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Review

Progress in Research of Flexible MEMS Microelectrodes for Neural Interface

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Abstract: With the rapid development of MEMS (Micro-electro-mechanical Systems) fabrication technologies, manifolds microelectrodes with various structures and functions have been designed and fabricated for applications in biomedical research, diagnosis and treatment through electrical stimulation and electrophysiological signal recording. The flexible MEMS microelectrodes exhibit multi-aspect excellent characteristics beyond stiff microelectrodes based on silicon or SU-8, which comprising: lighter weight, smaller volume, better conforming to neural tissue and lower fabrication cost. In this paper, we mainly reviewed key technologies on flexible MEMS microelectrodes for neural interface in recent years, including: design and fabrication technology, flexible MEMS microelectrodes with fluidic channels and electrode-tissue interface modification technology for performance improvement. Furthermore, the future directions of flexible MEMS microelectrodes for neural interface were described including transparent and stretchable microelectrodes integrated with multi-aspect functions and next-generation electrode-tissue interface modifications facilitated electrode efficacy and safety during implantation. Finally, the combinations among micro fabrication techniques with biomedical engineering and nanotechnology represented by flexible MEMS microelectrodes for neural interface will open a new gate to human lives and understanding of the world.

Keywords: MEMS; microelectrodes; neural interface; conducting polymer; nanotechnology

1. Background

The typical system configuration of implantable neural interface is illustrated in Figure 1. In the whole neural interface system, acting as the tissue-machine interface, the MEMS microelectrodes interconnect the biological tissue with the implantable devices and transmit electrophysiological signals and control orders to each other, which influences the overall efficacy of the system. The relationship among the implantable neural interface system, MEMS microelectrodes and electrode-tissue interface is shown in Figure 2.

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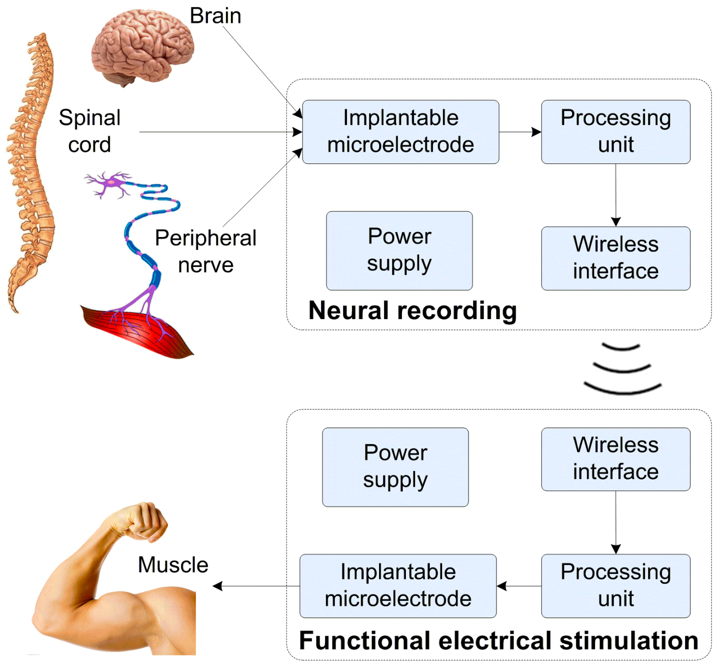

Figure 1 Structural illustration of implantable artificial nerve system.

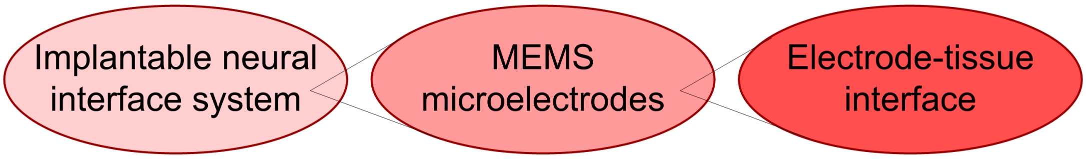

Figure 2 The relationship among the implantable neural interface system, MEMS microelectrodes and electrode-tissue interface.

With the rapid development of micro fabrication technology, biomedical devices can be manufactured considerably tiny and structurally diverse, which minimize the damage during and after implantation for both short term and long term requirement [1]. Nowadays, some dense electrode arrays and tenuous electrodes are developed to undertake complex and precise electrophysiological research with providing excellent spatial selectivity and low power consumption [2-4]. The problem is that smaller size, certainly lowers the damage to the tissue, would inevitably damage the performance and safety of the electrodes [5]. Because decrease in the size of electrode will lead to an increase in impedance and a drop in charge storage capacity (CSC), which, as a result, means poor recording signal quality and high stimulating current that may damage tissue. Considering this fact, the interface material plays a significant role to improve the electrode performance. Many efforts are made to develop more ideal electrode-tissue interface materials with properties including: electrical property containing low impedance, high CSC and high charge injection limit; stability for long term work or implantation without significant property variation; biocompatibility ensuring direct contact with tissue without inducing severe tissue response, toxicity or even necrosis. The characteristics of ideal implantable electrode-tissue interface are shown in Figure 3.

