Interfacing neuron-motor pathways with stretchable and biocompatible electrode arrays

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Conspectus

In the field of neuroscience, understanding the complex interactions within the intricate neuron-motor system depends crucially on the use of high-density, physiological multiple electrode arrays (MEAs). In the neuron-motor system, the transmission of biological signals primarily occurs through electrical and chemical signaling. Taking neurons for instance, when a neuron receives external stimuli, it generates an electrical signal known as the action potential. This action potential propagates along the neuron's axon and is transmitted to other neurons via synapses. At the synapse, chemical signals (neurotransmitters) are released, allowing the electrical signal to traverse the synaptic gap and influence the next neuron. MEAs can provide unparalleled insights into neural signal patterns when interfacing with the nerve systems through their excellent spatiotemporal resolution. However, the inherent differences in mechanical and chemical properties between these artificial devices and biological tissues can lead to serious complications after chronic implantation, such as body rejection, infection, tissue damage, or device malfunction. A promising strategy to enhance MEAs' biocompatibility involves minimizing their thickness, which aligns their bending stiffness with that of surrounding tissues, thereby minimizing damage over time. Yet, this solution has its limits; the resulting ultrathin devices, typically based on plastic films, lack the necessary stretchability, restricting their use to organs that neither stretch nor grow.

For practical deployments, devices must exhibit certain levels of stretchability (ranging from 20% to 70%), tailored to the specific requirements of the target organs. In this

account, we outline recent advancements in developing stretchable MEAs that balance stretchability with sufficient electrical conductivity for effective use in physiological research, acting as sensors and stimulators. By concentrating on the neuron-motor pathways, we summarize how the stretchable MEAs meet various application needs and examine their effectiveness. We distinguish between on-skin and implantable uses, given their vastly different requirements. Within each application scope, we highlight cutting-edge technologies, evaluating their strengths and shortcomings. Recognizing that most current devices rely on elastic films with Young's modulus value between ~0.5 MPa and 5 MPa, we delve into the potential for softer MEAs, particularly those using multi-functional hydrogels for an optimizing tissue-device interface, and address the challenges in adapting such hydrogel-based MEAs for chronic implants. Additionally, transitioning soft MEAs from lab to fab involves connecting them to a rigid adapter and external machinery, highlighting a critical challenge at the soft-rigid interface due to strain concentration, especially in chronic studies subject to unforeseen mechanical strains. We discuss innovative solutions to this integration challenge, optimistic that the development of durable, biocompatible, stretchable MEAs will significantly advance neuroscience and related fields.

Key References

- Jiang, Z.; Chen, N.; Yi, Z.; Zhong, J.; Zhang, F.; Ji, S.; Liao, R.; Wang, Y.; Li, H.; Liu, Z.; et al. A 1.3-micrometre-thick Elastic Conductor for Seamless On-skin and Implantable Sensors. *Nat. Electron.* **2022**, *5*, 784-793.[1] *This work*

reports the design and fabrication of an ultrathin elastic physiological MEA that can forms a seamless interface with rats' sciatic nerves, enabling high-fidelity neural signal recording and efficient neural modulation.

- Jiang, Y.; Ji, S.; Sun, J.; Huang, J.; Li, Y.; Zou, G.; Salim, T.; Wang, C.; Li, W.; Jin, H.; et al. A Universal Interface for Plug-and-play Assembly of Stretchable Devices. *Nature* **2023**, *614*, 456-462.[2] *This work reports a bind interface comprising of self-healing polymer and Au nanoparticles, enabling the simple assembly of stretchable MEAs and rigid components with tough interfacial strength for both 21-channel EMG detection and various acute bio-signals detection in vivo.*
- Pan, L.; Wang, H.; Huang, P.; Wu, X.; Tang, Z.; Jiang, Y.; Ji, S.; Cao, J.; Ji, B.; Li, G.; et al. Enhancing Prosthetic Control through High-Fidelity Myoelectric Mapping with Molecular Anchoring Technology. *Adv. Mater.* **2023**, *35*, 2301290.[3] *This work designed a soft hydrogel that can be coated onto stretchable MEAs to significantly reduce the impedance between devices and human skin, and as-fabricated MEAs can help disabled people manipulate a robot through EMG signals on the remaining limbs.*

Introduction

The discovery of unknown knowledge in neuroscience is accompanied by the invention of new techniques and tools. Among these tools, commercialized silicon-based physiological electrodes and sensors are widely used in laboratories, assisting researchers to understand the electrophysiological features of neural systems and to develop strategies to treat neural diseases[4]. For example, cell probes were developed to record the electrical activity of individual cells, including neurons[5]. This allows researchers to monitor parameters such as action potential and membrane potential changes, aiding in the study of cell function, physiology, and the effects of drugs[6,7]. Additionally, implantable high-density MEAs were utilized in studies related to neural repair and neuromodulation, enabling the stimulation of neurons to facilitate recovery or the monitoring of neural activity to comprehend the mechanisms of specific diseases[8-11]. Moreover, combined with prosthetic devices and machine learning, implants can help disabled people regain the capability to feel, move, and talk[12-15]. Despite the rapid development, there is an intrinsic limitation for current rigid MEAs that target chronic stable implantation: due to the huge differences between rigid devices and living tissues, strong body rejection and even organ inflammation can happen, resulting in device failure and/or threats to organ health[16-18].

Developing biocompatible physiological MEAs is urgently required for both hospitals and laboratories. For hospitals, such devices are safe and can be implanted for a longer time with better functionality[19]. For example, nanomesh-based MEAs with thousands of channels have been demonstrated to successfully record high-fidelity

neural signals in mice brains for 290 days without inducing strong body rejection, which outperforms the FDA-approved Utah electrode[20]. Such biocompatible MEAs show promise as human-brain interfaces for disabled people to regain the capability of feeling, walking, grasping, and talking in the future while bringing less damage to brain tissues[21]. For laboratories, the similar mechanical properties between tissue and devices may lead to discoveries of new behaviors and mechanisms because cell behaviors are different when they are cultured on substrates of different Young's modulus[22]. This theory can significantly influence the development of organ-on-a-chip for the screening process of drugs.[1] Therefore, recent developments of stretchable physiological MEAs have been focused on mimicking the mechanical properties of organs, including softness and stretchability, by designing new materials and structures[23-28].

