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Research Article

SOFT AND SELF-HEALING MATERIALS FOR NEURAL STIMULATION

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Abstract

Recently, soft bioelectronics have provided novel functionality to various kinds of device application. Neural stimulation and recording techniques play a critical role in understanding the complex functioning of the nervous system and developing effective therapies for neurological disorders. However, the use of conventional rigid materials in these applications often leads to limited biocompatibility, mechanical mismatch, and chronic tissue damage. In term of these requirements, alternative materials that offer softness, flexibility, and self-healing capabilities to improve the performance and longevity of neural interfaces have been developed for many years. In this paper, we review the development of soft and self-healing materials tailored for neural stimulation and recording applications. These new kinds of materials exhibit exceptional mechanical compliance, enabling seamless integration with the soft and dynamic neural tissues. They possess inherent stretch ability, allowing them to conform to the intricate shapes of the neural environment without causing excessive strain or mechanical trauma. Moreover, the self-healing properties of materials are a key feature, enabling them to autonomously repair any microscale damages caused by chronic usage or tissue movement. This property extends the functional lifespan of the neural interfaces, ensuring long-term reliability and minimizing the need for frequent replacements.

Keywords: Soft and self-healing, Neural stimulation.

INTRODUCTION

Neural stimulation and recording techniques have expanded our understanding of the nervous system and hold great promise for diagnosing and treating neurological disorders (Cogan, 2008; Das and Prusty, 2012). These techniques involve the use of neural interfaces, such as electrodes and recording arrays, to establish communication with the delicate neural tissues. Importantly, the biotic/abiotic interface is very important to for the interactions between bioelectronic device and biological tissue (Hong and Lieber, 2019; Farzin *et al.,* 2018). However, the traditional electrodes used in these interfaces, typically rigid and non-conformable, present several limitations that hinder their optimal performance and long-term viability. One of the key challenges faced by conventional neural interfaces is the mechanical mismatch between the interfaces and the soft, dynamic nature of neural tissues. The rigidity of these materials restricts their ability to deform or stretch in tandem with the surrounding tissue, leading to mechanical stresses and potential damage. This lack of mechanical compliance can result in chronic inflammation, scar tissue formation, and a limited lifespan of the interface, ultimately compromising the quality and longevity of neural recordings or stimulation. Moreover, the chronic use of neural interfaces is associated with various issues, such as device degradation and failure, due to repeated mechanical strains and fatigue. These challenges necessitate the development of materials that possess both stretch ability and self-healing properties to address the mechanical and long-term stability requirements of neural stimulation and recording applications. Stretchable materials can deform and stretch in response to the movements and expansion of neural tissues, minimizing mechanical stress and maintaining a stable interface between electrode and nerve (Figure 1).

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By matching the mechanical properties of the surrounding tissue, soft materials offer improved biocompatibility and reduce the risk of tissue damage or rejection. Additionally, the ability of these materials to conform to the intricate topography of the neural environment enhances the precision and effectiveness of neural stimulation and recording. In parallel, self-healing properties, which originates from novel chemistry, in neural interfaces can contribute to their long-term viability and functionality (Gai *et al.,* 2021). The ability to autonomously repair microscale damages sustained during chronic use or due to the dynamic nature of neural tissues can prevent performance degradation and the need for frequent replacements (Guimard *et al.,* 2011). Self-healing materials can also mitigate the risks associated with long-term implantation, such as chronic inflammation and foreign body responses, by maintaining the structural integrity of the interface and minimizing exposure of host tissues to potentially harmful materials. In light of these requirements, this paper aims to explore the importance and potential benefits of stretchable and self-healing materials for neural stimulation and recording applications. By addressing the limitations of conventional rigid materials, these advanced materials have the potential to significantly enhance the biocompatibility, mechanical compliance, and longevity of neural interfaces. The development of such materials holds great promise for improving our understanding of neural circuits, advancing neuroscience research, and enabling the development of more effective therapies for neurological disorders. Which is the biological path for providing nutrients and oxygen to all of our body, is essential part of our life.

Design and materials for stretchable electrodes

The use of metals in neural interfacing has been limited by their inert properties, which impede their interaction with surrounding tissues, leading to suboptimal performance. Metals are significantly stiffer than neural tissue ergo possessing a surface morphology that discourages tissue interaction.

