

Living Electronics

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ABSTRACT

Living electronics that converges the unique functioning modality of biological and electrical circuits has the potential to transform both fundamental biophysical/biochemical inquiries and translational biomedical/engineering applications. This article will review recent progress in overcoming the intrinsic physiochemical and signaling mismatches at biological/electronic interfaces, with specific focus on strategic approaches in forging the functional synergy through: (1) biohybrid electronics, where genetically encoded bio-machineries are hybridized with electronic transducers to facilitate the translation/interpretation of biologically derived signals; and (2) biosynthetic electronics, where biogenic electron pathways are designed and programmed to bridge the gap between internal biological and external electrical circuits. These efforts are reconstructing the way that artificial electronics communicate with living systems, and opening up new possibilities for many cross-disciplinary applications in biosynthesis, sensing, energy transduction, and hybrid information processing.

1. Introduction

Electronic and biological systems represent two limiting thermodynamic models in terms of functioning and information processing. Benefited from the advancement in nanotechnology and exponentially increasing level of integrations, modern electronics provide unprecedented storage density and processing speed with superb precision and reliability [1]. Meanwhile, the biological machinery has evolved capabilities through billion years of experimentations to process far more complex biophysical/biochemical inputs via unique

parallel pathways that are highly sensitive (sense/amplify minute signals from “noisy” background), dynamic (responsive to transient microenvironment changes), error-tolerant (self-detecting/accommodating internal processing errors), and energy-efficient (approaching fundamental thermodynamic limit) [1, 2]. Living electronics that converge the dynamic and self-adaptable features of biological machineries and the rationally defined/programmed functionalities of electronic components will open up new possibilities to effectively interrogate and direct many biologically significant processes, as well as

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inspire novel functional systems/device concepts for a range of engineering applications.

The intrinsic mismatches in physiochemical properties and signaling modalities at biotic/abiotic interfaces; however, have made the seamless integration challenging. Mechanically, conventional electronics made from solid-state metals/semiconductors are several orders of magnitude stiffer. When integrated with the much softer biological counterparts, for example in neural recording/stimulation, they could cause substantial tissue responses such as acute inflammation, neural degeneration, and glial scarring. Chemically, the inorganic surface is inert. The lack of adhesion proteins or bioactive molecules compromises cell/tissue integration and induces additional foreign body responses. These physical and chemical incompatibilities and the resulting deteriorations of interface qualities are considered as the major contributors to the degraded performance and the chronic failure of implantable bioelectronic devices [3-5]. In terms of signaling, electronics rely exclusively on the controlled transports of delocalized electrons/holes within rigidly defined matrices, while the biological processors exploit a range of water-compliant carriers from small ions to macromolecules to transmit information in a much more complex and noisier environment. Their distinct approaches in signal transductions have imposed significant challenge on the effective cross-system communications that underpin the living electronic design (Figure 1).

In the past decades, a variety of strategies have been developed to accommodate the physiochemical mismatches and forge the

structural integration of electronic and living components across different length scales. By reducing the size/dimension of traditional electronic devices, nano-electronic probes made from functional nanowires/nanotubes show substantially reduced invasiveness as compared with the bulk counterparts [6, 7] and achieve seamless bio-integration from subcellular [8-11] to tissue levels [12-14]. With synthetically encoded compositional, geometrical, and functional properties [15-20], they can be configured as either passive or active transducers that naturally match the length scales of biological building blocks and demonstrate significantly improved sensitivity and spatiotemporal resolution [7, 21]. By engineering the structural properties of device substrates, a great diversity of wearable and implantable electronics has been developed that further improve the compatibility of the flat/stiff wafer-bound devices and facilitate the seamless integration with the soft, three-dimensional biological systems [13, 22-26]. Additionally, electroactive biomaterials made of doped (e.g. with nanoparticles, nanowires, carbon nanotubes etc.) or synthetic conducting polymers (e.g. poly(pyrrole), poly(aniline) or their derivatives) are emerging as alternative interfacing platforms that provide enhanced tissue contacts, decreased electrode impedances, as well as attenuated inflammatory responses and reduced signal degeneration in chronic settings [27, 28].

In addition to the structural integration, which has been covered in many review articles [7, 29, 30], the functional coordination between electronic and biological machinery presents as

