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MINI REVIEW

Living electronics: A catalogue of engineered living electronic components

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Abstract

Biology leverages a range of electrical phenomena to extract and store energy, control molecular reactions and enable multicellular communication. Microbes, in particular, have evolved genetically encoded machinery enabling them to utilize the abundant redox-active molecules and minerals available on Earth, which in turn drive global-scale biogeochemical cycles. Recently, the microbial machinery enabling these redox reactions have been leveraged for interfacing cells and biomolecules with electrical circuits for biotechnological applications. Synthetic biology is allowing for the use of these machinery as components of engineered living materials with tuneable electrical properties. Herein, we review the state of such living electronic components including wires, capacitors, transistors, diodes, optoelectronic components, spin filters, sensors, logic processors, bioactuators, information storage media and methods for assembling these components into living electronic circuits.

INTRODUCTION

The fields of bioelectronics, synthetic biology and electromicrobiology are converging through the development of new living electronics where biological entities (e.g. biomolecules, cells or cellular communities) are directly integrated as electrical components into electronic circuits (Dunn, 2020). Biohybrid devices have been built that integrate a diversity of living electronic components spanning many length scales. Research in the field of bioelectronics is yielding materials innovations that improve the abiotic: biotic interface between biological entities and electrodes (Tseng et al., 2020). Synthetic biologists are leveraging concepts from electrical engineering as analogies when designing DNA-, RNA- and protein-based logic circuits to program predictable and dynamic phenotypes in cells and biomolecular networks (Brophy & Voigt, 2014; Gao et al., 2018; Green et al., 2017). Meanwhile, advances in electromicrobiology are providing a mechanistic understanding of molecular components underlying the ability of microorganisms to electrically interact with insoluble materials and other cells in their environment (Kracke et al., 2015).

The cross-disciplinary integration of the recently gained knowledge in each of these fields is uniquely poised to produce novel living electronics that leverage the unique capabilities of biological and solid-state systems. Herein, we summarize recent advances in the characterization of biological entities as electrical components, the integration of biological entities into electrical devices, and provide a prospective for new types of electrical devices that could be constructed using living components. Living electronics offer unique capabilities including the ability to self-assemble, self-power, repair, biodegrade, process molecular information and

store information in low-energy structures. Living electronics can be produced with renewable feedstocks at ambient temperature and pressures, thereby offering a path towards sustainable production of electronics. To leverage these unique capabilities the field needs a framework to integrate these components into conventional electrical circuits.

CATALOGUING LIVING ELECTRONIC COMPONENTS

Circuit engineering has benefited from having a catalogue of electronic components with well-characterized input–output relations, allowing them to be combined in a hierarchical manner. To integrate living components into electronic circuits it is useful to categorize these components according to their functions and behaviours so that they can be integrated into more complex devices.

Wires

One of the simplest electronic components is a charge-carrying wire or a conductive path. These components allow for the flow of current and have characteristic conductivities/resistances. Biological systems also take advantage of wires that exist at a range of length scales and conductivity to facilitate energy conservation and cellular communication (Figure 1).

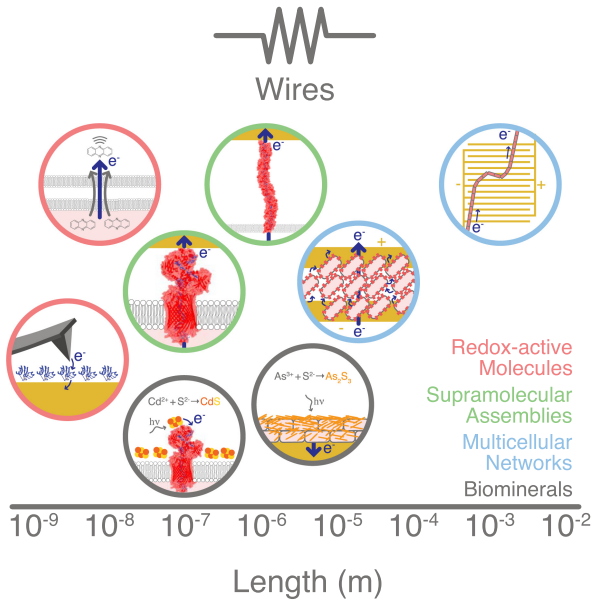

FIGURE 1 Living electronic wires span multiple length scales. Biological systems use diverse charge-carrying wires. The smallest of these are redox-active molecules (red circles) which include redox-active proteins which have been used for nanoscale molecular electronics and redox-active small molecules that function as diffusible electron carriers linking cells to distant materials in the environment. Cells also use supramolecular assemblies of proteins (green circles) enabling them to span many nanometres (MtrCAB, PDB: 6EF8) or micrometre distances (OmcS, PDB: 6R2Q). Electroactive microbes are also capable of precipitating nano-to-micrometre scale inorganic biominerals (grey circles) that can exhibit photoresponsive properties allowing for light-activated charge injection into cells or electrodes. The largest scale charge-carrying wires consist of multicellular networks (blue circles) which can span many microns as is the case for biofilms exhibiting redox-hopping transport and up to centimetre scale transport like that observed in cable bacteria.

Redox-active molecules as nanometre scale wires

All living cells form intracellular electron transfer (ET) networks using diffusible redox-active molecules that function as charge carriers coupling oxidative and reductive metabolic pathways. These ET networks enable energy extracted from substrates to be conserved in chemical bonds or membrane potentials, thereby allowing cells to perform work including active transport, biosynthesis, motility and cell division. Redox-active molecules include both organic small-molecules (e.g. nicotinamides, flavins, quinones and phenazines) and proteins (e.g. ferredoxins, flavodoxins, cytochromes, thioredoxins and azurins) (Atkinson et al., 2016). Redox-active molecules have a range of redox potentials at which they undergo ET and are compartmentalized in different regions of microbial cells including the cytosol, inner-membrane, periplasm and extracellular space. These properties constrain the connectivity of these ET networks and tailor their activity towards select chemical reactions.

In addition to forming intracellular ET networks, redox-active molecules can be excreted from the cell and used as mediators to form ET connections between cells and insoluble materials or other cells in their environment. This has been observed in electroactive organisms such as *Shewanella oneidensis* (Marsili et al., 2008; Xu et al., 2016), *Shewanella algae* (Turick et al., 2002) and *Pseudomonas aeruginosa* (Hernandez et al., 2004) that excrete flavins, melanin and phenazines respectively. The diffusible nature of these mediators enables them to function as charge-carrying shuttles that connect cells to distant materials in their environment. To increase electron flux, multicellular communities have also evolved strategies for concentrating these diffusible molecules into extracellular networks, which enables them to generate a gradient, or 'electrocline', of reduced and oxidized redox-active molecules (Bellin et al., 2016; Koley et al., 2011). For example, during biofilm formation, *P. aeruginosa* populations release extracellular DNA (eDNA) that binds and retains the phenazine pyocyanin while also functioning as a nanometre scale charge transporter to enable ET rates that are not limited by long-distance diffusion

of the phenazine (Saunders et al., 2020). However, using biofilms containing diffusible redox-active molecules to construct living electronic devices would be challenging as their conductive properties can change if there is a decrease in the concentration of the redox-active molecule within the biofilm environment (Saunders et al., 2020).

However, redox-active molecules have been used as nanoscale wires for the construction of molecular electronic devices where these molecules are covalently tethered to electrodes. While not the focus of this review, as they have been extensively reviewed elsewhere (Bostick et al., 2018; Cahen et al., 2021; Xiang et al., 2016), such devices have been constructed using carotene (Visoly-Fisher et al., 2006), Cu-azurin (Artés et al., 2012; Fereiro et al., 2018), c-type cytochromes (Amdursky et al., 2013, 2014; Futera et al., 2020) and ferredoxins (Zhang et al., 2004). Recently, proteins that do not undergo redox reactions in cellular contexts have been shown to carry charge likely via redox-active aromatic amino acids tyrosine and tryptophan in the peptide backbone rather than redox-active co-factors (Zhang et al., 2019, 2020). Such a non-traditional redox-active molecule has been employed as a molecular wire within scalable semiconductor chips with an ~25-nm-long alpha helical peptide containing metal binding domains enabling it to bridge pairs of ruthenium nano-electrodes (Fuller et al., 2022). Using this device, fluctuations in picoamp currents with an applied voltage of 0.7–1 VDC could be used to estimate the occupancy of biomolecules that bind to modified wires (Fuller et al., 2022). This exemplifies how nanoscale wires made of redox-active molecules can function as modular interfaces for biomolecular sensing (e.g. nucleic acids, peptides) in molecular electronics.

