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Materials and microfabrication processes for next-generation brain-machine devices

Wei-Chen Huang, Haosheng Wu, and Christopher J. Bettinger

Transfer printing microstructures onto novel hydrogel interfaces and customised composite electrodes could increase the compatibility and information transfer between body tissue and electronic devices.

Implantable devices such as pacemakers, cochlear implants, and deep brain stimulation devices enhance the quality of life for many people. Improving the integration of such devices with the body could enable the next generation of brain-machine interfaces (i.e., implantable devices that can record and modulate neurological function in vivo) to monitor physiology, detect disease, and deploy bioelectronic medicines.[1]

Current implantable devices are not well matched with body tissues in terms of their mechanical, chemical, and physical properties. The tissues that may be excited or interrogated by implants (e.g., brain, spinal cord, or cardiac muscle) are mechanically compliant, curvilinear, and perform their functions by modulating the flow of ions.[2] Conversely, most implantable silicon-based devices are mechanically rigid, and use electrons or holes as their primary information currency. These elements of mismatch reduce the overall performance of current implantable technology in three ways (see Table 1). First, the difference in mechanical properties (i.e., the elasticity) can cause local tissue damage that compromises the fidelity of measurements. Second, changing between ionic and electronic transduction decreases the information density and stimulation specificity. Finally, the materials that are typically used in microelectronic implants are susceptible to rapid protein adsorption, which initiates a cascade of local inflammation and scarring. The biological response to the presence of foreign material (such as an implant) can also compromise bidirectional communication.

Mechanically compliant electronics are ideal for neural interfaces because they can conformably meld with excitable tissue.[3] Flexible devices can also reduce the inflammatory responses that are associated with a mechanical mismatch at the tissue-device interface.[4] Integrating electronics with hydrogel-based materials may harmonize their mismatch (see Figure 1).[5] Fabricating such devices is challenging, however, as the processes involved require elevated temperatures, high vacuum, and exotic solvents. Such conditions are fundamentally incompatible with flexible swollen hydrogels. Transfer printing, in which a structure is printed onto a substrate and then lifted onto the hydrogel, is one technique that may be used to integrate large-area-format microelectronic devices with flexible substrates such as ultracompliant swollen hydrogels.[6] There are, however, a number of technical challenges associated with this methodology. These challenges include the appropriate selection of donor substrate materials and target substrates, and reduced adhesion in hydrated environments.

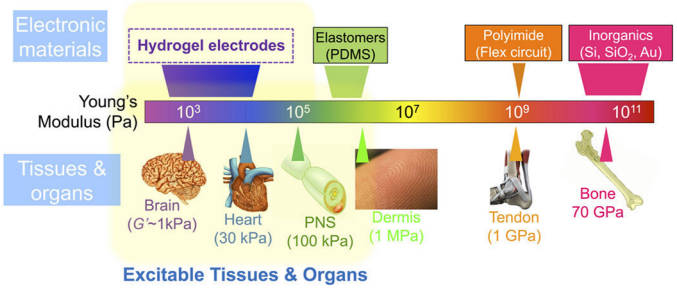

Figure 1. *The relative Young's moduli of a range of biological and electronic materials. Excitable tissues in the nervous and cardiac systems exhibit significantly smaller Young's moduli than materials that are commonly used in microelectronic fabrication. The ideal bioelectronic interface would integrate materials commonly used in microelectronic fabrication with hydrogel-based materials that can match the mechanical properties of the brain, peripheral nervous system (PNS), and even cardiac tissue. PDMS: Polydimethylsiloxane.*

In our work, we use a novel technique to transfer print metallic microstructures onto ultracompliant hydrogel-based

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Table 1. *The fundamental physical asymmetries that exist between excitable tissue in the nervous system and implantable, silicon-based biosensors (e.g., brain-machine interfaces and other bioelectronic devices). Biomimetic interfaces can potentially bridge the incongruities between natural tissue and synthetic materials, thereby improving overall device performance. PNI: Peripheral nerve interface. E_{Si}: Young's modulus of silicon. PNS: Peripheral nervous system. G': Storage modulus of a polymer or tissue. ECM: Extracellular matrix. $\gamma_{H_2O\text{-}material}$: Residual energy at the interface between water and a given material. CPs: Conducting polymers. Pt: Platinum.*

