevin's model can be used to simultaneously predict cross-sectional diameter and arterial pressure, describing how the viscoelastic properties are modified in space and time from the heart to the periphery. For a greater formalism, a mathematical model was developed based on the pressure and diameter measurements of the blood vessels, applying non-linear optimization techniques to compute those parameters of viscoelastic models that minimize the differences between the estimated and measured values. This work showed that the viscoelastic model captures the essential characteristics of the data significantly better than the traditional elastic model. These studies have confirmed that the elastic modulus changes along the vascular tree, being more rigid those that are further from the heart, in the proximal vessels, while the viscoelastic relaxation time remains constant or is not statistically significant throughout different measurement points of the arterial tree. In an analogous but more elegant way, the quasilinear viscoelastic theory was applied (Valdez-Jasso et al. 2011) in measurements obtained from the descending thoracic aorta and carotid arteries of ovine and human arteries. In a more elaborate step, a 1D-model was applied to mimic a dynamic network of the arterial system with 14 vessels to later integrate it into a series of 0D ex vivo temporal data to determine the dynamics of the cross-sectional pressure-area relationship in 11 male Merino sheep segments (Battista et al. 2015). The model was used concomitantly to estimate the input profile and the parameters corresponding to the resistance and total compliance of the distal network and to demonstrate the effects of incorporating wall viscosity. In one of the most recent works, viscoelasticity was described by a non-linear Kelvin-Voigt model in which the coefficients were adjusted using time series of pressure and radius measurements obtained experimentally in a sheep arterial network (Battista et al. 2015). A singular finding was that the viscoelastic relaxation time (defined by the relationship between the viscous coefficient and Young's modulus) was almost constant throughout the arterial network, giving rise to a new biological constant. Using this same scheme of a patient-specific 1D model (Casciaro et al. 2016), it was possible to evaluate pulse wave reflections when using different endovascular repair techniques for abdominal aortic aneurysm.

2.3 Cryopreservation Studies

An ideal arterial graft would be one with identical functional properties of the host artery. In this sense, surgical reconstruction of the common carotid artery is performed in various clinical situations, using expanded polytetrafluoroethylene prostheses (ePTFE) or saphenous vein (SV) grafts. The use of a fresh or cryopreserved/thawed artery appears as an interesting alternative based on the criteria previously described. One of the applications of our conceptual framework was to calculate functional properties of fresh and cryopreserved carotid and femoral arteries, and of venous and synthetic grafts (Santana et al. 2007). It was concluded that fresh and cryopreserved/thawed carotid and femoral arteries were more similar, both at viscoelastic and functional levels, than ePTFE and SV grafts.

It is well known that the characteristics of tissue donation and transplantation differ between Latin American and European countries, but the common denominator is tissue deficiency. To solve this problem, the feasibility of establishing an intercontinental network for tissue exchange was evaluated by studying the distensibility of ovine arteries divided into three groups: intact (in vivo tests, conscious animals), fresh control (in vitro tests immediately after artery removal, Uruguay), and cryografts (in vitro tests of cryopreserved-transported-thawed arteries, Spain). This work provided the transcendent result that between fresh control and cryografts there are no alterations in arterial distensibility neither due to cryopreservation nor to the intercontinental exchange network, despite the expected histological changes in cryografts. As a result, cryografts would guarantee less biomechanical mismatch (Bia et al. 2009) if they are used to replace ePTFE and SV grafts.

2.4 Endothelial Dynamics

The dynamics of the arterial system entails the analysis of its main components: arterial walls, blood flow and the interrelation between the two, which is governed by complex processes that can give rise to arterial diseases (Fischer et al. 2002; Pessana et al. 2013). One of the final objectives of this conceptual framework is to know the relationship between the elastic behavior of the wall and the shear stress of the blood in the wall caused by the endothelium. For this purpose, the arterial elastic behavior of intact and de-endothelialized sheep arterial segments (brachiocephalic trunk) was characterized and subsequently they were subjected to different levels of blood viscosity, keeping the flow levels constant. Essentially, the changes in the mean arterial diameter caused by an increase in blood viscosity were more pronounced in intact arteries than in arteries without endothelium. For the same levels of blood viscosity, the variations of the elastic modulus in relation to its baseline value, before and after removal of the endothelium, were significantly different. These results show that the elasticity of the arterial wall determined by its incremental elastic modulus is strongly influenced by blood viscosity (and by its shear stress), probably due to the presence or absence of endothelial relaxation factors or the activation of the arterial smooth muscle caused by direct shear stress on the muscle when endothelial cells were removed. The subliminal hypothesis of the article is that a healthy endothelium could protect the integrity of the ventricular-arterial coupling and, otherwise, in the presence of endothelial dysfunction, the increase in blood viscosity could imply changes in muscle tone with increased arterial stiffness, thus affecting the left ventricular function as an adaptive pressure pump (Pessana et al. 2013).

3 Applied Non-Linear Dynamics

3.1 Application of Fractional Models

Viscoelastic models are useful to better understand the mechanics of arterial walls under physiological and pathological conditions. As previously indicated, the behavior of viscoelastic materials is usually represented by simple models composed of elastic and viscous elements, which can be linear springs and dashpots. Fractional viscoelastic models make it possible to take a more elegant step in the characterization of arterial dynamics, since they can include a fractional element, also known as *spring-pot* (apocope of *spring* and *dashpot* in English). A 'fractal network' of springs and dashpots can be mapped to build similar fractional order dynamic models to address the biomechanical properties of tissues. The spring-pot element represents an intermediate behavior between a linear spring and a linear dashpot and has proven to be very efficient in the biomechanical description of rheological tissues. Two alternative fractional models were proposed (Craiem and Armentano 2007), with one and two spring-pots, applied on real data from anesthetized animals in control state and during activation of vascular smooth muscle. Only the model with two spring-pots correctly reproduces the state of muscle activation with the best approximation between model and reality. Human arterial stress relaxation was adequately described with this methodology in (Chironi et al. 2011) and its numerical model was developed in a doctoral thesis that resulted in a major scientific publication on in silico fractional models (Pérez Zerpa et al. 2015).

3.2 Complexity of the Arterial Tree: Analysis of Pressure Waveforms

The components of the fractional order models may also be related to fractal structures that could in turn be associated with complex collagen structures which are present in arterial tissues (Doehring et al. 2005). This fractal concept, strongly associated with the genesis of the arterial network, gave rise to a “holistic approach to the variations of the fractal dimension along the arterial network”, based on the complexity analysis of the arterial pressure waveform, both in health and disease conditions.

The idealization of the arterial system as a single closed conduit, with constant or variable properties along its length, has generated acceptable results in relation to low-frequency disturbances (Taylor 1965). However, in the case of high frequencies, the discrepancies are obvious. The justification for this situation lies in the fact that, although the arterial system is not a single conduit, it is made up of a set of tubular branches. Furthermore, the attenuation effect produced by the viscosity of the arterial wall on the waves that propagate through the network must also be considered. One of the most relevant aspects is the inverse relationship that exists between frequency and wavelength, since wavelengths corresponding to high frequencies will produce significant phase differences between waves from different reflection sites. For this reason, consideration of the stiffness gradient together with the distributed nature of the terminal branches significantly affects the general behavior of the arterial system (Taylor 1965).

The explicit references to the creation of vascular networks from fractal rules are profusely described in the literature (Bassingthwaighte et al. 1989), which are in line with the observations made on embryos by Taylor (1965). A fractal is a structure composed of subunits at multiple levels or scales (self-similarity), which resemble the structure of the entire object, and has a fractional dimension, thus breaking the values of the integer dimensions defined for Euclidean objects (1, 2 or 3). The fraction obtained (Fractal Dimension, FD) describes the existence of a highly detailed structure whose representation is absolutely ignored by traditional geometry. Various patterns found in nature (and particularly in biology) manifest fractal behavior. They can be observed in the arterial and venous branches, cardiopulmonary structures, bile ducts and also in physiological time series such as heart rate and blood pressure.

The effect of the arterial tree structure on the fractal behavior of blood pressure was confirmed in in vivo animal studies (Cymberknop et al. 2013). First, the fractal dimension was applied, as a non-linear measurement, in order to quantify complexity through the morphology of the waveform (or roughness) of the aortic blood pressure. Next, the stiffness of the aortic arterial wall was evaluated using the first derivative of the stress-strain relationship, while the effect of wave reflection was estimated from the augmentation index (AIX) measurements. In order to avoid reflections from distant peripheral waves, a pneumatic occluder made of silicone rubber was implanted around the descending thoracic aorta, proximal to the blood pressure and diameter transducers (piezoresistive and ultrasonic, respectively) driven externally with a cuff. Aortic stiffness was calculated by means of the purely elastic pressure-diameter relationship *P-D_elast* both in the baseline state and in the occlusion state (activation of the cuff and induction of total wave reflection). A biphasic model was adjusted, where the slope to the *P-D_elast* at low pressure levels was related to the elastin elastic response, while the slope to *P-D_elast* in the high blood pressure zone indicated the recruitment of collagen fibers. As a notable result, a significant decrease in the complexity of the aortic pressure waveform (indicated by a decrease in FD) was observed during the occlusion interval concomitant with the stiffening of the aortic wall and increased AIX. This unique situation was also found during the evaluation of the effect of arterial cross clamping (Politi et al. 2016) (a common strategy used in vascular surgery) on arterial stiffness, in humans. The rate of increase normalized to 75 beats per minute (AIx @ 75) and FD were calculated from radial blood pressure series during surgery. In aortic and iliofemoral procedures, after arterial clamping, the mean AIx @ 75 increased and FD decreased significantly following a mirror image; the opposite occurred after releasing arterial clampling. The complexity of blood pressure depends on the reflections.

3.3 Modeling Blood Pressure Using Solitons

As one of the most important objectives, especially at a formal level, the propagation of pulse pressure was studied, idealizing it as a combination of solitons (a solitary wave packet that maintains its shape while propagating at a constant speed) throughout the systemic circulation. The applicability of a compartmental model was used and validated for this purpose, in relation to the variation in the amplification of the pressure pulse associated with arterial aging (Alfonso et al. 2016). Arterial pressure waveforms were synthesized using solitons and then validated using waveforms obtained from individuals of well-differentiated age groups. Morphological changes in the arterial pressure waveform was verified as a consequence of the aging process (due to the increase in arterial stiffness) and were modeled by non-linear interaction phenomena present in the propagation of non-linear mechanical waves.

4 From the Laboratory Bench to Bedside

Our developments, taken to a non-invasive approach, allow all necessary studies to be performed -in one hour- to assess arterial health and the risk of events in patients, through the so-called tissue biomarkers, which are integrated into the **non-invasive vascular laboratory** (Santana et al. 2012b), with four main modules:

pulse wave velocity: arterial stiffness
flow-mediated vasodilation: endothelial function
intima-media thickness: arterial age-arterial remodeling
plaque characterization: personal vulnerability

This great clinical contribution that arises from cardiovascular engineering allows the detection of cardiometabolic disease before cardiac or cerebral complications and offers a unique opportunity to prevent many cardiovascular and cerebral events. Therefore, the combination of the estimation of risk factors with the early detection of cardiometabolic disease that our developments provide can help the doctor to identify those patients who need a therapy whose aggressiveness should be adapted to the level of risk. This approach, in addition to increasing the objectivity in the individualization of vascular risk, makes it possible to decide which individual needs preventive treatment or not, also allowing monitoring of the effectiveness of the treatment.

4.1 Vascular Age

In order to develop and apply strategies to improve cardiovascular risk stratification and the detection of subclinical vascular diseases, a computer tool was designed, developed and implemented to promote the diagnosis of subclinical disease, developing a centralized database to store information obtained non-invasively from anywhere. This allowed a biomathematical model to be developed integrating the values of arterial structure and function in the traditional evaluation of cardiovascular risk, to generate a detailed and comprehensive report for the specialist comparing patient data with reference data from the healthy population and to generate a similar report using a structural and functional arterial age algorithm to assess the condition of the patients' arteries (Santana et al. 2012a). The approach adopted was based on the determination of the presence of plaques in the common, internal and external carotid arteries, IMT and instantaneous diameter assessment, calculation of PWV, analysis of peripheral and central pulse waves, endothelial function (flow-mediated dilation), and the ankle-brachial index (Santana et al. 2012b). The 10-year risk of cardiovascular disease was estimated with the Framingham risk model (Valdez-Jasso et al. 2011; Chironi et al. 2011), considering age, LDL and HDL cholesterol, brachial pressure (continuous variables), sex (gender), tobacco consumption and diabetes (categorical variables). For a more systematic procedure, a linear regression model was applied to obtain an age value (calculated or theoretical) based on the non-invasive vascular markers (pulse wave velocity, IMT and AIx @ 75). Consequently, the obtained age value was used to calculate the Framingham risk to develop coronary heart disease in a period of 10 years. The consideration of the non-invasive vascular markers resulted in differences between the calculated (theoretical) and chronological age in subjects with cardiovascular disease, the former being higher. The estimated (or readjusted)

Framingham 10-year risk of cardiovascular disease (considering theoretical age) was greater than the Framingham risk score calculated before vascular assessment. Integration of vascular parameters to calculate arterial or biological age to calculate overall risk could aid in the individualization and precision of the risk (Santana et al. 2012a, b). Digital platforms for remote heart monitoring will include measurements of cardiometabolic variables, which will then be directly uploaded to the cloud in order to analyze the status of a group of patients and the evolution of their treatment (Armentano and Kun 2014) in a remote and non-invasive way.

5 Conclusions

Medical prevention aims to identify apparently healthy individuals from those who develop a disease and thus initiate preventive treatment for the latter. This identification of asymptomatic patients at risk is part of a preventive medicine which, according to what is advocated, will have to take on an ever-greater relevance in the coming years. Cardiovascular diseases are the main cause of death for both sexes in the Western world, one death every three minutes is of vascular, cardiac or cerebral origin. Regional factors, especially psychosocial ones, have contributed to an epidemic of type II diabetes as well as metabolic syndrome, which involve cardiovascular risk factors such as insulin resistance, visceral obesity, hypertension, and atherogenic dyslipidemia.

Thanks to technological advances in non-invasive exploration of human vessels, it is now possible to detect preclinical disturbances and thus select, among risk groups, people with silent alterations from those who are free from them. Those physical-mathematical models that integrate all the cardiovascular hemodynamic factors could be of considerable interest in daily clinical practice to predict the occurrence of cardiac events in greater detail than with the use of traditional risk factors. With this new approach, costs would be reduced, therapeutic management could be optimized, and results in patient follow-up and treatment could be improved. The cardiometabolic approach focused on the engineering of the arterial system, within the conceptual framework of the application of physics to life sciences in a realistic environment tending towards the domains of Integrative Physiology. This challenge fills a gap in the specialized literature that could be attributed to the fact that living organisms are highly complex dynamic systems: multi-fed, non-linear and with a certain hierarchical organization. These conditions that refer to the study of the rheological properties of living materials pose a number of specific problems, and often require a different approach from that uses the exact sciences. The relationships between measurable quantities and the parameters that describe the mechanical properties of materials are extremely complex and consequently require more or less complicated mathematical models, based on approximations that tend to become more realistic as measurement techniques become more precise. For this reason, the theoretical approach articulated with the experimental approach must be considered as a whole, a single conceptual unit. In this idea, the great advantage is in vivo studies in animal experimentation since it constitutes the closest approach to the human being to test new drugs and to improve non-orthodox therapeutic and diagnostic approaches without subjecting the patient to risky procedures.

It is through work on scientific experimentation and collaboration with interdisciplinary international groups that the author discovered the immense wealth of this unconventional research. This article is intended to position itself within a broader context, more fundamental than that of immediate application, taking into account the formal nature, contributing in its own way to answering that constantly renewed question about the particularities of the mechanisms put into service by nature to man, but that man has not yet put at its service.

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Engineering Special Medical Devices for Vulnerable Groups

M. Rocío Ortiz-Pedroza and Martha R. Ortiz-Posadas

Abstract As an example of what biomedical engineering can contribute to the solution of health problems that afflict the vulnerable populations, this chapter describes two clinical problems addressed in biomedical engineering developed at two public hospitals in Mexico City. The first project was developed at the National Institute of Perinatology, a tertiary-care hospital and, it is related to the vulnerable group of poor women with high-risk pregnancies. It is about the design and construction of a prototype of a perfusion system for cotyledon of human placenta, in order to study some drugs for the intensive care of the obstetric patient, such as antihypertensives and their possible affection to the fetus in utero. The second project is related to the vulnerable group of children in poverty, who have cleft lip and/or palate and come to the Pediatric Hospital of Tacubaya, a second-care public hospital, to be taken care of. The objective of this work was to develop a computational tool that would assist the physician in the assessment and prognosis of the rehabilitation of patients presenting with these congenital malformations.

Keywords Biomedical engineering · Clinical engineering · Vulnerable population · Perfusion of cotyledon of human placenta · Rehabilitation of cleft lip and palate

1 Introduction

Vulnerability is defined as the quality or state of being exposed to the possibility of being attacked or harmed, either physically or emotionally. Vulnerable populations are groups and communities at a higher risk for poor health as a result of the barriers they experience to social, economic, political and environmental resources, as well as limitations due to illness or disability (National Collaborating Centre for

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Determinants of Health). Among the vulnerable groups are women (violent, poor, pregnant), older adults, children and adolescents living on the street, refugees, people with HIV/AIDS, people with sexual preferences other than heterosexual, people with a mental illness or with disabilities, migrants, agricultural laborers and internally displaced persons. Additionally, health vulnerability refers to a lack of protection for specific population groups with specific health problems, as well as the disadvantages they face in solving them in comparison with other population groups. This major public health problem has multiple and diverse causes, including a shortage of trained health care personnel and the lack of family, social, economic, and institutional support in obtaining care and minimizing health risks. Health vulnerability is a dynamic condition arising from the confluence of multiple social determinants (Juárez-Ramírez et al. 2014). Vulnerable populations in healthcare include patients who are racial or ethnic minorities, children, elderly, socioeconomically disadvantaged, underinsured or those with certain medical conditions. Members of vulnerable populations often have health conditions that are exacerbated by unnecessarily inadequate healthcare (Waisel 2013). In Mexico, the population in poverty exceeds 50 million. According to the World Bank, 53% of Mexico's population is poor, living on less than $2 per day; while close to 24% is extremely poor, living on less than $1 per day. These families are "foodinsecure", meaning they cannot meet even their most basic nutritional needs for some or all of the year (The World Bank). All these people are vulnerable by definition.

Health services to the Mexican vulnerable populations must provide by the Ministry of Health. It has fourteen National Institutes of Health of different specialties, related to tertiary care and, in each Institute, there is a Department of Biomedical Engineering (DBE). On the other hand, health services in Mexico City are provided through 34 hospitals of second and third level of care and, there is a centralized network of biomedical engineering that manages medical technology in all these hospitals. The goal of a DBE is to contribute to the patient care through the development of medical technology. Design and supervise the construction and testing of special purpose equipment, when the requirements are not obtained with commercially available medical devices. Collaborate in advanced clinical studies, cost-benefit studies and clinical research that are carried out within the health institution.

The objective of this chapter is to show two contributions that biomedical engineering made in the hospital environment. We present two clinical problems approached from biomedical engineering in two public hospitals in Mexico City. The first one was developed at the National Institute of Perinatology and, it is related to the vulnerable group of poor women with high-risk pregnancies. The objective of this project was to design and construction of a prototype of a human placental cotyledon perfusion system for monitoring the effect of certain antihypertensive medications on fetal development. The second project was developed at the Tacubaya Pediatrics Hospital and, it is related to the vulnerable group of children living in poverty who have cleft lip-palate. The objective was to develop a computational tool that would assist the physician in the assessment and prognosis of the rehabilitation of these patients.

2 Project 1. A Perfusion System Prototype for Human Placental Cotyledon

2.1 Clinical Problem

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. In Latin America one quarter of maternal deaths have been associated with those complications. Pre-eclampsia (persistent diastolic blood pressure >140/90 mm Hg with substantial proteinuria >0.3 g/24 h) stands out among the hypertensive disorders for its impact on maternal and neonatal health. It is one of the leading causes of maternal and perinatal mortality and morbidity worldwide (World Health Organization 2018). In Mexico, preeclampsia is the main cause of maternal death. About 2.1 million pregnancies occur each year and about 300,000 have complications, consequently, each year 30,000 women are left with obstetric sequelae that make them disabled. However, although 85% of maternal deaths are preventable, on average, 1000 women still die annually (Jesús-García et al. 2018).

Pregnant women with pre-eclampsia receive treatment with antihypertensive drugs. The choice and route of administration of these drugs, is based primarily on the prescribing clinician's experience with that particular drug. The effects of antihypertensive drugs on the fetus are unknown. In this sense, studies of the human placental function are really useful for assess the effects on the fetus of certain drugs used during pregnancy. The use of an ex-vivo perfusion system of an isolated cotyledon is a good option for studying placental metabolism and, placental substances transfer between maternal and fetal circulations, and therefore for assess fetal exposure of different substances like obstetric drugs (Myren et al. 2007).

The Adult Intensive Care Unit in the Perinatology National Institute from Mexico provides care to obstetric patients by using some drugs for which there are no reported studies about transfer through the placenta from the maternal to the fetal circulation. These drugs are used for treating hypertension, and they lead cause of maternal death in Mexico. In order to study this metabolic phenomenon, we designed a perfusion system of an isolated cotyledon of human placenta, which recreates the internal placental conditions that allows simulating the fetal and maternal circulations. This system allows to control the main variables involved: pressure, flow, temperature and oxygenation (Sánchez-Castañeda et al. 2007, 2008).

The transfer studies of substances through the placenta will be successful, only if it is ensured that placental tissue still being functioning during all the study. Therefore, it is important that all variables involved in maternal and fetal circulations are kept in appropriate values in order to ensure the cotyledon vitality. These values depend on the characteristics of each part of the perfusion system. Pressures and flows, for example, strongly depend on diameter and length of the tubing that transports perfusion fluid to and from the cotyledon.