Supramolecular assemblies of proteins as nano-to-micrometre scale wires

Controlled assembly of charge carriers into supramolecular structures can extend the nanoscale electron transfer (ET) properties to enable electron transport (ETp) at micrometre scales (Ing, El-Naggar, & Hochbaum, 2018). This is best exemplified by microbial nanowires, conductive appendages that project out of microbial cells allowing them to reach insoluble substrates or other cells in their environment (Lovley & Yao, 2021). The term, microbial nanowires, has been used to describe a variety of disparate biological structures including conductive pili (Reguera et al., 2005; Walker et al., 2018), polymeric cytochromes (Filman et al., 2019; Wang, Gu, et al., 2019; Yalcin et al., 2020) and outer-membrane protrusions laden with cytochromes (Pirbadian et al., 2014). The charge transfer capabilities of these diverse supramolecular assemblies have been extensively studied using both dry, solid-state techniques as well as solution-based techniques including electrochemistry and spectroscopy. These measurements have revealed a range of charge transfer properties and suggested mechanisms including thermally activated hopping, diffusion-assisted hopping, delocalized band formation, flickering resonance and superexchange as extensively reviewed by Ing, El-Naggar, et al. (2018) (Table 1). When comparing these properties careful attention must be paid to both how these measurements are made (solid-state vs. solution based), the proposed mechanism of conductivity, the sample purity, the spatial geometry, the charge carrier concentration and what property is being reported (bulk conductance vs. intrinsic conductivity or electron diffusion coefficients).

Conductive microbial nanowires were initially discovered in *Geobacter sulfurreducens* (Reguera et al., 2005). These microbial nanowires extend micrometre distances away from the cell surface and based on early genetic studies were long thought to be electrically conductive pili (e-pili) consisting of polymers of a truncated pilin, PilA-N (Reguera et al., 2005), that contains a relatively high number of aromatic amino acids relative to other Type IV pilin proteins (Vargas et al., 2013). Many studies characterized the conductive properties of these wires without direct evidence of their molecular identity and suggested a mechanism of delocalized band formation through π-stacking of aromatic amino acids within supramolecular assemblies of PilA-N. Individual e-pili were found to form ~3 nm diameter wires with conductivity on the order of 10^{-2} S cm^{-1} as measured in hydrated conditions at pH 7 in a two-electrode configuration (Adhikari et al., 2016). In one of the most compelling studies linking a conductive function to PilA-N identity, using synthetic biology techniques Ueki et al. were able to determine the conductance of e-pili heterologously expressed in *Escherichia coli* using a four-electrode conductance measurement (Ueki et al., 2020). The conductance of films of these *E. coli* produced e-pili was found to be ~10^{-6} S under dry conditions, which is similar to the conductance of films of *G. sulfurreducens* produced nanowires measured under similar conditions (Walker et al., 2018). This synthetic biology approach helped to overcome the challenge of confounding alternative nanowires structures encoded in the *G. sulfurreducens* genome. However, in both studies, the purity and identity of the nanowires were not subsequently confirmed beyond targeted Western blots and scanning probe measurements of nanowire diameter (~3 nm) that do not preclude the presence of potential confounding conductive macromolecules such as B-DNA which has been observed in recent cryo-electron microscopy (cryo-EM) studies of *G. sulfurreducens* filament extractions (Wang, Mustafa, et al., 2022). To date, PilA-N filaments have not been structurally identified using cryo-EM approaches. However, heterodimeric PilA-N-C filaments have been observed (Gu et al., 2021; Wang, Mustafa, et al., 2022).

TABLE 1 Measurements of natural supramolecular wires. A description of the electronic measurements of natural supramolecular nanowires.

Organism	Charge carrier	Cofactor	Scaffold	Diameter (nm)	Conductivity ($S\,cm^{-1}$)	Conductance (S)	Measurement	Measurement orientation	References
G. sulfurreducens	PilA	–	Self-polymerized	3	10^{-2}	–	Hydrated solid-state 2-electrode	Transverse Individual	Adhikari et al. (2016)
G. sulfurreducens	PilA	–	Self-polymerized	3	–	10^{-9}	Dry solid-state 2-electrode	Cross-sectional Individual	Walker et al. (2019)
E. coli	gsPilA	–	Self-polymerized	3	–	10^{-6}	Dry solid-state 4-electrode	Transverse Film	Ueki et al. (2020)
E. coli	gsPilA	–	Self-polymerized	3	–	10^{-9}	Dry solid-state 2-electrode	Cross-sectional Individual	Ueki et al. (2020)
G. sulfurreducens	OmcS	Haem	Self-polymerized	4	10^{-2}	–	Hydrated solid-state 2-electrode	Transverse Individual	Wang, Gu, et al. (2019), Wang, Jones, et al. (2019), Wang, Zhang, et al. (2019)
G. sulfurreducens	OmcZ	Haem	Self-polymerized	2.5	10^{2}	–	Hydrated solid-state 2-electrode	Transverse Individual	Yalcin et al. (2020)
S. oneidensis	MtrCAB OmcA MtrDEF	Haem	Outer-membrane extension	10	10^{0}	–	Dry, Fixed solid-state 2-electrode	Transverse Individual	El-Naggar et al. (2010)
S. oneidensis	MtrCAB OmcA MtrDEF	Haem	Outer-membrane extension	10	10^{-2}	–	Hydrated solid-state 2-electrode	Transverse Individual	Grebenko et al. (2018)
M. huntgatei	Archaellum	–	Self-polymerized	10	–	10^{-8}	Dry solid-state 2-electrode	Cross-sectional Individual	Walker et al. (2019)
Cable bacteria (marine)[a]	unknown	Ni-S[b]	unknown	50 (26[b])	10^{-2}–10^{2}	–	Dry solid-state 2-electrode	Transverse Fibre-sheath	Meysman et al. (2019); Boschker et al. (2021)

[a]Unspecified genus assignment.

[b]Hypotheses from spectral studies of proposed metal centres (Boschker et al., 2021).

In 2019, a paradigm-shifting set of cryo-EM studies (Filman et al., 2019; Wang, Gu, et al., 2019) revealed the identity of certain nanowires isolated from *G. sulfurreducens* to be a polymeric assembly of the multihaem cytochrome OmcS (Yalcin & Malvankar, 2020). OmcS wires were found to form 4 nm diameter wires with closely spaced haems that have conductivities on the order of 10^{-2} S cm^{-1} as measured in hydrated conditions at pH 7 in a two-electrode configuration (Wang, Gu, et al., 2019). Subsequently, a different multihaem cytochrome, OmcZ, was found, using scanning probe techniques, to polymerize into 2.5 nm diameter wires with 1000-fold higher conductivity (~10^{1} S cm^{-1}) than what was reported for OmcS using a two-electrode configuration (Yalcin et al., 2020). Filaments of a third multihaem cytochrome, OmcE, were structurally resolved recently and found to share a conserved haem arrangement with OmcS, but have little sequence or structural similarity (Wang, Mustafa, et al., 2022). Recently, a thorough mechanistic study of OmcS revealed interesting temperature dependence in nanowire conductivity, resulting in a 300-fold increase in conductivity when cooled due to changes in hydrogen-bonding network that makes neighbouring haems more planar (Dahl et al., 2022). While questions remain about the specific roles of the multiple nanowires produced by *G. sulfurreducens*, they likely play different roles as the biofilm develops with PilA being important for the maturation and export of the polymeric cytochrome wires (Gu et al., 2021), OmcS being important for initial colonization and growth of the biofilm (Dahl et al., 2022), and OmcZ playing an important role as the biofilm thickens, enabling cells far from the surface to still maintain electrical contact as the local biofilm redox potential decreases (Yalcin et al., 2020).

S. oneidensis also produces nanowires that extend micrometres away from the cell (El-Naggar et al., 2008; Gorby et al., 2006), but in contrast to *G. sulfurreducens*, are not solely proteinaceous. Rather, nanowires from *S. oneidensis* consist of outer-membrane and periplasmic extensions that are packed with membrane-associated cytochromes (Pirbadian et al., 2014; Subramanian et al., 2018). When dried and chemically fixed, these membrane extensions form 8 to 10 nm diameter nanowires with conductivities of ~1 S cm^{-1} under dry, solid-state conditions in a two-electrode configuration (El-Naggar et al., 2010). However, such dry conditions do not reflect physiologically relevant conditions and individual nanowires measured under hydrated conditions yielded conductivity of 10^{-2} S cm^{-1} (Grebenko et al., 2018). This is especially important because the cytochrome charge carriers in these nanowires are mobile and diffuse along the cell surface and the nanowires (Chong et al., 2022). This diffusivity is thought to contribute to the overall conductivity of these nanowires in a collision-exchange mechanism whereby the lateral diffusion of cytochromes leads to collision and interprotein electron transfer via redox-hopping (Chong et al., 2022; Subramanian et al., 2018). Additionally, the individual cytochromes that span the outer membrane of *S. oneidensis* can be thought of as nanoscale wires spanning ~15 nm and have electron fluxes that are about 30-fold lower than *G. sulfurreducens* OmcS over similar length scales (Jiang et al., 2020).