Nature of asymmetry	Physical property	Silicon-based PNI	Biomimetic Interfaces	Neurons (PNS)
Large mechanical mismatch	*Elasticity (stiffness)*	Silicon (E_{Si} = 70GPa)	**Metallized hydrogels (G′ = 1kPa)**	Neurons in PNS (G'_{brain}∼1kPa)
Electron-Ion coupling	*Charge injection*	Platinum (pseudocapacitive)	**Flexible CPs (Faradaic)**	Ions
Glial response at interface	*Protein adsorption* ($\gamma_{H_2O\text{-material}}$)	Silicon/Pt (500mN/m)	**Zwitterionic gels** (∼0mN/m)	Cells-ECM Cells-ECM (∼0mN/m)

target substrates that incorporate bio-inspired chemistries to promote adhesion to inorganic materials in wet environments (i.e., the human body).[7,8] To achieve this, we have designed swollen hydrogels that include catechol, a compound that is present in marine organisms, to promote surface adhesion in wet environments.[9] These hydrogels exhibit storage moduli on the order of 10kPa, which is comparable to those of many excitable tissues, including cardiac muscle and peripheral nerves.[10] Our complementary transfer printing process—illustrated in Figure 2—enables microfabricated structures to be integrated with such bioinspired hydrogels. The key innovation of our process is the use of a selectively removable sacrificial release layer. This temporary release layer is composed of water-soluble poly(acrylic acid) (PAA) film that is crosslinked with divalent cations such as calcium. The film, which is spin-coated on silicon handling wafers, can be selectively dissolved through ion-exchange with aqueous solutions of monovalent cations. Using our method, materials that are commonly used in microelectric fabrication (e.g., metals, oxides, and polymers) can be transfer printed onto hydrated target substrates.[11] This technique requires device fabrication and a priori preparation of the hydrogel target substrate.

We have also developed a next-generation transfer printing process that enables catechol-bearing hydrogels to be formed, by rapid in-situ gelation, directly on top of pre-microfabricated structures that are laminated to a water-soluble sacrificial layer. Our gelation-assisted transfer printing method enables three processes (i.e., gel formation, the adhesion of microfabricated structures to target hydrogel substrates, and dissolution of the underlying PAA-based sacrificial layer) to take place simultaneously. This technique improves the prospects for bulk wafer processing and could enable the development of efficient manufacturing techniques for integrating microelectrode arrays with ultracompliant adhesive hydrogel-based substrates. This combination of target substrate composition and transfer printing is broadly generalizable and applicable for bioelectronic devices ranging from brain-machine interfaces to smart contact lenses.[12,13]

The deterministic design of composite electrode materials represents one strategy by which we hope to harmonize the mechanical asymmetries between the natural nervous system and implanted devices. Customized flexible materials must allow for the efficient transduction of information between neurons and biosensors. We plotted a number of existing electrode materials as a function of their Young's modulus and charge-injection capacity (Q_{inj})—both key figures of merit in stimulation electrode materials—to illustrate their suitability for this application: see Figure 3. The ideal material would have mechanical properties that approach those of excitable tissue (i.e., a Young's modulus less than 10kPa) and arbitrarily high Q_{inj} values. These characteristics reduce the area that is required for stimulation and therefore increase the spatial resolution of electrode arrays. Even elastomeric electrode materials would be able to accommodate the large strains that are often observed when flexible electronic devices are implanted in vivo. Many existing electrode materials are both rigid and exhibit Q_{inj} values that are an order of magnitude smaller than many conducting polymers, such as poly(3,4-ethylenedioxythiophene) and polyaniline. Conjugated (conducting) polymers conduct both ions and electrons and are therefore attractive coating materials for implantable biosensors.[14] Conducting polymers are often rigid and brittle, however, with Young's moduli approaching 10GPa.