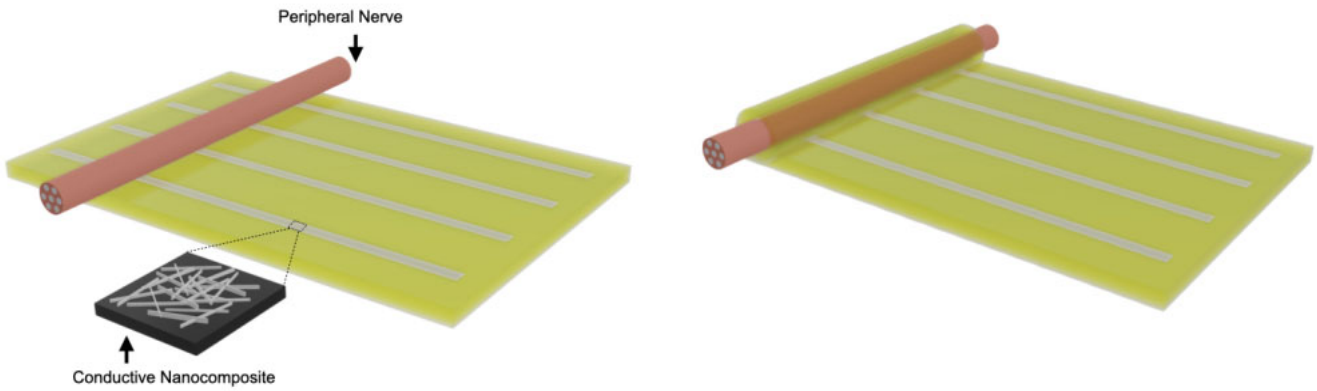

Figure 1. Schematic showing how to attach cuff electrode on nerve

Efforts have been made over several decades to modify metallic electrode arrays to create more flexible devices that can adapt to tissue movement and minimize inflammation (Heo *et al.,* 2016; Kaur *et al.,* 2015). Despite some success in developing flexible metallic arrays, challenges persist, such as the mismatch in strain and the absence of suitable sites for cell attachment, triggering a foreign-body response and the formation of scar tissue known as gliosis at the neural interface. In the past decade, researchers have focused on more complex materials that promote tissue interactions and enable more effective long-term neural interfaces. Organic materials, including conductive polymers (Lacour *et al.,* 2010), carbon nanotubes (McCallum *et al.,* 2017), hydrogels (Miao *et al.,* 2023) (including protein-based materials), and tissue-engineered constructs with cells, have gained popularity for developing advanced neural interfaces. These materials find applications not only in stimulating and recording devices but also in tissue engineering approaches for nerve and cardiac tissue regeneration. Organic electronics have emerged as a promising field, offering technologies that address the need for tissue-compatible interfaces while enhancing communication between tissues and devices. In particular, electro polymerized conducting polymers (CPs) have garnered significant attention due to their ability to transfer charge through both ionic and electronic mechanisms. To further optimize the performance of electrodeposited CPs, researchers have developed composite materials that allow for better control over the physicochemical properties. These composites enable tailoring of the mechanical, electrical, and biological characteristics of CPs. Hydrogels, elastomers, and biological polymers, such as proteins, have been widely explored as constituents of CP composites. Despite these advancements, challenges persist in the development of long-term neural interfaces, necessitating further research and innovation.

Conducting polymers (CPs) exhibit alternating single and double bonds (π bonds), creating a continuous pathway along their polymer backbone when effectively doped (Tian *et al.,* 2018). The delocalization of electrons along this backbone allows for the movement of mobile charge carriers, or dopants, resulting in electrical conductivity of CPs. Therefore, this reversible doping process enables intricate control over the electrical conductivity, spanning from insulators to metals. CPs can be synthesized through oxidative chemical or electrochemical polymerization, with negative counterions used for doping during polymerization to maintain charge neutrality. Although chemical polymerization is cost-effective for mass production, it offers less control over doping levels, leading to poor electrical conductivity.

