Chapter 16
Flexible Electronic Devices for Biomedical Applications

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Abstract Recent advances in material sciences and microfabrication technologies have enabled creating flexible electronic systems that are able to integrate with soft tissues with curvilinear and dynamic surfaces. Remarkable features of these flexible devices have opened an array of opportunities in controlling disease conditions, improving surgical procedures, and continuous health monitoring. The overarching goal of this chapter is to provide an overview of current advances in the field of flexible electronics with emphasize on biomedical applications. We will primarily discuss the fabrication strategies and materials for the development of physical-, chemical-, and biosensors. In the second part, the emerging applications of flexible electronics in wound healing, wearable electronics, implantable devices, and surgical tools as well as point-of-care diagnostic devices, will be explored.

Keywords BioMEMS • Flexible electronics • Biomedical engineering • Biosensors • Wound healing • Implantable devices • Surgical tools • Wearable electronics • Physical sensors • Chemical sensors • Point-of-care diagnostics

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1 Introduction

Flexible electronics is referred to the technology of integrating electronic circuits on stretchable substrates. The introduction of this technology goes back to 1960s when the flexible solar cell arrays were fabricated by forming thin layers ($\sim$100 μm) of crystal silicon wafer cells on a plastic substrate [1]. Flexible electronic devices offer several advantages over their rigid counterparts: they are lighter, portable, and could be manufactured using less expensive methods. Additionally, these devices are foldable and deformable, which make them excellent for applications that require smaller footprints or possess surfaces with curvilinear and irregular morphology. For instance, flexible solar cells are now being widely used to power satellites as they are lightweight and can be rolled up during the launch time and expanded after the satellite is placed in its orbit [2, 3]. Because of these alluring properties, this technology has been rapidly grown and found extensive applications in automotive industry [4], energy harvesting [5, 6], paper-like displays [7–9], robotics [10, 11], and medical devices [12–14].

Flexible electronics can be integrated with biological tissues by conforming to their soft and curvilinear shapes [13–15]. These systems can be bent, twisted, and wrapped around irregularly shaped objects without compromising their functionalities [13]. Due to these unique properties, innovative flexible electronic systems have been developed to measure electrophysiological signals [14, 16–19] and deliver therapeutic agents into or onto the human body [20, 21]. Additionally, recent advances in developing novel synthetic and naturally derived biomaterials enabled tailoring the substrate mechanical properties and controlling the rate of adsorption of different components of electronic systems in a programmable manner for implantable applications.

This chapter provides an overview of the recent advances in flexible electronic systems from the perspectives of their applications in biomedical applications. The first part of the chapter discusses flexible biomaterials including biocompatible substrates and conductive materials that have been utilized for this technology. We will explore different fabrication methods for creating flexible electrodes and will discuss their applications in the development of physical-, chemical-, and biosensors. The second part of this chapter will be dedicated to the emerging applications of the flexible electronics in wound healing, implantable devices, wearable electronics, and point-of-care diagnostic devices for early detection of human diseases. The chapter finally presents a perspective on the technology of flexible electronics and provides insights for the development of novel systems for emerging applications in biomedical engineering.

2 Flexible Electronics

2.1 Fabrication Strategies and Materials

Modern electronic devices are composed of a circuitry system made of semiconductors and a substrate that may be encapsulated in epoxy-based materials to protect delicate components. In flexible electronic systems, all components should comply with arbitrary deformations such as bending, stretching, twisting, and compression without losing their performance. One of the major strategies for fabricating flexible electronics is to manufacture complete circuits on a carrier substrate using conventional methods including lithography-based patterning techniques or chemical etching procedures, and further transferring the patterns onto a flexible substrate [22, 23]. In a study by Choi et al., silicon nanomembranes were fabricated from silicon-on-insulator wafers using reactive ion etching and the structures were subsequently transferred and bonded to a pre-strained polydimethylsiloxane (PDMS) substrate [22] (Fig. 16.1a). This construct exhibited biaxial and reversible stretching and compression with a linear response to applied forces. To improve the stretchability of the structures, they were formed into a noncoplanar mesh architecture to move freely out of the plane [23] (Fig. 16.1b, c). With such configuration, strains up to 100 % were achieved. Other structures such as noncoplanar serpentine [23] and coiled spring layouts [24] have also been used to achieve higher stretchability. Although this process enables the fabrication of high-performance devices with sophisticated structures on flexible substrates, it is expensive and can only cover small surface areas. Moreover, the manufacturing process is challenging due to small dimensions and mechanical fragility of the features.

An alternative approach for the development of flexible electronics is to fabricate the circuits directly on a flexible substrate. This approach requires conductive materials that can be grown on a foreign substrate and stretched without losing their functionalities. Existing techniques for direct patterning of conductive polymers include low-temperature assembly [25–27], solution processing and direct deposition [28, 29], contact printing using PDMS stamps [17, 30, 31], screen printing [32, 33], micro- and nanomoulding [12, 34, 35], and embedded 3D printing [36]. Typical organic/inorganic materials used in these techniques include eutectic gallium indium (eGaIn) [37, 38], carbon-based materials [39, 40], nanowires or nanotubes [39, 41], silver [42], and ionic fluids such as hydrogels and ionogels [43, 44]. A major advantage of these methods is their scalability that allows manufacturing of large-area electronic surfaces with high density. For instance, a 3D printing approach was utilized to directly embed a conductive material within a flexible substrate [36]. This method was used to create strain sensors for human-motion detection (Fig. 16.2a–c) [36].

Roll-to-roll fabrication of large-scale flexible electronic systems was demonstrated by direct deposition of monolayers of graphene films onto flexible copper substrates [29] and conductive polymers ITO:PET substrate [45] (Fig. 16.2d–f). However, any of these materials has its own limitations. For example, the fabrication

