Recent progress of wearable and implantable sensors for mobile health

Hanxiong Yang *

School of Advanced Technology, Xi'an Jiaotong-liverpool University, Suzhou 215000, China

* Corresponding Author Email: Hanxiong.Yang22@student.xjtlu.edu.cn

Abstract. With the multidisciplinary development of biomedicine, materials science, control science, and communication technology, the wearable devices market is developing rapidly. Flexible sensors are a core component of wearable devices. From monitoring to preventing diseases and being used in clinical trials to improve medical outcomes, the applications of sensors in the medical field are rapidly expanding. This paper will discuss some of the new medical applications of flexible sensor devices and summarise the progress in advanced medical research and development potential of the devices. Firstly, the paper discusses an overview of background information on wearable devices and sensors. This is followed by an overview of the materials used to manufacture flexible sensors. These are polymers, carbon-based materials, and hydrogels. Then, it compared the unique advantages of flexible sensors in terms of two modes which include in-vivo sensing and in-vitro sensing. Finally, the paper presents the current opportunities and possible future challenges for the sensor market.

Keywords: Flexibility; Wearable sensors; Implantable sensors.

1. Introduction

Over recent years, with the continuous development of 5G, artificial intelligence, and other technologies, the market and policy advantages of wearable flexible electronic devices have gradually emerged. It is one of the most promising high-tech devices. The flexible sensor market is expected to grow at approximately 9% per annum on average from 2022 to 2026, based on an industry research report published by Xinsijie Industrial Research Centre. Medicine is the major downstream market, accounting for 78% of the demand, mainly for wearable devices. Against the backdrop of COVID-19, the development of personalized wearable devices has been stimulated by successive epidemic prevention measures in various locations. This is coupled with an aging population and an increasingly epidemic population growth. Wearable flexible medical devices are better able to meet the needs of patients than traditional medical devices. Flexible wearables not only strengthen the reliability and stability of medical devices but also improve the comfort of wearing them. Such wearable devices are gaining increasing acceptance in the medical field.

Unlike traditional rigid electronics, stretchable and flexible electronics are designed to simulate the mechanical properties of elastic fabrics with human skin. Flexible electronics are highly deformable, stretchable, and flexible. They can meet the requirements of ductility and biocompatibility required for the manufacture of flexible devices.

In the last few years, the market for wearable sensor devices has grown rapidly. Flexible wearable devices for biomedical applications gain popularized. The technology for sensing is the key point of wearable devices. Combined with the cross-referencing of information technology, control science, bioelectronics, and other disciplines, this field has seen a breakthrough.

Biosensors have extensive applications in the medical field, with advantages such as high sensitivity, outstanding biocompatibility, low cost, and fast response time. Biosensors also have low mass and high flexibility, allowing for better portability and convenient limb movement.

With the continuous evolution of flexible electronics, sensors are allowed to be implanted or appended to the human skin and provide a good record of human blood pressure, body temperature, and other vital signs. Flexible electronic biosensors are more comfortable, lighter, and easier to carry

when compared with some traditional hard sensors. It also has less power consumption and provides more accurate measurements of human body conditions than traditional hardware sensors.