The goal of this study was to design and to assemble a perfusion system, as well as, to analyze if modifications in the tubing diameters have impact in pressure and flow values on maternal and fetal circulations.

2.2 Perfusion System

The design of the perfusion system considers the maternal and fetal circulations (Ruiz y García 2011). It consists of a uterine chamber with two compartments separated by placental cotyledon under study and a set of devices to simulate both circulations. In order to simulate the placenta physiological conditions there must be controlled the variables involved in both circulations: pressure, flow, volume, temperature, partial saturation of oxygen, carbon dioxide and nitrogen. The range for the values for the maternal and fetal circuits variables are shown in Table 1 (Mathiesen et al. 2010).

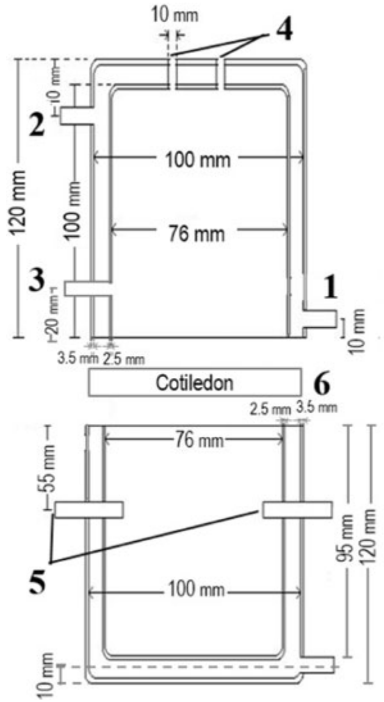
The perfusion system consists of three main parts: uterine chamber, fetal circulation and maternal circulation, described as follows.

Uterine chamber. The uterine chamber is formed by two compartments (Fig. 1a). The maternal compartment (top), (1) Bath input, (2) Bath output, (3) Maternal circulation output, (4) thermometer and catheter holes; Fetal compartment (bottom), (5) Fetal vein and fetal artery cannulas output holes; (6) Cotyledon. The uterine chamber prototype was made of glass at the glass workshop of the Universidad Autónoma Metropolitana Iztapalapa (Fig. 1b). The maternal compartment is made of two glass walls with the following characteristics: the external diameter is 10 cm, the internal diameter is 7.6 cm, the external height is 12 cm and the internal height is 10 cm. Distilled water is circulated at 40 °C between both glass walls (through input 2 and output 1 in Fig. 1a) as a mechanism for maintaining the cotyledon temperature. This is accomplished by using a bath with adjustable temperature, between 20 and 110 °C. There are two holes at the top of the maternal compartment (marked with 4 in Fig. 1a), which are used to

Table 1 Normal range for the variables involved in maternal and fetal circulation (Mathiesen et al. 2010)

Variable	Maternal circulación	Fetal circulacion
Pressure	80–140 mmHg	50–90 mmHg
Flow	9 ml/min	3 ml/min
Volumen	200 ml	100 ml
Temperature	37 °C	37 °C
pH	7.4	7.4
PO_2S*	95%	5%
PCO_2S**	5%	5%
PN_2S***	-	90%

* Partial oxygen saturation
** Partial carbon dioxide saturation
*** Partial nitrogen saturation



a) Uterine chamber design.

b) Uterine chamber prototype made of glass

Fig. 1 Uterine chamber

introduce a thermometer into the compartment and to insert a catheter to bathe the maternal part of the cotyledon with Hartmann´s solution. There is also an output (3 in Fig. 1a) localized in the internal wall of the maternal compartment, through which the Hartmann's solution leaves the compartment and goes to the rest of the system, as it will be described below.

The internal diameter of the fetal glass compartment is 7.6 cm and 9.5 cm height. The arterial and venous catheters used to cannulate the cotyledon are taken out from the fetal compartment by two side holes localized at 6.5 cm height from the base (marked with 5 in Fig. 1a). The previously cannulated cotyledon (marked with 6 in Fig. 1a) should be placed between the maternal and fetal compartments with the maternal side of the cotyledon up and the fetal side down. The maternal compartment is filled with 100 ml of Hartmann's solution.

Maternal circulation. As it is shown in the general schematic description of the entire perfusion system in Fig. 2, the maternal circulation begins with the output of the maternal compartment in the uterine chamber. This output is then attached, by using Tygon tubing, to a 250 ml Erlenmeyer flask with perforated rubber stopper, as a maternal reservoir. The flask is filled with 100 ml of Hartmann's solution as perfusion medium and it is oxygenated by direct bubbling with a gas mixture 5%

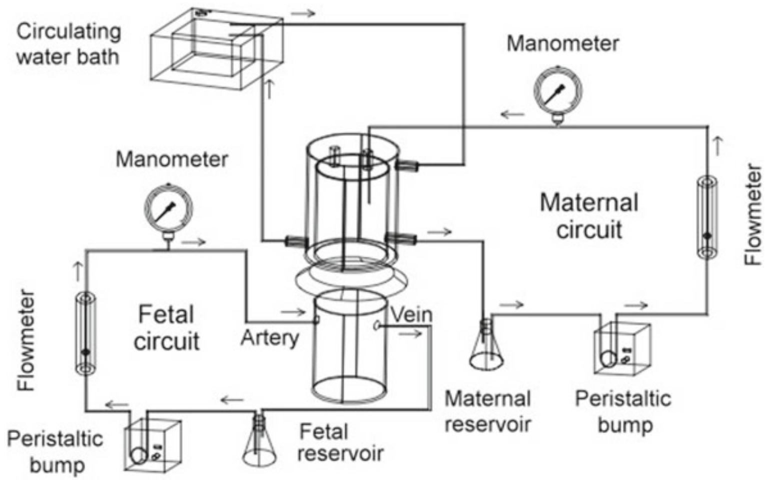


Fig. 2 Design of the perfusion system of an isolated cotyledon of human placenta (Ruiz y García 2011)

CO_2 and 95% of O_2. Circulation with Tygon tubing continues to a peristaltic pump (from 50 to 300 rpm; from 0.06 to 43 ml/min range) which controls the flow of the perfusion medium and drives it to a flowmeter (from 0.4 to 40 ml/min range). Tubing from the flowmeter is then attached, by a T-coupler, to a manometer (from 0 to 30 inHg range, 0.1 inHg resolution) which measures the perfusion pressure and to a cannula which bathe the intervillous space of the cotyledon in the uterine chamber.

Fetal circulation. The fetal circuit is very similar to that described for the maternal circulation (Fig. 2) and, the same materials characteristics and devices are used, except for the gas mixture bubbling in the fetal reservoir which is 5% CO_2, 5% O_2 and 90% N_2 and the circuit begins and finishes with the canalization of the fetal vein and the fetal artery, respectively. Canalization was made by using an 8F neonatal feeding tube AMA (Mathiesen et al. 2010) sutured to the tissue.

Placental tissue. Placental tissue consists of cotyledons obtained from the placentas of healthy women, nonsmoking and without complications during pregnancy. A peripheral cotyledon from four to six centimeters, provided with only one vein and one artery is dissected immediately after delivery. The cotyledon is separated from the rest of the placenta, leaving a margin of tissue around it to hold it between the two compartments of the uterine chamber. The following are considered as indicators of vitality of the cotyledon: glucose consumption, oxygen consumption and lactate production, to standardize the useful time of the tissue that effectively allows the transport of drugs.

The perfusion system was assembled as it is shown in Fig. 2 placing the uterine chamber at a height of 5.6 cm, maternal and fetal flowmeters at a height of 25 cm and manometers at a height of 16.5 cm from the table base that supports the entire system. For both circulations, a Krebs-Ringer-Phosphate-bicarbonate buffer solution with heparin (25 IU/ml), glucose (1 g/l) and dextran T40 (30 g/l) was used with a pH of 7.35 on the fetal side and (8.4 gr/l on the maternal side) at the same pH.

2.3 Fetal Circuit Diameter Modifications

As it was mentioned, pressure is one of the most important variables to control in the system to keep the placental tissue functional during a study of substances transfer from the maternal circulation to the fetal circulation and, the characteristics of the tubing are decisive to achieve that control. Therefore, a study was carried out to determine which of the commercially available tubing diameters allowed the pressure in the fetal circuit to be kept within acceptable limits.

Using a total tubing length of 185.5 cm for the fetal circuit and setting the fetal flow to 3 ml/min (by peristaltic pump), the fetal circuit pressure was measured by changing the diameter four times: $\phi_1 = 2$ mm, $\phi_2 = 3$ mm, $\phi_3 = 4$ mm and $\phi_4 = 5.25$ mm. Those measurements were repeated three times for each tubing diameter, so 12 pressure values were obtained for the fetal circuit (PFik), where $i = \{1, 2, 3, 4\}$ is the tubing diameter and, $k = \{1, 2, 3\}$ is the number of repetitions of the measurement for the same diameter.

The procedure for measuring the fetal circuit pressures was repeated for 3 placentas and was made as follows:

A cotyledon was placed in the uterine chamber and the entire system was assembled. The tubing diameters were modified following three different sequences (A, B and C), and fetal circuit pressure was measured for each diameter. The sequences are described below:

Sequence A. Tubing diameters changing in an ascendant way, from ϕ_1 to ϕ_4 and registering pressure values PF_{i1}.

Sequence B. Tubing diameters changing in a random way, registering pressure values PF_{i2}.

Sequence C. Tubing diameters changing in a descendant way, from ϕ_4 to ϕ_1, and registering pressure values PF_{i3}.

We change the tubing diameter by using different sequences because of three main reasons: (1) It could exist bias if we change diameter always in the same way; (2) Time could affect the cotyledon, physically or functionally (for example by losing stiffness), which could in turn alter pressure, and; (3) In order to know if there was hysteresis and for analyzing repeatability.

2.4 Results

Pressure values in fetal circuit for three cotyledons were obtained from three different placentas. The tubing diameter was changed by three different sequences: ascending (A), randomly (B) and descending (C)—named PF-A, PF-B y PF-C respectively—as shown in Table 2. Note that mean and standard deviation pressure values for placentas two and three, have a clear inverse relationship with the diameter showing that the pressure decreases when the diameter increases.

This behavior is not observed on mean pressure values for the placenta 1, where pressure seems to decrease from 69.4 to 48.2 mmHg when tubing diameters increases from 2 to 4 mm, but it increases again to 51.6 mmHg when the tubing diameter is 5.2 mm. Note that standard deviations on pressure values for placenta 1 are also the largest. It can be noticed an inverse relationship between pressure and diameter for placenta 1 when the sequence A was carried out, but not for sequences B and C. This behavior can be seen more clearly in Fig. 3, which shows the relationship between pressure and diameter on the fetal circulation for each placenta. Observe that if a linear fit with data is carried out for each placenta, there is an inversely proportional relation between diameter and pressure for placenta 2 and for placenta 3, with high R2 values (0.922 and 0.914 respectively), similar slop between them (−4.108 mmHg/mm and −4.682 mmHg/mm) and also similar intercept (74.59 mmHg and 77.06 mmHg). This inverse relationship is not present in placenta 1, where R2 is 0.289 and there is a wide dispersion of data around the fitted line.

As mentioned above, pressure values for placenta 1 were not as expected only for sequences B and C. We assume that the cotyledon of the placenta 1 may have suffered some physical damage or there were some technical problems when it was connected to the perfusion system during sequence B and sequence C.

Table 2 Pressures in fetal circuit for different sequence changes in tubes diameter

Placenta	Diameter (mm)	PF-A (mmHg)	PF-BV (mmHg)	PF-C (mmHg)	M ± ds (mmHg)
1	2	69.8	68.5	69.8	69.4 ± 0.8
	3	60.9	53.3	35.5	49.9 ± 13
	4	50.7	53.3	40.6	48.2 ± 6.7
	5.2	48.2	60.9	45.7	51.6 ± 8.2
2	2	68.5	68.5	63.4	66.8 ± 2.9
	3	63.4	60.9	60.9	61.7 ± 1.4
	4	58.3	58.3	57.1	57.9 ± 0.7
	5.2	53.3	53.3	53.3	53.3 ± 0
3	2	69.8	66	67.3	67.7 ± 1.9
	3	66	63.4	59.6	63.0 ± 3.2
	4	59.6	57.1	58.4	58.4 ± 1.3
	5.2	53.3	53.3	50.8	52.5 ± 1.4

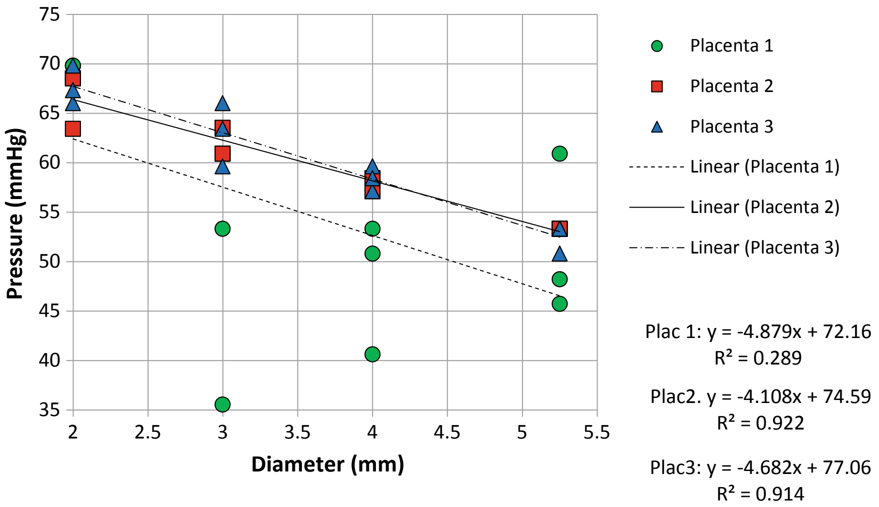


Fig. 3 Relationship between tubing diameter and fetal circuit pressure for three different placentas

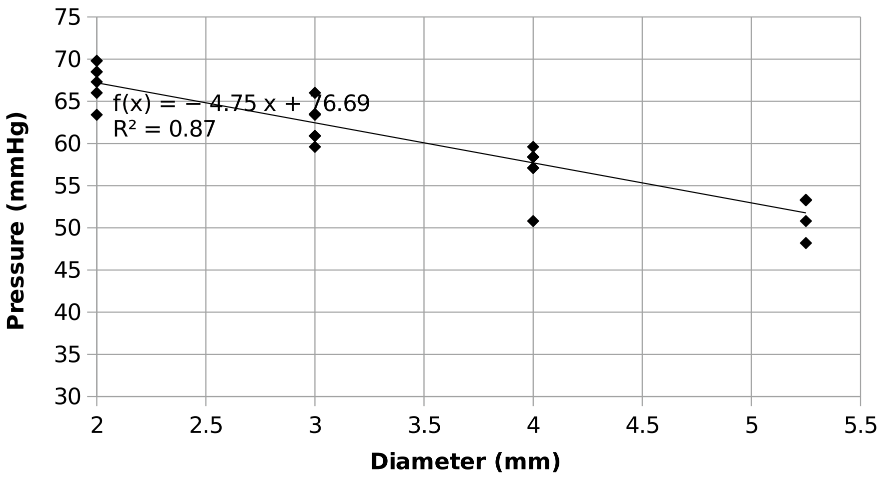


Fig. 4 Relationship between tubing diameter and fetal circuit pressure for all cotyledons

Data were plotted again without considering the values related with sequences B and C of the placenta 1, and a linear fit of these data were obtained (Fig. 4). It can be observed an inverse relationship between diameter and pressure, where R2 is 0.865, slope is −4.747 mmHg/mm and intercept is 76.69 mmHg. It is noteworthy that the smallest values of pressure observed in the graph, that were obtained for

4 mm and 5.2 mm diameters belong to placenta 1 again. It can be noticed that valid diameters for getting appropriated fetal circuit pressures between 50 and 70 mmHg are 3 mm and 4 mm. For the other diameter values (2 mm and 5.2 mm) observe that even almost all pressures are into the valid range, they are at the upper and the lower borderline, respectively.

2.5 Conclusion

The use of an ex-vivo perfusion system of an isolated cotyledon, is a good option for human placental transfer and placental metabolism studies, but this is not an easy task to achieve a successful experiment, because there are many variables which can influence the control of the parameters involved in the preservation of the cotyledon and in the transport measure procedure. Mathiesen et. al. (2010) for example, reported 92% of placentas successfully cannulated; 21% placentas for which they had a transfer of O_2 and no fetal leak; and only 15% in which they could measure the test substance.

In this work we designed and assembled a perfusion system and, we analyzed with which tubing diameters a better pressure control in the fetal circulation was achieved. The reason we made this evaluation was that we consider that two of the main variables to be controlled in this kind of perfusion systems, in order to conserve the cotyledon, are the pressure and flow in the fetal circuit so, we decided to fix flow and to explore which of the commercially available tubbing diameters were the best.

As it can be observed in these preliminary results, and as might be expected, the pressure varies inversely with the diameter. This results also show that even when all diameters explored seems to be useful for having pressure in the desired range (from 50 to 70 mmHg), 2 and 3 mm tubing diameters are preferable in order to have fetal circuit pressures values further away from the pressure levels limits.

The results obtained for sequences B and C in the placenta 1, confirms the statement we mentioned above, about the vulnerability of the results depending on the characteristics of the cotyledon, the characteristics of the components in the perfusion system and, of course, on the procedures carried out during the experiment. In this last sense, we think that possible reasons of these results could be some problems at the junction between one of the cannulas into the fetal artery and vein, or any damage to the cotyledon tissue before or during the assembly to the perfusion system. The results presented here should be completed by increasing the number of experiments in order to do statistics analysis of the results.

3 Project 2. A Computational Tool for the Prognosis of the Rehabilitation of Patients with Cleft Palate

3.1 Clinical Problem

The clinical problem consists of congenital malformations in the lip and/or palate, called cleft-primary palate and/or cleft-secondary palate, respectively. Surgical complexity for cleft reconstruction will depend on fissure complexity involving lip, nose and palate. As an example of this, Fig. 5 shows two different clefts, unilateral (a) and bilateral (b), before and after the surgery. Cleft lip and palate (CLP) are the more prevalent congenital craniofacial anomaly worldwide, affecting between 0.7 and 1.5/1000 newly live births. The prevalence of CLP in Mexico has been estimated in 0.6–0.9/1000 births (Gasca-Sánchez et al. 2019). Considering the average of this interval, there are about 120 thousand patients with CLP in the Country.

In order to do an integral rehabilitation, patients with cleft lip and palate are treated by a multidisciplinary team encompassing four medical specialties: reconstructive surgery, orthodontics, speech therapy and psychology. Reconstructive surgery is performed on abnormal structures of the body caused by congenital

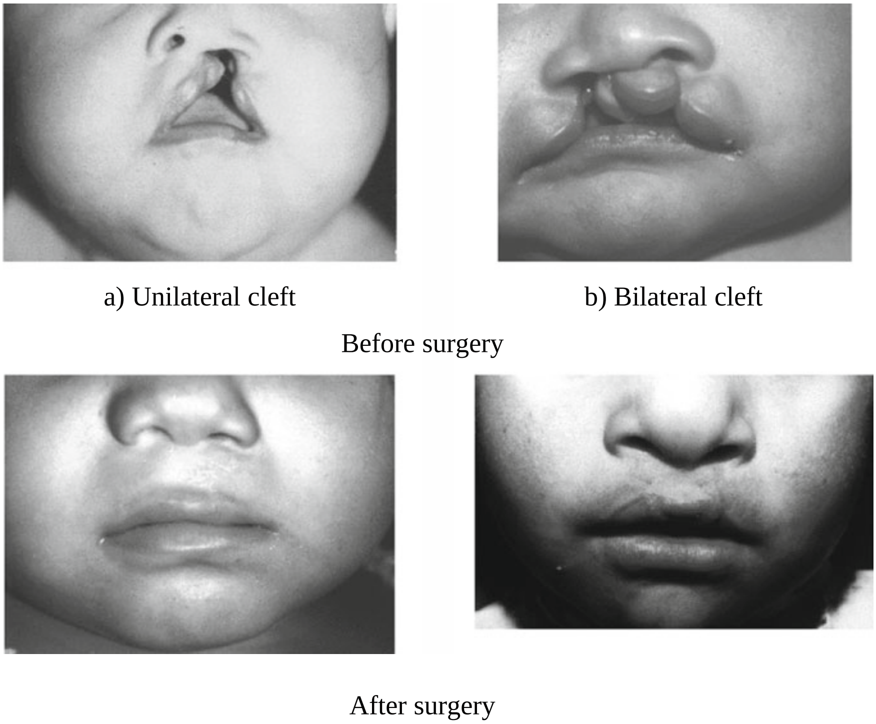


Fig. 5 Two primary cleft palates with different surgical complexities, before and after surgery

defects, developmental abnormalities, trauma, infection, tumors or disease. In facial surgeries, these can be performed to correct facial defects such as cleft lip and palate, breathing problems, or chronic infections, such as those that affect the sinuses, or even snoring. Orthodontic treatment (alignment of the teeth and their underlying supporting structures) can be used to intervene at almost any age from birth to teenage years, but the orthodontic cleft specialist must be cognizant of the burden of care for these patients. The speech and language therapists will evaluate the patient's ability to understand and use language and his speech resonance (oral and nasal tone quality). In addition, parents are often very shocked when they learn their child has a facial disfigurement. They need reassurance, support and time to assimilate the information. In this sense, the psychological care of the patient with a cleft begins at the time of diagnosis, even if this is before birth. With more involvement of specialist psychologists within cleft teams the importance of this is becoming increasingly apparent.

Cleft correction translates into a very slow and complex process because it is related to the growth and development of the patient and, it requires more than one surgical procedure. The importance of prognosis of the patient's rehabilitation, and subsequent evaluation of the surgical result, is the physician's self-feedback during all the rehabilitation process. The physician will learn if his/her work patient rehabilitation is adequate, or if it can be improved. This has a direct consequence in the future quality of life of the patient.

