100th Anniversary of Macromolecular Science Viewpoint: Soft Materials for Microbial Bioelectronics

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ABSTRACT: Bioelectronics brings together the fields of biology and microelectronics to create multifunctional devices with the potential to address longstanding technological challenges and change our way of life. Microbial electrochemical devices are a growing subset of bioelectronic devices that incorporate naturally-occurring or synthetically-engineered microbes in electronic devices and have broad applications including energy harvesting, chemical production, water remediation, and environmental and health monitoring. The goal of this Viewpoint article is to highlight recent advances and ongoing challenges in the rapidly developing field of microbial bioelectronic devices, with an emphasis on materials challenges. We provide an overview of microbial bioelectronic devices, discuss the biotic-abiotic interface in these devices, and then present recent advances and ongoing challenges in materials related to electron transfer across the abiotic-biotic interface, microbial adhesion, redox signaling, electronic amplification, and device miniaturization. We conclude with a summary and perspective of the field of microbial bioelectronics.

Introduction

Bioelectronics brings together the fields of biology and microelectronics to create new, multifunctional devices with the potential to address longstanding technological challenges. Example applications include brain-machine interfaces that treat diseases or control prosthetic limbs[1], ingestible biomedical devices that can sense and wirelessly transmit information about the gut[2], wearable devices for monitoring physiological activity[3,4], biodegradable implantable devices that stimulate healing[5,6], and a range of microbial bio-electrochemical devices that produce electricity, remediate wastewater, and produce fuels and other high-value chemical products[7,8]. Bridging the fields of biology and microelectronics comes with a number of challenges due to the different modes of electrical communication, mechanical properties, and chemistries most commonly found in biotic and abiotic systems. For example, biology commonly uses ionic and molecular signals for communication, while microelectronic devices rely on electronic signals. Biological systems are aqueous, soft, and pliable, while microelectronic devices are generally non-aqueous and rigid. Biology relies primarily on organic materials in aqueous environments, while the most powerful computing devices are based on silicon and metallic or inorganic components. Biological control systems are decentralized, with each cell contributing to an environmental response through its own metabolic process, while microelectronic devices have a central computing center. Additionally, biological systems require different types of energy sources and a safe environment to function robustly for necessary durations. Interfacing these two systems to create hybrid devices has therefore necessitated novel strategies to mediate these differences, including the development of novel architectures, synthetically engineered biological pathways, compatible and complementary sources of power, and new materials.

Microbial electrochemical devices are a growing subset of bioelectronic devices that incorporate naturally-occurring or synthetically engineered microbes within conductive materials. As shown in **Figure 1**, the applications are broad and include energy harvesting[9], the production of chemical fuels[10], the detection of environmental contaminants[11], water remediation[12], and monitoring chemical signatures of injury using ingestible devices within the gut[2], among others[13,14]. Microbial bioelectronic devices have significantly increased in complexity and functionality over the past 15 years with the discovery and engineering of new microbes that can couple electrically with materials, placing new needs and demands on materials. For example, microbial fuel cells have been demonstrated to be a viable power supply for meteorological buoys[15], and the use of highly porous, three-dimensional, conductive interface layers can significantly enhance current densities[16]. Bioelectrocatalysis has emerged as a powerful technique for producing chemicals

and fuels, with successes achieved with the reduction of nitrogen, production of chiral chemicals, and CO_2 fixation. However, the electronic resistance of the cell membrane presents challenges to achieving significant current fluxes with each of these reactions when mediated by microbial cells[10]. Redox-active polymer coatings have been effective at enhancing electron transfer from cathodes to *Escherichia coli* (*E. coli*) at low potentials, increasing the current available for microbial bioelectrosynthesis[17,18].

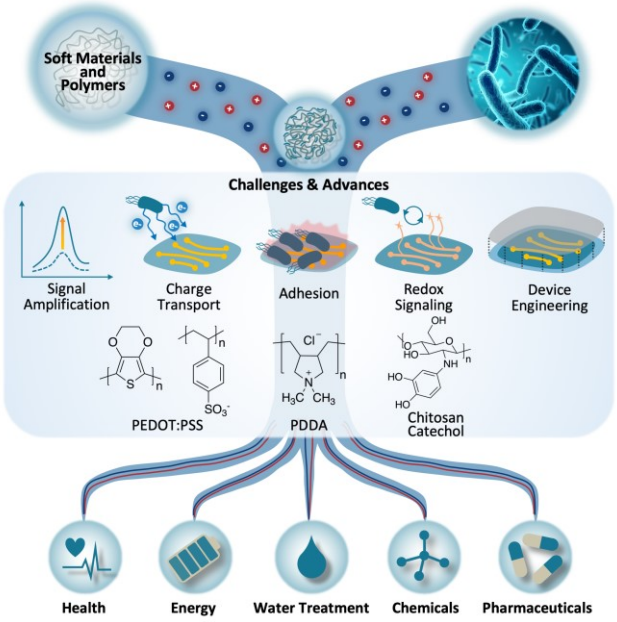

Figure 1. Interfacing microbes and soft materials enables a range of applications, but a number of challenges remain. Applications include fast sensing, energy storage, water treatment, electrosynthesis, and chemical production. Ongoing challenges include amplifying electronic and/or ionic signals, transporting charges over long distances, maintaining microbial adhesion to various electrode materials, achieving effective redox signaling, and proper device engineering. Microbe schematic adapted with permission from Paulista/Shutterstock.

There is a growing interest in expanding the capabilities of bioelectronic devices that better leverage the functionality and versatility of micron-scale microbes. Naturally-occurring exoelectrogenic microbes can perform extracellular electron transfer (EET) to electrodes, enabling electrical power generation from the oxidation of organic species or acting as biosensors that can detect toxic contaminants in the environment[19–24]. A related class of exoelectrophilic microbes can accept electrons from electrodes and catalyze the production of target chemicals and/or the utilization of target substrates such as carbon dioxide[8]. Since microbes can proliferate, microbial electrochemical devices can remain functional for extended periods of time[25,26], and they have the potential for self-healing capabilities. Microbial devices can also be miniaturized, multiplexed, and screen printed to generate multiple functions in a single device using low-cost processing strategies[13,27–29]. Finally, the tools of synthetic biology enable engineering the metabolic processes of microbes to, for example, produce a desired chemical[10,30], respond to a specific chemical target or chemical change in the environment[31–35], or perform a specific function in response to an electrochemical signal delivered externally[36]. There is considerable interest in taking advantage of synthetically engineered microbes for new device applications, and a growing number of programs and funding agencies have called for research inputs for synthetically engineered bacteria integrated in microbial devices. Also, a number of organizations and meetings have emerged to advance the development of microbial bioelectronics technologies. These include The International Society for Microbial Electrochemistry and Technology, the Asilomar Bioelectronics Symposium, and the Gordon Conference on Bioelectronics.