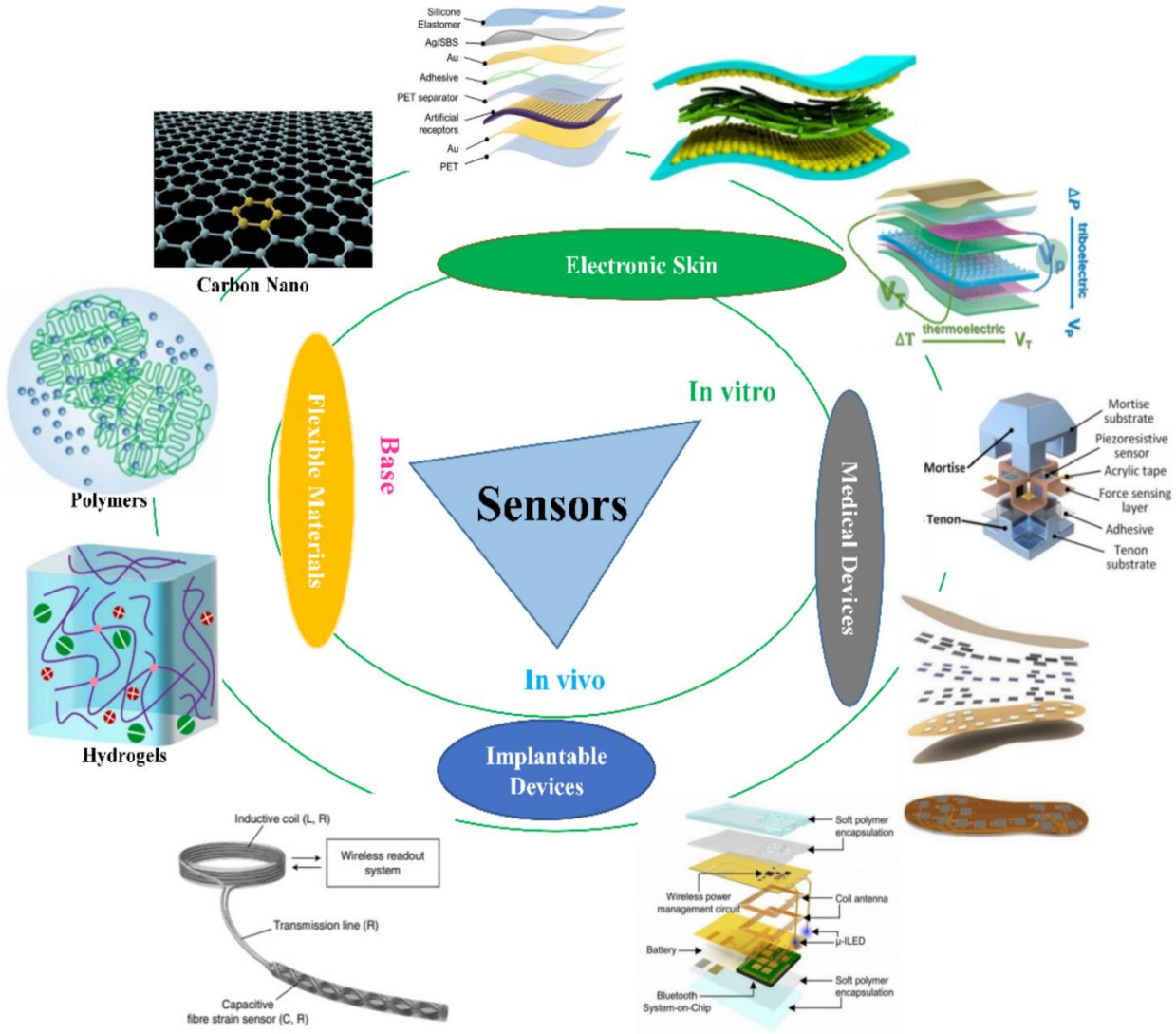


Fig 1. Wearable flexible sensor devices for biomedical applications [1].

This paper will develop an updated review of the medical applications of flexible wearable electronics. The overview of implantable sensors can be seen in Fig. 1. The concept of biosensors is first introduced and analyzed starting with the various types of flexible materials used in sensors. Then it presents the latest progress in the application of flexible electronic sensors from both in-vivo and in-vitro perspectives. Finally, the wearable technologies on sensors are summarised and future trends in biosensors are predicted.

2. Commonly used flexible materials for biosensors

In the modern scientific era, technological progress has played a key role in providing simple solutions. The development of biosensors is also an example of the advanced technologies that have become an essential component of human life. Biomedically oriented sensors place greater demands on the durability, flexibility, and electrical conductivity of flexible materials. For this reason, the selection of high-performance materials will play a significant role in determining the manufacture of biosensors. In this section, it will give a brief overview of flexible materials for the manufacture of biosensors, which are divided into polymers, carbon-based materials, and hydrogel.

