Nano Energy 65 (2019) 104039

Contents lists available at ScienceDirect

Nano Energy

journal homepage: www.elsevier.com/locate/nanoen

Review

Development of neural interfaces and energy harvesters towards self-powered implantable systems for healthcare monitoring and rehabilitation purposes

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ARTICLE INFO

Keywords:
Neural interface
Self-powered energy harvester
Healthcare monitoring
Rehabilitation

ABSTRACT

Despite its great promise, neural interface has yet to substantially impact modern healthcare monitoring and therapeutic interventions. However, considering the recent development of self-power solutions, data transmission technologies, and artificial intelligence, neural interface has the potential to transform future clinical applications. Together with the recent self-powered energy harvesting technologies, neural interfaces are evolving towards fully implantable systems. Here, we first review the progress and current status of neural interfaces, start from the well-established neuromodulation protocols and efforts to translational applications, then move on to milestones of neural interface development, and end with the review on considerations and requirements of active and inactive materials. With the knowledge of neural interface current status, we further review implantable systems which are built on top of the neural interfaces. Particularly, we review well-established powering solutions. Furthermore, we summarize the recent demonstrations of direct tissue stimulation with self-powered energy harvesters in chronological order. In the end, we discuss the future opportunities and challenges in the direction towards self-powered systems for healthcare monitoring and rehabilitation purposes.

1. Introduction

Luigi Galvani's discovery of electrically induced motor movements laid the foundation for current knowledge of neural signaling [1], moreover, started a new era of exploration into the decoding of neural functionalities and further introducing of therapeutic interventions by using electricity. Ever since 2005, when a single-component control tool of microbial opsin genes safely conferred to neurons was firstly demonstrated, optogenetics, yet another important toolkit using light, has fueled the exploration and intervention of neural functionalities to another level over the past decade [2,3]. For current neuroscience and neuroengineering research, right in the center of the enabling technologies lies the emerging field of the neural interface, which comes in direct connect with biological tissues to electrically and optically record and interfere with neural functionalities [4–7]. Furthermore, we have witnessed the recent convergence of neural interfaces with pharmacology, by combining drug delivery functions alongside the well-established electrical and optical methods to empower the multi-functional neural interfaces.

Neurological, neurodegenerative, psychiatric and neuromuscular conditions, for example, epilepsy, Alzheimer disease, depressive disorder, and multiple sclerosis, respectively, cause a huge social and economic burden on a global scale [8,9]. According to the Parkinson's Foundation, in the United States alone, nearly one million people will be living with Parkinson's disease by 2020, and the current combined direct and indirect cost of Parkinson's disease is estimated to be nearly $25 billion per year. These diseases have motivated the advance of neurotechnology, to develop novel tools combining well-established electrical and optical methods, pharmacology, and recent emerging ultrasound and magnetic methods to achieve observational and interventional purposes. Immense initiatives and funding projects are launched to support the fundamental research of neural mechanisms and translational research for the diagnosis and intervention of the diseases as well as brain-inspired intelligence technology, and examples include the United States' BRAIN Initiative [10], The Human Brain Project in Europe [11], China Brain Project [12], and Korea Brain

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https://doi.org/10.1016/j.nanoen.2019.104039
Received 4 July 2019; Received in revised form 8 August 2019; Accepted 17 August 2019
Available online 19 August 2019
2211-2855/

Initiative [13].

Here, we review the progress and current status of neural interfaces. Considering the versatile designs and wide applications, we first introduce the examples of neural interfaces employed on different biological tissues, with emphasis on well-established neuromodulation protocols and efforts to translational applications. Then, we move on to review neural interface milestones in terms of the central nervous system (CNS), peripheral nervous system (PNS), and muscle and organ applications, respectively, in chronological order. We finish the review on neural interface by discussing the considerations and requirements of conductive and non-conductive materials, as well as the new materials that enable novel features, such as biodissovable, self-adhesive, and stretchable.

From the perspectives of laboratory experiments and translational applications, the desirable neural interfaces have evolved towards implantable systems, to support long-term experimental observations, healthcare monitoring, and therapeutic interventions. With the knowledge of neural interface current status, we further review implantable systems which are built on top of the neural interfaces. Particularly, we review well-established powering solutions, which used to be a bottleneck technology on the way of developing sustainable systems, and reveal the recent trend of emerging self-powered solutions. Furthermore, we summarize the recent demonstrations of direct tissue stimulation with self-powered energy harvesters in chronological order. In the end, we discuss the future opportunities and challenges in the direction towards self-powered systems for healthcare monitoring and rehabilitation purposes.

2. Neural interface – protocols and translational applications

Electricity is the common language naturally spoken by various levels of biological tissues. Furthermore, recent advances in optogenetics have expanded the capability of selective gene modification from merely the cortex to various biological tissues, including the spinal cord, the peripheral nerves [14,15], skeletal muscle tissues [16–18], and cardiac tissue [19], providing an additional language for external observation and artificial intervention. To adapt neural interfaces to bidirectional communication with various biological tissues, there has been intense research on the versatile neural interface designs, in terms of three phases ranging from the preliminary research trials, well-established observation/intervention protocols, to translational applications (Fig. 1 shows the examples of neural interfaces designed for various biological tissues).

With the ever-increasing knowledge of neural signaling mechanism, electrical stimulation is becoming a powerful tool to treat the neurological, neurodegenerative, psychiatric and neuromuscular conditions. Some well-established neuromodulation protocols include FDA-approval deep brain stimulation therapy for the treatment of Parkinson's disease [20], epilepsy [21], and dystonia [22]. In addition, electrical spinal cord stimulation is applied to restore walking in humans with spinal cord injury [23,24]. Electrical recording from the brain has long been employed to decode motor intentions to achieve movement control [25,26], and more recently, it is proven that brain recording can be used to decipher complicated human speech [27]. Apart from these well-established observation/intervention protocols, there is an emerging trend of electroceutical, especially named for electrical stimulation targeting at the autonomic nervous systems, including the cervical vagus nerve, gastric vagus nerve, and sacral nerve [28,29]. Electroceutical is considered as a substitute for conventional medicines, to target specifically at the fine autonomic nerves by employing miniaturized devices to deliver localized electrical therapy, and thus is also named bioelectronic medicines. In 2013, pharmaceutical company GlaxoSmithKline (GSK) initiated the research on electroceuticals, followed closely in 2014 by the Electrical Prescriptions (ElectRx) program at DARPA and the NIH Stimulating Peripheral Nerves to Relieve Conditions (SPARC) initiatives. In 2016, Galvani Bioelectronics was formed through a partnership between GSK, and technology company, Verily Life Sciences, to specialize in the development of bioelectronic medicines.

