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Long-term flexible penetrating neural interfaces: materials, structures, and implantation

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Abstract Penetrating neural interface, which collects the neural electrophysiological signal and serves as a key component in brain-computer interface, has drawn great attention recently. The instability of chronic recording is the main challenge for the conventional neural interface. Novel neural probes with improved long-term performance have been developed based on advanced materials and engineered structures. Here, we review these emergent innovations contributing to chronic stable recording from the perspectives of materials, structures, and implantation methods. These advances make possible further developments in neuroscience research related to neural decoding, neural circuit mechanism analysis, and neurological disease treatment.

Keywords neural interface, long-term, flexible, minimally invasive, biocompatibility

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1 Introduction

The realization of seamless integration with the central or peripheral nervous system is a long-desired goal for bioelectronics [1–3]. Recently, electrical/optical/microfluidic interfaces between biological organisms and man-made devices have been established, which provide advanced platforms for biomedical researches and clinical applications. Of particular interest, electrical recording and stimulation have been considered as the gold standard method for mapping brain functions. The milestones in the field of electrical neural interfaces include a few commercialized products, such as deep brain stimulators [4], cochlear implants [5]. An important functionality of neural interfaces is to enable bi-directional communications between electronics and brains, which allows people to explore the mechanism of brains and treatments to neural diseases. Based on the location where the electrical contacts are placed, the existing neural interfaces can be divided into three categories: (i) non-penetration brain electrode caps placed outside the skull (for Electroencephalogram, EEG) [6], (ii) partial-penetration electrode arrays attached to the cortex (for Electrocorticography, ECoG) [7], and (iii) penetration neural interfaces (PNIs) for deep brain regions (for stereo-electroencephalography, SEEG). While non-/partial penetrating electrodes are widely adopted in the fields of entertainment and education due to their less risk at the current stage, penetrating ones are more promising for neuroscience thanks to their outstanding signal quality regarding spatiotemporal

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resolution and signal-to-noise ratio (SNR). Now PNI has been used in the reconstruction of neurological function [5, 8] and treatment of neurological diseases [4]. For example, patients who are paralyzed can now move a robotic arm by the brain-machine interface based on Utah array electrodes, which is a conventional PNI approved by U.S. Food and Drug Administration (FDA) for clinical applications. Deep brain stimulator is another clinical PNI that realizes specific pattern electrophysiological stimulation and regulation of neurons in deep brain regions, demonstrating the capability in treating neurological diseases such as Parkinson's disease and epilepsy.

Despite these remarkable accomplishments, a barrier to further applications of conventional PNIs is their limited long-term stability in tracking neuronal activity at a single neuron level without a seamless neural interface. While some chronic recording at the time scale of weeks has been reported using microwires and Utah arrays [9], the signal quality degrades over time regarding both SNR and the population of neurons that can be detected. Especially, tracking individual neurons on the monthly scale remains challenging, if not impossible at all. The lack of stable chronic recording capability, therefore, prevents people from understanding the evolution of neural networks and finding a long-term solution of brain-machine interfaces.

Mechanical and bio-chemical properties of the neural probe and the surgical method to implant the neural probes are essential factors that determine the chronic performance after implantation.

(1) The mechanical mismatch between PNI and brain leads to poor performance in long term for two reasons. Firstly, the stress at the implant interface causes damage to both cells and blood vessels, leading to nerve scars and glial cell growth around the implants [10–12]. The aggregative nerve scar encapsulates the implanted neural interface, resulting in reduced SNR and even diminished unit recording with prolonged implantation. Secondly, rigid materials of conventional PNIs cause relative displacement between the device and the tissue upon motions of animals or people, leading to variation of acquired waveforms even for the same neuron. Therefore, tracking individual neurons for a long time becomes difficulty [13, 14].

(2) The biochemical properties of the materials of which neural probes consist are also critical for chronic recording from two perspectives. Firstly, the minimal requirements include non-cytotoxicity for tissue health, chemical stability for preventing device failure, and cell attachment ability for seamless integration; Secondly, surface modifications are necessary for optimizing the electrical impedance and reducing inflammation at the neural interface.

(3) As we will discuss in Section 2, novel PNIs with flexible substrates have been developed to bridge the mechanical mismatch between neural probes and brain tissue. The flexible substrates, however, rise to new challenges for implantation methodology. Because buckle strength of ultra-flexible probes does not support direct penetration into the brain, stiff insertion shuttles become necessary. Those shuttle devices inevitably enlarge the footprint in the brain and break blood vessels like rigid probes thus undermine the bio-compatibility earned by reducing the dimensions of the neural probes.

To overcome the challenges mentioned above associated with chronic neural recording, great efforts have been made to develop advanced PNIs. These efforts include adopting emerging materials and micro and nanoscale structures in fabrications (Figure 1 [15–22]). First of all, flexible materials reduce the stress and the relative displacement at the neuron-electrode interfaces, while probing surface modifications with specially designed materials improve the electrochemical stability and biocompatibility. Secondly, the optimization of the structure reduces the dimensions and helps the seamless integration between PNI and neurons. In addition, advanced surgical methods and tools have been developed to implant the flexible probes at minimized tissue damages accompanied with implantation as well as surgical duration which eventually contribute to improved neural signal quality.

Here, we review recent progress in this field aiming at improving chronic performance. Materials that meet the above-mentioned biophysical and biochemical properties are introduced. The design of device structures that achieve seamless integration with neural tissue is discussed. The development of surgical methodologies is reviewed at last. A table of content of this review is given in Figure 2.

2 Materials

2.1 Polymer substrate for flexible neural interfaces

A key parameter that determines the degree of mechanical mismatch between the neural interfaces and

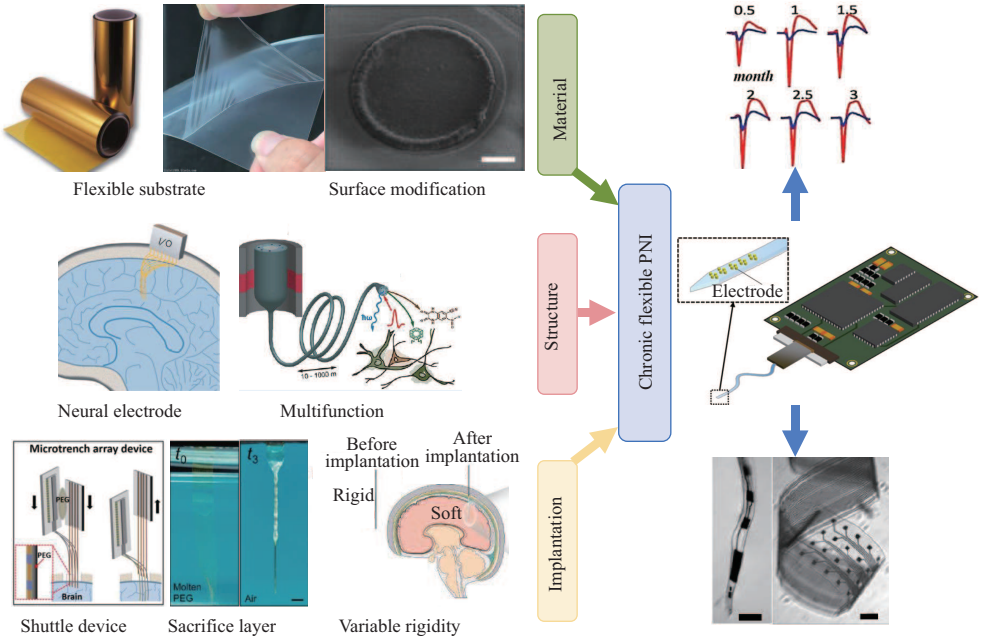

Figure 1 (Color online) Schematic diagram of the development strategy for long-term flexible penetrating neural interfaces. Surface modification: reproduced with permission [15] @Copyright 2017 Elsevier Science. Neural electrode: reproduced with permission [16] @Copyright 2015 Springer Nature. Multifunction: reproduced with permission [17] @Copyright 2018 American Chemical Society. Shuttle device: reproduced with permission [18] @Copyright 2019 IOP Publishing. Sacrifice layer: reproduced with permission [19] @Copyright 2019 American Association for the Advancement of Science. Variable rigidity: reproduced with permission [20] @Copyright 2020 Royal Society of Chemistry. Chronic flexible PNI: reproduced with permission [21] @Copyright 2017 American Chemical Society. Reproduced with permission [22] @Copyright 2017 American Association for the Advancement of Science.

