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Chapter

Perspective Chapter: Tissue-Electronics Interfaces

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Abstract

Tissue-electronics interfaces provide a two-way communication between biological tissue and external electronics devices to record electrophysiological signals and stimulation of the living organs. This chapter presents an overview of significant progresses in tissue-electronics interfaces. At first, we evaluate principal properties of the living tissue microenvironment important for tissue-specific equipment design. Next, we study charge transfer mechanisms in the biological tissues, bulk electrode materials, and tissue-electronics interfaces. After that, we highlight the current developing and promising advanced biomaterials for the neural electrodes, significantly leading to the development of bionanoelectronics and bionic organs. Finally, the challenges and future outlook of the neural interfaces will be discussed.

Keywords: bioelectronics, neural interfaces, biomaterials, composites, neural recording, electrical stimulation, charge transfer

1. Introduction

The discovery that human cells are capable of producing electrical signals and responding to electrical stimulation, has encouraged researchers to develop technologies based on monitoring the body’s electrophysiological activities and electrical stimulation of living tissues. To understand that how the electronic systems interact efficiently with biological tissues, dominating over the structural complexity and function of the host tissue is essential. Biological tissue often contains the cells distributed in an extracellular matrix (ECM). The ECM is a specific biochemical composition consisting of various sugars and proteins in an aqueous medium. In addition to mechanical support, the ECM has biochemical and topological properties that affect the cellular functions such as migration, proliferation, differentiation and growth mechanisms. The properties of the ECM are different according to the type of tissue. Therefore, the biomaterial’s performances can be different based on the microenvironment that the biomaterial is implanted in. Accordingly, to create harmony and constructive interaction between implantable devices and living tissues in a bioelectricity system, matching the properties of each component is vital [1].

Based on this, the need for new materials to extract data through advanced, immediate and accurate methods has developed different types of materials and methods to improve the interaction of implantable equipment with the biological organs, tissues and cells. Todays, developing of the new high efficient neural interfaces is progressing
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rapidly, which is mostly due to the development of new materials. Meanwhile, the current electrodes are usually made of the metals such as platinum (Pt), iridium (Ir) and other materials such as stainless steel and nickel-chromium (Ni-Cr) alloys. Figure 1 shows various commercial electrodes that are currently used in clinical applications. However, these materials have significant shortcomings such as mechanical mismatch, low biocompatibility, and weak electrochemical performances. Therefore, various new advanced materials such as hydrogels, conductive polymers, and hybrid composites have been developed, so that they are expected to cause the great improvements in bioelectronics and online health monitoring.

2. Essential considerations

2.1 Dynamics and mechanical properties

Reducing the damage to the biological tissue and minimizing the interfering effects on the function of the organ are fundamental considerations in the design and implantation of a device in the body. From the muscle dynamics caused by heart and lung activities to peristalsis of the digestive system and the mobility of bones and joints, may affect the performance of the implant. On the other hand, the presence of biomedical implants in the body can slow down or disrupt the activity of dynamic organs. The forces caused by continuous movements around the implant can easily lead to the destruction of the bioelectronic device. In addition, the stiffness of the
living tissue can also affect the performance of the implant. Most biological tissues, except bones and teeth, are soft and have an elastic modulus of less than 1 kPa (such as central nervous system) to higher than 100 kPa (such as lungs, kidneys, arteries) [2]. Meanwhile, pathological conditions can lead to the transformation and increase of stiffness of biological tissues [3]. Subsequently, changing the ECM’s stiffness affects the behavior and function of the cells. Therefore, the soft nature of most biological organs and tissues makes them highly vulnerable when faced with biological implants. Accordingly, it is important to understand the dynamics and mechanics of the living tissues.

2.2 Immune responses to implants

After implantation, a layer of proteins, such as fibronectins, collagens, laminins, are quickly absorbed on the implant’s surface [4]. This layer is determined by the immune system, leading to foreign body responses (FBR) [5]. The FBR is a phenomenon in which many immune cells undergo apoptosis. This compromises the immune system that may result in formation of a biofilm around the implant and tissue infection [6]. During this process, the formed fibrotic capsule around the implant separates the electronic device from the biological target.