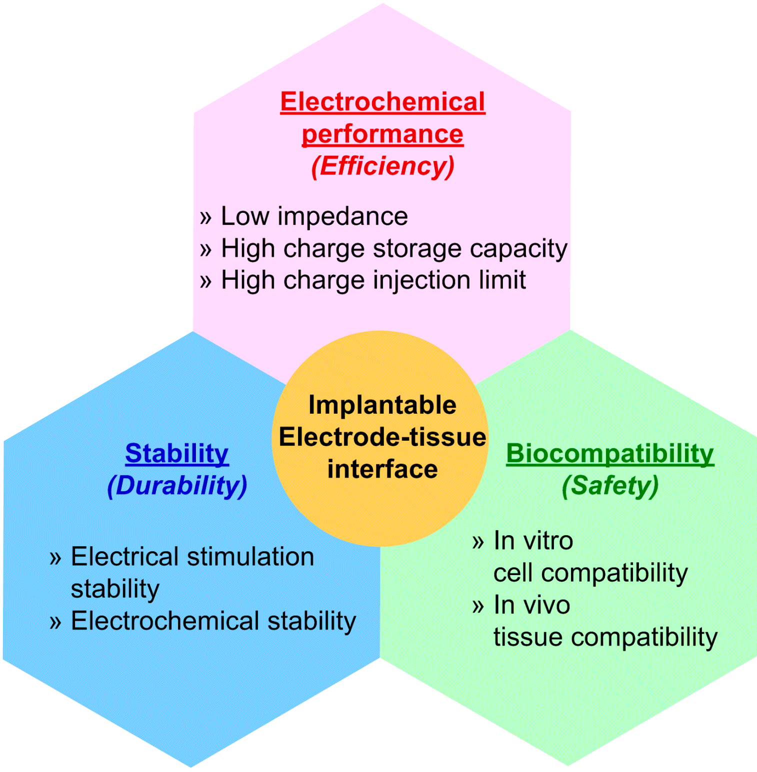

Figure 3 Characteristics of ideal implantable electrode-tissue interface.

1.1 Flexible MEMS microelectrodes for neural interface

One of the most significant components of the artificial prostheses is the microelectrodes which act as tissue-machine interface [6-8]. To functionalize well in live muscle and nerve tissue, the biomedical microelectrodes should meet the requirements including: 1) miniature dimension that minimizes the tissue damage and power consumption, 2) excellent performance that ensures effective operation of the prostheses device and, 3) good biocompatibility that guarantees relatively long term implantation without inducing severe immune response. Complying with these disciplines for biomedical electrodes mentioned above, various kinds of microelectrodes were developed to execute electrical stimulation and electrophysiological signal recording for paralysis recovery after spinal cord injury. Among these manifold electrodes, Michigan neural probes and Utah electrodes array are widely used in central nerve prostheses applications [9,10], while LIFE electrode are usually applied in peripheral nerve and intramuscular researches [7,11].

It is a significant symptom should be confronted that only electrical interaction between electrodes and muscle or nerve tissue without nutrition factor delivery would eventually lead to denervation-induced skeletal muscle atrophy [12-14]. Considering these facts, the microelectrodes integrated with micro channels for fluidic drug delivery were developed in recent year [15-17]. As majority of these studies focused on stiff electrodes which made of silicon or SU-8 for applications on central nerve system, only a few concentrated on flexible electrodes which made of parylene, polyimide (PI) and polydimethylsiloxane (PDMS) [18-20]. The problem that limits the precise stimulation by the polymer based flexible electrodes described above is that the electrode sites distributed on one side of the electrode. Moreover, most of the microelectrodes mentioned above were developed for neural applications, but rare electrode was designed for intramuscular research. The microelectrodes for intramuscular electrical stimulation and electromyogram (EMG) recording in recent years mainly were restricted to crude wire electrodes and simply constructed electrodes with single function [21,22]. For the current situations, it is necessary to design and fabricate multi-functional microelectrodes with circumferential electrode sites distribution for intramuscular prostheses.

1.2 Electrode-tissue interface of flexible MEMS microelectrodes for neural interface

In order to upgrade electrode performance of implantable MEMS microelectrodes, the ideal implantable electrode-tissue interface materials should satisfy requirements including excellent electrochemical performance, stability and biocompatibility. Therefore, manifold electrode-tissue interface materials have been developed to meet the practical demands. Nowadays, the most widely used electrode-tissue interface material remains noble metals, such as platinum, gold, iridium, tungsten and their alloys. These metals are chosen to be electrode-tissue interface because of their excellent chemical stability, which implies that they are able to be implanted in tissue without serious erosion. Nevertheless, the electrochemical performance of MEMS microelectrodes are restricted mostly by the high electrochemical impedance and low charge storage capacity (CSC) of bare metallic electrode-tissue interface. Some electrode-tissue interface was processed with porous structure and special profile to form a rough surface, which would consequently improve the effective surface area of electrode sites. In recent years, newly rising carbon nano materials, including carbon nanotubes and graphene, act as electrode-tissue interface to improve MEMS microelectrode performance for their multi-aspect excellent properties. Although the carbon nano materials possess extremely large specific area and excellent electrochemical performance that others could not match, the drawbacks comprising poor bonding effect with electrode substrate and the probably induced nanotoxicity by litters in tissue largely limit their applications in electrode-tissue interface.