Long-term flexible penetrating neural interfaces: materials, structures, and implantation	
Materials	Polymer substrate for flexible neural interfaces
	Surface modification for long-term stability
Structure	Structure of flexible neural electrodes
	Multi-function neural interfaces
Minimally invasive implantation	Shuttle device
	Sacrifice layer
	Neural interfaces with variable rigidity
Conclusion and outlook	The “ideal” neural interface in the future

Figure 2 Table of content of this review.

the nerve tissue [23, 24] is bending stiffness, which reads as [25]

$$\frac{F}{d} = \frac{4Ewt^3}{L^3}, \tag{1}$$

where F is the force, d is the deflection, E is Young's modulus, L, w and t are the length, width, and thickness of the device, respectively. From (1), bending stiffness is determined by both the geometric dimensions and Young's modulus. Therefore, choosing composing materials with low Young's modulus is an effective method to alleviate the mechanical mismatch. Reducing the cross-sectional area of the neural interface by advanced nanofabrication technique is another way to reduce the mechanical mismatch, which we will discuss in Section 3.

As a type of material that is widely used as substrate/encapsulation in the electronics industry, the

Table 1 Material properties of brain tissue, silicon and various polymers [27, 28]

	Young's Modudus (GPa)	Density ($g \cdot cm^{-3}$)	Melting/thermal decomposition temperature (°)	Possible thicknesses (μm)	USP class
Polyimide	8.83	1.10–1.11	>550	1–15	–
PDMS	0.5×10^{-3}–0.1	1.08	∼250	10–100 (spin coating)	VI
Parylene C	3.2	1.289	290	1–100	VI
SU-8	0.02	1.075–1.238	300–315	0.5–300	–
Human brain	1×10^{-6}–0.1	1.039–1.043	–	–	–

polymer has been adopted to the field of neural interface. Here, we discuss several representative polymer materials and their applications in PNIs. Note that a typical neural probe based on polymer substrate has conductive lines in the core layer encapsulated by an insulating polymer outer layer. Because the polymer layer usually takes the most volume of the probe, it dominates the mechanical property of the PNIs. In this sub-section, we mainly review 4 materials for fabricating flexible PNIs: (i) SU-8, (ii) Parylene, (iii) polyimide (PI), and (iv) polydimethylsiloxane (PDMS). Their basic chemical components, fabrication procedure, advantages and disadvantages will be discussed.

SU-8 is an epoxy-based negative photoresist compatible with the photolithography process, which is composed of Bisphenol A Novolac epoxy dissolved in an organic solvent (e.g., cyclopentanone) and mixed Triarylsulfonium/hexafluoroantimonate salt (10 wt%, photoacid generator). Upon excitation with UV light, the salt in SU-8 reacts to produce hexafluoroantimonic acid, which protonates the epoxy group. In the subsequent baking, the epoxy groups are completely polymerized. Further hard film baking can enhance the stability of the SU-8 structure and increase sidewall smoothness. Through spin coating, SU-8 films with thicknesses ranging from lower than 1 to 300 μm are feasible [26], providing great manufacturing flexibility. SU-8's low Young's modulus (20 MPa, see Table 1 [27, 28]) makes it suitable for substrate in flexible PNIs (Figure 3(a)) [22, 27, 29]. In addition, SU-8 has good light delivery capability in the wavelength band greater than 400 nm, supporting the development of a multifunctional neural probe with integrated optical stimulation functionality [30, 31]. A debate about using SU8 for the neural probe is about its bio-compatibility. Surface treatments, such as plasma treatment (enhance hydrophilicity for attachment of cell) [32], chemical treatment with acid and base (surface modification for immobilization of biomolecules) [33], and grafting of the surface with polyethylene glycol (optimize protein adsorption and cell attachment properties) have been demonstrated for improving the biocompatibility [34]. However, SU-8 contains a certain amount of antimony, which is biologically toxic. Although additional UV exposure and baking can reduce the antimony content [35], SU-8 has not been approved by the FDA for devices used for humans. In addition, SU-8 is brittle, which is the second drawback. For this reason, the Parylene C package is used to reduce the risk of breakage due to dangling and stretching during device implantation [17].

Parylene belongs to a family of polymer, whose repeating units are para-benzenediyl rings (-C_6H_4-) and connected by 1,2-ethanediyl bridges (-CH_2-CH_2-). In 1965, Gorham [36] proposed a solvent-independent method which provides pinhole defects-free films with a yield close to 100%, promoting the application of Parylene. The preparation method based on vapor deposition makes the Parylene film have excellent conformal covering ability [37], because the vapor monomer deposition process can easily enter the small gap area. Parylene film has good chemical stability (probe based on Parylene was placed in phosphate-buffered saline (PBS) solution at 75°C for 14 days without material degradation and delamination [38]) and electrical insulation properties. More importantly, Parylene is bio-stable and biocompatible (FDA approved for biological implants). The final deposition process of Parylene is carried out at room temperature, which improves its process compatibility. Many derivatives of Parylene are obtained by replacing hydrogen atoms on the phenyl ring or the aliphatic bridge with functional groups. Among them, the most widely used is Parylene C (a hydrogen atom on the benzene ring is replaced by chlorine). The outstanding advantages of Parylene C lie in the low cost of the precursor required for deposition and a good balance between insulation, corrosion resistance and ease of deposition. Therefore, a variety of flexible long-term neural interfaces based on Parylene C have been developed (Figure 3(b)) [15, 39–47]. In addition, Parylene C has high transmittance in the visible light range, facilitating the integration of the Parylene C neural interface with optical functions [48, 49]. However, the disadvantages of Parylene C lie in its poor mechanical properties, including high fragility and weakness.

PI has been extensively applied in the field of flexible electronics, and attracted interests in biomedical

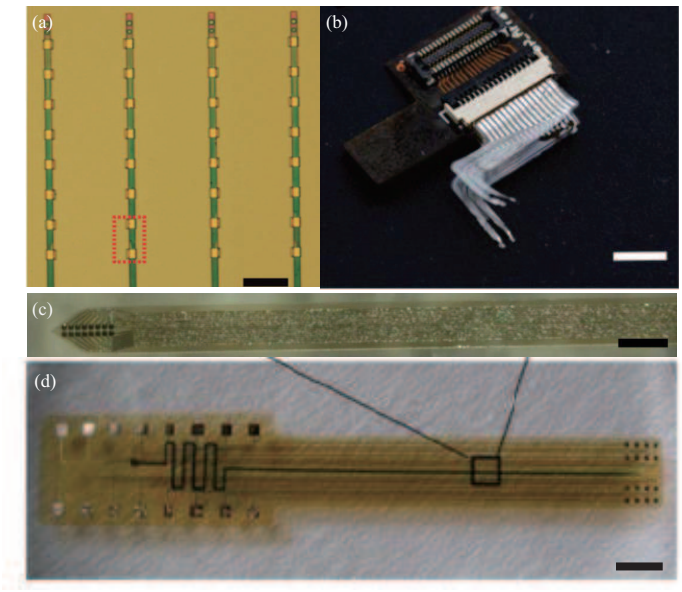

Figure 3 (Color online) Long-term penetrating flexible neural interface based on polymer materials. (a) SU-8; (b) Parylene C; (c) PI; (d) PDMS. Scale bars: (a) 50 μm; (b) 5 mm; (c) 150 μm; (d) 2 mm. (a) Reproduced with permission [27] @Copyright 2018 Wiley. (b) Reproduced with permission [43] @Copyright 2016 IOP Publishing. (c) Reproduced with permission [55] @Copyright 2020 IOP Publishing. (d) Reproduced with permission [60] @Copyright 2013 Elsevier Science.

applications over recent years. PI is a polymer of imide monomers. According to the types of interaction between its backbones, PI can be divided into two types: thermoplastic and thermosetting. Among them, thermoset PI has desirable chemical stability (remain stable for more than 20 months, at 60°C in PBS solution [50]) and mechanical properties (flexible and stretchable, Table 1). Although PI has not been approved by FDA for the application of implanted devices on human beings, the applications of PI in the manufacture of flexible PNIs have been explored (Figure 3(c)) which show promising biocompatibility [51–56]. In particular, the BPDA-PPD (4,4′-biphenyl dianhydride, BPDA, and p-phenilene diamine, PPD) is the most used polyimidic architecture in bio-related application [57]. PI's most prominent advantages lie in its heat resistance and stretchability. The thermal decomposition temperature of PI exceeds 550°C (Table 1), which makes it compatible with processes at elevated temperatures, such as plasma-enhanced chemical vapor deposition (LPCVD). And, its stretchability (breaking strength $\geqslant$100 MPa [28]) prevents it from easily rupturing after implantation. PI offers possibilities for complex structures; for example, microfluidic channels can be integrated on a flexible neural interface [53, 54]. The complementary metal oxide semiconductor (CMOS) circuit is manufactured on a silicon wafer, then transferred to the PI substrate via a transfer printing process, allowing monolithic integration of a flexible neural interface with the CMOS circuit [52]. This integration has been implemented on an ECoG array [56]. Esterifying the carboxyl groups and introducing photosensitive groups to obtain photosensitive PI can simplify the patterning step, but with limited resolution at micrometers [51].