Microbial bioelectronic devices come with a number of unique challenges. Effectively integrating microbes within devices requires developing interface layers with physical and chemical properties (conductive, porous, biocompatible) that maximize the interfacial area for electron transfer. The electrochemical interactions of microbes with electrodes are complex and can involve a combination of direct and indirect methods of electron transfer which vary in efficiency depending upon the design; the latter is mediated by soluble redox-active organic molecules that are produced by the microbes or added exogenously. To ensure cell viability, a food source must be provided to the microbes and released at the proper location, rate, and concentration for the desired duration. Detecting or producing electronic signals from microbes can be made more challenging by heterogeneities within a population[37]. Additionally, the incorporation of synthetically engineered microorganisms in devices raises a number of safety concerns due to the possibility that the microorganisms could be released to the environment. Mechanisms to prevent the spread and proliferation of engineered microorganisms may be required, such as genetically encoded "kill switches" that couple specific environmental cues to cell viability[38,39].

The goal of this Viewpoint article is to highlight recent advances and ongoing challenges in the rapidly developing field of microbial bioelectronic devices, with an emphasis on materials challenges. A number of excellent reviews have covered recent advances in the development of materials for bioelectronics[3,40–46]. However, these reviews have not focused on microbial electrochemical devices. In this Viewpoint, we first provide a brief overview of microbial electrochemical devices and discuss the biotic-abiotic interface of microbial bioelectronic devices, where many of the materials challenges arise. Next, we detail specific materials challenges for microbial electronic devices and review recent advances in materials and device developments. Finally, we conclude with a perspective on current challenges and future directions for research. We do not present a comprehensive review of materials for microbial bioelectronics or bioelectronics applications and instead refer the reader to a number of reviews about the design and engineering of electrodes[47–53], redox polymers[18], and conjugated polymers[40,41] for microbial bioelectronic devices.

Microbial Bioelectrochemical Devices

Microbial bioelectrochemical devices have a number of appealing qualities. First, microbial-based processes are already used in commercial and industrial applications including fermentation, wastewater treatment, and drug discovery and synthesis[54,55]. These processes are in general robust, scalable, and cost-competitive. Microbes are living and able to "self-heal" by replacing dead or sick cells with healthy ones. Microbial-based devices can be used in applications that vary widely in size and scale. For example, devices that harvest energy from the oxidation of organic matter in ocean sediment can power remote sensing devices. However, these devices require large-scale electrodes to achieve sufficient power. One design used multiple anodes with a footprint of 61 X 61 cm^2 and total geometric surface area of 2.2 m^2 [15], while another design used meter-long electrodes[56]. As an example of small-scale devices, Zhou and coworkers developed an electrochemical reactor with a 4 cm^2 footprint that used the exquisite sensing capabilities of microbes to report on dynamic changes in chemical and temperature perturbations[57]. Efforts to further miniaturize microbial devices that can be deployed in real environmental samples are underway[27], but it remains unclear how small microbial devices can be while maintaining functionality. Microbes are diverse and versatile and can be used for a variety of functions that include sensing, producing a chemical, and performing redox reactions to metabolize and decontaminate the environment. Finally, synthetic biology can be used to program microbial chassis with improved capabilities, such as increasing the efficiency of electrical coupling with materials[58], extending the sensing capabilities of microbes[59], and incorporating safety features that prevent release into the environment[38,39]. Altogether, microbial bioelectronic devices promise to integrate electronic communication, actuation, and control with microbial species which can perform multiple functions in parallel and can be potentially tailored for specific purposes. In this section, we briefly highlight examples of current and emerging bioelectronic technologies.

Microbial Fuel Cells (MFCs)

MFCs are microbial electrochemical systems that generate electricity from the oxidation of organic matter[7,14,15,48,60–63] (see **Figure 2A**). These devices take advantage of exoelectrogenic bacteria, such as *Shewanella oneidensis* (*S. oneidensis*) and *Geobacter sulfurreducens* (*G. sulfurreducens*), that are capable of oxidizing organic matter and transferring electrons to anodes in an electrochemical cell. MFCs provide a source of portable power and can also be used to simultaneously degrade environmental contaminants and pollutants. In benthic MFCs, a biofilm of exoelectrogenic microbes forms on the surface of an anode embedded in marine sediment, and these microbes deliver electrons to the anode during the oxidation of acetate or elemental sulfur. At the cathode, microbes living in an aerobic environment use these electrons to drive their metabolism and ultimately deliver those electrons to oxygen as a terminal electron acceptor. The current generated is sufficient to be harnessed as electrical energy and used to power portable buoys[15]. MFCs can also be applied to decompose and break down contaminants in wastewaters while recovering energy in the form of electricity[7,12,14], and companies (*e.g.*, Aquacyl) have emerged to commercialize MFCs for wastewater treatment. MFCs can also treat contaminants in the soil[64], including pyridine, perchlorate, and chlorinated organic solvents[65–68]. Finally, MFCs can be miniaturized to deliver high power densities[69] and used in portable devices or small-scale applications[13].

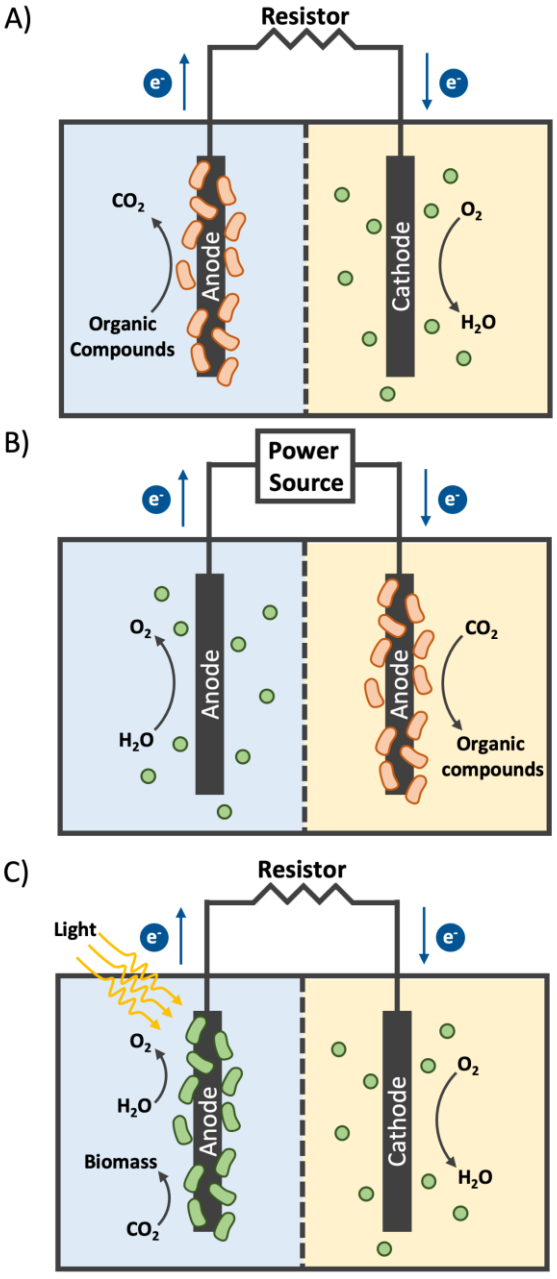

Figure 2. Example microbial bioelectrochemical devices including A) microbial fuel cell (MFC), B) microbial electrosynthesis system (MES), and C) biophotovoltaic (BPV).