Many of these stretchable physiological MEAs have been implanted on the surfaces of various organs in non-human primates, such as the heart, kidney, bladder, and the nervous system (including the cerebral cortex, deep brain, spinal cord, and nerve in **Figure 1**)[1,2,18,25,29-36]. Most of these flexible devices are adaptable to such 3D shapes due to their softness and low stiffness, while a seamless interface can only be achieved by certain types of devices. One is ultrathin devices that can be bent at a radius of several micrometers and thereby can fully replicate the microstructures of 3D tissue surfaces[1]. Another is hydrogel-based devices with Young's modulus of several kPa and good adhesion, which can be tightly bonded to textured surfaces under certain pressure[31]. Additionally, regardless of the targeted organs, the physiological electrodes have mainly two functions. One is used as a sensor to detect biological signals, and

another as a stimulator to deliver stimulus to tissues[37]. The signal type can be temperature, chemical concentration, PH, mechanical, and electrical signal, while the stimulus is usually mechanical, chemical, or electrical[38].

In this account, we focus the application scenery on the closed-loop neuron-motor circuit, summarize the latest progress on the device design and fabrication principles, introduce promising translational techniques from the application-driven perspective, and discuss future technologies toward stretchable physiological systems. For the fabrication principle of stretchable physiological electrode arrays, we mainly introduce the progress using polymeric materials, while hydrogel-based devices are listed as next-generation promising technologies. Next, we introduce two kinds of application-driven stretchable physiological electrode arrays for on-skin and implantation applications, which also have different device requirements. Then, we discuss the challenges for translational stretchable devices, mainly on multiple-functionality requirements and system reliability. We believe that reliable stretchable physiological MEAs with multiple functions will become a powerful tool in both academic research and industry related to neuroscience and beyond.

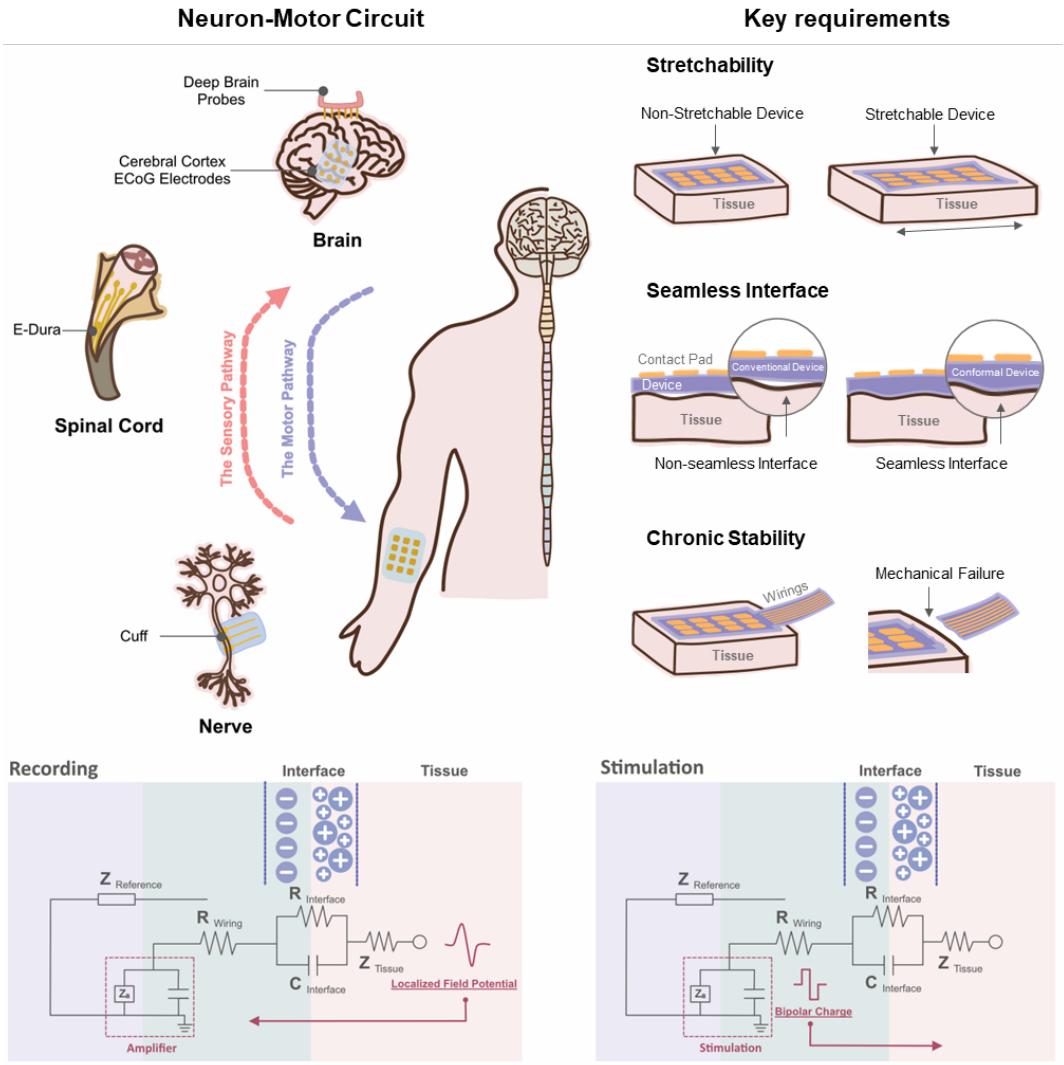

Figure 1. The concept and requirement of stretchable physiological MEAs as reliable and biocompatible interfaces for neuron-motor pathways and beyond. It is worth noting that chronic implants must be stretchable, form a high-quality interface with tissues, and maintain good stability over a long time. Their functionality, such as bio-signal recording and stimulation, highly depends on the tissue-device interfaces.