The objective of this work was to develop a computational tool to help the physician to assess and prognosticate the rehabilitation of patients with congenital malformations in the lip and/or palate, as well as to evaluate the rehabilitation advance of the patient. The prognosis is conceived as a supervised classification problem, using a classification algorithm of partial precedence called voting algorithm. The tool is based on a mathematical model that formalizes the clinical problem and it was tested with 95 patients attended at the Reconstructive Surgery Service of the Pediatric Hospital of Tacubaya in Mexico City. The information includes their corresponding prognosis and rehabilitation follow-ups.

3.2 Methodology for Rehabilitation Prognosis

The rehabilitation prognosis of patients with cleft lip and palate is carried out by considering the original condition of the patient and taking into account the degree of rehabilitation attained by previous patients cared for in the Hospital. Prognosis is made at the first visit of the patient to the hospital for being evaluated by the cleft lip and palate team. Prognosis is conceived as a result from a supervised classification problem, and it uses a learning matrix made from cleft descriptions from patients that already finished their rehabilitation and, a classification algorithm of partial precedence called voting algorithm (Ortiz-Posadas 2017). The learning matrix is divided into three post-surgical classes (excellent, very good and good). These classes were determined from the evaluation of the surgical result of each patient.

These classes provide the expert criterion (surgeon criterion) for evaluation (classification) of the degree of rehabilitation accomplished by the patient. Each patient is prognosticated (classified) by comparing his/her initial description with the initial descriptions of patients already included in the learning matrix. The most relevant patients for the prognosis will be those who are most similar to the patient one is about to classify. This means that the prognosis corresponds to the class that includes the patients most similar to the subject that will be classified. In this way, a patient will be predicted as very good if his/her description is most similar to patients from the learning matrix that were included in the very good class. In the same way, evaluation of rehabilitation advance is made using the patient's post-surgical description and applying the expert (surgeon) criteria which defined post-surgical classes mentioned above. The classification obtained will correspond to the patient's rehabilitation advance.

3.3 Mathematical Model

Variables. In order to describe the type of cleft it was necessary to define, in conjunction with surgeons, the variables related to the different anatomical structures affected. Eighteen variables were defined for initial description of the patient (Ortiz-Posadas et al. 2009): two for palate, nine for lip, and seven for nose. In addition, four variables were defined for post-surgical evaluation (after each surgical procedure). There was a total of 22 variables for patient's initial description and post-surgical evaluation.

Similarity function. The analogy between two clefts was formalized by the similarity function concept. This function is constructed by each comparison criterion defined for each variable x_i as:

> Let $\mathbf{C} = \{C_1, \ldots, C_n\}$ be a set of functions called *comparison criteria* for each variable $x_i \in \mathbf{X}$ such as: C_i: $M_i \times M_i \rightarrow \Delta_i$; $i = 1, \ldots n$ where M_i is the domain of the variable x_i. Depending on variable, the image of the function Δ_i can be of any nature (Boolean, k-valued, fuzzy, etc.), it is an ordered set and can be finite or infinite (Ortiz-Posadas 2017).

The characteristics of each comparison criterion (C_i) depend on the problem being modeled. However, it is important to remark that every C_i is designed individually to reflect the nature and interpretation of each variable x_i. The set **C** allows the differentiation and nonuniform treatment of the variables that describe the object (the cleft). Furthermore, it also gives the possibility to consider "absent information" in some variable values in the object descriptions. It is important to mention that all comparison criteria must be defined jointly with the experts, in order to incorporate his/her expertise. In the context of medical problems, the experts will be medical and paramedical staff (physicians, surgeons, nurses, among others) with knowledge, expertise, and the ability to provide criteria about medical problem being modeled (Ortiz-Posadas 2017). In this project, comparison criteria are of difference and of the fuzzy type, and they are represented by a comparison

Table 3 Difference comparison criteria for lip variables (Ortiz-Posadas et al. 2009)

Variable	(Mi)	Comparison criterion (Ci				
Symmetry of lip height						
Lip height normal			yes	almost	few	no
Muscular integrity	yes	yes	0	0.33	0.66	1
Skin integrity	almost	almost		0	0.33	0.66
Mucous integrity	few	few			0	0.33
Symmetry of lip thickness	no	no				0
Symmetry of filtral ridges						
Sulcus depth						
Presence of cupid arch						

matrix. Table 3 shows the comparison criterion for lip variables. It is a symmetric matrix (same values below the principal diagonal). These eight variables have the same 4-valued domain: M_i = (yes, almost, few, no). For example, the difference between two same values of these variables (yes vs. yes; almost vs. almost) is zero, because there is no difference.

C_i (yes, yes) = C_i (almost, almost) = C_i (few, few) = C_i (no, no) = 0

By the other hand, the difference between two different values of the variable, depends on the values compared: yes versus almost is 0.33; or yes versus few is 0.66.

C_i (yes, almost) = 0.33

C_i (yes, few) = 0.66

C_i (yes, no) = 1. This is the maximum difference because "yes" and "no" values are the extreme of the variable domain.

Evaluation of similarity between patient's malformation is made by the similarity function defined as:

Let $\beta : (M_i \times M_i)^2 \rightarrow \Delta$ be the *similarity function*, where Δ (as in the comparison criterion function) can be of any nature, it is an ordered set and can be finite or infinite. For I(Oi) and I(Oj) being two object descriptions in the domain $(M_1 \times \ldots \times M_n)$, the similarity function can be constructed from the comparison criteria in such away that β also can be expressed as:

$\beta(I(Oi), I(Oj)) = [(C_1(x_1(O_i), x_1(O_j)), \ldots, C_n(x_n(O_i), x_n(O_j)))]$, if C_i denotes similarity

$\beta(I(Oi), I(Oj)) = 1-[(C_1(x_1(O_i), x_1(O_j)), \ldots, C_n(x_n(O_i), x_n(O_j)))]$, if C_i denotes difference (Ortiz-Posadas 2017).

Classification algorithm. The classification algorithm of partial precedence is called voting algorithm. It is described in six steps: (1) Definition of the support sets; (2) Definition of the similarity function; (3) Determining the rule for evaluation of the similarity for one fixed support set; (4) Determining the rule for votes per class considering just one fixed support set; (5) Determining the rule for votes per class considering all the support sets in the system; and, (6) General solution rule for object classification (Ortiz-Posadas 2017).

3.4 Computational Tool Design

Once the mathematical model representing the clinical problem has been defined; we proceeded to design the computational tool. Four processes structure the tool: (a) Patient initial assessment; (b) Patient follow-up; (c) Consultations; and, (d) Administration (Ortiz-Posadas et al. 2000). These processes are described as follow.

Patient initial assessment. In this process one records the patient's data (name, age, gender, etc.) followed by recording a complete cleft description by the variables defined and, using the classification algorithm and the learning matrix a prognosis is made. The tool's output is a patient's rehabilitation prognosis and this result is store in the patient record. Figure 6 shows the three windows associated with the assessment of the cleft, lip and nose and, the rehabilitation prognosis for the registered patient according to the characteristics of his original fissure.

Patient follow-up. In this process one enters the patient's condition, after each surgical procedure and, it is compared to the prognosis result obtained in the first

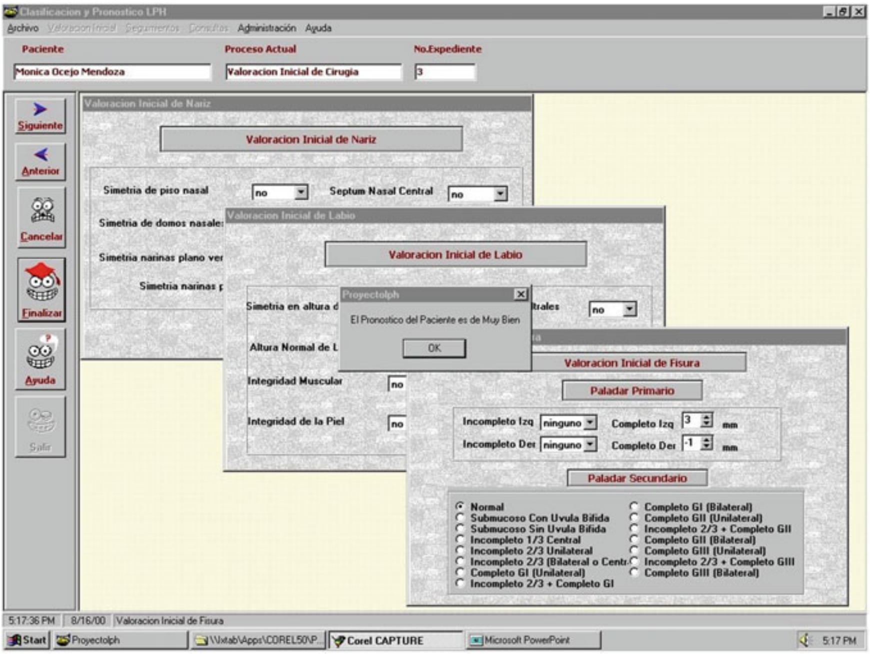


Fig. 6 System screen related to the patient rehabilitation prognosis

process (patient initial assessment). Additionally, the expert criteria are applied to learn about the patient's rehabilitation advance. The tool's output is the patient's rehabilitation advance.

Consultations (queries). Queries were designed, as a function of surgeon's information needs. For example, a useful information is the number of surgical procedures that a patient has had before; besides providing information on the surgical complexity of the fissure; it also provides information on the surgeon's abilities. In this way, one of the designed consultations was *patient versus procedures*. This query displays the patient's name and each one of the surgical procedures he/she has undergone. On the other hand, it is also important that physicians know how many times a surgical procedure of the same type has been performed. This will indicate to the physicians their experience in different surgical techniques, as well as their experience in different procedures used in reconstructing the cleft lip or palate. In this way, another possible query to do from the tool is *surgeon versus procedure*. In this case, the tool displays the name of the surgeon and the updated list of all the surgical procedures that he/she has performed.

Administration. This process is used to modify information related to physicians and patients and, includes three types of procedures: admission, discharge and modification. There are three types of information that can go through admission: (1) Medical admission, admits the name of a new surgeon not previously included in the database, entering his/her data in an active form. (2) Chart admission in the learning matrix, contains information from the learning matrix used for classification (prognosis), one can enter data from a new patient that has already finished his/her rehabilitation by retrieving the information from the database. (3) Procedure admission admits surgical procedure not considered previously in the already registered procedures. This process can also be done in an active way. The discharge procedure has two options: (1) Chart discharge from the learning matrix. In this process one eliminates the selected patient's record from the table related to the learning matrix. (2) Patient discharge from the database. In this process one eliminates every record from the requested chart from the database. In modifications on modifies fields related to the physician's name and specialty. Finally, there is also a *Help* module for providing a guide for using and managing the system.

3.5 Results

The prognosis methodology was tested with a sample of 95 patients cared for in the Hospital. Two matrices were made: learning and control. Matrices were made in a random way using a 1:2 ratio; for each patient entering the learning matrix, two were incorporated to the control matrix. The learning matrix consisted of 32 patients distributed in the following way: ten in the excellent (E) class, fourteen in the very good (VG) class, and eighth in the good (G) class. Similarly, the control matrix consisted of 63 patients: nineteen in E, 29 in VG, and fifteen in G. It is clear that the classification was made with patients from the control matrix and the results

Table 4 Classification results of the 63-patient sample (Ortiz-Posadas et al. 2000)

Class (algorithm)	E	VG	G	Total
Class (inference)				
Excellent (E)	**17**	2	0	19
Very good (VG)	0	**26**	3	29
Good (G)	0	1	**14**	15
Total	17	29	17	**63**

obtained are shown in Table 4. The diagonal highlights classification successes. Out of 19 patients in the excellent class, the algorithm correctly classified 17 and the remaining two patients were placed in the very good class. Of 29 patients located in the VG class, 26 were properly classified and three were classified as good. For patients in the good class, 14 stayed in this same class and only one was classified as very good. In general, 57 patients (90.5%) were correctly classified (Ortiz-Posadas et al. 2000).

Although the computational tool reached a good performence (90.5%), it should be noted that in the set of 63 patients not all possible fissures with their different surgical complexities are represented. In order to have a more representative sample, patients continue to be registered at the Hospital. A larger sample will allow obtaining more robust results and, where appropriate, adjusting the weights of the variables or the partial similarity functions for each structure (cleft, lip and palate), and analyzing whether it is possible to increase the classification percentage and therefore, a better performance of the tool.

3.6 Conclusion

The computational tool has been of great help for physicians at the Surgery Service. To be able to directly enter to the system the patient's general information (name, chart number, birth date, etc.) and his/her original condition in terms of cleft description, has resulted in a substantial speed increase in ambulatory consultation; since the patient's clinical chart is under better control. On the other hand, surgeons started to gather feedback on the results from their work; through consultations allowed by the computational tool. For example, knowledge on the number of surgical procedures of the same type performed by the physicians to learn how much experience they have gained or, learn about what type of surgeries need to be done for reconstructing a particular cleft, as a function of its surgical complexity, an element known from the initial description of the patient.

It is clear that the work carried out by the biomedical engineer in the hospital environment (also called clinical engineer) contributes to the care of patients in a specific way, according to the clinical problem solved. Biomedical engineering provides a more effective care of, in terms of developing health technology aimed at patients with some specific disease. In this sense, any biomedical engineering research carried out in health institutions whose medical services are aimed at the open population (population that still lacks coverage for the most essential health services) will be an invaluable effort for the benefit of Mexicans who belong to a vulnerable social group in our country.

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Serious Games and Virtual Reality for Rehabilitation and Follow up of Wheelchaired Persons

Marta R. Bez, Simone de Paula, Elias Pereira, and João B. Mossmann

Abstract This paper presents the development of a virtual reality environment for use in physical therapy with wheelchair patients for trunk control. The system was developed in order to insert several mini-games without changing the environment, and new movements and games can be incorporated. The methodology used in the development was exploratory, using Unity to build the games, C# for the back-end and the Gear-VR glasses. Professionals in computer science, physical therapy, and digital games participated in the project. The physiotherapist, at the beginning of the session can configure the movement angles according to the patient's needs for each mini-game. The environment stores variables that allow the physiotherapist-patient to follow the patient's evolution during the session, as well as over several consults. According to the physiotherapist, this type of environment can be of great help in the treatment and must be now validated in the clinic.

Keywords Physiotherapy · Rehabilitation · Virtual reality · Trunk control · Gear

1 Introduction

According to the World Health Organization, 1 billion people currently have some kind of disability. In Brazil, data from the Brazilian Institute of Geography and Statistics in the 2010 demographic census showed that approximately 24% of the population has some type of disability (IBGE 2010). The most prevalent disability

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is motor or physical disability, that occurring in 7% of the Brazilian population. Physical disabilities are define as the loss of quality of movement as consequence of a neurological, muscular and/or sensory alteration that interferes with posture and selective movements, compromising the performance of daily tasks.

In patients with physical disabilities, such as paraplegic individuals or those who have suffered a stroke, trunk control plays an important role in postural adjustments and balance reactions during Daily Living Activities (DLA). Physiotherapy is consider determinant for the functional recovery of this population. The trunk muscles allow the individual to perform the weight transfers necessary to perform functional activities against gravity, stabilizing the center of the body to perform movements in the extremities (Isho and Usuda 2016; Arienti et al. 2019).

Several therapeutic approaches have been use to optimize the balance reactions and functionality of neurological patients. This list of activities includes functional electrical stimulation, task-based training and kinesiotherapy (Vanoncini et al. 2008; Cabanas-Valdes et al. 2016; Tse et al. 2018). Due to the repetitive use of activities, the lack of motivational elements and the low patient compliance for the application of Physiotherapy protocols, the use of technology has been gaining space in the areas of assistance and research in Neurofunctional Reabitation.

In this scenario, the use of virtual games and virtual reality during Physiotherapy allows the development of a creative and motivating scenario. In this scenario, the patient can interact through kinesthetic, visual, tactile, auditive and/or sensory stimuli, producing satisfactory results, especially regarding balance (Morone et al. 2014) and the functionality of the upper limbs (Zoccolillo et al. 2015).

Deustsch et al. (2011) add that the real movements are convert, in this kind of game, to the virtual environment. Users actively practice sports, physical exercises in a playful way, and interact with the equipment, which makes them different from traditional video games, as they require physical effort and the practice of psychomotor skills during games.

Among the main advantages of these approaches are: the use of rewarding and more motivated tasks to perform the treatment, the possibility of immediate feedback during the activities, the storage of information and the great interactivity of the patient. The environment offers fun associated with rehabilitation in all age groups, especially in patients who need long-term treatment (Sveistrup 2004).

Despite favorable and recent scientific evidence, studies on the use of virtual games with patients with neuromotor dysfunctions are still limited. Moreover, currently the market does not have specific games for the stimulation of trunk control activities. In this sense, the objective of this article is to present a virtual reality environment that stimulates the balance reactions of the trunk in physical deficits through fun and playful therapeutic activities.

This chapter is thus constituted: it began with an introduction to the theme. In the sequence, the materials and methods used to develop a physiotherapy virtual reality environment is present. Structure and environment are present in the development part. As a result, the virtual environment, the mini-games and the beginning of validation are present. The conclusions are expose, with the limitations and future work.

2 Materials and Methods

This project was developed by an interdisciplinary team (Weingart 2000), formed by professionals in the areas of physiotherapy, computer science and digital games. We believe that a key to the project's success, a team where the health professional acts directly in the project. To structure the work and during the development, the team worked together so that the real needs of the physiotherapist were met. First, through meetings, the physiotherapist explained to the team of developers about trunk control, physiotherapy session and necessary movements. In addition, he highlighted the importance of a longitudinal follow up of the physiotherapy sessions, to check the evolution of the patient. Materials and methods.

The environment was design composed of several mini-games in order to keep the user entertained during the session, and not to make the environment repetitive. This was built using the engine 'Unity Engine', version 2018 (Unity), with the programming language C# (C Sharp) (Microsoft), in conjunction with the IDE (Integrated Development Environment) JetBrains Rider (Jetbrains).

The main limitation of the project was that a platform of easy access and mobility, as cables or expensive equipment would be an obstacle in the day-to-day use by the health professional. The 'Samsung Gear VR' (Sansung) was select as a platform. Another premise was that graphics and games could not demand heavy processing. Along with the optimization needed for the platform, the other challenge that the 'smartphones' provided was the lack of sensors to capture the position, rotation and movement of the device. For this, acceleration and rotation were use, averaging over the last frames, thus allowing know the movement the player made.

A structure developed to deal with the challenges of the project, detect the angle of the player without any reference of position in space and only with the sensors of the device (gyroscope and accelerometer), collect session data and maintain a flexible structure for future expansion. This way, it will be possible to complement the environment with more challenges and variations, only including new mini-games.

3 Development

From the integration among professionals, an environment was define to help wheelchair users exercise their torso and develop a better balance in the wheelchair while having fun with mini-games. The side effect of the game are the exercises defined by the physiotherapist. The player starts the experience in a scene where he must calibrate his device, and can then proceed to the main menu. The health professional can adjust relevant options to the game and start the session setup (difficulty level, angles and directions). At the end of the game, the player can choose to start again, exit or return to the main menu. At any time during the game, the option to stop, continue, restart or exit to the menu is available.

Data was collect and stored and the physiotherapist can follow the patient's results during the game sessions and afterwards. The basis of the entire environment is a manager that controls the entire navigation functionality, instructing which scene to load and maintaining control and access to class settings. During the execution, a controller is instantiated, being responsible only for it, since each one has its respective controller.

The user's central position has been set up as the zero mark for patient positioning. In this way, it is possible to compare the current inclination with the previously stored one. This allows to not only finding the direction and inclination of the player, but also set the device to a "neutral" position more comfortable for the player.

To store the data a serializable class used as data model. At each session, the game fills a class with the information of hits, errors and the player's inclination along with several other parameters and creates a '.json' file from each session. Every time a game event is generate by an object or angle detection, the data are add to be saved at the end of the game.

With the need to accommodate the environment for future expansion, the code has been structure from flexible prefabricated modules to work with various mini-games within the environment. Examples are the interface, menu, session configuration and data serialization that communicate with a class responsible for controlling the mini-game in question. It uses events to communicate data within the environment.

Figure 1 shows the diagram used for the environment. The controller and the mini-game scene are replaceable, and the system automatically takes the player to the next mini-game by replacing the controller and the game scene. The system actions presented in yellow and in white the components. Figure 2 shows the structure of the scenes. Arrows indicate access; the 'x' indicates that it is not possible to return to the previous scene.

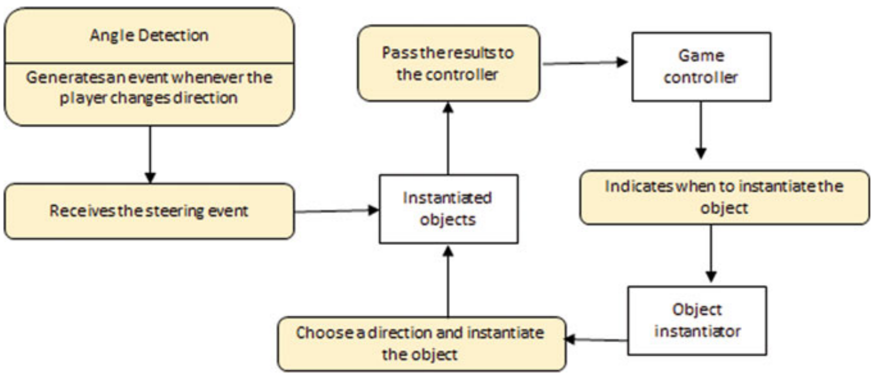

Fig. 1 Structure of the environmental development code (from the author, 2020)

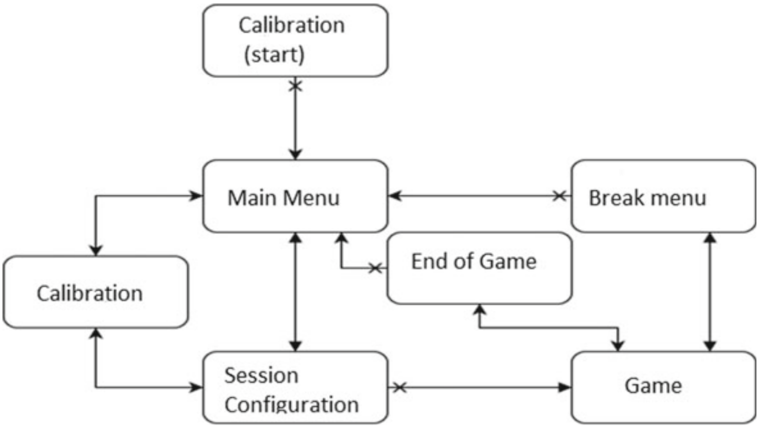

Fig. 2 Scene structure (from the author, 2020)

As the game time passes, and reached pre-defined conditions, the controller instantates the objects the player interacts with and passes parameters relevant to the difficulty to the player. The object itself checks if the player has reached the required movement, communicating the result to the controller. At the end of the mini-game, after storing the session data, the controller is destroy, allowing the manager to load another mini-game or return to the menu.

