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Materials approaches for modulating neural tissue responses to implanted microelectrodes through mechanical and biochemical means

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ABSTRACT

Implantable intracortical microelectrodes face an uphill struggle for widespread clinical use. Their potential for treating a wide range of traumatic and degenerative neural disease is hampered by their unreliability in chronic settings. A major factor in this decline in chronic performance is a reactive response of brain tissue, which aims to isolate the implanted device from the rest of the healthy tissue. In this review we present a discussion of materials approaches aimed at modulating the reactive tissue response through mechanical and biochemical means. Benefits and challenges associated with these approaches are analyzed, and the importance of multimodal solutions tested in emerging animal models are presented.

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1. Introduction

Many traumatic injuries and degenerative diseases in the central nervous system (CNS) are insufficiently or completely untreatable, and have a tremendous personal and societal impact. For example, spinal cord injuries (SCI) occur at a rate of 12,000 cases per year in the US, currently affect up to 400,000 Americans [104]. Additionally, there are at least 3.3 million Americans suffering from visual impairment [51] and about 750,000 affected by severe to profound hearing impairment [99]. The lack of sufficient treatments for sensory impairment and CNS injuries has stimulated research into using external devices to interface with the remaining healthy parts of the CNS as a means to restore or enhance lost neural function. Devices interfacing with the CNS can be categorized by size into macroelectrodes and microelectrodes. Deep brain stimulation (DBS) using macroelectrodes is FDA-approved and relatively widespread for the treatment of Parkinson disease [87,170,133,9,20], and is under investigation for the treatment of major depression [57,88,92,11,4] and chronic pain [81,26,14]. While DBS macroelectrodes are subject to biological reactions of brain tissue, they exhibit satisfactory long-term stability due to their size scale and exclusive operation in the stimulation paradigm [44,160,100,21,102,78,50]. On the other hand, intracortical microelectrodes have been used with varying degrees of success to treat blindness [101] and deafness [86,79] as well as enable bladder and muscle control in paralyzed patients [35]. The smaller size scale and the desired operation in both the recording and stimulation paradigms, however, mean that the quest for widespread clinical adoption of implantable intracortical microelectrodes faces a host of formidable obstacles. As such, intracortical microelectrodes and their mechanical and biochemical design considerations will be the subject of this review.

Intracortical microelectrodes are a major focus of research for implantable neural interfaces due to their ability to isolate smaller neuronal populations for recording and/or stimulation, as well as their ability to selectively target different cortical depths. While intracortical microelectrodes show great promise, they are unreliable in chronic settings, displaying a drop in signal to noise ratio (SNR), an increase in impedance, and a loss of neuronal discrimination with time post-implant [161,167]. This degradation in intracortical device performance is generally correlated with a reactive response of brain tissue. A recent retrospective analysis indicates that while acute mechanical failure is responsible for a large proportion of current device failures [8], the reactive tissue response remains a major factor in the decline of chronic device performance if acute failure is otherwise controlled.

This reactive tissue response is a complex aggregate of interdependent responses involving multiple native and invading cell types, including microglia, astrocytes, neurons dural fibroblasts, and blood borne cells. The immune response typically presents two distinct phases. An acute phase starts immediately following the insertion of the device, which causes the breach of the blood

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brain barrier (BBB), and the introduction and accumulation of blood borne components and cells [139]. Consequent edema, accumulation of proteins, and secretion of inflammatory cytokines results in the activation and recruitment of microglia to the surface of the inserted device, followed by reactive astrocytes [12,40]. This volatile stage transitions into a more stable chronic phase characterized by the encapsulation of the device in a tightly bound glial sheath accompanied by the loss of recording sensitivity over time. Recordings can be recovered temporarily by the application of DC pulses, which are hypothesized to disrupt the tight junctions of the astrocytes in the glial sheath [59,105], but maintaining reliably high fidelity chronic recordings remains challenging.

The exact biological pathways governing the progression of the reactive tissue response to intracortical devices are not well characterized. An important finding from recent years is the confirmation of the biphasic nature of the reactive tissue response [117], where a highly volatile acute stage that appears to respond well to various interventions transitions to a chronic stage that is more or less impervious to current treatment approaches. Changes in electrophysiological characteristics of the implanted electrode generally do not correspond well with observed cellular responses during the acute stage [120,121], questioning the efficacy of impedance monitoring in predicting the progression of the tissue response. Chronic damage to the BBB resulting from the indwelling of the implanted device appears to be one of the dominant factors in the extent of device failure [139,61]. Additionally, the reactive tissue response has been shown to be non-uniform and depth related [173], with stronger scarring closer to the surface of the brain. Transdural implants elicit a much higher response than subdural implants that are inserted completely below the meninges [93], and a recent retrospective analysis of intracortical microelectrode failure revealed widely variable meningeal reactions in non-human primates [8]. These findings collectively suggest that the introduction of dural fibroblasts and blood borne cells and proteins into the brain activates inflammatory pathways, and that this activation is strongest at the site of injury to these structures. Potential possible mechanisms include accumulation of reactive oxygen species and activation of toll-like receptor 4 (TL4) precipitating microglial activation and neuronal degeneration [116,127].