Conducting polymers attract much attention and have been broadly applied in multi-aspect research of biomedical domain for their unique characteristics comprising: low electrochemical impedance, high CSC, favorable plasticity, electrostriction and biocompatibility. Simultaneously, conducting polymers are capable to meet the requirements of electro-tissue interface material. In addition, as shown in Figure 4, conducting polymers possess characteristics including: modification through doping, electrically controlled drug release, molding through micro-nano processing and electro-spinning and surface modification by biochemical molecules. As two kinds of conducting polymers that widely used as electrode-tissue interface, poly (3,4-ethylenedioxythiophene) (PEDOT) exhibits better performance than polypyrrole (PPy) in electrical stimulation (better electrochemical performance) and cell culture (longer neurites growth) [23].

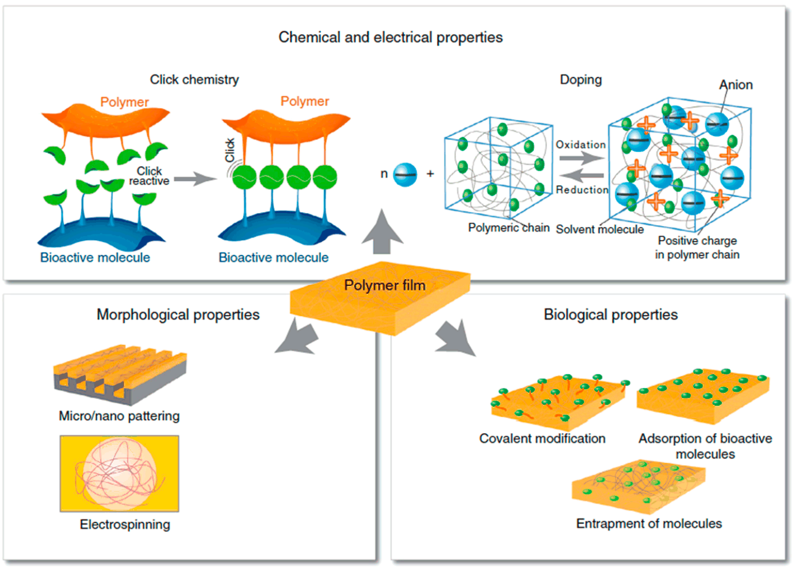

Figure 4 Schematic illustration of characteristics of conducting polymers.

2. Research progress

2.1 Flexible MEMS microelectrodes for neural interface

With the rapid development of MEMS fabrication technologies, researchers have developed various kinds of biomedical microelectrodes applied on electrical stimulation and

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electrophysiological signal recording for paralysis recovery. Among these manifold microelectrodes, Michigan neural probes and Utah electrode array are widely applied in central nerve system researches as stiff MEMS microelectrodes for neural prosthesis. Many research efforts have been devoted to developing novel flexible MEMS microelectrodes for their multi-aspect excellent characteristics compared with stiff microelectrodes, such as lighter weight, smaller volume, better conforming to neural tissue and lower fabrication cost. Owning these advantages, the flexible MEMS microelectrodes for neural interface have appealed extensive attentions and considered to have broad prospects for development in the future. The flexible MEMS microelectrodes mainly include: wire electrode, thin film electrode and mesh electrode.

