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The Rise of Soft Neural Electronics

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Neuroscience aims at gaining a better understanding of the mechanism and function of neural systems, but its development is usually limited by the available tools to probe and stimulate the neural system. Advanced electronic devices can receive and send physical/chemical signals from and to biological systems, thus opening opportunities for neuroscience. However, the soft mechanical nature of neural tissue poses challenges for conventional rigid electronics, as the implantation of stiff electronic devices causes a mixture of side effects, including immunoreaction, chronic damage to the surrounding tissue and device dysfunction. The emerging soft electronics offer promises to solve the mechanical mismatch between artificial devices and soft neural tissues. With multiple functions integrated, they are beneficial to complex behavior studies. In this perspective, we summarize the current design principles of soft neural electronics and give an outlook on future possibilities.

Neuroscience devotes to gain a deeper understanding of the biological mechanisms of the nervous system, and it lays the foundation to research fields including neural prosthetics design and neural disorder treatment [1, 2]. The development of this field relies on the availability of new tools to record and modulate the nervous system at the tissue, cellular or sub-cellular level [3, 4]. As one of the most complicated and vulnerable systems in mammals, neural tissues have low Young's modulus ranging from 100 to 10 kPa, and they are mechanically heterogeneous and bear constant micro-movements [5]. The traditional neural detection and stimulation methods, such as electroencephalography and deep brain stimulation, have fueled neuroscience for decades [6, 7]. However, they are struggling to meet the demands for chronic and free-moving behavioral studies due to the usage of stiff electrodes (usually with elastic moduli in the gigapascal range), resulted from an unstable tissue-device interface. To be specific, the relative movement between stiff devices and soft tissues under the dynamic physiological environment will cause severe immune response and scar formation during chronic use, creating a dense barrier between the device and tissue. This dense layer subsequently leads to electronics failures by blocking chemical or physical signal exchange between the device and tissue [8]. As a result, the mechanical mismatch between soft neural tissues and stiff neural implants remains a major challenge and hinders their development. A scheme of the ideal soft neural electronics is demonstrated in Fig. 1, the key to form a stable tissue-device interface is to design a mechanical compatible neural electronics to eliminate the effects of neural tissue micromovement. Recently, there has been a material-driven pursuit towards soft implantable tools to sense and modulate the activity of neural systems with high temporal and spatial resolutions [9]. Meanwhile, neural electronics with new structures evolved to be better integrated with the neural system. Furthermore, by adding multiple functions such as optogenetics and microfluidics into soft neural electronics, they have shown promises in complex animal behavioral and long-term experiments [10]. To get a better understanding of the rapidly developing soft neural electronics, in this Perspective article, we introduce their design principles with a few recent notable achievements, and then discuss the possible future directions.

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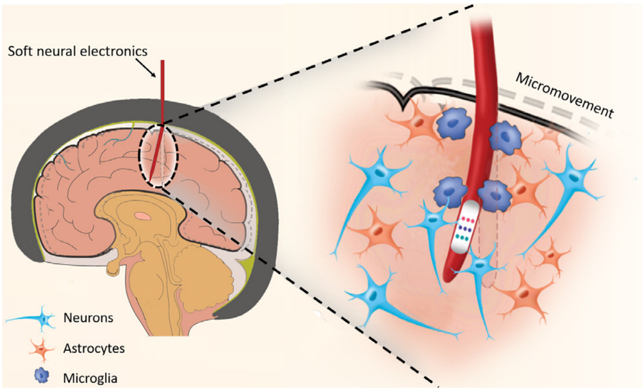

Fig. 1

The scheme of an implanted soft neural electronics in brain. The mechanical compatiblity between the device and tissue reduces foreign body reactions and allows the device to function in the long term.