The immune system reactions are altered based on the tissue. In the central nervous system, which is resistant to foreign antigens and immune response [7], the FBR causes the glial scar formation. The resulting scar isolates the bioelectric implant and ultimately impairs the electrical recording/stimulation function. Infections and glial scars caused by the presence of an implant in the body are generally attributed to various reasons such as the mechanical mismatch of the implant with the host tissue [8]. Hence, tailoring the mechanical properties to minimize the FBR is a major consideration when designing an efficient implant. Figure 2 shows the immune responses, including glial encapsulation and tissue/electrode separation processes, to the implants.

2.3 Chemical environment

The chemical microenvironment surrounding the implant plays an essential role in the stabilization, interaction and performance of the bioelectricity system. Biological tissues are moist and somewhat alkaline microenvironment, which may be aggressive to electronics system components such as sulfate, chloride, carbonate, and phosphate [10]. The combination of the chemical microenvironment with reactive oxygen species (ROS), which are produced during intracellular metabolic processes, can cause the FBR caused by oxidative processes. This disrupts the implant’s interaction with the biological tissue, and the subsequent entire functioning of the bioelectricity system.

Ideal biomedical implants should be compatible with the underlying living tissue. This adaptation results in a sincere but not restrictive interaction with the organ’s topography. Therefore, to minimize inflammation of the immune system, bioelectronic materials and designs must be biocompatible, and neutral to proteins absorption and immune cells stimulation. For example, applying an inert encapsulating material aims to reduce the direct interaction zone between the electrode and biological tissue, reducing electrical noise and potential electrode degradation. Hence, one of the most effective ways to reduce inflammation and infection, is designing new materials and modifying the implant’s surface to be more compatible with biological microenvironments.
3. Charge transfer mechanisms

3.1 Charge transfer at tissue-biomaterial interfaces

Accurate monitoring of the electrophysiological signals produced by the nervous system and operative tissue stimulation are important parameters for evaluating the performance of the tissue-electronics interface [11]. The generation and transmission of electrophysiological signals are conducted by stimulating ions to pass through the cell’s membrane and changing the charge concentration in the ECM. These ions carry the charges in the ECM, so their mobility makes a local electric field. The goal of a neural electrode is to create a two-way connection between the electronics device and biological tissue to record the changes of the electrophysiological field (signal recording) or change the field (electrical stimulation). Enhancing this two-way communication is the basis of what we consider for designing and construction of bioelectricity systems [12]. Figure 3 indicates the bioelectronics activities in the tissue-electronics interfaces and equivalent circuit models for stimulation and recording. It does not matter which communication mode (recording or stimulation) is performing at the interface, the important thing is that the applied electroactive materials ensure efficient charge transfer between electrons and ions in the bioelectricity system. Because, charge transfer in neural interfaces is done by electrons, while biological tissues transfer electrophysiological charges through ions [14].
In a way known as capacitive charge transfer, the transfer mechanism depends on the charging/discharging process of the capacitance made by the electric double layer (EDL) formed on the electrode surface. Upon the electrode generates an electrical pulse, the electrostatic charges concentration on the implant’s surface changes, which is accompanied with the alternating absorption and repulsion of ions in the ECM surrounding the implant. It is worth noting that during this process, there is no electron transfer between biomaterials and tissue. In fact, under these conditions, a layer of polarized water molecules is adsorbed on the electrode’s surface and acts as a dielectric for the EDL capacitor [15]. It means, no chemicals are produced or consumed in capacitive charge transfer. Therefore, electrodes whose function is based on capacitive charge transfer are more suitable for stable interaction with physiological environments. However, the charge transfer ability of a neural interface depends on the capacitance of the surface EDL, and the capacitance is positively dependent on the surface area of the electrode. Therefore, increasing the effective surface area of neural electrodes, without increasing their size, leads to improvement of the bioelectronics systems performance.