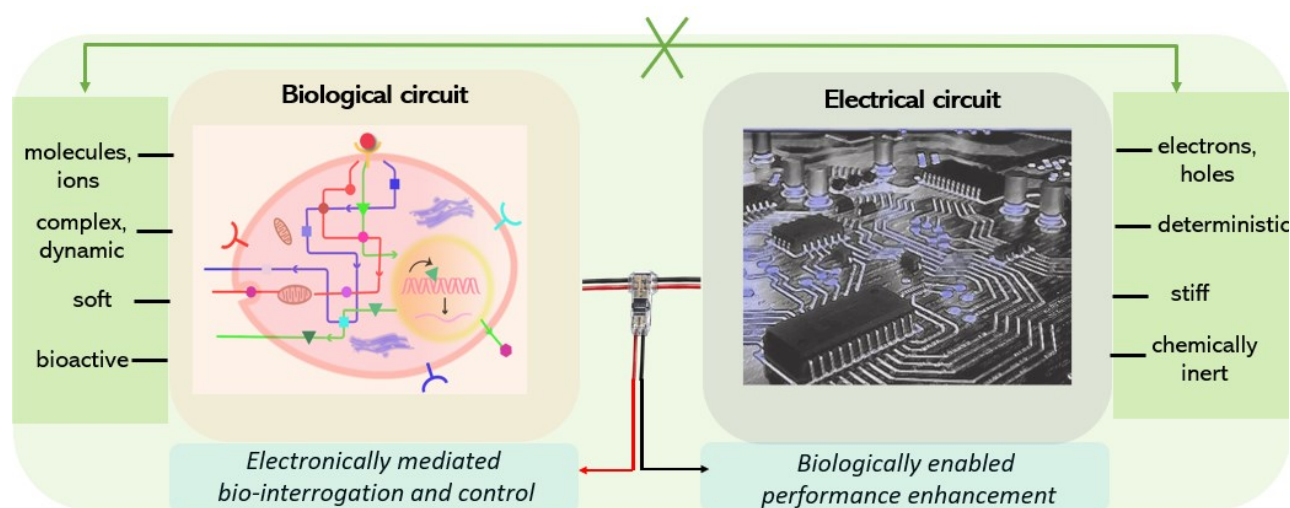


Figure 1 Living electronics paradigm by structurally integrating and functionally synergizing biological and electrical circuits.

another critical challenge that is ultimately central to the development of living electronics paradigm. The current review will primarily focus on the recent progress in synergizing biological and electronic processing through both engineering (biohybrid) and biological (biosynthetic) approaches, as well as the opportunities and prospects for future applications.

2. Biohybrid Electronics

Signaling in living systems is mediated through unique carriers as compared with traditional electronics (ions/molecules vs. electrons/holes) and algorithms (dynamic/nonlinear vs. deterministic), based on which complex biological functions, such as metabolism, development, and immunity, can be reliably programmed and regulated. Engineering of electronic interfaces with bioactive components which are capable of direct communications with biological machinery represents a promising strategy to bridge the distinct signaling modalities and enhance the interfacial coupling. This biohybrid electronic design holds great potential to facilitate the functional integration with living systems by rigorously translating/interpreting biological languages in the form of detectable electrical signals.

Biochemical signaling, where the synthesis, transport, and binding/unbinding of signaling molecules, regulates the downstream pathways, forms the foundation of cell signaling network and dominates many intracellular and intercellular processes. To actively interrogate the biochemical signaling, various electronic toolsets, including electrochemical [31] and field-effect transistor (FET) sensors [32, 33], have been developed to detect a broad library of biologically derived signaling molecules, such as secreted metabolites [34], cytokines [30, 35], and neurotransmitters [36, 37], in real time. The bio-electrochemical communication, or the electron exchange between biochemical and electrical circuits, is typically achieved through the electrode hybridization with redox active biocatalysts as primary transducers [38, 39]. For great majority of enzymes/redox proteins; however, their redox centers are deeply embedded within the insulating protein matrix and electrically inaccessible to conductive supports, thus substantially limiting the interfacial electron transfer rate which decays

exponentially with distance between donor and acceptor [40, 41]. Tremendous progress has been made to promote the electrical coupling at the biohybrid interface by electrically tethering the redox-active centers with nanoscale linkers to reduce the intra electron transfer distances [42], or immobilizing active biocatalysts within redox polymer matrices that serve as solid-state electron mediators [43, 44], yet challenges remain for complex bio-transducers, such as functional organelles/whole cells, as a result of the extra membrane shields [45, 46], or signaling molecules that are incapable of/incompatible with electrochemical transduction [47]. Bio-FET provides a more general strategy for biochemical signal transduction by detecting the surface potential changes induced by biological analytes or processes. Featuring favorable scaling effect (not compromising performance when reducing the device sizes), minimal invasiveness (without introducing potentiometric/amperometric perturbations), and low power consumption, it represents an ideal transducer platform for living electronics development. By functionalizing FET with molecular transducers, such as antibodies, enzymes, or single-strand DNA probes, the selective responses to specific targets can be achieved, which lead to the modulations of the carrier density in the semiconductor FET channel and transduce biochemical events into electrical conductivity changes with unprecedented sensitivities and spatiotemporal resolutions.

The effective Bio-FET sensing, however, demands intimate proximity and signal coupling between biological and electronic transducers. This becomes critically challenging under physiologically relevant conditions, where the outputs from the biological transducers may be quickly diluted and/or neutralized. Hence, the strength of electrical field/signals generated by charged analytes can be diminished at a distance of nanometer scales as a result of increased ionic strength and Debye screening [48]. To overcome this challenge, functional hydrogels have been recently exploited as interfacing materials to bridge the gap between the biotic and abiotic signaling and promote the cross-system transductions (Figure 2a) [49]. By modulating the local dielectric microenvironment with chemically conjugated polyethyleneglycol (PEG) [50], the electrostatic screening can be significantly reduced, enabling high-sensitivity detections of prostate specific antigen (10 nM) under high ionic strength conditions (100 mM