Fabrication approaches of stretchable physiological MEAs

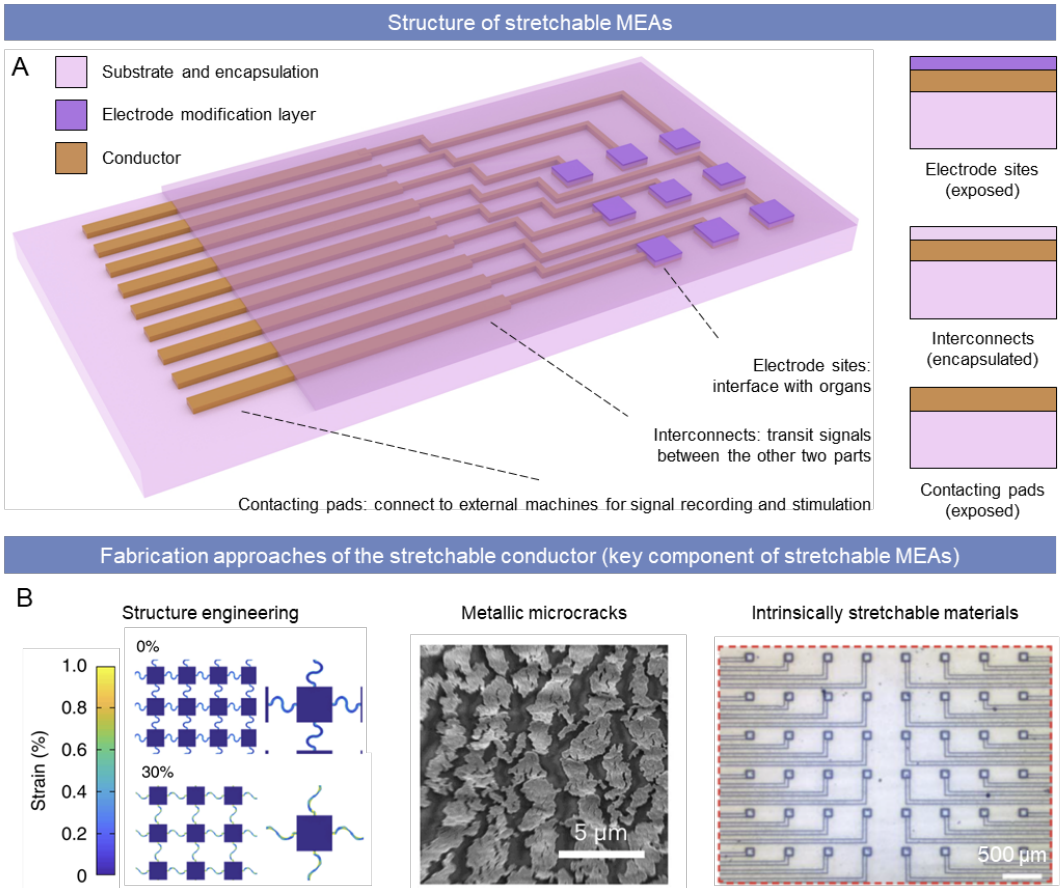

Figure 2. Structure of the stretchable MEAs and their fabrication approaches. A. Typical structure and components. From a device function perspective, stretchable MEAs consist of three parts: electrode sites interfacing with organs, interconnects, and contacting pads. Depending on the function of each part, their structure is summarized. **B**. Representative fabrication approaches for stretchable MEAs, including structure engineering (a stretchability of ~30%)[39], metallic microcracks (a typical stretchability of >100% strain)[1], and intrinsically stretchable materials[32]. Adapted with permission[39]. Copyright 2020 Springer Nature. Adapted with permission[1]. Copyright 2022 Springer Nature. Adapted with permission[32]. Copyright 2022 American Association for the Advancement of Science.

From a material perspective, physiological MEAs usually consist of 4 layers, including substrate, interconnection, encapsulation, and electrode sites (**Figure 2A**). The function of the substrate is to provide enough mechanical support and encapsulation from the bottom surface, and the function of encapsulation is to provide insulation for the underneath interconnections. The interconnection provides an electrical path between the electrode sites and tissues, and the electrode sites interact with tissues. The size, material composition, and surface structure of the electrode sites significantly influence their impedance and charge delivery capability, which have been summarized in previous reviews[37,44]. More attention should be paid to whether the electrode sites are mechanically durable and can remain stable *in vivo* for a long time and whether surface modification techniques of the electrode sites are compatible with the mass fabrication process.

To develop stretchable physiological MEAs, there are mainly three approaches, similar to the development of stretchable conductors but with higher requirements (**Figure 2B**). Based on stretchable conductors, stretchable physiological MEAs require a patternable encapsulation with exposed electrode sites and a surface modification process for the electrode sites in some cases. The first approach is the "structure engineering method", which involves designing stretchable structures that connect each electrode site to external readout circuits.[39] The stretchable structures can include serpentine, kirigami, and origami structures.[40] In this approach, the stretchability of the whole device depends on the stretchability of the structure and the ratio of dimensions between the serpentine interconnection and the electrode site. The advantage of this

approach is that it utilizes mature microelectronic fabrication techniques and plastic polymers with good encapsulation capability, and the devices are mechanically stable and strain-insensitive. However, the fabrication process is relatively complicated, and there is a trade-off between stretchability and array density.

The next approach is based on the stretchable micro-crack structure. Usually, the stretchability of metallic films, such as gold, aluminium, and copper, is limited to 1-2%.[45] Unlike conventional metallic films, when evaporating thin metallic films (50-100 nm) onto elastic substrates (for instance, Polydimethylsiloxane (PDMS) and Styrene-Ethylene-Butylene-Styrene (SEBS)), micro-cracks can form after the fabrication process possibly because of the thermal coefficient difference between metal and polymer[1,2,41]. Under stretching, these micro-cracks can propagate with strains while remaining on a conductive path. The encapsulation process for these stretchable conductors is usually very simple. In most situations, another layer of same-composition elastic film with patterns can act as the encapsulation. The encapsulation layer can be laminated to the stretchable conductive patterns, and the bonding between two parts can be achieved by plasma-assisted hydrogen bonding (for PDMS) or the self-healing process of the material itself (for SEBS). The advantage of this approach is that it is very simple and reliable. However, the resolution of this approach is usually limited to hundreds of micrometres because of the dimension of the micro-cracks. Also, there is non-negligible resistance increases when stretched, making it unsuitable for application scenarios involving substantial system deformation.

