Section 2.2. Enhanced interfaces for communication with living electronic materials

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Status

Alongside the advances in inorganic nano-assemblies that have fueled a technological revolution in microelectronics, biofabrication technologies are emerging to enable the assembly of biological molecules into structures for biotechnology [184]. Integrating biological systems with electronics enables the construction of devices with properties that combine the features of both but faces unique challenges for device fabrication, including engineering robust interfaces that bridge the material differences (*e.g.* stiffness, conductivity). This interface can be engineered across multiple hierarchical levels—ranging from physical adsorption at the molecular scale [185] to nano- and micron-scale entrapment using biosynthesized ECM [186] or ECM-inspired synthetic hydrogels [187] to create living electronic materials. Due to their inherent properties, hydrogels remain one of the most widely used platforms to assemble three-dimensional living structures on abiotic surfaces. Their crosslinked nano-scale matrices function as scaffolds to support cell retention and molecular exchange. Their high-water content provides a suitable environment for cell growth while their solid-like form allows easy handling and protects electronics from direct exposure to water. Complementing the use of hydrogels as scaffolds for biofabrication, spatial patterning techniques have been developed that use light [188], electrical [189–191], or mechanical [192] stimuli to control both material and cellular deposition.

In particular, electro-biofabrication, the use of electrical cues to control hydrogel structure and cellular localization, offers facile assembly of living materials on electrode surfaces and is uniquely suited for the fabrication of living electronics. A range of natural biopolymers, from chitosan to agarose, and cell types, from bacterial to eukaryotic cells, have been shown to undergo successful electrodeposition [193]. Electric field stimuli can be used to direct assembly of charged polymers at electrode surfaces, formation of ionic gradients that trigger phase transitions, or cellular motility to precise locations. Redox stimuli can also be leveraged to catalyze crosslinking of redox-active functional groups (*e.g.* disulfides, dityrosines) for electrodeposition or provide electron donors or acceptors to promote cell growth on electrode surfaces [194]. These electrical stimuli typically require imposing relatively low voltages (0.2–3 V vs Ag/AgCl) over short time frames (s–min), which is typically non-disruptive for cells [193], or can be directly catalyzed by the metabolism of electroactive organisms that function as living electrodes by performing extracellular redox reactions [195]. Hence, electro-biofabrication enables the creation of biological functional units (BFUs) by coordinating the assembly of living cells, hydrogel materials, and electrodes into user-designed structures that function collectively or in a spatially coordinated manner analogous to integrated circuits. With synthetic biology tools, BFU function can be tailored to specific applications by programming the cells to exhibit logic-like behavior, respond to diverse stimuli, and communicate electrochemically via redox-active signals or even electronically through extracellular electron transfer pathways [196–199].

These engineered BFUs, capable of sensing, computation, and actuation, pave the way for seamless integration between living systems and microelectronics. Such convergence can advance bioelectronics for environmental, health, biomanufacturing, and bio-machine interface applications.

Current and future challenges

To build robust living electronic devices or networks, envisioned as the 'Internet of Life' [194], an ongoing challenge lies in establishing efficient communication, or the transfer of information, between microelectronics, cells, the biotic-abiotic interface, and devices. Here, we outline key challenges across these components with a focus on communication.

First, the biotic–abiotic interface is where information transfer occurs through heterogeneous communication channels, and as a result, is susceptible to information loss. This is mainly due to the disparate communication modalities between electronics and biological systems, necessitating several forms of signal transduction to allow meaningful information transfer. For example, biological systems transmit information through ions and molecules and rely mostly on redox reactions for electron transfer