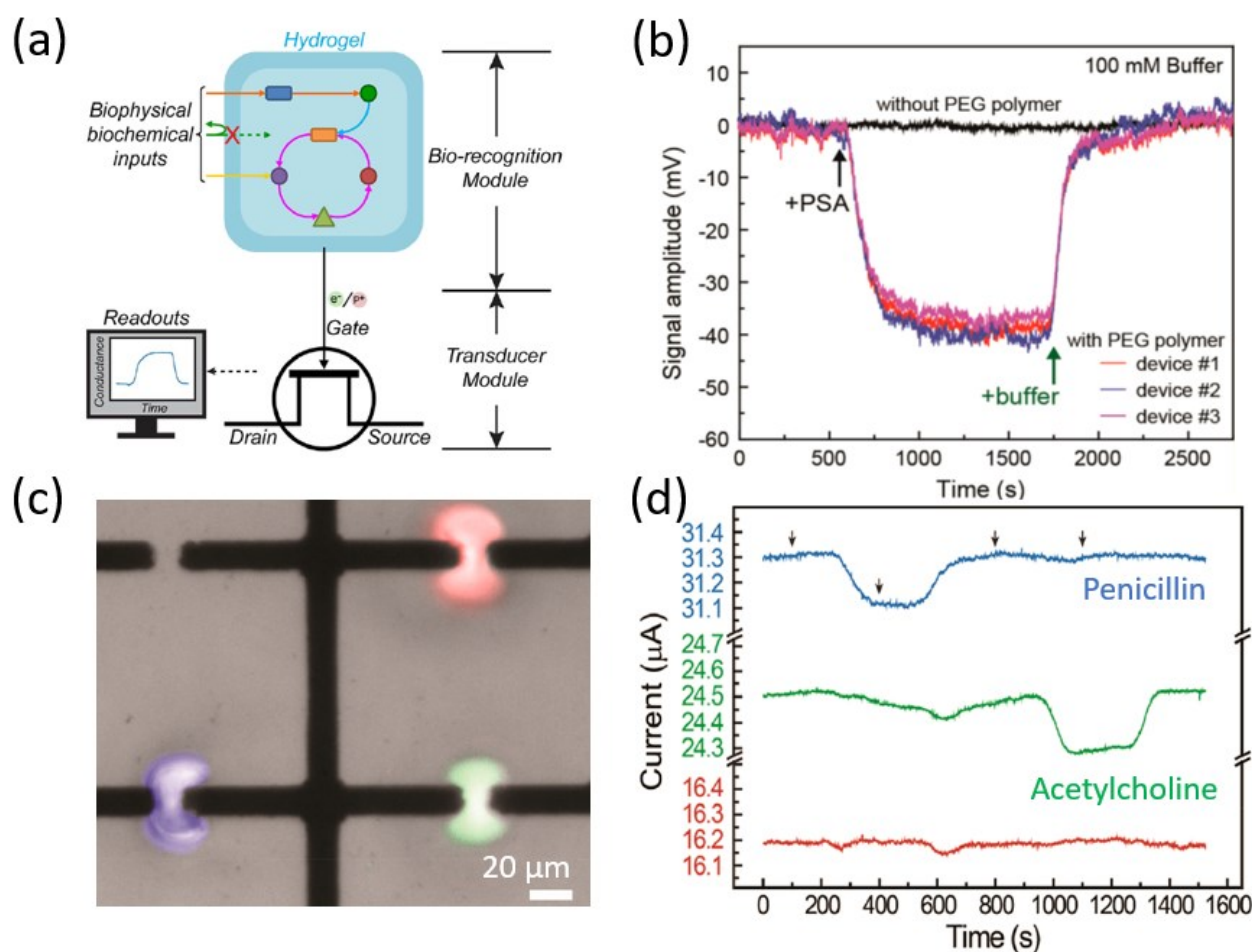


Figure 2 (a) Schematic representation of hydrogel-gate transistor design, where biological transducers (such as enzymes or functional organelles) are encapsulated within the hydrogel matrix with tunable physiochemical properties. The biochemical outputs from the bio-processor can be enriched/amplified in this confined microenvironment and effectively coupled with the electronic transducers. Reprinted with permission from Ref. [49], © American Chemical Society 2019. (b) Real-time PSA detection using Si nanowire FET sensors with and without PEG surface modifications. Reprinted with permission from Ref. [50], © American Chemical Society 2015. (c) Graphene FETs with biologically encoded hydrogel gates generated from spatially-defined photopolymerization (labeled with red, green and blue fluorescent dyes) and (d) Real-time multiplexed sensing of penicillin and acetylcholine chloride. Reprinted with permission from Ref. [51], © American Chemical Society 2018.

phosphate buffer) (Figure 2b). When programmed with spatially controlled photopolymerization (Figure 2c), biologically-encoded hydrogel gates can be precisely defined on top of individual FET channels, which offers controlled access to input molecules and highly localized enrichment/amplification of outputs from bio-transducers [51]. The multiplexed detection of penicillin and acetylcholine have been achieved with a minimal cross-talk. The hydrogel layer is also found to significantly reduce the

non-specific binding - another major obstacle toward applications in physiological fluids that typically present a high background of proteins/other biomolecules (up to tens of mg/mL). Additionally, by creating a biologically compliant microenvironment, the hydrogel matrices substantially improve the preservation and functioning of the bio-transducers by mitigating the progressive chemical and structural degradations over time.

