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Toward advanced neural interfaces for the peripheral nervous system (PNS) and their future applications

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Abstract
Modulation of nerve signals from the peripheral nervous system (PNS) is a growing field of neurotechnology for therapeutic effects of the human body and for interfacing with neural prostheses. For this, neural interfaces, that provide the basis for direct communication with neuron tissues and mapping neural signals, are preferentially developed. Even though various types of peripheral nerve interfaces have been developed for many years, advanced neural interfaces need to be developed in conjunction with cutting-edge technology for the modulation of the human body and advanced neural prostheses. This paper reviews the evolution of peripheral neural interfaces (PNI) and their applications. The emerging requirements of the next-generation PNI are also explored.

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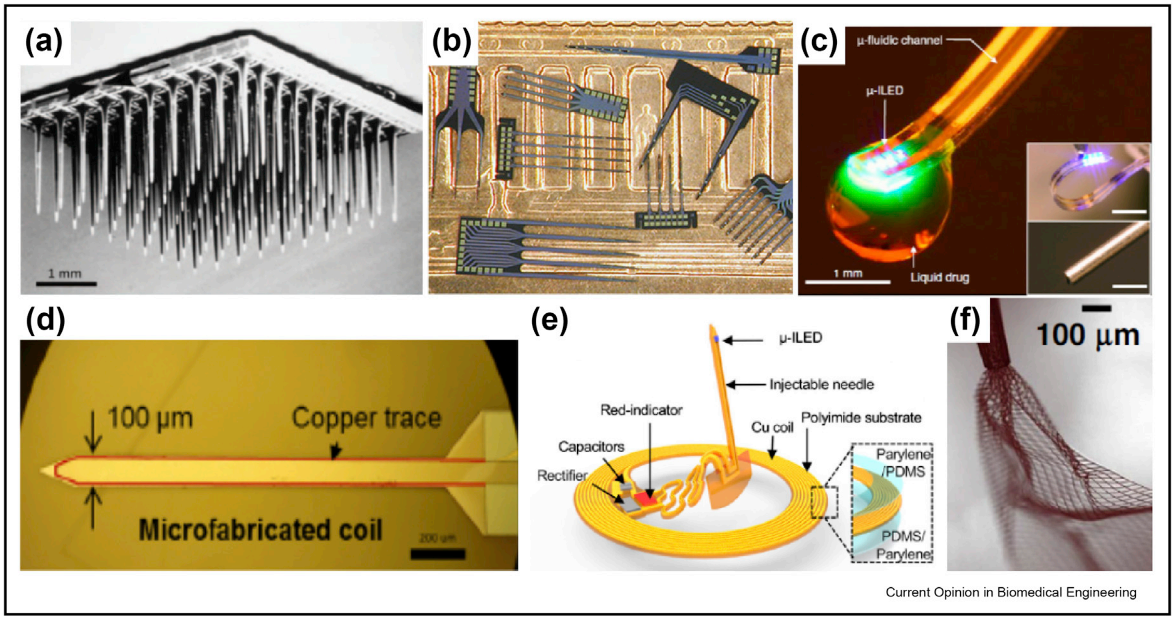
Bioelectronic medicine, Electroceutical, Peripheral nerve, Neural interface, Wireless neural interface, Self-sustainable platform.

Introduction

Neurotechnology has been developed for decades with the development of cutting-edge technology and neuroscience. From the discovery of electrical activity in the human brain in 1924 [1], variety of studies and tools have been demonstrated to explore the human brain. After demonstration of action potential recording from inside a nerve fiber by Hodgkin and Huxley in 1939 [2], neural electrodes have been widely used as a key tool to record action potentials from neurons or to stimulate neurons. Interfacing with the human nervous system opened new era of neurotechnology not only in neuroscience field to explore the human, but also in medical field to treat human neurological and psychiatric conditions. To investigate various neural characteristics of cortical and sensory areas in the brain, neural electrodes need to be implanted inside the brain. Multi-electrode arrays (MEA) such as Utah array (Figure 1a) [3] and Michigan probe (Figure 1b) [4] were designed and demonstrated using microelectromechanical systems (MEMS) technologies. However, higher density and resolution of neural electrodes are required constantly for a profound understanding of neuroscience, where limitations of those approaches are also reported. Accordingly, new approaches have recently been developed using optic (Figure 1c) [5,6], magnetic (Figure 1d) [7], and ultrasonic manners [8] for the next generation of neurotechnology. Those novel approaches meet with cutting-edge technology such as flexible and stretchable electronics (Figure 1e and f) [6,9,10], showing promising possibility of novel neurotechnology.