The last approach is to develop intrinsically stretchable materials, including

composites of insulating elastomers and conductive fillers, stretchable conductive polymers, and liquid metals[32,42,43]. These materials are usually in a format of paste or ink, allowing for suitability in solution-based processes like spin coating, screen printing, and inkjet printing. This, in turn, determines both the resolution of the conductive patterns and the methods used for encapsulation. For instance, screen-printed patterns usually have a resolution of several hundreds of micrometers while inkjet printing can achieve a resolution of several tens of micrometers.[46] After forming the conductive patterns, a matched encapsulation layer should be formed using a suitable printing process. It is worth mentioning that currently, high-resolution patterns with a feature size below ten micrometers can only be achieved by photolithography (on both the conductive patterns and encapsulation)[32]. Stretchable MEAs based on composites and stretchable conductive polymers have a similar limitation with those based on micro-cracks, i.e. non-negligible resistance increases when stretched. Fortunately, stretchable MEAs based on liquid metals usually are strain insensitive thanks to their fluid nature. However, there are still several technical challenges, such as suitable fabrication techniques for high-density MEA arrays, reliable encapsulation methods, and their chronic *in vivo* durability. To solve these challenges, it is urgently required to develop both new materials and reliable processing techniques.

As physiological MEAs, a higher resolution usually means a better capability to interact with several cells or even a single cell, which is the main driving force to downscale the resolution of the conductive patterns. For implantable MEAs that are inserted into organs, such as brains, spinal cord, and nerves, it is highly possible for

certain numbers of pixels to form intimate contact with neurons (axons for nerves), thereby decoding the neural signals and modulating the neuron-motor pathways with a high level of spatiotemporal accuracy. The limitation of inserting devices into neural tissues is that it brings damage to neural tissues and has a high-risk potential. On the other hand, in many applications, MEAs are only implanted on the surface of living organs. In this way, forming selective contact with a single or even a few functional cells is difficult because there are fluidic layers and protecting layers (such as mucosa for cavities and ducts, meninges for the central nerve systems, perineurium for the peripheral systems) between the device and functional cells. Therefore, depending on the targeted application, choosing a suitable material type with satisfactory resolution is recommended before optimizing the processing steps for stretchable MEAs. Considering more of the application-driven requirements, such as impedance, maximum strain, chemical durability, biocompatibility, and the reliability of processing techniques, is encouraged.

On-skin applications of stretchable physiological MEAs

As the largest organ, the skin plays crucial roles in protecting, sensing, regulating, and enhancing appearance, all of which are vital for maintaining overall health and functionality in the human body. Attaching electronic devices to skin enables researchers to detect various physiological signals, including Electrocardiogram, Electromyography (EMG), Photoplethysmogram, Electroneurogram, Electroencephalogram (EEG), softness, temperature, and chemical signals, which are important for understanding the health status of the human body.[1,47-50] Because on-skin

electronic devices are non-invasive, their applications are accessible to everyone, particularly older individuals who require specialized everyday care and ongoing physical monitoring. In on-skin applications, both EMG and EEG signals need to be gathered by a high-density physiological MEA.[3] With real-time signal mapping over multiple skin areas from limbs to brains, researchers can understand the detailed movement information or certain thoughts/emotions of the testee via the combination with machine learning methods.

The application of high-density physiological MEAs for on-skin EMG signal detection can contribute to the development of prosthetics for disabled people, thousands of whom suffer from the loss of hand function with limited physical incapacity. It is of high practical value to utilize the EMG signals from the remaining functional part of limbs to control a soft robot or a prosthetics to conduct a precise movement. The challenge is to gather a clear EMG signal pattern over a large area of the limb via a relatively small maximum voluntary contraction (MVC) of the muscle to achieve the distinction between different movements without compromising comfortability.[3] To overcome this challenge, it is of significant importance to develop suitable on-skin EMG electrodes with low impedance, which can contribute to improving the detection of low-level myoelectric signals (especially those less than 10% MVC). For example, our previous work designed hydrophobic poly(N-vinyl caprolactam) (PVCL) gel electrodes that can penetrate the stratum corneum layer of skin, thus reducing the skin barrier effect with a lower impedance and promoting a tough bonding with the skin at the same time (**Figure 3**). This hydrogel can be coated

onto the surface of a stretchable EMG electrode array composed of PDMS and metallic patterns with a micro-crack structure, enabling it to be easily attached to the human body.[3] Combined with wireless communication and machine learning, they developed a myoelectric prosthetic control system that can precisely control the movement of a robotic car (prosthesis). Apart from lowering the impedance between skin and devices, it is also important to consider the long-term functional capability of devices and skin health. Therefore, many efforts have been made to improve the adhesion between the device and skin under both dry and wet conditions. The easy dehydration problem of hydrogels and the breathability of the devices have also been addressed[1,51,52].