In another charge transfer process that is based on the Faraday mechanism, charge transfer depends on chemical reactions occurring on the electrode’s surface. Upon the electrode generates an electrical pulse, the reduction-oxidation (redox) reactions occur at the tissue-electrode interface. The Faradaic charge transfer is associated with the reduction or oxidation of chemicals, which establishes as electrons pass through the interface. According to whether new stable products are produced during charge transfer or not, the Faradaic process is divided into two types of reversible or irreversible. During the irreversible Faradaic process, the redox reactions not only lead to the collapse of the electrode, but also damage the living tissue by changing the ECM’s conditions such as pH and releasing harmful products into the tissue microenvironment. So, it is preferred to avoid charge transfer processes by irreversible Faradaic paths. Meanwhile, in reversible Faraday charge transfer mechanism, new materials produced on the electrode’s surface are converted to their original state during the opposite electric pulse. Hence, in the
reversible Faradaic process, new products are not introduced into the living biological tissue. Accordingly, charge transfer through reversible Faradaic processes is safe and desirable. It is very important that the corresponding redox reactions occur during charge injection in the reversible Faradaic method, because they indicate that the neural interface can hold more charges. Consequently, the electrodes with a reversible Faradaic charge transfer mechanism are preferred compared to the electrodes based on irreversible charge transfer. Figure 4 indicates capacitive and faradaic charge transfer mechanisms at tissue-electronics interfaces and their cyclic voltammetry (CV) responses.

3.2 Charge transfer in biomaterials (electrode)

Due to the type mismatch of charge carriers in the biological tissues and electronics systems, the stable and effective data transmission using the neural interface is a significant challenge. So far, we have discussed charge transfer mechanisms in the biological tissues and the tissue-electrode interfaces. Next, we will describe charge transfer mechanisms in biomaterials (electrode material). Charge transfer in the electrode materials are divided into three main categories, which are:

1. Charge transfer by electrons: This type of charge transfer is often observed in traditional electrodes, which are often made of metals and carbon materials. These materials generally use free electrons as charge carriers to establish connections with biological tissues [16]. Due to the high electrical conductivity and long-term biological stability of metal and carbon electrodes, these materials have been widely used in construction of the neural electrodes [17].
2. Charge transfer by ions: Ion-conducting materials such as hydrogels often have inherent biocompatibility, flexibility and excellent adaptability to the living tissues, which are considered as promising characteristics for the neural interfaces [13, 18, 19].

3. Charge transfer through hybrid electron-ion transfer: This transferring method is often done by conductive polymers (CPs), and their composites with hydrogels and electron conductive materials. In addition to hybrid electron-ion charge transfer mechanism, the excellent mechanical biocompatibility of the CPs has drawn this materials more attention [20].

In the next section, we will describe the notable electrode materials based on their charge transfer mechanisms.

4. Current developing neural interfaces

Tremendous production progresses of new materials, reducing dimensions while increasing efficiency of bioelectronics systems. In addition, the mechanical adaptability and improving the electrical properties of neural electrodes to better interact with biological tissues have always been on the research programs. The improvements of the conventional electrode’s properties and design of new electrodes, lead the bioelectronics present in various applications such as heart pacemakers, deep brain stimulators, retinas, contact lens, electronics skin and etc. In this section, we will introduce different types of these electrode materials, manufacturing processes and their functional mechanisms.

4.1 Neural interfaces that transfer charge by electrons

4.1.1 Metal electrodes

Until now, most neural electrodes are mainly produced by electron conductive materials, namely metals and metal composites such as platinum (Pt), gold (Au), silver (Ag), and iridium. However, the practical applications of these materials as electronic-tissue interfaces are limited due to their weak biocompatibility and insufficient electrical activities. It should be noted that the electrical activity of the electrode depends on different electrochemical parameters such as electrochemical impedance, charge injection limit (CIL) and charge storage capacity (CSC). It means, the high electrical conductivity of metal electrodes does not necessarily mean in that they have good electrical activity. For example, it has been demonstrated that although some conductive polymers suffer from lower electrical conductivity, they show higher electrical activity than platinum [21]. Therefore, a material with low electrical conductivity is not necessarily a weak electroactive material, although increasing the electrode’s conductivity usually improves its electrical activity [22]. In the following, we will discuss the recent approaches for improving the biological behaviors and electrical activities of the metal electrodes.