4 Results

The environment and two mini-games with the necessary information for the physiotherapist has been develop. Throughout the development, this professional accompanied validating the environment and the mini-games. To attend patients with different age groups, the scenario chosen for the game had a cartoon-like appearance. A small town, like a ‘playground’, with a ‘low-poly’ aesthetic. Nearby are a forest and a river with a waterfall. In this scenario are houses, roads and a park. The user hears the sound of the waterfall. Fragments of this scenery are presents in the Fig. 3.

The gameplay consisted of several objects appearing in front of the player with an arrow indicating the direction in which the player needs to lean. If the player can lean correctly, he gains a point and “collects” the object. If not, the object releases its place to the next one and considers that the player failed to make the correct inclination.

The system works by using a collider to detect if the player is looking at the object and detects the inclination of the device to determine if the player is leaning correctly. The objects chosen in the mini-games were a helicopter or a butterfly.

Fig. 3 Environmental scenarios (from the author, 2020)

The environment has a data and progress saving system. The following data are stored for future analysis of the health professional: Identification data (Name and age of the player), Use and session data (Date and time of the session, Duration of the session, average slope for each direction), Game data (Mini game identifier, Minimum slope angle, Time to validate the input, Level of difficulty, Mini games used in the session, Angle and direction of each input, Position of each of the objects or obstacles appeared, Quantity of hits and errors, score).

A Gear glasses and a cell phone given to a physiotherapist after the development of the environment was completed. In the cell phone, the environment installed and configured. For a good use, the physiotherapist received a three-hour training in which he used the glasses, learned how to use the environment, calibrate the options and analyze the data of each training session.

The physiotherapist is with the material and performing analysis. Two sessions of partial validation were performed, the first with a four year old child and the other with a woman over 60 (Fig. 4). The validation consisted in checking comfort and usability with people of different ages. In this test, the glasses and environment were well accepted and, more than that, the users did not want to stop the session. According to their report, it was very good to have fun and they didn't even notice that the movement performed was the same as in traditional physiotherapy sessions.

The validations were interrupt due to the Covid-19 pandemic, because as the glasses are place on the patient's face, it chosen not to run the risk of contamination due to the glasses. While waiting for effective use, another mini-game is under development, totaling three available in the environment.

As it was not possible to perform a longitudinal validation with the focus population, evidence sought in the literature about its effectiveness. Laver et al.

Fig. 4 Partial validation (of the author, 2020)

(2017), when conducting a systematic review, analyzed 72 randomized and almost randomized clinical trials on the effectiveness of VR use in stroke patients. The authors found reports of a significant favorable difference in the use of VR, both in treatment and daily activities of participants.

Aramaki et al. (2019) analyzed a rehabilitation protocol using user-centered VR (10 patients, for 12 weeks, at 40 min/day, 3 days/week). A diary was use to record the frequency and adherence of each participant and an interview was used to analyze the participants' perception of the program. They found that there was a statistically significant and clinically relevant improvement in the performance and performance satisfaction flow. The majority of participants had more than 75% consecutive attendance and there was 100% adherence to the program. In the interviews, the participants reported the post-CA difficulties; how the VR environment motivated their engagement in rehabilitation; and the improvement of occupational performance and social participation after participating in the program.

5 Conclusions

This chapter presented the development of a VR environment for use in physiotherapy, in trunk control for wheelchair users. The environment is modeled and functioning with two mini-games.

As a limitation, it was not possible to validate the use of the environment with patients due to the Covid-19 pandemic. Preliminary tests conducted with a child and an elderly woman, seeking to validate the usability and comfort of wearing the glasses and satisfaction. The environment is installed in a smartphone and was delivered together with the GEAR VR glasses to the physiotherapist, who at home is validating.

For future work, large-scale validation and longitudinal follow-up with patients will be perform. The small number of specific VR environments for physiotherapy and the fact that the health professional maintains the patient's evolution data are noteworthy. Another important aspect is the modularity that easily allows the insertion of new mini-games, diversifying the physiotherapy sessions.

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Society 5.0 and a Human Centred Health Care

Violeta Bulc, Bret Hart, Margaret Hannah, and Barbara Hrovatin

Abstract The concept of Society 5.0 is inviting us to move towards a human-centred society. It is balancing economic, political, societal and personal developments within the collective awareness, building on our interdependencies and capacity to deliver solutions collectively. We argue that Society 5.0 needs a human-centred health ecosystem, Health 5.0, with a high level of transparency, and integration of digital and artificial intelligence solutions as supporting tools. It is the authors' humble intention to encourage and curate the progressive development of such an ecosystem. We believe that ITC and AI are a must in the world of medicine and healing, yet we argue that they need to serve not dictate. The intention of this chapter is, therefore, firstly, to explain the political framework within which the Health 5.0 is evolving. Secondly, to show how elements of systemic thinking are developing in medicine through person-centred care approaches and the new paradigm of personalized or precision medicine. Thirdly, we describe the "clinical gaze" which provides the cognitive frame for healthcare practices. We explain how this frame poses limits to the value of technological solutions for achieving positive outcomes in health. We offer pathways towards more integrative solutions. Fourthly, we use a real-life example to show the challenges and benefits of a human-centred health system. The authors argue that there is no turning back. We hope you will walk and co-create the human-centred future with us.

Keywords Human-centred health · Care · Digitalization · Medical avatar · Clinical gaze · Anthropocene

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1 Introduction

The World Health Organisation constitution of 1948 sets out a definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". This sets out a broad agenda for health that extends beyond clinical treatment and care to include community and societal well-being. For over fifty years, progress was made on both fronts with people living longer and in better health than in previous generations. However, since the financial crash in 2008 and now, in the midst of a global pandemic, this progress has slowed to a halt. Furthermore, inequalities in health both between and within countries have widened. More concerning still, the scale of human activity has grown to threaten the very life-sustaining systems of the Earth that we rely upon for our existence.

We are living through profound societal change prompted by the financial crisis, Covid pandemic, climate change, new technologies, the challenging aging structures, and different needs of patients. We will argue in this article, that we need a new paradigm to address health in a holistic way, with an ecosystem perspective, human-centred approach and with an emphasis on preventive care. The 2020 pandemic has revealed many of the weaknesses of the existing health systems, regardless of the ownership structure behind them. On the one hand it has revealed a shortage of appropriate protocols to handle pandemics efficiently. Countries were left alone with scared and shocked citizens, improvising in the first few weeks, lacking proper medical equipment, drugs or vaccine, and even enough staff, diagnostic and testing capacities. In addition, there was a clear absence of people to address social effects, emotional traumas and people's fear. The pandemic showed yet again how important investments and investment plans for public health systems are. It also showed a lack of experience and skills for horizontal cross-sectorial cooperation, and the devastating consequences of political confusion. On the other hand, the pandemic once again showed incredible human capacities for compassion, solidarity and dedication which deserve to be supported by better health systems.

In this chapter, we first take a global political view over the current context—the existing technologies and the political stance on people-centric care with a special focus on the actions by the European Union (EU). Then we dive deeply into person-centred care as a parallel or co-existing health practices alongside personalized health and its possible challenges, especially from the point of view of technology. Next, we explore the dominance of the clinical gaze in today's health practice, its limitations and possible ways forward. Finally, we share with you some hands-on experiences from Australia on biomedical devices and applications used in their Health System.

2 Key Challenges

Conditions around the World do not allow us to rest. Democracy is being challenged everywhere, people are losing faith in honesty and compassion, conflicts are putting powerful toys in the hands of angry, sad and neglected people, across the whole spectrum of our society. Yet, every harm done to another human being, is a harm done to us. As we have seen it in the past, when pushed to the edge of human decency and, in addition, being confused with the chaos related to the Covid-19 pandemic, an emergence of new qualities arises. These qualities are changing social, political, economic, scientific, organisational, and leadership perspectives. They are also contributing to a structural transformation of the systems towards more inclusive, transparent, human-centred systems, supported by AI and ITS tools.

The emergence of Industry 4.0, Health 5.0 (Kowalkiewicz 2018) and the first initiatives around the possible new (eco)civilizational paradigm are calling for a new type of health system which can efficiently adapt to ever changing global, regional and local conditions. Along with the health crisis, societies are dealing with climate change, digitalisation, globalisation and an uneven distribution of wealth. Altogether these crises are causing ever growing development gaps between regions, social groups, creating more challenges than solutions. Directly or indirectly these conditions are impacting the health of people as well as creating health inequalities.

Along with the current state of the world, many transformative powers are shaping underlying systems. Self-centric, egoistic society is exhausting itself, approaching the edge of decadency and an entropy of no repair, which by its nature is creating more and more injustice in the world, increasing poverty, dehumanisation, and devastation. At the same time people are resisting, creating a self-healing move towards eco-centric self-determining society, searching for ways to tune-in with the laws of nature, the planet and fellow beings. We are realising the singularity in technology is not bringing us the inner satisfaction, peace and societal well-being. It is not creating a life balance we internally seek, but it is rather destroying the essence of our existence and potentially humanity itself.

Technologies have brought many new features and positive outcomes to the medical world, as well. Telemedicine, diagnostic and analytical tools, on-line consultations, live global cooperation, are just a few among many. Yet, there are moral and ethical challenges emerging from the use of new technologies, as well. We are becoming aware that the consequences of the use of technology are designed by the creator's intention. The owners of the digital tools play an essential role not only in the use of technology, but also in designing the outputs of these technologies. Such a vulnerability creates an opportunity for misuse, a technocratic approach and maximisation of profit rather than value. More and more the question of who controls the creator is raised. For example, AI is questioned on its preferences, priorities, gender equality, racial discrimination, preferred physical condition, geographical positioning, or even human characteristics. With such a vulnerability, special care needs to be exercised at an early stage of technology development, ensuring transparency and compliance with value in terms of clinical outcomes.

Social media seems to be a particularly sensitive for health topics in the form of unregulated drugs, uncertified advice, and untested solutions which are flooding the digital market (Social and Dilemma 2020). At the same time, it seems that users are hardly aware, that the Internet-based marketplace is a place where the players trade with our human future. With the help of digital tools, especially social media, we see an increasing presence of polarisation among users, pushing scientific arguments and evidence to the bottom of the available information and news. Corporations with a vested interest are already penetrating health systems, influencing the decision-making processes, value networks and revenue streams. With a disinformation-to-make-money business model, providers profit by pushing unregulated messages to the followers, often only to keep them on-line. It seems as if we are at the edge of a bizarre autocratic dysfunction. The health sector is not an exception. There are more and more health-related pages emerging in the digital world with no regulation, no quality control and dubious moral values. The medical world needs to pay special attention to such a behaviour and develop strong communication tools to overcome the abuse and raise awareness of the risks for people who are searching for help.

In these formative conditions Health 4.0, and Health 5.0 are inheriting the same challenges that other computer and AI based systems are facing. For example, deriving a digital avatar for every patient is very appealing, keeping the entire history of an individual in one place, accessible to all doctors she-he might visit. However, we need to be aware, that such a solution is still only an avatar, stripped of the socio-economic conditions of the person. Being aware of these limitations is essential to bypass possible misuse or superficial interpretation of raw data.

Medical informatics is defined as a study and application of methods to improve the management of patient data, clinical knowledge, population data, and other information relevant to patient care and community health (EU data protection rules [Internet] 2020). It is our duty to make sure that the IT and AI in the health system stay tools in the hands of those with good intentions, serving the needs of patients in their entire life cycle: from preventive care, to diagnostics, cure, and the post treatment phase, addressing not only the physical conditions of a body but all human levels of existence, minimizing physical interventions when the root socio-economic causes can be addressed. In order to achieve that we will have to go back to our core human values and align these technologies to strong transparent governance systems. It can be done, it has to be done, to have a viable future for humanity.

How is the EU responding to these challenges? In spite of political turmoil, projects of joined interest are evolving. After the conceptualisation of the Digital Health and Care a more holistic and EU-centred approach started to emerge. For example:

- General data protection rules (GDPR) (EU data protection rules [Internet] 2020), regulation setting the digital users' rights as foundation for the market and legal relationships in the virtual world, creating a user centric digital regulation. In addition, Health has been added to the Digital Union and the Single Market horizontal priorities as an integrated part with other portfolios.
- Appropriate funding (Anonymous 2015) for health, demographics and general well-being.

- A stronger EU health security framework (Draguet 2020) including a new Regulation on serious cross-border threats to health, strengthening preparedness, reinforcing surveillance, improving data reporting including the health systems indicators and a declaration of an EU emergency situation.
- The EU Health Union (Building a European Health Union [Internet] 2020), strengthening epidemiological surveillance via integrated systems enabling real-time surveillance, preparedness and response planning, reporting and auditing, provision of non-binding recommendations and options for risk management, the capacity to mobilise and deploy EU Health Task Force to assist local response in Member States, and building a network of EU reference laboratories and a network for substances of human origin while reinforcing the European Medicines Agency's mandate.

It is time to make a stronger effort to readjust our thoughts, awareness and consciousness, to see the beauty instead of pain, to see the light instead of sorrow, to offer a hand instead of a machine, to use the achievements, scientific or operational, for making our lives better, more sustainable, healthier and more safe. For that, the people behind the technologies, information systems, the engineering, business and social solutions, need to put people at its core, need to embed humanity into everything we do. And we invite the medical sector to stand firmly behind this position.

So, what is really missing in today's business world to keep technology aligned with the basic principles of humanity? Well, we can start with the fact that human brain, capacity to learn and understand, has not been proportionately evolving along with the technology and its capacity to manipulate. So, besides strong public pressure, we have two formal choices: either we come together and establish a strong global regulator, with monitoring and enforcing authority over the social media market, as well as, over the technology overall, or we close the social media market, for example, as we have successfully done in the past with the market of human organs and with slavery, for example.

The EU has done the first decisive steps with the GDPR Regulation, putting the user in charge of his/her data. The other two models, corporate-centric in the USA, or government-centric in China, for example, fail to meet the needed privacy and freedom rights. An enlarged global will is needed to get this river to flow towards a humane and sustainable society.

That is why it is so important to keep the patients' rights at the core of the health systems, to really understand the needs of a physician, a nurse and other medical staff, the processes they are engaged in, and the type of information they need to arrive at quality decisions. This should not increase the administrative burden and isolate the patient but rather increase the time patient and medical staff spent in a relationship with each other. Meanwhile a quality digital health system takes care in a smooth and almost invisible way of the processes behind, providing numerical data, historic trends and comparisons, and help to make consultations and interactions rich and useful.

Within the EU there is a growing movement for person-centred medicine, which provides people-centric health practices. It is relevant not just because of the human values it expresses, but because it suggests better results in patient recovery time, lower costs, improved social welfare and happier societies (Gottlieb 2013). The EU is walking the path towards a "user-centred approach" with users deciding what to do with their digital data, ensuring privacy and equal treatment, which is particularly important for medical records and diagnostics.

But even in the EU we are just at the beginning. There is a genuine and urgent need for global cooperation, putting the public health and patient privacy at the core of a modern, open, inclusive society. And responsible technology is at its core.

3 Towards Personalized Medicine: Hopes and Challenges

There are many names for this data-driven endeavour—European region favouring "Personalized" medicine, while in the USA "Precision" medicine is commonly used. Other common synonyms are "systemic" (bio)medicine (deriving from systems biology) and "P4" medicine—the four Ps' standing for the key characteristics of the future medicine, which is to be (more) predictive, preventive, personalized, and participatory (Vogt et al. 2016). In one of the definitions, Personalized medicine refers to "a medical approach that uses molecular insights into health and disease to guide decisions with regard to the prediction, prevention, diagnosis and treatment of illnesses" (Scholz 2015).

Personalized medicine is a new hope for the future of twenty-first century medicine, which would harness the power of big data to make risk assessments, diagnosis and therapies more precise and timelier. Big data can be described as high volume, velocity, variety and variability (Hulsen et al. 2019). They entail continuous interplay of data from imaging, electronic health records, social media, new biosensors and self-tracking technologies, environmental and lifestyle data and "omic" technologies (suffix "-ome" means "totality of"), such as genomics, proteomics, metabolomics …, with a risk of leading to overdiagnosis and overmedicalisation (Vogt et al. 2019).

The individually fine-tuned therapies, often summarized as "the right treatment, for the right patient, at the right time" (Scholz 2015) would achieve more efficient health care and better health. Initial breakthroughs are encouraging, e.g., Herceptin as specific breast cancer drug in patients with positive HER2 receptors; computer algorithm efficiently diagnosing brain cancers from routine blood samples (Podnar et al. 2019), yet challenges of measuring and monitoring »everything about everybody« throughout individuals' lifespan are many.

Huge investments into technologies are intended to enable constant gathering, storing, comparing and analysing big data of each individual. The dynamic data cloud, emerging at intersections of these enormous volumes of data, being continuously gathered (starting already in-utero) will be representing a quantified uniqueness: a medical or health avatar (Vogt et al. 2016; [Internet] 2020). This digital twin of each citizen is to be compared to a "generic virtual physiological human" in order to help monitor and manage health. Investments and enthusiasm regarding a broader concept of digital health and Personalised medicine, can be understood as reflecting the "ubiquitous social ideology of technological progress and technological fix" (Šimenc 2017, 2018). In western cultures science in general and technologies in particular are seen as obligatory enablers of progress as objective realities, untainted by human subjectivity. In their study of telehealth Greenhalgh and colleagues described a "modernist discourse", where technologies are depicted as "smart", "precise", "in-control", "always available", "error-free" and ethically "benign" solutions for what is exposed as the ever-expanding problem of chronic diseases and aging with health-care systems already reaching a critical point, in danger of collapse (Greenhalgh et al. 2012).

The idea of medical or health "avatar" emerging through unprecedented screening of every quantifiable aspect of human health and well-being is redefining bodies as transparent, high resolution networks and individuals as databases. Big data driven insights are intended to quantify individuals' estimations of risks, identify different responses to drug therapy, develop new disease classification and discover new biological markers. In the process, health and disease boundaries are blurred. They tend to be remapped as something concrete and objective in large data sets of biomarkers and molecular networks outside the organic confines of the human body (Vogt et al. 2016; Hulsen et al. 2019). Through those processes living human beings are further abstracted into virtual reality.

Planned as one of big data entries, the Electronic Health Records (EHR) are already ubiquitously used in clinical practice. The obligatory use of computers, the necessity of filling in pre-designed formats and algorithms with all the relevant patient's data, lab tests, diagnostic codes, referrals and prescriptions, has often been perceived as superfluous and futile administrative task, taking away from already limited time with the patient, while serving mostly for insurance billing and control, a burdensome bureaucratic intrusion in clinical encounter (Šimenc 2017). The uncomfortable co-existence of digital technologies and everyday clinical practices is well documented—physicians' descriptions such as tethered, distracted, frustrated, burned out, speak about clinical reality, where computer screens are capturing more than half of working hours (Toll 2012; Arndt et al. 2017; Gawande 2018). Juggling the needs of computer with those of patients rise concerns about vulnerability of caring doctor-patient relationship as a deeply human to human connection in the era of digital technologies. Staring into screens, "clicking", "filling in" and "ticking off" is taking focus away from the patient and clinical interactions, as described elsewhere in this book. Physicians often feel like turning into administrative workers (Hunt et al. 2017), while patients seem to be receding into a standardized, ever expanding dataset sometimes referred to as the "iPatient" (Verghese 2008).

Development of new technologies plays a crucial role in Personalised medicine vision of studying health and disease, which is enabling an ever deeper and all-encompassing technological gaze into the biology of human life. In the framework of such technoscientific holism (Vogt et al. 2016), complexities of human beings are recognized as important, yet reduced to biomedically quantifiable, predictable and actionable (controllable). Actionable opportunities for optimization of health and enhancement of wellness ("scientific wellness") can be discovered even in healthy and become new important spaces in need of biomedical monitoring and management, shifting health care's scope (and resources) from patients and diseases to all people and life itself (Vogt et al. 2016; Vegter 2018).

The deep technological gaze into the complex interplays of human biology and computer algorithms analysing, predicting and suggesting its management could be examined as a new step in the historical shifting from person-oriented towards object-oriented medical cosmology (Vegter 2018; Jewson 2009; Nettleton 2009), carrying a tendency to be disempowering and dehumanising.

The aura of technological and political neutrality of "smart" solutions can blur our discernment regarding broad array of interests integrated into the digital technological agendas (in the case of EHR, designed by expert engineers, removed from clinical work and the lived experience of illness) (Greenhalgh et al. 2012). Also staying mostly unexamined, is the potential of digital tools restructuring clinical reality—not only surveying, noting down, making transparent, but shaping what is going on, the practices themselves—what we have to do, what is important, what can be overlooked.