One step further from the well-established observation/intervention protocols, some neural interface technologies have become successful translational applications, including retinal prosthesis, cochlear implant, and pacemaker. Cochlear implant represents the mature neural interface technology for translational applications [30,31], which bypasses the peripheral auditory system and electrically stimulates nerves inside the inner ear. By 2018, worldwide recipients of cochlear implants manufactured by Cochlear and Advanced Bionic have reached 450, 000 and 79,000 respectively. Another example of successful translational applications is a retinal prosthesis, which involves the use of electrode arrays surgically implanted on the retina to restore functions of the damaged light-activated photoreceptor cells by directly stimulating the retinal nerve cells with electrical pulses [32–34]. In 2015, the Argus® II Retinal Prosthesis System became the first FDA-approval treatment for individuals with severe Retinitis Pigmentosa. Starting from 2016, IRIS® II Epi-retinal bionic vision system is going through clinical trials for treatment of retinal dystrophies.

3. Neural interface – research roadmap

Biological tissues that are constituted of neurons or innervated by nerves naturally communicate in the language of electricity. Thus, certain diseases related to neural signaling in these biological tissues can potentially be treated by employing neural interfaces to observe and modulate the electrical signals. Structural design is of crucial importance for neural interface development to target different biological tissues. Central nervous system (CNS) and peripheral nervous system (PNS) constitute the two major parts of the nervous system in vertebrates. In addition, muscles innervated by nerves can also be targeted by the neural interface. These biological tissues come in dramatically different structures. The CNS consists of the brain and the spinal cord, where the brain is soft and has a layered structure. The PNS consists mainly of nerves, which are enclosed bundles of the long fibers or axons, that connect the CNS to every other part of the body. Although both are constituted of muscle tissue, skeletal muscles, and organs, including heart, and bladder come in different structures. Application on these different biological tissues represents different preference, requirement, and limitation in terms of the neural interface design. The delicacy of the biological tissues and the complexity of the neural signals need to be considered during the design of the neural interface. Particularly, intimate localization can be of crucial importance for the application of electrical, optical, or pharmacological solutions. Here, we review the milestones of neural interface development in CNS, PNS, skeletal muscles and organs respectively (Fig. 2).

3.1. Neural interface for central nervous system (CNS)

The tradeoff between selectivity and invasiveness is a major limitation in CNS neural interface design [44,45]. For both recording and stimulation purposes, high selectivity requires the intimate location of the neural interface to the targeted biological tissue, which at the same time inevitably increases the invasiveness. The brain tissue naturally works as a low-pass filter, to allow only low-frequency electrical signals to propagate further. Electrical recording from the scalp, dura, or the pia can only capture low-frequency electrical signals propagated from the deep brain tissue, while losing the high-frequency neural spikes that encode the temporal and spatial firing information of individual neurons. Thus, to record high-frequency neural spikes requires invasive neural interface design, while surface EEG and ECOG can be used for learning low-frequency oscillation information. The early neural interface designs for recording purpose employed multiple-channel silicon probes, including Michigan probe and Utah electrode array (UEA) [46,47]. Syringe injectable electronics emerged in 2015, as a novel

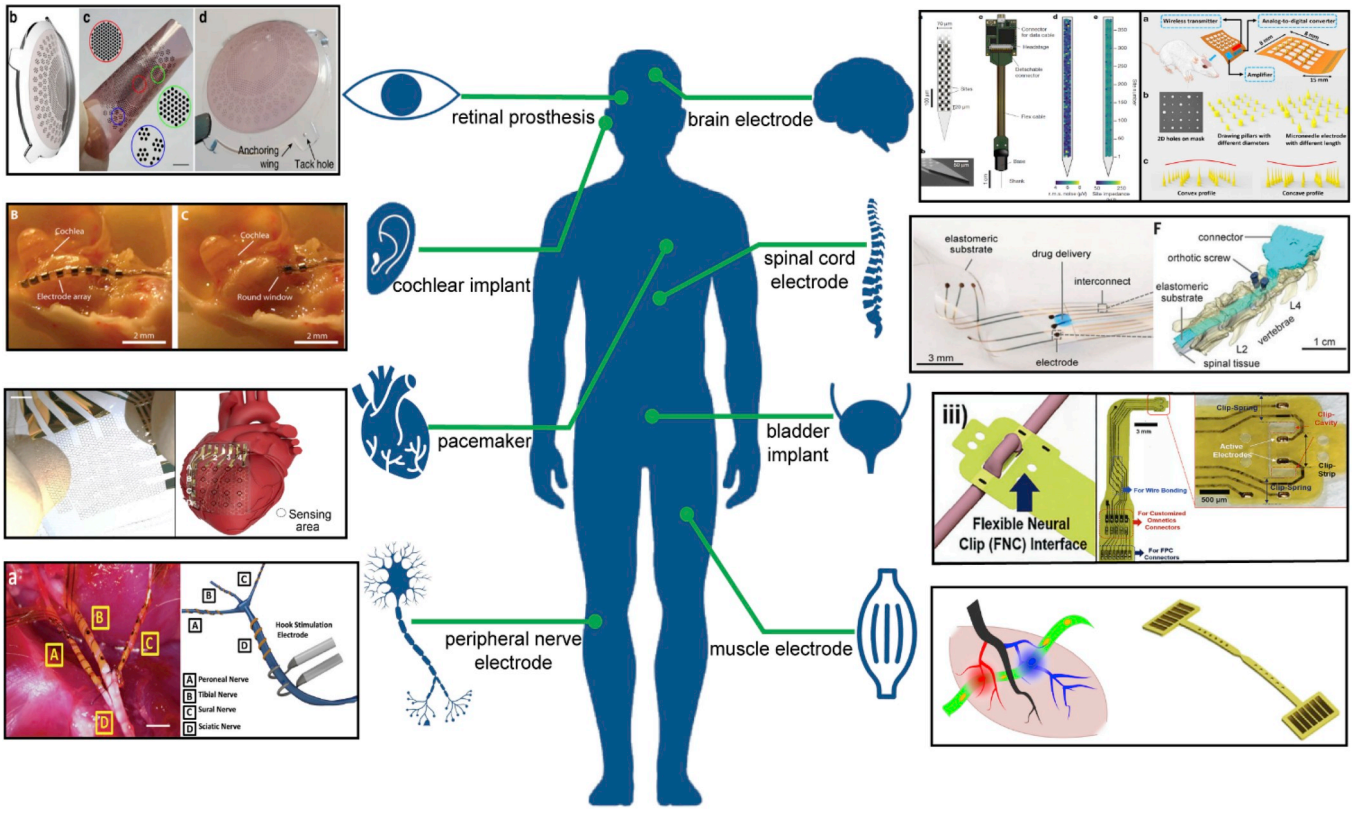

Fig. 1. Well established neuromodulation protocols and translational applications of neural interfaces. Neural interfaces can be widely applied to different biological tissues, examples include retinal prosthesis [35], cochlear implant [36], cardiac pacemaker [37], peripheral nerve electrode [38], brain electrode [39,40], spinal cord electrode [41], bladder implant [42], and muscle electrode [43].

invasive neural interface structure to reduce brain tissue damage [48]. More recently in 2017, 384-channel Neuropixels [39], the first fully-integrated silicon CMOS digital neural probe, leads the development of high-density invasive recording probes.