- Nanostructured metal electrodes

Do more with less, this is the mantra of nanotechnology. Considering the urgent need for small bioelectricity systems, increasing the number of channels and charge
In recent years, biocomposites have become a popular choice in the development of neural electrodes. These electrodes are designed to mitigate the high injection density of neural electrodes while reducing their dimensions, with nanoscale features [23, 24]. However, these electrodes still face unavoidable limitations, which are: (I) the possibility of bending and placing in unspecified places due to the excessive fineness and frangibility. (II) To design these tiny electrodes, the materials with high hardness and stiffness are needed, which may cause activation of the immune system, formation of glial scars and tissue inflammation. (III) Nanometer electrodes may have relatively high electrochemical impedance and low charge injection capability, which leads to weakening the performance of the bioelectricity system. However, some approaches such as introducing nanopores in the electrode structure for increasing its effective surface area, can reduce the electrochemical impedance of the neural interface [25]. Recently, composite coatings made of electrodeposited iridium oxides with Pt gray were developed to fabricate IrO$_x$/Pt gray neural electrode. It demonstrated that the large surface area of the nanoporous Pt, leading to firm adhesion of the iridium oxide to the substrate accompanying with superior mechanical and electrochemical stability of the electrode [26]. Other example are the diamond-titanium porous composites produced by deposition process to fabricate hybrid neural electrodes. These composite electrodes have demonstrated high electrochemical capacitance, low impedance, and excellent biocompatibility assessed in vitro using cortical neurons [27]. Moreover, the nanostructured electrodes have shown greater compatibility with the ECM [28]. The flexibility of nanostructured electrodes in line with the weak movements of the brain and other dynamic biological organs, is another advantage of nanometer electrodes [29].

- Metal composite electrodes

High impedance and low biocompatibility are the unfavorable characteristics of traditional metal electrodes for monitoring electrophysiological signals and tissue stimulation. Accordingly, metal composites have been developed to overcome the mentioned challenges and improve the long-term stability of metal-based neural interfaces. Avoiding parasitic effects should be considered for design of metal composites, so combining the materials with similar characteristics is more preferable. In addition, it has been proved that the nanocomposites, which have high specific surface area and more compatibility with the ECM, improve the performance of the neural interface. Also, fabrication of nanostructured composite coatings on the electrode, could be a method to create the preferred properties. The composite coatings are usually deposited by electrochemical deposition, sputtering and thermal evaporation methods. Currently, gold (Au) is considered as a promising candidate for improving the properties of neural electrodes. The excellent biocompatibility and encouraged performance of the Au-coated electrodes have been proven [30]. Compared to the pure silver (Ag) surface, the Au-Ag nanocomposite electrodes have shown lower impedance and more biocompatibility, which has resulted in accurate, high-quality, and stable recording of electrocardiogram (ECG) and electromyogram (EMG) signals. Moreover, the traditional neural electrodes generate wide signal void (no functional magnetic resonance imaging (MRI) signal) in ultrahigh field (UHF) MRI scanners. This is an important shortcoming when simultaneous MRI signal acquisition and neural monitoring is desired, for example in studying the functional mechanisms of deep brain stimulation (DBS). Recently, new gold-aluminum (Au-Al) composites have been presented for neural interfaces to overcome the signal voids. The Au-Al composites significantly reduce the magnetic susceptibility difference
between the brain tissue and electrode, resulting in greatly reduced regions of the signal voids. The Au-Al composites produced less field distortion and signal loss compared to the pure Au and Al electrodes, leading to MRI scanners of lower magnetic field strengths as well [31].

Despite the conventional electrode metals such as the toxic Ag nanowires [32], liquid metals (LM) have good biocompatibility, excellent mechanical flexibility, and significant electrical conductivity. The LM composites include bismuth-indium-tin (Bi-In-Sn), indium-gallium eutectic (EGaIn) and gallium-indium-tin (GaInSn), are widely used in the preparation of neural electrodes. However, these LM electrodes have obvious challenges, including (I) removing the oxide layer of LM particles inside the ink to connect the electrode paths, (II) overcoming the surface tension of the LM and converting it into desired shape, (III) solving the problem of connection fragility of the LM to other components of the bioelectricity system, and (IV) encapsulating the LM to prevent leakage into the biological microenvironment, and subsequent tissue damages.

4.1.2 Carbon-based electrodes

At present, carbon-based materials such as carbon nanotubes (CNTs) and graphene, are outstanding candidates for the design and fabrication of nanoscale, flexible, and multifunctional neural interfaces.