Material

The exploration of new materials is at the center of the development of soft neural electronics. Soft neural electronics usually consist of electrode and substrate materials. For traditional rigid metal electrodes, flexible polymer based substrate materials are generally used, such as polydimethylsiloxane, polyimide and silk, to achieve a certain degree of flexibility [11]. However, because of the mismatch between the modulus of the metal and the flexible substrate, the adhesion between the two materials is often not optimized. Some efforts have been devoted to improving the adhesion between the substrate and electrode materials by surface modification [12]. On the other hand, new electrode materials such as conducting polymers, carbon nanomaterials and hydrogels are attractive candidates to decrease Young's moduli of electronic devices [13-15]. For example, Fig. 2a shows the design of polymeric microelectrode arrays for neural recording and stimulation, which used polypyrrole nanowires as electrodes material and showed low Young's modulus (450 kPa) [16]. Other than signal component electrode materials, a recent study has shown the incorporation of ionic compounds as additives in conducting polymers, for example, in poly(3,4-ethylenedioxythiophene) polystyrene sulfonate, can further increase their flexibility as soft electronics [17]. Recently, carbon materials such as carbon nanotube (CNT) fibers showed both high stability and mechanical softness, and they represent ideal candidates for neural electrodes [18-21]. Fig. 2b shows the structure and image of a calcium ion crosslinked sodium alginate coated CNT fiber neural electrode [20]. The CNT fiber-based electrode was mechanical compliant with soft brain tissue. The electrode formed a dynamically and adaptable interface and enabled continuous 4-week monitoring of neuron activity. Compared to traditional metal electrodes, the CNT fiber electrode is suitable for chronic electrophysiology, offering a new tool for neuroscience studies. The hydrogel electrodes are also promising as they are mechanically compliant with soft neural tissues (on the order of 10 kPa). With suitable modifications, hydrogel electrodes are capable of loading drugs for controlled release or used to stimulate nerve repair [22]. Future efforts will be devoted to improve their low electrical conductivity and simply the fabrication process of hydrogel electrodes [23].

The removal of neural electronics after it completes its mission usually requires secondary surgery, may cause additional pain and suffer to the user. To address this problem, a class of degradable materials, which are chemically active after implantation, could remove the requirement of a second surgical operation after the device completed its mission [24, 25]. For example, a recent study illustrates an example of biodegradable soft neural electronics, as shown in Fig. 2c [26]. The poly(diketopyrrolopyrrole-*p*-phenylenediamine) based transistors can be fully disintegrated after 30 days. As it was hard for the degradation process to be precisely controlled, it is desiring to synthesize new materials