The tradeoff between selectivity and invasiveness also affects the design of the neural interface for stimulation purposes. Intrinsically, electric field tends to spread out in the brain tissue. Thus, electrical stimulation delivered by electrodes implanted on the scalp, dura, or the pia will spread out and have difficulty in targeting at a specific spatial location. Considering the recent progress of applying temporally interfering electric field for spatial location selectivity [49–51], implantation of several electrode arrays on the scalp, dura, or the pia may have improved spatial selectivity. In addition to surface electrode arrays, novel designs of fiber-based penetration electrodes integrate electrical, optical, and pharmacological functions, to enable selective therapy delivery to targeted brain areas [52,53].

3.2. Neural interface for peripheral nervous system (PNS)

Similarly, the neural interface for PNS also faces the tradeoff between selectivity and invasiveness. The peripheral nerves contain afferent sensory fibers and efferent motor fibers. Both afferent and efferent nerve fibers are grouped in fascicles surrounded by connective tissue (epineurium, perineurium, and endoneurium) in the peripheral nerves. Such nerve fiber grouping is based on their destinations instead of their functions. In this way, nerve fascicles provide a topographic organization to peripheral nerves. To selectively record or stimulate specific nerve fibers requires the neural interface to penetrate the nerve tissue and form intimate contact with nerve fibers. Yet, the neural interface for PNS faces another challenge, and that is the small dimension of the peripheral nerves, especially the autonomic nerves which are largely concerned with functions not normally under voluntary control. The small dimension of the peripheral nerves dramatically increases the difficulty for neural interface design, as advanced micro-machined fabrication technology is needed to achieve multiple channel neural interface within small footage.

Three are two types of micro-machined PNS neural interface, namely extra-neural interface and intra-neural interface. Extra-neural electrodes are implanted to tightly surround the peripheral nerve, and examples include flat-interface nerve electrode (FINE) [54], self-adaptive neural ribbon [38], pelvic nerve clip electrode [42], twining electrodes using shape memory material [55]. The intra-neural interfaces include intra-fascicular, penetration, and regenerative interface. Penetration electrodes access individual nerve fibers for high selectivity, and examples include transverse intrafascicular multichannel electrode (TIME) [56], longitudinal intrafascicular electrode (LIFE) [57], slanted Utah electrode array (SUEA) [58], and highly selective 3D spiked ultraflexible neural (SUN) interface [59]. Different from the conventional penetration electrode, axon-guiding electrode, such as the SIEVE electrode [60], aims at guiding and improving the nerve regeneration after severe damage.

3.3. Neural interface for muscles and organs

As compared to the peripheral nerves where hundreds of nerve fibers are tightly packed together, skeletal muscles generally are of larger sizes and are easier to operate on. Another important fact is that skeletal muscles adapt better to external implantations, which reduces the possibility of deteriorating the electrodes due to inflammatory reactions. Both the larger size and better adaptation to external implantations make the geometric design of skeletal muscle electrodes easier as compared to the peripheral nerve electrodes. The well-established skeletal muscle electrodes fall in two categories, namely epimysial electrode and intramuscular electrode. The epimysial electrode is

applied on the surface of muscles and fixed by suturing to the nearby tissue and is preferably fabricated of PDMS to allow conformal adhesion during muscle contractions [61,62]. The intramuscular electrode is implanted into the muscle tissue, to access motoneurons deep in the muscle tissue [43,63,64]. In addition to the skeletal muscles, cardiac muscles also receive great research attention. By monitoring the cardiac activities and delivering therapy when a cardiac abnormality occurs, the neural interface can be an effective solution to cardiac diseases. The recent cardiac patches come in stretchable material that wraps around and deform with the heart, with integration of the ECG sensors, temperature sensors, and electrical stimulation electrodes [37,65,66].

4. Neural interface – material aspects

The neural interface is the bridge connecting the biological tissue and external electronics. In terms of recording, neural interfaces serve to record bioelectrical signals from the biological tissue to obtain sensory information or motor intentions. In terms of stimulation, neural interfaces inject charge into the biological tissue to modulate biological functions. The physical interaction between neural interface and biological tissue can be complicated, and this is an important consideration when choosing the active electrode material. For the inactive electrode material (e.g., insulating material), biocompatibility and biostability are the important considerations. Here, we will discuss the criteria for active electrode material and inactive electrode material. Then, we will review the emerging materials that enable novel features, such as biodissovable, self-adhesive, and stretchable (Fig. 3).

During stimulation and recording on the biological tissue, disturbing electrical events can occur at the active electrode material surface. For metal electrodes, electrons serve as the carriers. For the biological tissue, cations and anions are the carriers. Because of the different carriers, there is an interface between electrodes and tissue where they interact with each other. This electrode-tissue interaction can be capacitive, faradaic, or a combination of both capacitive and faradaic, depending on the active electrode material properties. The difference between capacitive and faradaic charge injection lies in whether redox reactions happen. In terms of capacitive charge injection, there is no redox reaction. It works similarly as parallel plate capacitors, as electrons accumulate in the metal and the attracted cations accumulate on the electrode surface, which forms a double layer (Helmholtz fixed layer, and Goy-Chapman diffuse layer which is neglected for well-conducting electrolytes). Electrodes made of materials that only employ capacitive charge injection are named perfectly polarizable electrode. Perfectly polarizable electrodes are ideal for stimulation because they will not corrode (electrode corrosion can happen in faradaic charge injection). A capacitor is used to describe the