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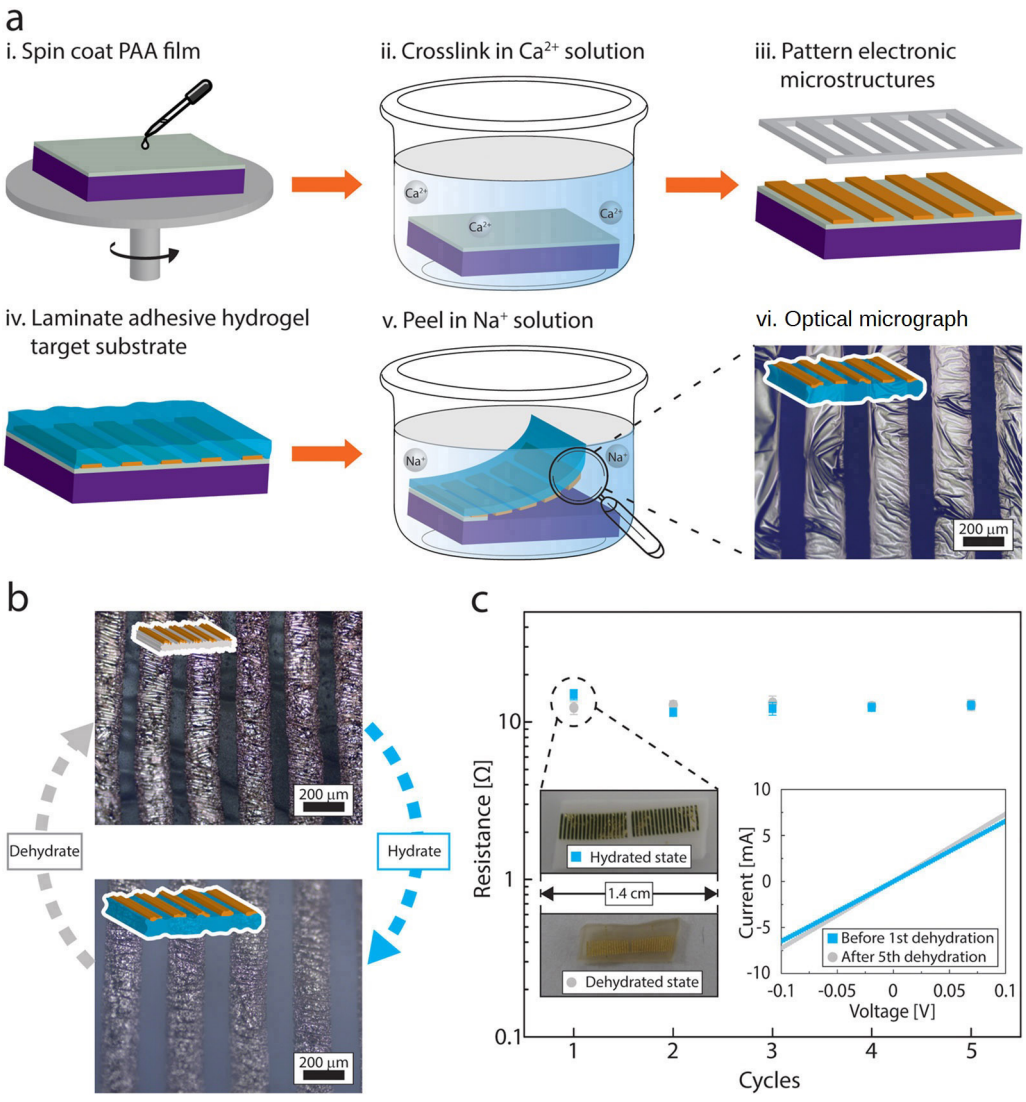

Figure 2. *(a) The transfer-printing process. Donor substrates for transfer printing are prepared by (i) spin-coating a sacrificial layer of water-soluble poly(acrylic acid) (PAA) and (ii) crosslinking in an ionized calcium (Ca^{2+}) solution prior to (iii) fabricating gold microelectrodes onto the PAA-Ca^{2+} surfaces. (iv) Adhesive-swollen hydrogel-based target substrates are conformably laminated on the donor substrate surface for five minutes and then (v) removed from the donor substrate in an ionized sodium (Na^{2+}) solution, resulting in the transfer of gold microstructures onto the hydrogel substrate. (vi) An optical micrograph showing a portion of the gold microstructures on the hydrogel substrates. (b) Optical micrographs of gold microelectrode arrays. The hydrogel substrates are cycled between hydrated and dehydrated states, demonstrating robustness in adhesion at the hydrogel-electrode interface. (c) Resistance values for gold microelectrodes indicate that the electrical conductivity is preserved for five hydration/dehydration cycles. Reproduced from Wu et al.[7] with permission. Copyright American Chemical Society 2016.*