Microbial Electrosynthesis Systems (MESs)

MESs are MFCs operated in reverse: a microbial biofilm on the cathode utilizes externally supplied current to catalyze the production of a desired product or chemical[8,10,70,71] (see **Figure 2B**). MESs can be utilized for nitrogen reduction,

ammonia production[72], chiral chemical synthesis[73,74], carbon fixation[75,76], and biofuel production[77]. MESs can provide environmentally friendly routes to produce useful chemicals and biofuels because they leverage cell factories created using metabolic engineering, which provide high yields of specific chemicals at moderate temperatures without the need for large energy inputs. In fact, MESs can improve upon yields obtained using standard fermentation protocols since they can provide additional reducing power for the reactions of the biosynthetic pathway. Call et al. showed that hydrogen production using MESs had greater yields than fermentation and higher energy efficiency than water electrolysis[78]. This potentially enables the use of MESs to generate and store renewable energy in biochemical products with low potentials, like hydrogen and alpha-keto acids, hydrocarbons and alcohols.

Biophotovoltaics (BPVs)

Biophotovoltaics are microbial bioelectrochemical systems that convert solar energy into electricity[79–82]. Similar to MFCs, microbes on the anode produce the electrical energy that can be harnessed. However, unlike MFCs, phototropic organisms such as photosynthetic algae and cyanobacteria are used in BPVs to capture light, split water, and produce electricity (see **Figure 2C**). When compared to traditional, solid-state photovoltaics, the microbes used in BPVs offer advantages such as self-sustainability and the ability to produce electricity even at night[83], but the current outputs from BPVs are still orders of magnitude lower than MFCs[84]. A new class of BPVs has emerged that are generated by coating heterotrophic microbes with semiconducting nanoparticles that are photosensitive. These BPVs can be used for light-driven enzymatic synthesis by precipitating these materials on cells to create shells that harvest light to drive cellular metabolism[85].

Microbial Sensors

Microbial bioelectronic devices can also be used as sensors by leveraging the exquisite abilities of microbes to monitor different physical and chemical conditions in their local environment[11,33,34]. A sensor with an MFC architecture can be used to detect the presence of organic matter or toxic contaminants by monitoring the current produced by microbes whose metabolism is linked to the presence of those chemicals in the local environment. Oxidizable organic matter produces an increase in current while toxic contaminants such as heavy metals can produce a large drop in electronic current. Since the devices harness electric energy, they can also be self-powered[33]. Cellular growth allows a microbial biosensor to power itself for a longer functional lifetime compared to enzymatic biosensors. The use of microbes also endows the biosensors with ability to work under relatively harsh conditions such as sensing in oilfield wastewater[86]. Microbial bioelectronic sensors are still in their infancy and are only able to report on a small number of analytes compared with the total number of parameters sensed by microbes.

Synthetic Microbes within Devices

An emerging strategy for extending the capabilities of microbial devices is to program the microbe to produce non-native enzymes and oxidoreductases using synthetic biology[32,87]. This approach can extend the capabilities of devices by creating increased specificity towards the detection of specific analyte, allowing electrical control over the biosynthesis of target chemicals such as antibiotics, converting easy to program strains like *E. coli* into exoelectrogenic bacteria, and making safe microbial components by incorporating "kill switches" that turn off microbes on demand. As an example, Mimee et al. developed an ingestible micro-bio-electronic device (IMBED) for detecting gastrointestinal bleeding that combined engineered microbes that produced a fluorescent response upon sensing heme and microelectronics for wirelessly transmitting real-time information[2]. In another example, Zhou and coworkers developed a miniaturized, autonomous bioelectronic sensing system (BESSY) capable of producing an electrochemical response to fumarate[57]. Both of these examples take advantage of synthetic biology to engineer a specific microbial response to a target chemical and advances in microelectronics to produce a miniature, autonomous, wirelessly connected device. Synthetic biology not only engineers and expands the input and output targets of microbes, but also empowers microbes with novel functionality by taking synthetic biology toolkits from other organisms. For example, Jensen et al. implemented the Mtr pathway originating from *S. oneidensis* to build a synthetic electron conduit in *E. coli*, which is unable to transfer electrons across membranes without this synthetic modification[58]. Furthermore, a growing number of studies are programming cells to construct modular and orthogonal logic gates for precise, desired cell behaviors[88]. While most efforts to date have focused on genetic logic gates that require slow transcriptional processes, the recent development of chemical-dependent protein electron carriers suggest that fast living sensors can be created that function orders of magnitude faster than existing technologies[89,90]. By coupling synthetic biology with the design of microbial bioelectronic devices, it is possible to build complex information-processing circuits for diverse applications. Furthermore, methods for signal processing, as have been applied to neural recording[91,92], can aid in interpreting signals from multiple channels and enable multimodal sensing.

The Biotic-Abiotic Interface in Microbial Bioelectronic Devices

A number of materials challenges occur at the biotic-abiotic interface, which also underlies the novelty and functionality of microbial bioelectronic devices. The interface in microbial bioelectronic devices is complex, generally heterogeneous, and can vary widely in terms of structure, chemistry, and electronic properties. Structure and phenomena occur across multiple length scales, and include the size of pores at the interface, the nature of charge transport, and the interactions between microbes and the specific surface chemistry, and some of these phenomena and structural features are depicted in **Figure 3**. Here, we describe and classify microbial bioelectronic interfaces in terms of structure, biocompatibility, and electronic properties.