PANI, known for its high environmental stability and ease of charge transport, has garnered relatively less interest in neural interfaces due to reported issues with cell adhesion and growth. PPy, extensively investigated for neural applications, demonstrates superior solubility in water, excellent mechanical actuation, a flexible preparation method, and cytocompatibility. On the other hand, PEDOT, a newer CP, exhibits high electrical conductivity, outstanding chemical stability, and in vivo biocompatibility, establishing its dominance in the research field of CPs for neural interfacing over the past decade. An ideal CP should have a high charge-transfer capacity in an aqueous environment to function effectively as an electrode. However, rough CPs formed with smaller dopant anions (e.g., PEDOT/pTS) tend to have fragile mechanics, limiting their use in implantable devices. Smoother CPs (e.g., PEDOT/PSS or PPy-based films) offer improved biocompatibility due to cohesive film properties but compromise charge-transfer capacity and may delaminate during electrical cycling. Ultimately, a trade-off between mechanical, electrical, and biological properties must be considered, as there is no single combination dominating the field. While conducting polymers (CPs) possess favorable qualities as neural interfacing materials, their full potential observed in vitro has not yet been fully reflected in the in vivo environment. There are two primary challenges that hinder the performance of homogeneous CPs in the biological setting: their mechanical properties and the occurrence of scar tissue encapsulation. Conventional electrodeposited CPs tend to be stiff and prone to fragmentation, with elastic moduli typically ranging from 1 to 8 GPa. These materials often experience significant material loss, when applied as coatings, exceeding 15% in tape tests conducted according to the standards set by the American Society for Testing and Materials (ASTM). Moreover, CPs have been observed to delaminate under electrical stimulation therefore limiting the application of electrodeposited CPs as standalone materials and prompting the development of new electroactive hybrids or composite materials with softer and more robust mechanical properties. Examples include CP-hydrogel blends, CP-elastomer combinations, carbon nanotube composites, and CP nanotubes with gel-like cores. Although the electrical properties of CPs can be preserved when combined with hydrogels, there is ongoing interest in further enhancing the mechanical performance of CP-based materials. Researchers have explored fully flexible bioelectronics that eliminate the need for metallic substrates, leading to neural interfacing devices without metal tracks or electrodes. Hydrogels offer softening properties to CPs, mitigating material loss, but they still exhibit brittleness and can experience delamination and cracking, thereby

compromising the electrical connection. CP composites have yielded a variety of flexible and multifunctional materials that can be tailored for specific tissue-interfacing applications. However, their long-term performance in vivo remains relatively unknown, with only a limited number of acute studies reported in the existing literature.

Soft self-healing materials and its mechanism

Advanced functional materials play a vital and indispensable role in our daily lives, serving as the foundation for numerous technological advancements. The development of materials has always been driven by the relentless pursuit of cost-effective solutions that exhibit exceptional strength, durability, and reliability. In conventional way, these materials primarily consisted of natural resources, which underwent basic processing techniques such as alloying and compositing, primarily to fulfill structural or passive functions. However, as technology progressed and our understanding of material science expanded, more scientific characteristics are required for materials that could be precisely tailored to meet the specific demands of various applications. This demand leads to the concept of "smart" materials, which possess the remarkable ability to respond to selected stimuli in a controlled and predetermined manner. Among the diverse classes of smart materials, self-healing materials have emerged as an area of intense focus and research over the past decades. Self-healing materials exhibit a fascinating capability to autonomously repair damage, thereby extending their functional lifespan and enabling them to withstand harsh operating conditions. This remarkable characteristic has drawn intensive attention of scientists, engineers, and researchers, who are increasingly exploring the potential applications and possibilities offered by these materials.