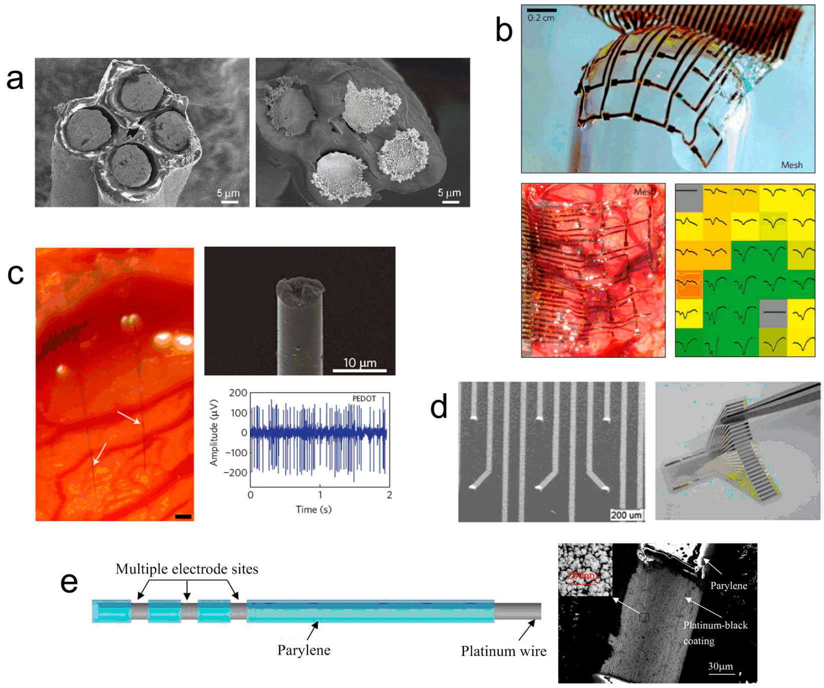

Figure 5 Research progress of flexible MEMS microelectrodes for neural interface. **a** Tetrode composed of four micro wire electrodes; **b** Thin film microelectrode array with silk fibroin covered as substrate; **c** Carbon fiber microelectrode; **d** Thin film microelectrode with 3D raised hemispherical electrode sites; **e** Micro wire electrode with multiple cylindrical electrode sites.

John E. Ferguson and A. David Redish et al. of University of Minnesota developed tetrode made of four micro wire electrodes for neural signal recording on freely moving live animals in 2009 [24]. As shown in Figure 5a, the tetrode was composed of four Ni-Cr alloy micro wires with diameter of 12.7 μm which coated with polyimide as insulation on the surface. The micro wire electrodes were cut to expose the cross-section as electrode sites, and the electrode sites were electrodeposited with gold to improve their electrochemical performance. The micro wire electrode was easy to fabricated, and the electrode with micro dimension was suitable for cortical implantation with little tissue damage. However, the micro wire electrode was not convenient to precisely implant into target position at deep brain area.

Dae-Hyeong Kim and John A. Rogers et al. of University of Illinois at Urbana-Champaign developed thin film microelectrode array based on polyimide for electrocorticogram (ECoG) recording in 2010. The microelectrode array was reinforced by silk fibroin, which acts biodegradable substrate, to improve the conformal attachment on the brain tissue surface [25]. As displayed in Figure 5b, the thickness of the 5 × 6 grid-like thin film microelectrode array was approximately 2.5 μm, and the dimension of the electrode site was 500 × 500 μm. Moreover, it can be observed from Figure 5b that the thin film microelectrode array tightly attached on the sphere surface when the silk fibroin dissolved. The biodegradable silk fibroin surface coating facilitated the conformal cover of the mesh electrode on the rough surface of brain. Apart from this, the mesh electrode could be fabricated

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thinner and the electrode sites could be designed smaller to further improve the conformal attachment on brain and accuracy of neural recording.

Takashi D. Yoshida Kozai, Nicholas A. Kotov and Daryl R. Kipke et al. of University of Michigan developed composite fiber electrodes consists of carbon fiber core and poly-p-xylene insulation coating in 2012 [4]. As shown in Figure 5c, the diameter of the carbon fiber core was 7 μm. The poly-p-xylene insulation coating with thickness of 800 nm was covered on the carbon fiber surface by chemical vapor deposition. Moreover, conducting polymer was electrochemically deposited on the cross-section to improve the electrochemical performance. The ultra-small dimension facilitated the microelectrode penetration into brain tissue and induced little tissue damage. Also, the mechanical property of the carbon fiber microelectrodes superbly fitted the inherent mechanical property of brain tissue. The carbon fiber electrode could be further fabricated into multiple channels to satisfy complex neural recording.

Yuefeng Rui and Jingquan Liu et al. of Shanghai Jiao Tong University developed flexible 3D microelectrode array with raised hemispherical electrode sites in 2011 [26]. The electrode sites arranged in 5×5 array, which diameter was 50 μm, and the gap between two adjacent electrodes was 600 μm. As exhibited in Figure 5d, compared with flat electrode sites, the micro scale 3D hemispherical electrode sites facilitated the contact to nerve tissue, increased the effective contact area and reduced the interfacial resistance. Thus, the electrical stimulation and neural signal recording performance was improved. In addition, the research group developed flexible micro wire electrodes in 2012 [27]. As shown in Figure 5e, compared with flat microelectrode array, the micro wire electrodes not only facilitated the implantation process and reduced the tissue damage, but also could be arbitrarily bended to adjust specific circumstances. The cylindrical electrode sites of micro wire electrode contacted well with the bioactive tissue, thus the impedance per unit area was decreased. Furthermore, the electrode sites with diameter of 100 μm were electrodeposited with platinum black by ultrasonic current pulses to improve their electrochemical performance. Compared with conventional micro wire electrode, the cylindrical electrode sites facilitated the tightly attachment of the electrode on the nerve and muscle tissue. The area of the electrode sites could be precisely reduced to further improve the spatial selectivity.