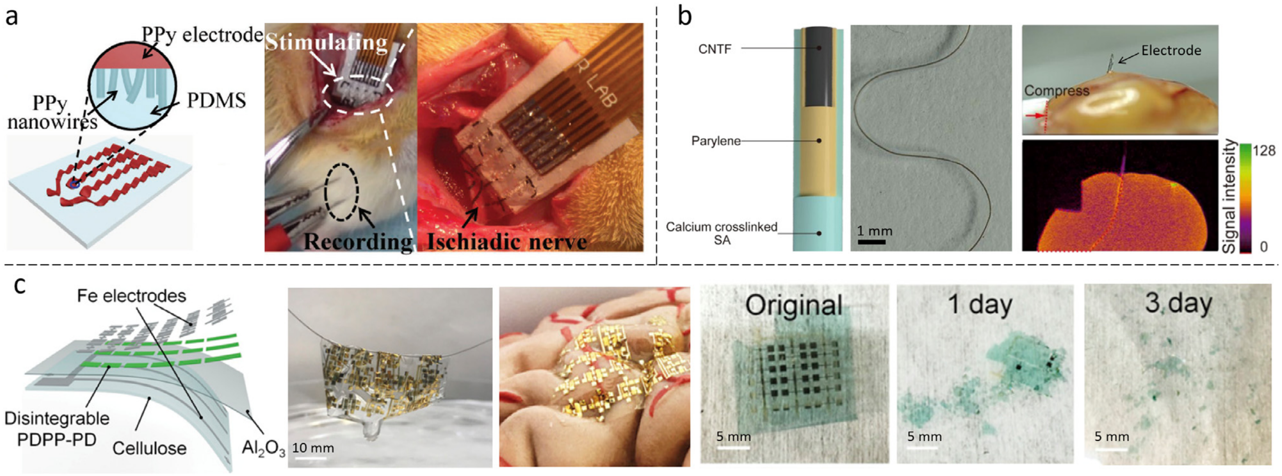

Fig. 2

Materials selection for soft neural electronics. (a) A mechanical compatible polymeric neural electrode for neural recording and stimulation. Reproduced from ref. [16] with permission of Wiley-VCH. (b) Carbon nanotube (CNT) fiber-based soft neural electrode, offered dynamically adaptable tissue-device interfaces. Reproduced from ref. [20] with permission of the Royal Society of Chemistry. (c) A poly(diketopyrr olopyrrole-*p*-phenylenediamine) (PDPP-PD) based biodegradable soft neural electronics. Reproduced from ref. [26] with permission of the National Academy of Sciences of the USA.

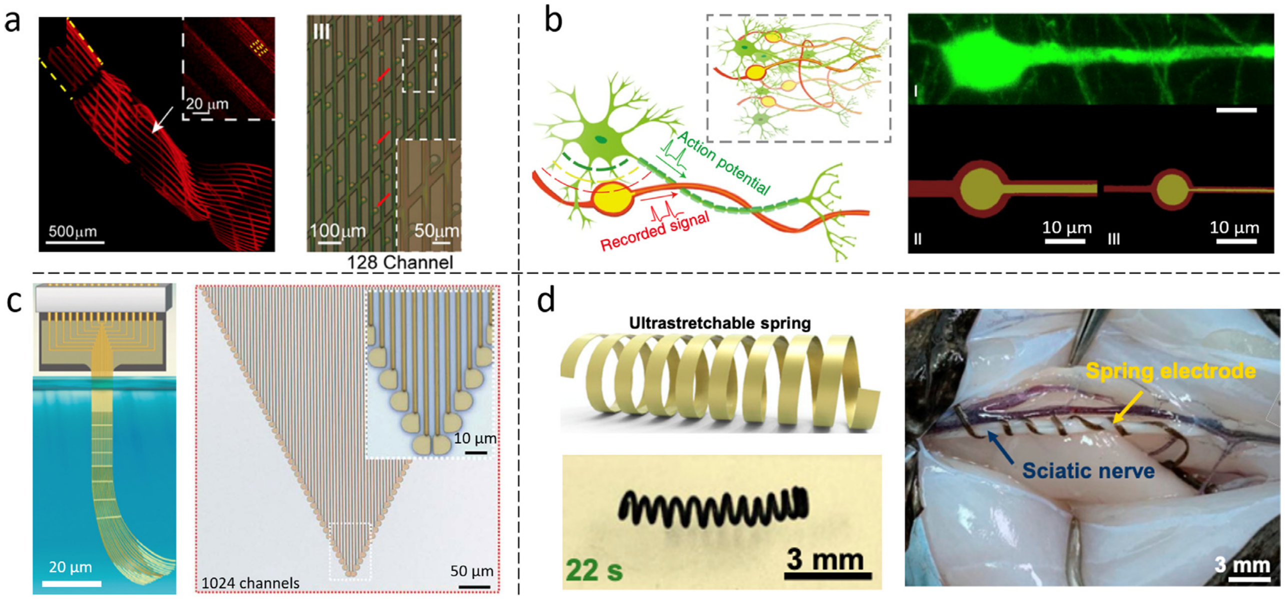

Fig. 3

New structures to improve the stability of the tissue-device interface. (a) Microscope images of multichannel mesh electronics, the electronics is suitable for stable chronic brain electrophysiology. Reproduced from ref. [29] with permission of the National Academy of Sciences of the USA. (b) Neuron-like electrodes mimicking the structural features and mechanical properties of neurons, which provides a structurally and functionally stable interface with the neuronal and glial networks. Reproduced from ref. [30] with permission of the Springer Nature. (c) Self-assembled multiple channel neurotassel for neural activity recording. Reproduced from ref. [31] with permission of the Springer Nature. (d) Ultra-stretchable spring electrode for sciatic nerve stimulation. Reproduced from ref. [32] with permission of the National Academy of Sciences of the USA.