2.1. Polymers

The polymer material is commonly utilized as a coating material or substrate for superior performance by virtue of its good biocompatibility and electrical conductivity. Polymers are organic macromolecules consisting of repeating monomers. Benefiting from the extensive use of monomer synthesis and chain engineering in the biomedical field, polymers can also be engineered as insulators, semiconductors, and conductors with a wide range of electrical and mechanical properties. Polymers can be used to make good conductive and thermally conductive materials [2], composite films [3], temperature or pressure sensors [4], or as the primary material for flexible electrodes [5].

Xu et al. proposed a hybrid composite material based on a conductive polymer [2]. This inorganic material has a high thermal conductivity. Meanwhile, the organic component acts as a stabilizer and the dispersants can enhance the stability of the inorganic component in solution. By combining CPs and inorganic fillers, the strategy can inherit the merits of both and optimize electrical performance. This combined strategy not only improves current transport significantly but also tends to block low-energy carriers through a filtering effect, in which the performance of the polymer matrix is dramatically boosted. Inorganic materials for this application are generally inorganic semiconductors and carbon-based nanomaterials. Some carbon-based molecules such as PEDOT, and PSS can be uniformly distributed in the polymer liquid state.

Polymers are also prepared as polymer composite films by layer-by-layer deposition techniques, forming multilayer structures with appropriate strip arrangements [3]. Such structures have unprecedented Seebeck coefficients and electrical conductivity comparable with outstanding inorganic semiconductors such as bismuth telluride at common room temperature. These are capable of being utilized as coatings for flexible surfaces, such as fibers on clothing. The mechanism at work behind such structures is known as modulation doping, and it accounts for the diffusion of carriers through energy changes. Most crucially, for organic/inorganic composite systems, the top priority challenge is to bring the two morphologically differentiated components into uniform dispersion and close contact, and finally to achieve a mixing effect. This must be taken into account in the process of material fabrication, otherwise the system of composite will not outperform any substrate and the material with which it is polymerized.

Cho et al. presented an all-polymer rubber temperature sensor that was tested at a mechanical strain range of 0% to 30% [4]. It is a generally recognized range for skin stretching during movement. The resistance of the prepared all-polymer rubber temperature sensor decreased with a rise in temperature from 27°C to 45°C where the effective carrier density in the semiconductor material increased with increasing temperature. The sensor exhibited the typical nonlinear behavior of a semiconductor thermistor. Another example application of an all-polymer rubber sensor is a pressure-sensitive rubber used for making sensory skin [4]. Sensory pixels are dispersed on the fingers of the robot [4]. The device is grounded via a shunt resistor that reduces the resistance significantly when pressure is applied. Therefore, the skin can clearly show the change in pressure by the change in voltage when the pixels sense pressure.

Conductive polymer fibres offer the advantages of mechanical flexibility, inherent conductivity and electrochemical activity. The optical and electrochemical properties of conductive polymers are attributed to the extended conjugation along the backbone and the ease of doping the system. In recent research, PEDOT fibres have been used in a wide diversity of frontier applications [5]. Polymer fibres with a very small diameter can maximise intrinsic conductivity, electrochemical activity and mechanical flexibility. The discovery is of considerable assistance for fibre devices in fabric electronics. Polyaniline fibres are another type of polymer fibre. It has outstanding chemical properties and capacitance at less than 5μm. An ultra-thin, fully solid organic electrochemical transistor made from this material can be utilised as a tactile sensor to detect different levels of pressure and friction. Their effectiveness is far superior to that of other materials.

2.2. Carbon-based materials

In recent years, carbon materials have been widely used to develop flexible biosensors. For example, carbon dots have extensive applications in biochemistry [6]. Carbon nanotubes have superior flexibility, mechanical and electronic properties [7], with tensile strengths ranging from 11-50 GPa. Similarly, graphene has a tensile strength of 119.2 GPa. This property facilitates their transformation into one-dimensional fibres, two-dimensional films/sheets or three-dimensional structures.