2.2 Flexible MEMS microelectrodes with fluidic channels for neural interface

While the researchers focus on developing MEMS microelectrodes with smaller dimension, more complex structure and denser electrode sites distribution, they are also devoting many efforts to multi-functionalizing the MEMS microelectrodes. The nerve conduction and muscle contraction actions of denervated paralyzed nerve and muscle tissue could be restored by electrical stimulation based on MEMS microelectrodes for artificial neural system. However, long-term lack of supply of neural nutritional factors would eventually lead to denervation atrophy of nerve and muscle tissue, which meant irreversible loss of natural conduction of nerve system and contraction function of muscle. Therefore, some kinds of MEMS microelectrodes integrated with fluidic channels for drug delivery have been developed. Based on the inherent electrical stimulation and electrophysiological signal recording properties, the novel MEMS microelectrodes integrate functions of delivering fluidic drugs, nutritional factors and neural transmitters to target nerve and muscle tissue sites. The flexible MEMS microelectrodes with fluidic channels mainly consist of: polyimide, PDMS and parylene.

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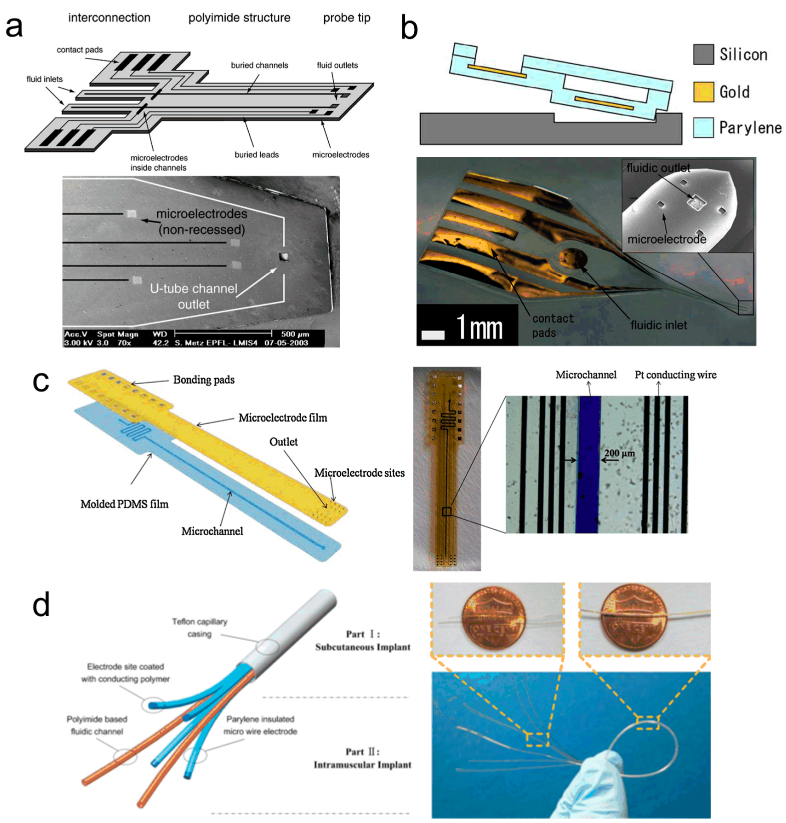

Figure 6 Research progress of flexible MEMS microelectrodes with fluidic channels for neural interface. **a** Thin film microelectrode array based on polyimide (PI); **b** Thin film microelectrode array based on Parylene; **c** Thin film microelectrode array based on poly-dimethylsiloxane (PDMS); **d** microelectrodes integrated polyimide micro fluidic channels and parylene micro wire electrodes.

S. Metz and A. Bertsch et al. of École polytechnique fédérale de Lausanne developed flexible MEMS microelectrodes with fluidic channels based on polyimide (PI) in 2004 [18]. As displayed in Figure 6a, the thickness of the microelectrode array was 10~60 μm, and the dimension of electrode sites was 50 μm × 50 μm. The cross-section dimension of inner fluidic channels was 5 μm × 50 μm or 20 μm × 200 μm, and the cross-section dimension of fluidic channel exits was 30 μm × 30 μm or 50 μm × 50 μm. The thickness of the PI microelectrode array was relatively small, which was suitable for cortical implantation and neural recording. However, the one-sided distribution of electrode sites affected the functional scope of neural recording and stimulation.

Dominik Ziegler and Shoji Takeuchi et al. developed flexible MEMS microelectrodes with fluidic channels based on parylene in 2006 [28]. As shown in Figure 6b, the thickness of the microelectrode array was 18 μm, and the dimension of electrode sites was 40 μm × 40 μm. The cross-section dimension of inner fluidic channels was 15 μm × 80 μm, and the cross-section dimension of fluidic channel exits was 100 μm × 100 μm. The parylene microelectrode array was quite thin, which benefited the conformal cover on brain cortex. However, the parylene thin film electrode was too thin to withstand the internal pressure produced by tissue motion, which might lead to the closure of the fluidic channel and disability of drug delivery.