Another research trend has been developed to connect the human nervous systems to devices or robotic systems, called neural prostheses, replacing or enhancing sensory, motor, and cognitive modalities of the human [11]. Starting with cochlear implant development in 1957 [12], visual [13] and motor prostheses [14] have been demonstrated. Naturally, the target of neural interfaces extended from the brain to the spinal cord, and then to peripheral nerves, changing the type and requirements of neural interfaces. Brain neurons are located under stiff skull and connected complicatedly each other and, making precise and functional modulation difficult (Figure 2a). The spinal cord is a long, thin, tubular bundle of nervous tissue, acting as the main pathway for information connecting the brain and the peripheral nervous system (PNS) [15]. Furthermore, with newly reported results by M. Capogrosso et al., there is increasing interests in the brain-spine interface research to support locomotion after spinal cord injury (Figure 2b) [16]. Peripheral nerves extending from the spinal cord are functionally separated than the spinal cord and can be experimentally accessed with less risk than approaching the brain (Figure 2c). This paradigm-shift approach from the brain and spinal cord to peripheral nerves provides higher and promising possibility of modulating bodily function via peripheral and visceral nerves with cutting-edge technologies. This field is now requiring advanced neural interfaces, opening another era of neurotechnology.

Figure 1



Photos of (a) Utah array with 400 μm shank spacing and 100 channels demonstrated in human studies [3], and (b) several designs of silicon-based Michigan probes [4]. (c) A picture of microfluidic channel integrated with micro-ILEDs delivering light and drug simultaneously. The inlet image shows a comparison of the flexible device (top) and conventional metal cannula (bottom) [6]. (d) Schematic of the microfabricated coil consisting of a copper trace (red) on a silicon substrate (yellow) [7]. (e) Schematic illustration of the overall construction, highlighting a freely adjustable needle with a m-ILED at the tip end, connected to a receiver coil with matching capacitors, a rectifier, and a separate μ-ILED indicator [9]. (f) A bright-field microscope image showing partially ejected mesh electronics with significant expansion in solution [10].

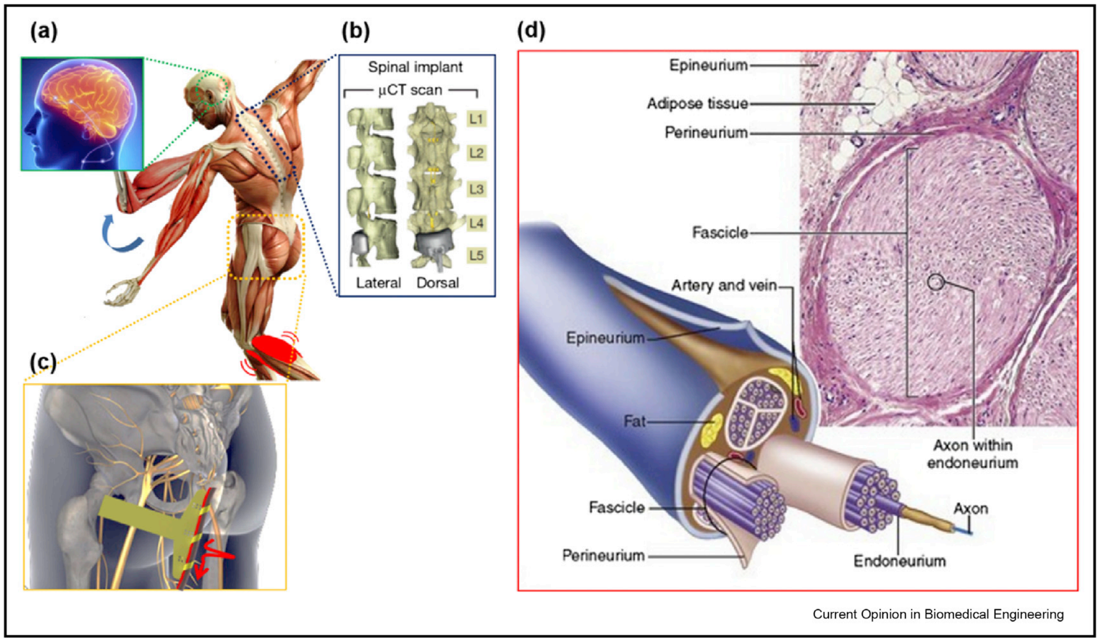
Neural interface for the peripheral nervous system (PNS)