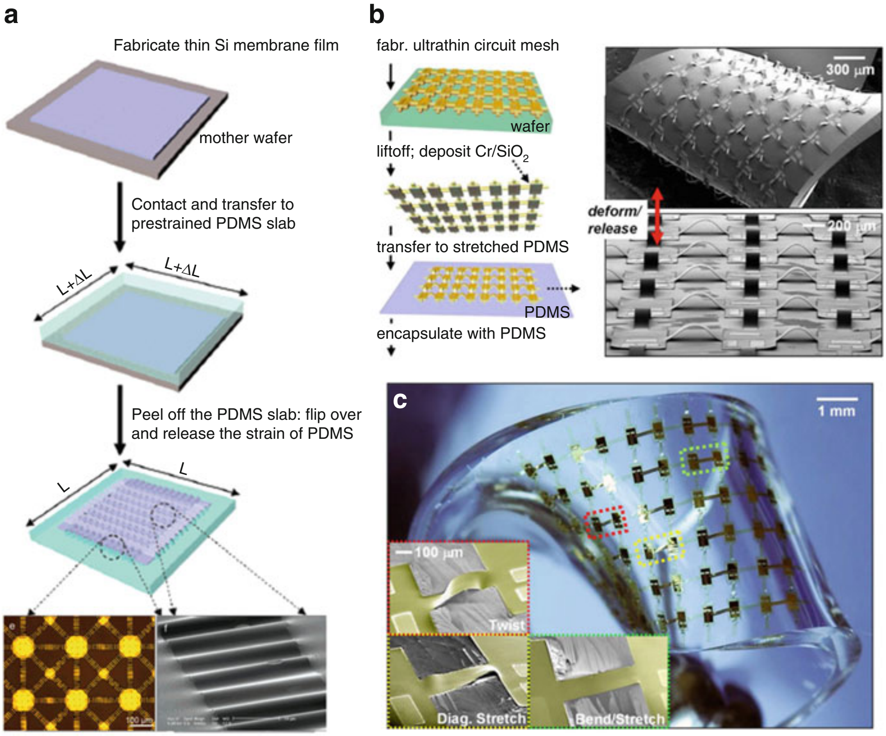

Fig. 16.1 The stretchable features transferred and bonded to elastic substrates. (**a**) Fabrication and transfer of wavy features on PDMS. Reprinted with permission from [22]. Copyright 2007 by American Society of Chemistry. (**b**) Fabrication process of noncoplanar stretchable electronics. The circuit mesh was fabricated on a silicon wafer and then transported to a pre-strained PDMS substrate and encapsulated within PDMS. (**c**) Flexible device underwent various stretching modes including diagonal stretch, twisting, and bending. Reprinted with permission from [23] Copyright 2008 by Proceedings of National Academy of Sciences

routs of using liquid metals are complex as they possess high surface tension and complex surface phenomenon [46]. On the other hand, ionic fluids and conductive inks can be patterned easier, but they have non-uniform electrical resistivity because of particle network disruption at high strains [36] or changes in water content as a result of evaporation or hygroscopic effects [47].

Flexible electronics with the ability of conforming to curvilinear surfaces require patterning of electronic components on stretchable substrates [48]. Metallic free-standing microstrips have been successfully utilized for brain mapping [14]. However, having a flexible substrate improves the mechanical stability of the device and enables fabrication of advanced drug delivery systems and smart wound dressings by encapsulating drug carriers in the substrate. Paper and PDMS are probably the most used substrates in flexible electronic devices [13, 23, 49, 50]. These materials are biocompatible, low cost, and permeable to air. In particular, the nanoporous structure of paper makes it an excellent candidate for rapid diagnostic

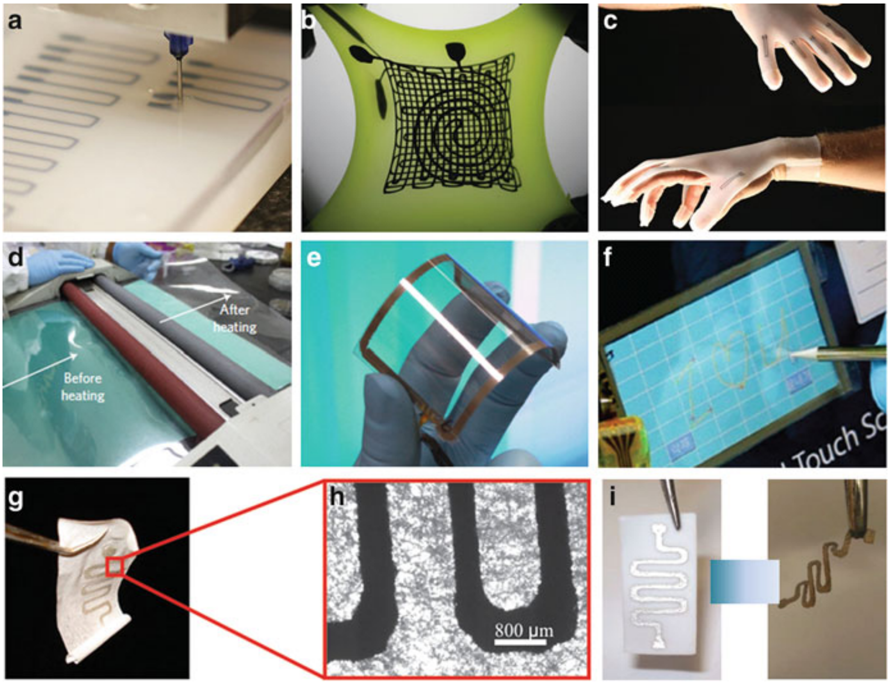

Fig. 16.2 Manufacturing of flexible electronics. (**a**) Embedded 3D printing of conductive ink into an elastic substrate. (**b**) Image of a stretched multilayer strain and pressure sensors fabricated by embedded 3D printing technique. (**c**) A glove with strain sensors made by embedded 3D printing. Reprinted with permission from [36]. Copyright 2014 by WILEY-VCH Verlag GmbH & Co. (**d**) Roll-to-roll fabrication of a large-scale flexible electronic device with (**e**) excellent flexibility. (**f**) A touch screen panel resulted from the graphene-based stretchable electronic. Reprinted with permission from [29]. Copyright 2010 by Macmillan Publishers Limited. (**g**) A patterned electrode on an electrospun PGS-PCL mat. (**h**) Scanning electron microscopy image of the electrode on the mat. (**i**) Flexible electrode before (*left*) and after (*right*) degradation of the PGS-PCL substrate in 500 mM NaOH. Reprinted with permission from [32]. Copyright 2014 by WILEY-VCH Verlag GmbH & Co

tests. However, paper is not elastic and loses its mechanical integrity in aqueous environments. PDMS is a soft elastomer that has been extensively used in food and cosmetic industry. PDMS can be processed easily to create stamps for transferring conductive materials on different substrates [51]. Due to the existence of –OH groups on the PDMS surface, strong covalent bonds (Si–O–Si) between the pattern on the top and the substrate can be formed. Other materials such as silk [52], polyester [15], poly(imide) [53], poly(4-vinylpyridine) [54], paper, poly(lactic-*co*-glycolic) acid (PLGA) [55], and poly(caprolactone)-poly(glycerol sebacate) (PGS-PCL) [32] have also been used as substrate materials. A notable example is an electrospun PGS-PCL mat used to fabricate bio-resorbable temperature and strain sensors and heaters by screen-printing of silver ink and iron oxide (Fig. 16.2g–i) [32]. These fibrous substrates offer several advantages such as high biodegradability, considerable suturability, high in-plan thermal conductivity, and high permeability to air and body fluids [32, 56, 57]. Similar to paper substrates, electrically conductive materials can be patterned on these substrates using screen printing, inkjet printing, and contact printing.

Overall, elastic electronics that are able to form a conformal contact with non-flat surfaces require an elastic substrate and stretchable conductive materials. The fabrication process should maintain the contact between the conductive layer and the substrate without losing its performance. For biomedical applications, the material should also be biocompatible and does not induce allergic reactions. Implantable electronics should degrade into non-toxic compounds in a controlled manner. Moreover, these materials should be compatible with the existing fabrication processes and enable the fabrication of large-scale devices.