The hydrogel-mediated enhancements of both

signal transduction and biocompatibility also have the potentials to facilitate the structural and functional integration at higher biological levels. Traditional electrochemical/FET biosensors could yield important “analytical information” which answers the questions of whether and how much of a certain signaling molecule is present, but with limited capability for comprehensive interpretation of sophisticated biological signaling/function, such as apoptosis or immune responses. By integrating more complex biological machineries, such as whole cells or functional organelles, as primary transducers, the living electronic platform will be implemented with unique capabilities to process parallel biophysical/biochemical inputs through a series of signaling pathways and respond with

biologically relevant patterns that deliver direct functional information [52]. By placing hundreds of T-cells on top of nanowire FET sensors, for example, antigen-specific immune responses can be electrically detected with a great temporal resolution after exposure to external stimulus, making the technique very appealing to elucidate the fundamental kinetics of activation induced immune activities (Figure 3a) [53]. Similarly, by tethering isolated mitochondria to graphene FET sensors and monitoring the local pH change in response to outer membrane permeabilization, the intrinsic mitochondrial pathway of apoptosis can be interrogated in real time (Figure 3b) [54]. These works provide important proof-of-concept demonstrations of more complex living transducer designs, but currently are still limited

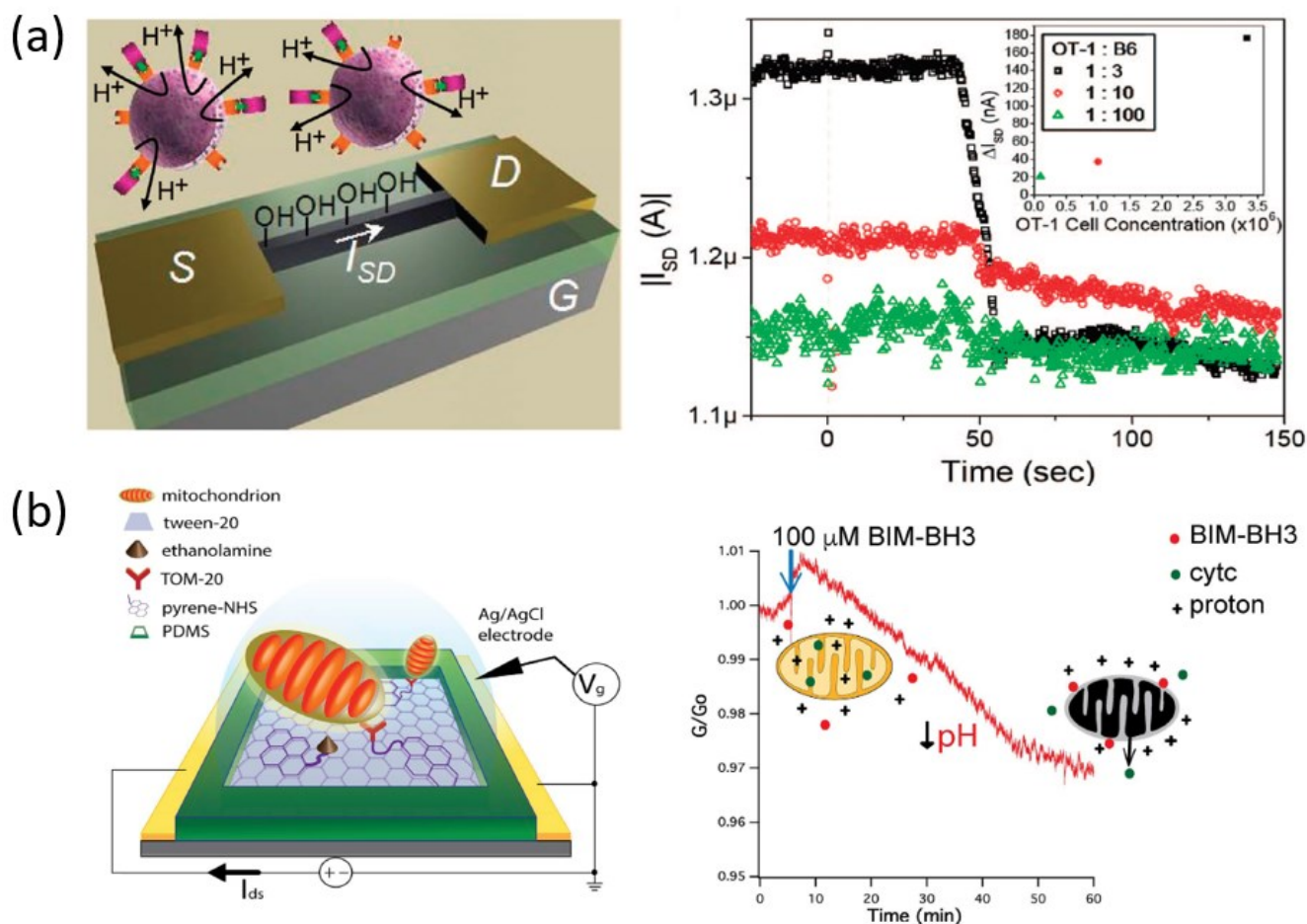


Figure 3 Bio-FET with higher level biological machineries integrated: (a) antigen-specific T-cells integrated nanowire FET sensors for the detections of antibody-induced extracellular acidification. Reprinted with permission from Ref. [53], © American Chemical Society 2008. (b) mitochondria integrated graphene FET for the sensing the mitochondrial outer membrane permeabilization. Reprinted with permission from Ref. [54].

by the lack of effective signal coupling (mainly rely on extracellular acidification) and short life-time of the living components. To generate meaningful signals, decreased buffer concentrations and/or increased number of cells/organelles are also typically required, which not only compromise the viability and spatiotemporal resolution, but also restrain the capability to address biological heterogeneity at single cell/organelle levels. Future developments in engineered the bio-interfaces (e.g. with hydrogels or other functional biomaterials) that are capable in synergizing the biological and electrical signaling could open up new possibilities for biohybrid, living electronic designs.