Peripheral nerves have different anatomical and physiological characteristics compared with the brain and spinal cord. Axons are surrounded by insulating myelin, then bundled into fascicles which are further surrounded by dense protective outer layers, known as the perineurium and epineurium (Figure 2d) [17]. It makes us difficult to elucidate which specific pathways, or fascicles, signals are originating from. Furthermore, any neural signals that one may achieve to record are inherently weaker than the brain or cortex, and are always with additional interfering sources such as electrical signals, caused by muscle contraction, and movement artifacts that might corrupt measurements from peripheral nerves. In addition, nerves are typically affected by physiological motion (respiratory and cardiovascular movement) and kinematic movement (muscles and organs), so that considerable compliance and flexibility of peripheral neural interface are highly required. The ideal peripheral neural interfaces should have the highest selectivity for recording and stimulation with the minimal invasiveness. The neural interface should also be implanted for longer period without degradation of own functionalities. Due to the anatomical characteristics of peripheral nerves, selectivity and invasiveness are trade-off. Accordingly, various types of peripheral neural interfaces have been investigated for many years, such as extraneural (CUFF, FINE) [18,19], intrafascicular (LIFE and TIME) [20,21], penetrating (USEA) [22] and regenerative interfaces [23] (Figure 3a).

The regenerative interface may ultimately allow to interface a high number of nerve fibers for bidirectional communication between a nerve and a prosthetic device or system. However, it is difficult for regenerating fibers to reconnect to its original target since the fibers randomly grow. As a result, the success of functional recovery remains challenging. In addition, slow regeneration (1−2 mm per day) and progressive reduction in the capacity of Schwann cells to support regrowth result in neuronal apoptosis and muscle atrophy [24]. To overcome these issues, several approaches were investigated such as use in biomaterials [25,26] as well as applying external energies such as electrical stimulation [27] and pulsed electromagnetic fields [28].

Multi-electrode arrays (MEAs) also used for peripheral nerves as a penetrating interface. To minimize the number of redundant electrodes and to enhance the selectivity of fascicles within the nerve, Utah Slanted Electrode Array (USEA) was demonstrated for neuromodulation in the PNS [29]. Some critical issues, however, should be seriously considered for penetrating electrodes. Firstly, this interface typically has stiff

Figure 2



Schematic representation of neurotechnology in (a) a brain, (b) a spinal cord [16], and (c) peripheral nerves [40]. (d) Schematic diagram of peripheral nerve organization [17].

electrode arrays which are enough to be penetrated in nerves, leading to the damage of the nerve or fascicles as well as electrode during the implantation and movements of the object due to mechanical mismatch between the nervous tissues and the electrodes [30]. Secondly, selectivity is limited in the area where electrodes inserted. Thirdly, the large number of electrodes is not efficient for selective stimulation or recording as well as requires many wires and connectors, which demands additional and complicated mapping procedures.