PDMS, also known as silicone rubber, is widely used in the biomedical field and has been approved by the FDA for long-term clinical studies. The synthesis of PDMS bases on silane precursors (e.g., $Si(CH_3)_2Cl_2$) and is terminated with silanol groups (-[$Si(CH_3)_2OH$]). Reducing the methyl groups and increasing acid-forming groups in the silane precursor introduce branching or cross-linking in the polymer chain to obtain PDMS with higher Young's modulus. Therefore, PDMS has a large adjustable range of Young's modulus over four orders of magnitude, from kPa to MPa [58], so as to best match the target tissue. Within the organism, PDMS is not prone to degradation or aging (material properties do not significantly change after two years of implantation in the organism) [59]. A variety of microfabrication methods (standard photolithography and etching, as well as laser cutting and nanoimprinting) that are compatible with PDMS provide convenience for flexible PNIs based on it (Figure 3(d)) [28, 60, 61]. However, the minimum thickness of PDMS film (10 μm, Table 1) limits its application as ultra-thin PNIs. PDMS is often combined with other polymers as a substrate. For example, embedding structured Parylene C foil in silicone rubber is one approach used to improve substrate durability [62,63]. Mechanical characterization proves that the sandwich structure of PDMS-Parylene C-PDMS significantly enhances the ultimate fracture strength of the material and reduces the possibility of fracture after implantation.

2.2 Surface modification for long-term stability

The surface of electrode contacts is where the electronics meet tissues directly, therefore the chemical components at the surface largely determine the signal quality and tissue reaction to the implants. Lowering the electrode impedance and reducing tissue inflammation are two main factors that have been taken into consideration regarding contact surface modification.

Arguably, a lower impedance of the electrodes leads to better data quality [64]. Conjugated conductive polymers effectively reduce electrode impedance from the order of mega-Ohms to kilo-Ohms at 1 kHz, and protect the electrode from degradation during long-term implantation [15,42,65–69], therefore particularly suitable for the modification of neural interface electrodes. Poly(3,4-ethylenedioxythiophene) (PEDOT) is a conjugated conductive polymer that receives widespread attention for its excellent electrical conductivity, biocompatibility, and chemical stability [67, 70, 71]. Thermal aging experiments performed after PEDOT deposition demonstrated that impedance remained roughly unchanged for more than one month, confirming the material's excellent stability [67]. Among various methods for depositing PEDOT on an electrode surface, electrochemical polymerization has the advantage that allows depositing PEDOT in targeted locations [68].

Lecomte et al. [15] developed a PEDOT-modified Parylene C-based PNI which achieves stable recording for up to six months. PEDOT modification of the electrode is achieved using electrochemical methods in EDOT: PSS (3,4-ethylenedioxythiophene: polystyrene sulfonate) solution. After 29 weeks of immersion in artificial cerebro-spinal fluid (ACSF) (in vitro aging experiment), the impedance of the electrode at 1 kHz did not significantly change (Figure 4(a)). Throughout the experiment, the median impedance measured is in the range of 10–25 kΩ. After 30 weeks of implantation, scanning electron microscope (SEM) images show no evidence of delamination or expansion of the PEDOT layer after implantation (Figure 4(b)). And the SNR also remained stable in the range of 10–20 during the implantation period, further confirming the long-term stability of PEDOT.

Suppressing inflammation response is another goal of contact surface modification. It has been demonstrated that the use of biomaterials, such as curcumin, nerve growth factor (NGF), brain-derived growth factor (BDNF) and dexamethasone (DEX) can effectively improve integration of the implant and the tissue interface by promoting neuron growth and inhibiting inflammation [43, 72–77]. For example, Lein et al. [78] used Matrigel (BD Biosciences, San Jose, CA, serve as a base matrix which supports neuronal growth, attachment, and differentiation) as a substrate to coat biomolecules and hormones on PNI, which promoted the formation of a seamlessly integrated neural interface. Within 14 weeks of implantation, the SNR of the uncoated probe was comparable to Matrigel+ coated (Matrigel coating containing NGF, BDNF and DEX) probe which remained stable at around 6. However, the firing rate indicated the positive effects of Matrigel+ coating (∼0.65 spikes/s for Matrigel+ coated, ∼0.2 spikes/s for uncoated) (Figure 4(c) and (d)) [43].

From the tissue side, genetic modification can improve the anti-damage and anti-inflammatory capabilities of the neural tissue itself. The expression of a virus construct based on the Caveolin-1 gene increases expression of neurotransmitter receptors and promotes the growth of neuronal dendrites, thereby improving neuron survival and growth [43]. In mice, a PNI implanted after pretreatment with the viral construct AAV9-SynCav1 (encoding the Caveolin-1 gene) shows better long-term electrophysiological recording ability (SNR: ∼6.4, firing rate: ∼0.5 spikes/s, Figure 4(c) and (d)). This combination of probe surface modification with biomolecules and genetic modification of neuronal cells promises to improve biocompatibility and optimize the interface between the implant and surrounding nerve tissue.

In short, the material properties at the neural interface are the primary factor that determines the long-term recording performance of PNI. Despite weaknesses associated with individual material (such as delamination of PI, a limited minimum thickness of PDMS) which deserve further investigations, polymers with low Young's modulus have been demonstrated as promising substrate/encapsulation materials for flexible PNIs affording mechanical matching between brain tissue and PNIs. In addition, the surface modification could improve electrode impedance and reduce tissue inflammation, which overall contributes to the long-term performance of the PNI in the recording.

3 Structure

3.1 Structure of flexible neural electrodes

Besides adopting flexible materials as a substrate for PNIs, reduced dimensions and specially engineered

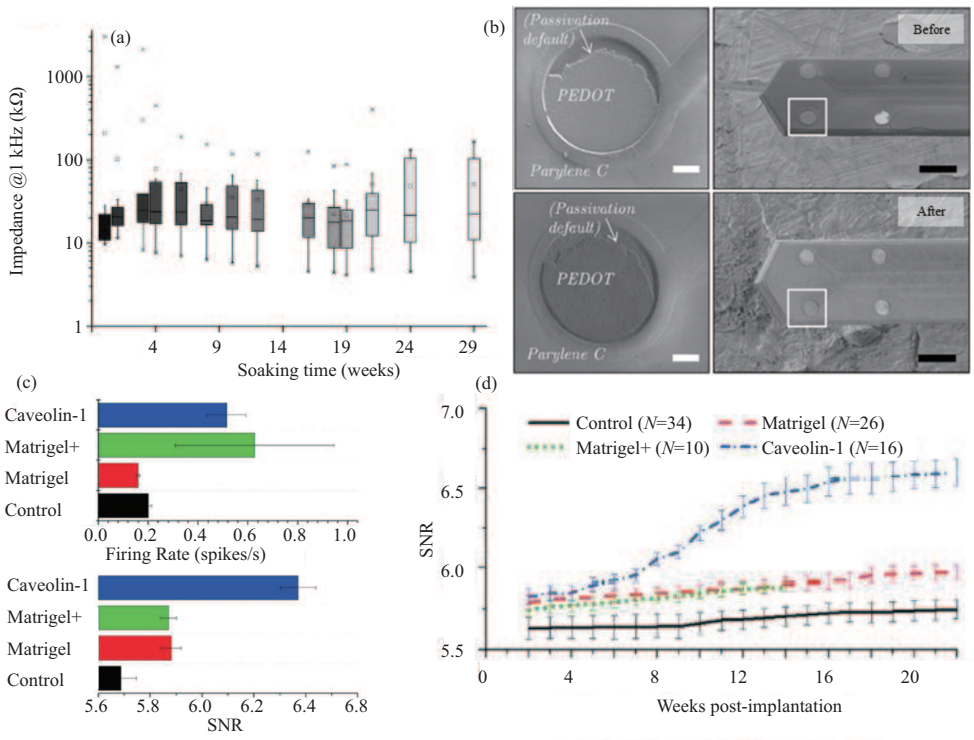

Figure 4 (Color online) Surface modification of long-term flexible penetrating neural interface. (a) The impedance of 16 electrodes modified with PEDOT at 1 kHz varies with time immersed in ACSF solution. (b) SEM images of PEDOT-modified electrodes before and after implantation in a mouse hippocampus for 30 weeks. (c) Firing rate and SNR of electrophysiological signals recorded under different conditions, such as Caveolin-1 virus transcription, Matrigel coating, and control. (d) SNR of the signal changes over time under different conditions, such as Caveolin-1 virus transcription, Matrigel coating, and control. Scale bar: (b) white: 10 μm, black: 100 μm. (a) and (b) Reproduced with permission [15] @Copyright 2017 Elsevier Science. (c) and (d) Reproduced with permission [43] @Copyright 2016 IOP Publishing.