Kunpeng Gao and Gang Li et al. of Shanghai Institute of Micro-System and Information Technology (Chinese Academy of Sciences) developed flexible MEMS microelectrodes with fluidic channels based on poly-dimethylsiloxane (PDMS) in 2013 [20]. As shown in Figure 6c, the thickness of the microelectrode array was 125 μm. The cross-section dimension of inner fluidic channels was 50 μm × 200 μm. The thickness of the PDMS microelectrode array was relatively large, which was unfavorable for flexibility and conformal attachment on tissue.

Hongchang Tian and Jingquan Liu et al. of Shanghai Jiao Tong University developed flexible MEMS microelectrodes integrated polyimide micro fluidic channels and parylene micro wire electrodes in 2014 [29,30]. As shown in Figure 6d, the integrated flexible microelectrode was composed of three parts: (1) the micro wire electrodes as electrical interfaces; (2) the PI capillaries (outer diameter of 110 μm and wall thickness of 10 μm) for fluidic drug release as chemical interfaces; and (3) the Teflon capillary (outer diameter of 650 μm and wall thickness of 140 μm) casing for packaging. The integrated microelectrode with drug delivery function was easy to fabricated and change parameters. More electrode sites and fluidic channels and smaller dimension of the electrode sites and fluidic channels were required to satisfy more complex and precise neural recording and stimulation.

2.3 Electrode-tissue interface for neural interface

Functional interface possesses the ability to combine physical effects, such as electrical [31], magnetic [32], mechanical [33] or optical [34] stimulations, with modified substrates for further exploration and manipulation of stimuli sensitive cell. Majority of existing studies have already incorporated conductive biomaterials involving electrical stimulating character as electrode-tissue interface in neural engineering investigations [35-37]. Park et al. and Huang et al. reported that the differentiation and maturity of neural stem cells can be promoted by electrical stimulation on graphene plate and carbon nanotube rope, respectively [38,39]. Zhao reported the effects of skeletal myogenesis on comb pattern substrate by adjusting frequency of electrical stimulating [40]. Lee and his colleagues demonstrated that polypyrrole coated nanofibres were able to induce directional growth of neurons [41]. These researches suggest that conducting substrates with variable structure have great potential in modulating excitable cells for neural engineering.

Appeared to attract widespread attention, conducting polymer possesses various distinctive characteristics including high charge storage capacity, low impedance, excellent plasticity, volume electrostrictive effect [42-44]. Meanwhile, conducting polymers with good biocompatibility is widely applied in biomedical area such as biomedical imaging [45], biosensor [46,47], artificial muscle [48], drug release controller [49], cancer biomarker [50] and neural interface [51,52]. One of the most important roles conducting polymer plays is in the electrode-tissue interface material for neural engineering, as it can be facilely fabricated into multiple structures [53], modified by different doping [54,55] and regulated to undertake electrical stimulation [56,57].

The fundamental properties of conducting polymers including surface morphology, electrical stimulating performance, stability and biocompatibility heavily depend on the characteristics of the negatively charged dopants which are also termed counterions. For instance, mechanically strong macromolecules have the ability to enhance the stability of conducting polymer composites [58]. Similarly, nano-materials with excellent conductivity, such as carbon nanotubes, are capable of improving the electrical performance of composite film [59]. Therefore, it is of great significance to assess the influence on conducting polymer induced by doping different counterion components. As one of the frequently used conducting polymer for interfaces to different cells, polypyrrole (PPy) doped with generally accessible molecules of electrode-tissue interface. The conducting polymer electrode-tissue interface mainly referred to PEDOT combined with: water soluble molecules, bio-molecules, carbon nanotube (CNT), perchlorate (ClO_4^-) oxide groups and graphene oxide (GO). Typical conducting polymer (PEDOT) electrode-tissue interface for neural interface discussed.

Xinyan Cui and David C. Martin et al. of University of Michigan doped polystyrenesulfonate (PSS) as negatively charged counter ion into PEDOT to form PEDOT/PSS composite as electrode-tissue interface [60]. As exhibited in Figure 7a, the rough and porous structure of PEDOT/PSS composite greatly increased the effective area of electrode-tissue interface, thus improved the electrochemical performance. After that, the PEDOT/PSS composite became one of the most widely used conducting polymer materials.

Maria Asplund and Hans von Holst et al. of Royal Institute of Technology doped hyaluronic acid (HA), heparin and fibrinogen as negatively charged counter ion separately into PEDOT to form PEDOT/bio-molecule composites as electrode-tissue interface [61]. As exhibited in Figure 7b, the three kinds of composite electrode-tissue interface doped with bio-molecules differs from each other in their characteristics including: surface morphology, effective area determined by surface

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roughness and thus induced electrochemical performance. The addition of bio-molecule might improve the biocompatibility of the conducting polymer electrode-tissue interface. Furthermore, bio-active drug and nutrition factors could also be added to the PEDOT/bio-molecule composites to produce drug-loaded functionalized electrode-tissue interface.