3. Biosynthetic Electronics

Life is intrinsically driven by the flow of electrons. From photosynthesis to cellular respiration, biological machineries have established efficient energy transductions through diverse electron transport complexes. Design and programming of these biosynthetic pathways to interconnect biological and electrical circuits represent another promising strategic approach for living electronics developments. While most biological electron transports occur intracellularly at molecular scales, certain marine microorganisms, such as *Shewanella* and *Geobacter*, have evolved a unique capability to complete redox half-reactions outside the cell through bidirectional extracellular electron transfer (EET)

at much longer length scales (nano- to centi-meter) [55-58]. These electrochemically active bacteria (EAB) can directly exchange metabolic electrons with solid-state donors/acceptors (such as metal electrodes) [59], thus naturally bridging the internal biological and external electrical circuits (Figure 4). EET occurs through both direct and indirect routes, where the outer membrane cytochromes (OMCs) [60], nanoscale proteinaceous filaments (referred to as pili or nanowires) [61-64], or secreted redox-active “electron shuttles” [65-68], are exploited to implement electron transfer across different scales. These biologically enabled electron conduits along with their self-assembled nanostructures represent a category of biosynthetic interfaces that is very different from the engineered bioelectronics and can initiate new signaling gateways between electronic and living systems.

From a perspective of materials chemistry, EAB function as cellular factories for self-regulated production of mechanically compliant and biologically relevant electroactive materials with genetically encoded properties. In contrast to the conventional platform that relies on high-quality metal/semiconductor materials and sophisticated fabrication/assembly under strictly-defined conditions, the capability of EAB to self-immobilize, grow, and inter-connect under nontoxic, room temperature, and aqueous conditions makes the manufacturing extremely facile and reproducible [69]. Furthermore, the

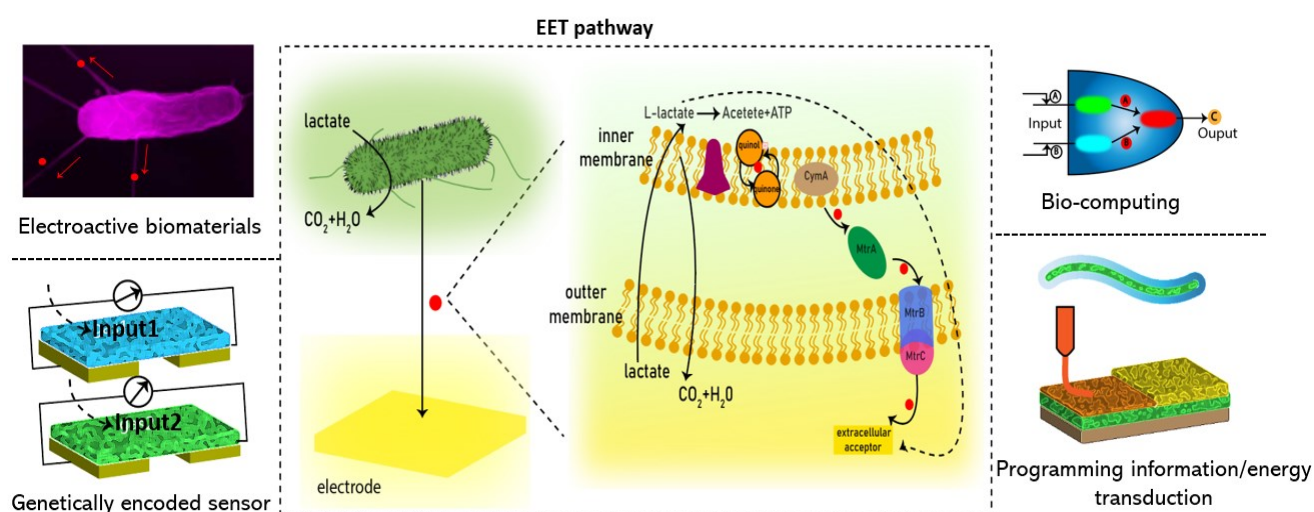


Figure 4. Scheme about the paradigms of biosynthetic electronics.

possibility to program device sensitivity and specificity through synthetic biology tools has the potential to completely transform the way that bioelectronics are designed and produced [70, 71]. For example, Leang et. al. modify the capacity of *G. sulfurreducens* for EET by deleting a gene responsible for encoding protein with a PilZ domain. The deletion results more production of pili and pili associated OmcS and contribute to a 6-fold increase of conductivity in formed biofilms [72]. As part of the EET pathway, microbial nanowires can also be independently engineered to regulate their electrical conductivities through genetic manipulation of the abundance of aromatic amino acids in the monomer peptide [73]. Based on the structure-function understanding acquired from EAB models, Altamura et.al build an artificial electroactive biofilm using synthetic nanowire scaffolds, where prion domain is attached to the redox protein rubredoxin, functioning as self-assembling unit and charge carrier, respectively [74]. These

examples demonstrate the feasibility and effectiveness of modulating inter-molecular, redox-mediated electron flow from bottom up via synthetic gene editing.