2.2 Physical Sensors

Physical parameters such as temperature, stress, strain, and pressure are important indicators of different diseased conditions in various organs and tissues [58–60].

2.2.1 Temperature Sensors

Temperature is an important marker for monitoring the body's health as its variation can be an indicator of inflammation or bacterial infection [58, 59]. Moreover, precise measurement of significant changes in temperature is central for improving the accuracy of other chemical and physical sensors [61]. For the majority of temperature sensors, the principle operation is based on the variation of the resistance as a function of temperature change. Resistive metallic sensors are the most common types of sensors, for this purpose [61]. Platinum is the best material among readily available metals that provides a linear temperature-resistance coefficient and is compatible with conventional microelectromechanical systems (MEMS) technology [15, 62–64]. Other materials such as graphite, silver, and carbon nanotubes (CNTs) have also been widely used for the fabrication of flexible temperature sensors [65–68].

2.2.2 Strain Sensors

Strain sensors are used for measuring the amount of displacement in a moving object. The basic of strain sensors relies on the piezoresistive properties of a conductor, where the electrical conductivity varies with applied strains mostly in a linear fashion [15, 39]. A mechanotransduction system inspired from kidney cells relies on the mechanical interlocking of metal coated nanofibers [12]. Such nanofibers can be made from high-aspect ratio Pt-coater polymeric nanofibers grown on thin layers of PDMS substrates (Fig. 16.3a). This configuration can be used to measure strains as small as human heart beats and as large as the impact of a water droplet on a super-hydrophobic surface with reproducibility of 10,000 cycles

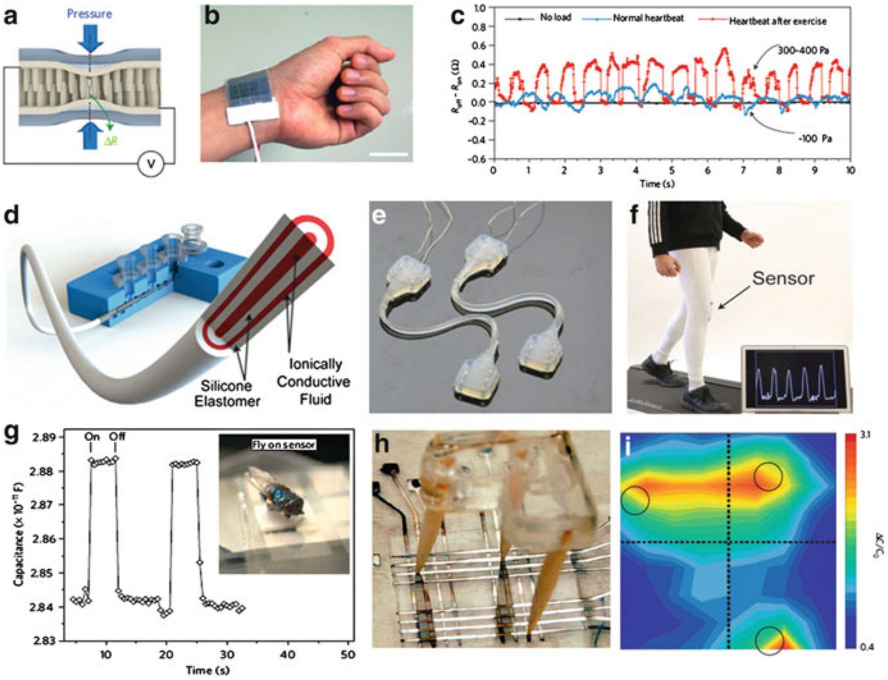

Fig. 16.3 Flexible physical sensors. (**a**) Schematic of the strain sensor made from high-aspect ratio Pt-coater polymeric nanofibers grown on thin layers of PDMS, which was used for (**b**, **c**) human heart beat measurement. Reprinted with permission from [12]. Copyright 2012 by Macmillan Publishers Limited. (**d**) Schematic of a multicore-shell capacitive strain sensor for human motion measurement. (**e**) Multicore-shell strain sensors fabricated in two different lengths. (**f**) A stain sensor integrated with a fabric across the knee for human motion measurement. Reprinted with permission from [69]. Copyright 2015 by WILEY-VCH Verlag GmbH & Co. Ultrasensitive flexible pressure sensors capable of measuring ultralight weights of a (**g**) fly and (**h**, **i**) miniaturized tripod. Reprinted with permission from [35]. Copyright 2010 by Macmillan Publishers Limited

(Fig. 16.3b, c) [12]. Embedded 3D printing of a viscoelastic conductive material into an elastomer using a nozzle has been also used to create flexible strain sensors capable of measuring strains up to 450 % [36]. Capacitive sensors are another class of strain sensors, which have been recently used to measure strains up to 700 % [69]. These sensors are composed of a dielectric layer sandwiched between two conductive layers. The strain signal is determined by measuring the alteration in the thickness of the layers as a function of applied deformation [43, 69, 70]. In particular, strain sensors that are made from fibre materials can be integrated into smart fabrics and further used for the measurement of human motion (Fig. 16.3d–f).

2.2.3 Pressure Sensors

Pressure measurement is essential for applications in soft robotics, smart artificial hands, and electronic skin (e-skin) that imitates the functions of human skin [8, 35]. To sense the applied pressure on a large surface, fabrication of an array of flexible pressure sensors capable of mimicking the tactile sensing of natural skin is required. Organic field-effect transistors (FETs) integrated with rubber pressure sensors are the most cost-effective methods for fabrication of large-scale flexible pressure sensors [10, 11]. Organic transistors are inherently flexible and offer several advantages including the ability to be manufactured on plastic films at ambient temperatures using inexpensive methods [53, 71, 72]. Higher sensitivities can be achieved by using a compressible rubber in the dielectric layer (Fig. 16.3g–i) [35].

Integration of the sensors with other electronic components such as power supplies and communication elements is central for long-term measurement of the physical markers [15]. An important factor in designing such systems is to ensure long-live and robust electrical contacts that do not cause discomfort and irritation for the skin. In a notable study, a multifunctional sensing system composed of temperature, strain, and electrophysiological sensors, light-emitting diodes, transistors, resistors, wireless power coils, along with a high frequency communications [15]. This sophisticated system was integrated on a 30 μm gas permeable polyester sheet and was able to undergo different stretching forces without losing its functionalities. Such advanced technology can be further used to measure the electrical signals generated by heart, brain, and skeletal muscles for gathering information about the human body health in long term.