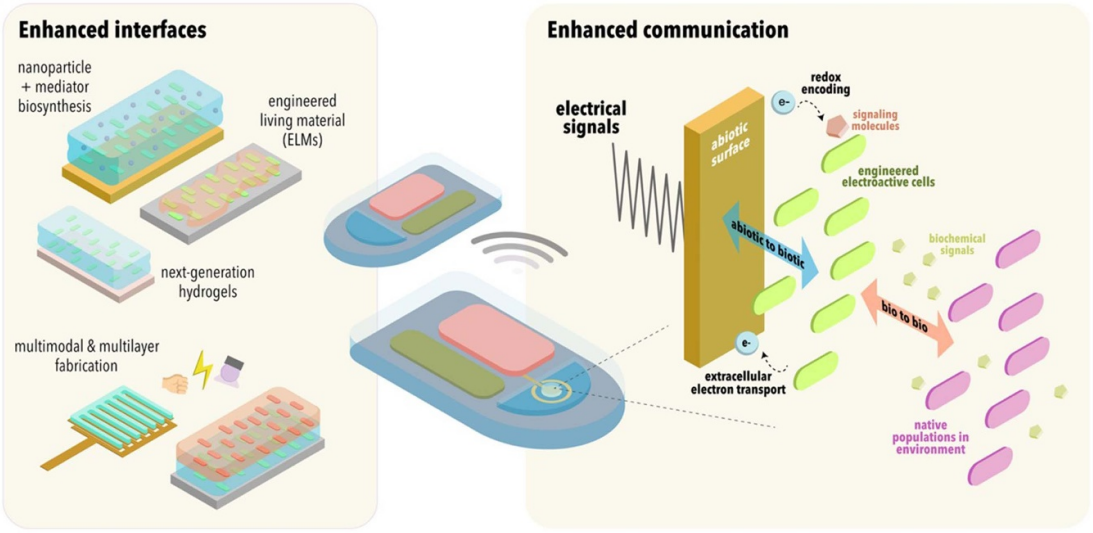


Figure 10. Enhanced abiotic-biotic interface toward efficient communication between biological systems and electronics. Enhanced interfaces may feature complex structures built using advanced fabrication techniques and next-generation hydrogels that encapsulate engineered cells programmed to collectively improve information transfer between devices and communities of cells.

where electrons are localized to molecules; whereas electronics use materials that allow delocalized electron movement. Therefore, electrical signals sent from electronics must be encoded into molecules for biological systems to interpret. While certain redox-active molecules can bridge the two systems by participating in redox reactions at electrode surfaces [199], these molecules can be short-lived (*e.g.* reactive oxygen species) and their transport is constrained by diffusion. Thus, matrices constructed at the interface not only need to provide physical support of biotic components on the electrode surface but to localize signal transfer at the interface to ensure an efficient exchange of information. Nevertheless, a stable and robust matrix is essential, as most living electronics are intended to remain functional *in situ* over extended periods. Strong structural support is needed to immobilize and prevent cell escape, which can otherwise lead to non-homogeneous signal transfer. Current hydrogel platforms often fall short in these requirements, exhibiting low mechanical strength, poor electrical conductivity, uncontrolled degradation, and insufficient containment of smaller cell types (*e.g.* microbes) due to relatively large pore sizes. These material limitations are further compounded in environmental deployment scenarios, where inadequate containment raises biosafety concerns, including unintended organism release, horizontal gene transfer, ecological competition, and long-term persistence in natural ecosystems [200]. In addition, while incorporation of conductive (*e.g.* polythiophene, polyaniline) or redox-active (*e.g.* quinone-based) materials can confer electroactivity and promote more uniform charge transport [201], their cost and potential biocompatibility concerns may limit scalability, underscoring the need for next-generation hydrogels that balance flexibility, stability, electroactivity, and biocompatibility.

Within living electronics, the encapsulated cells play the most vital role, as they are responsible for carrying out the advanced tasks ranging from biosensing to bioproduction. Although most cells are equipped with native machinery to decode redox signals generated from electrodes, the number of these machinery that have been rewired to control the activity of cells for user-specified tasks remains limited (*e.g. soxRS, oxyRS, Keap1–Nrf2*) [197]. Additionally, certain redox-active molecules with high potential can damage cellular components and induce cytotoxicity. Hence, one major challenge lies in balancing efficient redox-based information transfer while maintaining cell viability and productivity. Additionally, although high cell density on the electrode is essential for compact bioelectronic devices (especially in tasks related to bioproduction), electrochemical signals can be degraded by cellular uptake and catalytic turnover resulting in non-uniform signal transmission even within the localized area. For aerobic systems, oxygen also becomes a limiting factor for cell viability and in some cases electrochemical signal generation [194]. Like traditional bioreactor systems, managing cell growth remains a significant challenge.