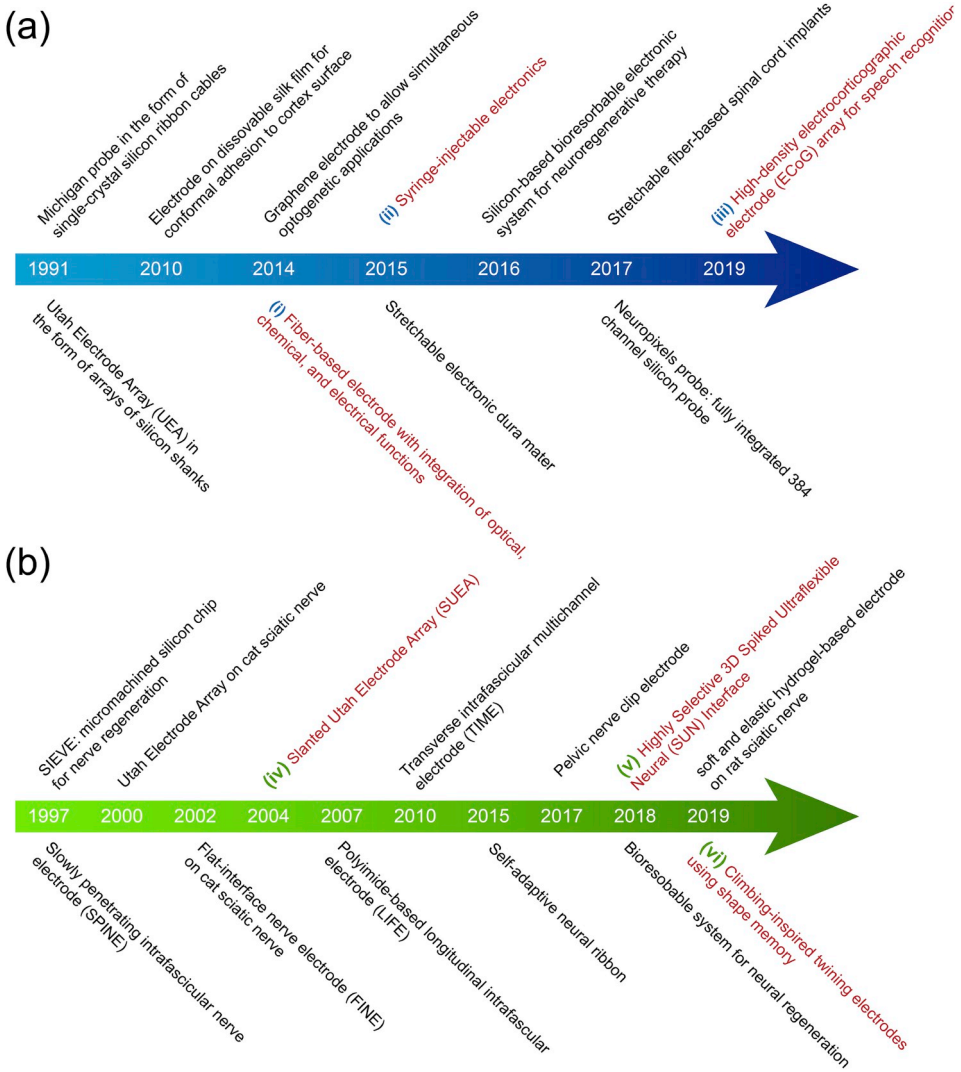

Fig. 2. Research roadmap of neural interfaces. (a) Milestones of CNS neural interface development [27,39,41,46–48,52,53,67–69]. (b) Milestones of PNS neural interface development [38,42,54–60,70–73]. (c) Milestones of skeletal muscle and organ neural interface development [37,43,61–66,74]. (d) Structural design of CNS, PNS, skeletal muscle, and organ neural interfaces.

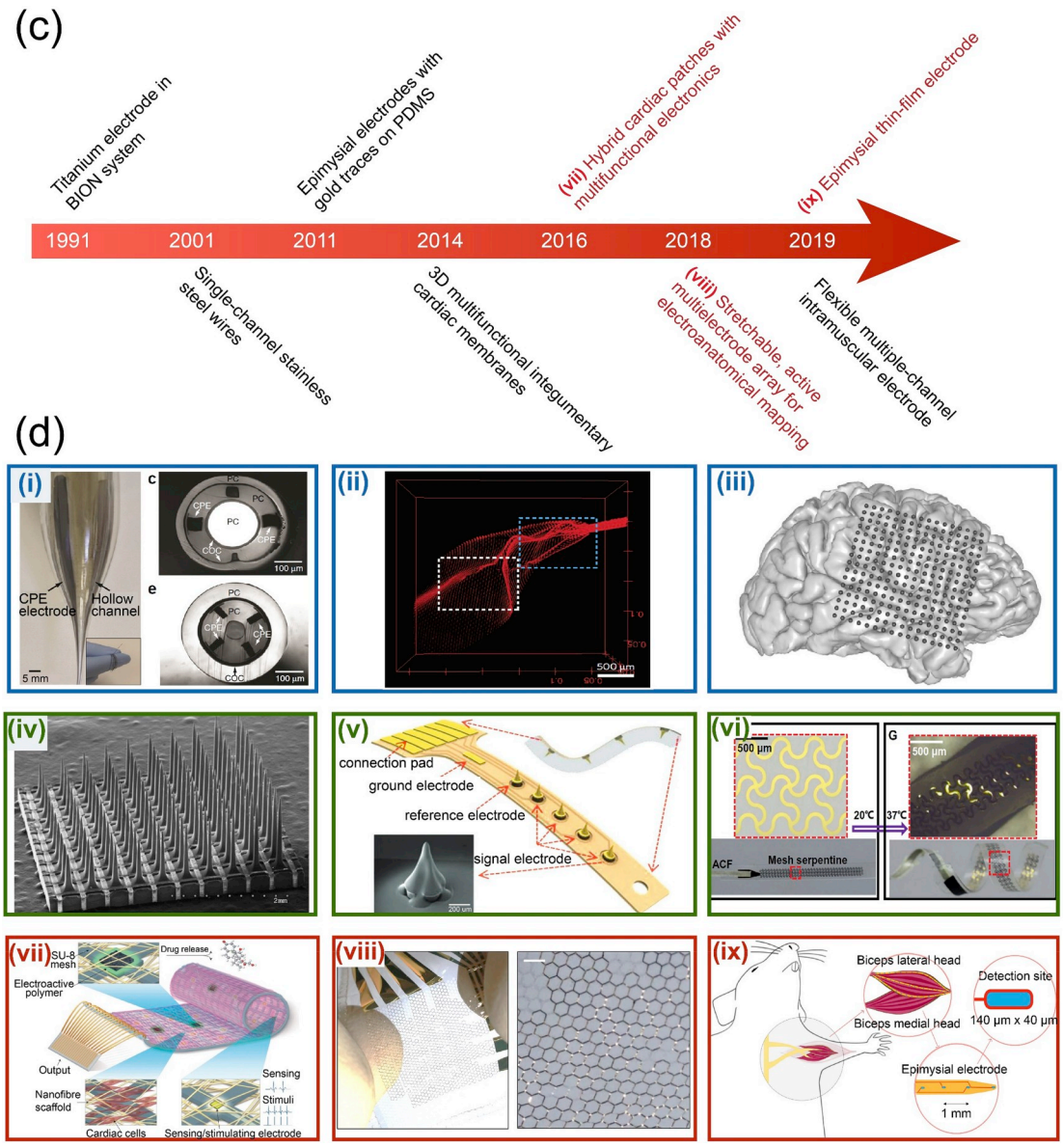

Fig. 2. (*continued*)

capacitive charge injection. In terms of faradaic charge injection, redox reactions are involved. It seems like the electrons just flow into the tissue from the metal electrodes, while the true physical process is that the electrons are transferred into the tissue in redox reactions. Thus, a resistor is used to characterize the faradaic charge injection. Electrodes made of materials that only employ faradaic charge injection are named perfectly non-polarizable electrode. Perfectly non-polarizable electrodes are ideal for recording, because they show the same impedance at all frequencies, so that not to induce filtering effect on signals of different frequencies. Faradaic charge injection may cause electrode corrosion, depending on whether the redox reaction is reversible. Materials employing reversible redox reaction can also be used for stimulation, and these materials often offer higher charge injection capability as compared to pure capacitive charge injection materials, which is desirable in stimulation.