neural probe structure also improve the integration between probes and the brain. For example, based on micro-machining technology and multi-layer wiring design, Luan et al. [22] developed a novel PNI called nanoelectronic thread (NET, Figure 5(a)) with reduced the cross-section leading to ultra-flexibility. In order to minimize implant volume, the electrodes and the interconnection layer were located on different layers and were electrically connected by the vertical interconnect access (VIAs) on the insulating layer. The cross-sectional area of NET was as small as 10 μm×1.5 μm where the bending stiffness decreased to the order of 10–15 $\mathrm{N{\cdot}m^2}$. The shear-force from the probe to a nearby neuron was in the nano-Newton range, equivalent to the traction force between cells, thereby significantly improving biocompatibility [79]. In this study, NET electrodes were implanted in the visual and somatosensory cortex of mice for four months. During the first 1.5 months, average impedance and noise levels decreased, while the number of single-units with detected action potentials (AP) remained stable (impedance, noise, yields of multi-unit and sortable single-unit recording are ∼600 kΩ, ∼5 μV, ∼75% and ∼25%, respectively) for the following 2.5 months (Figure 5(b)). Three-dimensional reconstruction of vasculatures around probes two months after implantation through in vivo 2P microscopy demonstrated the minimally invasive performance of the NET probe (intact blood-brain barrier lasting two months, Figure 5(c)).

The dimensions of NET probes can be further reduced by using deep ultraviolet lithography (DUV) or electron beam lithography (EBL) which are able to pattern conductive wires at the resolution of nanometer scale. In Wei et al's work, a minimal width of metal wires of 200 nm has been demonstrated, reducing the cross section of the second-generation NET probe to 8 μm×0.8 μm (Figure 5(d)) [27]. Such a small implant volume resulted in a reduced inflammatory response. Importantly, after two months of implantation, the SNR of the required data was still greater than ten with little deterioration (Figure 5(e)). Note that as EBL components cannot be manufactured in parallel, only the tip of the probe is processed by EBL, while the other metal connection parts were processed using traditional lithography (Figure 5(d)) to reduce the total cost of the fabrication.

Biomimetic electronics help optimize the design of flexible PNIs with the goal of manufacturing probes

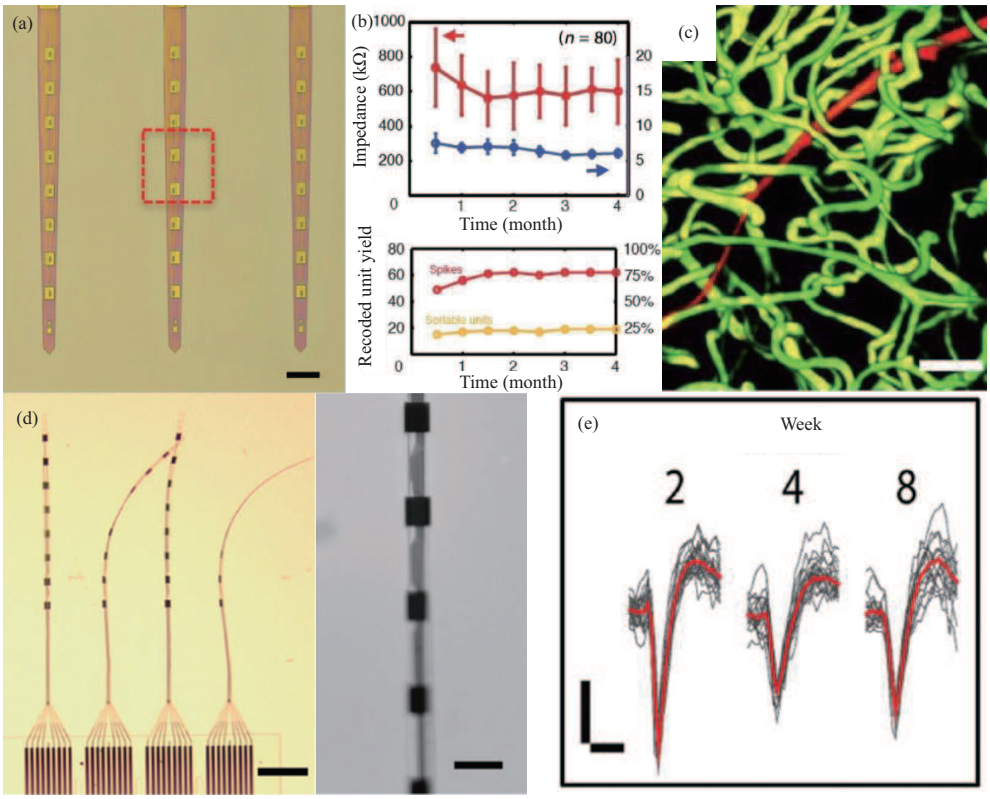

Figure 5 (Color online) NET and NET-e probes with neuroelectric signal recording function. (a) Optical image of NET probe. (b) Above: impedance (red) and noise level (blue) of NET probe as a function of time. Below: number and percentage of electrodes that recorded unit activities (red) and sortable single-unit APs (orange) of the NET probe as a function of time. (c) Three-dimensional reconstruction of two-photon imaging after NET implantation. (d) Microscope image of EBL section of the NET-e probe. (e) Spikes recorded by NET-e probe over eight weeks post-implantation. Scale bar: (a) 100 μm; (c) 50 μm; (d) left: 20 μm, right: 10 μm; (e) vertical: 50 μV, horizontal: 0.5 ms. (a)–(c) Reproduced with permission [22] @Copyright 2017 American Association for the Advancement of Science. (d)–(e) Reproduced with permission [27] @Copyright 2018 Wiley.

that are structurally and mechanically similar to neurons at the subcellular level, further reducing the difference between the implant and the brain tissue [80]. Yang et al. [81] developed a macroporous mesh PNI called neuron-like electronics (NeuE). The bending stiffness of NeuE was comparable to that of axons, and the geometric size of its recording electrodes matched somatic cells and neurites of typical pyramidal neurons (Figure 6(a) and (b)). In addition, the thin polymer insulating layer resembled a myelin sheath surrounding the axon. The NeuE constructed a 3D electronic grid similar to a neural network structure with a volume ratio of only 0.07%–0.3%, confirming its ultra-low invasiveness to neural tissue. These biomimetic designs helped to form seamless contacts, reducing displacement and stress between the neural interface and brain tissue. During the three-month implantation period, there was no loss of neuron tracking, demonstrating the long-term recording stability of NeuE (Figure 6(c)). A major feature of NeuE and other mesh PNIs is the coating of nerve cells inside the probe, rather than completely excluding nerve cells from the probe (Figure 6(d)) [16, 82–84].

The structural optimization of the mesh probe has further improved its biocompatibility and signal quality. Considering the factor that smaller geometry leads to higher flexibility, Viveros et al. [84] developed a flexible 2D/1D PNI with reduced cross section. Optimizing the geometry of the mesh probe allowed implanting through a needle with an inner diameter of 100 μm (Figure 6(f)). In addition, Xie et al. [16] developed a mesh PNI with three-dimensional distribution electrical recording sites. As a result of the compressive strain element on the lateral interconnection line, the probe automatically formed a cylindrical shape after implantation, such that the electrical recording points were evenly distributed around the cylinder (Figure 6(g)). Local tensile strain elements in the supporting arms of each electrical recording site made these arms bend outward (Figure 6(h)). This design positioned the electrical recording site far away from the site of implantation injury (100 μm away from the cylindrical probe surface), which was beneficial to avoid the influence of nerve scars and glial cells on the electrophysiological recording and allowed researchers to obtain high signal quality.