Intrafascicular electrodes show a higher level of selectivity for stimulation and recording by implanting inside a nerve as well as has considerable compliance and flexibility for peripheral nerves using flexible materials [31]. However, the successful use of these interfaces strongly depends on implantation techniques such as an implantation angle between the electrode and a nerve, implantation depth and secure fixation of the interface on the surface of a nerve. Furthermore, it is doubtful to implant intra-neural approaches on autonomous nerves for electroceutical applications. This is because these approaches themselves potentially cause nerve damage [32], which leads to serious side effect.

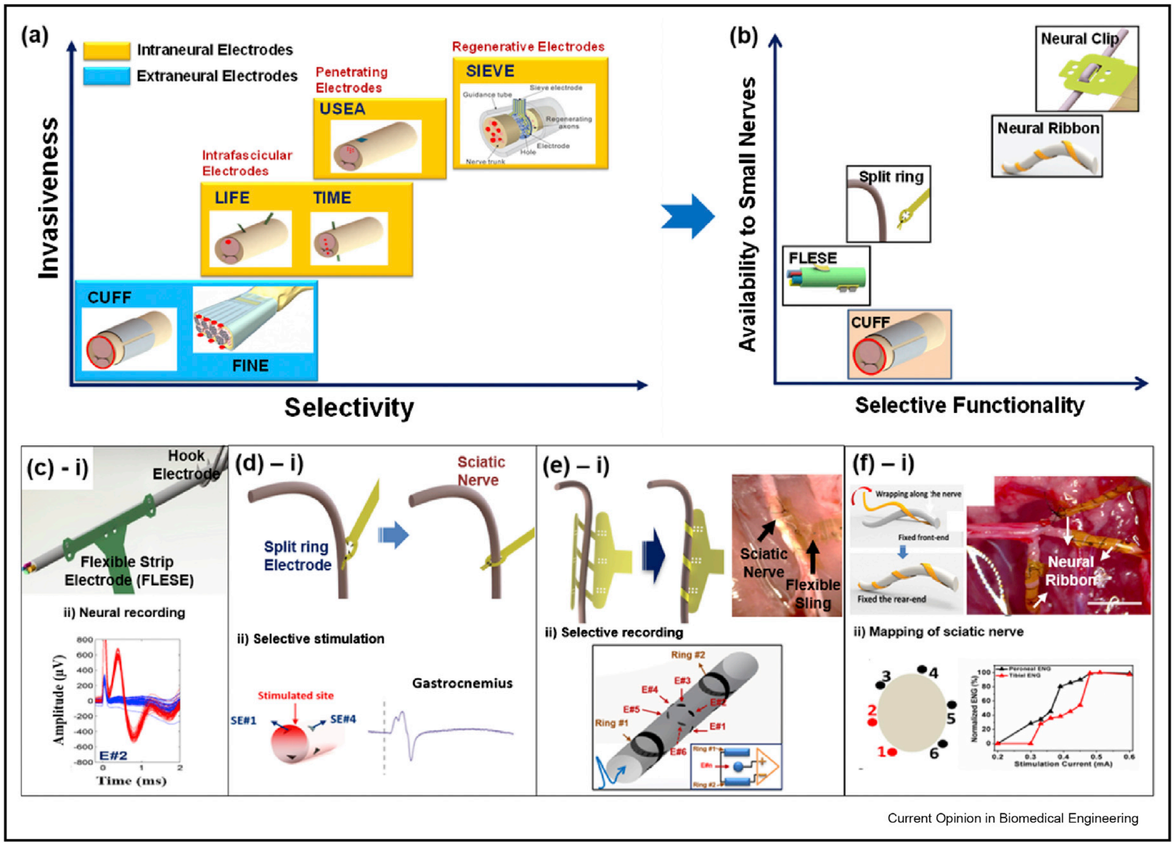
On the other hand, extraneural interfaces are relatively non-invasive approach and allow easy implantation, showing reasonable effective selectivity for stimulation [33]. However, the low signal-to-noise ratio (SNR) remains a major challenge of the cuff-type electrodes for recording since tight cuff for achieving close contact to a nerve could causes eventual nerve damage during long-term implantation [34]. In addition, a long length (at least 20 mm) of cuff is usually required for high amplitude signal recording when tripolar configuration of recording is used [15]. It is also limited due to higher possibility of foreign body response, biomechanical issues and difficulty of implanting on small nerves for long term implantations [35].