Hopes and expectations for digital technologies and AI in the framework of Personalized medicine to free health care professionals to bring time and presence to the care of patients—the real work of medicine, are yet to be fulfilled. Some of the most important considerations awaiting to be thoughtfully addressed in order for large investments into Personalized medicine to bear fruit are: deepening technological gaze, taking our attention further away from the first-person accounts of the lived experience and further from understanding the immeasurable human beings-in-relation, the threats of medicalization of life itself with rising risks of overdiagnosis and overtreatment, the misbalanced focus on individual rather than structural interventions that would build and strengthen health-enabling social environments.

4 Person-Centred Care in the Age of Technology

Person-centred (health) care is another important initiative for a more holistic (integrated) view of patients as persons in health care systems. Both—Personalized medicine and Person-centred care can be thought of as responses to fragmented ways of seeing people in biomedicine, both carrying the word "person" in its name yet approaching the challenge from quite different ends of the spectrum. At a glance, these two movements might easily be understood as opposite poles, as either/or, yet further exploration shows no such easy distinctions. Through explorations of Person-Centred and Personalized medicine we can discover ways of possible thinking towards improvements of medicine and healthcare, ways that are embodying important challenges for the medicine of the future while uncovering the often-hidden assumptions of what is true and valid, what is at all possible and where we are to be moving as a society in medicine and healthcare (and beyond).

Person-centred care (PCC)—or sometimes a broader term "Whole person care" is used (Hutchinson 2011) has become a guiding principle of healthcare, deepening the biopsychosocial approach in providing compassionate and respectful care. PCC is guided by patients' values, needs and preferences, where the patient is recognized as an equal partner in therapeutic relationship. Over and beyond autonomy and access, PCC obliges us to take into account the self-aware, meaning-seeking, purposeful and relational nature of human beings (Miles et al. 2011).

One of the core qualities of person-centred relationships is compassion and quite a few studies are showing that compassionate relationships in clinical encounters lead to improved health-care outcomes (e.g., management of blood sugar in diabetes, duration of common cold, intensity of postsurgical pain) (Rakel 2018; Trzeciak et al. 2019). Social support has been found to be the most important modifiable factor for morbidity and longevity, trumping cessation of smoking and regulation of high blood pressure (Holt-Lunstad et al. 2010). At least as importantly, compassionate intervention also works outside of the healthcare system and in connection with it—in community, for example by reducing emergency admissions to hospital in a population—the Frome compassionate communities project has affirmed how love and laughter, sharing companionship and values connects through caring, reducing isolation and loneliness, increasing belonging (Frome Model [Internet] 2020).

In his more recent works, Arthur Kleinman, the renowned physician and medical anthropologist, writes about caregiving as an existential act that defines our humanity. Caregiving is a basic response to human vulnerability, uncertainty and suffering (Kleinman 2009, 2013, 2019). The focus on caregiving can be discouraged or even disabled in the structures of medical training and health care systems, where the balance between science-technology and art is clearly shifted far towards the former (Kleinman 2008). Kirkengen and colleagues reflect on "Medicine's perception of reality", critically exposing consequences of a depersonalized view of the human-as-body, which gets separated ("liberated") from its subjective context of lived life. Naturalistic worldview, its most prominent criteria for quality being objectivity and value neutrality, helped to establish dichotomies of mind-body, nature-culture, objective-subjective, facts-values as natural distinctions (Kirkengen et al. 2016).

The vulnerability of our attention to a persons' lived experience in enabling health becomes even more important in the light of more recent, ground-breaking scientific evidence, demonstrating the indivisible interrelatedness of human biology and biography. The interdependency of the material (body) and the social (environment, life experience) is confirmed in abundant research, one of notable examples being the Adverse Child Effects studies (ACEs), showing dose response relationship of childhood trauma and adult morbidity. ACEs are linked to chronic health problems (significant increases of diabetes, autoimmune and cardio-vascular diseases, cancer, and substance abuse—among others—decades after the negative childhood experiences such as: violence, abuse, or neglect; living environment undermining sense of safety, stability, and bonding). ACEs can also negatively impact education and job opportunities (Felitti 2002; Shah et al. 2014).

The indivisibility of human being in her lifeworld is confirmed also in studies showing that socioeconomic gradients can influence morbidity and mortality. Conditions of life worlds, where people are born, grow up, work and age—termed also as »causes of causes«, and socioeconomic inequalities deriving therefrom, determine health and length of life (Marmot and Bell 2012; Braveman and Gottlieb 2014).

Scientifically, we can now better articulate how lived experience gets under the skin. Allostatic overload (McEwen and Gianaros 2011) denotes a chronic over-taxation of bodies adaptive responses to stress. Not only to physical trauma, but also to psychological-existential threats, where betrayal, isolation, neglect, humiliation, guilt, shame and integrity violations are igniting the pathophysiology of deficiency and helplessness, with chronic inflammation and dysregulation of vital systems such as immune, hormonal and neurological. What can collectively be termed as biology of disadvantage is often presenting as multimorbidity and medically unexplained syndromes, a growing cause of suffering and challenges in health care (diagnostic, therapeutic and economic) (McEwen and Gianaros 2011; Getz et al. 2011).

How does the biography become embodied under the skin (in biology), is getting visibility also through discoveries of epigenetics—the burgeoning scientific field arising in the post-Human genome project era. The surprising outcomes of a decade long and much awaited project were the vast »noncoding« areas of DNA (comprising 98,8% of DNA), now seen as the site of "epigenome", where molecular reactions are constantly responding to internal and external environments, regulating gene's expression. So instead of reaffirming genetic determinism (we are our genes—what we bring to this world), the post-Human genome project era brought even more complexity—the fluid, constant interplay between inner and outer environments, now technologically discernible on the molecular level. Instead of the executive suite, our DNA became a more fluid concept, a potential for emergence at the intersections of nature and society, bodily structures and lived experience (Meloni 2019). The growing field of epigenetics is changing scientific understanding of the body interior, making clear—in the words of Margaret Lock, "that human bodies are permeable and mutable to environmental stimuli while in utero and throughout life" (Lock 2013, 2017). All together, these studies challenge biomedically entrenched separation of nature/nurture and object/subject, making them untenable and call for an ethically informed epistemology appraising the values and meanings of the human lifeworld in medical research and clinical practice (Kirkengen et al. 2016; Kirkengen and Thornquist 2012).

These discoveries are even more significant in the light of Anthropocene—the era of profound destructive impact of human activities on Earth and all living beings, which together with wars, poverty and discrimination lead to more inequalities and suffering (Lock 2017).

Along with new technologies we need to research, develop and support ways of encountering one another, opening the healing potential of intersubjective space, enabling trust through recognizing, acknowledging and affirming a fellow human being (Charon et al. 2016), with compassion and care. We need ways of studying and teaching how to be present and connected, so that the vast biomedical knowledge and technologies can run through the fundamental substance of human relationships, which strengthen, evoke, support healing on both sides of the stethoscope. It is our human relationship that enables us to balance technological advances of managing risks and diseases with whole person care, balancing the »doing to« frame of thought with presence of »being with«. Therefore, it is the human relationship that is the fundamental basis for integrating our traditional medical focus on what is wrong (pathogenesis) to be discovered, calculated, fixed or prevented, with what is right with you (what matters to you), to be supported in human relationships—salutogenesis (Rakel 2008). Despite the lure of vast potentials of technological aids, we might look in vain for healing, the transcendence of suffering, (Egnew 2005) in future data clouds, or in the words of Abraham Verghese, the founder and director of The Stanford Presence Canter: "Good patient care is found not in the computer but in being truly present with patients" (Verghese 2016).

Challenges of human suffering and the limits of current biomedical paradigm, increasingly acknowledged also through the science of biomedicine itself, beseech us to move closer towards causes of causes, where we find, again and again, the indivisible nature of complex systems, their interrelatedness and emergent properties, with relationships at the core of Life. Can we transcend the naturalistic framework of biomedicine towards better understandings of healing of whole living beings? Can technologies help us to develop better understandings of the person in her lifeworld, supporting and creating compassionate communities?

5 The Clinical Gaze

Modern medicine is based on an objective perspective of ill health which is located in the body and/or the mind of individuals. This perspective derives from seventeenth- and eighteenth-century discoveries such as by William Harvey who discerned that the heart functioned as a pump for the circulation of blood. This accumulation of knowledge constructed a mechanical view of the body with diseases regarded as breakdowns in its functioning. To this day, diseases are categorised based on sets of symptoms and signs and grouped by systems of the body: neurological, circulatory, digestive etc. Confirmation of these diseases may require multiple and potentially invasive investigations and a diagnosis reached based on certain thresholds in measurement being exceeded. Treatments have been developed to address diseases as defined by these categories. Their aim can often be to remove, control or suppress the cause of symptoms. Or they can replace or substitute a deficit or defect in the body. Learning to understand and practice in this world takes years of training. Often medical doctors have to specialise so they can focus on particular groups of people with particular patterns of illness. The physical design of clinics and hospitals matches this clinical paradigm. The algorithmic access to consultations and treatment on-line follow the same patterns.

All of this may seem obvious, but the consequences of this medical paradigm are substantial and often over-looked. By focusing on diseases, the objective perspective of the clinician minimises personal, relational, cultural and societal aspects of ill health. This “clinical gaze”, as described by Foucault (1973) shapes the power dynamics of modern medicine and leads to over-investigation and treatment. For example, a neurologist may refer a woman for a cranial CT scan to investigate her headaches rather than find out she is in an abusive relationship. A general practitioner may order a set of invasive investigations for a man with weight loss and change of bowel habit before having a longer conversation and discovering he has lost his job and is drinking heavily. Rather than spending time to understand personal, relational, cultural and societal influences on their health, investigations are the default option for clinicians to “rule out” serious disease.

A further problem with the clinical gaze is the use of numerical values in investigations to describe thresholds for intervention. This is particularly problematic for so-called risk factors for cardio-vascular diseases (Hannah 2014). Thus, elevated cholesterol or blood pressure measurements are taken as reasons for lipid or blood pressure-lowering medication. These thresholds are determined through meta-analyses of research into links between these factors, risks of stroke or heart disease, and the effects of reducing their levels by medication. Often this research is backed by the pharmaceutical industry, recommendations for treatment sanctioned by the publication of clinical guidelines, and implementation requirement from health regulators.

The net result is millions of people are put on medication for elevated blood pressure measurements. A more in-depth conversation might have found that they are experiencing stress, maybe problems of bullying in the workplace, financial worries, relationship difficulties. There are not many clinicians who ignore clinical guidelines required by regulators and instead explore ways whereby people can address their adverse life circumstances.

Notwithstanding the extraordinary success over the last century of this reductionist, objective clinical gaze, it has become of more limited value today. Undoubtedly effective for single conditions, often acute ones (e.g., a bone fracture), the clinical gaze is nevertheless not able to embrace complexity. There is an important difference between complicated and complex. A car engine is complicated, but a good mechanic can identify a fault and put it right. The impact of the car on culture and society is complex. From the day the first Model T Ford came off the production line, who could have imagined the extent to which cars have shaped our lives in the subsequent 100 years?

The same is true for patterns of disease. One hundred years ago, the main causes of hospital admissions were infections and trauma (often work- or birth-related). Whilst infections remain a challenge, particularly during a global pandemic, far more hospitalisations are for chronic, non-communicable diseases, often in older people. Part of the reason is that modern medicine has reduced death rates from conditions such as heart disease and cancer. As a result, people are living for many years, often decades after their initial diagnosis with these conditions. Another reason is an increase in the proportion of older people in the population who are at higher risk of chronic, non-communicable diseases. This is made worse by the fact that many people with a chronic condition will have more than one. For example, a cross-sectional study in Scotland showed more people over 65 years had two or more conditions than a single condition (Barnett et al. 2012). It is not easy to manage two diseases in a single person: drug treatments can interact and generate complications. As the number of conditions grow, these risks escalate: the situation is no longer complicated but complex.

Our healthcare system is locked in by its legacy focus on infections and trauma and maladapted for chronic, complex conditions. By focusing on a fix or cure for one disease at a time, clinical practice is divorced from the notion of health as the potential for "complete physical, mental and social wellbeing" to use the 1948 WHO definition. Fortunately, the tide is turning. Clinicians around the world are exploring more person-centred ways of interacting with those seeking their help whilst also providing active treatment and care. They are not just focusing on the absence of disease but exploring with people their potential for complete physical, mental and social wellbeing (The Compassion Project [Internet] 2019). This progress is particularly marked in palliative care, where there is no likelihood of cure, so the focus is on living life to the full in one's final days.

These clinicians see the whole person, not just their disease. Rather than concentrating on problems, they help people identify their strengths and they find out what is important to them in their lives. Instead of asking "What's the matter with you?", they ask "What matters to you?". One such example is the Fife Shine Programme which is enabling people to thrive not just survive with long-term health conditions (Leicester 2018).

Putting people at the centre of decision-making has a powerful effect on the power dynamics and radically changes the culture of healthcare. What might be the role for technology in this new paradigm—healthcare 5.0?

6 The Role of Technology in Healthcare 5.0

The global pandemic of Covid-19 has accelerated many innovations in technology, particularly in relation to remote consultations. Telemedicine and telecare play a vital role in providing access to help for people needing urgent clinical advice and treatment. However, when the presenting picture is complex rather than complicated, the challenge is to provide settings for people and their healthcare providers to have honest and open conversations. With the right support, people can understand their situations better and find solutions which fit their context.

If remote consultations are within an enabling, humanising culture, which seeks to create the conditions for building quality relationships, they can be very supportive. But if the underlying culture of healthcare is one of alienation and fragmentation, such technology might be deployed for more sinister, surveillance purposes. The same is true for personal diagnostics and monitoring technology. If people own their data, use it to support their personal decisions and feel they can still contact their healthcare provider if they want advice, the use of personal health devices can be life enhancing. On the other hand, if these technologies are used for coercion and control and are a substitute for human care, they are likely to cause more harm than good.

A further risk is exploitation of personal health data by technology providers. Without safeguards around confidentiality, trust can be breached and seriously undermine the culture of healthcare. Lastly, the challenge for health technology in the new paradigm is to examine how the disease focus embedded within the clinical gaze can be balanced with the person-centred perspective. This means supporting decisions as far as possible in real time, often using existing ICT rather than inventing new forms. Managing two-way information flow is essential so that people can let their providers know how they are and receive prompt responses: both sides work in partnership for optimal health and wellbeing.

7 Pathways to More Integrative Solutions

In the 1960's, Edward Lorenz made a profound observation in his work on weather systems, noting that small changes in initial conditions of his experiments produced large changes in long-term outcome. He subsequently went on to describe this phenomenon as the "butterfly effect". This has important consequences for technology in healthcare and particularly the use of artificial intelligence. With algorithms built on the perspective of the clinical gaze, artificial intelligence cannot capture the richness or complexity of the circumstances that bring people to healthcare seeking help. No matter how impressive the detail and range of the variables used, if they miss out on the lived experiences which have generated the pattern of disease in the person seeking help, they close off the potential for new possibilities and novel pathways to recovery.

In short, advanced technology in healthcare needs to be used with caution and not fall into the trap of focusing its attention on a map derived from one point of view. It needs to recognise the map is an abstraction from the territory which is inhabited by those with ill health. In Healthcare 5.0, integrative solutions are needed where the best of analytic and deterministic science is enmeshed within humanistic and life-enhancing care. How might they be found?

International Futures Forum (IFF) uses a Three Horizon Framework to make sense of the changing landscape of society from three perspectives on the present moment—the first, second and third horizons (Sharpe 2015) as shown in Fig. 1.

The first horizon (H1) perspective is managerial and focused on keeping current systems going. It drives the current dominant system—'business as usual'. But as the world changes, so this dominant system is losing strategic fit and will be superseded by a radically different pattern of activity in the future—the third horizon.

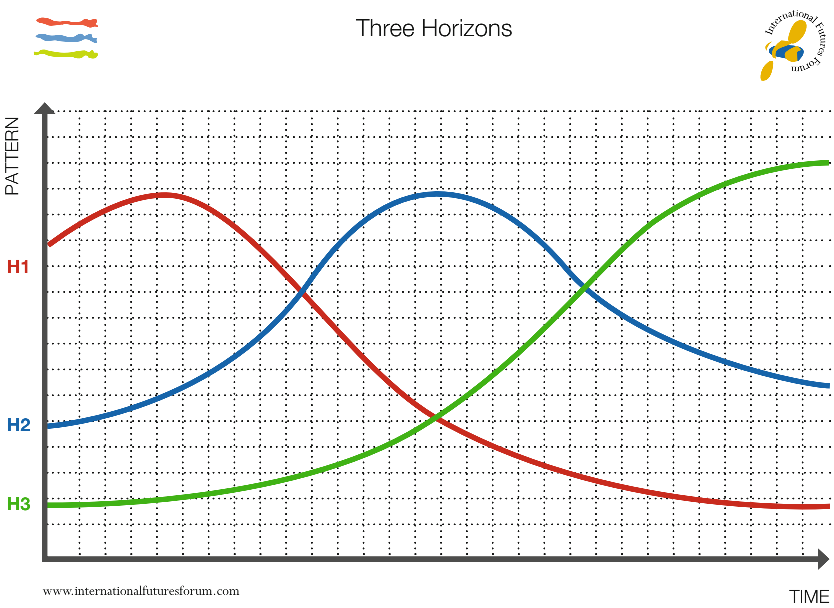

Fig. 1 The three horizons framework (Sharpe 2015)

The third horizon (H3) perspective is visionary and aspiring for a better way. Committing to a better future, the visionary perspective inspires the growth of the third horizon from fringe activity in the present to the eventual successor to the dominant H1 system—perhaps a generation from now.

The second horizon (H2) perspective is entrepreneurial and eager to try out new ways. The entrepreneurial perspective drives innovation and looks for opportunities to do things differently. Some innovations will be absorbed into the H1 systems to improve them and to prolong their life. Others have the potential to pave the way for the emergence of the radically different H3 system.

IFF has used this framework for engaging people in thinking about the future healthcare system. The three perspectives can be teased out through interviews or conversations. On deeper probing, tensions emerge between the values and assumptions of the H1 perspective and those of the visionary H3 perspective (Fig. 2).

To use an example, the H1 managerial perspective may put value on using technology for efficiency. It helps manage scarce resources in time, people and skills. A great example of this is digital imaging which can be taken in Accident and Emergency centres 24/7, sent and read remotely by radiologists and results returned in minutes. The H3 visionary perspective in contrast may put value on technology to enable people. They are inspired by young people teaching older people how to use video-conferencing platforms, enabling them to be in touch with their families.

Another example might be H1 putting value on personal health data as a resource to exploit which could conflict with the H3 value of personal privacy.

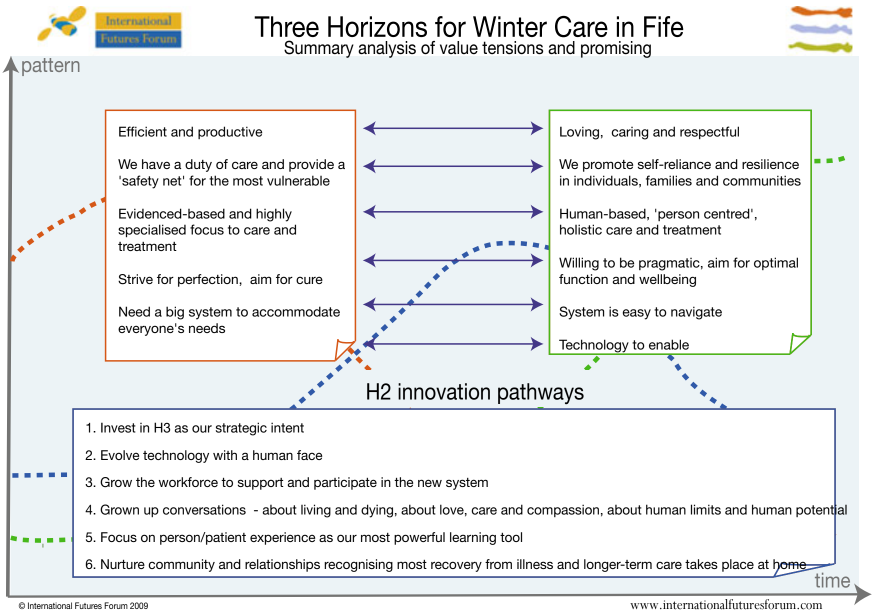

Fig. 2 The three horizons for winter care in Fife (Sharpe 2015)

Typically, the H1 value tends to win out against the H3 value which is often why our current systems are resistant to change. Instead of seeing these tensions as either permanently in conflict or one dominating the other, they can be considered dilemmas. Using dilemma resolution methods, it becomes possible to generate innovative pathways (H2) which optimise the expression of both H1 and H3 values. The aim is for integrative solutions which are the "best of both worlds".

Work on these technology dilemmas in Scotland, generated an innovative pathway as "evolving technology with a human face". This pathway led to technology being used in ways that contributed to a humanising environment for people seeking help and their providers. One simple example was a mobile phone booking system for home care. This used familiar technology, but because of the culture it was embedding into, the communications between care giver and the person needing care were to help them both develop a trusting relationship. In a different culture, the same technology could have been used to sanction staff for being late or taking too long with a client.

Many other examples are now emerging. The Play List for Life programme (2020) encourages families of people with dementia to have a playlist of personal music which they can use at any time, but particularly when they are in hospital or care homes. This provides people with dementia with something they recognise amidst the confusion of a healthcare setting and can be of great comfort to them and their families. Care providers can see more of the person, the music lifts their spirits. People engage with the music and can sometimes find their voice and sing when previously they were mute.

Southcentral Foundation in Alaska (2017a) provides primary care health services for Alaskan Native people. They base their approach on the culture and values of the community with conversations and relationships at its heart. They call their approach, the “Nuka Model of Care” where Nuka is an Alaskan Native word for a “large living structure”. Their consulting rooms are designed on a basis of partnership between healthcare provider and people (formerly known as patients). To this end, the computer is put in the middle of the desk with two equal chairs on the same side so both can see the screen. This prevents the computer dominating the interaction and puts the relationship at the heart of care.