In recent years, the pursuit of smart materials capable of withstanding a multitude of environmental stresses, including oxidation, radiation, abrasion, impact, thermal decomposition, and moisture, has garnered increasing attention. The central aim of this research is to develop materials that exhibit self-healing properties, mirroring the regenerative abilities observed in living organisms when they sustain injuries. The potential benefits of such self-healing materials are manifold and encompass enhanced security, prolonged lifespan of components and systems, reduced incidence of failures, and diminished maintenance and cost requirements, all of which hold immense significance across diverse industries. While certain polymers display inherent self-healing capabilities, the vast majority of these common materials necessitate human intervention for repair, employing conventional methods such as resin injection, reinforcing patch application, or welding. These methods, however, often result in repaired regions that are weaker than the rest of the material, compromising overall structural integrity. Furthermore, the challenge of dealing with damage in inaccessible areas further accentuates the need for alternative self-healing approaches. The ultimate objective in designing self-healing materials is to achieve healing at the microscopic or even nanoscopic level, effectively arresting crack propagation and restoring the material's original physico-mechanical properties. Researchers have primarily explored two main avenues to attain this goal: intrinsic healing through the establishment of reversible chemical bonds and extrinsic healing by incorporating a pre-added healing agent that can be triggered upon damage occurrence. Self-healing materials can be broadly categorized based on their response mechanisms. Some materials autonomously initiate the healing process in response to mechanical damage, ensuring timely restoration without external intervention. Conversely, other self-healing systems require predetermined external triggers, such as optical, thermal, electrical, ballistic, or chemical stimuli, to activate the healing process. In both cases, the primary objective is to mend microscopic cracks before they propagate and lead to catastrophic failure, effectively extending the material's longevity and reliability. Over the past decade, significant strides have been made in the development of diverse self-healing materials, each offering unique capabilities and characteristics. While some materials exhibit autonomous healing properties, others require specific external conditions or human involvement to trigger the healing process. Understanding the intended application of the self-healing material is crucial in assessing its suitability for a given context. Factors such as healing rate, repeatability of healing at the same fracture point, restoration of physico-mechanical properties, system complexity, stability, and cost play pivotal roles in determining the viability and practicality of these materials.

In the pursuit of self-healing materials, early developments focused on mechanisms triggered by mechanical cues. One notable example is the reinforcement of concrete with cyanoacrylate-filled fibers, which was later extended to polymer composites. Additional advancements included two types of self-healing fiber-reinforced polymer (FRP) systems: a two-part reagent system and a two-part system where one component is encapsulated or embedded within the polymer matrix. Extensive research has been conducted to optimize various parameters such as fiber or capsule thickness, diameter, size, concentration, healing agent, catalyst type, and incorporation method. These optimizations aim to enhance the controlled release of healing agents and the subsequent polymerization rate upon encountering a mechanical trigger. To improve stability and cost-effectiveness, recent efforts have focused on using alternative components instead of air-sensitive and expensive materials like Grubbs' catalyst. For instance, a tin-based catalyst has been utilized to catalyze the polycondensation of siloxane-based macromonomers released from microspheres. While FRP and microcapsule-based systems share similarities, the latter provides greater flexibility in tailoring material properties through careful selection of microcapsule material, size, and concentration (Xue *et al.,* 2015). The use of microencapsulated repairing agents offers advantages such as autonomous healing, adaptability to different polymers, and the potential for achieving quantitative healing. However, the development of an ideal system remains a goal as the optimal approach depends on the specific application. Ongoing research focuses on discovering new, stable, and straightforward encapsulated healing agent-based systems that possess desirable properties. A significant limitation of self-healing FRPs and micro/nanocapsule-polymer composites lies in their inability to repeatedly heal the polymer at the same location due to limited distribution of healing agents. To address this challenge, researchers have turned to biomimetic self-healing polymer systems inspired by the capillary network of the dermis layer in animals. These systems feature refillable microvascular networks, allowing for multiple healing cycles at the same fracture site. Although human intervention is required to replenish the microvascular network with healing agents, this approach surpasses the capabilities of FRPs and microcapsule-based self-healing polymers. While extrinsically self-healing materials have

demonstrated advantages for specific applications, there is a growing interest in developing autonomously and intrinsically healing materials composed of dynamically bonding components. Current research focuses on reversibly bonded materials with the aim of designing materials with tailored properties for specific applications. These materials rely on dynamic bonds capable of repeated healing at the same damage site. Autonomously self-healing bonds, such as supramolecular interactions including hydrogen bonding and metal-ligand complexation, have shown promise. However, materials solely based on these supramolecular interactions often exhibit limited physico-mechanical properties, making them less suitable for industrial applications. Nevertheless, ongoing studies aim to overcome this limitation and explore other dynamic bond types, both covalent and non-covalent, that require heat, light, or chemical stimuli to trigger healing. With these self-healing polymers, we could fabricate self-healing conductive composite for bioelectronics. As similar with previous methodology, conductive particle or polymers could be embedded in self-healing matrix. When the mechanical damage arise, composite could be healed autonomously due to re-crosslinking of matrix, allowing conductive particles or polymers to be rearranged for conductive path. In terms of it, self-healing conductive composite has both mechanical and electrical healing property as shown in Fig. 2.