In addition to the intrinsic electrical properties of the bioderived materials, the charge transport across the biotic-abiotic interface represents another important aspect for biosynthetic electronic design. The unique interplay between cell metabolism and external electron acceptor (electrode) offers the possibility to directly interrogate and program EET through electrochemical gating. Systematic studies have been carried out to elucidate the effect of electrochemical potential on EET pathways [75-77]. *G. sulfurreducens* grown on poised anode, for example, has been found to synthesize more extracellular cytochromes such as OmcS at lower potentials [76]. Recent advancements in nanomaterial synthesis/integration provide additional opportunities to further enhance the electrical coupling between the two distinct

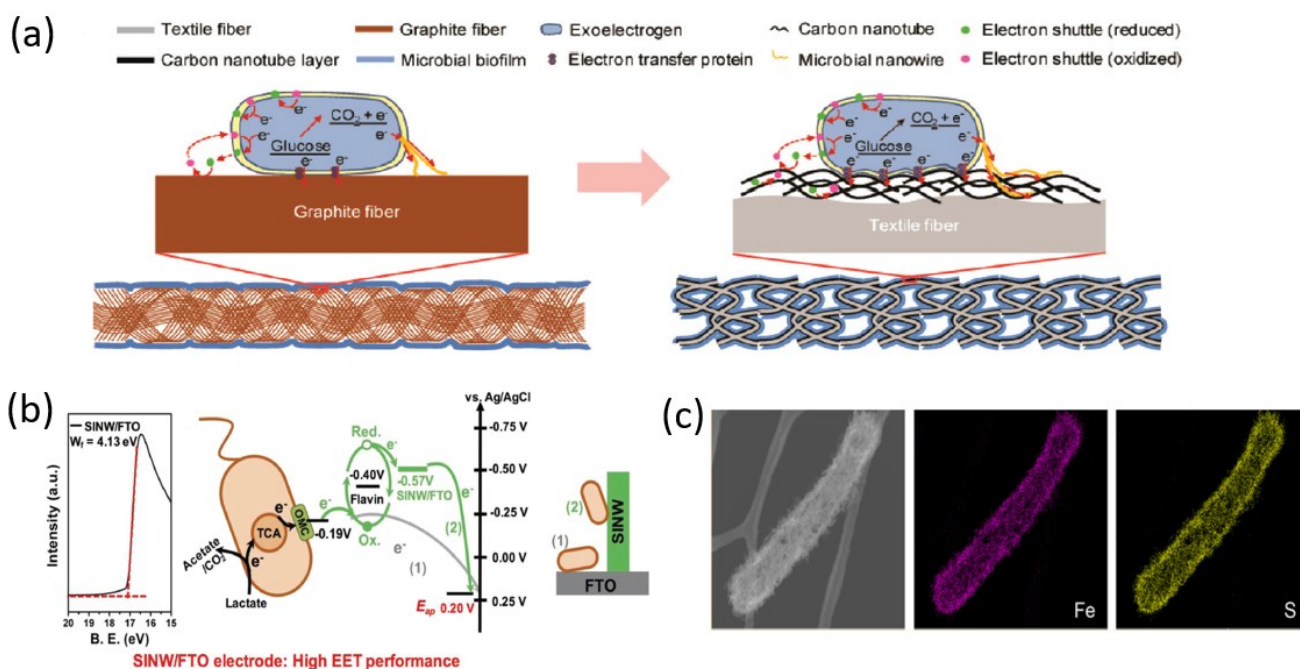


Figure 5 Schematic illustration of strategies used to facilitate electron transfers at biosynthetic interfaces. (a) Schematic of the electrode configurations and electron-transfer mechanisms for the CNT-textile anode (right), compared with the widely used carbon cloth anode (left). Reprinted with permission from Ref. [79], © American Chemical Society 2011. (b) SINW/FTO electrode for facilitating both direct and indirect bacterial EET. (left) The cut-off energy region of UV photoemission spectra of the SINW/FTO electrode. (right) Schematic of the cascade of EET across the bacteria/FTO interface with SINW mediated energy levels. Reprinted with permission from Ref. [80]. © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018. (c) Bright-field STEM image and corresponding EDX elemental mapping of a PV-4 cell coated with nanoparticles. Reprinted with permission from Ref. [84], © American Chemical Society 2014.

charge transport systems [78]. By increasing the active interface area in a hierarchical and microporous CNT-textile anode, the charge transfer resistance can be reduced by 90 % (Figure 5a) [79]. The fermi levels of the semiconductor electrodes can also be precisely tuned, as demonstrated in a composite In_2O_3 nanowire/FTO design, to match OMCs' energy level and mitigate the charge transport barrier (Figure 5b) [80]. Additionally, EAB are known for their capability for dissimilatory reduction/biogenic production of a broad range of inorganic nanomaterials, such as metal nanoparticles [81, 82] or reduced graphene oxide [83], through EET. The process creates materials that are closely coupled with OMCs and actively wired the redox active centers. The effective integration of biomineralized iron sulfide nanoparticles have been demonstrated to substantially improve the microbial fuel cell performance by electrically contacting and interconnecting *S. loihica* cells (Figure 5c) [84].