Recently, flexible epineural electrodes have been suggested and investigated (Figure 3b), where contact electrodes are closely on epineurium of nerves (Figure 3c) or partially implanted in epineurium (Figure 3d), not only to reduce pressure applied on the nerve, but also to enhance selectivity of recording and stimulation [36–39]. Selective stimulation and recording of rat sciatic nerves were demonstrated with less pressure on the nerve by the interface than that applied by a commercial cuff electrode (Figure 3e) [40]. The high quality of neural recordings was demonstrated in branches of sciatic nerves in a rat to map a sciatic nerve and leg muscles (Figure 3f) [41] as well as sensory information was decoded to restore sensory feedback [42].

Peripheral neural interface for neuroprosthesis and future direction

Neural prostheses are assistive devices or systems that replace or restore sensory, motor and cognitive functions of the human resulting from neural damage [11]. Cutting-edge bionic limb as a motor prosthesis has been developed with robotics, engineering, and 3D printing

Figure 3



Schematic diagrams of various types of peripheral nerve interfaces; (a) invasiveness versus selectivity and (b) availability to small nerves versus selective functionality; (c–i) Schematic diagram of flexible strip electrodes and (c-ii) the result of neural recordings [38]; (d–i) Schematic diagram of split ring electrodes and (d-ii) the result of selective stimulation [36]; (e–i) Schematic diagram and picture of flexible sling electrodes and (e-ii) the result of selective recording [40]; (f–i) Schematic diagram and picture of flexible neural ribbon electrodes and (f-ii) the result of mapping a sciatic nerve in a rat [41].

technologies to replace arms or legs of amputees. Sensory feedback plays an important role in improving the performance of the neural prostheses to achieve finer and dexterous movement control [43]. Natural touch perception was elicited by electrical stimulation on the peripheral nerves in amputees [44], and tactile sensations in patients who cannot benefit from peripheral nerve sensory stimulation was also evoked by intracortical microstimulation of the primary somatosensory cortex [45]. These studies have started to use fairly dense electrode arrays, which make difficult to stimulate neurons that represent different parts of the body as well as to represent different sensory modalities [46]. Currently, artificial sensors are employed on the skin surface to collect sensory information, however, it is difficult for these artificial sensors to substitute the functions of the natural tactile and proprioceptive receptors due to their density and complexity. These peripheral receptors, together with the primary sensory neurons that relay their signals to the CNS, are typically intact in persons with tetraplegia due to spinal cord injury. Recording of sensory signals from these primary sensory neurons that are part of the PNS, and the transformation of the information into a feedback signal, provides an alternative but yet relatively unexplored way to restore high-fidelity sensory feedback to persons with tetraplegia. With the recent developments of implantable self-powered energy harvesters [47], it may now be possible to realize long-term nerve recording for sensory feedback. The PNS of the upper and lower limb conveys both afferent sensory information to the brain and efferent motor commands to the muscles. Although the peripheral nerves are small in size, they are made up of several nerve fascicles holding hundreds of nerve fibers. As an example, the human median nerve trunk, which has around 20 nerve fascicles (with an average area of 0.16 mm^2), holds 20,000 axons [17]. Thus, an effective neural interface needs to record from a large number of nerve fibers in a highly selective manner. To achieve this, various intrafascicular multichannel neural interfaces have been developed, including LIFE, TIME, and UEA. To extend the UEA along the nerve fiber direction, it is desirable to integrate the penetrating microneedle electrodes with a flexible substrate, which will deform with the nerve. A manually integrated stretchable microneedle electrode array has been shown to maintain stable contact with the muscle tissue during electromyographic recording and stimulation [48]. However, the manual integration process lacks precision, repeatability, and scalability compared to standard microelectromechanical systems (MEMS) fabrication process. Recently, a highly selective 3D spiked neural interface was demonstrated to decode peripheral nerve sensory information [42]. Furthermore, prosthetic electronic skin was developed for mimicking the skin's ability to sense and generate biomimetic signals [49]. By integrating these two technologies, advanced bionic arms could be achieved (Figure 4).