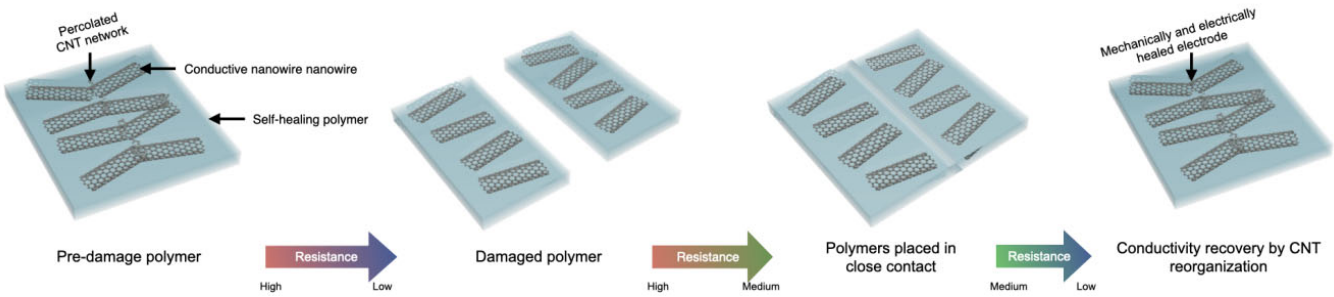

Figure 2. Schematic showing self-healing mechanism of conductive composite

Cuff electrode for neural stimulation and recording

Recording Devices

The literature on in vivo performance of Conducting Polymers (CPs) has primarily centered around their application as recording electrodes for brain-machine interfaces, research, and diagnostic devices. However, a significant challenge in this area arises from the size discrepancy between conventional metal electrodes and individual cells. The larger size of metal electrodes restricts researchers to sample only a few neurons out of the billions present within an organ, making the study of large networks of neurons problematic. To overcome this limitation, researchers have proposed the use of electrodeposited CPs, which offer the advantage of fabricating smaller, more sensitive electrodes capable of detecting action potentials from individual cells. The reduction in electrode size Small area electrode not only improves sensitivity but also allows for the miniaturization of the electrode array. This miniaturization is shown to be beneficial during thefor implantation process, as it helps could minimize damage to neural cells. Implantation trauma is known to create a "kill zone" around the implanted device, hampering the recording of neural activity in the device''s vicinity from cuff electrode. Several studies have been conducted to investigate the effectiveness of CPs as recording electrodes, and while some short-term results have shown promise, the long-term efficacy of CPs in this context remains largely unknown due to the limited time frames of the studies. In subchronic and chronic studies, foreign-body reactions have been observed to reduce the number of active recording channels, as scar tissue encapsulates the electrodes regardless of their coating type. This encapsulation process usually occurs within one to two weeks after implantation. Additionally, the use of stiff probe arrays for cortical tissue penetration may trigger an adverse immune response due to their limited ability to move with the cortex''s pulsatile motionrigidity that suppresses the pulsatile motion of cortex‘s. As a result, it is suggested that using a softer CP may not significantly improve the tissue interface, which is often dominated by the mechanical mismatch of the array. Two critical metrics for assessing recording electrodes are the signal-to-noise ratio (SNR) and the number of cell events or units detected. In most in vivo studies, CP-coated electrodes initially demonstrated improvements in both SNR and unit detection, as they exhibited an average halving of electrode impedance, leading to higher SNRs and spike counts. However, this positive effect was not consistently sustained across all reported studies. Specific materials, such as hydrogels, did not prove effective in enhancing the neural interface.

Although composites of CPs and hydrogels showed promise in mitigating the mechanical difference between stiff metal probes and soft neural tissues, they presented challenges related to swelling properties. Recently, a novel approach involving the direct electrode position of CPs around cells and tissues has shown potential benefits in maintaining connections with neural tissue over chronic time frames. However, the impedance benefits observed during acute wound healing periods of around 3-4 weeks were not maintained in the long term. Furthermore, the presence of CPs beyond the initial glial scar led to increased scarring due to the migration of inflammatory cells. Despite the advantages observed in vitro, the benefits of CPs in recording electrodes do not always translate to chronically implanted devices. Moreover, the limited number of studies investigating CPs applied to chronically implanted electrodes has made it challenging to establish standardized metrics across different research papers. It is therefore recommended that future studies focus on defining consistent metrics, enabling more meaningful comparisons between different approaches and providing a comprehensive understanding of the benefits and limitations of CP-based electrode coatings. At present, it is evident that CPs can offer some improvement in metal electrode impedance over subchronic time frames, but this benefit diminishes as scar tissue encapsulates the device, regardless of the material

composition. Nevertheless, some enhancements in SNR and the ability to record cell activity are still maintained in such conditions.