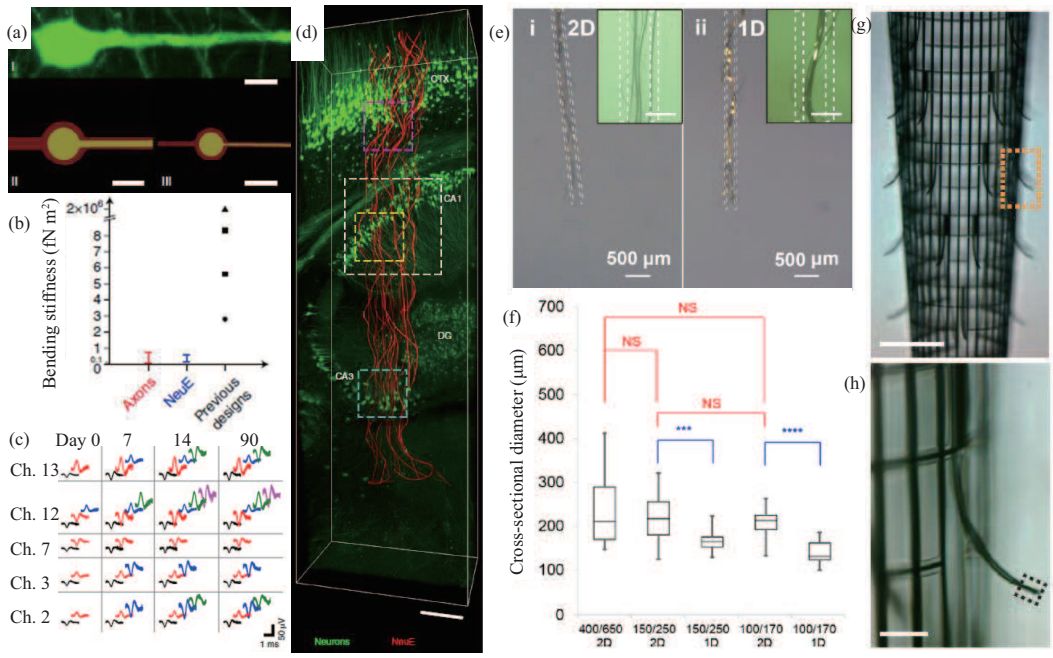

Figure 6 (Color online) Mesh neural interface with neural electric signal recording function. (a) Fluorescence microscope image of neuron cell and SEM image of NeuE. (b) Bending stiffness of axons, NeuE and previous mesh neural interface. (c) Spikes recorded by NeuE over 90 days post implantation. (d) Three-dimensional reconstruction of two-photon imaging of NeuE after implantation. (e) Microscope image of 1D and 2D mesh neural interface injected into agarose hydrogel. (f) Cross-sectional diameters of 1D and 2D mesh neural interfaces. (g) and (h) Microscope image of 3D mesh neural interface. Scale bars: (a) 10 μm; (d) 200 μm; (g) 200 μm; (h) 50 μm. (a)–(d) Reproduced with permission [81] @Copyright 2019 Springer Nature. (e) and (f) Reproduced with permission [84] @Copyright 2019 American Chemical Society. (g) and (h) Reproduced with permission [16] @Copyright 2015 Springer Nature.

3.2 Multi-function neural interfaces

The above discussion of neural interfaces focuses primarily on electrophysiological recording functions. Another critical goal in the study of neural circuit mechanisms is the precise interrogation and manipulation of neuronal cells, which require neural interfaces that integrate multiple functions, including optical stimulation and drug delivery.

Combining multiple electrical, optical, and microfluidic devices is a simple way to achieve multifunctional PNIs. However, stacking multiple components increases implant volume, resulting in larger implant damage. To overcome this issue, Zhao et al. [21] developed nano electronic coating (NEC) method, which was able to attach ultra-thin and flexible electrical neural probes to the surface of optical fibers and glass pipettes, thereby achieving functional integration without increasing implant volume (Figure 7(a) and (b)). NEC had the advantage of high-resolution multi-channel recording. A large number of electrical recording sites were arranged at the site of optical stimulation or drug delivery on the optical fiber or glass pipette tip (the electrode spacing is only 30 μm). In this way, the response of neurons after stimulation can be accurately recorded. The optical fiber of diameters ∼150 μm was integrated with NEC, and implanted into the prefrontal cortex (mPFC) of mice transfected with the gene Thy1-mhChR2-YFP. The signal demonstrated that blue light irradiation leads to a significant and reversible increase in the firing rate of neuronal action potentials (Figure 7(c)). In another experiment, a micropipette (diameter <30 μm, injecting antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) at rates of 5–50 nL/s) integrated with NEC was implanted into the mPFC. The firing rate decreased significantly during drug injection, and reversed after drug injection stopping (Figure 7(c)). The aforementioned experiments demonstrated the integration of NEC with other components in optical stimulation and drug delivery applications.

Canales et al. [85] developed a new type of multifunctional fiber probe through the thermal drawing process (TDP) which was universal for optical fiber manufacturing. This technique requires a variety of materials with similar melting points or glass transition temperatures and low viscosities ($<10^7$ P) at the drawing temperature, such that they can be heated and stretched at the same time, to constitute the fiber probe. Cyclic olefin copolymer (COC), polycarbonate (PC), and conductive polyethylene (CPE)

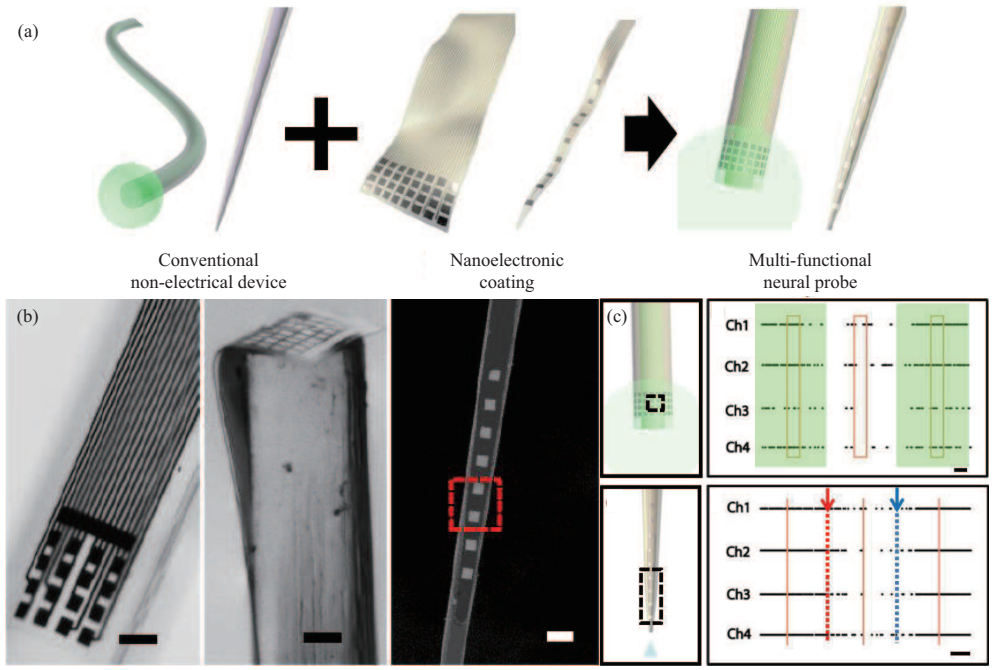

Figure 7 (Color online) Realization of a multifunctional neural interface based on NEC. (a) Schematic diagram of NEC integration with optical fiber and glass pipettes; (b) microscope image of NEC integration with optical fiber and glass pipettes; (c) demonstration of electrophysiological recording of neuronal cells combined with optical or drug regulation. Scale bars: (b) 100 μm; (c) top: 2 s, bottom: 1 min. Reproduced with permission [21] @Copyright 2017 American Chemical Society.

were feasible materials to construct a multifunctional PNI (Figure 8(a)) [85]. After thermal stretching, the cross-section significantly reduced more than 100 folds, but the designed structure remains intact (Figure 8(b) and (c)). Figure 8(d) demonstrated the light delivery capability in the PC (with light attenuation of 1.6 dB/cm). The neuronal action firing potentials related to light stimulation remained observable two months after implantation (Figure 8(e)). Experiments in which CNQX was injected through the microfluidic channel also demonstrate drug-related suppression of action potentials.

In addition, by the TDP method, fiber probes with various sensing functions have been demonstrated, including fluorescence intensity detection fiber probe by Abouraddy et al. [86, 87] and chemiluminescent detection fiber probe by Stolyarov et al. [88, 89]. Furthermore, Rein et al. [90] introduced μLED chips and tungsten wires, which are non-stretchable, into the TDP process (Figure 8(f)), allowing simultaneous light stimulation and electrical recording, respectively (Figure 8(g)).