for stable tissue-device interfaces and being able to degrade on demand. The resulting new devices may minimize foreign body reactions and avoid second surgery after use.

Electrical impedance determines the recording performance of electronic devices including signal-to-noise ratio and detection range. For instance, high-impedance electrodes (1–5 MΩ) were normally used to record neuron action potentials, and lowing the impedance increased the detection radius and cell population [3]. Future electronics are expected to have a self-tunable detection range to adapt to the research requirements, achieving this requires the electrodes to own tunable electrical impedances, possibly by using semiconductors and photo-responsive materials.

Structure

Another effective approach to building a stable tissue-device interface is enabled by the structure design. Decreasing the device thickness reduces the bending stiffness, as the latter scales cubically with the thickness [3]. This scaling rule has been used to guide the design of electronic devices with a broad spectrum of materials, including conventional rigid materials [27]. Two main types of structures are commonly used for neural electronics, either penetrating implants or planar implants. Penetrating implants are designed to reach deeper regions of the brain due to their small sizes with minimized impact on surrounding neural tissue. For example, fibrous neural electronic devices showed low bending stiffnesses and were capable to record electrophysiological signals with the single-cell resolution for up to a few months [27]. However, they are expected to further match the dynamically and mechanically heterogeneous nature of neural tissues when crossing different regions, which is crucial for providing a more stable brain-machine interface in free-moving animal models. Planar implants are generally used to study the function of the cortex, and a successful example is the Utah electrode arrays. The relatively larger surface areas of this type of electrodes allowed them to sense and modulate a large population of neurons [28].

Recently, a few new structures have been developed to improve the stability of tissue-device interface and to expand the function of neural electronics. For example, to further decrease the size of a neural electrode, injectable electronics with the mesh-like structure were developed and it demonstrated advantages such as high tissue biocompatibility with promises for chronic applications, as demonstrated in Fig. 3a [29]. Later, to further decrease the size of neural electronics, neuron-like electronics (Fig. 3b) showed similar structural features and mechanical properties to neurons was developed. The neuron-mimicking devices can form structurally and functionally stable interfaces with neuronal and glial networks *in vivo* [30]. The electronics demonstrated stable single-unit recording of individual cells and enabled high-quality recording from shortly after implantation to at least 3 months, Further, to minimize the footage of the implanted neural electrode, a fibrous stucture of self-assembled multiple channel Neurotassel was developed for chronic recording (Fig. 3c) [31]. The Neurotassel was fabricated *via* elastocapillary interactions when withdrawn from a molten polymer and can be readily scaled up to 1024 microelectrode filaments. Due to the similar structure of fibrous implants to neuron cells, they may be useful to enhance the integration between neuron and device. Other than penetrating and surface structures, a 3D spring shape electrode was recently developed, which can be comfortably