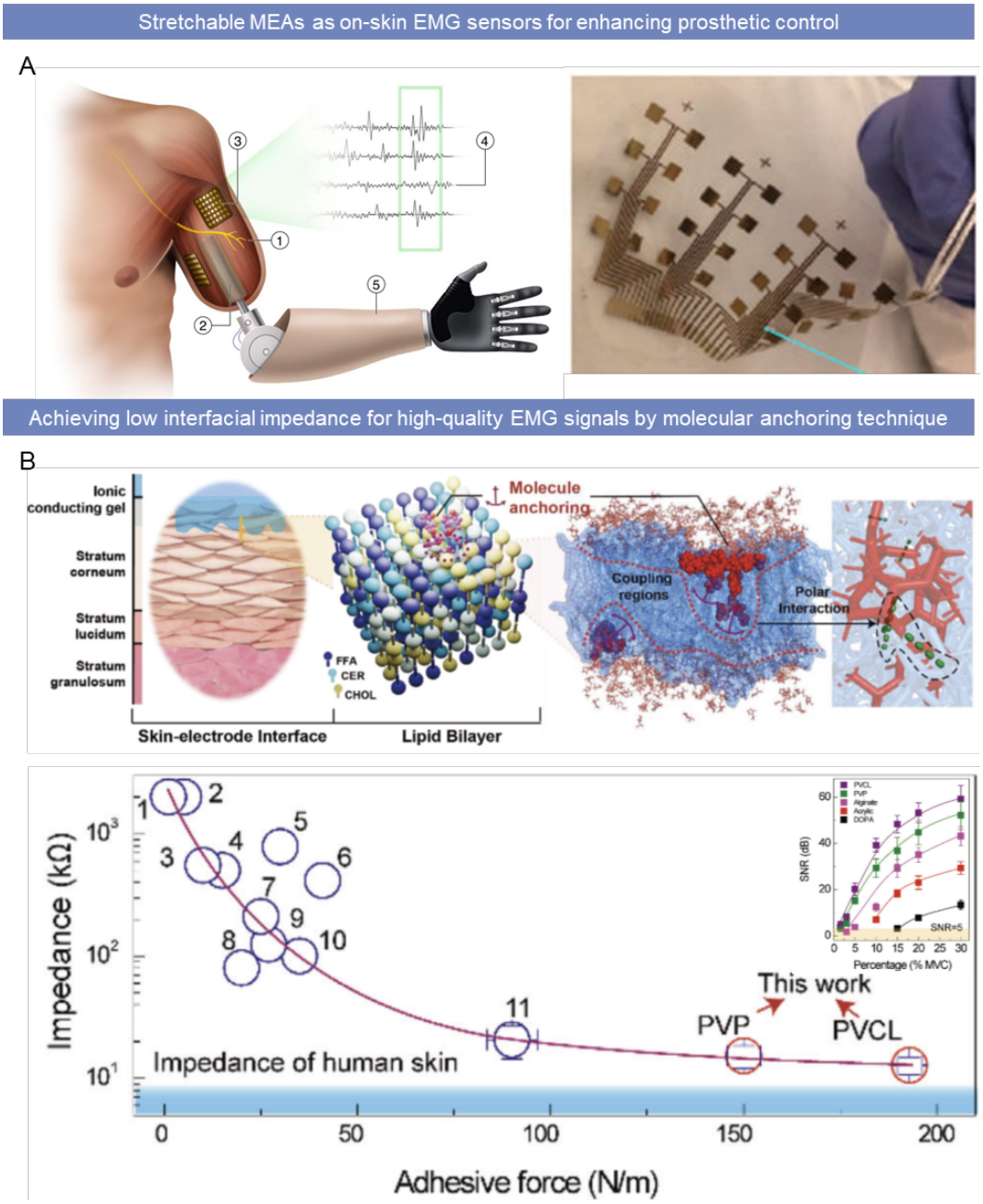

Figure 3. Stretchable MEAs for on-skin applications. A. Schematic showing the usage of on-skin EMG MEAs for controlling a prosthetic arm[53], and a photograph of a stretchable EMG electrode array based on PDMS and metallic micro-crack structure[3]. Adapted with permission[53]. Copyright 2023 Springer Nature. Adapted with permission[3]. Copyright 2023 Wiley-VCH GmbH, Weinheim. **B**. Schematic showing an ionic conducting gel electrode embedded into the stratum corneum layer of the skin (up),

which leads to a low impedance between the devices and skin (bottom) and high signal quality (inserted picture)[3].

Wearable EEG arrays are being used as non-invasive tools to decode brain activities. Compared with commercialized EEG electrode systems (mesh cap on the scalp with stiff metal electrodes), conformal stretchable EEG arrays are considered to be more user-friendly because they allow long-term signal recording in a skin-mounted mode, with no involvement of discomfortable rigid electrodes or sticky conductive gels and its frequent reapplication[54]. The conformal skin attachment of soft electrodes onto various brain locations, such as the forehead, outer ear (the auricle), and inner ear canal, facilitates brain-computer-interface related applications, including robotic limb control, sleep monitoring, emotion evaluation, etc[55]. Further multi-functional device integration with electrochemical sensors and power sources for body biomarkers analysis will contribute to detecting and monitoring neurodegenerative diseases.

Implantable applications of stretchable physiological MEAs

Physiological MEAs as neural interfaces have been proven to be a valuable tool for studying neural physiology and treating neural diseases[4]. Generally, neural systems consist of the central and peripheral nerve systems. Their requirements for physiological MEAs are different depending on their mechanical property and anatomical structure. Here, we summarized the representative techniques, focusing on the biocompatibility and tissue-device interfaces in different parts of neural systems.

The cerebral cortex, i.e., the brain's outermost layer, plays a critical role in

advanced cognition, perception, motor control, emotions, and thinking, enabling us to engage in complex cognitive and behavioural activities to adapt to different environments and tasks. Placing a stretchable physiological electrode onto the cerebral cortex involves craniotomy surgery (incising the cranial bone and dura mater), which is a high-risk surgical procedure[33]. Therefore, minimization of the incision (<1 cm^2) is considered to be a practical approach to reduce the risk of postsurgical complications, including inflammatory responses and scarring, morphological changes to the brain, and neurological deficiencies. This requirement is challenging because it requires the stretchable physiological MEAs to have a high resolution and array density. Additionally, considering that the space between the cerebral cortex and the skull is limited, stretchable physiological MEAs are required to have a relatively thin thickness without any possibility of exerting pressure on the cerebral cortex. For example, a deployable electrocorticography (ECoG) system was reported with the capability to be inserted through a small burr hole in the skull and unfold itself to form contact with the cerebral cortex over a large area (**Figure 4A**)[33]. The unique design with two layers of elastic membranes that were bonded at the edges enabled the actuation of the device by loading and unloading fluidic pressure, which led to the insertion of the deployable ECoG system. The deployable system (<400 μm thickness) with a layout of a three-by-four electrode array (0.3-mm diameter, 1.5-mm centre-to-centre pitch) can be used in an anaesthetised Göttingen minipig model and was able to record somatosensory evoked potentials at the surface of the brain in response to the electrical stimulation of the snout. At different electrode sites, the neural signals with peak amplitudes

reaching >30-μV displayed location-specific characteristics of amplitude and waveform.