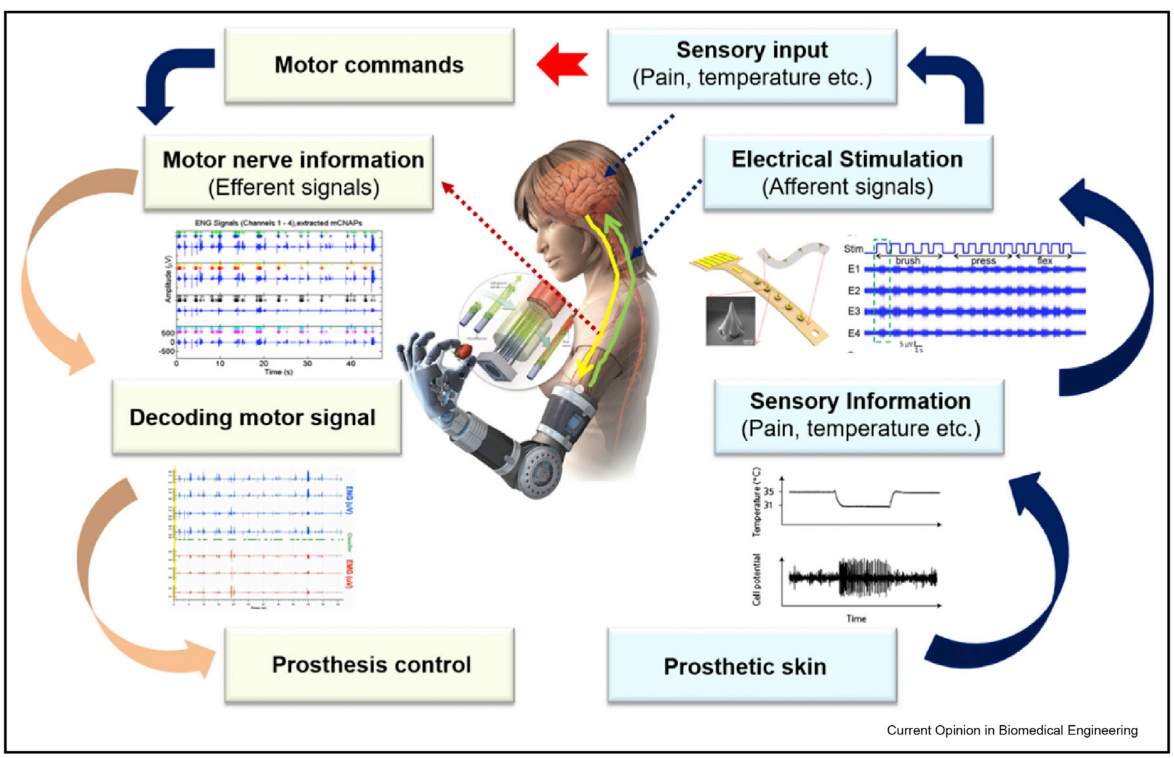
Advanced neural interface

With the development of cutting-edge technology of engineering and materials combined with neuroscience, neurotechnology is opening a new era of advanced biomedical fields. An advanced neuroprosthesis, which is replacing the bodily function, constantly requires an advanced neural interface, becoming parts of the human body.