- **Graphene electrodes**

  Graphene is a single layer of carbon atoms that are connected to each other in the form of a two-dimensional honeycomb network by sp² hybridization. Recently, graphene has been used as a successful high efficiency material in the neural interfaces [33]. Among the prominent features of the graphene, the following should be mentioned: (1) very high mechanical strength while maintaining extraordinary flexibility, (2) excellent electrical conductivity (single layer resistance of 100 Ω sq. −1) with a carrier mobility of ~15,000 cm² V⁻¹ s⁻¹ at ambient temperature [34], (3) large surface area that provides a favorable template for cell attachment and charge transfer, thereby enhancing electrical recording/stimulation capability, and (4) biocompatibility. Additionally, the modified surface functional groups of the graphene, makes it more compatible as an operational nanostructure for various applications. By manipulating or functionalizing graphene, some modified structures such as graphene oxide (GO), reduced graphene oxide (rGO), graphene fibers and other derivatives can be produced, which brings more choices for bionanotechnology [35, 36]. Graphene can be coated on the electrodes using different methods such as chemical vapor deposition (CVD) [37], spraying [38], and electrochemical routes such as cyclic voltammetry (CV) [39]. However, weak adhesion of the graphene to the substrate, resulting in coating instability and destruction of the electrode, is one of the main challenges of the graphene electrodes.

- **CNT electrodes**

  Carbon nanotubes (CNTs) are one-dimensional nanostructures created by twisting the graphene sheets. The CNTs have been widely used in the construction of neural electrodes, due to their following desirable characteristics: (1) they have high electrical conductivity, facilitating the ballistic electron transfer from the
electronics-tissue interface to the electrode material. (2) They have a high surface-to-volume ratio, which can reduce the electrochemical impedance and increase the charge injection capability of the electrode [40, 41]. (3) The CNTs benefit from surface functional groups that are easily modified by biological molecules, leading to tunable anisotropic properties adequate based on the application. In addition, (4) The CNT-based electrodes have presented superior biocompatibility, mechanical strength, flexibility, and worthy adhesion to the nerve cells [42, 43].

There is a trade-off between the size of the neural electrode and its electrochemical impedance, so that by decreasing the electrode size decreases, its impedance increases. It should be noted that for high resolution and accurate recording of the electrophysiological signals, the small electrodes with low impedance are needed. Although the size and electrochemical properties of neural electrodes have been continuously improved, weakening the mechanical performances during miniaturization have always been an important challenge for practical applications [44]. Therefore, the CNTs are suitable nanomaterials to overcome this challenge. In addition, the improvement of biocompatibility, reduction of impedance, promotion of more stable micro-environmental ability of the conventional electrodes modified with the CNTs have also been reported [45]. The researchers have evaluated conductive CNTs/collagen composites for studying the cellular responses on the neural interfaces. The results indicated that by increasing the collagen content, the cells show enhanced attachment on the electrode’s surface, which could be due to the high ability of the collagen to improve the adhesion and viability of the nerve cells [46].

4.2 Neural interfaces that transfer charge by ions

Signal transmission in biological media is conducted through the movement of ions and small molecules, contrary to the electron-hole in electronic devices. Accordingly, the ion-conducting neural interfaces can interact more efficiently with the living tissue. The finding this tissue-electronics charge transfer interaction has caused the ion-based interfaces to receive more attentions. However, the use of liquid ion-conducting materials such as electrolyte solutions and ionic liquids, which have high ion transfer capability, are limited due to the need for a mold to maintain the shape of the electrode [47]. As a result, the solid ion conductors have attracted more attentions. Recently, hydrogels have been broadly applied in biological applications, including cell culture, smart drug delivery, tissue repair and regeneration, due to their intrinsic biocompatibility, biological functionality, flexibility, and adaptation to living nerve tissue. The outstanding capabilities of the hydrogels have caused these materials to be considered promising candidates for designing and manufacturing flexible bioelectronic systems [48].

4.2.1 Hydrogels

Hydrogels are soft solid ion-conducting materials that are composed of interconnected polymeric configuration. This polymeric structure can absorb water that enables free ion movement in aqueous-based network, creating ionic conductivity. This ability has caused hydrogels to be used in various applications such as artificial muscles, ionic skin, artificial axons and connections of the central nervous system, whose functions are performed through ion conduction. Conductive hydrogels are usually synthesized by (1) constructing distinct component networks through
self-assembly or self-polymerization CPs/fillers, (2) building interpenetrating networks by doping CPs/fillers, (3) diffusing free ions, and (4) embedding conductive fillers/free ions into an existing non-conductive hydrogel matrix (Figure 5).