While these recent findings shed more light on the biological mechanisms governing the progression of the reactive tissue response, they suggest the importance of simultaneously examining multiple components of the reactive tissue response at multiple time scales. Reductionist approaches to understanding and mitigating the reactive tissue response have had limited success. This suggests that the problem is multi-dimensional, and likely non-linear. Thus, single-factor or other limited experimental designs are unlikely to provide meaningful data, particularly in the chronic phase of the tissue response. Despite the limitations of these reductionist approaches, several factors have shown to modulate the reactive tissue response, particularly the acute phase. Two of the most significant factors have been: (1) the mechanical structure and size of the substrate of the device and (2) modulation of the local biochemical environment around the device. In the following sections we will review these mechanical and biochemical intervention strategies with respect to the reactive tissue response and device performance.

2. Mechanical approaches

2.1. Substrate material

2.1.1. Mechanical mismatch between device and tissue

A significant difference in stiffness exists between brain tissue and electrode materials. Conventionally used substrate materials such as tungsten, silicon, platinum, steel, and glass have a Young's modulus (i.e., a measure of stiffness) of 6–7 orders of magnitude greater than that of the brain tissue [77,156]. Due to this mismatch, micromotion generated by respiratory and pulsatile movement can perturb the surrounding tissue over a long period of time by exerting shear stress on the tissue and/or by cutting off the tissue with sharp edges [76,32,39].

To identify the effect of rigid electrode materials to brain tissue, several parameters including geometry, material properties, buckling load, and estimated force were taken into consideration [34]. Mathematical modeling studies using finite-element model (FEM) were conducted to evaluate the extent of shear stress induced by micromotion [153,76,180]. These results suggest that the implanted devices indeed generate strong enough stress on surrounding cells to stretch-activate ion channels and cause deformation. *In vitro* cell culture studies verified that an increased level of astrogliosis and neuronal death may happen in excessive strain conditions [29]. Furthermore, the use of soft materials can potentially reduce the shear stress by several orders of magnitude and minimize the possibility of damaging the surrounding tissue, leading to a healthy neuronal environment. In addition, neurons were found to extend their projections more actively to a preferred range of stiffness, mostly at lower moduli than that of conventional materials, and this further strengthens the idea of using soft materials [75,31,64].

2.1.2. Flexible substrates

Early generation electrodes specifically designed to meet the flexibility constraint were polyimide-based microelectrodes [152,136,77,156]. The fabrication of these devices involved metal sites sandwiched by thin film of polyimide using standard planar photolithographic techniques. Fig. 1 shows examples of polyimide-based electrode architecture. Parylene-C is also considered to be a suitable material which can serve as a flexible substrate backbone [154,111,132,68]. These types of electrodes reduced the strain forces between the tissue and the devices caused by micromotion, which can potentially enhance the devices' functional longevity. However, these materials did not show an improved surface chemistry over silicon as evidenced by cytoarchitectural examinations [168]. While flexible substrate materials offer advantages in providing a lower Young's modulus and ease of prototyping/fabrication, their major disadvantage is their need for aid in insertion. Since the stiffness of the electrodes made out of compliant materials is targeted to match with the brain tissue after insertion, the electrodes are likely to buckle on the surface of the cortex when attempting to penetrate into the meninges [76].

Insertion of flexible devices has been enabled by using insertion platforms that provide increased rigidity to push the electrode through the pia mater. The device surface can be coated with an agent that is rigid, biocompatible, and rapidly biodegradable while breaking down into biocompatible metabolites. Coating the device with carboxyl monolayer, poly(ethylene–glycol) (PEG), gelatin, or tyrosine-derived resorbing polymers has been proposed to provide enough rigidity for insertion [73,24,84,82]. With such insertion aids, the mechanical properties of electrodes were successfully modulated within physiological conditions. Side effects, however, may exist as these carriers increase the surface area of the shank, evoking greater tissue damage. Dissolvable insertion shuttles might also subject their cargo to substantial fluid forces [126]. In addition, flexible electrodes that are insertion-guided by carriers will need to consider the long-term effects of the carrier need to be considered in order to accurately examine the performance of flexible substrate material itself.

A solution to such potential pitfalls might be the use of mechanically adaptive nanocomposite materials. One example uses rigid cellulose nanofibers embedded within a soft polymeric matrix,

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