In summary, reducing dimensions of the PNI by employing advanced micro- and nano-techniques minimizes the invasiveness of PNI. Moreover, innovations in geometry including multi-layer wiring design, biomimetic mesh, and TDP-based fiber probe enabled long term stable and multifunctional neural signal recordings. Researchers are still committed to reducing foreign body reactions through further structural optimization thus achieving a seamlessly integrated neural interface.

4 Minimally invasive implantation

While the flexibility of neural probes leads to less tissue damage, it brings up a challenge for implantation. In contrast to the stiff neural probe of which the buckling strength is sufficient for direct insertion, the buckling strength of flexible probes is less than the insertion stress needed.

According to Euler's formula, the critical bending stress of the neural probe is calculated as

$$F = \frac{\pi^2 EI}{L^2} = \frac{\pi^2 Ewt^3}{12L^2}, \tag{2}$$

where F is the critical bending stress, I is the moment of inertia, E is Young's modulus, L, w and t are the length, width and thickness of the probe, respectively. Two strategies have been developed to deliver the flexible probes into brain tissue, either by a stiff shuttle device or by temporarily reinforcing the buckling strength of the flexible probe.

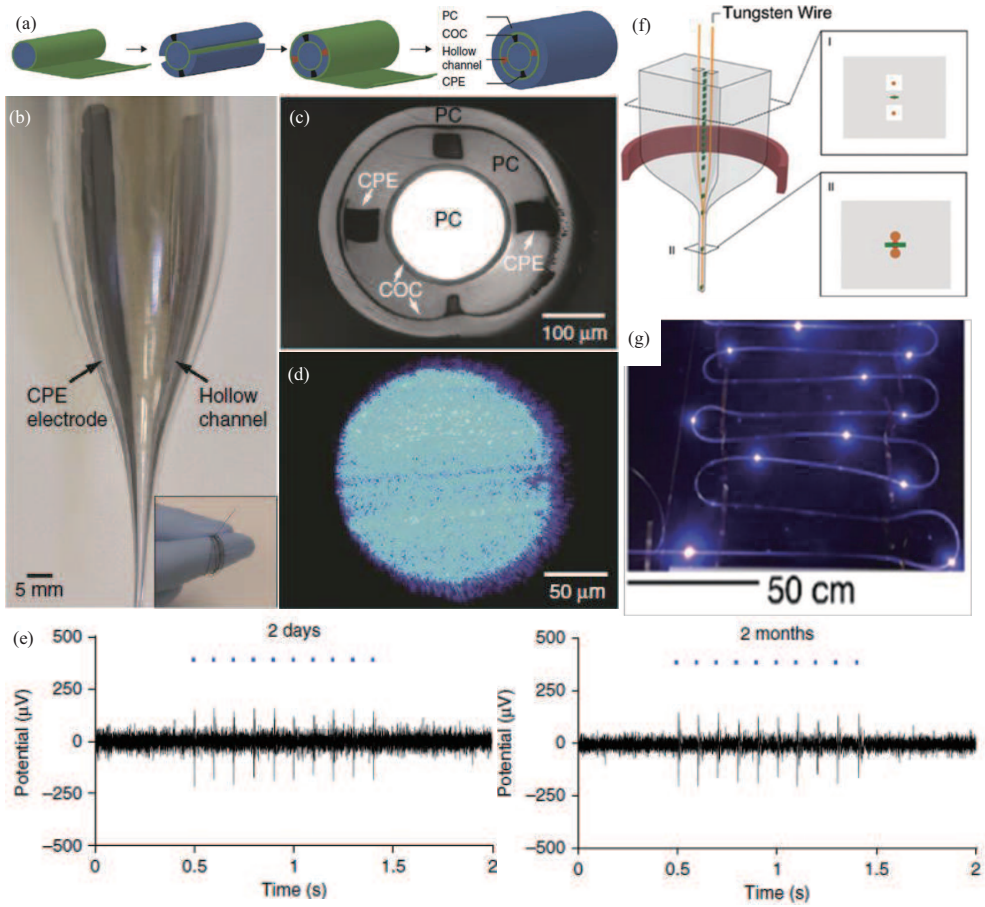

Figure 8 (Color online) Multifunctional fiber probe based on TDP. (a) Schematic diagram of the fiber probe manufacturing process; (b) image of the TDP process; (c) optical image of fiber probe cross-section; (d) image of light traveling along the fiber probe; (e) simultaneous optogenetic stimulation (blue marks) and electrophysiological recording performed two days, one week, one month and two months after implantation; (f) schematic diagram of the LED chip integration process; (g) LED chip integration allows light stimulation. (a)–(e) Reproduced with permission [85] @Copyright 2015 Springer Nature. (f) and (g) Reproduced with permission [90] @Copyright 2018 Springer Nature.

4.1 Shuttle device

For the first strategy, one basic approach is to use a stiff shuttle device, such as a stent or microneedle, to deliver the flexible neural probes [18, 22, 91–96]. For example, Luan et al. [22] used a tungsten wire of diameter 7 μm as a shuttle device which pulled the flexible PNI to the desired depth with an implant footprint at the cellular scale (10 μm), resulting in negligible acute injury (Figure 9(a) and (b)). However, this method did not have the capability of parallel implantation, leading to low implantation efficiency.

To improve the implantation efficiency, Zhao et al. [18] developed a parallel implantation approach. Multiple tungsten wire shuttles were aligned paralleled along grooves defined by photolithography method (Figure 9(c)). Then both shuttles and probes were dipped in polyethylene glycol (PEG) solution. As a result of surface tension, the probes are automatically attached to the tungsten wire when taken out from the solution (Figure 9(d)). After implantation, residual PEG dissolves leading to detached probes from the tungsten wire array, followed by drawing tungsten wire array out and completing the implantation operation (Figure 9(e) and (f)). Additionally, tetra fluoroethylene (PTFE) microtubes fixed by epoxy resin helped assemble a three-dimensional tungsten wires array for more possible arrangements (Figure 9(g) and (h)).

The parallel method has heavily relied on human-labor efforts to pre-assemble the neural probes and shuttles. In contrast, engineers from Neuralink developed a robotic machine to implant one neural probe shank at a time where minimal pre-assembly is required (Figure 9(i) and (j)) [97]. Specifically, the robotic machine was equipped with a motor-driven tungsten wire for inserting neural probes. In addition, multiple cameras working at 405, 520, and 650 nm were employed for visual guidance and improving implantation accuracy. 405 nm light induced fluorescence from the PI probe, so as to accurately locate the position of

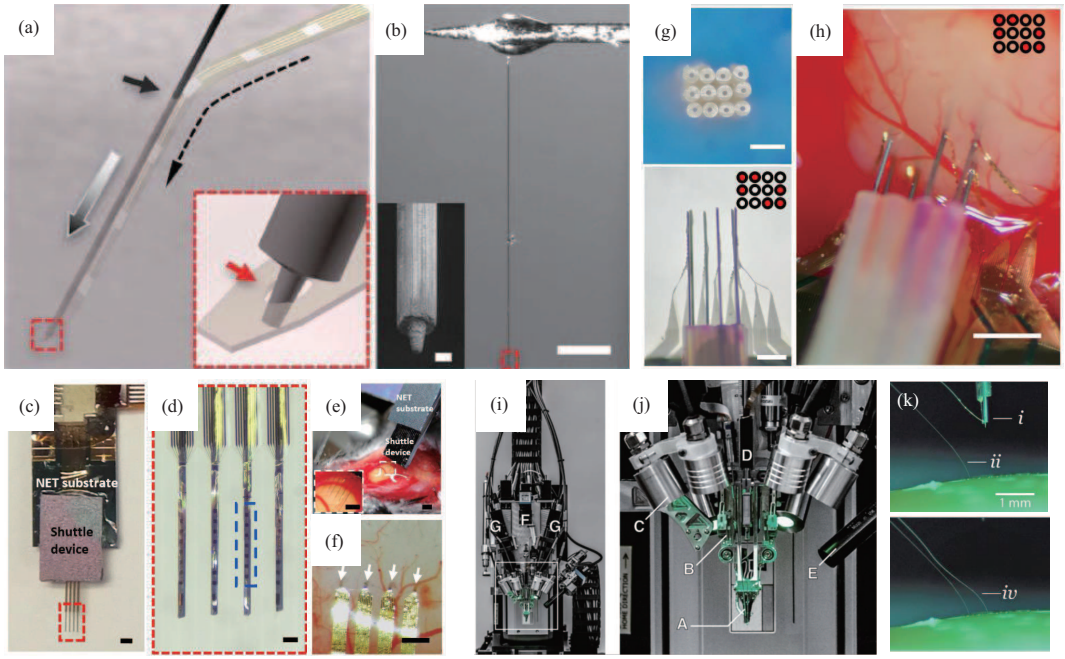

Figure 9 (Color online) Flexible probe implantation method based on shuttle device. (a) Schematic diagram of manual implantation method based on tungsten wire; (b) microscope image of flexible probe assembly with tungsten wire; (c)–(f) image of parallel implantation based on additional shuttle device carrying chips; (g) and (h) image of parallel implantation based on PTFE microtubes; (i) and (j) image of the surgical robot; (k) image of the probe implantation process based on the surgical robot. Scale bars: (b) 500 μm, insert: 2 μm; (c) 500 μm; (d) 50 μm; (e)–(h) 500 μm. (a) and (b) Reproduced with permission [22] @Copyright 2017 American Association for the Advancement of Science. (c)–(h) Reproduced with permission [18] @Copyright 2019 IOP Publishing. (i)–(k) Reproduced with permission [97] @Copyright 2019 J M I R Publications, Inc.