The conventional active material is noble metal, such as platinum and gold [75]. However, platinum and gold suffer from low charge delivery capability, the electrodeposition method is developed to increase the surface roughness by introducing conductive polymer PEDOT-PSS and CNT [76,77]. In addition, shape memory alloy is demonstrated as an active material, to allow curling to tightly wrap around the biological tissue at the same time of providing conductive surface [78]. To allow simultaneous optogenetics observations together with electrical stimulation, graphene is developed as an optically transparent active layer [68]. Bioabsorbable active material including magnesium and silicon oxide opens a possibility to future transient electronics [71].

In addition to the consideration of electrode-tissue interaction, all neural interfaces have to fulfill general requirements to become approved as a medical device: they must not harm the body and should stay stable and functional over a certain life-time which is in most cases in the range of decades [79]. To not harm the body, the electrode materials need to be biocompatible. The biocompatibility can be considered in two aspects: surface biocompatibility (whether the material is toxic to the tissue), and structural biocompatibility (whether the material matches the mechanical properties of the tissue). All surgical procedures will cause an inflammatory response. If the electrode material fails to fulfill the biocompatibility requirement, the inflammatory response will get worsen. The inflammatory response includes both acute response and chronic response. Acute inflammation can be characterized by the presence of erythrocytes, activated platelets, clotting, and factors released from disrupted blood vessels [80–82].

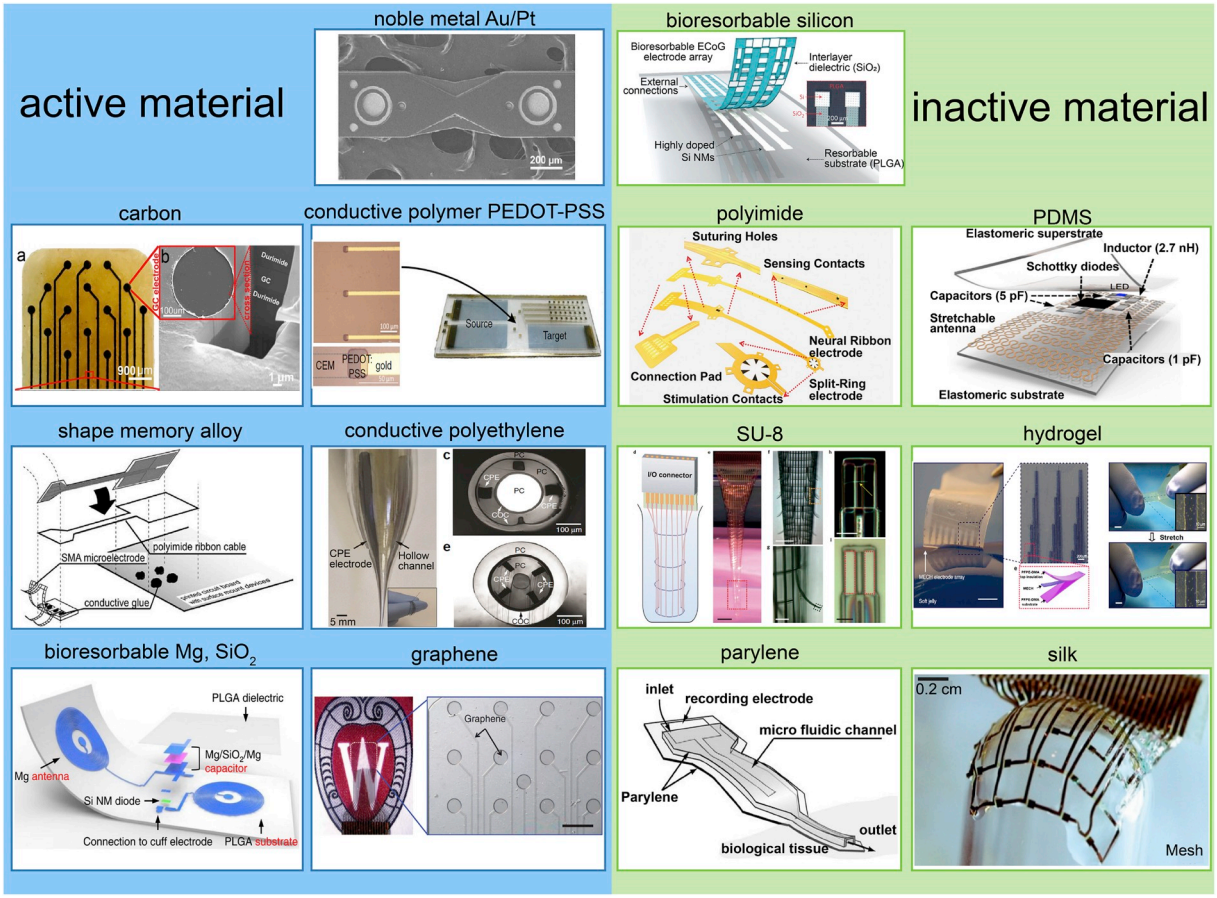

Fig. 3. Progress of neural interface active and inactive material development [53,67–69,71,72,76–78,83–87]