Fife Homecare Services (2020) in Scotland provide care and support for people living with chronic conditions in their own homes. A mobile phone management solution has enabled carers to co-ordinate their visits effectively in real time. It means they are using all their time more effectively, yielding a day and a half per week increase in productivity. Near Me (Video Appointments 2020) is a telemedicine system originally designed for remote consultations in Scotland. Since Covid-19, the system has been expanded for all areas and has enabled people to consult with their doctors and other care providers as required during the pandemic.

Increasingly, primary care physicians are working in ways which grow connections within local communities. With the use of a simple technology platform, people can access a range of services and opportunities to manage their health conditions and find better ways to keep well. Health Connections in Somerset, England is one such example. Using the power of human relationship, people are feeling more supported and are finding ways to support each other (Home [Internet] 2020).

8 Biomedical Devices and Apps in Health Systems: An Upstream Perspective from Australia

A true test of the benefit of medicine-based informatics, engineering, biomedical devices and apps is their potential to reduce the life expectancy gap between the First Nations People of Australia and the rest of the population. Reducing this gap has been an insurmountable challenge for Australia for too many decades (Close the Gap: Indigenous Health Campaign|Australian Human Rights Commission [Internet] 2020). The Australian government's annual “Closing the Gap” report was released on 12th February 2020 with data to demonstrate the inability of governments to meet most of the targets set in 2008 (Askew et al. 2020; Biddle 2020; Markham and Biddle 2020; Why we aren’t closing the gap: a failure to account for ‘cultural counterfactuals’ [Internet] 2020; Pha 2020). The previous statement could not be made if it wasn’t for informatics.

8.1 The Power, Promise and Problems with Informatics

Those working in Aboriginal health were pioneers in the use of medical informatics (Pathfinders—Aboriginal Health Informatics [Internet] 2020). For example, in the Northern Territory clinicians transitioned from, "who owns the information?" to understanding how important quality health records are to providing efficient health delivery. This spurred exploration of the use of Internet based electronic health records almost two decades ago in Western Australia. This ultimately became, with many teething problems, the nationwide "My Health Record" (MyHR). But it is no longer locally driven and is now administered from Canberra by the Australian Government under legislation.

Uptake of MyHR was and is slow due to privacy and security concerns following disclosures about data breaches such as the Cambridge Analytica imbroglio and problems with release of Medicare and Pharmaceutical Benefit Scheme data in Australia (Sweet 2020). In addition, there were doubts about the evidence to indicate whether any outcomes have been achieved relating to any of its objectives outlined in the 2012 My Health Records Act. This prompted the recommendation to research whether the MyHR system actually helped improve Australia's healthcare system (Mesquita and Edwards 2020).

Whilst research occurred, access to it necessitated a Freedom of Information request to the Australian Digital Health agency to review the studies of the over 2-billion-dollar system (My Health Record: almost $2bn spent but half the 23m records created are empty [Internet] 2020). When access was finally granted in November 2020, the reason for reluctance to share the information was revealed. It is one of the most expensive health interventions in Australian healthcare during the last 20 years and yet with no robust evidence of having any impact on what it was designed to do—improve patient clinical care (The 4.5 studies showing the My Health Record is on track [Internet]. 2020).

In the late nineties, in the remote Kimberley region of Western Australia (WA), Dr Ian Wronski envisioned how computers could make a major difference to public health in Aboriginal communities. He commissioned an IT company to build a patient public health database enabling the local Aboriginal Controlled Health Organisation (ACCHO) to track health care needs particularly in health prevention and health promotion of the Aboriginal people of the Kimberley. ACCHOs are also leaders in data analysis with the ability, for example to determine how many regular female patients with diabetes aged between 45 to 54 have an HbA1c (longer term measure of average blood sugar) of less than the recommended level (HbA1c test [Internet] 2020). Data are also used for online Community Health Reporting which is compulsory for all ACCHOs in order to obtain funding (Bartlett and Boffa 2001).

This begs the question of how much ACCHOs are in control not only in Australia but also in Canada and New Zealand with the first edition of the International Journal of Indigenous Health devoted to "governed by contracts" (Governance of Aboriginal Health 2013). Other commentators suggest that community control rarely leads to community empowerment but the entrenchment of the power of professionals (O'Neill 1992).

Community empowerment is not well understood or practiced by healthcare professionals with, for example, the previous UK National Health Service head Nigel Crisp witnessing disempowering behaviour by some UK trained nurses in developing countries (Crisp 2010). A way to convey the concept is to consider the following story relayed by University of New South Wales Associate Professor Jan Richie at the 1991 Public Health Association conference:

> Once upon a time, there were four villages. Each village drew its water from a well with a pump. One by one each of the pumps fell into disrepair, leaving the people to use contaminated river water to drink, and their children became ill.
>
> In the first village a nurse spent her time competently treating the children who became dehydrated due to severe diarrhoea or disease.
>
> In the second, a nurse was able not only to treat the serious ill children, but she also taught the mothers to use oral re-hydration solution in the earlier stages of the disease.
>
> In the third village not only could a nurse treat the disease and educate the parents but she was also able to contact the pump repair people and persuade them to come and mend the pump.
>
> In the fourth village, a nurse could treat, educate and collaborate with the engineers, but instead she chose to call a meeting of the villages and supported them while they negotiated with the pump repair people. Through their own actions, the people had the pump repaired very quickly.
>
> Sometime later, after all four nurses had moved on, as nurses tend to do, the pumps failed once again. Which village had then the best advantage of sustaining healthy children?

Another way to convey the approach is to consider the ancient quote of Lao Tzu: "Go to the people. Live with them. Learn from them. Love them. Start with what they know. Build with what they have. But with the best leaders, when the work is done, the task accomplished, the people will say 'We have done this ourselves'".

These concepts seem far removed from the technological revolution but in his book "Your Patient Will See You Now: The Future of Medicine is in Your Hands" Dr Eric Topol predicts that new innovative technologies will change the role of patients to becoming active participants in their own medical care (Topol 2015).

When community empowerment is fundamental to the provision of healthcare, impressive health outcomes can be achieved as demonstrated by the Southcentral Foundation's 'Nuka' system of care in Alaska (2017b). Similar to the First Nations People of Australia, the Indigenous people of Alaska that administer their own holistic health service recognised the importance of health informatics. They expanded their capacity to improve how Southcentral presents data as a basis for making operational decisions. This resulted in developing a more comprehensive database than most comparable primary and community providers in the United States. They also established a far more successful electronic patient record system than Australia's MyHR (Collins 2015).

Clearly informatics applied to the First Nations People of Australia was insufficient to inform the implementation of successful strategies in the past. The failure of mainstream healthcare to provide culturally appropriate services to First Nations People precipitated the establishment of their own medical services in the early seventies (Bartlett and Boffa 2001). Whilst these Aboriginal Medical Services "cure more than illness," (Baba et al. 2014) they are still part of "the health system" which only partially contributes to the health of a population. The impact of COVID-19 has highlighted "… the long-known fact that 90% of our health and wellbeing are influenced by factors other than access to clinical services" (Stein et al. 2020).

8.2 Does the Benefit of the Technological Revolution Outweigh the Cost?

Informatics, engineering, biomedical devices and apps applied to medicine will be revolutionary and will make it smarter and better according to a group from Taipei Medical University (The Times they Are a-Changin'—Healthcare 4.0 Is Coming!| SpringerLink [Internet] 2020). These developments herald the beginning of Healthcare 4.0 with the potential to assist health practitioners. However, this benefit will contribute only a fraction of the 10% that determines the health and wellbeing of the community (Stein et al. 2020). But this benefit comes at a price. For example, the World Economic Forum refers to the 4th Industrial revolution which led to advances in cell therapy for cancer treatment—but this can cost well over $1 million for one treatment for a single patient (Goy et al. 2019). This prompts an alternative to the Prevention Paradox of the late Professor Geoffrey Rose which states that a preventive measure that brings large benefits to the community offers little to each participating individual (Institute of Medicine (US) 2003). In view of opportunity cost of Healthcare 4.0, a 'Treatment Paradox' might need consideration.

In his book, "Bigger Government: The Future of Government Expenditure in Advanced Economies", Mark Robinson predicts government health spending, which is responsible for approximately 70% of total health expenditure, will need to grow enormously mainly because of this technological revolution (Bigger Government 2020; Press Release 2020). Because of these growing costs, he predicts welfare spending will have to be pruned in countries with the most comprehensive welfare states. This is an example of the 'treatment paradox'; austerity measures needed to fund smarter medicine will damage health and lead to premature death (Bambra 2019).

Meanwhile, whilst the health of the community in the future is potentially under threat from not only funding Healthcare 4.0 but also from the economic consequences of managing COVID-19. Despite this, it is claimed that "the future is bright for healthtech". In an article with this title, there is a paragraph with the somewhat oxymoronic heading, 'HealthTech Leading the Patient-led Healthcare Revolution' (The Future is Bright for HealthTech—[Internet] 2020). This indicates healthtech is not so much responding to demand from the community, but it is the digital revolution that's driving its own momentum. Birgit Mahnkopf suggests in her article on the '4th wave of the industrial revolution' that the revolution is occurring blind to the social consequences and ecological impact. Accordingly, she recommends we should consider all the challenges and risks of this revolution and then decide whether to resist or foster the trend (Mahnkopf 2019). This is consistent with the aim of health impact assessments (HIAs) which are, according to the WHO, "used to judge the potential health effects of a policy, programme or project on a population, particularly on vulnerable or disadvantaged groups. Recommendations are produced for decision-makers and stakeholders, with the aim of maximising the proposal's positive health effects and minimising its negative health effects" (Health impact assessment 2020). Unfortunately, HIAs do not seem to figure highly in considering the influence of medicine-based informatics, engineering, biomedical devices and apps in health systems. However, a European team has developed a framework to assess what they describe as a new paradigm: 'Connected Health'. They describe Connected Health (CH) as "a promising vehicle for the incorporation of telehealth and integrated care services, covering the whole spectrum of health-related services from the ones directing the healthy subject (as a citizen who seeks health service support or a wellness service consumer) to those addressing the chronic patient as an integrated (tele) care service beneficiary." The team describes the application of their 'Connected Health Impact Framework' in the hope it will "…evolve toward the creation of a CH impact tool and contribute to the generation of a service registry for further comparison and investigation" (Chouvarda et al. 2019). Meanwhile, it is important to define and be reminded of the function of health systems—whether they are connected or not.

8.3 What's in a Name? Misnomers, Malapropisms and Misunderstandings

"*Every system is perfectly designed to achieve the results it gets*."

Paul Bataldan, Institute for Health Care Improvement

According to past President Institute of Health Care Improvement, Don Berwick, "…most hospitals and physicians' offices are repair shops, trying to correct the damage of causes collectively denoted 'social determinants of health'" (Berwick 2020). The social determinants of health (SDoH) are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life (Wilkinson and Marmot 2003).

Unlike the appeal of technological advances, informatics, engineering, biomedical devices and the popularity of apps, the phrase "Social determinants of health" is described as "…one of those ostentatiously bland phrases that seem engineered to deter interest in the topics they name" (Heath 2020). The term is also liable to be confused with socialism which is not alleviated by the suggestion that there should be a new profession—'socialists' (Hatzigeorgiou and Joshi 2019).

Perhaps the poor 'branding' of SDoH, and being tainted with a leftist brush, led to Australia's right wing government's lack of action on the recommendations stemming from the 2013 Senate Inquiry into Australia's domestic response to the WHO's 'Closing the Gap in a Generation' report (Smith et al. 2018).

SDoH for many First Nations People of Australia are compromised so the previous lack of action is likely to have contributed the inability of government's failure to meet most of Australia's 'Closing the Gap' targets. In addition, the UK derived SDoH fail to consider the impact of the history of dispossession, colonisation, attempts at assimilation, racism, and denial of citizenship rights on the First Nations People of Australia (Anderson et al. 2007).

Whilst these issues seem far removed from what informatics, engineering, biomedical devices and apps can offer, it was claimed in 2014 that "Aboriginal Health in Australia may be one of the most successful areas of development in Health Informatics." This observation was based on the fact that First Nations People appreciate that health care is more than a visit to the doctor. They have witnessed and/or experienced the devastating effect of chronic disease well before the non-Aboriginal community. They want to prevent these diseases in their children hence the focus on prevention and public health. In addition, they want healthcare to be sensitive to their culture which is best achieved by employing First Nations People as local health workers (Pathfinders—Aboriginal Health Informatics [Internet] 2020). However, a recent study has revealed a decline in some Australia States and Territories in the workforce due to external family pressures, lack of career progression, mismatch between clinical responsibilities and training, and the 2012 requirement of new Health Practitioners to obtain a Certificate IV in Aboriginal and Torres Strait Islander Primary Health Care (Wright et al. 2019). The latter will be impossible for those who are illiterate and yet many would have much to offer as they have their finger on the pulse of the local community. They would overcome the missing element from SDoH—the cultural determinants of health. Aboriginal Cultural Carers used to fulfill this role in WA before the State Government's Health Department cut the funding (AIS Report 2013).

Aboriginal Cultural Carers attuned to local issues would have provided valuable insights into what has been described as "social informatics". This is a subset of informatics which informs, "… how to approach the unique data, interoperability, execution, and ethical challenges involved in integrating social and medical care" (Pantell et al. 2020). However, a preferable term would be "societal informatics" in that this incorporates the broader societal determinants of health which refer to, "… the political-economic order and structures of power, in which health inequities derive from elite groups wielding power against oppressed groups. As such, addressing the societal determinants of health requires fundamentally rectifying unequal political power" (Birn 2011). This is particularly relevant for the First People of Australia whose latest attempt to wield some political influence was crushed with the Federal Government's dismissal of their Uluru statement (Mayor

2018). Additionally, a societal determinants of health framework has been suggested in order to move the Global Mental Health Movement from narrow individualized interventions to a more emancipatory direction (Cosgrove et al. 2020).

8.4 *Moving Upstream from Repair Shops*

More hospitals are not the solution to health challenges (Duncan et al. 2020). Whilst 'repair shops' are necessary, there is also the need to take action on the causes of the causes of diseases by tackling upstream factors (Kiran and Pinto 2016). But the swim upstream is going against the tide thanks to the anomaly of how healthcare system measures its activity. This was criticised by the Australian Financial Review in 2010 saying that "Failures (death rates) are measured well, but success is not–not measuring patient improvements is akin to a business that does not measure profit (Scott 2010)."

Societal informatics could not only be useful but also could be revolutionary in countering this anomaly by contributing to a greater understanding of causes of morbidity and mortality. For example, societal informatics could be used by doctors

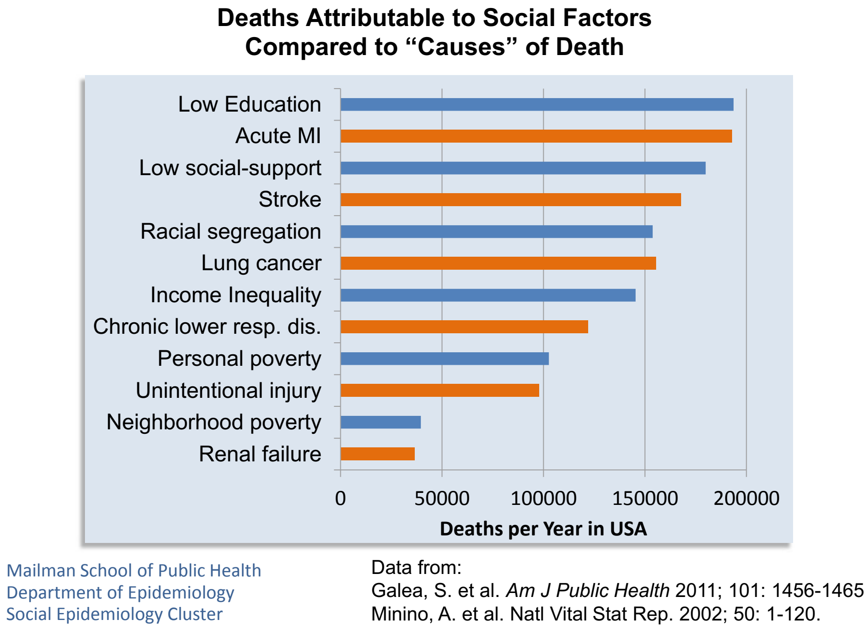

Fig. 3 Deaths attributable to social factors compared to "causes of death". From Galea et al. (2011) and Minino et al. (2002) Graph created by and reproduced with permission from Andrew G. Rundle, Social and Spatial Epidemiology Unit, Department of Epidemiology, Mailman School of Public Health

to decide what to write on death certificates as contributing factors to the causes of death. This idea was prompted by studies published by Professor Sandro Galea and his team. The following graph demonstrates the results of their estimation of the number of deaths attributable to social factors in the United States comparable to the number attributed to pathophysiological and behavioural causes. Their findings argue for a more expansive policy approach that considers how social factors can be addressed to improve the health of populations (Galea et al. 2011). As shown in Fig. 3, education level is one the most powerful social influences on health which is in accord with the well-established association between the level of education and health (Albert and Davia 2011; Cohen and Syme 2013; Fiske et al. 2014; Ahmady, Akbari and Lakeh 2015). It is particularly relevant for the First Nations People of Australia (Hart et al. 2017). Whilst the association is not causal, a Mendelian randomisation study suggests there is causal relationship between the common causes of death, coronary heart disease and educational level (Tillmann et al. 2017). This adds to the argument for investing in education for the greatest return on investment in achieving health outcomes (Campbell et al. 2014).

A corollary from this is that one of the most valuable societal informatics would be a measure of child development. Indeed, such a measure, the Early Development Instrument (EDI), was developed in Ontario, Canada (Janus and Offord 2007) and trialed for applicability in Australia (Hart et al. 2003). A follow up study of the cohort of 5-year-old children who participated in the WA trial revealed associations between the early development instrument at age 5, and reading and numeracy skills at ages 8, 10 and 12 (Brinkman et al. 2013). Accordingly, there is the potential to predict the future health of children from the EDI (Forget-Dubois et al. 2007). Australia is the first country to adopt a slightly modified version of the EDI to become the triennial Australian Early Development Census in 2012 generating almost a thousand articles and many interventions in late 2021 according to Google Scholar.

Do medicine-based informatics, engineering, biomedical devices and apps pass the test of their potential to reduce the life expectancy gap between the First Nations People of Australia and the rest of the population? The potential to do so is possible with some modification. Rather than medicine based, but societal determinants-based informatics are already proving to be valuable especially if they will be applied to assess the new 16 revised Closing the Gap targets with more than half focussing on the early years and childhood (Williamson and Markham 2020). Biomedical Engineering could step up to the mark in helping First Nations Children to hear—otherwise it is difficult to learn (Su et al. 2020) whilst awaiting action on the social determinants of otitis media. (DeLacy et al. 2020).

9 Conclusions

The challenges the societies all over the world are facing are calling for people-centric, horizontal approach to health and well-being where care is the prevailing driver of the doctor-patient relationship. Quality of life means less expense for the state, therefore the accountability and stewardship over health and well-being is a societal asset. Caring means stronger community sense, helping to minimize loneliness which is more damaging to health than smoking. There is a universal truth that one cannot be healthy alone. So, we need an holistic approach to national, international, and global health with a global regulator overseeing the implementation of digital solutions.

Relationship-based health system, focusing on preventive care, means better society, less sick leaves, better cooperation with Nature, more content individuals. We have enough empirical data to lead the transformation of the health system towards sustainable solutions. We have enough empirical data to create new metrics of progress to see what delivers desired results, focusing us on indicators and analysis, honouring the real sources of health distress, like socio-economic factors, climate, genetics, and organize the health systems around them.

There is no good example of a sustainable national health solution available today, however, positive examples from smaller communities fuel the optimism that it can be done. Investors hold an important key for better outcomes in health systems, especially since the money currently invested in the health system is not creating healthier people. We hope that with green agenda being prioritized all over the world, health will get more attention and smarter measures of success.

There is room for disruptive innovation that can lead to improvement in health and well-being. But above all, we are at the crossroads, health included, deciding on the future of humanity. There is an attractive proposition unfolding from a possible new civilizational paradigm, where technology could potentially be used only as a tool, and the quality of relationships will prevail as the primary value generator. We acknowledge that technology is a powerful tool and is here to stay. However, that does not mean that we can ignore the responsibility for its possible negative outcomes, especially, when they are penetrating such a sensitive area as health care systems. Human-centred health care is a decisive step into this direction. Health 5.0 is walking along the same path. Let us co-create it together.

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Clinical Practice, Patient-Physician Relationship and Computers

Alvaro Díaz Berenguer

Abstract Despite that technology organizes most tasks at lower costs and higher efficiency, human communication uses speech intonation, listening attitude and body language. As a special type of communication, the patient physician relationship enacts a particular exchange that simultaneously uses multiple languages and codes, all typical of human interaction. Patient physician relationship, even more so than other human communication, is based on the fact that the sender is able to perceive what the receiver perceives of the sender's own perception. In addition to gestures, body language, glances and barely perceptible elements like perspiration, the smell of skin and piloerection, clothes also communicate, such as white gowns worn by health care personnel, or the stethoscope. In the words of Lacan, two desirers meet during patient physician relationship: one that needs to be healed and other who needs to heal in an act of giving which comforts both. Through communication, physicians channel their power in a beneficial way: the introduction of computers may alter this channel. Computers in Medicine, as they are currently used, could become an obstacle for a proper patient physician relationship which may become alienating and the "other" disappearing as a person. Communication is then transformed into a sterile interaction ignoring the other's dignity which turns the patient into a machine-toy-cog. It is because of this, that some clinicians state that the most important element in the consultation room is not the stethoscope, nor the computer, but the chair.