the probe tip. Submicron vision under the illumination of 650 nm light guided the insertion of probes. Monocular extended depth of field calculation under the illumination of 520 nm light accurately estimated the cortical surface position, further promoting accurate implantation of the probe at the required depth. Establishing a universal coordinate system with integrated depth tracking helped avoid the blood vessels in the brain tissue once the implantation path had been planned, thereby minimizing the inflammatory response. Up to six flexible probes can be inserted in automatic mode per minute. Among 19 operations, the average implant success rate was 87.1%±12.6% (mean ± standard deviation).

4.2 Sacrifice layer

Despite the successful delivery of neural probes, the shuttle-method inevitably introduces an extra footprint to the probe, which is not favorable for tissue health. To minimize the footprint, a second strategy, where the mechanical strength of flexible probe is reinforced before insertion but relaxed to flex after implantation, has been gaining many interests. There are two methods to temporarily make the probe stiff, i.e., from the structure and material perspectives. The key of structure-method is to bundle multiple flexible probes together by biocompatible materials which automatically degrade after implantation [19, 29, 98, 99].

For example, Guan and colleagues [19] developed a PEG-based method that assembled multiple microwires into bundles for subsequent implantation. They fabricated a flexible neural interface called Neurotassels composed of multiple flexible microwires, each of which included a metal microwire encapsulated in PI layer with a total thickness of 1.5–3 μm [19]. The Neurotassels formed a cylindrical shape with a total diameter of 55 μm due to surface tension when pulled out from molten PEG (Figure 10(a) and (b)). While a single microwire cannot be inserted alone, the bundled Neurotassels can be directly implanted. Studies have shown that the use of PEG as a sacrificial layer to help implantation does not increase foreign body response [100]. The implantation yield of more than 95% verified the effectiveness of this implantation method (Figure 10(c)). After six weeks of implantation, the electrophysiological signal from the neuron could be stably recorded, proving that the implantation method results in minimal implantation damage. Additionally, it is worth mentioning that with the hollow cylindrical probe structure, optical fibers can be integrated into the cavity without increasing implant volume, making it

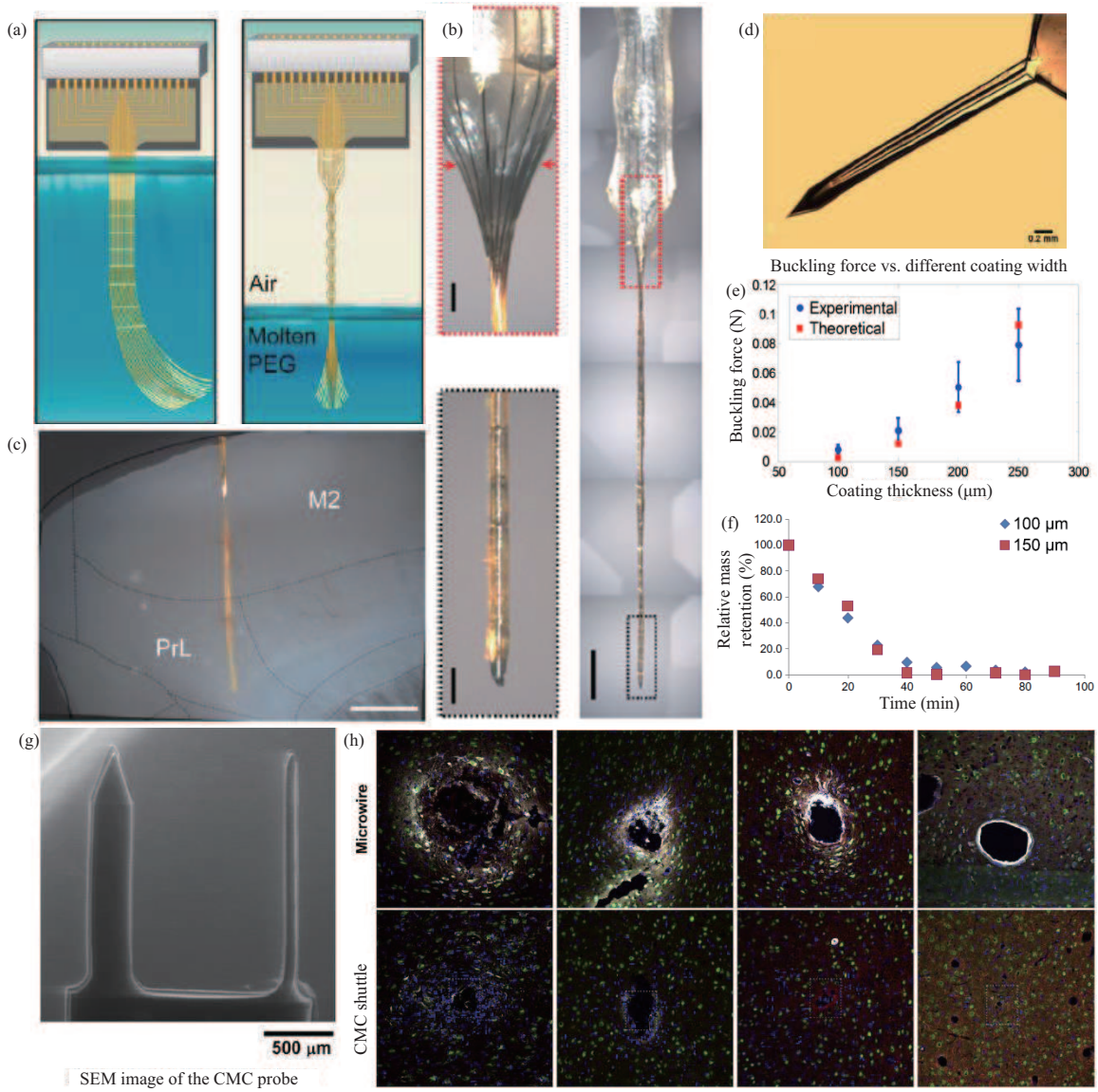

Figure 10 (Color online) Implantation of a flexible neural interface based on a sacrificial layer that can be degraded in vivo. (a) Schematic diagram and (b) microscope image of flexible neural probes self-assembled into bundles. (c) Microscope image of brain slice and implanted neural interface. (d) Microscope image of E5005(2K) sacrificial layer. (e) Buckling force as a function of E5005(2K) sacrificial layer thickness. (f) Relative mass retention of the E5005(2K) sacrificial layer as a function of implantation time. (g) SEM image of the CMC sacrificial layer. (h) Images of NeuN (green), Neurofilament (red), BBB Leakage (IgG, white), and cell nuclei (blue) after implantation of CMC sacrificial layer and microwire for 1, 7, 28, and 84 days. Scale bar: (b) left: 100 μm, right: 500 μm; (c) 500 μm; (d) 200 μm. (a)–(c) Reproduced with permission [19] @Copyright 2019 American Association for the Advancement of Science. (d)–(f) Reproduced with permission [29] @Copyright 2015 Springer New York LLC. (g) and (h) Reproduced with permission [98] @Copyright 2014 Pergamon.

convenient to transform Neurotassels into a photoelectric probe.