Unlike the above application, which places stretchable MEAs on the surface of the brain cortex, deep brain applications insert devices into brain tissues. Since it is a high-risk surgery, the minimization of the insertion in three dimensions should be considered. Additionally, after insertion, there is a low possibility for devices to be stretched unless the brain grows. Therefore, one popular research direction of the soft MEAs for brain applications is to thin the device with a small in-plane area, and those devices typically are based on plastic substrates with a grid/mesh configuration[29]. For example, ultra-thin shuttle monolithically integrated mesh electronics (less than 1 μm) were reported, and they can be implanted across multiple brain regions with an open mesh structure (**Figure 4B**).[29] The open mesh structure can be interwoven with the neural network in the brain, enabling immune-response-free implantation and long-term stable 3D electrode-neuron integration (over the entire adult life of the mice until natural death). The challenge is that there is wiring between the mice and external recording systems, limiting the free movement of mice in the 3D environment. Adding certain stretchability to both soft MEAs and systems can be a potential solution in the future.

Apart from good biocompatibility and less tissue damage, improving the interface quality between tissues and devices is important. Conventional stretchable MEAs utilize a thick substrate of hundreds of micrometers. However, the space between neural tissues and other protecting layers is limited. Such thick devices potentially exert certain pressure on neural tissues, especially after the growth of the fibroblast layer around the

devices and also the change of body weight, leading to degraded tissue-device interfaces over time[41]. In our recent work, the thickness of PDMS films can be significantly decreased to 1.2 μm by spin coating diluted solution at high speed (**Figure 4C**).[1] We developed a protocol to handle such thin, soft elastic films, i.e. adding a temporary frame around it to avoid the curling. Then we formed the micro-cracked Au electrodes (50 nm) on it by thermal evaporation; the ultrathin PDMS-Au electrodes had a thickness of 1.3 μm, which is much thinner than that of facial stratum corneum (10-20 μm). Thanks to the ultrathin configuration, stretchable MEA with a cuff configuration can form seamless contact with rats' sciatic nerves (diameter of ~1 mm) while there is a clear gap between the nerves and a 100-μm-thick device. This seamless device-tissue interface facilitates the electron/ion coupling process, leading to a lower stimulation current threshold from devices to nerves to activate muscle contraction and low-noise, stable neural signals recorded by devices from nerves.

Another requirement of the tissue-device interfaces is the capability to customize them freely depending on different organs. Typically, different organs are of different shapes and dimensions. Therefore, it is important to form such shape-adaptive devices using simple techniques. For instance, a fully printed stretchable MEA was reported, whose components (substrate, wiring, electrode sites, and encapsulation) are all printed with different ink by different printing methods. In this way, it is easy to change both the array density and configuration of the stretchable MEA (**Figure 4D**) for different organs[25]. Moreover, even for one specific organ, it is important to customize the configuration of MEAs for the required functionality. Taking spinal cords, for instance,

it is important to achieve selective activation of a specific region because there is a clear definition of different sections of spinal cords, and each section is connected to different peripheral nerves for different functions. With this requirement, the same group further reported selectively stimulating different sections of spinal cords using customized MEAs, activating different muscles (such as musculus iliopsoas and musculus gastrocnemius)[25]. The decerebrated cats showed good foot placement and well-coordinated hindlimb movements in the step cycle[25]. It is worth mentioning that such selective activation of different muscles was reported to assist disabled people with spinal cord injury to regain walking capability by utilizing flexible electrodes based on polyimide substrate[14].

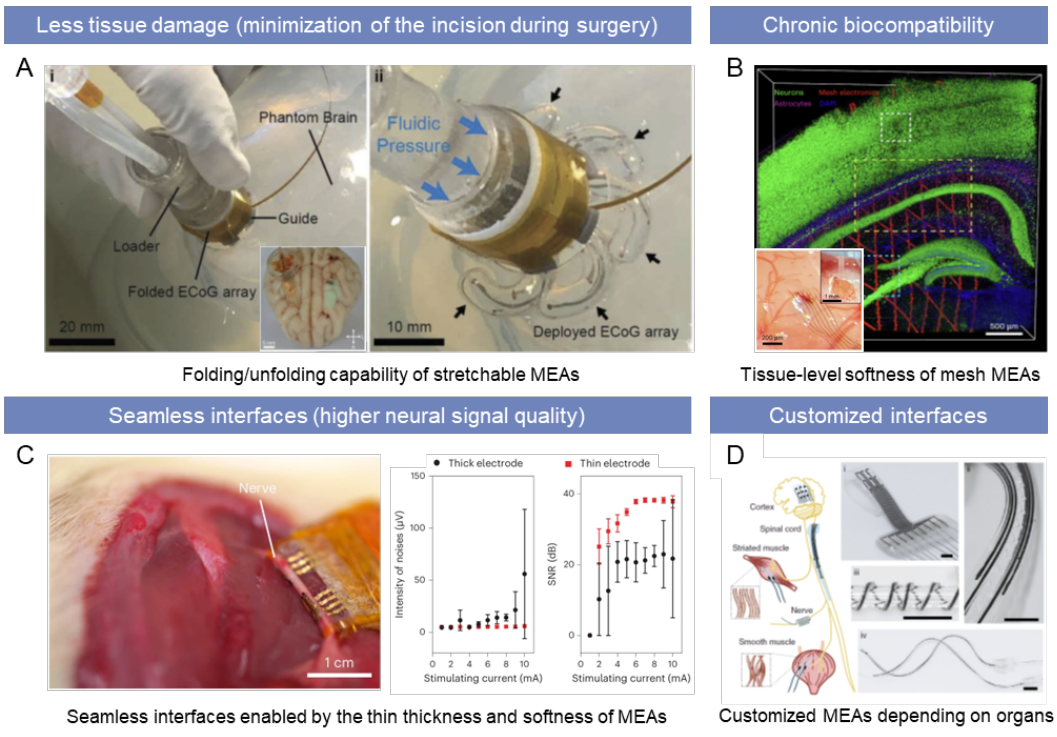

Figure 4. Stretchable MEAs for implantable applications. A. self-unfoldable MEAs that can be inserted through a minimized hole in the skull to contact the cerebral cortex. Adapted with permission[33]. Copyright 2023 American Association for the

Advancement of Science. **B**. Ultrathin bio-compatible MEAs that can be inserted into the deep brain to chronically record neural signals for a long time. Adapted with permission[1]. Copyright 2022 Springer Nature. **C**. Ultrathin MEAs that can form a seamless interface with peripheral nerves with a cuff configuration. Adapted with permission[25]. Copyright 2020 Springer Nature. **D**. Customized stretchable MEAs that can interface with various organs. Adapted with permission[29]. Copyright 2023 Springer Nature.