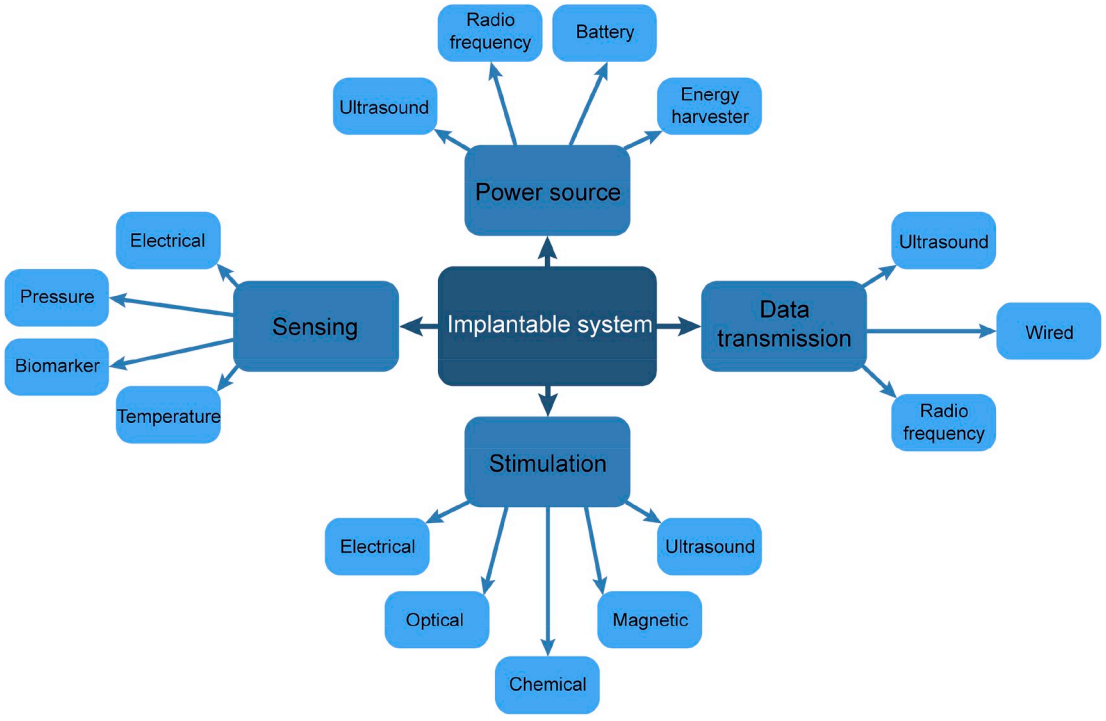

Fig. 4. Overview of the implantable system. Implantable system consists of four functional modules, including power source, data transmission, stimulation, and sensing module.

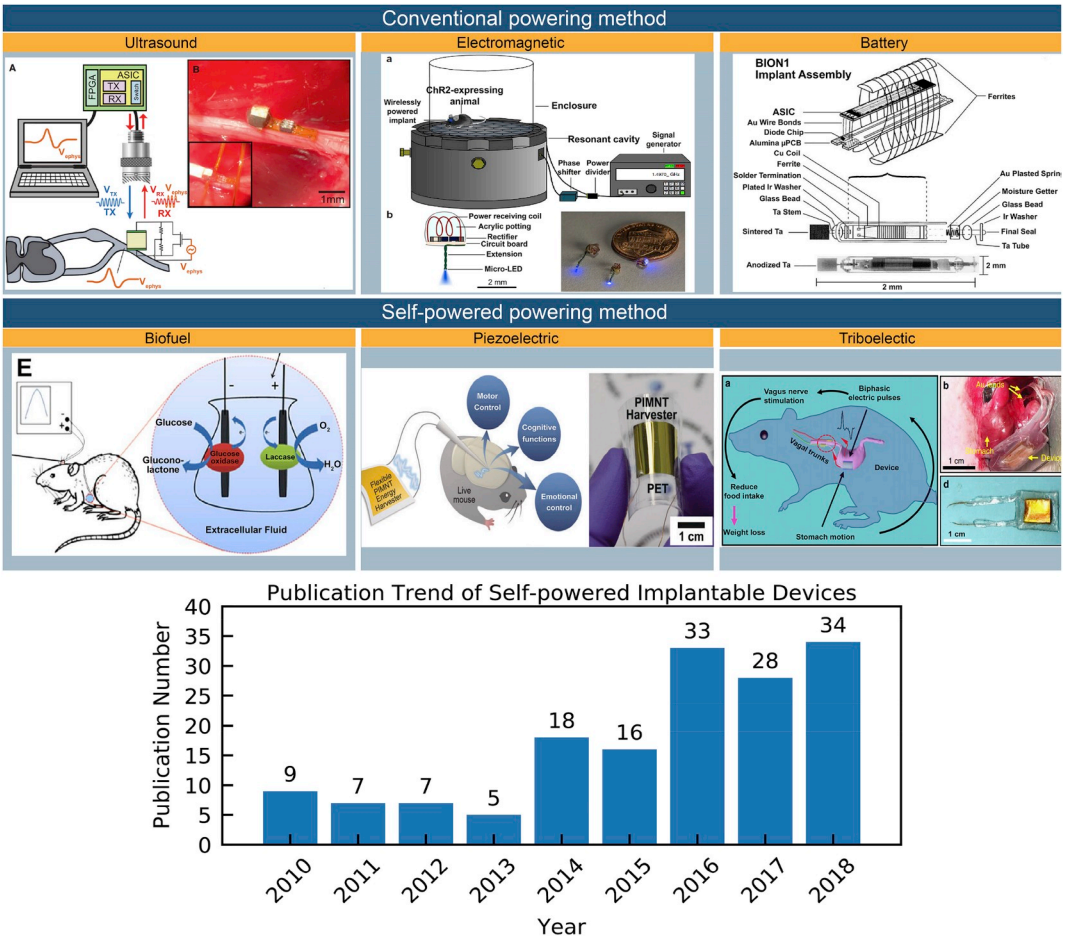

Fig. 5. Progress of current available powering solutions, including ultrasound [92], electromagnetic [15], battery [117], biofuel [102], piezoelectric [112], and triboelectric [111]. Summary of recent publications by searching for 'TS = ("self-powered" AND implant*)' in Web of Science.

Once acute inflammation declines, the chronic response will initiate, which can be characterized by the presence of both reactive astrocytes and activated microglia that form a glial scar. These glial scars will isolate the electrodes from the surrounding neural tissue, making it more difficult to either stimulate the tissue or record signal. In addition, the electrode materials need to be biostable to ensure long-term functionality after implantation. In vitro soaking tests, for example, in physiologic saline, Ringer's solution or cell culture media allow a first approximation of the biostability of the materials and are often performed at higher temperatures to accelerate the diffusion processes and thereby their influence on aging and the mean time to failure.

Polymer materials have been widely explored for the applications of neural electrodes. With considerations of biocompatibility and biostability, well-established polymer materials include polyimide [83], PDMS [83], Parylene [83], and SU-8 [84]. Compared to the rigid materials like silicon, these polymer materials match well with the tissue mechanical properties, which help to reduce inflammatory reactions caused by the implantation. Conventional silicon is engineered into ultrathin silicon layers to explore dissolvability of the silicon-based neural interface [84]. In addition, hydrogel is also employed as inactive substrate material, rendering the properties of high stretchability to allow accommodation to biological tissue movement [72]. Natural polymer materials are also used as inactive substrates, such as silk, which dissolves to enhance adhesion to the biological tissue surface [69].

5. Implantable systems – overview

Moving forward, neural interfaces are evolving towards implantable systems, to enable long term applications, including observational experiments on animal models, and translational therapeutic solutions. As shown in Fig. 4, a fully implantable system requires power source (supply power through ultrasound, radio frequency, implanted battery, or energy harvesters), data transmission (transmit power through ultrasound, radio frequency, or the wires), sensing modules (to record electrical signals, pressure, temperature, or concentration of biomarkers [88–90]), and stimulation modules (to deliver electrical/optical/magnetic/ultrasound/pharmacological treatment), to realize closed-loop control. Take the well-established pacemaker as an example, a pacemaker typically consists of a battery, a computerized generator, and electrodes. The electrodes simultaneously serve two purposes, on the one hand, they detect heart's electrical activity and send data through the wires to the computer in the generator, on the other hand, they deliver electrical stimulation to modulate and control abnormal heart rhythms. Similar close-loop principle also applies to diabetes therapy, which employs implantable continuous glucose monitor for blood glucose level to control implanted insulin pumps for drug delivery, and the on-going research targeting at vagus nerve stimulation to treat epilepsy, which employs implantable pacemaker-like devices to monitor brain activity patterns to detect seizures before they happen and deliver electrical stimulation or drug to stop the seizure.