Other microbes have recently been discovered to produce diverse conductive structures that function as supramolecular wires. In the archaean *Methanospirillum hungatei*, conductive atomic force microscopy was used to show cross-sectional electron transport in the archaellum that is thought to arise from a core of tightly packed aromatic phenylalanine residues (Walker et al., 2019). Anaerobic methanotrophic archaea (ANME) express multihaem cytochrome/surface-layer fusion proteins that have been implicated in direct interspecies electron transfer with sulfate-reducing bacteria (McGlynn et al., 2015). While the structure and electron transport properties of ANME cytochrome/s-layer fusions have not yet been investigated, they hold exciting promise for engineering self-assembling 2D conductive materials (Charrier et al., 2019; Schuster & Sleytr, 2013). Recently, extracellular flavinylated proteins have been found in a wide array of Gram-positive bacteria including multi-flavinylated proteins that may serve similar functions as multihaem cytochromes (Light et al., 2018; Méheust et al., 2021). While it remains to be seen if similar micron-scale falvinylated proteins exist, there are exciting opportunities for developing conductive nanowires that do not require metallocofactors for conductivity but instead harbour redox-active organic molecules such as flavins.

In addition to these natural examples, there are examples of synthetic proteinaceous nanowires that have been engineered to facilitate micrometre-scale electron transport (Table 2). Synthetic nanowires use scaffolding proteins to self-assemble into nano- or micro-metre length fibres that are often modified with metal binding moieties or metalloproteins that endow these fibres with conductive properties (Altamura et al., 2017; Nguyen et al., 2014; Scheibel et al., 2003; Seker et al., 2017). Frequently, amyloid-fibril-forming proteins are used for the scaffold, such as fungal prions (Altamura et al., 2017; Scheibel et al., 2003) and bacterial curlins (Nguyen et al., 2014; Seker et al., 2017). These scaffold proteins have relatively low intrinsic conductivities (Del Mercato et al., 2007; Dorval Courchesne et al., 2018; Kalyoncu et al., 2017). To confer metallic conductivity to these nanowire scaffolds, the monomer can be functionalized to bind exogenously supplied metal nanoparticles by fusing them to metal binding moieties such as surface-exposed cysteines (Scheibel et al., 2003), poly-histidine (Chen et al., 2014; Seker et al., 2017), or metal-binding peptides (Nguyen et al., 2014; Seker et al., 2017). Redox-hopping conductivity has been engineered into nanofibres by fusing amyloid-forming

TABLE 2 Measurements of synthetic supramolecular wires. A description of the electronic properties of synthetic supramolecular nanowires.

Scaffold	Charge carrier	Cofactor	Diameter (nm)	Conductivity ($S cm^{-1}$)	Conductance (S)	Measurement	Measurement orientation	References
Amyloid (CsgA)	Colloidal Au	Colloidal Au	–	–	10^{-2}	dry solid-state 2-electrode	Transverse, Film	Scheibel et al. (2003)
Amyloid (CsgA)	Internal aromatic amino acids	–	–	–	10^{-9}	dry solid-state 2-electrode	Transverse, Film	Dorval Courchesne et al. (2018)
Amyloid (prion fibrils)	rubredoxin	Fe	8	10^{-6}	–	hydrated solid-state 2-electrode	Transverse, Film	Altamura et al. (2017)
ACC-Hex Alpha helical bundle	Internal aromatic amino acids	–	2.3	10^{0}	–	dry solid-state 2-electrode	Transverse, Film	Ing, El-Naggar, et al. (2018), Ing, Spencer, et al. (2018)
Gamma prefoldin subunit (Q58064)	Cytochrome c3 (CytC3)	Haem	3.6	–	10^{-7}	dry solid-state 2-electrode	Transverse, Film	Chen et al. (2020)
No scaffold (crystalized monomer)	CctA	Haem	–	~10^{-9} $cm^2 s^{-1}$	–	solution spectroscopic	Transverse, Crystal	Huang et al. (2020)

monomers to rubredoxin, a metalloprotein containing an $Fe^{2+/3+}$ centre enabling electron hopping with a conductivity of ~10^{-6} $S cm^{-1}$ in both hydrated electrochemical measurements and in solid-state two-electrode measurements (Altamura et al., 2017). Similarly, the bacterial curlin CsgA has been engineered to display a minimal cytochrome domain, but charge transport of these engineered curli was not measured (Chen, Yang, et al., 2022). To generate nanofibres with intrinsic conductivity based on band conduction with π-stacking, the amyloid-forming scaffold CsgA has been engineered to increase the number of amino acids with aromatic side chains through peptide fusion (Kalyoncu et al., 2017) and site-directed mutagenesis (Dorval Courchesne et al., 2018). The CsgA modified to have more aromatic residues resulted in nanowire films with enhanced conductivity relative to WT CsgA that, when characterized as dried fibre mats, displayed conductivities of ~10^{-9} $S cm^{-1}$ and ~ 10^{-8} $S cm^{-1}$ for the WT and mutant CsgA respectively (Dorval Courchesne et al., 2018). These studies illustrate the flexibility of amyloids as a platform for generating engineered conductive biomaterials.

Other fibre-forming scaffolds have been leveraged to generate conductive nanowires. For example, alpha-helical bundles with internal aromatic amino acids form micrometre length nanofibres with an exceptionally high conductivity of ~1 $S cm^{-1}$ as measured in solid-state conditions using a two-electrode configuration (Ing, Spencer, et al., 2018). Mechanistic electron transport measurements revealed that these nanowires had properties of ohmic charge conductors rather than those of redox-hopping or π-stacked charge conductors (Ing, Spencer, et al., 2018). The archaeal filament-forming protein gamma-prefoldin (γPFD) from *Methanocaldococcus jannaschii* has been engineered to assemble the tetra-haem cytochrome c3 (Cytc3) from *Desulfovibrio vulgaris* (Chen et al., 2020) into filaments in a modular way using the SpyTag/SpyCatcher system (Zakeri et al., 2012). γPFD-cytc3 fibres formed 3.6 nm diameter nanowires that display redox-hopping-based conductivity in electrochemical measurements and displayed conductances of 10^{-7} S when characterized using a solid-state, two-electrode configuration (Chen et al., 2020). This modular bioconjugation strategy could be adapted to assemble other redox-proteins into nanowires.

Synthetic wires have also been constructed that are not based on linear scaffolds but rather three-dimensional networks of charge carriers. Crystals of a tetra-haem cytochrome from *S. oneidensis*, CctA, have been generated and studied for their charge-carrying properties in solution using photoreduction and spectroscopy (Huang et al., 2020). These measurements revealed electron hopping between cytochromes travelling ~100 μm through the crystal lattice with apparent electron diffusion coefficient of ~10^{-9} cm^2 s^{-1} but

such crystals have not yet been probed using electrical characterization techniques (Huang et al., 2020). Mats of bovine serum album have also been shown to be proton conductors with proton conductivities of 10^{-5} S cm^{-1} (Amdursky et al., 2016) and, when doped with an electron carrier like Fe-containing haem, they can reach electron conductivities of ~10^{-3} S cm^{-1} (Amdursky et al., 2017). Subsequent studies of BSA mats doped with porphyrins containing different metal centres or protoporphyrin-IX containing no metal at all were also found to increase electron conductivity to ~10^{-3} S cm^{-1} leading the authors to suggest this results from the conjugated π-system of the porphyrin ring and not hopping between metal centres (Agam et al., 2020). Hydrogels made from the aforementioned alpha-helical bundles have also been constructed. AC conductance measurements of these materials have returned values on the order of 10^{-7} S when measured using two-probe configuration under hydrated conditions (Ing, Spencer, et al., 2018).

From the above-mentioned review of supramolecular wires, it is possible to glean important trends that are influencing our understanding of charge transport and structure–function relations. One trend is an increasing emphasis on developing electron transport measurement techniques that go beyond dry, solid-state conditions to hydrated or in-solution electrochemical measurements. This development is key to understanding electron transport in living electronics under physiologically relevant conditions. Moreover, there is increasing emphasis on reporting the intrinsic conductivity (or electron diffusion coefficients), rather than conductance, finally allowing detailed comparisons across studies in a way that is not confounded by contact resistances or electrode/biomaterial geometries. Moreover, with the increasing availability of structures, it is finally possible to make the link between these structures and the key thermodynamic and quantum mechanical parameters that control electron transport (Jiang et al., 2020). This increasing emphasis on structure–function studies, and the emergence of synthetic structures that promise to rationally control these parameters, are providing unprecedented mechanistic insight into both the limitations and potential of biological wires.