Xiliang Luo and Xinyan T. Cui et al. of University of Pittsburgh doped acidified carbon nanotube (CNT) as negatively charged counter ion separately into PEDOT to form PEDOT/CNT composite as electrode-tissue interface [62]. As exhibited in Figure 7c, the PEDOT/CNT composite exhibited rougher surface than other PEDOT electrode-tissue interface, which facilitated the improvement of electrochemical performance though increasing effective area. The neuron grew well and tightly attached on the PEDOT/CNT composite film, which indicated that the PEDOT/CNT neural interface possessed good biocompatibility. The loose and porous structure of PEDOT/CNT composite was attributed to addition of nano-scale carbon nanotube, which sharply increased the effective area. Moreover, due to the outstanding electrical and mechanical performance, the PEDOT/CNT composite possessed excellent electrochemical property and stability.

Mohammad Reza Abidian and Daryl R. Kipke et al. of University of Michigan doped perchlorate (ClO_4^-) as negatively charged counter ion separately into PEDOT to form hollow nanotube structure as electrode-tissue interface [63]. As exhibited in Figure 7d, the PEDOT nanotube intersected and stacked together to form loose and porous extensional organization on the electrode surface, which improved the effective surface area of electrode-tissue interface. The hollow structure of PEDOT nanotube further increased the electrode-tissue interface area, which resulted in the improvement of electrochemical performance.

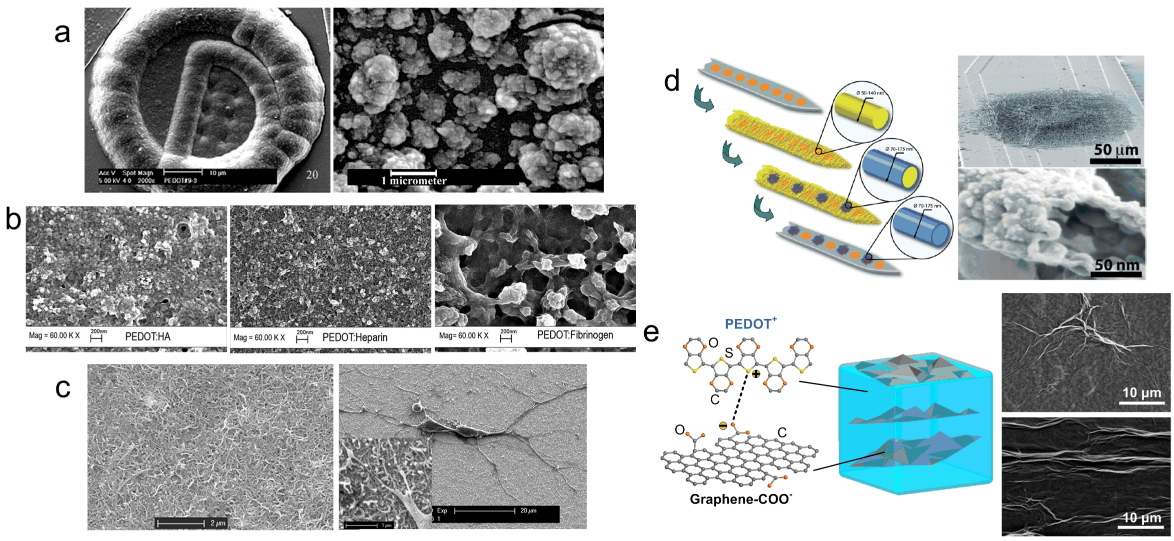

Figure 7 Research progress of the electrode-tissue interface modification technology of flexible MEMS microelectrodes for neural interface. **a** PEDOT/PSS composite film; **b** PEDOT/biomolecules composite film; **c** PEDOT/carbon nanotube (CNT) composite film; **d** PEDOT composite nanotubes; **e** PEDOT/graphene oxide (GO) composite film.

Hongchang Tian and Jingquan Liu et al. of Shanghai Jiao Tong University doped graphene oxide (GO) as negatively charged counter ion separately into PEDOT to form PEDOT/GO nanocomposite film as electrode-tissue interface [64-66]. As shown in Figure 7e, in PEDOT/GO composite film, GO disorderly distributed as the structural material to form three dimensional crossover networks, while PEDOT served as stable charge transfer medium was interspersing among the interspaces of graphene nets. Like rebar in concrete, GO doping enhanced the mechanical property of conducting polymer film. Meanwhile, the conducting polymer encapsulation prevents GO from dispersing to the tissue during recording or stimulation process, which greatly abates the possibility of cytotoxicity induced by carbon nano material diffusion while contacting with tissue directly. Like carbon

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nanotube, the nano-scale graphene oxide also possessed multi-aspect excellent property, which facilitated the improvement of the performance of the conducting polymer electrode-tissue interface.

