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PERSPECTIVE

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Electronic tissue technologies for seamless biointerfaces

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Abstract

Bioelectronic interfaces establish a communication channel between a living system and an electrical machine. The first examples emerged in the 18th century when batteries were used to "galvanize" muscles and nerves. Today bioelectronic interfaces underpin key medical technologies such as the cardiac pacemaker and emerging ones such as neuroprostheses and brain-machine interfaces. Despite compelling applications in living systems, bioelectronic interfaces employ materials from microelectronics that are rigid, impermeable to water and bioinert. In contrast, electrical phenomena in soft tissues such as muscle and nerve are mediated by ions and molecules solvated in water. This disparity leads to missed opportunities for achieving seamless interfaces and communication that extends beyond electrical stimulation and recording. In this perspective, I discuss opportunities presented by hydrogel materials for building bioelectronic interfaces. This will require new types of hydrogels that support both ionic and electronic conductivity combined with key functions of the extracellular matrix.

KEYWORDS

bioelectronics, conductive hydrogel, electrode arrays, neural interfaces

1 | INTRODUCTION

Bioelectronic interfaces emerged in the late 18th century, at a time when knowledge about electricity was advancing through observations of its effects on human or animal bodies. In one famous experiment, Alessandro Volta connected the terminals of his battery of electrochemical cells to metal rods and proceeded to touch their rounded ends to his eyes or insert them in his ears.[1] The description of flashes of light and crackling sounds he perceived is intriguing as is his warning against repeating such experiments in the future. It is now known that electrical phenomena in biological systems are connected to the movement of ions solvated in water while those in metals are due to movement of electrons.[2] These differences define some of the fundamental challenges encountered when building bioelectronic interfaces even to this day. On one side of the interface are circuits of biological cells, and on the other are circuits of transistors. The biological cells are embedded in a viscoelastic electrolyte (extracellular matrix, ECM) while transistors are made on silicon and are encapsulated in watertight packages. The role of the interface is to establish a communication channel between the biological and electronic computer. Considering the vast differences in the physical properties of the constituent materials this is not a trivial task, especially when engineering implanted interfaces.[3,4] Despite this, more than 200 years after Volta's experiments, systems that deliver electrical stimulation to the retina (visual prosthesis) or the inner ear (cochlear implant) via implanted microelectrodes restore auditory and visual perceptions in patients with degenerative loss of the

relevant receptors.[5,6] One of the fundamental questions in human-machine interfaces is if machine and biological system can be seamlessly integrated? If this is possible, can such an interface offer improved or radically new healthcare technologies or fundamental insights into the biology of living systems?

2 | MATERIALS AND DESIGNS INSPIRED BY MICROELECTRONICS

Today, the workhorse of the bioelectronic interfaces is the electrode. It is a conceptually simple device consisting of a metallic conductor embedded in an insulating material.[7] At one end, a portion of the conductor is exposed and contacts the biological system, at the other it is connected to equipment that records or generates electronic signals. When many electrodes are integrated, an array is formed where multiple contact sites establish a spatially defined interface.[8] Arrays with thousands of passive or actively switched contacts have enabled monitoring network dynamics in neuronal cell cultures with high spatiotemporal resolution.[9] In clinical practice, with far fewer (several to several 10s) electrodes, neuroprosthetic implants have benefitted patients with hearing loss, Parkinson's disease, chronic pain and more recently paralyzed patients.[10] Electrode arrays rely on a single mode of operation – induction or detection of depolarisations in single or ensembles of cells. The range of materials employed is inspired by microelectronics and includes metals and their alloys (Au, Pt, PtIr, stainless steel) which are encapsulated in a dielectric polymer (parylene, polyimide, silicone).[11] Charge exchange is determined by reduction–oxidation reactions and (dis)charging of electrochemical double layers which are confined to the surface of the electrode, where electrolyte and solid conductor meet (Figure 1A).[12] Despite many successes, challenges with biointegration limit outcomes. Inside the body electrodes persist as a bulky foreign body, susceptible to corrosion, delamination, immune response, fibrotic encapsulation, blood–brain-barrier disruption.[13] In vitro, planar, rigid form factors make interfacing three dimensional cell culture models such as organoids challenging.[14]

A key feature of the second generation of interfaces is their improved biointegration. One strategy is to engineer