Beside PEG, other biodegradable biocompatible materials, such as polycarbonate [29, 99], carboxymethyl cellulose (CMC) [98], and poly(D,L-lactide-glycolide) (PLGA) [101], are also candidates. Specifically, Lo et al. [29] integrated the tyrosine-derived polycarbonate (E5005(2K)) polymer with the SU-8 based flexible probe through micro-molding in capillaries (MIMIC) process, leading to a smooth and uniform polymer coating on the probe surface, thus reducing acute implant damage (Figure 10(d)). E5005(2K) is biocompatible and degrades into non-cytotoxic tyrosine and PEG. Modulating polymer composition controls its degradation rate. Figure 10(e) showed the influences of different coating thicknesses on the mechanical properties of the probe. The relative mass retention of E5005(2K) decreased after implantation (Figure 10(f)), until the probe became flexible. Note that the degradation time is ∼40 min which is acceptable for an implantation surgery.

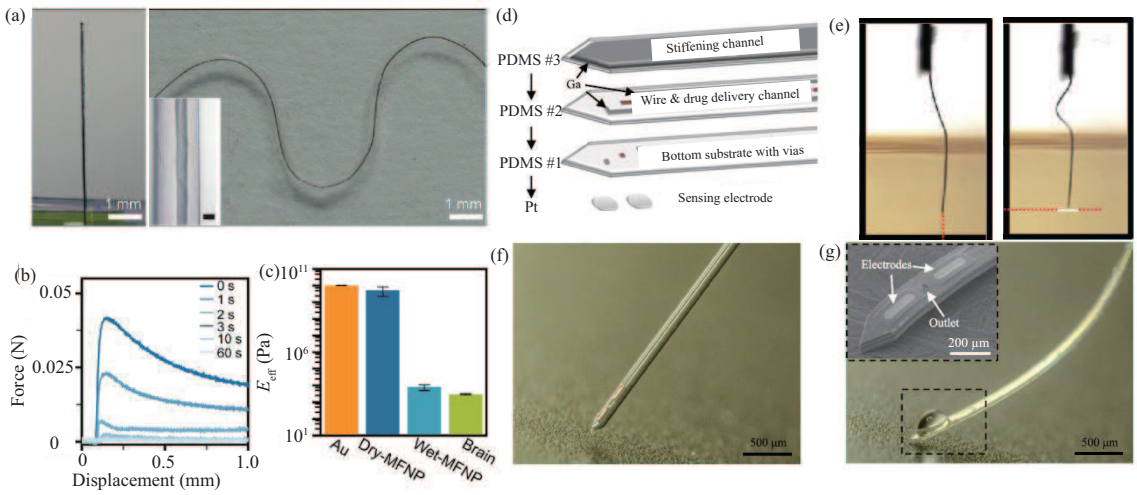

Figure 11 (Color online) Neural interface with variable rigidity before and after implantation. (a) Fiber probe based on calcium cross-linked sodium alginate before and after reaction with water; (b) stress of the fiber probe under different reaction times as a function of displacement; (c) Young's modulus of Au wire, Dry-MFNP, Wet-MFNP and brain tissue; (d) schematic diagram of the Ga-based rigid variable probe; (e) schematic diagram of Ga-based probes recovering flexibility after insertion into agar; (f) and (g) images of Ga-based probes in rigid and flexible states. Scale bar: (f) and (g) 500 μm. (a)–(c) Reproduced with permission [20] @Copyright 2020 Royal Society of Chemistry. (d)–(g) Reproduced with permission [103] @Copyright 2019 Elsevier Science.

Kozai et al. [98] used another biodegradable biocompatible material, CMC, as the sacrificial layer for flexible neural interfaces implants. CMC is a naturally occurring water-soluble polysaccharide, and its degradation products are non-cytotoxic. A CMC sacrificial layer can be manufactured through a molding process (Figure 10(g)). After implantation of the CMC sacrificial layer, the NeuN, Neurofilament and cell nuclei near the implantation site recovered to their pre-implantation levels over time (Figure 10(h)). These demonstrated harmless degradation of the CMC sacrificial layer in the body. However, the controversy about CMC is that it does not completely degrade after implantation. Rather, it becomes gelatinous and still wraps around the probes, potentially affecting the performance of the neural interfaces.

4.3 Neural interfaces with variable rigidity

Although the degradation products of the sacrificial layer-based implantation method are non-toxic and harmless, one cannot exclude the possibility that the degradation process and byproducts may affect the performance of the implanted neural interface (e.g., incomplete degradation products encapsulate the devices). Therefore, materials with tunable mechanical strength have been explored for fabricating PNIs. Ideally, a neural probe would be rigid for direct implantation, then become flexible after implantation for chronic recording.

Materials, which have different mechanical strengths before and after implantation due to environment dependent chemical reactions, have been explored. For example, Tang et al. [20] developed a fiber-shaped neural probe with a variable rigidity based on calcium ion cross-linked sodium alginate (SA). The device was a coaxial structure, where the center contained a carbon nanotube fiber (CNTF) microwire with a diameter of 20 μm for electrophysiological recording while the out layer was Parylene for insulation. The probe is cured in SA to obtain a Young's modulus at the order of 10 GPa, which is sufficient to support direct insertion. After implantation, the Young's modulus of the probe decreased to the order of ∼10 kPa, similar to that of brain tissue (Figure 11(a)–(c)). Currently, researchers have achieved four consecutive weeks of neuron electrophysiology monitoring. However, there are two aspects that need to be further improved: (i) the material has not yet been compatible with standard microfabrication processes; (ii) the fiber probe has its only electrical recording site at the tip and cannot achieve multi-channel electrophysiological recording.

Besides chemical reactions, a flexibility-tunable PNI can also be realized by physical processes, such as melting and solidification. One candidate material is metal gallium (Ga), chosen because of its high fluidity, high conductivity, and low melting point (30°C, close to body temperature) [102, 103]. Wen et al. [103] developed a Ga-based variable-rigidity probe composed of a stiffening layer, a wire & drug delivery layer, and a substrate layer (Figure 11(d)). One channel in the wire & drug delivery layer was for drug

delivery, and the other two channels were filled with Ga as recording electrodes and metal interconnects. In this technique, before implantation, pressurized liquid Ga in the probe was frozen to a solid state, enabling direct insertion. After implantation, the Ga was melted down at body temperature and partially drawn out to reinstall the flexibility of the probe (Figure 11(f) and (g)) for chronic electrophysiological recording. A simulated implantation operation using an agar block had verified the feasibility of this implantation method (Figure 11(e)).

In short, flexible probes have better longevity than conventional rigid probes, but the self-buckle strength of flexible probes does not support direct penetration into the brain. Therefore, several implantation strategies, including using shuttle devices, sacrifice layer, or temporarily stiffening neural interfaces, have been developed to insert the flexible probes into the brain. In addition, the semi-automatic robotic surgeon has been developed to facilitate the implantation procedure. These methods overcome the challenges associated with implanting flexible probes which in turn contribute to the chronic recording performance.

5 Conclusion and outlook

The challenge of solving the mysteries of the brain stems from the vulnerability and complexity of the brain. An ideal neural interface would be able to chronically probe the brain at large coverage without interrupting the neural circuit under test. Towards such a goal, advanced neural interfaces have been developed by employing emerging materials and fabrication technologies, with chronic stability at a single-neuron level and multimodality of electrical and optical signals. In this review, we discuss recent advances in PNIs development focusing on the improved chronic recording by adopting flexible materials and reducing the physical size to imitate the mechanical property of the brain, modifying neural interface to improve signal quality, and developing new implantation strategies to reduce tissue damages.

We envision that PNIs with long-term stable recording capability will continue to be pursued in neuroengineering and neuroscience fields. Further technological innovations in three major directions are needed to develop the 'ideal' neural probes. (i) Novel biocompatible materials are to be explored to fully match the mechanical and biological properties of brain tissue, based on which the PNIs should not be considered as "foreign body" by the immune system. Recent progress in conductive flexible polymer paves the way to producing all-organic PNI which holds promising for improved biocompatibility due to less heavy metals usage in the probes [104]. (ii) Neural probes with shrinking size yet boosting recording channel count enabled by advanced nano-fabrication technologies would have a smaller footprint in the brain while simultaneously record a large number of neurons in a brain. For example, the total channel count, electrode density and spatial resolution of PNIs based on state-of-the-art CMOS technique of feature size at nanometer scale could be potentially improved by a factor up to 100 in comparison to existing probes. (iii) For future clinical translation, it is necessary to develop a new surgical method capable of automatically implanting flexible probes in parallel with high efficiency and precision without increasing implant volume. For instance, by combining existing robotic surgery machines with artificial intelligence, it is possible to identify and avoid blood vessels automatically and precisely during insertion. These innovations that promote chronic recording capabilities will ultimately benefit the field of neuroscience, especially for the study of brain evolution and development, such as understanding how memory is stored and lost at the single-neuron level, and the changes of neural network that occur over the lifespans of animals.

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