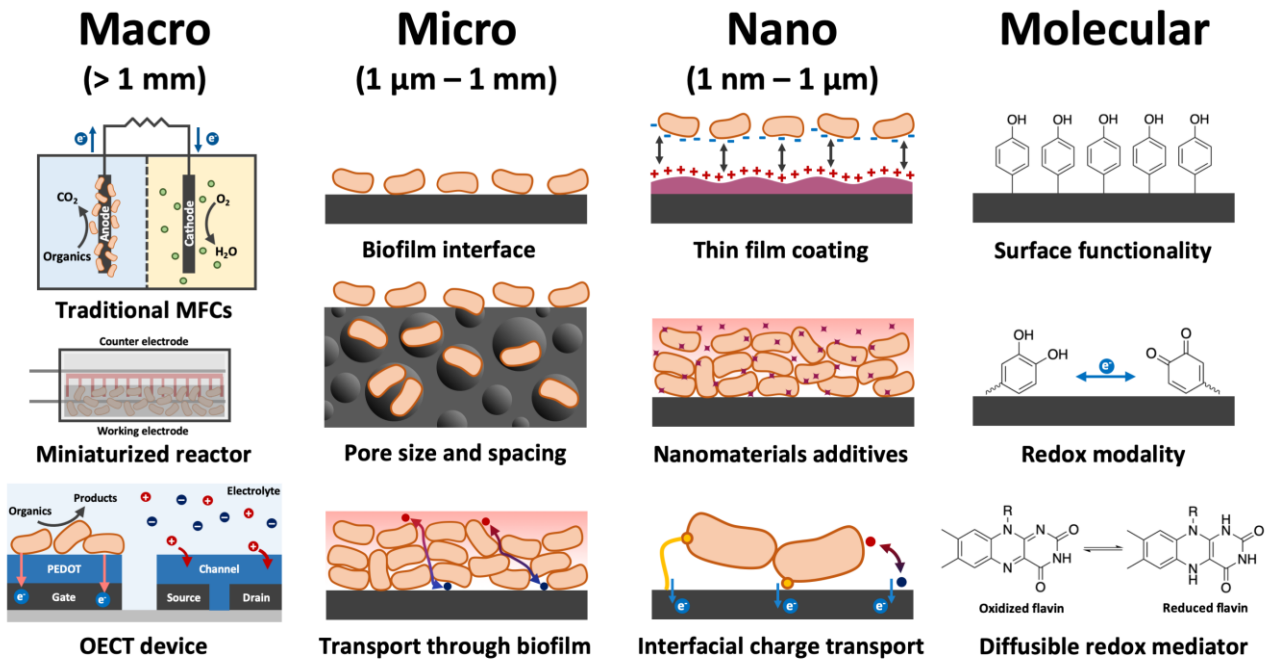

Figure 3. Microbial bioelectronic devices and interfaces have distinct features at dimensions ranging from the macroscopic to molecular level. (OECT device image is modified with permission from Ref. 93)

Interface Structure

The structure of the biotic-abiotic interface can vary widely, from a hard boundary, such as a biofilm on top of metal electrodes[94] to a diffuse interface, such as microbes dispersed within a conductive polymer matrix that is 80 µm thick,[95] to an interface involving indirect charge transfer via diffusible mediators[36]. The structure of the interface plays an important role in determining the dominant mode of charge transport and the maximum current flux that can be generated. The structure also influences the biocompatibility and electronic properties of the interface. Porosity enables microbes to infiltrate and populate the interface and may be important to microbial survival by allowing organic materials and other nutrients to freely diffuse into and away from the interface[52,96,97].

Relevant structural features occur across various length scales. At the molecular level, the specific chemistry of the interface will influence microbe viability, affect microbe adhesion, and control electronic properties. For example, the deposition of a cationic polymer coating can improve adhesion, but at the cost of adversely affecting microbial viability[98]. In another example, increasing the surface area using nanomaterials may actually decrease current fluxes as hydrophobic conductive surfaces can deter microbial attachment and biofilm formation[51]. In the case of metallic electrodes, a metal oxide coating can form on the electrode surface, changing the surface chemistry, structure, and electronic properties[99,100]. At micrometer length scales, the structure of the interface influences microbial adhesion and viability. Interface layers with pores of 10 µm or larger enable microbes to penetrate and proliferate. With redox active coatings, charge transfer is governed by diffusion of soluble mediators between microbes and redox-active sites[36]. In these cases, the chemistry of the redox active film will influence the diffusion of the mediators. Finally, macroscopic structural features are important in determining the maximum power densities that can be achieved and the ultimate dimensions of the microbial device. While it is clear that there are tradeoffs between material structure and cellular interactions, there is a need for additional studies to understand the best material designs for coupling with natural and engineered microbes.

Interface Biocompatibility

Biocompatibility should be thought of as a system property rather than that of a particular material[101] and will involve a number of interfacial characteristics including adhesion of microbes to the interface, cytotoxic responses to either the primary interface material or contaminants that may be present at the interface, the porosity of the interface material, and electronic properties of the interface material. The porosity of the interface influences microbe viability, with large (10 µm or greater) pores enabling the infiltration and propagation of microbes within the interface layer[16,69]. The presence of residual contaminants (*e.g.*, unreacted monomer[95]) or surface charge[98] influences microbial viability. Finally, electronic properties of the interface can also influence viability. Hu et al. prepared a conductive DNA hydrogel containing carbon nanotubes and silica nanoparticles and found that exoelectrogenic *S. oneidensis* microbes preferentially populated the conductive hydrogel [102]. However, we do not yet understand the underlying cause of these behavioral differences to anticipate how biocompatibility will vary across different microbial species and strains.

Interface Electronic Properties

The electronic properties of the interface are perhaps the most relevant to bioelectronic device applications. The interface will mediate communication between electronics and microbes by influencing electron transport, which can occur through both direct and indirect routes. In direct electron transfer, electrons are shuttled directly between the electrode and microbe through conductive cytochrome proteins or pili. Direct electron transfer occurs with exoelectrogenic bacteria[19,21,23,103] (*e.g.*, *S. oneidensis* and *G. sulfurreducens*) and may be a more useful mechanism for engineering a specific connection to a unique metabolic processes[22,35]. The indirect route involves mediated electron transfer, in which electrons are shuttled between microbes and electrodes via soluble mediators such as flavin, anthraquinon-2,6-disulfonate (AQDS), neutral red, and methyl viologen. The interface plays a role in multiple ways, including by providing pathways for microbe-microbe or microbe-electrode electron transport. While prior work has established how interface chemistry and structure can influence charge transport, there remains a need for general approaches that can be applied to effectively increase charge transport for various applications and in different environments.

Structure, biocompatibility, and electronic properties are useful for classifying and understanding the interface, and it is important to note that they are all interconnected and need to be considered in parallel when designing or optimizing interface materials for microbial bioelectronics. The structure (e.g. porosity, thickness, and roughness) of the interface influences cell viability by influencing the ability of the microbe to penetrate the interface and affecting the diffusion of nutrient and waste into and out of the interface layer. The structure also impacts electronic properties by determining the available surface area for interfacial charge transfer and, through the thickness and chemistry, influencing the resistances involved. Biocompatibility and electronic properties can also be interconnected[102].

Advances and Challenges for Soft Materials for Microbial Bioelectronics

In this section, we highlight specific materials challenges within the broad field of microbial bioelectronics. In each topic, we highlight recent research advances and innovative approaches and also provide a perspective on remaining questions and challenges. This is not a comprehensive discussion of materials challenges in the field, but rather a selection of topics that are of current interest. We specifically emphasize challenges in increasing charge transport at device interfaces, adhesion of microbes to the synthetic bioelectronics interface, materials for redox signaling, amplifying electronic signals in microbial bioelectronic devices, and miniaturization.

