Soft Materials in Neuroengineering for Hard Problems in Neuroscience

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http://dx.doi.org/10.1016/j.neuron.2014.12.035

We describe recent advances in soft electronic interface technologies for neuroscience research. Here, low modulus materials and/or compliant mechanical structures enable modes of soft, conformal integration and minimally invasive operation that would be difficult or impossible to achieve using conventional approaches. We begin by summarizing progress in electrodes and associated electronics for signal amplification and multiplexed readout. Examples in large-area, surface conformal electrode arrays and flexible, multifunctional depth-penetrating probes illustrate the power of these concepts. A concluding section highlights areas of opportunity in the further development and application of these technologies.

Introduction

Breakthroughs in fundamental science often follow from advances in technology and methodology. In neuroscience, development of functional magnetic resonance imaging (fMRI) led to key insights into the patterns of activity that occur across the entire brain (Logothetis, 2008). Confocal microscopy and two-photon techniques with genetically encoded fluorescent indicators of membrane voltage, ion concentrations, and synaptic transmission, yielded similar advances in understanding through real-time monitoring of neuronal activity with improved spatial and temporal resolution (Denk and Svoboda, 1997; Fine et al., 1988). Positron emission tomography provided molecular level neuroimaging capabilities for diagnosing brain disorders such as Alzheimer's disease (Phelps, 2000). The emergence of optogenetic techniques (Deisseroth, 2011), methods for rendering brain tissue optically transparent (Chung et al., 2013), miniaturized fluorescence microscopes for cellular-level brain imaging in freely moving animals (Flusberg et al., 2008; Ghosh et al., 2011), and transgenic multicolor labeling strategies for neurons (Livet et al., 2007) represent some of the latest examples in which new technical approaches are enabling fundamental discoveries.

Recently launched, large-scale research initiatives seek to build on these and other technologies to revolutionize our understanding of the human brain. An ambitious goal is to develop neural interface systems that can reveal the interactions of individual cells and entire neural circuits in both time and space. Although optical and chemical techniques can play important roles, capabilities for electrical measurement and stimulation are essential not only to this type of fundamental research in neuroscience, but also to the development of procedures for treating Alzheimer's disease, Parkinson's disease, epilepsy, depression, and many other conditions that originate from aberrant neural behavior. Modern electrical neural interface systems build on a long history, largely involving the development of advanced electrode technologies. Penetrating pins formed in micromachined silicon represent popular means for interfacing directly to brain tissue (Campbell et al., 1991; HajjHassan et al., 2008), whereas bulk metal electrodes and coupling gels provide for measurement through the skin of the scalp (Niedermayer and Lopes Da Silva, 2005). Although effective for many purposes, such systems rely on hard materials in geometrical forms that establish a poor match to the soft tissues and the curved, textured surfaces of the brain and the skin; they also often constrain and frustrate the dynamic, natural motions of these organs. Consequences include discomfort, irritation, and adverse immune responses at the critical interfaces (Grill et al., 2009; He and Bellamkonda, 2008; Polikov et al., 2005; Ward et al., 2009), thereby creating challenges in non-invasive initial integration and subsequent chronic operation. Furthermore, the basic architectures of the readout electronics do not scale effectively to the geometrical areas and the numbers of independent channels thought to be indispensable for recording neural data that span the dynamics of isolated neurons to individual neural circuits, to the entire brain. Such circumstances demand alternative materials, component devices, and functional systems for a next generation of neural interface technology.

This review summarizes recent progress in these directions, with an emphasis on approaches that embed soft materials and compliant mechanical structures in active electronic designs with potential to achieve spatiotemporal resolution across all relevant scales. The article begins with an overview of electrodes with unique capabilities in direct electrical interfaces to the surfaces or depths of the brain, and indirect ones through the skin. Subsequent sections illustrate means for combining such electrodes with electronic circuits capable of active, multiplexed readout, per-channel signal amplification, wireless transmission, and multimodal operation, in each case with representative neural data to illustrate the functional possibilities.