Depending on the additives and dominant conducting mechanisms, the synthesized hydrogels can be classified as electron-based, ion-conducting, and hybrid electron–ion conductive hydrogels. The ionic conduction is mainly based on a non-Faradaic (capacitive) charge transfer mechanism, without materials or charges passing through the neural interface. This transmission possesses the transmitting high-frequency electrical signals over long distances [50].

There are three types of widely used hydrogels for the electronic-tissue interfaces, which are (1) ion-conducting hydrogels (ICHs), (2) ion-conducting organohydrogels (ICOHs), and (3) hydrogel composites. In the following, we will focus on hydrogels in which the electrical conduction is conducted only through ions. Other hydrogels in which the charge transfer process is carried out by hybrid electron-ion transfer will be discussed in the next section.

The ICHs are classified as highly hydrophilic gels with a massive three-dimensional (3D) hydrated network structure [51]. Since ions can move freely in this 3D network, ICHs can achieve high ionic conductivity in the range of 3.4–5.5 Sm⁻¹ [52, 53] by permeating salts such as NaCl, LiCl, FeCl₃, acids such as HCl, H₃PO₄, or ionic liquids [54–56]. In addition, the ion conduction mechanism of hydrogels is similar to biological tissues, so they can efficiently exchange data through ion diffusion [48]. This makes hydrogels immune to the challenges of converting electronics and ion-based signals to each other and related problems [50, 57]. It should be noted that this group of hydrogels contain large amounts of water, which can act as a buffer environment during the side effects, to prevent adverse problems for the living tissue. Most ICHs are adhesive, transparent, and self-healing, so their applications in bi-electronic systems such as wearable sensors, implantable epidermal electrodes, digital tattoos, and many others are being developed [58, 59].
However, the prepared ICHs by salt compounds, have unfavorable biocompatibility and low stability due to the release of excess ions, which can lead to the damage of bioelectronic devices. It has been proven that compared to traditional metal electrodes, the ICH-based electrodes can generate contractile forces using lower voltages, which indicates the capability of the electrodes for bioelectrical stimulation. In addition, it should be noted that the undesired gaps formed between the electronic interface and the biological tissue, resulting by muscle contraction or skin bending (surface electromyography abbreviated to sEMG), leads to significant noise/error in the identification of electrophysiological signals. These gaps can be eliminated using soft hydrogel interfaces and making electrostatic interactions between the electrode's surface and tissue [60]. However, the ICH-based electrodes lose conductivity, flexibility, and even morphology due to rapid water loss, which limits their practical applications [61]. At present, some solutions have been proposed to overcome this problem, including (I) addition of dehydrating reagents [62, 63], (II) mixing of ionic-polymeric liquid gels [59], (III) binding of sealing materials [64], and (IV) mixing of deep eutectic solvents (DESs).

As mentioned, the water losing is one of the major shortcomings of hydrogels in practical applications. Recently, adding organic solvents to hydrogels for producing the ion-conducting organohydrogels (ICOHs) has been considered to overcome the dehydration of hydrogels. This modification is based on the premise that the organic solvents can compensate some of the lost water of hydrogels, and enhance their dry immunity and maintain ionic conductivity [65]. In addition, the ICOHs retain some advantages of the hydrogels, including biocompatibility, soft mechanical properties, and considerable shape design ability [66, 67]. Adding organic solvents to hydrogels can be conducted through three methods, which are (1) solvent replacement [68]; (2) the desorbed hydrogel network is injected with organogel precursors, and then is subjected to in situ polymerization [69]; and (3) gelation in a binary solvent [70].

It is worth noting that although the solvent displacement method could be done easily, the ICOHs prepared by this method have relatively weak forces between the hydrogel's polymer network and the replaced solution, resulting in solvent leakage and tissue damages [71]. Meanwhile, ICOHs synthesized by the gelation method in binary solvents have overcome this challenge and also presented the advantage of high electrical conductivity. While, high electrochemical impedance and insufficient long-term adhesion to biological tissue are some problems of the ICOHs, which have limited their usage in the bioelectronics.

4.3 Neural interfaces with hybrid electron-ion charge transfer mechanism

An ideal tissue-electronics interface should provide the charge transfer requirements of biological tissues and electronics devices simultaneously. Hence, the materials with hybrid electron-ion charge transfer are more appropriate for design and construction of the neural interfaces. Recently, conducting polymers (CPs) have attracted many attentions to create neural interfaces due to their hybrid electron-ion charge transfer capability.