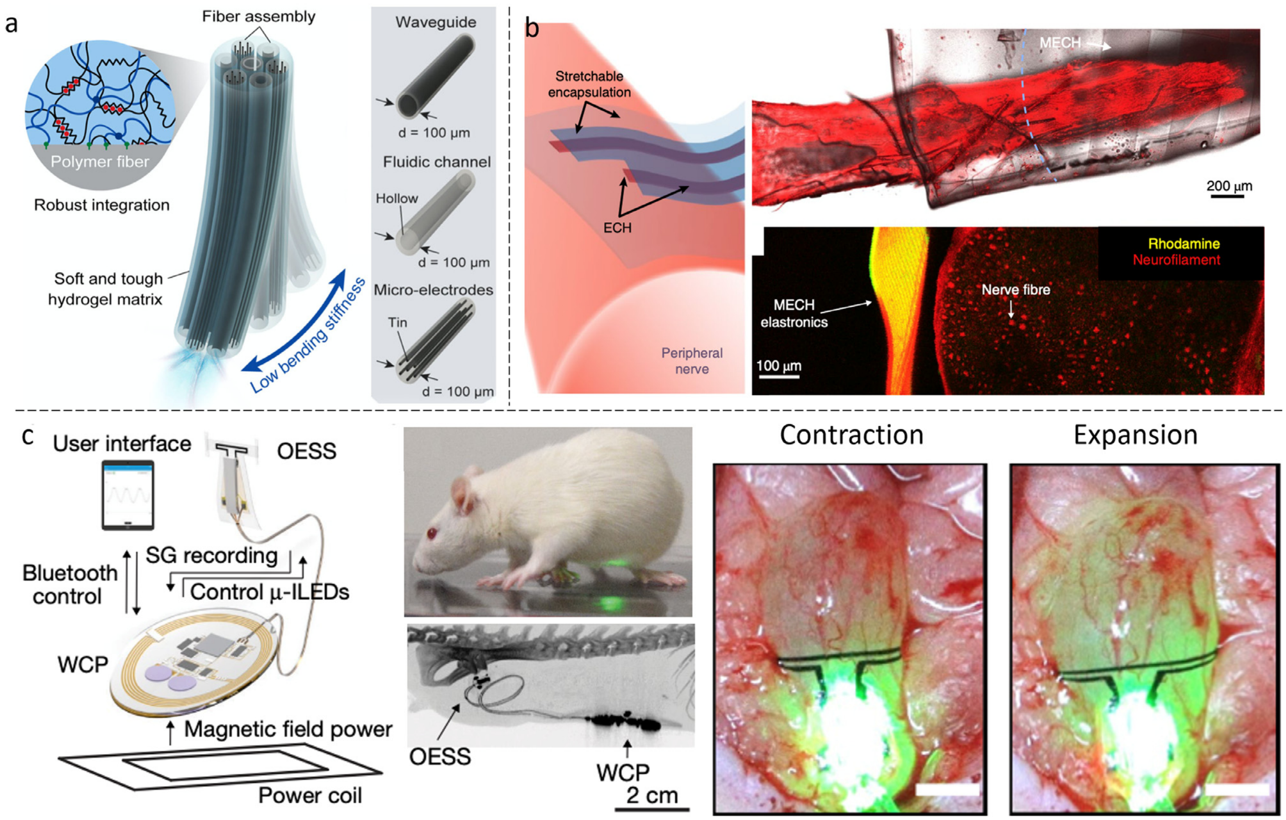

Fig. 4

Functions and integrated systems of soft neural electronics. (a) Hydrogel hybrid probe consisting of multiple functions including electrophysiological, fluidic delivery and optogenetics. Reproduced from ref. [39] with permission of the Springer Nature. (b) A soft electrically conductive hydrogel electronics for peripheral nerve stimulation. The microelectrodes formed a stable interface by wrapping around a sciatic nerve. Reproduced from ref. [40] with permission of the Springer Nature. (c) Wireless closed-loop electronics system for optogenetic neuromodulation of the bladder. The soft, high-precision biophysical sensor system continuously measured bladder volume while the optogenetics module controlled bladder function. Scale bar, 2.5 mm. Reproduced from ref. [41] with permission of the Springer Nature.

wrapped around the sciatic nerve for neural stimulation, as shown in Fig. 3d [32]. The newly developed neural electronics with these new structures showed excellent compatibility with neural tissue, which holds promises for neuroscience studies.