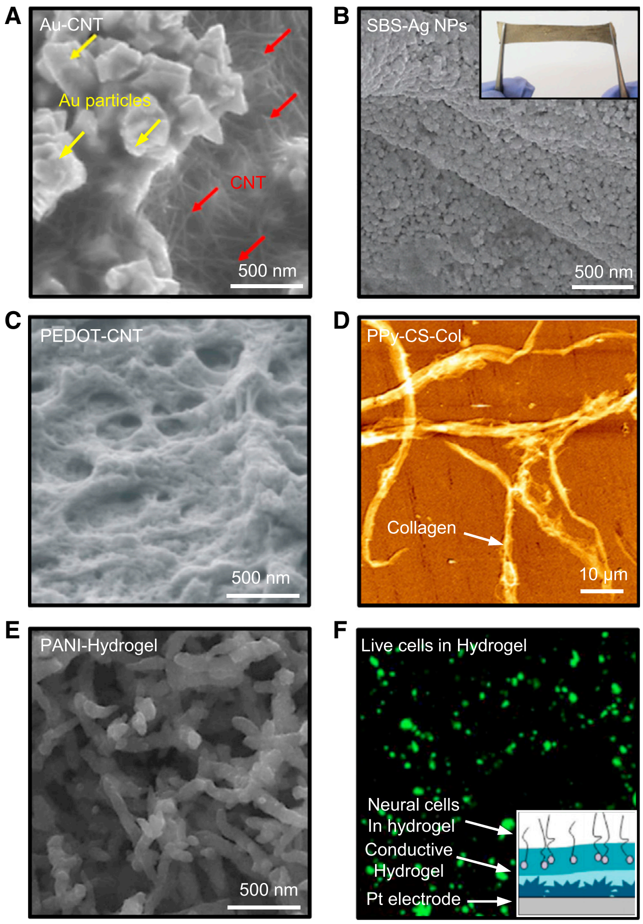

Figure 1. Soft Materials for Neural Interfaces
(A) Scanning electron micrograph of a percolating network of gold (Au) nanoparticles (yellow arrows) and carbon nanotubes (CNT, red arrows) in a polyimide matrix (Xiang et al., 2014).
(B) Scanning electron micrograph of a styrene-butadiene-styrene (SBS) triblock copolymer rubber with a percolating network of silver nanoparticles. The inset shows a picture of this material while stretched (Park et al., 2012).
(C) Scanning electron micrograph of a PEDOT/CNT composite. Electropolymerized PEDOT/CNT offers low impedance (15 kΩ with a diameter of 30 μm at 1kHz) compared to an Au electrode (330 kΩ with a diameter of 30 μm at 1kHz) (Gerwig et al., 2012).
(D) Atomic force micrograph of Polypyrrole (PPy)/chondroitin sulfate (CS)/collagen (Col) composite. Collagen fibrous matrix consists of small individual fibers of collagen with diameter of 150 to ~200 nm (Liu et al., 2011).
(E) Scanning electron micrograph of a polyaniline (PANI) / hydrogel composite. The dendritic nanofibers of PANI (~100 nm diameters) form a 3D interconnected network (Pan et al., 2012).
(F) Fluorescent optical micrograph of P12 neural cells in a sericin hydrogel (Green et al., 2013).

Soft, Compliant Neural Interfaces

Neural interfaces provide two-way communication between electronic devices and biological tissues for purposes of measurement and/or stimulation. The materials that serve as the electrodes play critically important roles, where interactions involve redistribution of charges (capacitive) and/or transfer of electrons and ions (Faradaic) at the double layer that forms between the electrode and electrolyte (i.e., surrounding biofluid) (Cogan, 2008; Merrill et al., 2005). The charge injection capacities and the impedances are generally thought to be most relevant to stimulation and sensing, respectively. Over the past 50 years, various metals, metal alloys, metal oxides, doped semiconductors, conductive polymers, and carbon nanomaterials have been explored. Platinum (Pt) and its alloys with iridium represent popular classes of metals, due to their chemical stability, bio-compatibility, and excellent electrical properties (Merrill et al., 2005; Petrossians et al., 2011). Here, Faradaic and capacitive mechanisms can be equally important, partly due to the modest injection capacity of Pt (0.05–0.15 mC/cm^2), as defined by the maximum amount of charge per unit surface area that can be delivered in the leading phase of a stimulation pulse, without causing irreversible electrochemical reactions. Another widely used material is iridium oxide, due to its capability for charge injection via fast, reversible Faradaic reactions (Mozota and Conway, 1983) associated with oxidation and reduction between multiple valence states of Ir in the oxide. Resulting capacities (1–5 mC/cm^2) can be greater than those of Pt (Merrill et al., 2005). Similar performance based on capacitive coupling within a regime of reversible electrochemical processes (Cogan, 2008) is possible with titanium nitride (TiN; ~1 mC/cm^2), also commonly used for neural electrodes. In all cases, texturing the electrode surfaces increases their areas, and therefore lowers the electrochemical impedance, with examples in porous TiN and sputtered iridium oxide (Cogan, 2008), and enhances the charge injection capacity (Petrossians et al., 2011).

Although these and other established materials are useful, they are mechanically hard (~50–500 GPa modulus, ~1%–5% elastic strain limit) and, in conventional forms, they offer shapes and structural properties that are highly dissimilar to those of targeted tissues. These and other drawbacks create interest in alternative, soft materials, such as conducting polymers and nanomaterial composites, which combine low modulus mechanics (1 MPa to 5 GPa modulus, 5%–500% elastic strain limit) and good biocompatibility (Asplund et al., 2009; George et al., 2005; Humpolicek et al., 2012) with an ability to be molded, printed or cast into complex, curvilinear shapes matched to tissues of interest, with or without additional nanotextures. These features facilitate integration on soft, moving biological surfaces with minimized inflammatory reactions and gliosis. Conducting polymers such as poly(3,4-ethylenedioxythiophene) (PEDOT) and polypyrrole (PPy), are attractive due to their low electrochemical impedances and high capacities (>15 mC/cm^2) (Cogan, 2008). Their modest conductivities can be addressed through the addition of nanomaterials to yield advanced composites that often also increase the active surface areas, without compromising the soft mechanics. Figure 1 shows some examples, including a dispersion of carbon nanotubes (CNTs) and gold nanoparticles in a polymer host (polyimide) (Figure 1A), silver nanoparticles in a soft elastomer (Figure 1B), and CNTs in a conductive polymer (Figure 1C) (Castagnola et al., 2014; Gerwig et al., 2012; Park et al., 2012; Xiang et al., 2014). In the first, electrodeposited nanoparticles decorate a 3D, percolating network of CNTs (Figure 1A) (Tsang et al., 2012; Zhang et al., 2014). The CNT/Au composite (< 100 kΩ for a 500 μm × 300 μm pad at 1 kHz) offers much lower impedances compared to those with Au (~1 MΩ for a 500 μm × 300 μm pad at 1 kHz) at all frequencies from 10 Hz to 100 kHz. The mechanics of this type of