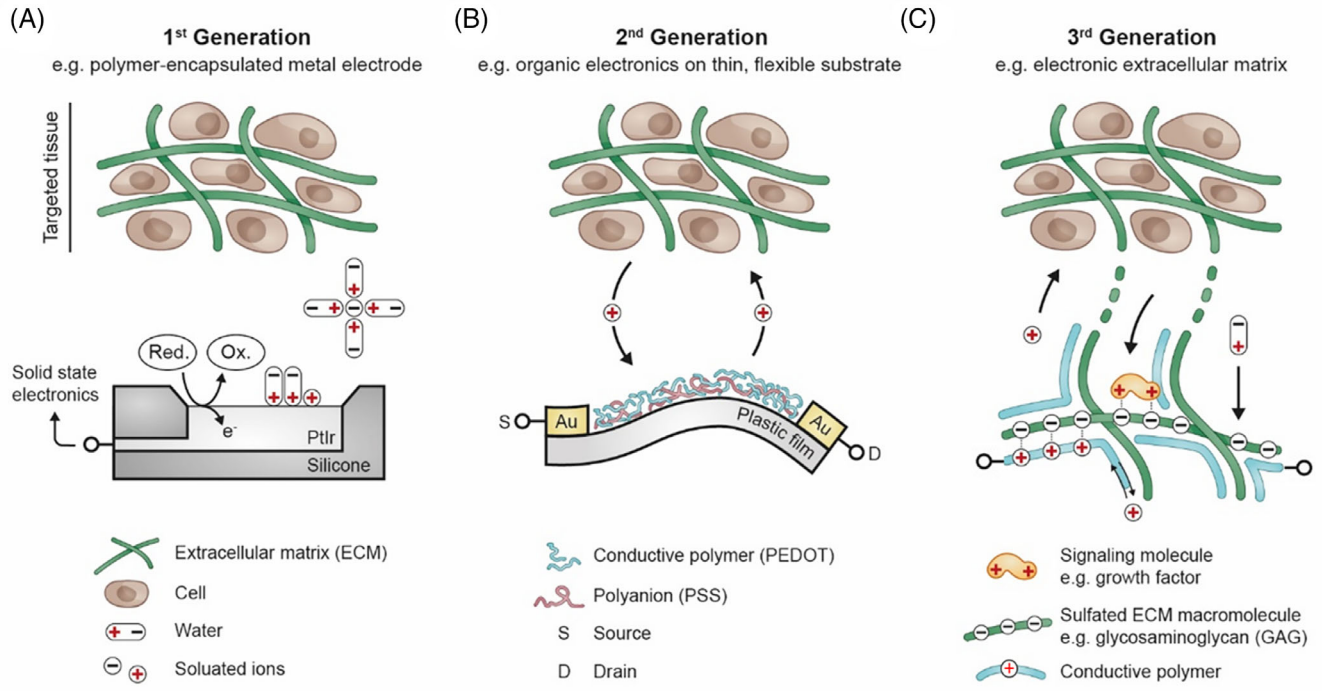

FIGURE 1 Generational taxonomy of technologies for bioelectronic interfacing. (A) Electrodes are a key first generation technology where electrochemical reactions on the surface of a conductor transduce electronic to ionic currents. (B) Thin, flexible and stretchable devices have enabled improvements in biointegration at the cell, tissue and organ levels. Organic semiconducting materials such as PEDOT:PSS support mixed electronic-ionic conductivity and have contributed more efficient mechanisms of charge exchange. (C) Electronic tissues are fully hydrated polymer networks that mimic the physical properties and some functions of the ECM. A defining feature emerges from the presence of an organic semiconductor network, which enables on-demand switching of properties. This may enable several key functions such as modulation of ionic currents, sequestration/release of signaling molecules and mechanical actuation (water swelling/de-swelling).

arrays with mechanical properties that mimic those of the biological host. Two approaches have gained traction and have been demonstrated in various animal models. They are characterized by intrinsically soft materials (e.g. composite conductors combining metal particles and elastomer) or radically thinned substrates.[15–18] Both demonstrate elasticity and can conform to curvilinear objects for example the outer surface of stem cell spheroids, the spinal cord or brain.[19,20] Designs based on thin-strut meshes have achieved intermingling of individual electrode sites among neurons in the brain and within the cell mass of 3D cell cultures.[21,22] Wireless connections linking the implant with control electronics have eliminated bulky connector cables.[23,24] In addition to silicon, metals and plastics, the palette of materials has expanded to include organic electronic materials.[25–28] Many examples are conjugated polymers (CPs) which are typically p-type semiconductors. When mixed with a polyanion, doping enables high hole mobility along the CP backbone as exploited in blends of poly(3,4-ethylenedioxythiophene) and polystyrene sulfonate (PEDOT:PSS). Organic electronic materials are mechanically softer than their inorganic counterparts and support both electronic and ionic conductivity.[29] Such mixed mode conductivity is essential for linking the ionic currents in tissues to solid-state electronics. For example, some device types such as the Organic ElectroChemical Transistor (OECT), require access to the interstitial electrolyte (Figure 1B).[30] This means an actively switched device can be paced closer to the biological source, which combined with stretchable or thin substrates can drastically improve signal quality.[31] Organic electronic materials have also enabled devices for delivery and detection of small molecules such as neurotransmitters.[32] They are biocompatible and may even be assembled in vivo among living cells.[33] Second generation interfaces have achieved remarkable progress in embedding electrical machines in tissue as evidenced by reduced foreign body response, smaller neuronal kill zone and better signal quality in pre-clinical models.[21,34,35] Ongoing and future clinical trials using neurotechnological devices may potentially translate some of these advantages to the clinic.[36–38]