After these advancements, future surface implants should be able to cover the convoluted surface of the brain by closer physical contact with tissues to provide higher spatial resolutions. Such envision could be achieved by using three-dimensional printing or high-resolution photolithography for personalized neural electronic devices. Also, they still need a less invasive implantation method.

Function

Neural functions rely on electrical and chemical signaling among neuron cells, so soft neural electronics should be able to detect these diverse biological signals in long term. A chemical biosensor is usually more complicated regarding to the structure and component compared to neural electrodes, as they rely on an additional step to translate chemical signals to electric signals on the electrode surface [33]. Some advances have demonstrated using chemical sensors to chronically detect neurotransmitters and key chemicals in the brain (e.g., dopamine, glutamate and choline) with various behavior models [4, 34-36]. For neural modulation, optogenetics using light to control genetically modified neurons is now a wildely used technology to probe neuron function [37]. The search of better soft photoelectric materials (such as semiconductors) and fabrication technique has accelerated the development of soft optoelectronics [38]. These importantant technologies, along with but not limited to drug delivery and neruon stimulation, are the key to the development of neuroscience. Recent attempts have integrated these modules into a signal device [10]. An example of a recently developed soft hydrogel hybrid probe that consisted of these functions is demonstrated in Fig. 4a [39]. Such a highly integrated flexible system could simplify the multiple-step operations that are commonly involved in neuroscience study, offering a real-time readout platform for in *vivo* and behavioral experiments.

Meanwhile, other than central neural systems, peripheral neural systems are also an important research direction. Several pioneer works have demonstrated the use of soft electronics for peripheral neuromodulation. For example, soft and elastic hydrogel-based microelectronics can be used to wrap around the peripheral nerve and stimulate it with low voltage, as shown in Fig. 4b [40]. Another pioneering work showed the design of a closed-loop electronics system for the modulation of bladder function (Fig. 4c) [41]. The device consists of a soft biophysical sensor, optical stimulation module, and a control module, which can be used for closed-loop optogenetic neuromodulation of bladder function. Another example showing soft morphing electronics could be integrated with multiple functions, including chronic neuromodulation, nerve growth monitoring and conduction velocity testing. Such a device was consisted with viscoplastic conductive polymer and an insulating and self-healable viscoplastic polymer, could grow 2.4-fold in diameter to accomplish the study in the fastest growth period of rat model [42].

In the future, we are expecting soft neural electronics will find more applications in nervous system disorders, such as in the treatment of neurogenic gastritis and distal muscle weakness. Recently, the pursuit to find the chemical changing during behavior animal model attracts attention. Such function can be incorporated with optogenetics for behavior study to reveal the functions of neural circuits [43]. Further, decoding the information obtained from neural electronics is important. The collaboration with big data analytics and machine learning may become another important direction. Finally, the reliable powering system of soft neural electronics remains challenging. The power management module of the soft electronics should be safe, minimized and reliable. Recently developed implantable soft battery, biofuel cell or nanogenerator may offer solutions for continuously powering these devices [44, 45]. Another direction of soft neural electronics is to design neuromorphic devices such as artificial synapses to mimic the behavior of neuron function. Recent work reported the example of artificial synapses that can transform the chemical doping process into electric signals, and has shown to be compatible with neuron cells [46]. Such devices may further be incorporated with soft neural electronics and demonstrate their application *in vivo*.

After all, we have witnessed the rapid development of soft electronics in the past few years. However, the clinical translation of soft neural electronics remains challenging and will require new understandings and technologies not only in neuroscience, but also in multiple disciplines including materials science, physics, chemistry and engineering. The complicated fabrication process, safety, high cost and ethics problems (e.g., data collection and cloud analysis) are the main obstacles to commercialize these soft neural electronics. However, with careful material selection, structure design and function integration, soft neural electronics will keep advancing related fields such as neural prosthetics and neural disorder treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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