4.3.1 Conductive polymers

The CPs benefit from unique features, which include (1) simultaneous electron-ion conductivity [72], leading to reduction of the electrochemical impedance and improvement of the electrical recording/stimulation. (2) Their inherent adaptive mechanical
properties lead to bridging at electronic-tissue interfaces. (3) Fibers and nanostructures of the CPs, which could be synthesized by low-cost and simple methods, have high specific surface areas that result in facilitating electron-ion exchange at neural electronics-tissue interfaces. (4) Mixing the CPs with different materials such as polyelectrolytes (polystyrene sulfonic acid, polyacrylic acid, polymethacrylic acid) and bioactive molecules [73] can be easily conducted, which improves the biocompatibility and stability of the CPs-based electrodes [74]. In the following, some well-known CPs materials, which have shown promising performances as the neural electrodes, will be presented.

- Neural electrodes made from polypyrrole

Polypyrrole (PPy) is an intrinsic CP that has high conductivity, biocompatibility, facile processing, water solubility, and slight potential for its monomers oxidation, which has made it a capable candidate for the neural interfaces [75]. An ideal CP should have independent decent properties and performances as much as possible, without adding extra reinforcements. To achieve this goal, the CPs need to have mechanical and chemical stabilities in biological microenvironments. However, contrary to the mentioned worthy properties of the PPy, it is prone to irreversible oxidation and easily fails under the change of chemical conditions such as pH and disrupts the bioelectronics interfaces. This characteristic has limited the PPy applications, resulting in more attentions to alternative CPs such as the poly (3,4-ethylene-dioxythiophene) (PEDOT).

- PEDOT electrodes

The PEDOT is an intrinsically CP that appears to be more attractive than PPy due to several reasons, including (1) PEDOT has a narrow band gap [76], changing charges in the polymer chains. (2) PEDOT has a higher electrical conductivity that increases the electrode’s capabilities [22, 77]. (3) PEDOT has shown great electrochemical stabilities [78], which are necessary for the electrical recording/excitation stabilization in a bidirectional communication. In addition, (4) the PEDOT has better biocompatibility than PPy [79, 80]. Although the CPs have many advantages in bioelectronics, their brittleness and excessive stiffness have limited their use in neural electrodes. Therefore, the design and construction of soft and elastic composites based on conductive elastomers (such as PEDOT:PSS) distributed in a soft elastomer matrix (such as polyurethane, PU), and or using the laser micromachining technology for converting the CPs into a flexible electrodes array, have been proposed [81].

- CPs composite electrodes

In addition to the CPs-based electrodes, surface modification of traditional electrodes using the CPs and their composites has given innovative capabilities to the electrical recording/stimulation processes. Improving the performance of electrodes with the CPs-based coatings, could be due to (1) reducing the electrochemical impedance of the electrode, (2) making a soft compatible surface for the electrode while being strong to improve the tissue-electronics interface. In addition, (3) increasing bioactivity in comparison with the bio-inert metallic electrodes, results in decreasing immune responses, tissue inflammation and implant infections. The CPs not only increase the electrode’s stability, but also their highly porous structures, such as electrospun fibers, can improve the electrochemical performances [82]. The biological
fluids can flow in the pores of fibrous structures and interact with a high surface area to increase the electrophysiological signal transmission efficiency. Additionally, making porous composites such as fibrous CPs/CNTs can also enhance the polymer’s conductivity and increase the electrode’s effective surface area. The results have also shown that the neural interfaces based on the CPs/CNTs composites have lower impedance and more charge storage capabilities. These improvements can be due to the presence of CNTs as impurities to make a strong interaction with the CP chains, leading to fast electron transfer processes, formation of three-dimensional structures, and increasing the effective surface of the composite electrode [83].

- Neural electrodes made from hydrogel composites

Hydrogels can make ionic conductivity through the absorption and transfer of the ions present in their structural water, which is a process similar to the transfer of electrophysiological signals. Although this hydrogel’s property has made them attractive, activation electron transfer mechanisms is the key for successful bioelectronics application of the hydrogels [84, 85]. Fortunately, the hydrogel’s porous structure provides adequate space to incorporate with the electron-conducting materials such as metals, carbon-based materials, conductive polymers, etc. with the aim of forming a composite of hybrid electron-ion transfer network. Accordingly, it is possible to improve the electrochemical properties of the hydrogels, including electrochemical impedance and CIL, without weakening their excellent biological properties [49, 86].