2.3 Chemical and Biological Sensors

Flexible chemical- and biological sensors designed for the detection of biological parameters such as pH, biomarkers, enzymes, chemokines, toxic or explosive agents, or environmental pollutants. These sensors have been used for a wide range of applications including healthcare, military, sport, and environmental monitoring [73]. Development of miniaturized and minimally invasive biosensors for the detection of biomarkers and cytokines continues to be an important application of flexible biosensors [73]. Among a variety of different detection systems, electrochemical detection techniques such as amperometric and voltammetric methods have received a broad attention. Various flexible materials including polyethylene terephthalate (PET), polyethylene naphthalate (PEN), Mylar, Parylene, and Kapton have been used as the substrate for electrode patterning [74]. Graphene is an exceptional candidate as an electrode for flexible biosensors due to its high deformability, conductivity, and transparency [17]. Also its high surface area helps to provide high sensitivity for a large number of markers [75]. To use graphene for biosensing applications, its surface can be functionalized with various biomolecules, e.g., antibodies and linkers through covalent, non-covalent, or ionic bonds [76]. In the most common application of graphene for biosensing, the surface is functionalized with reduced graphene oxide (rGO) [77, 78].

2.3.1 pH Sensors

pH is one of the critical parameters affecting many reactions in the body and is an indicator of the bacterial infection especially in chronic wounds [79]. The pH of digestive tract also changes in gastrointestinal diseases such as inflammatory bowel and gastroesophageal reflux diseases or infection from *Helicobacter pylori* [80, 81]. Traditional pH sensors are glass-based potentiometric devices that reveal open circuit voltage with respect to the pH of the solution based on Nernst equation [82]. These devices are rigid and bulky, and cannot be used for wearable and in vivo applications. Solid-state pH sensors contain two electrodes, a working electrode and a reference electrode. Working electrode is fabricated by deposition of metal oxide such as platinum oxide, iridium oxide, and ruthenium oxide on flexible substrates [83–86]. These metals can be deposited using physical metal deposition including sputtering, e-beam evaporation, electroplating, screen printing, and sol–gel coating [85, 86]. The thickness of the deposited layer is small and does not affect the flexibility of the device. Conductive polymers such as polyaniline (PANI) or polypyrrole (PPy) are other materials that could be used as working electrodes in pH sensors [87, 88]. Their chemical structure allows protonation and deprotonation in acidic and basic environments to generate the potential voltage between working and reference electrodes [89]. Solid-state pH sensors demonstrated a linear response within the pH range of 2.0–12.0 with a sensitivity of 58.73 ± 0.41 mV/pH and a rapid response time of 0.5–5 s depending on the solution pH [90].

2.3.2 Glucose Sensors

The ability to monitor the glucose level in vivo over a long period of time enables intensive control of blood glucose concentrations in diabetic patients. Additionally, such long-lasting implantable sensors reduce the frequency of implantation and replacement, which can lead to less discomfort for patients. A flexible thick-film biosensor was developed using Nafion/GOx/carbon enzyme-functionalized electrodes for in vivo detection of glucose (Fig. 16.4a) [91]. The mechanical deformation testing demonstrated reliable performance for such flexible enzyme/polymer electrode (Fig. 16.4b). It was also shown that the sensitivity of the sensor substantially enhanced following the strain application. A potential reason could be the increase in biocatalytic area for the reaction though the response was stabilized after a few bending cycles. However, the alteration in sensitivity under mechanical loading was not observed for other agents such as hydrogen peroxide, catechol, and potassium ferrocyanide. Another glucose sensor with flexible structure and suitable optical transparency was constructed by immobilizing graphene oxide (GO) with glutaraldehyde solution onto the Indium/Tin Oxide (ITO)-electrode [92]. The sensor was able to measure glucose ranges from 0.06 to 1.24 mmol/L with accurate reproducibility [92]. In another study, a glucose sensor was fabricated using membrane-entrapped GO on a flexible polyimide substrate and integrated with a pH sensor based on a PVC-based neutral carrier membrane [91]. By incorporation of

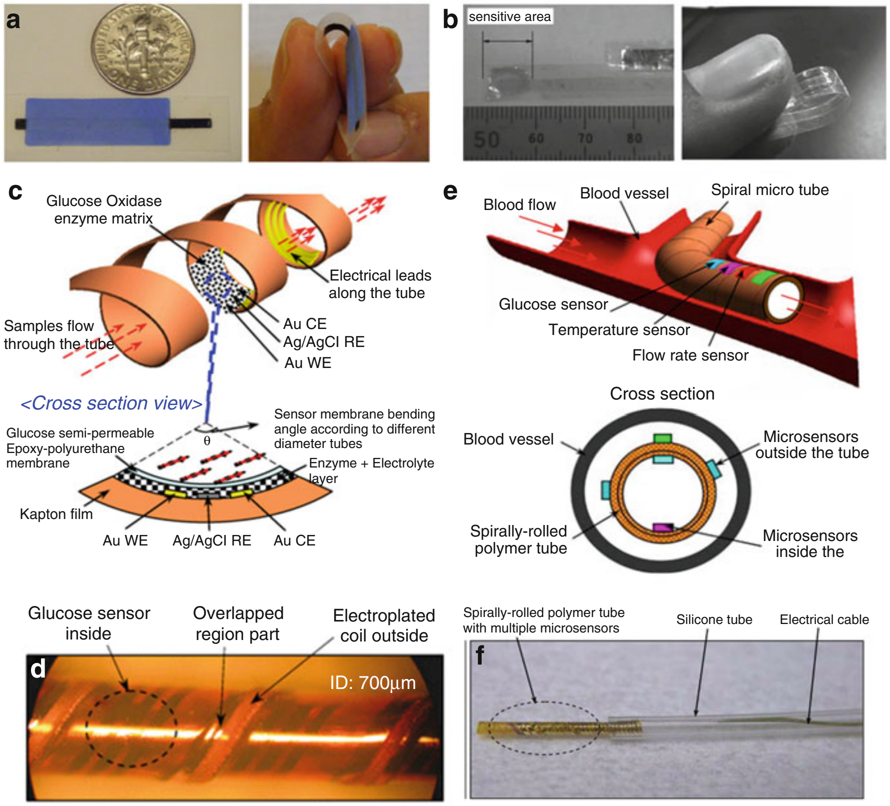

Fig. 16.4 Flexible biosensors. (**a**) Bare electrodes on a flexible Mylar substrate. (**b**) Electrodes during a 180° inward bend. Reprinted with permission from [91]. Copyright 2010 by Elsevier. (**c**) Schematic of a rolled glucose sensor and (**d**) image of the sensor. Reprinted with permission from [98]. Copyright 2007 by Elsevier. (**e**) Glucose biosensor integrated into catheter. (**f**) The fabricated glucose biosensors in rolled configuration. Reprinted with permission from [99]. Copyright 2008 by Elsevier

several pretreatment and heat curing steps as well as an electrochemical preconditioning step, the sensor performed with minimal background noise and settling time. The biosensor was designed for the short-term monitoring of glucose and pH in intensive care units particularly for neurosurgical applications. This sensor had profound performance with high specificity in detection of glucose in buffer solutions, serum, and whole blood [91].