Xiaoyang Kang and Jingquan Liu et al. of Shanghai Jiao Tong University also developed iridium oxide (IrO_x) as an important electrochemical modification material for neural interface, which exhibited considerable value in neural stimulation and recording applications [67-71]. There were various kinds of preparation methods for IrO_x, including: sputtering iridium oxide film (SIROF), activated iridium oxide film (AIROF) and electrodeposited iridium oxide film (EIROF), as shown in Figure 8a-c. For SIROF, the iridium atom combined with oxygen atom under vacuum condition to form IrO_x. For AIROF, iridium atom reacted with water in solution to form IrO_x hydrate. The SEM of the iridium oxide as SIROF, AIROF and EIROF are shown in Figure 8d-f. For EIROF, iridium complex compound drew off carbon dioxide to form IrO_x, which generally was in the form of IrO_x hydrate. The SIROF prepared under optimal condition exhibited dendrite surface morphology with porous structure. The AIROF displayed rough and porous structure which facilitated fast ion exchange. The EIROF were suitable for short-time electrical stimulation for its relatively high charge storage capacity (CSC) and low impedance. The SIROF possessed better stability than the other two IrO_x since no water existed in sputtered IrO_x, which was more suitable for long-term electrical stimulation. The AIROF was more suitable for neural recording, because the phase angle shift of electrochemical activated IrO_x was smallest among the three kinds of IrO_x.

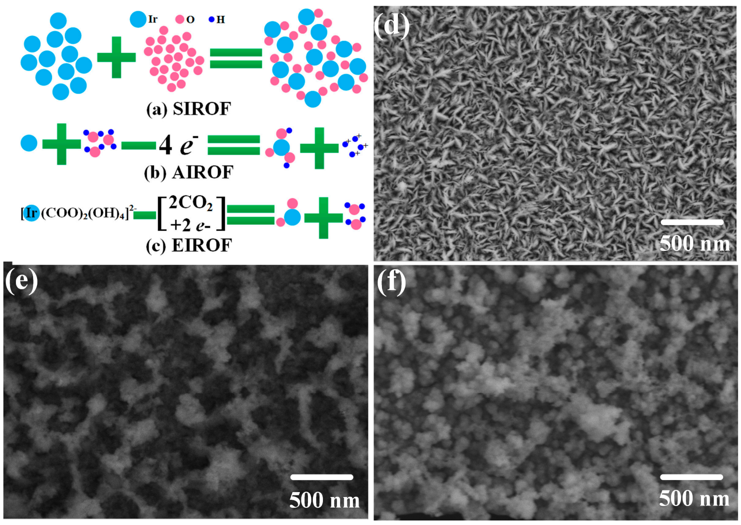

Figure 8 Research progress of iridium oxide as an important electrochemical modification material for neural interface. **a-c** Three preparation methods for iridium oxide as SIROF, AIROF and EIROF; **d-f** SEM of the iridium oxide as SIROF, AIROF and EIROF.

3. Future development prospect

In the research area of flexible MEMS microelectrodes for neural interface, the development of microelectrodes with tiny dimension and multiple functions will be the goals for researchers. Moreover, transparent flexible MEMS microelectrodes facilitated fluorescence observation of neural tissue and stretchable flexible MEMS microelectrodes for conformal covering on brain tissue will become new direction in this research area. Furthermore, in terms of electrode modifications for electrode-tissue interface, an ideal tissue engineered interface proposed by Ulises A. Aregueta-Robles et al. that incorporating combined coating approaches of conductive polymers, hydrogels and attachment factors with neural cells will be able to give considerations to each requirement of electrode-tissue interface [72].

In recent years, the applications of optogenetics in neuroscience also attracted much attention of neuroscientists. Although electrical stimulation exhibited remarkable efficacy in controlling and exploring the function of discrete brain regions and providing therapeutic solutions, it was unable of targeting genetically specified neuron types. The defect of electrical stimulation could be overcome with genetically encoded actuators [73]. As a consequence, flexible MEMS microelectrodes integrated with optical stimulation capability for neural interface will be point of special interest in future research.

Besides, the integration of flexible MEMS microelectrodes for neural interface and other flexible sensors, such as flow rate sensors, will be promising in future. Single element or single function will not satisfy the requirements anymore, so a device with multiple sensors, like the impedance wire integrated with two capacity sensors [74], will be convenient to obtain more information at the same time. In brief, flexible MEMS microelectrodes integrated with sensors are in great demands later on.

In addition, the newly rising nanotechnology and biomedical engineering will open a new gate for the development of flexible MEMS microelectrodes for neural interface. The interdisciplinary research of micro fabrication technology with nanotechnology and biomedical engineering will lead the future developing orientation [75-78]. The combination of these cutting-edge subjects will undoubtedly collide to burst shinning sparks and greatly influence people's daily life and understanding of the world.

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