Multicellular networks as micron-to-centimetre scale wires

Just as redox-active molecules and supramolecular structures can carry charge, groups of cells can themselves come together to form multicellular networks that act as charge-carrying wires over length scales from microns to centimetres (Table 3). Model electroactive organisms such as *S. oneidensis* and *G. sulfurreducens* naturally cluster together and form

TABLE 3 Measurements of multicellular wires. A description of the electronic measurements of multicellular assemblies as microwires.

Organism	Charge carrier	Cofactor	Conductivity (S cm^{-1})	Conductance (S)	Measurement	Measurement orientation	References
G. sulfurreducens	Multihaem cytochromes	haem	10^{-6}	–	hydrated, electrochemical gating	Transverse, cell-containing film	Yates et al. (2015)
S. oneidensis	Multihaem cytochromes	haem	10^{-9}	–	hydrated, electrochemical gating	Transverse, cell-containing film	Zhao et al. (2022)
S. oneidensis	Multihaem cytochromes	haem	10^{-3}	–	hydrated, solid-state 2-electrode	Transverse, core/shell encapsulated cable	Hsu et al. (2018)
E. coli	AuNP	Ni-NTA-AuNP	–	10^{-9}	dry, solid-state 2-electrode	Transverse, cell-containing film	Chen et al. (2014), Seker et al. (2017)
Cable bacteria (marine)[a]	unknown	Ni-S[b]	10^{-2}–10^{2}	–	dry, solid-state 2-electrode	Transverse, single cable filament	Meysman et al. (2019)

[a]Unspecified genus assignment.
[b]Hypothesis from spectral studies of proposed metal centres (Boschker et al., 2021).

current-producing biofilms on electrodes. To probe in vivo biofilm conductance, biofilms have been cultivated on interdigitated arrays (IDA) of source and drain electrodes where electrochemical gating measurements have shown that these networks of cells form conductive channels capable of bridging the insulating gaps between the two electrodes (Xu et al., 2018; Yates et al., 2015). Temperature-dependent electrochemical gating measurements have revealed that these biofilms conduct electrons using a thermally activated redox hopping mechanism, where electrons travel through the biofilm, from source electrodes to drain electrodes, by hopping across the haem centres of the cells' outer-membrane cytochromes (Xu et al., 2018; Yates et al., 2015). In vivo biofilm conductivity, a fundamental material parameter that requires a conduction channel of known dimensions in order to be calculated, has also been determined for *S. oneidensis* and *G. sulfurreducens*. By constraining the physical dimensions of the conduction channel during electrochemical gating measurements, using the defined IDA geometry in the case of *G. sulfurreducens* and using light-patterned biofilms in the case of *S. oneidensis*, conductivities were found to be on the order of 10^{-9} S cm^{-1} for *S. oneidensis* and 10^{-6} S cm^{-1} for *G. sulfurreducens* (Yates et al., 2015; Zhao et al., 2022). With these fundamental, quantitative electron transport results, more in depth characterization can be performed on these systems and they can inform the construction of microbial-based living electronics.

While conductive multicellular networks have typically been studied in the form of micron-scale 2-D and 3-D biofilms on surfaces, the study of 1-D conductive multicellular networks was recently enabled by the discovery of cable bacteria, centimetre-scale filamentous chains of conductive cells. Cable bacteria were first discovered in aquatic sediments in Denmark in 2012 and were found to link sulfide oxidation occurring centimetres below the sediment surface to oxygen reduction occurring at the surface (Pfeffer et al., 2012). To connect these spatially separated redox reactions, cable bacteria evolved to form 1.5 cm to 3 cm long chains of cells that contain thousands of cells linked end-to-end (Schauer et al., 2014). Ultrastructural studies using cryotomography and nanodissection revealed that each individual cell in the chain has an individual inner membrane while the entire chain of cells shares a common outer membrane and periplasmic space (Cornelissen et al., 2018; Jiang et al., 2018). Within this shared periplasmic space, cable bacteria contain a network of 15–60 parallel ridge-structures (Cornelissen et al., 2018; Jiang et al., 2018). These periplasmic ridges consist of 10–50 nm diameter fibres that run along the long-dimension of individual cells (~3 μm) and join together into cartwheel structures at cell–cell junctions forming a sheath-like cage around each cell within the cable and are continuously connected over the centimetre length of the cables (Cornelissen et al., 2018; Jiang et al., 2018). This conspicuous structure suggests that these fibres are the conductive components enabling long-distance electron transport in cable bacteria.

To determine the charge-transfer characteristics of cable bacteria, they have been interrogated using both solid-state and electrochemical techniques. As implied by their geochemical activity, solid-state measurements of intact cable bacteria confirmed that they are capable of long-distance electron transport along their length using a two-electrode configuration (Meysman et al., 2019). Both cyclic and differential pulse voltammetry of intact cables on modified gold electrodes revealed redox-active molecules with potential near 0.155 V versus standard hydrogen electrode (V vs. SHE) that, based on resonance Raman spectroscopy, likely correspond to c-type cytochromes (Meysman et al., 2019). Conductive atomic force microscopy performed on the surface of intact cables directly implicated the periplasmic fibres as the conductive structure within the cable bacteria (Thiruvallur Eachambadi et al., 2020). The periplasmic fibre sheaths have been extracted from cables and directly studied using two-electrode and three-electrode field effect transistor (FET) measurements yielding conductivity values ranging from 10^{-2} to 10^{2} S cm^{-1} and electron mobility of 10^{-1} cm^2 V^{-1} s^{-1}, making these fibres one of the most conductive biomaterials studied to date (Bonné et al., 2020; Boschker et al., 2021; Meysman et al., 2019). Spectroscopic analysis of the extracted fibre sheaths revealed that, unlike the intact cables, they do not have c-type cytochrome signatures (Meysman et al., 2019) and suggests that they may contain a novel sulfur-ligated nickel cofactor that is important for the fibre-based long-distance electron transport (Boschker et al., 2021). There is much work to be done to understand the charge transfer properties of cable bacteria including determining the structure of the charge-carrying periplasmic fibres and characterizing the properties of diverse cable bacteria species. Currently, these organisms are the only known examples of macroscopic-scale living conductors and present some of the most conductive biomolecular structures known.

In addition to studying multicellular assemblies that self-assemble, electroactive bacteria have been directed to assemble into different structures using material encapsulation. Approaches for encapsulating multicellular assemblies often incorporate additional charge carriers such as polypyrrole (Song et al., 2017), polydopamine (Yu et al., 2020), PEDOT:PSS (Zajdel et al., 2018) or metallic nanoparticles (Atkinson et al., 2022; Chen, Kang, et al., 2022) making it challenging to directly measure cell-mediated conductivity. However, in some cases, researchers have examined composites where cells are encapsulated only using non-conductive materials. Inspired by cable bacteria, Hsu et al. utilized calcium-alginate hydrogels to form

quasi-1D assemblies of *Shewanella loihica* packed into 2-cm-long core/shell cables and studied their conductivity using a two-electrode configuration revealing conductivities of ~10^{-3} S cm^{-1} depending on the density of cells packed into the core/shell cable (Hsu et al., 2018). Further exploration at this interface of materials science and electromicrobiology will yield generalizable platforms for analysing microbial conductivity and generate interesting new components for bioelectronic devices.

Conductive multicellular networks have been demonstrated to transport electrons over micron (biofilms) and centimetre (cable bacteria/encapsulated cells) length scales. Further characterizing their fundamental electronic properties could lead to the development of novel living electronics that leverage the unique biological ability to sense and respond to environmental stimuli, self-assemble and self-repair. In the context of cable bacteria specifically, further electronic, spectroscopic and structural characterization of their periplasmic fibre network may reveal novel mechanisms responsible for their unprecedented long-distance biological conduction. Additionally, the further study of cable bacteria periplasmic fibres could lead to the development of biomimetic materials that are both flexible and share the long-distance electron transport efficiency of the fibres. Such materials could act as biocompatible wires in the development of new bioelectronic devices.