Keywords Patient communication · Clinical practice · Machine-toy-cog · Medical informatics

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1 Introduction

The history of humanity is intimately related to the development of tools to master nature. Human intelligence interacts in a virtuous circle with the creation of different tools. Each one of such tools further enhances the capacity to create other tools in a meteoric path to evolution, a geometric evolution. Thus, human power is substituted, first by animals, and then by machinery. As from the twentieth century, elemental, "intelligent" processes of humankind have been taken over by computing and robotics. This has become even more relevant in the twenty-first century with the development of artificial intelligence, which mimics cognitive processes such as in machine learning. Scientific development occurs in parallel with this technological evolution, including Medicine in terms of knowledge and technology, as described in this book in the chapter by Vienni and Simini.

This process has left many workers relegated to the margins of the labour market. First of all craftsmen, then other employed workers after them. In the last decades, scores of white collar workers have suffered the same fate. Meanwhile, "Information and Communication Technology (ICT) specialists" are needed. This process, fostered by market in search for low-cost labour, has been evolving towards the creation of an "artificial being". Such a being would replace its flesh and blood creators in performing tasks at the lowest possible cost. Ultimately, an artificial slave (etymological origin of the word robot) would be created.

History seems to indicate that we humans look for someone or something to replace us in basic tasks necessary to live. We aim to create some being—identical to ourselves—which would obey us, but towards whom we have no moral obligations. Will physicians also be replaced by artificial beings, and thus, be redundant in the future? Will future physicians actually be robots?

2 Patient Physician Relationship

Let us consider the field of human communication, so typical of clinical activity, which cannot be substituted by computers, at least from a current-day perspective. Communication is a way of exchanging information based on the interaction between two entities, using for that purpose a specific tool called language. A language is based on a code which implies that both entities can decode it. Moreover, such decoding capability is determined and limited by a certain context.

In human communication, every language implies the existence of the "other", recipient and emitter. The very concept of "other" is a consequence of some language. It is thanks to language that we can recognize, consider and include the other (Díaz and Díaz 1997). The patient/physician relationship is based on communication, enacting a particular exchange that simultaneously uses multiple languages and codes, all typical of human interaction. Its fundamental substance is empathy; a perceptive resonance of the other, unto which the receiver projects itself to decode a message. Such projections are based on previous experiences, which begin to develop since the first moments of existence. Maternal stimuli and a cultural background that supplies the necessary codes, are essential to this process (Díaz 2004).

The following sentence is not a wordplay: ***human communication is based on the fact that the sender is able to perceive what the receiver perceives of the sender's own perception***. In this game of mutual resonance, of perceiving what the other perceives, it is possible that, for example, a mere look creates the obligation of responding to it (Díaz 2010, 2012). Namely, a greeting. The need of the other's recognition underlies all human communication; at the heart of it, recognition is what all human beings need. As stated by Lacan (1971), every human's desire is the desire of the other. Human language is based on what the other needs. Heidegger (2000) said that "language is the house of being"; it is the house of the existence of everything that surrounds us, thanks to the act of naming. Indeed, in solitude we still coexist with other(s). Even in silence, if another person appears on scene, their very mutual presence communicates and gives rise to moral considerations without actually having the intention to do so.

Human communication is also characterized by the use of multiple simultaneous languages, and therefore, multiple codes that vary depending on the context. It uses intonation and the intensity of the voice, beyond words and language. It employs gestures, body language, glances, and barely perceptible elements like perspiration, the smell of skin and piloerection, all of which are residues of archaic forms of animal communication. Clothes also communicate. The symbolic efficacy of white coats or gowns worn by health care personnel, or elements like the stethoscope, is undeniable. The same phenomenon occurs with the shaman's garbs, in prehistoric tribes or present day tribes hidden in the Amazon jungle. Several such codes are innate, and many others are learnt within a certain culture. In this regard, we do not need to look further than language, including expressions singular to distinct groups. Furthermore, the premises in which people interact, like the medical office and everything that is inside of it, are also a part of the communication system.

Something which we share with many animals, especially with gregarious animals, is yelling as a way of showing pain, as an alarm call to our kind. Compassion in the face of pain and human suffering can only be understood as part of an archaic and innate language, of which yelling is part of. The foundation of such language is empathy. Yelling evidences the existence of the other even in the absence of that other, given that pain triggers yelling even when there is no one there to hear it. In our subconscious mind, the other is always present.

3 Complementarity of Patient and Physician

In clinical medicine, human communication is remarkably important. It is the foundation of the dignifying process of the patient who is afflicted by denigrating sufferings. The essence of the patient/physician relationship can be found in communication. The term “communication” stems from the Latin word “communicare”, which means “make others part of what oneself has”. Communication implies an intimate act of “giving”, of “sharing”, where mutual desires and a cultural norm are implicit. “Giving” implies a certain sacrifice for the other and a pre-feeling of what the other feels. Coming from the notion of the other as a peer “like me”: this is related to a prehistorical morality which states that “do not wish for others what you do not wish for yourself” and, vice versa, “wish for others what you wish for yourself”.

Pedro Laín Entralgo defined the patient/physician relationship as an encounter between two beings in need, two desirers (in the words of Lacan), one that needs to be healed and other who needs to heal (Entralgo 1990). There is an act of giving between them which comforts both. This way of picturing the patient/physician relationship is only possible through an intimate, close communication, free of other interests.

Jacques Lacan said “and every word calls for a reply” (Lacan 1971). When communicating with a patient, the physician must always give an answer; which is what the patient is waiting for. Every patient brings questions and a call for help. In a way, physicians are seen and culturally understood as powerful and protective beings, able to predict the future, to give advice and to change destiny. A blend of doomsayer, magician and confident, the patient comes to them when any of such functions are needed, oftentimes with a visible narrative, sometimes with a hidden one, but always with a clear goal: help me and tell me what will happen to me.

Frequently, disease comes with feelings of shame and guilt (disease as a punishment). Hence, the physician must go deep into the sociocultural environment of the afflicted patient through the patient’s own narrative. The importance of this fact determined the birth of a particular way of re-elaborating communication known as “narrative medicine”, which emphasizes the assessment of the patient's biographical and social facts.

Through language we include or exclude, dignify or denigrate; we can get to know what the other fears and ignores, we can give hope, encouragement or discouragement. “Soulove” is a verb invented by Jacques Lacan which intertwines the words “soul” and “love”; thus, love restores the soul of the loved person. It is similar to the verb “to animate”. Such neologism brings back the concept of the soul from oblivion; a concept run over by science and almost outdated in the field of scientific medicine.

4 What is Essential is Invisible to the Biological Eye

The physician must clear out the relevant symptoms entangled in the patient’s discourse to build a scientific model of disease. In order to do so, the physician is required to have the skill to decode multiple languages and to grasp the situation of the patient, not only with respect to organic suffering, but also in terms of sociocultural environment, which is not always easy to do. Such phenomena as the exaggeration (or in the contrary, minimization) of the symptoms, sanity or deceitfulness, shame or guilt, must be evaluated and modulated by the irreplaceable experience of the examiner: a physician.

When building a scientific model of the disease to operate technically, the physician must dive deep into the model of disease that the patient has built to explain what is happening to him or her (Kleinman's 1981 anthropological interpretive model of illness). Thus, the physician must decode the patient's discourse in terms of fear, malignant influences, demonic possessions, bad luck, beliefs, guilt, relationship problems, and many other circumstances of daily life. The physician must intuitively understand the psychological problems in such a model, i.e., anxiety, depression, negation, and fury. Much of this construct remains hidden if we only focus on pathologies from an organic perspective; as Francisco Maglio said, reminiscing of Saint Exupéry "in Medicine what is essential is invisible to the biological eye". Just like the moon, patients have a hidden face, which can only be reached making use of empathy, compassion and special sensitivity.

All of the above shall be necessary not only for diagnosis, but also to establish a relationship of mutual trust, without which it is not possible to get the patient's approval and involvement in the treatment to be followed, as well as to address prognosis and its implications. Therefore, in order to lower pain, a painkiller is not always enough, but it is also necessary to help the patient understand the meaning and location of his/her existential reality, which also needs trust in the protective figure of the physician. Accordingly, the physician's response will be able to "soulove" the patient. The act of listening and the subsequent hopeful, inclusive, dignifying, human and supporting speech has a beneficial placebo effect. On the contrary, listening dismissively, and answering with a discouraging, pessimistic, exclusive, and denigrating speech produces a maleficent nocebo effect. Both forms of communicating (placebo and nocebo) have biological implications: they act as modulators of pain, achieving relief or exacerbation of such pain.

Through communication, physicians can channel their power in a beneficial, or in the contrary, a maleficent way. The absence of answers, and even partial answers, caused by interferences which make communication difficult, work towards establishing a maleficent effect.

In the current status of Medical Informatics, it is not possible to replace the physician in Semiology: i.e. to extract the basic elements of the disease model of the patient. It is also impossible to replace the physician in the communicative function of "giving" what the other (the patient) needs. Clinical approach begins with "questioning" or anamnesis. Francisco Maglio, with his acute human sensibility, prefers to use the term "listening booth/stage" ("escuchatorio"), because he considers the word "questioning" to be based on a forceful obtention of information, which in turn reveals a warlike conception of medicine. Such conception would look at diseases as the enemy in a war, in a similar fashion to the interpretation of the militaristic metaphors of Susan Sontag: therapeutic arsenal, magic bullets, etc. The patient, then, is exclusively the "terrain" in which those militaristic actions happen, excluding him/her from being considered the crucial element. The term "escuchatorio" (literally a booth to listen to) proposed by Maglio is based on the premise that the obtention of data in the first place comes from a spontaneous discourse of the patient which naturally derives into the assessment of his or her suffering.

5 Introduction of Computers

The inclusion of computers, as they are currently used, may be an obstacle for a proper patient /physician relationship. The threat of introducing computers in the clinical environment was already brought to light by Francisco Maglio: "The patient/physician relationship is *technologized* and *dehumanized* (Maglio 2012). That is why it is alienating and the "other" disappears as a person".

There are several kinds of interferences in communication. For example, a bad disposition to connect humanly with the patient due to permanent or circumstantial personal reasons of the practitioner, the lack of empathy and motivation, or even burnout. There can also be reasons unrelated to the physician, like environmental noise, fragmentation of the health care system, exaggerated demands from the patient, defensive medicine, imposition of guidelines and protocols for action regardless of the specific patient, or an ill designed computer program interfering from the PC screen. Oftentimes in these circumstances the patient may ask the physician—or at least think—"Doctor, please look at me, not at your PC monitor".

The overwhelming development of technology and computing has caused a loss of trust in good old medical semiology, both in physicians and patients. The technological aspect is overrated, especially in relation to the diagnosis. At the same time, there is a tendency towards automation; towards "cybernetic medicine" of Eric Fromm, centered around the body as a "bio machine". Guidelines and protocols have also been overrated and applied without taking the singular characteristics of each patient into consideration.

Therefore, with intrusive computers and unadapted guidelines, communication is transformed into a sterile interaction ignoring the other's dignity which turns the patient into a machine-toy-cog. This overlaps with last century's perspective of human beings, as a product of an assembly line as first described by Henry Ford: uniformity and automation extrapolated to clinical medicine. It would not be surprising that in such circumstances the patient's narrative is relegated to the background, which means that the patient himself or herself is left out of the scene. This situation causes feelings of mistrust and being disregarded which hamper any relationship with the physician. Questions regarding "the future" or related to the guilty sense of "sin" of the disease, do not come to the surface and are therefore left unanswered. The patient leaves the physician's office in a state of discouragement and hopelessness. Without reciprocal trust, the patient/physician relationship and related communication are diluted, as well as any subsequent adherence to indications.

"Screenism", or addiction to the computer monitor, does not only affect children and teenagers who wander the streets and squares without looking at their environment, but it also infiltrates the intimacy of homes and workplaces in our society today. The same happens in medical practice, where it isolates people from direct contact. In such a scenario, physicians are distracted from their main objective of making a patient physician interaction come true.

Medical Informatics (MI) has the potential to be an extremely valuable medical tool which must be utilized in a way that does not interfere with the clinical process. MI must not decrease the time spent on human relationships and should not hinder achieving the necessary depth in communication. MI must be careful NOT to place too much attention on monitors and automation. Indeed, MI should help to avoid non-critical clinical guidelines compliance to avoid displacing the traditional semiological technique in favor of technology, and to avoid transforming physicians into automata, mirroring some software designed from outside Medicine.

Although computers can be of help in the clinical process, it is also a tool of control and oversight over medical practices, reducing the freedom of action of the once accepted "professional" discretion. The physician liberal profession has been lowered in hierarchy or proletarianized and, as such, has been regulated around the concept of productivity, following industrial or commercial models. And this was done concomitantly with the introduction of computers in clinical practice. Using software conceived from an industrial production point of view, physicians are forced to comply with administrative algorithms or institutional protocols. The level of satisfaction of the patient as a user is also being controlled, as well as the medical visit time, the number of patients seen per hour, and the number of prescriptions ordered or diagnostic procedures issued per month. The physician is then reprimanded when some standard is not fulfilled.

6 Conclusion

In many ways, all members of the globalized and technological society of today rely heavily on computers and ICT, which also means everyone is being controlled, observed, assessed, valued, manipulated, and judged. It is increasingly frequent that patients bring their own diagnosis out of the Internet and expect that the physician performs some specific procedure, hindering all opportunity to follow the different stages of the clinical process. The patient, manipulated by the marketing of expensive medicine, may demand diagnostic procedures or treatments which are not available locally, or that are not publicly available or even not applicable to the case at hand. Every refusal, or even a mere questioning, from the physician is received with distrust. Usually the physician, fearing a potential lawsuit, complies with the demands of the patients, even in disagreement. This situation creates an unnecessary increase of procedures and medication prescriptions that could even be hazardous, in addition to unnecessary costs.

Sigmund Freud, in the advent of the twentieth century, disclosed the power and scope of the spoken word. The power such a tool has over human beings is the basis of psychic treatment. For this to be executed in clinical medicine, i.e. beneficence as the main objective above any other, communication must happen in a certain intimate “context”: with enough time, in a quiet place, patiently and serenely, with all the attention placed upon the person in front of us, physician in need of “an other” to heal. Not in the sense of a psychoanalytical treatment; but as the treatment that someone who consults for low back pain, flu or a tumor should receive. It is because of this, that some clinicians state that the most important element in the consultation room is not the stethoscope, nor the desk, or the computer, but the chair.

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Interdisciplinary Collaboration Within Medicine-Based Informatics and Engineering for Societal Impact

Bianca Vienni Baptista and Franco Simini

Abstract This chapter elaborates on the challenges and opportunities that interdisciplinary collaborations have for Medicine, Informatics and Engineering. It argues that interdisciplinarity is a means to better approach current societal challenges and therefore to achieve meaningful impact on current problems, as the ones presented in this book. We seek to open a fruitful pathway to reflect on the urgent demand to bridge knowledges, perspectives and insights, that help to overcome crisis such as the current Covid-19 pandemic. In so doing, we identify challenges coming from a national and international perspective and we analyze them in the light of a Uruguayan interdisciplinary program: the Núcleo de Ingeniería Biomédica of the Universidad de la República (Uruguay). This program has been working for almost 40 years in the interface between Medicine and Engineering, training scientists and researchers in how to foster meaningful solutions to health problems. Lessons learnt and successful narratives are presented as means to promote interdisciplinary collaborations between these and other fields of knowledge. We also build on general and also specific research strands that have historically pursued collaborations among different disciplines to approach complex problems. Several examples have also been provided in this book so as to include two powerful ideas to leverage BME and MI as means to achieve socially robust solutions for health and well-being. As chapters in this book show, the development of biomedical devices, software and systems must stem from clinical wish lists and desiderata. Technology follows, in these cases, medical specifications applying an interdisciplinary approach.

Keywords Interdisciplinary research · STEM disciplines · Biomedical engineering · Uruguay · University programme · Societal impact

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1 Introduction

Science and technology have interacted in an ever increasing depth since the beginning of speculative thought, which is approximately the time when civilizations have started their written history, i.e. when documents in writing were produced.

Ancient Greek culture was the place and time where the pleasure of thinking and the satisfaction of intellectual speculation were developed and socially valued. Philosophy was made possible by long hours with no material nor practical burden on the shoulders of free citizens. Within an ideal framework of social interactions, geometrical theorems and other speculative forms of science were considered to be of great importance, challenging and reaching the aesthetic characters of beauty. The practical aspects of life—left to be taken care of by slaves—dealt with the evolution of technology, be it food preparation, house building, crop growing or materials management. Very little contact—if any—was developed to enhance technology using results of thinking, speculation and theorem demonstration. Different people and different communities dealt with each activity of the dyad science and technology.

Therefore, the origins of Science and Technology are different and clearly separated, the former being originated by intellectual curiosity and the latter by practical barriers to be overcome. The increasing sophistication and complexity of our culture is having the effect of bringing Science and Technology to a close synergy, together with society in three vertexes bidirectional dialogues. By doing so, the original dyad was challenged to include the societal perspective in this equation. Science, Technology and Society studies (STS) have become a means to understand and to problematize the relationship among these (Hackett et al. 2008; Jasanoff 2005).

Technology tackles complex problems today to produce simple usable goods and services. Its complexity implies an interdisciplinary approach to better approach multidimensional problems that foster improved quality of living conditions. The complexities of practical problems call for new knowledge which is the result of research devoted to augment the scope and specificity of technology (Bammer 2008; von Bertalanffy 1968).

In an ever increasing fashion, Science, Technology and Society interact closely as a system according to the observations and theory put forward since 1940 by von Bertalanffy (1968). With the difference that almost a century ago, von Bertalanffy and contemporaries longed to “improve communication among specialists” (von Bertalanffy 1968) while full scale interdisciplinarity (ID) is necessary in the present century.

This chapter elaborates on the challenges and opportunities that interdisciplinary collaborations have for Medicine, Informatics and Engineering. It argues that interdisciplinarity is a means to better approach current societal challenges and therefore to achieve meaningful impact on current problems, as the ones presented in this book. We seek to open a fruitful pathway to reflect on the urgent demand to bridge knowledges, perspectives and insights, that help to overcome crisis such as the current Covid-19 pandemic. In so doing, we identify challenges coming from a national and international perspective and we analyze them in the light of a Uruguayan interdisciplinary program: the NIB (Núcleo de Ingeniería Biomédica of the Universidad de la República, Uruguay). This program has been working for almost 40 years in the interface between Medicine and Engineering, training scientists and researchers in how to foster meaningful solutions to health problems. Lessons learnt and successful narratives are presented as means to promote interdisciplinary collaborations between these and other fields of knowledge.

The chapter is organized as follows: first, we look at the definition of interdisciplinarity and present the challenges that Science, Technology, Engineering and Mathematics (STEM) currently face as separate disciplines. We argue for more collaboration between them and Arts, Humanities and Social Sciences (AHSS). More specifically, we analyze the implications of the challenges of integration in collaborative research. We then detail the historical conditions that helped integrate Medicine into STEM. Next, we provide the example of the interdisciplinary program NIB, as a successful example of such encounters. We conclude with some insights on how these interdisciplinary collaborations provide a fertile territory for societal impact outcomes within STEM and Medicine (STEMM).

2 Interdisciplinarity and STEMM Disciplines

The progress of interdisciplinary collaboration is fundamentally entwined with the process of social research and the societal context of doing science (MacMynowski 2007). Within this framework, our perspective on ID corresponds to a twenty-first century vision of the problem of how different disciplines interact and collaborate towards approaching current societal challenges (following Bammer 2008). In this section, we present the main challenges of what we understand as interdisciplinary collaboration(s) between STEMM (Science, Technology, Engineering, Mathematics and Medicine) and AHSS disciplines (Arts, Humanities and Social Sciences).

Interdisciplinarity is a widely used term, particularly as part of present efforts to transform the relations between research, economy and society. Most generally, ID is understood as:

> a mode of research (…) that integrates data, tools, (…) perspectives, concepts, and/or theories from two or more disciplines to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline (National Academy of Sciences 2005: 4).

Beyond this specific understanding of the term, other definitions are possible and coexist within the academic literature (Vienni Baptista et al. 2019). When facing the challenge of defining ID, these concepts still represent contested discourses that reveal an interwoven set of different understandings of the term (e.g. Barry and

Born 2013; Klein 2017; Lury 2018; Lyall 2019). Differences are meaningful when thinking the implications for the roles assigned to different disciplines in collaborative work (Vienni Baptista et al. forthcoming).

A main feature of all definitions include the important role that integration has in interdisciplinary research. Integration is a process to combine and synthesize different concepts, methods and/or theories from two or several fields of knowledge in different stages of the research process. It is considered "the core methodology" (Pohl 2008: 421) of collaborative research.

ID implies activities ranging from individual to large-scale team-based initiatives integrating insights from other disciplines, such as the one we present in this chapter. The purpose of interdisciplinary collaborations varies depending on the research aims and specific questions it addresses; both determining the scope that the synthesizing process may achieve. For instance, Mäki (2016) contrasts managerial top-down interdisciplinarity with practitioner bottom-up interdisciplinarity. In what follows, we focus on the second type of interdisciplinary initiatives.

Integration, as the basis to build a collaborative endeavor, needs to be guided using different methods and tools (Pohl et al 2021). One challenge of successfully fostering integration is finding adequate forms of collaboration between researchers and practitioners (Pohl and Wülser 2019). Violeta Bulc (in this volume) argues that these bridges are necessary and require specific skills from researchers and societal actors to build a common ground for collaboration. The "Society 5.0" concept includes ID as a distinctive and identifiable aspect of modern and future human life organization.

The promotion of ID has come to be central to the governance of research (Barry and Born 2013). Despite the long history ID has in different fields of research, integration is still weak between some disciplines. Many factors that hinder ID are associated to what Snow (1964) defined as the "two cultures" as it constitutes a significant influence in attempts to bridge AHSS and STEM.