Nanotechnology has contributed significantly to the improvement of the sensitivity and specificity of flexible biosensors. CNTs have shown promising results for the development of electrochemical biosensors due to several specific properties including strong electrocatalytic activity, minimized surface fouling, and high flexibility [3], and therefore have been used for the detection of electroactive species such as hydrogen peroxide and reduced nicotinamide adenine dinucleotide (NADH). A flexible glucose sensor was fabricated using immobilization of glucose oxidase (GOx) enzyme over plasma-functionalized multiwalled carbon nanotube (MWCNT) films on gold coated PDMS substrate [93]. The GO/MWCNT/Au/PDMS electrode exhibited highly sensitive performance within the detection limit of glucose in human body. Oxygen plasma-functionalized CNTs significantly enhanced electrocatalytic activity and electron transfer due to production of oxygen-contained groups over CNT surface, verified by X-ray photoelectron spectroscopy [18].

Temporary transfer tattoos with electrochemical-based function and compliant with the skin have been used for electrochemical analysis of physiologically relevant agents such as ascorbic and uric acids with high sensitivity [73]. The ability of these tattoos to withstand extensive mechanical loading and chemical degradation in the skin has provided reliable transdermal wearable biosensors. However, there are still challenges in the integration of electrodes onto both textile substrates and the adhesion to the epidermis. Also further improvements are required to integrate power sources to the biosensors to enable communication and data transfer via wireless infrastructure, to assess interaction of liquids at the printed electrode-epidermis interface, and to improve absorption of moisture on the surface [94].

A more advanced model of flexible biosensors is called “flexible rolled biosensors”, suitable for integration into catheters for minimally invasive amperometric detection of biomarkers [95–97]. A stretchable biosensor patterned on a polyimide substrate was developed for rapid and sensitive detection of dynamic changes in glucose, norepinephrine, and dopamine [95]. To integrate such biosensors into medical catheters, textile-based thick-film sensors with highly porous substrates were effectively utilized to survive large deformations [96]. Such textile-based biosensor was further developed to achieve a flexible and low-cost solid-state sensor [97]. Since the flexible fabrics had hydrophobic properties, they prevented hysteresis behaviour and therefore enabled repeatable electrochemical sensing [97].

In a notable study, a novel glucose sensor was demonstrated by patterning electrodes on Kapton material, followed by spirally rolling it into polymer micro tube [98]. The comparison between the spirally rolled glucose biosensor with its planar counterpart showed that the rolled sensor provided reliable sensitivities under various working temperatures (Fig. 16.4c, d) [98]. This biosensor can be effectively used for in vivo monitoring of glucose using microcatheters. In a more complex system, bio-chemical and physical sensors were integrated into a flexible polymer tube mounted within a catheter for measuring physiological (temperature, pressure, and flow rate) and biochemical data (glucose concentration) (Fig. 16.4e, f) [99]. The sensors were assembled on the inside and outside wall of the polymer without the need to external wiring. The fabricated sensors demonstrated acceptable performance in planar and spiral configurations as one step forward to develop patient-specific “smart” catheters.

2.3.3 Other Biosensors

Flexible biosensors are crucial for the fast, simple, reliable, and in-field detection of biological and toxic agents on the battlefield for security applications [100–102]. In particular, electrochemical biosensors have offered a unique opportunity for field screening to identify various explosives or toxic agents [101]. Nitroaromatic explosives (e.g., 2,4,6-trinitrotoluene, TNT) with redox activity have made them ideal for electrochemical-based detection [100]. Various materials such as cotton, polyester, and Gore-Tex with different hydrophobicity have been used as flexible substrates for electrochemical detection of such agents [73]. Among these materials, fabrics made from Gore-Tex have shown a profound waterproof properties that are suitable for stable detection of nitroaromatic explosives such as TNT and 2,4-dinitrotoluene (DNT) in both the liquid- and gas phases [73]. The ability to print electrodes in multiplexed arrays has enabled the fabrication of multiplexed electrochemical sensor [102].

In addition to the application for gas-based detection of explosives, the stretchable biosensors have shown their ability in diagnosis of security threats and environmental contaminants in aqueous solutions [101, 103]. For instance, isolation and transport of sea water samples to the laboratories for further analysis is costly, labour-intensive, and time-consuming, indicating the need for portable devices for on-site analysis of water samples [101]. Moreover, in military activities with a requirement of hands-free operation, a built-in biosensor facilitates their performance and provides the user with a real-time assessment of the environment. For such applications, neoprene-based electrochemical electrodes have been integrated into flexible substrates to provide effective wearable electrochemical-based biosensors for on-site assessment of the presence of contaminants and hazards, such as copper and phenolic pollutants [101]. Toward achieving a fully integrated electrochemical portable biosensor, integration with miniaturized potentiostats [103] has been utilized to detect phenols with the possibility of visual indication and warning system alarming the divers and surfers about toxic level of the environment. The future application of these fully miniaturized sensors is to integrate them into suits worn by divers, surfers, and swimmers, for continuous monitoring and security hazards.

3 Emerging Applications

3.1 Wound Healing

A large number of compromised and chronic non-healing wounds in our ageing population have imposed a significant health and economic burden [104]. This problem is intensified when combined with other complications such as diabetes, vascular disease, and long-term immobility [105]. The current trend in the global wound care market is now expected to raise from $15.6 billion in 2014 to $18.3

billion in 2019 [104]. Therefore, developing novel therapeutic approaches for treating skin wounds has been one of the most active areas of research during the past few decades. The existing approaches for management of skin wound vary from simple coverage of the wound with a sterile patch [106] to smart wound patches capable of measuring the wound environment [81], and releasing the drug on demand [21]. An ideal wound patch should be oxygen permeable, maintain the moist environment of the wound, prevent bacteria and fungi growth, and cover the entire wound area without imposing discomfort and irritation.

Quantitative monitoring of the wound environment during the healing process is of great importance in effective management of the wounds [15, 107, 108]. For example, the ability to measure pH of the wound provides useful information about the stage of the healing process and the possibility of bacterial infection. Another parameter that affects the wound healing process is hydration [107], as the ability to control the moisture balance at the wound surface, central for a successful healing. The hydration of the wound surface can be assessed by measuring the wound temperature and humidity sensors [108]. Measurement of other important markers such as oxygen level, cytokine release, the level of hormones and enzymes at the wound site also provides useful information about the healing process [85].

Multifunctional skin-like electronics capable of covering the wound area have been recently emerged as a promising approach for wound management applications [16, 108]. These electronic systems are composed of metallic microstrips that precisely measure the temperature and thermal conductivity of the wound (Fig. 16.5a, b) [108]. The material characteristics and mechanical properties of the substrate that holds the electronic circuit can be tuned to comfortably cover the wounded area. Electronic devices can also be fabricated in the form of sutures. These “smart” sutures were instrumented with high quality inorganic and biocompatible semiconductors to perform sophisticated sensing and therapeutic actions (Fig. 16.5c, d) [16]. The materials used in these sutures can be biodegradable or permanent [109], while the sutures can be loaded with drugs, growth factors, or stem cells for promoting the wound healing process [110]. Smart sutures can be assembled into complex mesh-like patches using textile technologies for treatment of large-scale wounds.