Based on these configurations, we have designed intrinsically flexible conducting polymers based on polyaniline that can preserve the native electronic properties typical of such materials and exhibit intrinsic elastomeric properties (see Figure 3).[15] The key discovery that enabled this breakthrough is the use of block-copolymer templates to control the morphology of in-situ polyaniline synthesis. The result is an elastomeric conducting polymer that can facilitate charge injection and improve the overall performance of flexible bioelectronic interfaces. Elastomeric conducting polymers show great promise as coating materials for metallic leads. Such coatings could accommodate the

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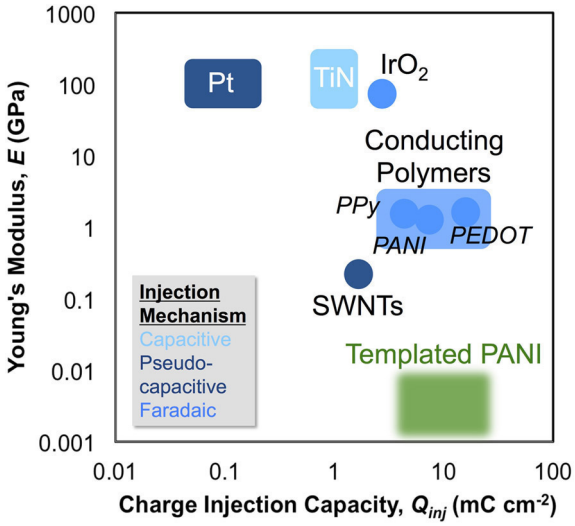

Figure 3. *The Young's moduli and charge-injection characteristics of a range of organic and inorganic electrode materials. The charge-injection mechanism of each material is color-coded: green for capacitive; dark blue for pseudo-capacitive; and light blue for faradaic. Next-generation electrode materials must exhibit unique combinations of physical properties including elastomeric mechanical behavior (to accommodate flexibility) and efficient charge injection (to facilitate electrode miniaturization). Common electrode materials, such as Pt, titanium nitride (TiN), and iridium oxide (IrO_2) can inject charge efficiently, but are not elastomeric. Organic electrode materials such as poly(3,4-ethylenedioxythiophene) (PEDOT), polypyrrole (PPy), and single-walled carbon nanotubes (SWNT) offer improved charge-injection performance, but have rigid mechanical properties. Next-generation materials may include templated conducting polymers, such as polyaniline (PANI), that exhibit high charge-injection capacities in combination with elastomeric mechanical properties.*

large strains that may be experienced by implantable microelectrode arrays, thereby improving their reliability. We are particularly interested in evaluating the in-vivo performance of these materials to identify the fundamental limits of electrode size. A 50-fold improvement in Q_{inj} could reduce the characteristic length scale of electrodes from 50μm to less than 10μm, thereby leading to enhanced specificity of neuron stimulation.

In summary, we have developed a transfer-printing process that enables electronic microstructures to be printed directly onto flexible hydrogel substrates. Furthermore, we have shown that the resulting microelectrode arrays are robust enough to maintain their electronic properties after five cycles of hydration and subsequent dehydration. Bioelectronic interfaces that can transduce information between tissues and devices will have exceptional utility in future biomedical applications, and should find application in both diagnostic tools and therapeutic modalities. Improving the reliability of such interfaces to achieve these aims requires advances in material synthesis and microfabrication techniques. Additionally, developments in these areas will also help to harmonize the intrinsic physical asymmetries between the natural and synthetic domains. We believe that next-generation bioelectronic interfaces will seamlessly meld tissues and devices by incorporating novel biomimetic materials, non-conventional microelectronic fabrication techniques, and comprehensive device integration strategies. In the next stage of our work, we plan to design and fabricate fully packaged and ultra-compliant adhesive microelectrode arrays for in vivo recording.

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Christopher J. Bettinger is an associate professor. He directs the Biomaterials-based Microsystems and Electronics laboratory, which is broadly interested in the design of novel materials and interfaces to integrate medical devices with the human body.

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