Materials for Increasing Charge Transport between Microbes and Electrodes

A number of materials and novel approaches have been implemented to achieve higher current densities between microbes and electrodes[47,50–53], and this translates to a number of performance enhancements in microbial bioelectronic devices, including a higher rate of electrical energy generation in MFCs, greater sensitivity to target chemicals for microbial biosensors, and greater rate of chemical fuel production in MESs. Among the most successful approaches has been the development of three-dimensional, porous, conductive matrices. These materials provide a large interfacial area for contact and charge transport, support long-range charge-transport through the conductive material, and are compatible with microbial viability within the matrix. However, achieving an interconnected, porous, conductive matrix with microbes dispersed optimally throughout remains a challenge. For example, a number of studies attempted blending microbes with conductive additives (*e.g.*, carbon black, graphene, or carbon nanotubes) along with a polymeric binder to form a slurry that is deposited on an electrode surface.[97,104–107] These approaches experienced challenges in significantly enhancing current densities due to the poor viability of the microbes inside the matrices, possibly due to mass transport limitations in the composite layer[52]. More recent work has explored alternative materials and approaches to effectively interface microbes with a conductive, porous interface that ensures microbial viability and provides bi-directional communication between the microbes and electrodes[16,69,95,108]. Below, we describe three different classes of materials that have been used to increase electronic currents across microbial bioelectronics interfaces.

In situ chemistries for conductive polymer interface layers. Conductive polymers have been widely used in bioelectronics since they are generally biocompatible due to their mechanical properties. Two recent studies are notable for the use of in situ chemistries to fabricate conductive polymeric networks and coatings in the presence of microbes. Song et al. coated individual exoelectrogenic microbial cells of *S. oneidensis* in a conductive polypyrrole (PPy) coating (see **Figure 4A**). This was achieved by adsorbing Fe^{3+} catalyst onto the microbe surface and then initiating the growth of conductive polypyrrole from the bacterial surface. The researchers found that the microbes remained viable after producing the conductive polymer coating, and they fabricated an MFC anode by depositing the polypyrrole-coated microbes onto a conductive carbon cloth. The resulting device produced order of magnitude increases in current densities and reductions in the charge transfer resistance relative to a similar device with unmodified microbes[108]. In another approach, Zajdel et al. embedded *S. oneidensis* in a conductive poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) matrix (see **Figure 4B**). PEDOT:PSS is a commercially available solution-processible conductive polymer widely used in bioelectronics and other electronics applications[41,109,110]. Zajdal et al. performed an in situ electrochemical polymerization to embed microbes within a conductive PEDOT:PSS matrix. The researchers found that 3,4-ethylenedioxythiophene (EDOT), the monomer used in the synthesis of PEDOT, was toxic to microbes, and they developed a flow chemistry approach to minimize contact time of the mi-

crobes to the monomer while performing an in situ electropolymerization and encapsulation. The final material consisted of microbes embedded in a porous and conductive PEDOT:PSS matrix that produced a 20-fold increase in current relative to microbes deposited on an electrode[95].

These in situ chemical approaches have shown significant potential as interface layers that can encapsulate a high density of cells, but it remains unclear how these layers compare with other approaches to conductive interface layers and how scalable and practically relevant these approaches will be. There is also a need for further development of these approaches that are compatible with patterning, printing, and/or selective deposition of microbes.

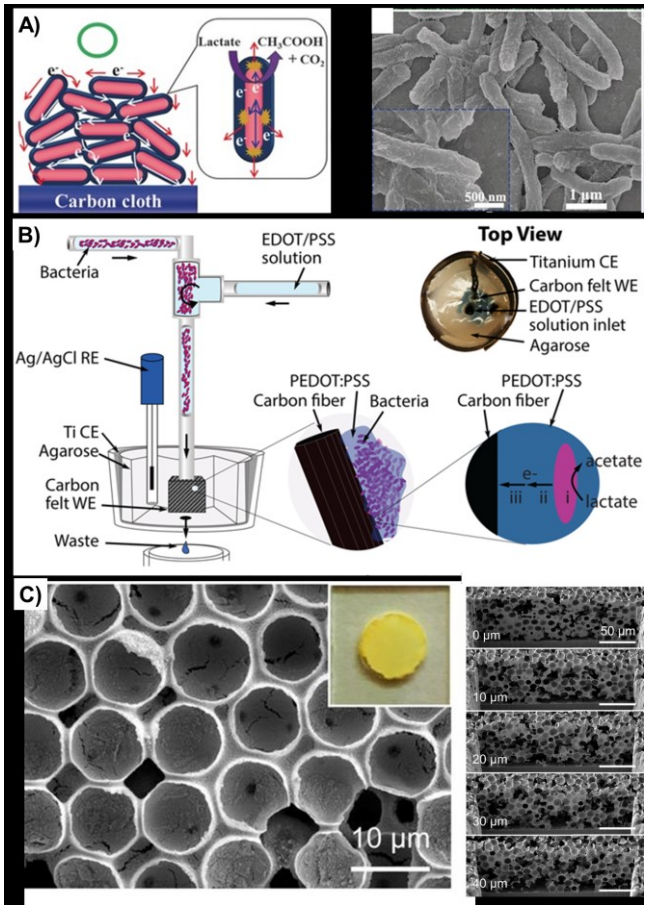

Figure 4. Three-dimensional conductive interface materials enhance charge transfer across the biotic/abiotic interface. A) Schematic for and scanning electron micrograph of a PPy coating on microbes that can enhance charge transfer in a biofilm. The coating is shown in dark purple in the schematic and results in a rough, conformal coating apparent in SEM micrographs. Reproduced with permission from ref. 108. B) Schematic for PEDOT:PSS interface produced in a flow cell and involving the in situ electrochemical polymerization. Reproduced with permission from ref. 95. C) Scanning electron micrographs of a porous ITO template produced using an inverse opal method. Reproduced with permission from ref. 16.

Interface layers with large (> 10 µm) pores significantly enhance current densities. Two recent studies demonstrated the importance of large (10 µm or greater) pores in the design of 3-D biocompatible conductive scaffolds. In a 2016 study, Ren et al. fabricated a 3-D, conductive, macroporous graphene scaffold on a nickel foam template. The nickel was subsequently removed to produce a freestanding porous graphene scaffold. The pores were spaced by 100 - 200 µm, which enabled microbes to enter the pores and populate the interior of the scaffold. The device produced a volumetric current density of 10 mA/cm^3, a record at the time the study was published[69]. In a more recent study, Fang et al. fabricated an inverse opal indium tin oxide (ITO) electrode[16]. Inverse opal materials are formed using colloid crystals as templates, around which macroporous, photonic structures can be formed[111]. Fang et al. used colloidal polystyrene spheres to construct a conductive and porous inverse opal ITO scaffold with spherical, interconnected pores of 8 - 10 µm in size (see **Figure 4C**). Microbes were able to penetrate and proliferate inside the pores, and the device produced a record volumetric current density (500 mA/cm^3)[16].

These two examples clearly demonstrate that conductive materials with micrometer-sized pores are effective for interfacing with microbes, both for providing large interfacial area for charge transfer and for enabling microbes to infiltrate and populate the interface. However, we do not yet know how the pore size may affect molecule diffusion, cell growth, cell penetration, and cell immobilization for different interface chemistries and microbial species. Also, these two examples involved the preparation of a porous, conductive matrix followed by infiltration by microbes. Alternative approaches that encapsulate microbes within a matrix of controlled pore size may be more effective.