Emerging technologies of stretchable physiological MEAs based on hydrogels

The above-discussed stretchable MEAs are all based on polymers with Young's modulus of over 500 kPa. Recent advances in hydrogel-based MEAs show the possibility of further lowering Young's modulus of the device and achieving multiple unique functions for more specific applications, including high transparency, growth with tissue, and tissue adhesion (**Figure 5**)[18,31,56,57]. The first unique tissue-device interface is enabled by a highly transparent stretchable conductive hydrogel based on silk fibroin, poly(ethylene glycol), and poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS). The device achieved high transparency of >95%, high stretchability of ~260%, and moderate impedance[56]. It is further demonstrated that based on the highly transparent hydrogel, stretchable MEAs showed superior electrical recording and stimulation capability than the non-transparent controls in a rat photothrombotic acute stroke model. The second unique tissue-device interface is enabled by an all-printed adhesive stretchable MEAs, which were based on different

hydrogel materials for different layers, including hydrophilic polyurethane as the substrate and encapsulation, hydrophilic polyurethane/PEDOT:PSS as wiring and electrode sites, adhesive hydrogel as adhesion layer[31]. The same group demonstrated that adhesive stretchable MEAs can stably stimulate various organs, such as rat sciatic nerves, spinal cords, and hearts, for 4 weeks. The third unique tissue-device interface is enabled by a morphing MEA that can grow with rat sciatic nerves without exerting stress on nerves during their growth in 8 weeks[18]. This unique property was enabled by the mechanical property of viscoplastic polymer, whose stress under deformation can disappear gradually. The above advances in hydrogel-based soft MEAs can facilitate new functions and applications. However, for their translational applications, there are some challenges to be solved in the future, including the swelling issue and chemical residuals that may induce strong body rejection and the intrinsic *in vivo* stability that may influence the device's durability.

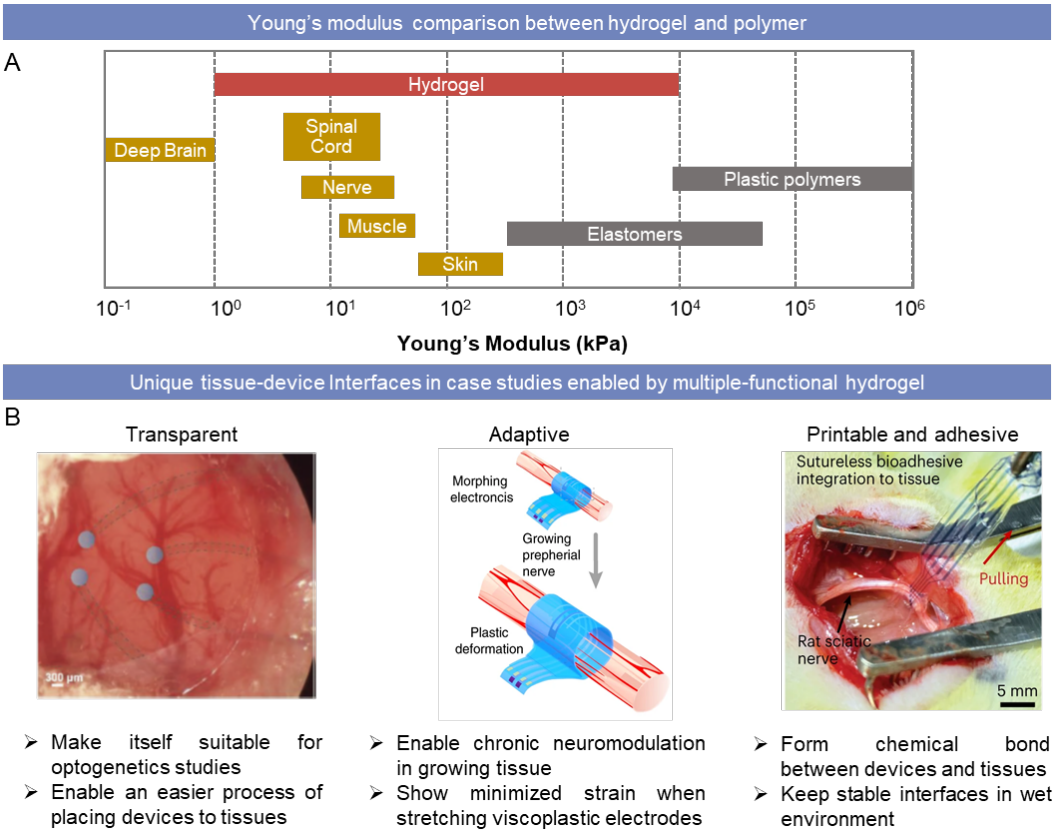

Figure 5. Hydrogel-based stretchable MEAs with unique tissue-device interfaces. **A**. A comparison of the Young's modulus values of different materials and organs. **B**. Unique tissue-device interfaces enabled by multiple-functional hydrogels, including transparent[56], adaptive[18], and adhesive features[31]. Adapted with permission[56]. Copyright 2021 Wiley-VCH GmbH, Weinheim. Adapted with permission[18]. Copyright 2020 Springer Nature. Adapted with permission[31]. Copyright 2023 Springer Nature.

Bottleneck of translation stretchable physiological systems

For translational stretchable physiological systems, a practical configuration is the combination of stretchable MEAs and flexible/rigid wirings that connect to external physiological machines. For both freely moving animal models and human-targeted applications, a wireless system with a few rigid components of limited volume is