Stimulating Devices

The integration of conducting polymers (CPs) into neuro-stimulating electrodes is driven by the imperative to reduce electrode size while upholding the safety and efficacy of these devices. The pursuit of smaller electrode sites in stimulating devices holds significant advantages, as it facilitates the development of densely packed arrays. This advancement, in turn, enhances the resolution of biological responses in implant recipients, leading to potential improvements in sound perception for cochlear-implant users and the ability to discern facial expressions more effectively for visual-prosthesis recipients. The ultimate goal is to establish an optimal neural interface that can effectively communicate with individual cells, necessitating the operation of electrode technologies on the micro and nanoscales. Traditionally, commercial stimulating electrodes have been crafted from platinum, but this material exhibits limitations in safely injecting charge. When charge-injection limits are exceeded, chemical reactions occur at the interface between the platinum electrodes and the surrounding tissue, causing local pH changes and gas generation. Consequently, tissue damage and electrode dissolution may ensue. As an alternative, CPs, particularly PEDOT, have demonstrated higher charge-injection limits compared to platinum, presenting a promising avenue for improved electrode performance. However, successfully translating this enhancement from in vitro settings to in vivo scenarios poses a significant challenge. A comprehensive understanding of the role and benefits of CPs in stimulating-electrode applications requires addressing several key issues. Among these are the development of appropriate methods for measuring injection limits in both controlled laboratory environments and the complex in vivo setting, advancements in electrochemical and optical assessments of CPs in situ, and a deeper comprehension of protein interactions with roughened electrodes, which can affect charge-transfer mechanisms. Addressing these challenges is not only vital for CP neural interfaces but also for electrode interfaces in general. Evaluating the performance of electrodes in the in vivo environment is particularly challenging due to spatial constraints, the intricate biological milieu, and mechanical disparities between tissues and implants. Studies have highlighted that electrical stimulation can impact the mechanical integrity of CPs, leading to delamination and failure. Progress in this area relies on the development of accurate assessment techniques that can be applied in real-world situations. To ensure the durability of CP coatings for stimulating electrodes, it is essential that they remain firmly adhered to the underlying metallic electrode under various conditions, including implantation, explantation, polymer aging, and exposure to electrical stimulation in a biological environment. One promising approach to achieve this is through mechanical interlocking, which involves roughening the metallic electrode surface before applying the CP coating. This technique has demonstrated considerable potential in significantly extending the usable lifetime of CP-coated electrodes, allowing for the delivery of a large number of pulses, even at clinically extreme levels. Despite extensive research into CPs as electrode coatings, challenges persist in achieving consistent and robust performance for stimulating neuro-prosthetics. While CPs show promise in delivering substantial improvements in electrical performance, a thorough understanding of the neural interface is imperative before drawing definitive conclusions. Notably, the issue of scar-tissue encapsulation remains a relevant consideration, but the presence of CPs may enable safer charge delivery at the interface, bypassing scar tissue and maintaining the activation of target neurons. To achieve the full potential of CP-coated electrodes in stimulating

Conclusion

Beyond conventional cuff electrode, soft self-healing cuff electrode is a promising and innovative technology with significant potential in the field of bioelectronics and healthcare. To provide summary, this electrode type offers several key advantages: biocompatibility for stable bio-interfaces, self-healing Properties for adaptive and long-term functionality. Importantly, Soft self-healing cuff electrodes demonstrate excellent long-term stability in terms of their electrical performance, ensuring accurate and reliable signal acquisition over extended periods. Overall, the soft self-healing cuff electrode holds great promise for improving patient outcomes and advancing our understanding of the nervous system. As research and development continue, this technology has the potential to revolutionize the way we interact with and treat the human body. However, it's important that the technology might still be in the early stages of development, and further studies and trials will be necessary to fully realize its potential and ensure its safety and efficacy in various medical applications.

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