Self-doped conjugated polymers enhance conductivities of microbial biofilms. Another approach recently explored the use of a conductive, water soluble polymer to produce a "living" bioelectrochemical composites. Unlike the *in situ* polymerization strategies, McCuskey et al. used a conductive and water soluble polyelectrolyte that could be simply blended with *S. oneidensis* and deposited onto a conventional electrode[112]. They relied on self-doped conjugated polymers, which contain a conjugated backbone along with ionic functional groups and counterions, resulting in more stable backbone doping and electronic conductivity[113,114]. The researchers used a conjugated polyelectrolyte termed CPE-K and found that blending CPE-K with microbes increased microbial growth, presumably due to increased electronic conductivities of the biofilm. The polymer also self-assembled to form a 3D framework, driven by interactions between the ionic side-chains and bridging counterions. When used as an additive at concentrations as high as 30 mg/mL, the resulting biofilm exhibited significantly higher current densities compared with either a pure biofilm or a pure CPE-K film[112]. In addition to enhancing electronic conductivities of the biofilm, CPE-K also exhibits significant ion conductivity[115], which may also contribute to improved charge transfer.

These studies demonstrate self-doped polymers are promising additives for increasing charge transport, but several questions remain. For example, we do not understand structure-property relationships in these types of polymers

for increasing charge transport in biofilms. It is also unclear whether these polymers primarily increase charge transport through the biofilm or across the biotic-abiotic interface, and the potential role of combined ion and electron transport by these materials is unclear[115].

Materials for Enhanced Microbial Adhesion

A related issue important to enhancing current densities is achieving good adhesion. Adhesion between microbes and an electrode surface plays an important role in the effectiveness and biocompatibility of an electrode. A number of highly conductive carbon-based materials exhibit poor performance as electrodes due to hydrophobicity of the surface and poor adhesion[51]. Diverse approaches including surface modification, charged coating deposition, and co-coating of microbes with other materials have shown promising results in the improvement of microbial adhesion[116], and here we highlight two innovative examples. A 2010 study encapsulated microbes within a strongly adhesive silica layer, which resulted in strong binding to and immobilization on a graphite felt electrode. The microbes remained viable, and the device exhibited improved stability over control devices without silica[117]. While the goal of the study was to develop a standardized anode to assess different MFC designs, the work effectively demonstrated the importance of adhesion to achieving reliable performance. In a more recent study, a cationic polymer, poly(diallyldimethylammonium chloride) (PDDA), was deposited on the surface of an electrode, providing an electrostatic force driving microbes to the surface of the electrode. Despite the cytotoxicity of PDDA, the researchers were able to optimize deposition conditions and concentrations to enhance microbial adhesion, reduce start-up time, and increase power densities[98].

This demonstrates how proper material selection and design can provide simple strategies to enhance interfacial interactions, resulting in improved device performance and stability. However, it is unclear how microbial proteins mediating electron transfer contribute to the improved adhesion and if contact and interaction with the material can be improved further.

Materials for Electronic Control through Redox Signaling

While the majority of strategies for bidirectional electronic communication with microbes have focused on enhancing electronic conductivity of interface layers, an alternative approach is to utilize redox modalities for bidirectional communication. Electron shuttling using redox-active mediators is the primary mode of electron transfer in some microbes, such as exoelectrogenic microbes *S. oneidensis*[118], and synthetic redox-active materials can be leveraged for bidirectional communication with microbes. This approach has several attractive features, as detailed in recent review articles[119,120]. Most notably, the approach is compatible with traditional instrumentation for electrochemical analysis and can be used to communicate with and/or monitor redox-active biomolecules. The method can be used to detect redox-active biomolecules or to leverage the biomolecules as reporters that can actuate a desired biological response (see **Figure 5A**). A drawback of this approach is that redox-active mediators can in general interact with a variety of molecules and processes, making it more difficult to control or interpret electrochemical signals[120].

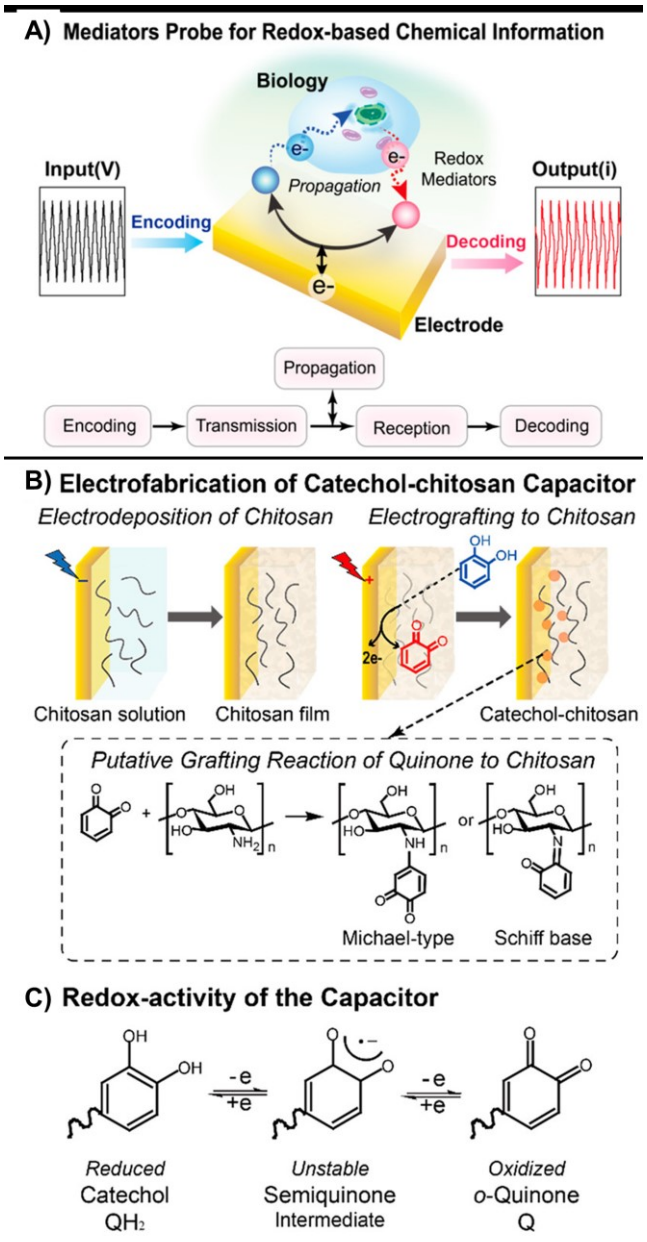

Figure 5. Electronic control is enabled through redox signaling. Schematics for A) signaling and communication through redox-active mediators, B) fabrication of redox capacitor using chitosan and catechol, and C) redox-activity of catechol in the capacitor. Reproduced with permission from ref. 120.