desired[29]. In such a system, the bottleneck is the interconnection between the stretchable MEAs and flexible/rigid components. Using commercially available adhesive layers for bonding soft and rigid components, detachment at the interfaces between them can happen during deformation because of high-stress concentration, which will lead to the failure of the whole system (**Figure 6**)[58]. Additionally, mechanical failure was reported as the dominant failure mode in animal physiological studies[59]. To solve this issue, new bonding techniques and materials for bridging soft and rigid components have recently been developed[2,58,60,61]. For example, a universal interface was reported that can reliably connect soft devices with rigid modules in a plug-and-play manner[2]. This is enabled by developing a new stretchable conductor whose surface is composed of interpenetrating SEBS polymer and Au nanoparticles. The unique surface structure gives the SEBS-Au three properties: conductivity, stretchability, and self-healing capability. With the modification of this layer on the contact pads of other components, including flexible/rigid wirings and chips, stretchable hybrid systems were developed for on-skin EMG applications and acute implants in various animal models. Another report developed a stretchable anisotropic conductive film (S-ACF) that can electrically connect high-resolution stretchable circuit lines to other electrodes of different mechanical formats[60]. The S-ACF was composed of Au microparticles and a thin layer of SEBS, where the Au microparticles penetrate the thin SEBS to form a vertical electrical pathway, and the thin SEBS forms chemical bonding to another substrate whose surfaces have been modified. The advantage of this technique is the high resolution (~50 μm) and the anisotropic conductivity. Such novel bonding techniques

targeting soft/rigid interfaces have shown great promise in translational stretchable systems. However, there are still limitations to these new bonding techniques, including complicated requirements for surface modification on both soft and rigid components, concentrated stress at the interfaces, and reliability issues.

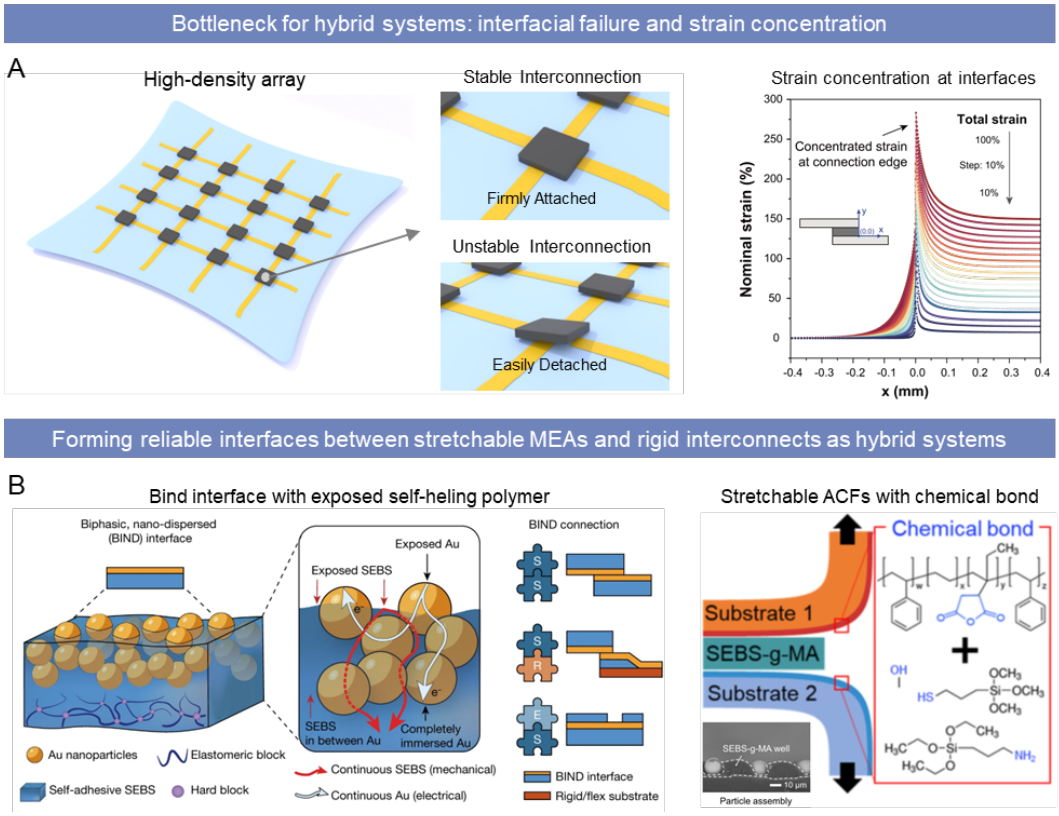

Figure 6. Developments for solving the bottleneck of stretchable hybrid systems. **A**. Illustration of the bottleneck of stretchable systems, including the detachment at the interfaces between soft and rigid components under deformation and stress concentration at their interfaces. Adapted with permission[2].Copyright 2023 Springer Nature. **B**. New materials for connecting soft and rigid components, including a bind interface with exposed self-healing polymer[2] and stretchable anisotropic conductive films (ACFs) with chemical bond[60]. Adapted with permission[60].Copyright 2021 American Association for the Advancement of Science.

Conclusion and Perspectives

In this account, we have systematically summarized the latest progress in the development and deployment of stretchable physiological MEAs for neuroscience and beyond. We have introduced state-of-the-art devices in each application and summarized their advantages and disadvantages in terms of fabrication methods, material innovation, practical durability, and biocompatibility. These stretchable physiological MEAs have been proven to be powerful tools in academic research. However, for their translation from lab to fab, there are still some challenges and potential future directions, as listed below:

1. Device performance improvement. Compared with rigid and flexible MEAs, there is still plenty of room for stretchable ones, including resolution, pixel number, areal impedance/charging capability, and *in vivo* chronic durability. Further device improvements will be possible by combining new materials, processing techniques, and device design.
2. System-level stretchability and bio-compatibility. Currently, most stretchable MEAs still need to be connected to rigid interconnections that connect to external machines. The rigid interconnections are usually embedded in muscles or under the skin and typically induce a thick fibroblast layer encapsulation. This undesired fibroblast layer can be a problem in the long-term implantation while attracting less attention. Additionally, the joints between soft devices and rigid interconnections are mechanically unstable, posing significant risks to the system during extended

implantation periods.

3. Neural signal comprehension and multiple-type signal gathering. Most stretchable MEAs demonstrate their functionality in acute signal measurement with healthy animals. The next step will be utilizing such valuable tools in chronic applications in disease models. Understanding the relationship between neural signals and animal behaviours is important for understanding diseases' causes and developing corresponding treatment strategies. Additionally, apart from electrical signals, gathering other types of signals, such as chemical signals and temperature, will certainly help provide a more comprehensive understanding. Finally, developing a suitable signal analysis protocol with the combination of machine learning methods will be necessary when analyzing a huge amount of signals recorded by high-density MEAs.

Notes

The authors declare no competing financial interest.

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Conspectus graphic