Finally, we wish to touch on how charge transfer limits electro-biofabrication. While electrodeposition allows precise and real-time tuning of the structure height, it is ultimately constrained by the

diffusion limit of electrons or mediators from the electrode surface. This limitation hinders the ability to pattern complex, multilayered structures, such as multicompartment architectures that can house arrays of cells each with distinct functions. This provides opportunities for using multiple orthogonal stimuli (*e.g.* optical, mechanical) to control living material deposition for device fabrication.

Advances in science and technology to meet challenges

We anticipate discoveries in materials science can bring forth next-generation gel-forming polymers or composites that (*i*) enhance charge/information transfer, (*ii*) provide sufficient structural integrity, and (*iii*) are cost-effective and sustainable. Novel bio-derived polymers may carry useful functional groups to allow covalent linkages with other molecules, for example, to incorporate nanoparticles, redox-active moieties (*e.g.* catechol), and other CPs to improve electron transfer. These functional groups may also support different stimuli-responsive deposition techniques, leading to improved multilayered spatial patterning. When coupled with micro- and nanoscale electrode design, complex cell-gel architecture may increase surface area and promote efficient charge transfer [202, 203]. In addition, these next-generation polymer materials should resist degradation from exposure to cellular and electrochemical byproducts as well as diverse environmental conditions when deployed in the field. Such materials may even co-develop with embedded cells, forming dynamic composites that change shape or mechanical properties in response to cell growth or in response to external stimuli [204]. Lastly, advances in biorefining may generate suitable materials derived from waste feedstocks to promote environmental sustainability.

Synthetic biology continues to expand its toolbox for generating 'designer cells' with precisely regulated and customizable functions, offering several strategies for improving abiotic-biotic information transfer. First, cells can be programmed to synthesize nanoparticles [205] or stable redox-active mediators (*e.g.* phenazines, flavins) [199] to facilitate charge transfer. Secondly, cellular sensitivity to electronic signals can be heightened by regulating the intracellular sensor machinery so less signal is required for activation. Thirdly, synthetic electron transport chains can be generated to control how electrons flow through cellular components of devices that can be used to control bioproduction or signal generation by electroactive cells [206, 207]. Furthermore, cell–cell communication networks can be leveraged to relay highly-localized electronic signals to *ex situ* biological populations, establishing communication between device-immobilized cells to their surrounding environment after deployment [196].

To limit excessive proliferation, synthetic biology offers a wide range of growth-rate controllers, employing a wide range of cues to modulate population dynamics [197]. Oxygen limitations in high-density milieus can be mitigated by engineering cellular resilience to hypoxia through genetic constructs. Alternatively, anaerobic organisms are promising candidates for integration into bioelectronic systems. Cells may also be engineered to synthesize reinforcing materials to enhance the structural integrity of their encapsulating matrix and limit their own escape from the gels [186].

Although microelectronics is a relatively mature field, we advocate for greater integration and design optimization with biological applications in mind. For instance, devices can incorporate oxygenation modules to periodically deliver oxygen and provide convective flow to enhance diffusion. They may incorporate various modules with detectors and processors to combine optical and electrochemical interfaces to enable multi-modal communication with biotic components [194]. Finally, machine learning offers powerful tools for interpreting complex, noisy signals from multi-component consortia or arrays and implementing adaptive feedback control to fine-tune system behavior in real time [208].

Concluding remarks

The convergence of biofabrication, synthetic biology, and microelectronics is rapidly transforming our ability to engineer intelligent, multifunctional living electronic devices. We and others [196, 198] anticipate that continued interdisciplinary advances, will generate synergistic solutions to overcome limitations from each individual field and propel the development of living electronic materials with unprecedented capabilities. Key challenges to be addressed include achieving efficient communication between components, establishing robust and sustainable interfaces, maintaining long-term cell viability, and fabricating complex structures with high spatial precision.

Looking forward, the development of dynamic, cell-responsive materials will be crucial to support growth, cell containment, and communication within living electronics. Engineered cells will play increasingly central roles, not only as biosensors or actuators, but also as active participants in structuring their environments, and mediating electron flow. At the same time, machine learning will be essential in managing the complexity of biological data and enabling bioelectronic devices to evolve over time, moving closer to realizing adaptive, autonomous platforms capable of interfacing with the complexity of

life. Ultimately, such systems promise to open opportunities across therapeutics, diagnostics, bioproduction, energy recovery, environmental remediation, and beyond.

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