Microorganisms host metabolic functions inside cell membranes and draw energy feedbacks from their environments to self-grow and organized into highly hierarchical structures in response to external stimuli via intrinsically defined genetic pathways [85, 86]. With recent breakthroughs in elucidating genetic pathways of EABs [87–89], synthetic toolkits provide opportunities to

incorporate additional functionalities by directly rewiring their cellular signaling pathways to change how they interact with the environment, i.e. affinity to different substrates, sensing ability and even light utilization [90]. By reconstructing the Mtr pathway with arsenite-responsive transcriptional circuit, for example, *S. oneidensis* can be engineered to function as living electronic sensors with genetically encoded specificity, where the peak bio-electrochemical current is correlated with the arsenite concentration (Figure 6a) [91]. The electronic actuation of gene expression has also been demonstrated using redox mediators as signaling molecules, where the applied voltage can induce quick, reversible cellular responses that are dependent on the amplitude and frequency of the electronic inputs (Figure 6b) [92]. This bi-directional electrical linkage with biological circuits is opening up new possibility for real-time bio-computation with bioelectric I/O that streamline the processing and integration (as compared with the traditional optical readout) [93–95]. In particular, with the synchronization of multiple modalities, complex Boolean logic gate networks can be realized, where the inputs are processed in-parallel by living bacteria through their regulatory/metabolic pathways and respond with electrically readable signals. Based on a similar concept, Li et al. build a bacteria-based AND gate using *Pseudomonas*

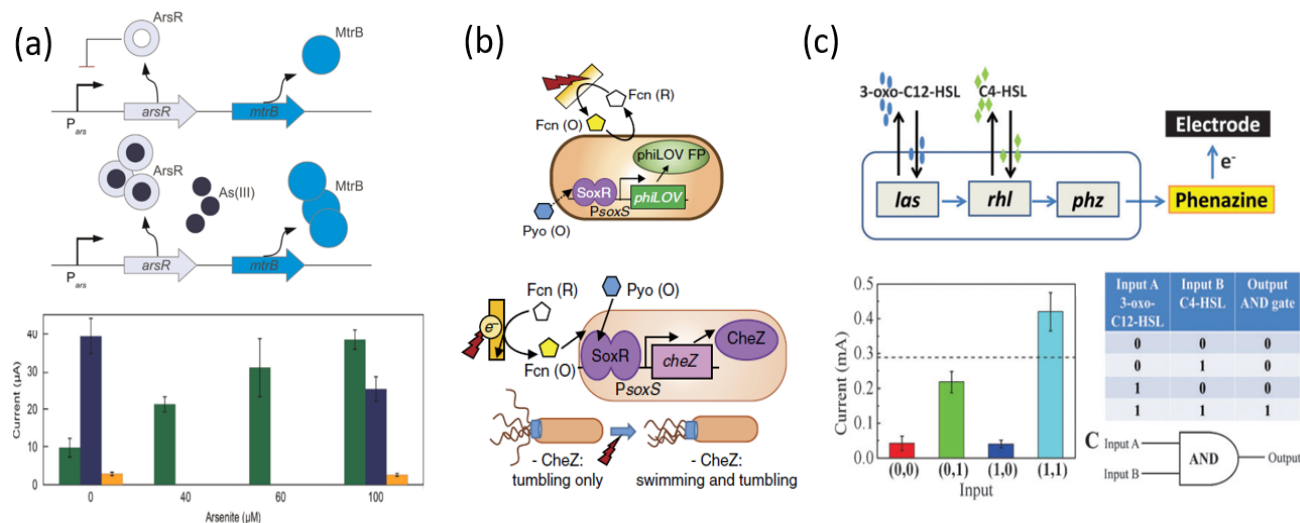


Figure 6 Using synthetic tools to engineer bio-directional communications between bacteria and electronics. (a) Design of arsenite-responsive transcriptional circuit in plasmid pArsR/MtrB. As arsenite enters the cell, ArsR dissociates from the operator, which leads to an increase in *mtrB* expression. Reprinted with permission from Ref. [91], © Elsevier B.V. 2014. (b) Schematic of the electronic control of cell fluorescence and electronic induction of the cell mobility. Reprinted with permission from Ref. [92]. (c) Bacteria-based AND logic gate to control phenazine synthesis by *P. aeruginosa*. Four different input combinations regulate the Phenazine-based current production. Reprinted with permission from Ref. [96]. © Royal Society of Chemistry 2011.

aeruginosa (PA 14) *lasI/rhlI* double mutants which are two important regulatory systems for cell-cell communications (Figure 6c) [96]. The electrical outputs can be effectively regulated as a function of two signaling molecules, 3-oxo-C12-HSL and C4-HSL, that are involved in the biosynthesis of phenazine/current generations. Moreover, by genetically modifying microorganisms that natively lack EET pathways, researchers can further expand the library of biosynthetic electronics with additional functionalities that are hard to achieve using traditional engineering methods, e.g. by expressing EET conduits to electrically link the membrane-shielded photosynthetic charge transport system for bio-energy harvests and transductions [97].