Biogenic synthesis of solid-state wires by electroactive microorganisms

In addition to producing conductive biomolecules or forming multicellular conductive networks, electroactive organisms can enable the mineralization of metallic and semiconductor nanomaterials by reducing metal and chalcogenide ions in solution. While this biomineralization phenomenon is often studied in the context of bioremediation and formation of catalytic nanoparticles, reviewed elsewhere (De Corte et al., 2012; Gadd, 2010; Shedbalkar et al., 2014) here, we discuss the relevance of biomineralization to the formation of electronic components. Biomineralizing microbes can produce inorganic materials that can act as wires or as more advanced electronic components such as photoresistors and transistors. Biogenic formation of inorganic nanomaterials can: (1) enable the synthesis of technologically relevant materials at ambient temperature, pressure and near neutral pH, without the resource-intensive conditions required for conventional chemical or solid-state material fabrication (Estroff, 2008); (2) allow use of synthetic biology tools to control material morphology and chemical composition (Chellamuthu, Naughton, et al., 2019; Chellamuthu, Tran, et al., 2019) and (3) allow the formation of cell-nanomaterial hybrids that combine the properties of both microbes and solid-state material (Ng et al., 2019).

Diverse strains of *Shewanellaceae*, such as HN-41, ANA-3 and MR-1, have been used to generate micron-long, nanoscale fibres consisting of metallic and semiconductor materials including selenium, goethite, telluride, uranium and arsenic-sulfide (Ho et al., 2010, 2015; Jiang et al., 2009, 2011; Kim et al., 2012, 2013; McFarlane et al., 2015; Tam et al., 2010). *Shewanella* sp. HN-41 can reduce Se(IV) to form extracellular Se nanoparticles when selenite is provided as the sole electron acceptor (Tam et al., 2010). When mercury chloride is present alongside Se(IV), HN-41 forms Hg-Se nanoparticles (Ho et al., 2015). Se and Hg-Se nanowires are formed when the cells and either type of Se nanoparticles are washed and resuspended in various solvents including acetone and DMSO (Ho et al., 2010, 2015). HN-41 also reduces the Fe(III)-oxyhydroxide akaganeite to form goethite nanowires that were evaluated as anodes materials for Li-ion batteries (Jiang et al., 2013). *S. oneidensis* MR-1 was demonstrated to reduce Te(IV) to Te(0) resulting in the formation of intracellular Te nanorods, when sodium tellurite was provided as the sole electron acceptor (Kim et al., 2012). However, in the presence of Fe(III), Te(0) nanorods were formed extracellularly (Kim et al., 2013). Such bacterially derived elemental tellurium nanostructures have been explored for their unique photonic properties (Wang, Zhang, et al., 2019). Similarly, when uranyl acetate is supplied as the sole electron acceptor, MR-1 formed U(VI) nanowires (Jiang et al., 2011).

HN-41, ANA-3 and MR-1 generate arsenic sulfide nanofibres by simultaneously reducing thiosulfate to sulfide and As(V) to As(III) (Jiang et al., 2009; McFarlane et al., 2015). As-S nanofibres harvested from HN-41 cultures demonstrated metallic-like conduction, with conductance decreasing with increasing temperature (Lee et al., 2007). While HN-41, ANA-3 and MR-1 have been shown to be electroactive, only the electrochemistry of MR-1 has been characterized in detail (Bretschger et al., 2010; Wu et al., 2013; Xu et al., 2016, 2018). To improve methods for the biogenic generation of these materials and for creating microbe-nanomaterial electroactive biomaterials the electrochemical activity of additional strains should be studied further. The electrochemical and biomineralization capabilities of electroactive microbes are often examined separately. However, a recent review by Ostermeyer et al. discusses the potential for using microbial fuel cell (MFC) and microbial electrolysis cell (MEC) technology with biomineralizing microorganisms for the industrial-scale bioremediation of metallurgic plant wastewater, with the additional potential of generating some energy from this process (Ostermeyer et al., 2022). In addition to wastewater treatment, MFC and MEC technology combined with microbial biomineralization should be used for the reclamation of precious metal and semiconductor materials (Capeness & Horsfall, 2020).

Capacitors

In addition to charge-carrying wires, capacitors are another important electrical component (Figure 2). Capacitors are circuit elements that store electrical energy as accumulated charge. Redox molecules, including biomolecules like those outlined above, can function as pseudocapacitive components of supercapacitors. Monolayers of redox-active proteins including cytochrome c (González-Arribas et al., 2018) and rusticyanin (González-Arribas et al., 2018) adsorbed onto the surface of electrodes is a facile way to increase the areal capacitance to ~10^{-4} F cm^{-2}. Redox-active molecules can also be stored within supramolecular assemblies (Cao et al., 2017; Liba et al., 2013) and multicellular networks (Bonanni et al., 2012; Esteve-Núñez et al., 2008; Malvankar et al., 2012; Schrott et al., 2011; Uría et al., 2011) resulting in increased capacitance. Supramolecular hydrogels of the aminopolysaccharide chitosan have been engineered to have capacitive moieties including catechol (Liba et al., 2013) and Li^+/Ag^+ (Cao et al., 2017) reaching areal capacitances of 10^4 F cm^{-2}.

Similar to the redox moieties in supramolecular assemblies, the cytochromes associated with *G. sulfurreducens* (Bonanni et al., 2012; Malvankar et al., 2012; Schrott et al., 2011) and *S. oneidensis* (Uría et al., 2011) have been shown to store charge when cells are starved of terminal electron acceptors. Individual *G. sulfurreducens* cells were found to be capable of storing ~10^7 electrons cell^{-1} when cytochrome discharge of cells starved of terminal electron acceptor was measured

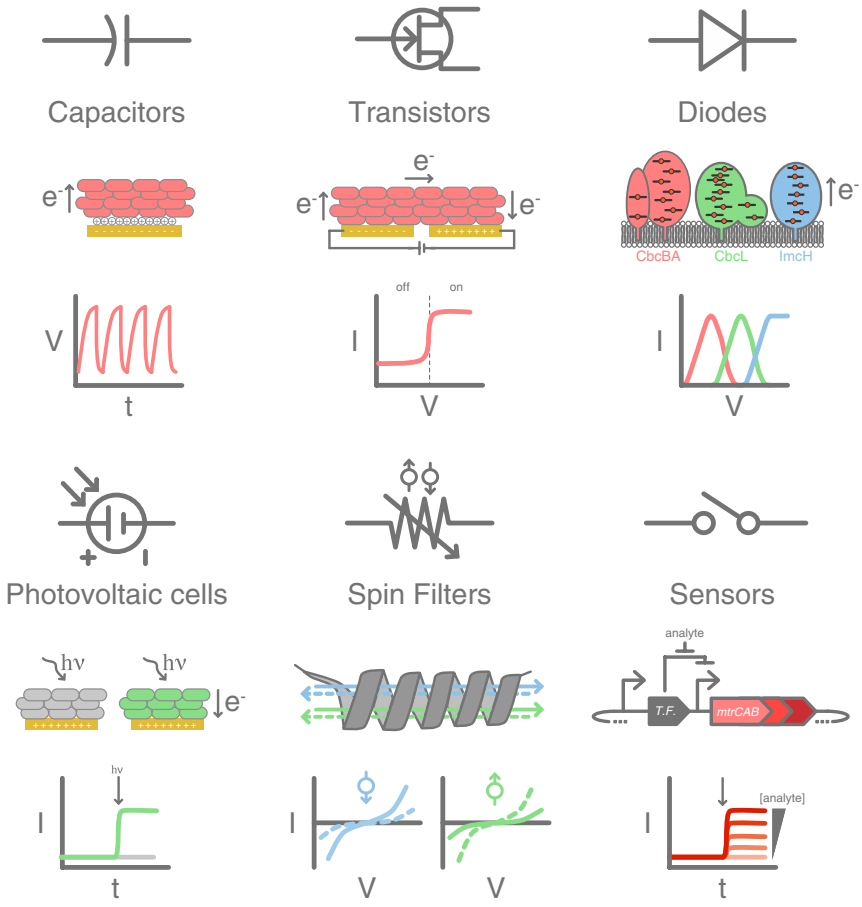

FIGURE 2 A catalogue of living electronic components. Capacitors can be formed by depositing electroactive bacteria (red) or biomolecules onto the surface of electrodes (gold). Resulting in a characteristic pseudocapacitive galvanostatic charge–discharge profile (V–t curve). Transistors can be constructed by depositing electroactive bacteria (red) or biomolecules as a current channel between source and drain electrodes (gold). Resulting in a transition between 'off' and 'on' states at a characteristic gate potential (I–V curve). Diodes can be envisioned being constructed by utilizing engineered microbes containing different inner-membrane quinone reductases (red, green and blue) that only transfer electrons at discrete potential windows (I–V curve). Photovoltaic cells can be constructed by depositing photosynthetic bacteria (green) onto electrode surfaces (gold) which generate photocurrents (I–t curve) when exposed to light relative to non-photosynthetic cells (grey). Spin filters can be constructed using chiral biomolecules which preferentially transmit electrons of either spin Up (green lines) or Down (blue lines) depending on the orientation of charge transfer through the molecule (left-to-right or right-to-left). This results in electron spin- and biomolecule orientation-dependent I–V curves. Sensors that respond to chemical analytes and generate electrical signals can be constructed by using analyte-dependent transcriptional promoters (arrows) to control the expression of EET-related genes, such as *mtrCAB*, in engineered microbes. This results in current production that is dependent on the concentration of the analyte (I–t curve).