As a new carbon-based material with a wide range of applications, carbon dots offer widespread use. Carbon dots have a unique nanostructure with a characteristic diameter of under 10 nm and were discovered opportunistically in the process of purifying single-walled carbon nanotubes. The manufacturing techniques for carbon dots can be categorised as both top-down and bottom-up approaches. Particularly, these top-down methodologies simplify large volumes of material into smaller complex structures and forms, which include electricity discharge, electrochemical or chemical oxidation and laser ablation. Conversely, the bottom-up approach transforms or accumulates smaller build-up structures into carbon dots. As a consequence of their superior biocompatibility, low toxicity and photostability, carbon dots also supply promising probes for the effective targeting and imaging of cancer cells to identify and detect bacteria by their properties or modified ligands [6].

Likewise, carbon dots have significant energy applications such as supercapacitors, rechargeable batteries, and fuel cells. Carbon dots possess good optical properties, huge specific surface areas and conductivity, low cost and low toxicity. An excellent metal-free porous graphene framework was developed by a simple, extensible hydronic thermal method and subsequent annealing process [7], and the framework utilized a heteroatom-doped carbon dot as a dual-function oxygen electrocatalyst for a metal-air cell.

Carbon nanotubes have unique mechanical and electronic properties. After fullerene was discovered in 1985, this carbon 60 species was considered to be of functional value and considerable chemical [8]. Carbon nanotubes have unique mechanical and electronic properties.

Similarly, due to their Superior mechanical strength, thermally conductive properties and electrical, carbon nanomaterials offer many possibilities for tailored roles and properties within the central nervous system. As such they are often considered to be the best candidates for neurobiomedical applications. These materials can interact with brain tissue and can efficiently perform imaging, neurite growth, and neuroprotection and drug delivery tasks [9]. Similarly, carbon nanomaterials can be used for the treatment and diagnosis of brain diseases through research on the central nervous system [9]. Carbon nanomaterials are promising, are being explored for biomedical applications and are making a positive contribution to neuroscience applications.

Graphene is a sheet of carbon atoms as thick as an atom. Graphene is well-suited for use in supercapacitors, electrodes, and transistors [10]. Similar to carbon dots, graphene possesses good mechanical and electronic properties, as well as both thermal and optical properties, and graphene also allows for synthesis through multiple top-down and bottom-up strategies. Graphene is used as a functional material in composites.

2.3. Hydrogel

The hydrogel material is flexible, biocompatible and has tensile properties. This material is durable and sensitive enough. The specific requirements of flexible sensors can be met. Considerable progress has been attained in the field of hydrogels for wearable sensors. Hydrogels also have multiple applications in wearable sensors, which include as a material utilized for sampling sweat and making flexible electrodes. Hydrogels can also be made to have the desired properties by choosing different synthesis methods and h or by combining them with other materials. Hydrogels have made considerable progress in the field of capacitive sensors and battery-powered sensors. This progress will provide further opportunities and developments in the medical and monitoring fields.

Nagamine et al. developed a hydrogel-based contact sensor pad which was used for non-invasive abstraction and in situ sweat composition analysis [11]. This sensor pad consists of a combination of

reference electrodes and electrochemical biosensing working, completely overlaid with agarose hydrogel. A sweat-lactate biosensor was prepared for the sampling and measurement of human sweat. The experiments were modelled on an enzyme-based l-lactate sensor, which stabilized the electrical potential of the parameter electrode in the perspiration extraction solution.

Electrodes made from hydrogels are biocompatible, adhere well to the skin and have accurate signal transduction [12]. Chen's group reported a robust hydrogel- elastomer hybrids. The mechanical interlocking structure not only ensures high adhesive strength, but also achieves mechanical flexibility.

3. Medical applications of flexible wearable sensors

Flexible biosensors have a broad range of promising applications in the medical field. In this chapter, in-vivo sensing and in-vitro sensing are discussed respectively. In vivo sensing is much more challenging with higher safety requirements and the complex physiological environment of the human body.

3.1. In-vivo sensing

In vivo sensing has an instrumental role in maintaining environmental homeostasis within the human body, sensing external stimuli, information transfer and adaptation to the external environment. The internal body is in a complex physiological environment and flexible medical devices communicate with data through embedded sensors. Medical devices can have a range of geometries and a greater variety of sensors and more sensing data than electronic skin, all of which promise to improve diagnosis and treatment.