The CPs are ideal materials for making hydrogel-based composites, because (1) the similar soft and high flexible mechanical properties of the CPs and hydrogels, avoiding mismatch dynamics and extra stresses to the electrode. (2) The CPs have high compatibility and affinity to the hydrogels that results in potential hybridization. In addition, (3) the unique polymeric and organic properties of the CPs make them facile to be modified. It should be noted that (4) some CPs such as PEDOT have a hydrogel-like form in wet environments, which corresponded to their hygroscopicity or swelling properties when exposed to water [13]. This behavior makes this kind of CPs more similar to the hydrogels’ properties, leading to more integrated and consistent composites.

The CPs are usually used as the electron conducting additives in hydrogel composites. The polymeric nature of CPs allows the molecular scale structures, forming interpenetrating network (IPN) hydrogels. The IPNs not only minimize potential trade-offs in mechanical properties, but also meaningfully reduce probable heterogeneity in electrical and mechanical behaviors. The IPN-based hydrogels could be generally synthesized via three main approaches, including (a) direct mixing of CPs and the hydrogel’s precursors, (b) in-situ polymerization on CPs in the hydrogel matrix, and (c) in-growth polymerization of CPs into the hydrogel matrixes. Figure 6 shows schematic illustrations of the IPNs production processes.

Making nanocomposite using electron-conducting nanostructures, including carbon nanotubes, liquid metals, graphene, metal nanowires, is another approach to increase the hydrogels’ conductivity. Carbon-based materials are preferred candidates for mixing with hydrogels, because their excellent conductivity, high effective surface area, good chemical stability in wet environments, and especially the ability to form covalent bonds with different polymeric network groups. In addition, under the premise of satisfying improved biocompatibility and electrochemical behavior,
Five. Conclusion and outlook

Tissue-electronics interfaces are the key component of bioelectronics systems. These interfaces provide a two-way communication between biological tissue and external electronics devices to record electrophysiological signals and stimulation of the living organs. In biological tissues, the charge transfer is done through ions, while the electronic systems generally use the electrons as electric charge carriers.
Accordingly, the neural interfaces with a hybrid electron-ion charge transfer mechanism can improve the charge transfer processes at bioelectronics. There are two main charge transfer mechanisms at the tissue-electronic interfaces, including capacitive (based on EDL) and Faraday charge transfer. In addition, the biocompatibility, which can reduce FBR and glial scar formation, is an essential parameter for tissue-electrode adhesion improvement that results in accurate and stable signal transmission. Recent general methods to increase the biocompatibility of neural interfaces include reducing the biomaterial's stiffness and elastic modulus, biocompatible coatings, and developing new bioactive materials and composites. Although significant progress has been made in the design and fabrication of tissue-electronic interfaces, some challenges must be overcome before the bioelectronics interfaces can be efficiently operated, including (I) the weak adhesion of the neural electrode materials to biological tissues. This problem may be due to the high hydrophobicity and insufficient biocompatibility of the current interfaces. (II) Inadequate biocompatibility of the electrode materials that leads to FBR, glial scar formation and subsequent tissue-electronics separation. The challenge is that although the electrode materials should have low stiffness and elastic modulus to avoid mechanical mismatch with host living tissue, the weak mechanical properties, especially in dynamic organs, can lead to electrode destruction and failure. Therefore, adapting the properties of the implant to the host living tissue, is important for successful implantation and long-term stability of the electrode. The efficiency of the neural recording/stimulation process depends on the biocompatibility, electrochemical properties such as impedance, charge storage capability, and charge injection limitation of the electrode. High electrochemical impedance reduces the accuracy of electrophysiological signals recording. Reducing methods of the electrochemical impedance mainly include the following: (1) enhancing the conformal capability between the neural interfaces, (2) improving the tissue-electronic adhesion, and (3) modifying the electrode's surface characteristics to adapt with the ECM. In summary, the prospect of developing high efficient tissue-electronic interfaces due to rising the new materials and strategies is expected. To achieve this goal, the main neural biomaterials' properties such as biocompatibility and electrochemical performance must first be improved. It is believed that the development of neural interfaces can contribute to the progress of bioelectronics medicine, neuroscience, and online health monitoring.

Conflict of interest

The authors declare no conflict of interest.
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