Payne, Bentley, and coworkers have developed and extensively explored polymeric films that can serve as a "redox capacitors." These films are comprised of redox-active molecules tethered to a non-conductive polymer network, and analogous to capacitors which store electronic energy in the form of electronic or ionic charge, redox capacitors store energy in the form of oxidized or reduced organic moieties[120,121]. As an example, Kim et al. developed a redox-

capacitor film by producing a chitosan hydrogel with grafted catechol moieties[122] (see **Figure 5B**). Chitosan is a pH-responsive polymer that can be electrodeposited onto the surface of an anode while catechol is a redox-active molecule that can be reversibly switched between reduced (catechol) and oxidized (*o*-quinone) states (see **Figure 5C**). Charge is accumulated in the film in the form of *o*-quinone, which reacts with the chitosan network. Since *o*-quinone is covalently bound to the non-conductive chitosan film, reduction and oxidation only occurs in the presence of diffusible mediators, which are added to the system. These films are electrochemically active within the thermodynamic window set by the oxidation and reduction potentials for catechol and *o*-quinone. At these potentials, reduction or oxidation of the redox-active molecules in the film can occur, resulting in a large current. These films therefore provide a method to probe redox-active molecules and processes at controllable oxidative and reductive potentials[120,123]. This approach is versatile, and redox-active capacitors have been used to detect redox active metabolites, such as signaling molecules from pathogenic microorganisms[124].

The redox active molecule can be designed to target different analytes. A recent study by Tschirhart et al. demonstrated that redox modalities could be used to build microbial biosensors that respond to specific targets. Tschirhart et al. engineered a genetic circuit responsive to quorum-sensing molecule autoinducer-2 (AI-2) and utilized a redox capacitor to electrochemically monitor the output of the genetic circuit, β-galactosidase[125]. This enabled electronic detection of the target analyte in real time in a whole cell biosensor, which is generally not possible for microbial biosensors with an MFC architecture.

Only a limited set of materials have been studied for electronic communication with microbes through redox modality, and significant material challenges remain. While the chitosan-catechol redox capacitor films can be fabricated quickly through electrodeposition, other processing strategies (*e.g.*, solution casting, printing) may be desirable. Chitosan only remains crosslinked at basic pH, and therefore a new polymeric matrix material may be needed for stability in lower pH-environments. There is an extensive library of redox active molecules that have been developed for electrochemical applications, including redox polymers[18,126] and other organic electrode materials for energy storage[127] that could potentially be incorporated into redox capacitors. This approach also has the potential to utilize multiple, different redox capacitor films that can detect different molecular targets or actuate different genetic pathways. To achieve this, the reduction and oxidation of the various redox-active molecules chosen should occur at different potentials. Alternatively, materials could be developed to uptake or enable the diffusion of specific mediators to the target film. A drawback of the redox modality approach is that it requires the addition of diffusible mediator, which may not be possible or be undesirable for some applications.

Using Materials to Amplify Electronic Signals from Microbes

Organic electrochemical transistors (OECTs) are organic electronic devices that can amplify ionic and/or electronic signals[128]. OECTs consist of a semiconductive polymer film channel that connects source and drain electrodes. A gate electrode is used to control doping of the polymer channel, resulting in significant changes in the channel conductivity and, as a result, the source-drain current. Doping occurs due to ion injection into the channel with changes in the gate potential. By monitoring changes in the electronic conductivity of the channel, OECTs can detect small changes in the gate voltage and/or charge or ion injection into the channel. Importantly, they are functional in biologically-relevant media and can be used to monitor various biological electronic processes[128], including neural activity[129,130], muscular action potentials[131], and cellular attachment[132]. PEDOT:PSS is the most widely studied active material for OECTs, but recent work has identified a number of other semiconductive polymers that can be used in OECTs[133,134].

A recent study by Mehes et al. reported the use of OECTs to amplify extracellular electron transfer (EET) from exoelectrogenic microbes *S. oneidensis*. The researchers fabricated an OECT with PEDOT:PSS as the channel and a PEDOT:PSS/PVA-coated gold electrode as the gate. *S. oneidensis* were deposited onto the gate electrode, which had a total surface area of only 0.25 mm^2. By monitoring the conductivity of the channel, the researchers could detect EET from the microbes to the electrodes. The researchers observed changes in the channel conductivity with variations in the amount of lactate added, demonstrating a connection to microbial metabolism. Compared with conventional chronoamperometric or electronic impedance spectroscopy (EIS) measurements, the OECTs were able to detect currents from a much smaller electrode and lower density of microbes. For comparison, a miniaturized biosensing device used an electrode surface area of 2 cm^2 and required several hours for a measurable response, compared with a surface area of 0.25 mm^2 and response time of 40 min for the OECT. The researchers also noted a much faster response in their device, which they attributed to improved sensitivity. This work provides an approach for monitoring extracellular electron transfer processes in exoelectrogenic microbes[93].

Significant opportunities are available for creating new microbial devices and enhancing performance through proper material selection and processing. For example, an open question is whether the sensitivity of OECTs can be enhanced to enable detection of EET from a single microbe or a small population of microbes. A variety of channel materials have been developed specifically for OECTs that can improve sensitivity and provide a "turn-on" rather than a "turn-off" response that is characteristic of PEDOT:PSS devices[133]. More sophisticated methods for microbial deposition could enable producing arrays of OECTs coupled to different microbial species. Finally, lessons can be learned from material developments for MFCs to enhance charge

transfer can likely be applied to OECT devices to more effectively integrate microbes with the gate electrode and/or the channel.

Processes and Materials for Miniaturization of Microbial Bioelectronic Devices

There is significant interest in the miniaturization of microbial bioelectronic devices for sensing[33], environmental monitoring[57], providing power[13], and performing medical diagnostics[2]. These emerging technologies require autonomy, wireless communication, compact size, and biodegradability. To realize these characteristics, a combination of novel materials, processing, and design strategies need to be implemented.

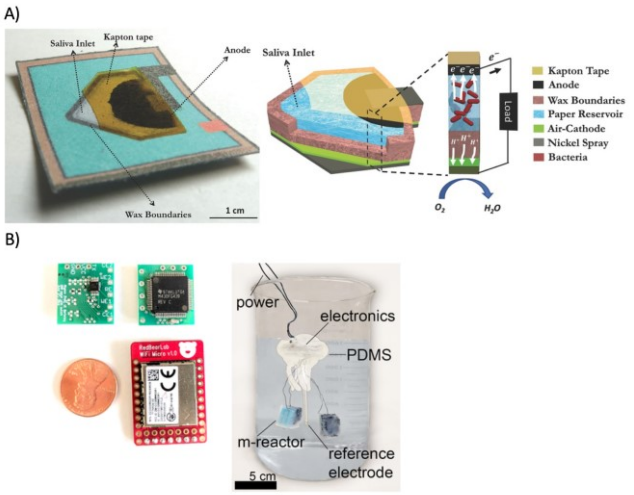

Figure 6. Microbial bioelectronic devices can be miniaturized for applications that require portability. A) Image and schematic diagram of paper-based biobattery. Reproduced with permission from ref. 135. B) Image of deployable microbial bioelectronic sensing system BESSY including miniaturized potentiostat and WiFi micro board (left), and final BESSY setup in aqueous environment (right). Reproduced with permission from ref. 57.