Zhao et al. integrate polymers into an active material to enhance the flexibility of this composite [14]. It also enables strong intermolecular interactions and significantly improves the adsorption capacity. Nitrides and two-dimensional transitional metal carbides were prepared and integrated with versatile interface chemistry and high-level metal conductivity to present excellent sensing properties. The physicochemical characteristics of the two-dimensional materials were revised to produce high-performance ammonia sensors to develop strong, chemically stable, thin and flexibly laminated electronic films which are better suited for soft robotics applications. The results of this experiment greatly improve biocompatibility and safety. This electronic technology offers new directions for future sensors for medical prosthetics. MXene films cross-linked with PVA with powerful hydrogen bonds demonstrate outstanding structural stability [15].

Guan et al. proposed a new self-powered, wirelessly controlled, neurostimulated e-skin for in vivo sensing. The e-skin comprises micro-individuals of flexible photo-sensitive frictional electrical MAPbI3/ PDMS [16]. The electrical neurostimulation signal output by the e-skin is generated by human activity in an unimplanted battery. Through light illumination, the photosensitive e-skin allows for functions during neurostimulation and wireless control. The state of switching off the neurostimulation can be controlled by the recording of the switching state for the light illumination. Here, Guan et al. fabricated a self-supporting, wirelessly controlled, electrical neurostimulation which can be controlled by a wireless switch [16]. As a demonstration of the application of electronic skin in characterising synaptic changes, the researchers attached a device for connecting the hippocampus to the brain of mice. By attaching the device to the hippocampus of the mouse brain, the researchers discovered that the e-skin could successfully engineer postsynaptic responses and thus characterise in-vivo synaptic plasticity. This self-supported, light-operated e-skin offers new possibilities for realising battery-free, wirelessly controlled, electrically neurostimulated medical devices.

In vivo medical equipment for haptic perception requires precise manipulation of the in-process to provide detailed data on moments and forces in the x, y and z orientations. For surgical purposes, Hu et al. designed a six-dimensional flexible force sensor with a mortise and tenon interlock structure based on ancient Chinese architecture [17]. This sensor uses a concave and convex interlocking structure to allow for the development of six directional sensing modules in the flexible sensor. This

structure allows for clear sensing of external force information and biochemical signals. The collection and sensing of additional sensing information helps to monitor the complexity of the external environment. The flexible sensor is integrated into the braces through six-dimensional orientations and its high-precision design facilitates the precise alignment of teeth. This helps the dentist to obtain information about the different forms and stages of the teeth. This will make the treatment process more efficient.

A precise multi-axis procedure is a fundamental requirement for orthodontic treatment of tooth movement. Even though flexible multidimensional force sensors can effectively sense multidimensional forces, the challenge they still face is the simultaneous presence of three-dimensional forces and moments in a flexible force sensor. Six-dimensional force sensing permits the successful manipulation of objects relying heavily on directional tracking and the accurate monitoring of complex multi-axis stimuli. The uniquely flexible six-dimensional force sensor offers a new approach to the design of multi-dimensional force sensors. What it paves the way for is the advancement of intelligent robotics, innovative interactions with human-machine interfaces and sophisticated prosthetics.

A team at Stanford University has proposed an organization-mimicking, extensible neurochemical bio interface called "NeuroString", fabricated by laser-fabrication of metal composite polyimide into an interlinked graphene/nanoparticle network embedded in an elastomer [18]. Neurowire sensors enable chronically real-time, multichannel and multiplexed monoamine sensing, in vivo, throughout the brains of behaving mice, together with the measurement of serotonin dynamics and interference with peristaltic motility in the gut in the absence of undesired stimuli and disturbances. The researches on resilient and coherent biosensing interfaces described have broad potential to be extended in terms of neurotransmitter effects on the communication between gut microbes and the brain which possibly eventually to biomolecular sensing of other soft organs throughout the body.

3.2. In-vitro sensing

Flexible, in-vitro devices can measure the movement of different body parts, contributing to disease diagnosis and providing a greater degree of human-machine connectivity. In addition, they are a prominent area of interest for in vitro sensing.