One of the main design parameters for a wound dressing is the ability to maintain the wound in a moist environment [111]. Hydrogels are 3D polymeric materials containing high water content, and thus are suitable materials for wound dressings [112]. Hydrogels can be impregnated with drugs and growth factors to modulate the vascular formation and also inhibit bacterial growth at the wound site. In addition, other biocompatible materials such as glycerol can improve the flexibility of the hydrogel-based materials and improve their ability to maintain water content over long periods of time [21]. Conductive materials such as gold can be patterned on hydrogel substrates to create electronic circuits for sensing and actuating purposes. For example, a heating element was patterned on an alginate/glycerol sheet using screen printing method to stimulate thermo-responsive drug-loaded microparticles that were embedded within the alginate sheet (Fig. 16.5e, f). This system can be used for on-demand release of antibiotics and growth factors in a programmed manner.

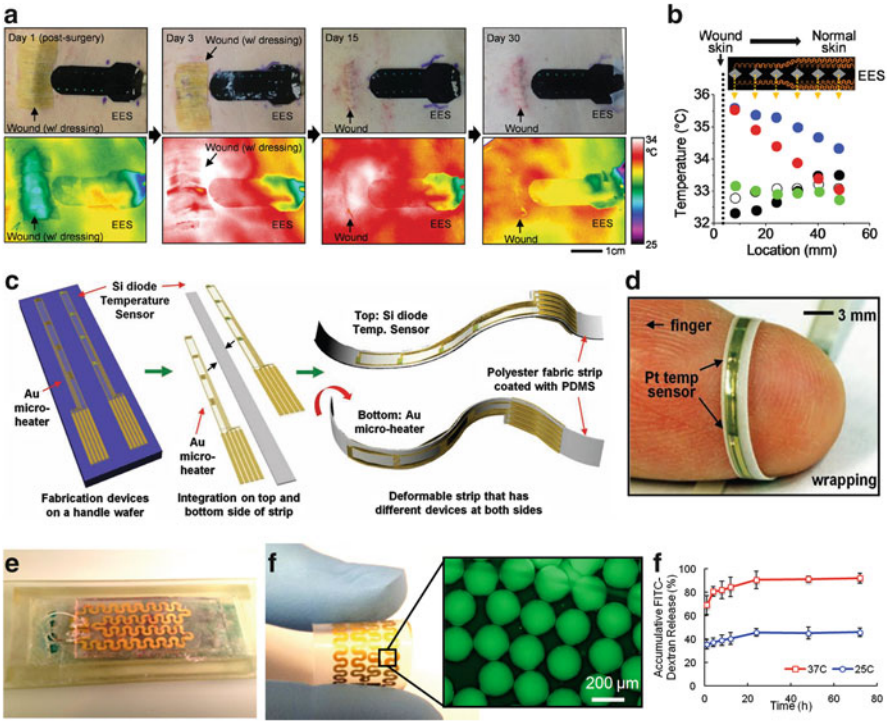

Fig. 16.5 Flexible electronics for wound healing application. (**a**) An epidermal electronics system capable of measuring the wound temperature during the healing process. Infrared images show the temperature distribution over 30 days. (**b**) Temperature distribution measured by the flexible electronic system. Reprinted with permission from [108]. Copyright 2014 by WILEY-VCH Verlag GmbH & Co. KGaA. (**c**) Smart sutures made from strips of biocompatible semiconductors on a polyester fabric. (**d**) Smart suture measuring wrapped around a finger and the temperature. Reprinted with permission from [16]. Copyright 2012 by WILEY-VCH Verlag GmbH & Co. KGaA. (**e**) An integrated hydrogel-based flexible electronic system capable of releasing drugs and small molecules on demand. (**f**) A flexible hydrogel-based substrate with encapsulate thermo-responsive microparticles (*inset*). Release profile of the particles at different temperatures. Reprinted with permission from [21]. Copyright 2015 by WILEY-VCH Verlag GmbH & Co. KGaA

3.2 *Implantable Devices and Surgical Tools*

Implantable devices are battery-powered electronics that are placed into the body for diagnostics and therapeutic applications. These devices are able to measure several body parameters such as temperature, oxygen content, and pH level, and determine electrophysiological mapping of heart and brain [113]. Current implantable electronics including pacemakers, deep brain stimulators, and epilepsy management devices are composed of electrodes that are in contact with the targeted tissue and a control unit system that monitors each electrode individually [14, 114]. These electrodes are fabricated on flexible substrates such as silicon-based materials [114] or directly patterned on the tissue by a sacrificial substrate that was dissolvable

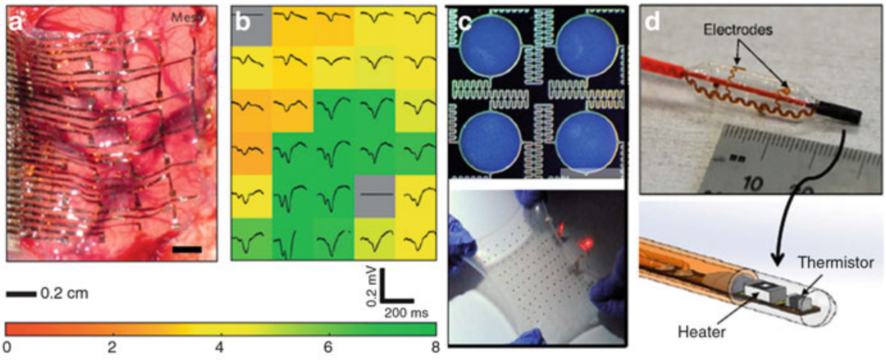

Fig. 16.6 Flexible implantable devices and surgical tools. (**a**) Electrode arrays implanted directly onto a soft brain tissue. (**b**) Measured brain activity signals using the flexible electrode array. Reprinted with permission from [14]. Copyright 2012 by Macmillan Publishers Limited. (**c**) Fractal-like design for fabrication of stretchable batteries. Reprinted with permission from [120]. Copyright 2013 by Nature Publishing Group. (**d**) A balloon catheter system with integrated electrodes for measuring blood flow in real-time and to perform ablation. Reprinted with permission from [19]. Copyright 2015 by Elsevier

in vivo (Fig. 16.6a) [14]. The advantages of these electronic systems are their ability to conform on dynamic and 3D surfaces such as heart or brain and provide electrophysiological mapping of the tissues by means of an array of micropatterned electrodes (Fig. 16.6b) [14]. For example, 2016 silicon nanomembrane transistors were fabricated on a thin plastic sheet and implanted on the surface of a beating porcine heart to record its electrophysiological signals [114]. Unlike conventional electrodes, this technology did not require repositioning of electrodes, and therefore provided a high-resolution and real-time map of the heart.