This could involve active neural interface platform where integrated or wired with active component (such as amplifiers for neural recording and stimulators for neural stimulation). Furthermore, neural interfaces that have the capability of high quality of selective stimulation and recording are required to record motor intention signals as well as to stimulate sensory information on peripheral nerves. Emerging field of bioelectronic medicine or electroceutical is also requiring an advanced neural interface which could be closely attached to very small visceral nerves for high quality of recording and reliable stimulation as well as long-term usage without causing damage of nerves. Accessing such deep nerves associated with the autonomic nervous system is a grand challenge due to physiological and anatomical characteristics of the nerves. The nerves are highly compliant and associated with moving organs so that neural interface should have considerable compliance and flexibility. In addition, quick and mechanically secure implantation of neural interface is an important consideration in the presence of physiological motion such as respiratory and cardiovascular movements. Furthermore, such neural interfaces should target only the signals that elicit a desire effect without altering non-target functions since the autonomic nervous system has complex innervation of the organs or muscles [50]. This is because visceral nerves are vulnerable and the damage of visceral nerves cause consequence side effect that may finally case serious health problems.

Another requirement of the neural interface for this field is to achieve lasting effect of modulation, which requires long-term use of the interface with a reliable power source in the human body. Some feasible solutions include external energy sources, which are outside

Figure 4



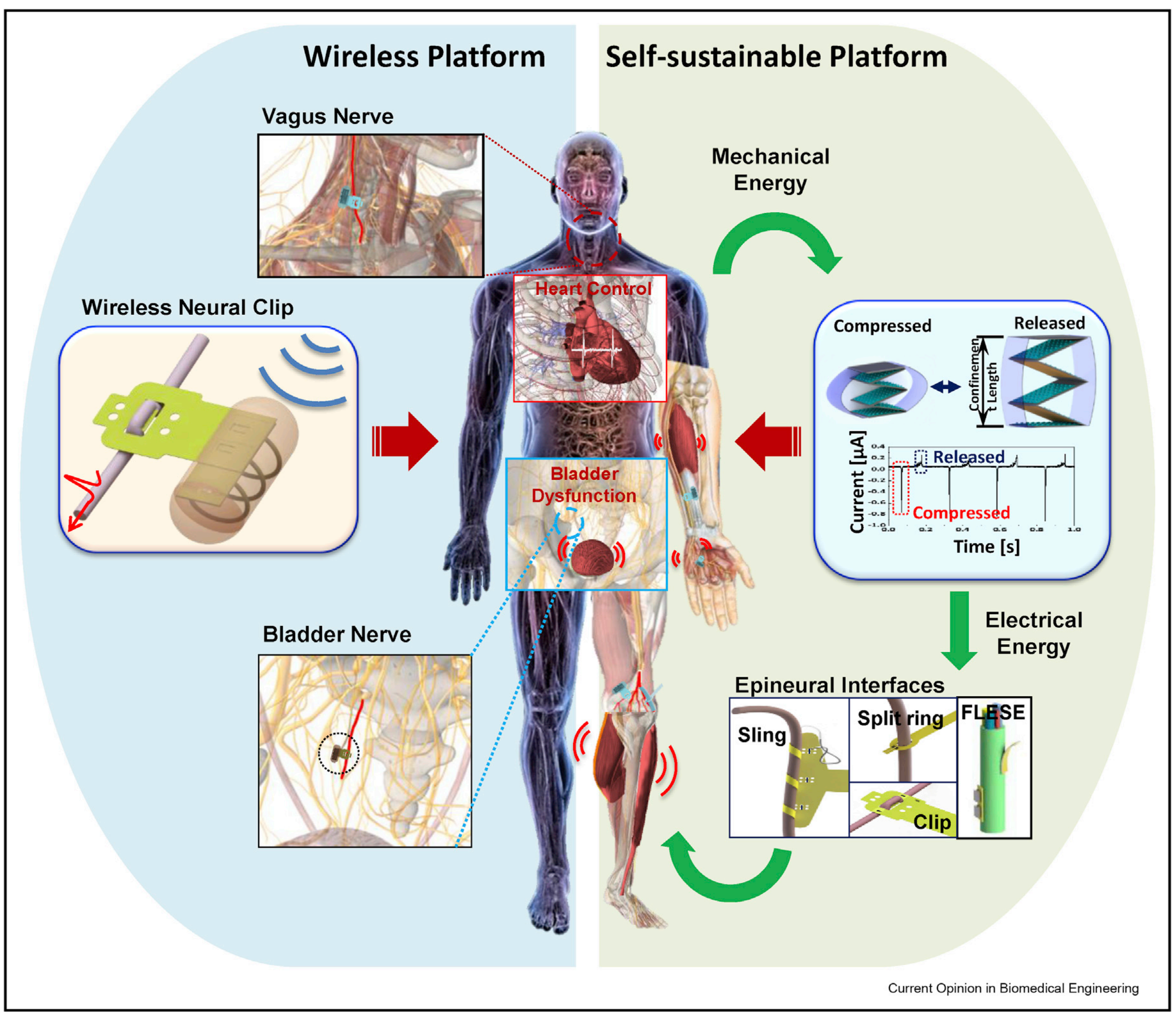
Conceptual diagram of the advanced bionic arm systems.