Efforts to connect disciplines are present in different countries as part of science policy efforts. Currently, the Irish Council of Research (2018), to give one example, characterizes its legacy as "STEAM" research: this is research combining knowledge from Science, Technology, Engineering, Art and Mathematics. In a recent study at the European level, Medicine was also included in this equation, defining STEMM as Science, Technology, Engineering, Mathematics and Medicine (Vienni Baptista et al. 2019, 2020a). It can be argued that none of these terms are new but need to be incorporated more widely into policy to have a real effect on practice (Irish Research Council of Research 2018). In this regard, ID that focuses on challenge-based research accompanies current trends from funders and policy makers world-wide (Kania et al. 2019; Bammer et al. 2020).

STEAM approaches are crucial to understand the social and environmental interactions and their implications and impacts on solutions to grand challenges (De la Garza and Travis 2018). Emerging fields of knowledge and bridges between them build interactions on boundary-crossing exercises and experiments (Klein 2005). These cross-fertilizations are becoming more relevant than ever (de la Garza and Travis 2018), especially in fields as the ones this book focuses on. A multitude of science policy actors, such as research funders, policy makers, journal editors, think tanks and research lobby organizations, all seem to agree that the future of science is to be found outside of firm disciplinary boundaries (Stamm 2019: 376) and well into interdisciplinary research.

In this sense, Arts, Humanities and Social Sciences are also faced with the need to position themselves as part of the current realm of knowledge; including their own definitions of ID. Not only by taking roles that might have an instrumental function, but also by facing conditions that affect their success or failure as disciplines in the scientific environment. We argue that instrumentalization of AHSS disciplines has pervasive consequences on potential interdisciplinary research (Vienni Baptista et al. 2020a) as the evidence from a recent Horizon2020 project confirmed. The project "Shaping interdisciplinary research practices in Europe" (SHAPE-ID)[1] has done an extensive literature scanning exercise on a large set of academic and policy literature on inter- and transdisciplinary research (Vienni Baptista et al. 2019). Authors proved that the Social Sciences and STEM interactions are more diverse than in the case of AH-STEM. While AH connects strongly with Social Sciences, Engineering, and Computer Science; Social Sciences connect strongly with Arts and Humanities, Environmental Science, Business Management and Accounting, Medicine, Computer Science, Engineering, Economics Econometrics and Finance, Psychology, Earth and Planetary Sciences (Vienni Baptista et al. 2019).

This shows that the AHSS-STEMM gap remains a significant challenge in practice and policy (Stamm 2019). MacMynowski (2007: 3) considers that.

> evaluations of interdisciplinary research in journals targeted at biophysical scientists include virtually no citations from the social science literature on disciplinarity and interdisciplinarity; even of one of the most widely cited books on the history, theory, and practice of interdisciplinarity is absent (i.e., Klein 2005). Likewise, in the social science literature, there are virtually no citations from the biophysical literature. The two discussions are running in parallel with stunningly little crossover.

The academic and policy literatures show successful examples of AHSS integration in interdisciplinary research should look like, but there are few factual ideas about how this integration can actually be achieved (Fletcher and Lyall 2020). Examples from practice as the one developed by NIB and described in this book by Martha Ortiz, Marta Bez and Violeta Bulc provide meaningful suggestions that can be replicated in diverse academic contexts associated with social initiatives. For its part, a recent movement within the British Academy proposed the acronym SHAPE for Social Sciences, Humanities and the Arts as a joint movement for the people and the economy (British Academy 2016). SHAPE is:

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[1] Some of the outcomes detailed in this section are framed in the project "Shaping interdisciplinary practices in Europe (SHAPE_ID)", which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 822705. More details on the project: shapeid.eu.

> a new collective name for those subjects that help us understand ourselves, others and the human world around us. They provide us with the methods and forms of expression we need to build better, deeper, more colourful and more valuable lives for all (British Academy 2016: 1).

While policy reports frequently advocate for the contribution AHSS disciplines can make to solving societal challenges, the academic literature suggests that there is often a perception that humanities researchers have little to offer and their contributions are difficult to understand and integrate (Callard and Fitzgerald 2015). There are indications that few in the sciences are aware of what humanities researchers can contribute, and that few in the humanities are aware of it either (Robinson et al. 2016). Following Snow, Robinson et al. (2016) argue that the lack of interdisciplinary interaction involving scientists and humanists is less about hostility and more about mutual ignorance.

One of the main challenges that AHSS currently face is related to how disciplines are grouped under the labels used to refer collectively to the Arts, Humanities and Social Sciences—'AHSS' and 'SSH'—. These labels obscure important differences between disciplines that bear on the different ways they position themselves in relation to doing interdisciplinary research and to interactions with other disciplines like the STEMM (Vienni Baptista et al. 2019).

Interdisciplinary collaborations also have long traditions in Latin America (Simini and Vienni Baptista 2017) but differences between countries pose difficulties to researchers in finding a community of practice and participating in associations and networks. Moreover, scientific papers are published in different journals, partly due to the lack of specialist publications, and researchers often face substantial obstacles trying to publish their results. Gaps in the literature, widely dispersed findings and scattered literature are key challenges in interdisciplinary research, as also proved in the European context (Vienni Baptista et al. 2020a).

These challenges cause that ID is not yet mainstream and is questioned by institutions, policy makers and researchers alike (Vienni Baptista et al. 2020a). It is rendered invisible in many academic spheres and its outcomes are not always taken into consideration by research institutions, policy makers and funders (Fletcher and Lyall 2020). This implies that systematizing the features that ID has in different contexts is an intricate task: scientific papers, reports and internal documents from funding agencies and research organizations, randomly and selectively promote the advantages of interdisciplinary research.

Above all these levels of complexity imposed to the concept, ID reveal differences that have to be taken into consideration when AHSS disciplines are to be integrated. Callard and Fitzgerald (2015), for example, consider that there are real opportunities for collaboration between the social sciences and the neurosciences. These opportunities are often occluded by the narrow discursive range of contemporary understandings of interdisciplinarity. We argue that many problems related to interdisciplinary research and its conceptualization relate to the current state of research and its obstacles (Vienni Baptista et al. 2020b). There are specific challenges that ID needs to face in order to transform factors into positive conditions for research. Interdisciplinary research imposes a new level of complexity to research practices, one that is it still not yet fully understood by researchers and funders at large (Vienni Baptista et al. 2020b).

Committing to interdisciplinary research pose different risks and benefits for researchers in terms of the balance of transaction costs and collaborative benefits (Feng and Kirkley 2020). The motivation for researchers to participate in interdisciplinary research highly depend on the evaluation of such perceived risks and rewards. Increasing attention is directed toward better understanding the factors driving collaborations among researchers (Boix Mansilla et al. 2016). Nevertheless, further research is also needed to explore the conditions affecting the success of research collaborations in interdisciplinary research (Feng and Kirkley 2020) and specifically concerning how STEMM disciplines can facilitate integration processes (Vienni Baptista 2009, 2020a), as shown in the next section.

3 Opportunities for Medicine Within STEMM

After centuries all branches of knowledge which included Astronomy, Mathematics, Engineering and fine Arts, experienced deep interrelations during the period known as the Renaissance (Snow 1964). The paradigmatic case of Leonardo can be mentioned as an engineer solving mathematical problems, studying Anatomy and producing remarkable paintings. But in modern times, special careers and specialists arose which separated the different disciplines to meet the requirements of the new phenomenon of industrialization. Medicine was left to the medical corporation, engineering to engineering schools and professional bodies, while science took a different path adopting the speculative attitude, taking distance from production, the fine arts and human experience. For two centuries specialization took Science, Technology, Engineering and Mathematics apart, arriving at the beginning of the XXI century as substantially separate bodies of knowledge. The first reaction may have been the theory of systems by von Bertalanffy (1968: 29) who at the beginning of the second chapter of his most cited book reveals:

> Modern science is characterized by its ever-increasing specialization, necessitated by the enormous amount of data, the complexity of techniques and of theoretical structures within every field. Thus science is split into innumerable disciplines continually generating new subdisciplines.

As a reaction to this specialization and the growing complexity of problems to be solved along with the sophistication of the products expected by an increasingly demanding market, the concept of ID arose (Vienni Baptista et al. 2020b). One could say that the Renaissance approach is again present in researchers who follow ID, but in a less “amateurish” way, if the expression is allowed. A Renaissance person could have notions of what became known as different fields of knowledge, such as Anatomy, Geography, Engineering, Mathematics, History and Humanities. The relatively incipient nature of these areas was such that the synthesis could be made by a single person during a lifetime. A similar interaction of diverse knowledges happens in ID, not within an individual but as collective work of several cooperating specialists. By introducing ID, contemporary organization of research is reinstalling the broad scope of methods, models, and information which characterized the Renaissance. Additionally, the production of goods and services is increasingly associated with academic research. The cooperation between Science and Engineering, sometimes also including Mathematics, is a specific characteristic of twenty-first century industry (Sábato 1979).

Biomedical Engineering has been developing during more than a century to provide Medicine with instrumentation of growing complexity and specificity as technology and theoretical tools became available (Bronzino 2006). To the initial cooperation of Engineering and Medicine, Informatics—which is a specialized branch of Engineering—is also added in the design of technologies to be used in Medicine. Medical Informatics starts to produce clinical software shortly after computers were used for the first time in ballistic, scientific or commercial applications. Informatics was first seen in hospitals as payroll and administrative systems, later also in electronic clinical records systems. The mutual interaction of Informatics and Medicine has allowed over the decades to develop a separate field of study and a profession devoted to clinical records and patient management. Albeit initially the Informatics approach to Medicine has been limited to a mere translation of commercial processing concepts from “products” and “transactions” to “patients” and “physician/patient relationship”, over the years interdisciplinary cooperation modified Medicine. Physicians now use more statistics, expect clinical records to be available over the internet and make some use of diagnostic aids (Simini et al. 2019).

In a reciprocal way, once clinicians grasped the telematic potential, they are inducing Medical Informatics to be conceived from a medical perspective and help to abandon the simple paradigms of early industrial or commercial systems. Personal assistants to help “solve” patients in less time and with higher chances of success are designed based on typical medical intellectual itineraries rather than product stocks or sales logic. One typical example is PRAXIS (Simini et al. 2019), a software designed to acquire medical office data and to turn them into a powerful “suggestion machine” for each future patient, based on the accumulating experience of the MD user. Additional evidence of Medical Informatics being reformulated to adopt a medical starting point is found in the recently patented concept of “prescription Apps” (Simini et al. 2019) by which a personalized App is installed in the patient´s mobile phone to perform follow up tasks. Thanks to the telematic capacity of recent Medical Informatics, the follow-up becomes active, personalized and omnipresent in everyday life, at very low costs. Pregnancies can benefit from close monitoring (Simini et al. 2019), cardiac failure can be managed for long periods of time optimizing quality of life (Simini et al. 2019) as opposed to frequent drop-outs with sometimes ominous consequences and persons with diabetes can be helped on a regular basis with reminders or active inquiries triggering useful tips over the years.

The societal impact of Medicine with Medical Informatics tools is relevant because it has the potential to foster optimal adherence to treatments and compliance to preventive Medicine practices. Medical Informatics acquires an indirect relevant role in people's health by allowing a better medical care at very low costs and therefore available to increasing cohorts of citizens. The societal impact of MBEI may be evaluated looking at medical and epidemiological statistics, where the extent of disease or quality of life can be estimated. For example, during the current COVID-19 pandemic, a Bluetooth based App can help trace contacts after an infected case is detected, thus cutting to some degree the contagious spread of the disease.

In a mutually stimulating fashion, clinical work and engineering tasks adopt each other´s mindset to accomplish biomedical engineering and informatics projects of ever increasing complexity. This is the result of putting in practice the interdisciplinary approach to complex problems (Vienni Baptista and Simini 2018). As a consequence, medical perspective changes when exposed to engineering methodology, nomenclature and reasoning. After a Medical Informatics course during the last year of medical training, students admit their perspective and expectations change with respect to Electronic Medical Records or to diagnostic assistance. From a semi “magic” concept of cybernetic mysterious tools, they acquire the general concepts of data processing, data matching, artificial intelligence and algorithms. All of which stimulate their clinical use of new MBEI tools (Vienni Baptista and Simini 2018).

Conversely, consider the following example: last year Engineering students who declare a preference for biomedical applications are asked to be present during neuro-pediatric rehabilitation visits. Study of the biomechanical, cognitive and communication difficulties of every child, and conversation with clinicians after patient and family have left, allows the engineering students to suggest tools, Apps or instruments to overcome the disability they have seen. The clinical perspective has thus modulated the engineering capacity to suggest either existing or new technological solutions, case by case. Not to mention the empathy stimulated in the engineering student as motivation for further work and study.

The Núcleo de Ingeniería Biomédica (Universidad de la República, Uruguay) described in the next section is but one of hundreds of academic groups in Latin America devoted to the identification, specification, design and testing of new devices, models and software tools to be used in clinical practice. Medicine comes into the interdisciplinary space both giving and receiving ideas for creativity, innovation and further societal impact.

If technological elements are clearly influencing Medicine, the opposite can also be found in examples of biological models turned into technology to be used in all areas of Engineering. For instance, consider the well-known “Schmitt Trigger” which is an electronic circuit opening in a ON/OFF fashion as a consequence of some input signal compared to a given threshold (Schmitt 1938). The circuit evolved from neurophysiology research performed by Otto Schmitt, on the firing of giant squid neurons taken as an animal model of human neurological transmission. This case can be taken as an example of a Biological or Medical contribution to Electronic Engineering, since the Schmitt Trigger has been used extensively as a building block in the design of circuits of all sorts and for decades.

The interaction within once-separated knowledge branches such as Science, Engineering, Technology must include Medicine as a major partner, not only as a beneficiary of new techniques but also as an original source of problems and requirements to stimulate theoretical and applied research. Societal impact of such encounters are also larger as the interaction with patients allow for solutions that are problem-based. This has proved to be a fertile space in Latin America and specially in Uruguay, as detailed in the example we present in the next section.

4 The Núcleo de Ingeniería Biomédica: A Fertile Landscape for Interdisciplinary Encounters

Biomedical Engineering (BME) has proved to be a fertile territory for introducing new technology to develop research and teaching formats that adequately involve interdisciplinary collaborations. Although this is true, ID still needs a great amount of personal interaction and face—to—face work to achieve its full potential. In this case, the permanent contact and active relationship with patients and clinicians are the basis for a better development of prototypes in contexts where these interactions are rare and may derive into unwanted health problems, as the experience of Núcleo de Ingeniería Biomédica shows (Biomedical Engineering Node) (NIB for its acronym in Spanish) (Simini and Vienni Baptista 2017; Vienni Baptista and Simini 2018).

NIB is an interdisciplinary group of the Faculties of Medicine and Engineering of the Universidad de la República in Uruguay. Founded in 1985, it has focused on the development of BME as a contribution to the solution of medical challenges. The group is placed at the boundaries between physiopathological and clinical approaches through the development of engineering prototypes to support research, teaching and outreach (Simini and Vienni Baptista 2017; Vienni Baptista and Simini 2018). The study areas of NIB have allowed to go beyond the rationale of each discipline, fostering the solution of medical problems by means of technology transfer (Simini et al. 2019).

The NIB has an interdisciplinary approach to train professionals in Biomedical Engineering, capable of facing the challenges of medical and biological instrumentation. This approach is translated into research projects and students thesis. NIB is an example of how interdisciplinary collaboration can be achieved in Higher Education research and teaching activities with a focus on Biomedical Engineering and Medical Informatics. By evaluating these scientific research and teaching practices we aim at contributing to the definition of institutional policies that better support them. Systematizing the similarities and the learning strategies within the university context may favor the conduction of research on societal problems and scientific democratization through a better use of new technologies, including Informatics.

NIB seeks the immersion of engineers in a clinical environment and the joint work of scientists of different academic backgrounds to favor a gradual osmosis of knowledge and even language (jargon), values and work objectives. For these reasons, students and researchers at NIB are embedded in a meaningful dialogue to understand clinicians and physiology researchers. The culture, the habits of communication and reasoning of an engineer differ from those of physicians, whose training follows different intellectual processes and therefore develops different mental reflexes.

A Biomedical Engineering or Medical Informatics project usually starts from a problem in clinical practice, management or some adverse result. All are interdisciplinary by definition. The general description of the desired instrument, software or setting is seldom given by clinicians alone as there is a need to refine or confirm the goal during engineering sessions. BME and MI are intrinsically a two sided activity where medical concepts are enhanced with all available theoretical and practical assets. The following is a review of only three case studies taken from the extensive experience of NIB in the last decade, from 2010 to 2020 (other examples are described in Simini and Vienni Baptista 2017).

A. The problem: Chronic patients are lost to follow up. Cardiac failure patients are asked to periodically come to medical visits where clinical evaluation allows to adjust medication, nutritional counseling based on clinical records, measurements and lab results.

SIMIC (Spanish acronym for Cardiac Failure Management System) is the result of an interdisciplinary discussion where the goal of securing patients and keeping in contact with them was revisited. No personal calls are possible, no human memory is enough to manage hundreds of patients and to keep them informed and willing to come to consultation. A new concept arose (Patented), that of a "prescription App". SIMIC would be a set of recommendations, questions and alerts which the physician agrees with the patient to install in his/her mobile. During normal life SIMIC acts as a constant, and yet discreet, reminder and data logger, analyzing data to emit alerts based on algorithms taken from best practices. Additionally, ominous combinations of variables and timing trigger alerts dispatched to the health care team.

B. The problem: Parkinson patients need more rehabilitation hours. Guided gait is limited by staff availability.

PARKIBIP (Spanish acronym for PARKInson disease rehabilitation by BIP sound feedback stimulation during gait) is the result of an interdisciplinary discussion where the goal is to have patients walk with no professional assistance and yet be stimulated by sound and continuous guidance. PARKIBIP is an active wearable device which detects all movements of both limbs, analyses gait and emits sounds (bip) or words to encourage the patient, at the right time, to lengthen the step or to reduce gait frequency.

C. The problem: Pregnant women seldom comply with recommendations. Treatment opportunities are lost due to delayed consultation. Active Medical Follow up is not possible due to cost and staff availability.

SEPEPE (Spanish acronym for Personalized Perinatal Follow-up) is the result of an interdisciplinary discussion where the goal of detecting signs during normal life at home suggested an App. The spirit of the existing Perinatal Information System (SIP) is enhanced using ubiquitous communication and information technology (TIC): the perinatal passport in the hands of the pregnant woman was only used during medical visits at the antenatal clinic, while SEPEPE is programmed to be used recording data and answering questions at all times, under the initiative of the App. Two levels of alerts are available, one for the woman and the other for the health care team, only when a very serious situation is found to be compatible with data collected or missing data.

As part of the Universidad de la República, NIB has developed the three university missions: research, teaching and extension, which in turn gave its characteristics to the group and to the interdisciplinary work. These three missions share interfaces that help to conceive interdisciplinary work as part of "integral activities" (Arocena 2010; Tomasino and Rodríguez 2010). The University missions, in addition, contribute in their complementarity to the construction of dialogue, research and development processes of biomedical solutions. Core activities include: (1) teaching courses and seminars, (2) research and development based on thesis (3) consultancies to other departments of the Faculty of Medicine, (4) strong relationships with institutions, publications and exchanges and (5) technology transfer to industry. In all these activities, NIB has been using ICTs as a fundamental tool to develop the interdisciplinary interface needed.

5 Conclusions

Complexity occurs in an increasing number of activities which play an important role in the production of knowledge. These activities include interdisciplinary networks, loans, shared interests, learning communities of faculties (Medicine, Engineering, Nursing, among others) and participation in different fields. The growth of BME and Medical Informatics in the last years responds to the availability of technological solutions to which researchers access to solve problems of increasing diversity. The clinician resorts to ID and the engineer proposes new solutions as a consequence of the existence of an integral practice. Prototypes can be tested with phantoms and simulators before going to clinical application once safety and legal clearances are satisfied (Simini and Vienni Baptista 2017; Vienni Baptista and Simini 2018).

This concluding chapter elaborates on general and also specific research strands that have historically pursued collaborations among different disciplines to approach complex problems. Several examples have also been provided in this book so as to include two powerful ideas to leverage BME and MI as means to achieve socially robust solutions for health and well-being. The limitations of technology should no longer be considered as the starting point of design, because technology is so generous and abundant. Nevertheless, following technological capabilities alone can lead to irrelevant so-called medical applications. On the contrary, chapters in this book show that the development of biomedical devices, software and systems must stem from clinical wish lists and desiderata. Technology follows, in these cases, medical specifications applying an interdisciplinary approach.

BME and MI should merge into a single body of knowledge to better follow the demanding clinical challenges of modern Medicine. Interdisciplinary methods and theories developed in the last few decades provide promising means to achieve this (Bammer et al. 2020). Having mastered problems to be solved for survival, to repair physiological impairmentand to reduce pain, BME and MI are now asked to start from bedside and develop sophisticated tools to deliver better quality of life for increasing cohorts of ageing populations.

Within this framework, the book includes chapters of diverse authors addressing a range of fields wide enough to give the reader an overview of what to expect in the coming decades in BME and MI concerning new medical software systems, pervasive medicine, intelligent follow-up and implanted devices. This will also have a great impact on electronic clinical records and data analysis. The point of view of the book follows the academic experience of authors from different countries around the world, including Latin American entrepreneurs and scholars.

BME and MI have proved to constitute a fertile territory for introducing new technology to develop research and teaching formats that adequately involve interdisciplinary collaborations. Although this is true, our analysis of NIB practices has confirmed that ID still needs a great amount of personal interaction to achieve its full potential and overcome the challenges inherent to collaborative practices. An active relationship with clinicians is the basis for a better development of prototypes and societal impact (Simini and Vienni Baptista 2017; Vienni Baptista and Simini 2018).

Interdisciplinarity constitutes an important and rewarding practice in current times. If we acknowledge the fact that collaborative research has a substantive role in addressing and framing the complex socio-technical problems the world is facing today, we need new and sustained pathways to develop interdisciplinary research between AHSS and STEMM disciplines. To achieve this, change is needed urgently in research institutions, funding mechanisms, societal participation and policy measures.

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