The spatial organization is another hallmark of microbial life, where the complex functions depend on having the right cells/bio-components in the proper places [98, 99]. In the context of EET, the capability to rationally program the interaction between EAB and/or their external electron donors/acceptors has the potential to significantly advance the biosynthetic electronics

paradigm. One-dimensional assembly of EAB has been recently demonstrated in the form of core-shell bacterial cables [100]. Confined in porous hydrogels with tunable geometries and physicochemical properties, their microenvironment and cellular interactions can be precisely engineered to regulate EET and generate a library of conductive bacterial cables with encoded electrical properties (Figure 7a). These bacterial cables can also serve as living building blocks to construct complex bioelectrochemical systems, in which both charge and mass transports can be designed and optimized at biologically relevant scales to maximize the system performance. These research endeavors are currently benefiting from the rapidly progressing bioprinting technology, which enables the 3D integration of biologically relevant materials/structures with unprecedented resolution and throughput. In particular, the recent advances in bio-ink design makes it possible to effectively incorporate and spatially organize living components [101-104]. Exploiting freeze-dried cells as both active biocatalysts and fillers, for example, Qian et al. demonstrate

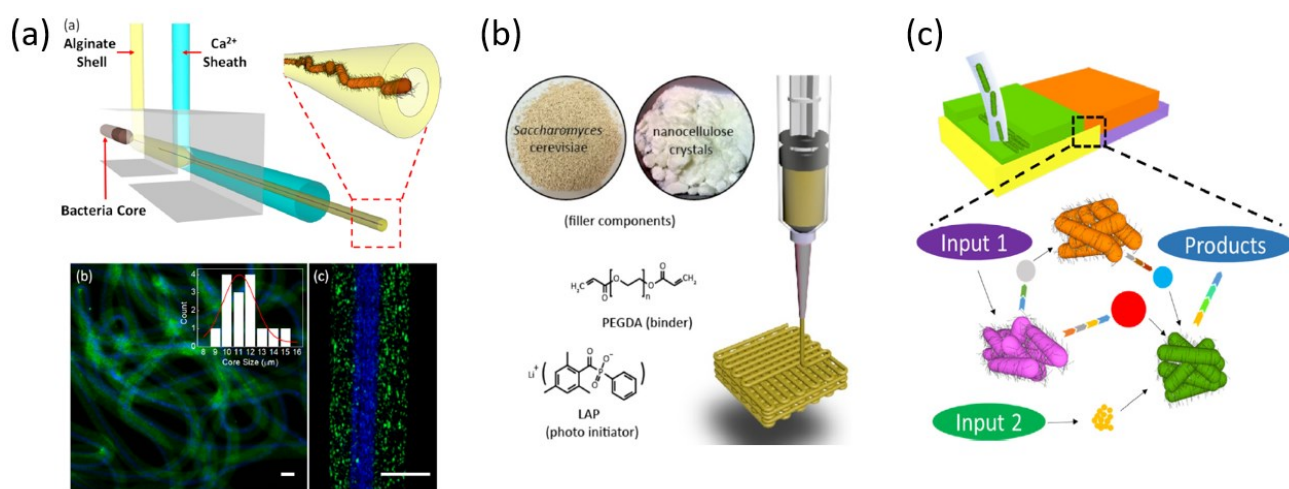


Figure 7 Schematic illustration of using the “bottom-up” assembling strategy to spatial pattern bacteria with microenvironment and other communities. (a) (Top) Microfluidic generation of core/shell bacterial cables generation. The EAB-containing core stream (brown) is flow focused before entering the alginate shell stream (yellow). The core/shell hydrogel fiber is formed at the end of the device when a CaCl₂ sheath flow is introduced to cross-link the alginate. (Bottom) Low- and high-magnification fluorescent images of as-fabricated core/shell fibers; green color indicates the alginate shell mixed with Dextran nanoparticles and blue indicates the bacteria with Hoechst nuclei staining. Reprinted with permission from Ref. [100], © American Chemical Society 2018. (b) Schematic preparation and printing of bioinks with tunable cell loading. Ink components include fillers, binder and photoinitiator. Reprinted with permission from Ref. [105], © American Chemical Society 2019. (c) Multidimensional integration of living and synthetic components for programming biological processing and system functionality from the bottom up. Reprinted with permission from Ref. [106], © Elsevier Ltd. 2019.

significantly enhanced cell loading density and viability while providing desirable rheological properties for high-resolution 3D printing (Figure 7b) [105]. The consolidation of these sophisticated engineering approaches will significantly expand the scope of traditional synthetic biology (which has been primarily focused on molecular level engineering), by rationally designing the biotic-abiotic interfaces, spatially modulating the bio-physical/biochemical microenvironments, directing the system-level electron flows, and programming the ensemble behaviors to create new synthetic functionalities (Figure 7c) [106].

4. Summary

In summary, recent progress in forging the structural and functional synergy between biological and electrical circuits is transforming the traditional bioelectronics field. By seamlessly integrating biological processors at molecular, organelle or cellular levels, biohybrid electronic devices are being developed to process multimodal, dynamic physiochemical inputs and deliver physiologically relevant functional information. By re-constructing and programming charge transport pathways across different length scales, various biosynthetic strategies are being explored to naturally bridge biological and electrical circuits, allowing electrical “reading” and “writing” of biologically significant functions. Multi-dimensional systems are also being developed with structured distribution of biotic/abiotic components and programmed energy and information flow. These efforts are blurring the distinction between living systems and artificial electronics, and could revolutionize how biological functions can be designed and interpreted.

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