using both fluorescence (Esteve-Núñez et al., 2008) and electrochemical (Bonanni et al., 2012; Malvankar et al., 2012) approaches. Using similar electrochemical charge–discharge cycles, *S. oneidensis* biofilms have been found to store up to ~10^{14} electrons cm^{-2} (Uría et al., 2011) and individual cells are estimated of storing ~10^5 electrons $cell^{-1}$ within the haems of c-type cytochromes (Sturm et al., 2015). Leveraging this capacitive property of electroactive cells, Malvankar et al. constructed supercapacitors using multicellular biofilms of *G. sulfurreducens* that spanned a 50 μm gap between gold electrodes (Malvankar et al., 2012). Electrochemical impedance spectroscopy and equivalent capacitive circuit modelling revealed biofilm areal capacitance of 10^{-4} $F\,cm^{-2}$ and a specific capacitance of 10^2 $F\,g^{-1}$. C-type cytochromes served as pseudocapacitive components within this biofilm-based supercapacitor, increasing the capacitance beyond the double-layer capacitance of the medium, and yielded charge–discharge cycles consistent with pseudocapacitive behaviour which could be eliminated when treated with a cytochrome inhibitor (Malvankar et al., 2012).

Living capacitors hold great promise as charge-storage devices that could be used as power sources for electrical devices. They can be easily coupled to enzymatic-power generation systems, making them self-powered energy storage devices for deployment in resource-limited environments including the human body and environmental settings (González-Arribas et al., 2018; Malvankar et al., 2012). Many of the previously mentioned wires function using a redox-hopping mechanism that also makes them potential capacitors and should be explored for their capacitive properties. While living capacitors have limited energy density relative to traditional battery chemistry, there is potential for improving on these early designs. Their limited resource requirements and facile construction make living capacitors an attractive option for energy storage devices to help address the need for renewable energy storage.

Transistors

Transistors are switchable circuit elements that can be controlled to either allow (on-state) or block (off-state) current from flowing through them (Figure 2). The on- and off-states of solid-state transistors, of which there are up to several billions of in modern computational devices, act as the physical bits that enable complex digital logic processes. Solid-state transistors are constructed from doped semiconductors, whose electronic properties enable gating of current flow through the device (Neamen, 2011). Soft-matter transistors in the form of organic electrochemical transistors (OECTs) have also been constructed in solution with conductive polymers acting as the switchable current channel (Friedlein et al., 2018; Rivnay et al., 2018). Additionally, some of the above-discussed conductive solid-state and biological materials produced by electroactive microorganisms have also been used as switchable current channels in dry, transistor device setups (Bonné et al., 2020; Leung et al., 2013; McFarlane et al., 2015). While transistors can enable digital logic processes, they can also be used to characterize fundamental electronic properties of the channel material, such as identifying the majority charge carrier type and charge mobility.

Transistor measurements where biogenic conductive materials serve as the conducting channel enable the extraction of additional fundamental properties, including charge carrier mobility. Measurements of the aforementioned As-S nanofibres harvested from ANA-3 cultures revealed a mixed population of both n-type (electron majority charge carrier) and p-type (hole majority charge carrier) semiconducting fibres (McFarlane et al., 2015). Leung et al. showed that current through the *S. oneidensis* outer-membrane extensions could be gated using an electric field, with the conduction interpreted to be p-type with an estimated hole mobility of 0.1 $cm^2\,V^{-1}\,s^{-1}$ (Leung et al., 2013). More recently, fibre sheaths extracted from marine cable bacteria were used as channels in transistor measurements, illustrating that current through these structures could be gated. From these measurements, the conduction was interpreted to be n-type and an electron mobility was estimated to be on the order of 0.1 $cm^2\,V^{-1}\,s^{-1}$ (Bonné et al., 2020), a value similar to charge mobility in some organic semiconductors and the hole mobility in *S. oneidensis* outer-membrane extensions. While these examples are few, the use of biologically synthesized solid-state semiconductors and biological conducting materials as transistor channels demonstrates their potential application in the construction of more complex bioelectronic devices.

Looking forward, transistor measurements offer an additional avenue to further characterize electron transport in biogenic materials. In addition to revealing the majority charge carrier and charge mobility of materials, transistor measurements can be used to investigate the speed at which the current flowing through channels can be switched on and off, as well as how many on/off cycles the channel can support before degrading. Since transistors can be used as amplifiers, transistor measurements can also be used to investigate how well current channels made of biogenic materials amplify input current and voltage signals. Thus far, conductive supramolecular assemblies and biogenic semiconductor materials have been the focus of transistor-based characterization; however, multicellular networks, such as the patterned biofilms discussed earlier, could also be used as device channels. Since electroactive biofilms act as redox conductors, when a constant applied source-drain potential offset is applied, there are

applied gate potentials that enable current flow through a biofilm spanning source and drain electrodes that can be switched on and off. The characterization of biofilms as transistor channels may prove useful as multicellular networks can self-assemble, are patternable and may be engineered to respond to environmental stimuli. Taking inspiration from how solid-state semiconductors can be doped to tune electronic properties, biofilms can also be engineered for tuneable expression of electron transport proteins (West et al., 2017) or with metal or semiconductor nanomaterial binding sites to modulate their conductivity (Seker et al., 2017).

Diodes

Diodes are useful components in electrical circuits because of their ability to control the direction through which current can flow. Recently, separate EET pathways in the model electroactive organism *G. sulfurreducens* have been identified that activate depending on the potential of an external electron acceptor (Figure 2). Similar to their diversity of extracellular nanowires that serve different functions depending on the biofilm stage, *G. sulfurreducens* also uses a variety of inner-membrane quinol oxidases to input electrons into the EET pathway. With higher potential (> −0.1 V vs. SHE) electron acceptors the inner-membrane cytochrome ImcH is triggered (Levar et al., 2014), while use of the inner-membrane cytochrome CbcL is triggered when the biofilms exchanges electrons with lower potential (< −0.1 V vs. SHE) (Zacharoff et al., 2016), and at very low potentials (< −0.2 V vs. SHE), near the energetic limit of respiration, *G. sulfurreducens* use the inner-membrane cytochrome CbcBA (Joshi et al., 2021). The existence of such potential-dependent EET pathways raises the intriguing possibility of building living electronic components (at the cellular or biofilm scale) with asymmetric conductance features, in a manner analogous to traditional electron rectifiers and diodes.

Optoelectronic components

Adding to the above list of circuit elements, biomineralized and biological materials have been used for the development of a diverse set of living optoelectronic components. This can include hybrid components that use inorganic semiconductors that are photoresponsive and alter their material properties in response to light such as photoresistors. Other living optoelectronic components such as biophotovoltaic cells use biological structures to harvest energy from photoexcited electrons. Additionally, components can be built that utilize cells engineered with optogenetic circuits, allowing photon absorption to trigger alterations in gene expression such as the production of redox active biomolecules that can interact with electronic devices.

The earlier described As-S nanofibres biomineralized by *Shewanella* sp. HN-41 display photoactive properties and were used for the construction of a photoresistor after being harvested from cell cultures. Increased current was observed when As-S fibres were illuminated with UV light while a DC voltage was applied across the fibres (Lee et al., 2007). In addition to being capable of natively biomineralizing photoactive nanomaterials, microbes have also been engineered to act as scaffolds for the abiotic formation of photoactive semiconductor networks. Recently, Wang et al. engineered *E. coli* to produce curli fibres with transition metal binding sites (Wang, Zhang, et al., 2022). This then allowed photoactive CdS nanoparticles to spontaneously form along the fibres when Cd^{2+} and S^{2-} ions were introduced to the cell culture. When formed on the working electrode surface of a three-electrode bioreactor setup, the cell and curli fibre scaffold network of CdS was shown to produce a photocurrent upon illumination with blue light. This system was also leveraged for the development of an artificial photosynthesis scheme in which electrons generated by the photoexcitation of the CdS-cell network were used to drive enzymatic chemical production (Wang, Zhang, et al., 2022). One limitation of using such semiconducting nanoparticles is the need for sacrificial electron donors (often exogenously supplied cysteine or unspecified cellular metabolites) to fill holes generated during semiconductor photoexcitation.