3 | INTERFACES FROM BIOINSPIRED MATERIALS

A third generation of bioelectronic interfaces is in its infancy. It may be characterized by a major shift from excluding water to working with water. A defining feature may be the absence of a distinct boundary between the electronic machine and living host system.[39,40] A continuum of hydration will facilitate exchange not only in the ionic but also molecular and mechanical languages native to living matter (Figure 1C). In addition to stimulation and recording, this will enable tapping into the control loops that regulate growth, maintenance and remodeling of the biological system.[41–43] These key functions will be electrically addressable and linked to artificial intelligence enabled by the computational power of solid-state electronics.[44] Inspiration for the design of this new type of interface may be sought by examining the structure and function of the ECM.[45] In addition to mechanical support, ECMs are a key orchestrator of tissues including presentation of cell instructive molecules, attachment sites, mechanobiological cues and cleavable locations that enable plasticity.[46–48] An interesting example are perineuronal nets, fine arborized meshes of proteoglycans found to surround mammalian neurons. In addition to their ECM role, they are implicated in regulation of memory and the speed of axonal conduction.[46]

The materials to realize ECM-like bioelectronic interfaces are still missing. The existing palette is unlikely to fulfill all requirements because its constituents are not bioactive, nor permeable to liquid water. A promising approach may involve engineered hydrogels, a class of water-swollen polymer networks whose properties and function are amenable to rational design.[49–51] They can be constructed from the same molecular building blocks that constitute the ECM.[52] Although its full complexity is challenging to recreate, defined hydrogels have achieved progress in recreating stem cell, wound healing and neuroregenerative microenvironments.[53–56] Unfortunately, hydrogels are poor conduits of electrons (or holes). However, due to liquid water and network mesh sizes on the order of 10s of nanometers, they have good ionic conductivity and essentially behave as viscoelastic electrolytes ($\sigma \sim 1$ S/m in physiological saline).[57] These properties have already been exploited in non-conventional electronics.[58] In hydrogel iontronics, space charge (due to fixed charged groups on the hydrogel polymer network) enables permselective ionic conductivity. This has been exploited for building water-based diodes, mechanical actuators, pressure sensors and even a reconstruction of the electrogenic organ of the electric eel.[59–62] Incorporation of an electronically conductive network within the hydrogel would be attractive, because it renders the hybrid with dual conductivity. Thus, unlike iontronic hydrogels or other smart polymers activated by external stimuli (e.g. light, temperature change, pH change, electric field),[63] dual-conductive hydrogels will respond to direct injection of electronic charges. The modes of operation may extend beyond the electrical domain and include release and sequestration of signaling molecules and neurotransmitters and even mechanical actuation. Machines made from them will operate at low voltages ideally within the water window which is an important consideration when interfacing living systems.[64]

Hydrogels with dual conductivity have been under development for a number of years.[65,66] Recently, elastic moduli in the range of soft tissues (1–100 kPa), stretchability exceeding 100% and overall conductivity of up to ~50 S/cm have been achieved in various systems.[67–72] Typically, the electronically conductive material is a CP or a network of metallic or carbon nanoparticles.[73,74] In experimental bioelectrodes, such hydrogels demonstrate efficient (e.g. low voltage) stimulation in the nervous system and mimetics of tissue mechanics.[67,75] As already alluded to, perhaps the missing component needed for third generation bioelectronics or electronic tissues are soft and hydrated materials whose biological function can be electrically switched. This will enable the construction of sensors-actuators arrays and circuits that fluently converse in the many languages used for communication within living systems.

Electronic tissues may bring the recreation of the in vivo environment in a dish a step closer. Successful growth of organ-like constructs outside the body is at present limited by the lack of a supporting microenvironment and reproducibility of outcomes.[76] New approaches are needed to emulate the organizational centres delivering biochemical, electrical and physical morphogens present during development in vivo. If this can be achieved, organoid cultures may reflect more mature stages of development. This may contribute to delivering the promise of organoid technology for transformative discoveries in developmental biology, drug screening and even the generation of replacement tissues for human repair.[77–79] Electronic tissues have great potential to disrupt the design of future bioelectronic implants. They may be transformed in three distinct directions of superior biointegration, longevity (or programmed lifetime) and enablement of multimodal operation.[80,81] Designs may altogether dispose with metal, plastics and silicone components and instead incorporate water rich organic materials. Current challenges resulting from corrosion, loss of hermeticity and delamination in the mechanically and chemically hostile environment of the body will be less detrimental to long-term operation.[82] Such technologies may enable the creation of miniature implantable laboratories for in situ repair of the human body.

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CONFLICT OF INTEREST STATEMENT

The author is a member of the scientific advisory board of Neurosoft Bioelectronics and is a co-inventor on the following patents US Patent 10,828,486 (2020), US Patent 10,695,555 (2020), US Patent 10,448,514 (2019).

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