Miniaturized integrated batteries are essential to supply the power required for long-term function of the implantable devices [115]. The batteries should be able to generate high energy or power densities in a small footprint. Two-dimensional (2D) thin-film batteries supplied high power densities; however, they need large footprints to deliver high energies required for activating some of the electronic components [115]. It has been shown that colloidally templated 3D mesostructured electrodes could improve the efficacy of power density production by delivering significant energy due to high surface to volume ratios [116]. This technology can take advantage of 3D holographic patterning techniques to allow precise control over the microstructure of the electrodes. Stretchable batteries can be fabricated from stretchable electrodes using wavy and wrinkled designs from conductive materials such as polypyrrole [117]. The fabrication methods are similar to the methods used for patterning of sensors on elastomeric substrates. Other design configurations such as origami [118], serpentine [119], and fractal-like [120] patterns have also been recently developed to achieve high power densities and larger stretchability (Fig. 16.6c).

Catheter-based diagnostic and treatment approaches are non-invasive methods that rely on the local delivery of sensing elements and therapeutic payloads. Catheters, instrumented with recording and stimulating electrodes, are flexible and therefore can interface with the soft tissues within the human body. Balloon-based catheters with multiple electrodes have been developed to map the electrical activity of the heart and perform ablation therapy [13]. The fabrication strategy includes patterning of ultrathin conductive layers and inorganic nanomaterials on inflated elastomeric balloon substrates using plasma treatment, transfer printing, and interfacial adhesives [13, 121, 122]. Another application of balloon-based catheters is to manage vascular diseases such as coronary artery diseases using an approach referred as percutaneous transluminal coronary angioplasty [121]. These catheter-based methods are usually combined with drug-eluting stents for local delivery of therapeutic agents [123]. To improve the functionality of these balloons, blood sensors and actuators have also been integrated into the electronic system to monitor the blood vessel health in real time (Fig. 16.6d) [19]. These sophisticated platforms enable performing surgeries faster with less instrumentation and higher vascular intervention efficiency.

3.3 Wearable Devices

Wearable systems are defined as a new class of the health monitoring and therapeutic platform that can be embedded into the user clothing or accessory [124]. These systems enable collection of physiological information over a long term without introducing inconvenience to the patient [124]. This ambulatory technology allows real-time monitoring of the key markers in patients with chronic conditions, not necessarily in the hospital. Miniaturization, lightweight, and conformability of the components are the key requirements of wearable systems. These systems contain different electronic and sensing components integrated into a single flexible platform such as bandage and wristband [125, 126].

In the past few years, several wearable devices have been introduced for monitoring of the heart rate [127] [128], the blood pressure [129, 130], electrocardiography [131], and physical activity [39, 132]. In a notable study, a wearable strain sensor was fabricated from aligned thin films of CNTs on PDMS as an elastic substrate [39, 133]. CNTs were aligned perpendicular to the strain axis. This system was able to measure strains up to 280 % and was used to assimilate various dynamic motion of the human (Fig. 16.7a–c).

To enhance the adaptability on a rough skin surface, the same group developed a dry adhesive patch for in vitro diagnostics [134]. They presented a simple method for fabricating an enhanced dry adhesive skin patch by utilizing modulus-tenable composite micropillars made of stiff and soft PDMS materials (Fig. 16.7d–f). The method consisted of direct replica moulding of rigid bottom micropillars (curing agent 15 wt%) and selective inking of soft tip layer (curing agent 5 wt%). Such monolithically integrated composite micropillars provided a large normal adhesion

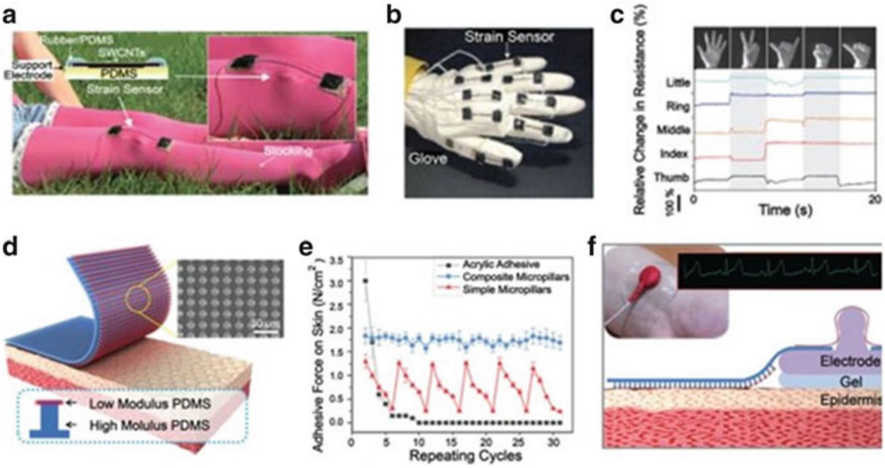

Fig. 16.7 Flexible wearable devices. (**a**–**c**) Wearable stretchable human-motion detector, strain-gauge sensors and signal patterns of attachment on knee and a glove. Reprinted with permission from [133]. Copyright 2011 by Nature Publishing Group. (**b**) Enhanced skin adhesive patch with composite micropillars with (**d**) a schematic illustration and scanning electron microscopy (SEM) image of heterogeneous micropillars. (**e**) Plot of the enhancement of adhesion, and (**f**) ECG signal measurement with an electrode attached on the skin. Reprinted with permission from [134]. Copyright 2013 by WILEY-VCH Verlag GmbH & Co. KGaA

force up to 1.8 N cm^2 (maximum: 2 N cm^2) on the human skin as well as high durability (30 cycles) without notable degradations. Using the composite micropillars electrocardiograms (ECGs) were successfully recorded in real time for the time period of 48 h with minimal side effects [134].

Wearable chemical sensors are also recently introduced. Smart bandage with embedded oxygen sensors and readout electronics allows continuous monitoring of chronic wound oxygenation (Fig. 16.7g, h) [135, 136]. In addition, electrochemical sensors with screen-printed electrodes on underwater garments are proposed for monitoring of environmental pollutants [137].

Another important application of the wearable devices is the electronic artificial skin (e-skin) [8, 10, 35, 40, 41, 138]. Development of an artificial skin capable of detecting external environmental stimulus is a great interest for the humanoid robotics and prosthetics [10, 35, 41]. E-skin should be implemented on a highly flexible and soft substrate to mimic the human skin. Currently, there has been a great deal of research focusing on the development of e-skin including physical sensors, such as pressure and temperature sensors. The e-skin design generally contains two components, an active layer containing organic transistors, switches, etc. covers the flexible substrate. The second layer includes physical sensors to measure pressure and temperature, and to collect the environmental information. Information of the second layer is read by the first layer as an active layer [41]. Someya et al. presented a net shape e-skin including flexible pressure and temperature sensors implemented on a polyamide substrate in contact with organic transistors [10, 11]. The platform was conformable to 3D surfaces and enabled the e-skin to extend by 25 %.

3.4 Point-of-Care Devices

The cost of public healthcare is significantly increasing in the modern societies. Point-of-care devices and portable instruments can play essential role to shift from expensive healthcare to low cost care [139]. These devices can be used in diagnosis, prevention, and treatment of diseases to improve the clinical outcome in health care. Such devices are expected to be rapid, cost-effective, portable, multifunctional, with integrated sample preparation, detection and processing systems. Stretchable sensors with high flexibility and sensitivity, and possibility of real-time detection can be miniaturized and function under considerable physical deformation with the potential application in development of point-of-care devices.