of body and provide energy to the devices via wired and wireless communication. The integration of neural interface with wireless powering by either ultrasound [51] or electromagnetic powers [52] is a promising direction for future bioelectronic medicine. Therefore, next generation of neural interface for bioelectronic medicine should have been adapted and miniaturized enough to interrogate visceral nerves non-invasively, wirelessly and securely.

Recently, nanoclip interface was suggested and demonstrated in a very small vagus nerve for stimulation and recording [53], but it still needs to be connected to the outside of sources or components via wires. High performance wireless powering at low gigahertz frequencies combined with neural cuff was demonstrated to regulate heart rate and blood pressure in a porchine animal model [54]. Flexible neural clip interface was suggested and demonstrated in branches of sciatic nerves, vagus nerves and bladder pelvic nerves for leg muscle activation, heart rate control and modulation of bladder function, respectively, then finally demonstrated wireless bladder modulation combined with the mid-field powering (Figure 5) [55].

Furthermore, the self-powered concept using various mechanisms could be a promising solution for achieving lasting effect of modulation, which is recently attracting significant attention for biomedical devices as a novel self-sustainable platform for long-term use [56]. For instance, triboelectric nanogenerators (TENGs), that are operated by any mechanical sources, generate rising exponential waveforms as an output signal which can be used for direct neuro-stimulation as a power source. This has an advantage in that a rising exponential waveform stimulated neuron more effectively than a square-wave pulse [57–59]. Previous study showed clear muscle activations with TENGs by stimulating a sciatic nerve and branches [40], and TENGs show a promising candidate for a battery-free stimulator

Figure 5



Schematic diagram of wireless and self-sustainable platforms for advanced neural interfaces and their applications.

(Figure 5b). Furthermore, comparative demonstration of the efficiency of nerve stimulation induced by exponential and square pulsed waveforms was verified that TENGs can effectively stimulate nerves and are good candidates for neurostimulators [60].

Also, with the development of cutting-edge self-powered device, any kinds of mechanical movements of muscles or organs from the human body could be used for sustainable power sources of TENGs. This could act as not only a battery-free stimulator by combining neural interfaces, but also a self-sustainable power source for neuroprostheses.

Summary and outlooks

Neural interfaces for peripheral nerve applications have shown promising potential in emerging research field, such as modulation of the human bodily function and fine connection with bionic prostheses. For neural prostheses, bidirectional communication between prostheses and peripheral nerves will be required with neural interfaces that record the high quality of motor signal to control the prosthesis as well as stimulate a peripheral nerve with sensory information to provide sensory feedback. For bioelectronic medicine, neural interfaces should non-invasively and securely stick on visceral nerves. Integration of energy sources with neural interfaces in small form factor may lead to novel self-sustainable neuroprostheses.

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Conflict of interest

The authors declare no conflict of interest.

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- •• of outstanding interest

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