While interfacing cell networks with photoactive nanomaterials can confer optoelectronic properties, biophotovoltaic systems have been developed that harness the intrinsic light-harvesting and electroactive properties of photosynthetic microbes to harvest energy (Figure 2) (Tschörtner et al., 2019). For example, films of *Synechocystis* sp. PCC6803 (*Synechocystis*), a model photosynthetic bacterium, deposited onto the working electrodes of three-electrode reactors present enhanced EET currents when they are illuminated with light (Cereda et al., 2014; Thirumurthy et al., 2020; Zhang et al., 2018). Control experiments using photosystem II (PSII) inhibitors confirmed that electrons from this light-enhanced EET are derived from water oxidation rather than coming from another electron donor (Cereda et al., 2014; Zhang et al., 2018). While the mechanisms for how electrons from PSII cross the cell membrane and reach the electrode are not currently known, redox-active molecules have been implicated as soluble electron shuttles in this process (Cereda et al., 2014; Kusama et al., 2022; Saper et al., 2018; Shlosberg et al., 2021; Thirumurthy et al., 2020; Zhang et al., 2018). In addition to pursuing a better mechanistic understanding of the EET pathways in photosynthetic microbes, the field of biophotovoltaics has focused on optimizing these systems (Wey et al., 2019). This work has included enhancing biofilm formation (Wey et al., 2021), creating porous

electrodes with increased surface area (Wenzel et al., 2018; Zhang et al., 2018), disrupting the cell surface (Kusama et al., 2022; Saper et al., 2018; Wey et al., 2021), introducing additional redox-active molecules (Clifford et al., 2021) or EET proteins (Meng et al., 2021; Schuergers et al., 2017; Sekar et al., 2016) and creating microbial consortia where photosynthetic microbes use light to produce electron donor chemicals that other electroactive microbes can use to produce current (Zhu et al., 2019). Biophotovoltaic devices using *Synechocystis* have proven functional as continuous power sources for low-powered electronics such as a digital clock (McCormick et al., 2011) and a microprocessor (Bombelli et al., 2022).

Producing living optoelectronic components by leveraging the ability for electroactive microbes to produce solid-state semiconductor materials and for photosynthetic microbes to harvest light has great potential for enabling new types of living electronic circuits that use light as both a stimulus and a power source. One unexplored avenue for living optoelectronics is using optogenetic tools, commonly used by synthetic biologists, to control EET protein expression or activity in electroactive cells (Baumschlager & Khammash, 2021). Another interesting unexplored research area is using living electronic circuits to generate nanoparticles that undergo radiative emission of light when electrically stimulated to function as optical displays. Using electroactive microbes to both generate such semiconducting nanoparticles as well as functioning as living electrodes for interfacing these particles with electronics could provide a more sustainable route for manufacturing such devices.

Spin filters

Spintronics are an emerging class of devices that exploit the spin degree of freedom, in addition to the electron charge, to control the storage and flow of information (Wolf et al., 2001). Such devices often employ magnetic interactions and/or spin-filtering components to make conduction dependent on the spin state of the electrons (Up or Down) (Figure 2). In simplified terms, the resistance of these materials depends on the spin state of the electron passing through the device and can be influenced by magnetized layers (Moodera et al., 1995) or an external magnetic field (Baibich et al., 1988). Such spintronic devices have revolutionized magnetic recording and memory (Bhatti et al., 2017; Wolf et al., 2001). Components that leverage the impact that spin has on electron transmission are typically constructed using inorganic metals, oxides, and semiconductors, but recently have begun to employ organic molecules (Naaman & Waldeck, 2015). Chiral molecules have been shown to preferentially transmit electrons with one spin orientation over the other. This phenomenon has been dubbed chirality-induced spin selectivity (CISS) (Naaman & Waldeck, 2015).

CISS was first reported in 1999, when Naaman, Waldeck and colleagues (Ray et al., 1999) observed a correlation between the transmission of polarized photoelectrons and the chirality of L- or D-stearoyl lysine thin films. The effect involves the breakdown of spin degeneracy in chiral molecules, leading to a coupling of the electron spin with its linear momentum (Naaman & Waldeck, 2012). The favoured spin depends on the handedness of the chirality, where if one enantiomer favours a particular spin along an axial vector, its mirror image will favour the other along the same vector (Zwang et al., 2016). In all cases, the spin polarization depends on the energy of the incident electrons, and has been observed to vary nonlinearly in current–voltage curves (Xie et al., 2011). Interestingly, the spin polarization observed in organic molecules can be very large relative to inorganic materials (Naaman & Waldeck, 2015). The extent of spin filtering due to CISS in some supramolecular organic polymer-based nanofibres has been observed to be as high as 85% (Kulkarni et al., 2020). Devices constructed using organic molecules displaying CISS include magnetoresistive random access memory (MRAM) (Ben Dor et al., 2013), memristors (Al-Bustami et al., 2018) and a 9-bit optical memory device (Al-Bustami et al., 2020).

In addition to organic molecules, the CISS effect has been observed in many biological materials, including DNA (Göhler et al., 2011; Mishra et al., 2020), oligopeptides (Kiran et al., 2017; Mishra et al., 2020) and proteins (Carmeli et al., 2014; Mishra et al., 2019). In the case of DNA and linear oligopeptides, spin selectivity is observed to increase with increasing molecular length while total electron transmission decreases (Mishra et al., 2020). Recently, spin selectivity was demonstrated in monolayers of metalloproteins including photosystem I from *Synechocystis* (Carmeli et al., 2014), azurin from *P. aeruginosa* (Sang et al., 2021) and the multihaem cytochromes OmcA and MtrF from *S. oneidensis* (Mishra et al., 2019). While the role that CISS plays in the physiological function of these metalloproteins remains unknown, the electron transport properties of these biomolecules make them a promising new material for the development of spintronic components.

Sensors

One powerful use for integrating living cells with electronics is for applications in sensing. To thrive in diverse and changing environments, microbes are capable of sensing, integrating and dynamically responding to a variety of physical, chemical, and biological stimuli (Del Valle et al., 2020; Wan et al., 2021). Efforts in synthetic biology have enabled the construction of microbial sensors

that produce diverse phenotypic outputs including the production of electrical currents (Atkinson et al., 2022; Dundas et al., 2020; Golitsch et al., 2013; Hu et al., 2015; Li et al., 2020; Ueki et al., 2016; Webster et al., 2014; West et al., 2017; Zhou et al., 2017), redox molecules (Li et al., 2011; Terrell et al., 2021; VanArsdale et al., 2019; VanArsdale, Hörnström, et al., 2020; VanArsdale, Pitzer, et al., 2020) and light (Mimee et al., 2018) that can be integrated into microelectronic devices as sensor modules. Sensor cells can be engineered by introducing stimuli-regulated transcriptional promoters that control the concentration of proteins that facilitate electron flow or the production of redox-active molecules (Figure 2) (Del Valle et al., 2020; Wan et al., 2021). Additionally, the activity of these proteins can be directly controlled by stimuli through insertion of stimuli-responsive domains to generate allosteric protein switches (Atkinson, Wu et al., 2019; Kanwar et al., 2013; Stein & Alexandrov, 2015). To date, living electronic sensors have been developed to respond to various chemical stimuli (Table 4).

Signal transduction using redox mediators

Biological systems natively produce and respond to molecules that undergo redox processes (Falkowski et al., 2008). These redox-active molecules undergo electron transfer reactions making them well-suited mediators for enabling communication between cells and electrodes (VanArsdale, Pitzer et al., 2020). Many bioelectronic sensors implemented that utilize redox mediator-based signal transduction require the addition of exogenous substrates that become redox active following enzymatic activation such as 4-aminophenyl β-D-galactopyranoside (PAPG) which is cleaved by β-galactosidase (LacZ) to form the redox-active molecule p-aminophenol (PAP) that can be detected electrochemically (Tschirhart et al., 2016; VanArsdale et al., 2019). Efforts have also been made to engineer cells that self-produce electroactive molecules such as phenazines (Feng et al., 2018; Li et al., 2011), riboflavin (Khan et al., 2020; Zhou et al., 2021) and L-3,4-dihydroxyphenylalanine (L-DOPA) (VanArsdale, Hörnström, et al., 2020) that can function as redox mediators for biosensing. As additional pathways for synthesizing and interacting with extracellular redox mediators are discovered (Coates et al., 2018; Glasser et al., 2017; Hernandez et al., 2004; Light et al., 2018; Mevers et al., 2019) it opens the potential for enabling multiple channels of cell-electrode communication in a single device.