A flexible paper-based electrochemical portable biosensor was fabricated based on free-standing graphene coated with nanocomposites of Pt/Au alloy and MnO_2 for the purpose of non-enzymatic amperometric detection of biomolecules [140] (Fig. 16.8a, b). The fabricated sensor offered enhanced sensing with high sensitivity, low detection limit, high reproducibility and stability under mechanical stress, with an acceptable selectivity. An impedance-based electrochemical biosensor was further fabricated by growing CNTs on flexible polyimide substrate, where the CNTs surface was coated with anti-human serum albumin (AHSA) for specific detection of HSA and with the potential application in the implant-based detection [141] (Fig. 16.8c).

Another flexible electrochemical biosensor was made of a graphene paper covered with Au/Pt core–shell nanoparticles for real-time monitoring the reactive oxygen species (ROS) and reactive nitrogen species (RNS), particularly nitric oxide [142]. The integration of metal nanostructures and graphene paper into functional electrodes was optimized to achieve a high electrocatalytic activity and sensitivity with a wide linear range and a low detection limit. Other flexible-based substrate electrochemical biosensors were developed by printing silver electrodes over PET substrate to detect D-proline, sarcosine, cadmium sulphide (CdS), and potassium chloride (KCl) [143]. Hg^{2+} ions exist in low concentrations in biological and environmental samples have extreme toxicity effects for both human health and environment, and may lead to fatal diseases like minamata disease, cyanosis, nephrotic syndrome pulmonary, or edema [144]. A liquid-ion gated FET was integrated into PEN-based flexible graphene apta-sensor with excellent mechanical properties for highly sensitive and selective detection of Hg (Fig. 16.8d) [73]. The sensor exhibited a rapid response of less than 1 s when the Hg^{2+} ion concentration was altered. Additionally, its performance was selective in a mixed solution containing several other metal ions as well as the real blood samples. The sensor was rapidly considered as an effective alternative for silicon-based electronics. Lactic acid is another agent important for environmental monitoring and

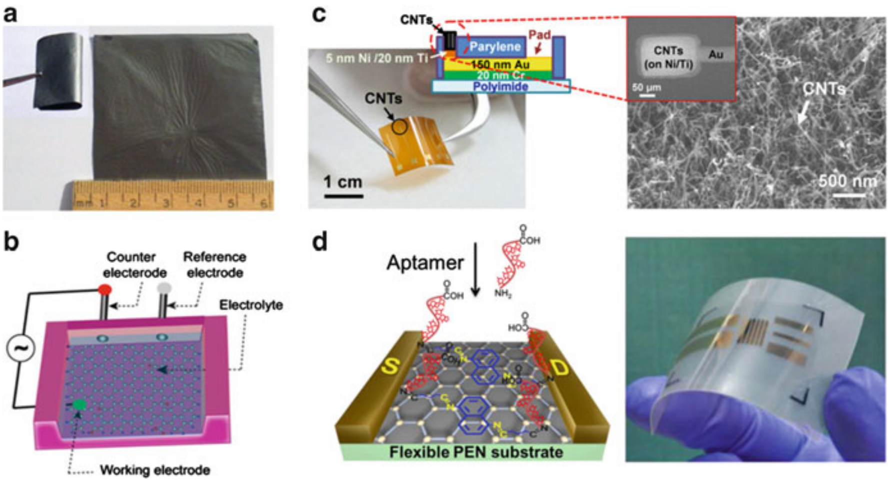

Fig. 16.8 Flexible sensors for point-of-care diagnosis applications. (**a**) Graphene nanosheets. (**b**) The schematic representation of the electrochemical set-up. Reprinted with permission from [140]. Copyright 2013 by Elsevier. (**c**) Flexible CNT electrode with a SEM image of the electrode coated with CNTs. Reprinted with permission from [141]. Copyright 2013 by Elsevier. (**d**) Flexible and transparent graphene-based biosensor deposited the gold electrodes [73]. Reprinted with permission from [73]. Copyright 2013 by ACS Publications

for clinical assessment. Therefore, the development of a flexible biosensor for POC-based detection of lactate is essential. Recently, a flexible graphene-based biosensor was developed to detect lactate under different mechanical bending conditions with the sensitivity of 0.1–20 μM. The performance of the sensor was shown dependent on the bending angle and the number of bending cycles [145].

Stretchable biosensors have also been used for early detection of cancer biomarkers from blood samples [146]. A FET-type apta-sensor was fabricated based on N-doped graphene using conducting polymers with heteroatoms as the carbonization precursor over a flexible substrate. The PPy-NDFLG conjugated with antivascular endothelial growth factor (VEGF) RNA aptamer was embedded into a liquid-ion gated FET sensing area to detect VEGF as angiogenesis biomarker useful for the detection of metastasis and growth of human tumour. The sensor demonstrated enhanced reusability and mechanical bendability required for a sensor for point-of-care application.

Wireless communication is an inevitable component of point-of-care devices for long-term monitoring of physiological signals. A wireless biosensor printed on a stretchable substrate with integrated antennas and interconnections between components was utilized to monitor biomarkers. A wireless biosensor with inkjet conductors printed over polyurethane substrate was also successfully utilized to detect organophosphate (OP) and p-nitrophenol hydrolysis with the measured reading range of 14 m distance from the body [147].

4 Summary and Conclusions

The advances highlighted in this chapter shed light on the exciting opportunities offered by the flexible electronics technology. These directions emerge from the unique characteristics of flexible electronic systems that allow integrating electronic components into soft tissues with irregular surfaces. Novel fabrication methods combined with advanced stretchable biomaterials enabled developing complex electronic devices that can monitor physical and biological signals within the body or from outer layers of skin and transport these valuable information to central unit for further analysis. Integration of the sensors with other electronic components such as power supply and communication elements is essential for prolong measurement of the physical markers. An important factor in designing such systems is to ensure long-live and robust electrical contacts that do not cause discomfort and irritation for the tissue. More advanced flexible biosensors have been developed that can be mounted on medical catheters for minimally invasive detection of biomarkers. These sensors can be delivered to the site of interest intravascularly, measure the markers and if needed release proper treatment locally. Another exciting application of flexible electronics is the development of smart dressings capable of on-demand release of antibacterial agents and growth factors at the site of injury. Flexible electronics can also be wearable to collect the physiological information over a long term without the patient inconvenience. This ambulatory technology allows real-time monitoring of the key markers in patients with chronic conditions, not necessarily in the hospitals. A major application of flexible electronics is in development of point-of-care devices and portable instruments that are essential for improving the quality of public health in low resource settings. These devices can be used in diagnosis, prevention, and treatment of diseases to improve the clinical outcome in health care. All together, flexible electronics technology holds a great promise for a wide range of biomedical applications. However, advances in the integration of wireless communication systems, substrate materials with tuneable degradation and mechanical properties, and manufacturing technologies that allow large-scale fabrication of electronic devices are necessary.

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