Choi and coworkers recently reviewed the development of microbial biobatteries, which in contrast to MFCs are compact, self-contained, and, in some cases, biodegradable[13]. As an example of such a biobattery, Lee and Choi fabricated a paper-based biobattery. The battery was thin and lightweight and could be stacked and folded into origami-like structures. The researchers used a combination of screen printing and spray deposition to deposit electrodes and wiring. Bacteria were loaded into the device by depositing a liquid suspension on an inlet port, and the bacteria were then drawn into the device through capillary action. The researchers demonstrated that they could generate currents by introducing various aqueous media, and the device produced a maximum output voltage of 1 V and output power of 48 nW[136]. In more recent work, the group demonstrated that bacteria could be lyophylized and then later rehydrated for use with saliva (see **Figure 6A**). The device remained functional even after storage for several months[135].

Another example is a miniaturized, deployable microbial bioelectronic sensing system (BESSY) that used *S. oneidensis* for in situ environmental monitoring. Zhou et al. miniaturized the potentiostat and electrochemical cell to produce a device with 2 X 2 cm² footprint (see **Figure 6B**). Their design replaced traditional potentiostat and electrochemical cells with a chip-like, low-power potentiostat that was portable and was able to function in remote regions. The miniaturized electrochemical cell included a reference electrode and a miniaturized reactor which integrated a working electrode that encapsulated *S. oneidensis* and a counter electrode in agarose gel. By integrating the homemade potentiostat and two pairs of three-electrode systems encapsulating different strains of *S. oneidensis*, the authors were able to detect fumarate with excellent sensitivity and in the presence of environmental perturbations[57].

These examples demonstrate how innovative combination of materials, device designs, and processing can produce a variety of functional and miniaturized microbial devices. More work is needed in order to take full advantage of the responsiveness and multi-functionality of microbes. For example, a device that could detect multiple analytes, transmit information about these analytes in real time, and respond by producing a specific chemical or target would be unprecedented but requires integrating MFCs for power, microbial sensors, and BESs to produce the desired chemical in response to the target, in addition to onboard electronics for wireless communication.

Summary and Perspective

Microbial bioelectronic devices have advanced significantly in recent years, and emerging devices will have growing applications in energy harvesting, chemical synthesis, water treatment, environmental and health monitoring, and treatment of disease. Materials scientists have made significant contributions to this growing field, and more materials innovations are needed to realize the full potential of these devices. For example, while recent studies have been successful in taking advantage of *in situ* biocompatible chemistries for producing conductive, encapsulating interface layers, the field has yet to take full advantage of biocompatible chemistries available. A number of efficient and mild click chemistries can be conducted in biologically relevant media under mild stimuli, including copper-free azide-alkyne cycloadditions, thiol-ene chemistries, and Diels-Alder coupling[137]. These reactive, selective, and orthogonal click chemistries can be used to form hydrogels, microgels, and nanogels under mild conditions. DeForest et al. synthesized three-dimensional cell microenvironments by performing sequential bioorthogonal click chemistries (copper-free azide-alkyne cycloaddition and thiol-ene chemistry) to form and then biochemically pattern a hydrogel. This study combined two click chemistries to create a hydrogel and conjugating biomolecules at specific locations, allowing for spatial cell manipulation[138]. Similar chemistries could lead to effective approaches to creating conductive hydrogels that encapsulate microbes. Another innovative and emerging materials chemistry approach involves the use of exoelectrogenic bacteria to initiate polymerization reactions[139,140]. While work so far has

focused on the synthesis of non-conductive polymers, extending this approach to conductive polymers would potentially enable the formation of conductive polymer shells around microbes, catalyzed by microbial metabolism.

Novel materials such as self-doped polymers can enhance the electronic conductivities of biofilms. Self-doped polymers are an example of a broader class of polymers with intrinsic ionic and electronic conductivities that have been recently explored for a range of organic electronic applications[141,142]. These materials have significant potential for enhancing the performance of microbial bioelectronic devices and have been shown to simultaneously increase storage capacities and rate performances in energy storage applications. Bio-mimetic conductive peptide nanofibers represent another interesting set of materials for bioelectronic devices. Mimicking the structure of naturally-occurring pili that are capable of long-range electron transport[143,144], Ing et. al developed synthetic peptides that self-assembled to form conductive peptide nanofibers[145]. These materials were used to produce multifunctional peptide-metal nanocomposites and shown to be relevant for applications including chemical catalysis and static charge detection[146].

The recent work with OECTs is an important example of how different device architectures can enhance sensitivity. Although the OECT device architecture is not new, it had not previously been applied to study exoelectrogenic electron transfer. In addition to detecting ionic and electronic signals, OECTs have also been applied to deliver ions to a specific location. This could potentially be leveraged to actuate or interact with microbes in a specific location. Furthermore, conjugated polymer films have been implemented as devices for neuromorphic computing, serving as domains for storing and releasing charge in the form of ions[147]. This capability can potentially be used to deliver or detect specific ionic signals.

Finally, advances in materials processing and engineering have produced a number of new applications for microbial bioelectronic devices, including as sources of portable power[13], implantable and ingestible diagnostics[2], sensors for environmental monitoring in remote and/or hard-to-access environments[57], and novel response to the environment[7]. Recent work has focused on miniaturized devices at approximately 1 cm^3 scales. Future work should address whether further miniaturization is possible, and whether functional devices approaching the size of individual microbes can be fabricated.

Through the design of novel materials and synthetic microbes with improved behaviors, a new era of hybrid electronic devices is expected to emerge with capabilities for precision sensing, wireless reporting, and tailored responsiveness to different chemical signals and/or environmental cues. These devices will have broad and revolutionary impact in fields as diverse as environmental reporters for detecting and responding to chemical signals to biomedical devices for diagnosing and treating disease.

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ABBREVIATIONS

AI-2, autoinducer-2; AQDS, anthraquinon-2,6-disulfonate; BESSY, bioelectronic sensing system; BPV, biophotovoltaic; CPE-K, conjugated polyelectrolyte; EDOT, 3,4-ethylenedioxythiophene; EET, extracellular electron transfer; EIS, electronic impedance spectroscopy; IMBED, ingestible microbio-electronic device; ITO, indium tin oxide; MES, microbial electrosynthesis system; MFC, microbial fuel cell; PDDA, poly(diallyldimethylammonium chloride); PEDOT:PSS, poly(3,4-ethylenedioxythiophene) polystyrene sulfonate; PPy, polypyrrole; OECT, organic electrochemical transistor.

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