With the knowledge of neural interface current status, we will move on to review the recent development and current status of power source, which used to be a bottleneck technology in the implantable

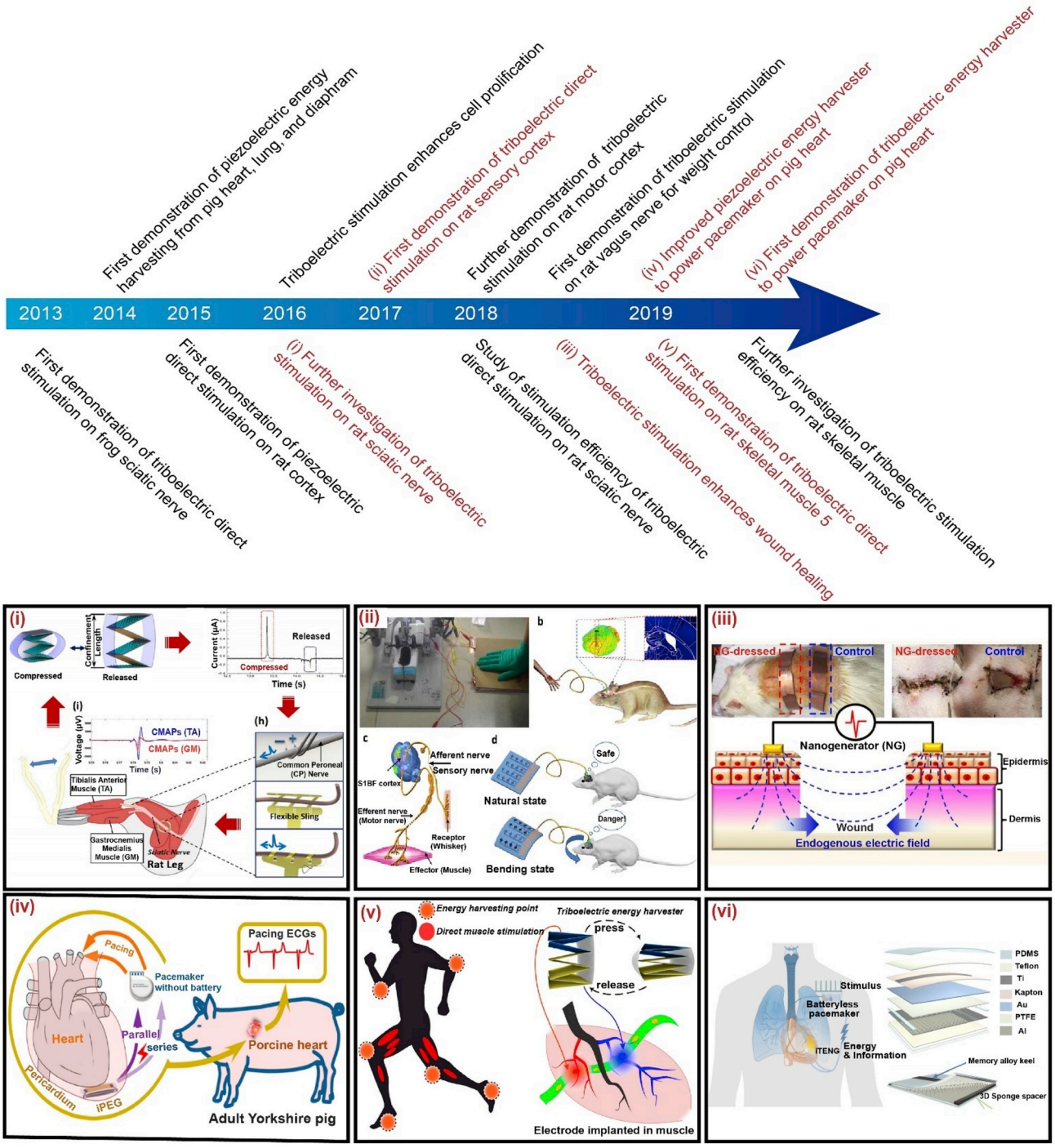

Fig. 6. Research roadmap of direct biological stimulation using piezoelectric/triboelectric energy harvesters [43,65,111,112,118–127]

system development. We will focus on the recent emerging energy harvester technology, and the novel demonstration of direct biological tissue stimulation using energy harvesters.

6. Implantable systems – power source solutions

Since the introduction of the first cardiac pacemaker in 1958, batteries have been the conventional solution for powering implantable systems. Although batteries are reliable energy sources with high energy density, and despite the features of low power electrical stimulation required by cardiac pacemakers, the cardiac pacemaker batteries still suffer from limited lifetime, which ranges between 5 and 15 years, and requires subsequent replacement. Besides the conventional batteries, powering solutions fall into two main categories, namely wireless powering, and self-power energy harvesting (Fig. 5).

Electromagnetic (EM) and ultrasound are commonly used for wireless power transfer [91]. EM power transfer can be generally classified into two categories, namely non-radiative (near-field), and radiative (far-field). Although EM power transfer is broadly used for implanted device powering, it has difficulty in powering devices deep in the body, as the electric or magnetic field (for near-field transfer) and the electromagnetic beam (for far-field transfer) suffers from dramatic decay in biological tissue. Another issue with EM power transfer lies in the high requirement of coil requirement, as a slight coil misalignment

decreases the energy transfer efficiency. Recent efforts on mid-field transfer show enhanced efficiency [15], however, it heavily relies on the proper engineering of source current and phase distribution in the antenna. In addition to EM power transfer, the recently reported ultrasonic energy transfer opens another possibility of wireless energy supply [92]. As compared to EM radiation, ultrasonic energy attenuates less in biological tissues and thus can achieve higher penetration depths. Although ultrasound technologies have long been used for other diagnostic and therapeutic purposes, the exploration of ultrasound energy supply for implanted devices has just started.

Besides wireless power transfer, self-power energy harvesting is receiving immense research attention in recent years [93–95]. Although wireless power transfer avoids the batteries' issues of limited lifetime and replacement, EM and ultrasound power transfer still requires an external energy source to supply power to the implanted device. A more desirable energy supply solution will be to harvest energy from biological tissues, whether it is due to body/organ motion or electrochemical energy, to ultimately eliminate the requirement of external power supply. Self-powered energy harvesting falls into three categories, namely biofuel energy harvester, piezoelectric energy harvester, and triboelectric energy harvester [96–101]. It is reported that implantable glucose biofuel cell based on carbon nanotube/enzyme electrodes generates sufficient power from a mammal's body fluids to act as the sole power source for electronic devices, by utilizing glucose oxidase for glucose oxidation and laccase for dioxygen reduction [102]. Different from biofuel energy harvesters, piezoelectric [103–105] and triboelectric [106–110] energy harvesters turn mechanical deformation into electrical power. By harvesting mechanical deformation energy from the contraction of heart, brain and vagus nerve stimulation are demonstrated by piezoelectric and triboelectric energy harvesters, respectively [111,112]. In recent years, there are emerging fully-implantable triboelectric energy harvesters [113–116].