Medical equipment and electronic skin are the two most common types of in vitro sensor devices. Consequently, flexible wearable technology has a high capacity for bending and stretching. These devices can be adapted to the body's limb movements. Most human surfaces can be effectively integrated as platforms for electronic skins, which have a thin and soft interface. The e-skin can detect physiological data within the body. The e-skin makes informed decisions when analysing data and detecting and monitoring disease. However, the built-in sensors must be precise and electronic.

Wang et al. proposed a non-invasive wearable biosensor to monitor metabolites in sweat continuously [20]. During strenuous exercise, sufficient quantities of biological fluids are often produced. This sensor can detect some metabolic foreign bodies at sufficiently high concentrations, and wireless communication and on-site signal processing from the puissant wearable sweat sensing technology "NutriTrek". It is capable of personalized and non-invasive metabolic monitoring, and prompt intervention. The combination of carbachol ion electrophoresis-based sweat induction and efficient microfluidic-based peripheral sweat sampling technology enhances the efficiency of continuous autonomous analysis of sweat for the precise detection of trace levels of several metabolites and nutrients.

In the biomedical field, thermal detectors are essential for assessing the condition of objects targeted from the environment through the human body. Optically based thermosetting tools have received considerable attention. One such method, a photonic upconversion process which has low autofluorescence and high tissue penetration depth, is considered to be an effective methodology for the monitoring of temperature. Ding et al. proposed an optical thermometer containing an optoelectronic device with integrated photonic upconversion [21]. Converting through infrared to visible light is done by an integrated optical receiving and transmitting device. In contrast to the

methods used for conventional materials, temperature sensing delivers an alternative method that is highly sensitive and low power when stimulated. Integrated arrays of large-area devices on similar semiconductor materials and architectures with wafer scales and pitches of a few microns can be easily archived for high-resolution thermograms. One of the limitations of the present generation of devices is red emission, which is outside of the transparent windows. Futuristic designs could include the absorption and emission of semiconductors for longer wavelengths. In summary, these concepts for materials and devices build a collection of power tools with a variety of applications in both the environment and healthcare.

The other medical application is the Triboelectric Nanogenerator Sensor Integrated with a Bistable Micro-Actuator made by Arab et al. for poor bladder control [22]. Furthermore, in cases of large bladder size or stiff bladder muscles, the capability permits multiple actuation of the device to achieve complete vacuity. A high level of sustained voiding efficiency resulted from the idea of building in the repair phase. The integrated TENG sensor detects bladder filling in patients with neurological degeneration and serves as a proof of concept for a future auto-control system for clinical applications. This bistable brake is used to clear the bladder in the first stage of the repair to create a complete voiding system that can be driven repeatedly, allowing the patient to achieve self-control over voiding, normalising the frequency and volume of urination per voiding and thus treating the symptoms of frequent urination.

4. Conclusion and outlook

This review systematically discusses cutting-edge research on flexible implantable sensors for applications in biomedical. It first delves into the selection and analysis of flexible materials and then presents a review of two types of sensors for in vivo and in vitro sensing. The use of these flexible wearable devices in biomedical will expand with the efforts and input of various other disciplines.

As previously mentioned, the detection of physical signals in the human body is expanding with the advancement of sensing technologies and new materials. With excellent performance on detection, flexible wearable sensors have far-reaching breadth and potential for development in the medical field. However, the future diffusion of flexible implantable sensor products faces many obstacles, such as research and experimentation with emerging materials to obtain sensor materials that offer higher performance. This is coupled with polymerisation and exploration between materials, cross-linking and modification. A range of technical challenges also exist, one of which is their security and privacy. Sensors are small and sensitive and can store large amounts of data. However, the potential for data loss has led to the need to develop more secure and encrypted wearable devices to reduce privacy and security risks. A future challenge in terms of technology is the in-person calibration of wearable devices. There are differences in body structure and function between individuals, and the factors that influence the individual experience of using them vary from person to person. How to make the sensors more personalised to the person is a major issue. Cross-disciplinary developments are driving the expansion of medical applications for flexible wearable devices. As technology continues to develop, the application of flexible wearable devices is set to become more comprehensive. A more scientific approach from the research and development stage to clinical trials and then to the market is worth further exploration.

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