Recently, there is an emerging trend of implantable self-powered energy harvesters. By searching 'TS = ("self-powered" AND implant*)' in Web of Science, which means search in title, abstract, and keyword for both exact "self-powered" and implanted or implantable or implants, we summarized the recent publication related to implantable self-powered energy harvesters in Fig. 5. The popularity and community of implantable self-powered energy harvesters gradually grew throughout these years and increased faster in recent years.

7. Direct stimulation with self-powered energy harvesters – current status

Piezoelectric and triboelectric energy harvesters can harvest mechanical energy generated by the contraction of organs and skeletal muscles, and it is possible to apply the collected energy for therapeutic purposes. In this way, a self-sustained system can be established as a treatment to some diseases. There is tremendous progress in the development of piezoelectric and triboelectric energy harvesters towards the self-sustained system (Fig. 6). For piezoelectric energy harvesters, in 2014, John A. Rogers's team first demonstrated a fully implantable system with conformal piezoelectric energy harvesting and storage from motions of the heart, lung, and diaphragm to power commercial cardiac pacemaker [65]. Later, in 2015, Keon Jae Lee's team reported direct cortex stimulation with the electrical current output from the piezoelectric energy harvester, which opens a new possibility to avoid using the complicated circuits and achieve direct cortex stimulation with the energy harvesters [112]. Furthermore, in 2019, Hao Zhang's team further improved the performance of piezoelectric energy harvesting from the motions of the heart [118].

Unlike the piezoelectric-based self-sustained system which was first developed as a fully implantable system in 2014 [65], only until recently in 2019, Zhou Li's team first successfully demonstrated fully implantable triboelectric-based self-sustained system which harvests mechanical energy from heartbeat motion and powers commercial pacemakers [119]. Despite the late report on the fully implantable triboelectric-based self-sustained system, there has been tremendous research achievement on exploring fundamental principles and various rehabilitation applications of employing triboelectric energy harvesters. In 2013, Haixia Zhang's team first demonstrated direct stimulation on the frog's sciatic nerve to induce muscle contraction using a triboelectric energy harvester [120]. Then, Chengkuo Lee's team and Xudong Wang's team individually demonstrated direct stimulation on the sciatic nerve, the pelvic nerve, and the vagus nerve by using triboelectric energy harvester, providing the fundamental knowledge on triboelectric stimulation efficiency and opened opportunities for wide applications on the peripheral nerve neuromodulation [111,121–123]. In addition to the peripheral nerves, triboelectric energy harvesters have been applied on cells [124], the cortex [125,126], to enhance wound healing [127] by generating an electric field. Different from the PNS and CNS with abundant neurons, skeletal muscles have much fewer neurons innervating the bulk muscle fibers. As a result, skeletal muscles have a much higher threshold as compared to the CNS and PNS. In 2019, the first paper reporting successful direct skeletal muscle stimulation using TENGs with μA-level output was published [43], and different approaches for muscle stimulation efficiency improvement are also reported [128,129], representing a step forward in the exploration of fundamental knowledge on triboelectric stimulation efficiency.

8. Summary and future perspectives

As shown in Fig. 7, in the past decades, neural interfaces have developed towards high density, multiple functions, reduced biological damage, and chronic implantation. Ranging from the commercialization of high-density brain probes, including the Neuropixels and Utah Electrode Array (UEA), to the exploratory stretchable peripheral nerve electrodes, neural interfaces have evolved for both CNS and PNS applications. In general, neural interfaces have evolved towards multiple-channels for high-resolution recording and simulation, multiple-

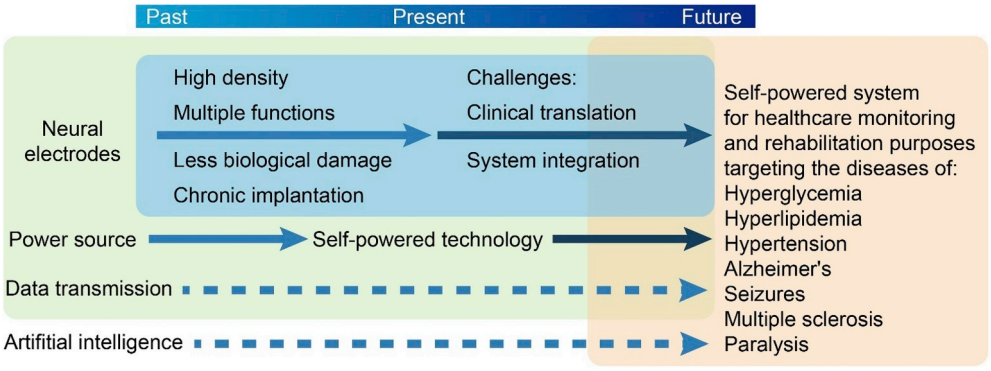

Fig. 7. Future perspectives.

functions with electrical/optical/pharmacological capabilities, and more flexible and stretchable to reduce potential damage to biological tissues. Parallel to the neural interface development, power source solutions have also evolved in recent years, from the conventional battery to wireless powering, and to the more recent self-power energy harvesters. Exciting progress is reported on direct stimulation using the piezoelectric and triboelectric energy harvesters.

Looking forward, new challenges of system integration with other functional modules and clinical translation are in front of the development of future neural interfaces. Neural interfaces show huge potential in healthcare monitoring of biomarkers, vital signs (body temperature, pulse rate, respiration rate, blood pressure), and bioelectrical signals. With the re-emerging of artificial intelligence into the scientific and public consciousness, augmentation or even transformation of neural interface applications is expected [130–132]. By integration with self-powered technologies, data transmission, and artificial intelligence, a close-loop implantable system can be realized. In this way, when a certain event is sensed, corresponding therapeutic intervention (electrical/optical/pharmacological) can be delivered to relief or eliminate the danger. Such event-triggered close-loop therapies optimize the intervention dosage and reduce social and economic cost of long-term monitoring of the patients. Although translating the research results into clinical applications is not straightforward, yet applications of neural interfaces have the potential to transform the conventional healthcare monitoring and rehabilitation methods. We wish to see the prosperous future development of self-powered intelligent systems for healthcare monitoring and rehabilitation purposes.

Acknowledgements

This work was supported by the following grant from the National Research Foundation: Competitive Research Project ‘Peripheral Nerve Prostheses: A Paradigm Shift in Restoring Dexterous Limb Function’ (NRF-CRP10-2012-01), and the grant from the HIFES Seed Funding: ‘Hybrid Integration of Flexible Power Source and Pressure Sensors’ (R-263-501-012-133).

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