Signal transduction using direct electron transfer

An alternative approach for enabling communication between cells and electrodes is to use direct electron transfer machinery from electroactive microbes to generate or receive an electrical signal. Bioelectronic sensors using direct electron transfer for signal transduction often engineer electroactive microbes to enable control over the production of critical components within the extracellular electron transfer pathway such as the synthesis of multihaem cytochromes or dehydrogenases. Because the EET pathways in *S. oneidensis* are well-understood (Bretschger et al., 2007; Coursolle & Gralnick, 2012), it has been engineered into bioelectronic sensors for a variety of stimuli by controlling the ability of electrons to reach extracellular electrodes. This has been implemented by several labs over the years by controlling the transcription of various EET genes including the inner-membrane quinol-oxidase *cymA* (Dundas et al., 2020), the periplasmic decahaem cytochrome *mtrA* (Dundas et al., 2020; Golitsch et al., 2013), the porin *mtrB* (Golitsch et al., 2013; Webster et al., 2014), the outer-membrane cytochromes *mtrF* (Golitsch et al., 2013) and *mtrC* (Dundas et al., 2020) as well as the endogenous operon encoding *mtrCAB* (West et al., 2017) or an engineered operon encoding *mtrFAB* (Golitsch et al., 2013). This strategy works well in organisms with well-understood EET pathways and limited redundancy in electron transfer pathways (Coursolle & Gralnick, 2012). In contrast, *G. sulfurreducens* utilizes a more complicated EET pathway with many built in redundancies that make controlling any single EET component challenging (Jiménez Otero et al., 2018). To overcome this challenge, Ueki et al. engineered control over how electrons enter the EET pathway by controlling flux through acetate metabolism by gating transcription of citrate synthase and acetyl-CoA transferase as well as controlling flux through lactate metabolism by gating transcription of D-lactate dehydrogenase (Ueki et al., 2016). This same strategy has also been successfully applied to build sensors for acetate and lactate controlling their metabolic fluxes in *Arcobacter butzleri*, an electroactive organism with unknown EET components (Szydlowski et al., 2020).

Enabling sensors with rapid response times

While using gene networks to build microbial sensors allows for the facile design of new sensors based on the plug-and-play nature of transcriptional promoters, one limitation is that they require minute-hour long response times to allow for transcription and translation of output proteins (Olson & Tabor, 2012). To overcome this limitation, proteins can be engineered into stimuli-regulated switches (Atkinson, Wu et al., 2019; Kanwar et al., 2013; Stein & Alexandrov, 2015). This approach has been used to build living electronic sensors where intracellular electron transfer is controlled by ferredoxins that have been engineered to function as chemically gated allosteric switches (Atkinson, Campbell,

TABLE 4 Bioelectronic sensors modules. A description of bacterial sensors that utilized electrical or redox signals as outputs to interface with electronics.

Analyte	Organism	Receptor	Regulated component	Output type	Measurement	Limit of detection	Linear range	Response time	References
arsenite	*S. oneidensis*	Promoter (AsrR – P_{ars})	MtrB	DET	Chronoamperometry	40 μM	100 μM	1.5 d	Webster et al. (2014)
Zn^{2+}	*E. coli*	Promoter (ZntR – P_{zntA})	riboflavin synthesis	MET	Microbial Fuel Cell voltage	20 μM	100 μM	ND	Khan et al. (2020)
Cu^{2+}	*E. coli*	Promoter (CusR –P_{cusC})	riboflavin synthesis	MET	Microbial Fuel Cell voltage	28 μM	500 μM	ND	Zhou et al. (2021)
IPTG	*S. oneidensis*	Promoter (LacI-P_{tac})	MtrA	DET	Microbial Fuel Cell voltage	10 μM[a]	ND	ND	Hu et al. (2015)
IPTG	*G. sulfurreducens*	Promoter (LacI-P_{tac})	GltA	DET	Chronoamperometry	1 mM[a]	ND	ND	Ueki et al. (2016)
IPTG	*E. coli*	Promoter (LacI-P_{trc})	phenazine-1-carboxylic acid synthesis	MET	Microbial Fuel Cell voltage	0.5 mM	ND	ND	Feng et al. (2018)
3-oxo-C6-HSL	*S. oneidensis*	Promoter (LuxR – P_{lux})	MtrA	DET	Microbial Fuel Cell voltage	10 nM[a]	ND	ND	Hu et al. (2015)
3-oxo-C12-HSL	*E. coli*	Promoter (LasR – P_{luxI})	L-DOPA synthesis	MET	Cyclic voltammetry	ND	10 nM	ND	VanArsdale, Hörnström, et al. (2020), VanArsdale, Pitzer, et al. (2020)
3-oxo-C6-HSL	*S. oneidensis*	Promoter (LuxR – P_{lux})	OmcAMtrCAB CymA riboflavin synthesis	DET MET	Chronoamperometry	0.024 nM	100 nM	ND	Li et al. (2020)
Autoinducer-2	*E. coli*	Promoter (LsrR – P_{lsr})	p-aminophenol synthesis	MET	Cyclic voltammetry	5 μM[a]	40 μM	2 h	Tschirhart et al. (2016)
Pyocyanin	*E. coli*	Promtoer (SoxR – P_{soxS})	L-DOPA synthesis	MET	Cyclic voltammetry	ND	0.5 μM	ND	VanArsdale, Hörnström, et al. (2020), VanArsdale, Pitzer, et al. (2020)
Paraquat	*E. coli*	Promtoer (SoxR - P_{soxS})	L-DOPA synthesis	MET	Cyclic voltammetry	ND	1 μM	ND	VanArsdale, Hörnström, et al. (2020), VanArsdale, Pitzer, et al. (2020)
Dicamba	*E. coli*	Promtoer (SoxR – P_{soxS})	p-aminophenol synthesis	MET	Cyclic voltammetry	0.9 mM[a]	4.5 mM	0.5 h[b]	VanArsdale et al. (2019)
Diquat	*E. coli*	Promtoer (SoxR – P_{soxS})	p-aminophenol synthesis	MET	Cyclic voltammetry	0.1 μM[a]	1.5 μM	0.5 h[b]	VanArsdale et al. (2019)
4-hydroxytamoxifen	*E. coli*	Protein Switch (sFd-ER-55)	Relative electron flux	DET	Chronoamperometry	12.5 μM[a]	ND	5–10 min	Atkinson et al. (2022)
Thiosulfate	*E. coli*	Thiosulfate metabolism	Relative electron flux	DET	Chronoamperometry	0.28 mM	20 mM	3–10 min	Atkinson et al. (2022)
L-arabinose	*S. oneidensis*	Promoter (AraC-P_{BAD})	MtrFAB	DET	Chronopotentiometry	0.2 mM	1 mM	2 h	Golitsch et al. (2013)
Lactate	*S. oneidensis*	Lactate metabolism	Relative electron flux	DET	Chronoamperometry	40 mM[a]	ND	ND	Zhou et al. (2017)
Lactate	*A. butzleri*	Lactate metabolism	Relative electron flux	DET	Microbial Fuel Cell voltage	ND	450 μM	ND	Szydlowski et al. (2020)
Acetate	*A. butzleri*	Acetate metabolism	Relative electron flux	DET	Microbial Fuel Cell voltage	ND	600 μM	ND	Szydlowski et al. (2020)
Trimethylamine *N*-oxide	*S. oneidensis*	Promoter (TorR-P_{torF})	MtrCAB	DET	Chronoamperometry	5 mM[a]	ND	ND	West et al. (2017)
Fumarate	*S. oneidensis*	Fumarate metabolism	Relative electron flux	DET	Chronoamperometry	1 mM[a]	ND	1.8 h	Zhou et al. (2017)

Abbreviations: DET, Direct electron transfer; HSL, homoserine lactone; IPTG, isopropyl β-D-1-thiogalactopyranoside; MET, Mediated electron transfer; ND, Not determined.

[a]LOD not formally determined, minimum tested yielding response.

[b]Minimum time tested.

et al., 2019; Wu, Atkinson, et al., 2020). These switches allowed for metabolic pathways to be rapidly turned on only in the presence of small-molecule signals. Coupling the metabolic pathway controlled by these ferredoxin electron transfer switches to an extracellular electron transport pathway enabled engineered cells to report on chemical concentrations in the cellular environment to electrodes with mass transport limited kinetics (Atkinson et al., 2022). A recent study probing the insertional tolerance of the multihaem cytochrome MtrA suggests that it may also be possible to build such allosteric switches from native EET proteins (Campbell et al., 2022).

Contrasting signal transduction mechanisms

Each of these signal transduction mechanisms have unique advantages and disadvantages. One advantage of mediator-based signal transduction is that the sensor output does not require metabolically derived electrons to generate a detectable signal. Rather, the quantity of the accumulated molecule is assessed using voltammetry techniques (current vs. electrode potential) which are sensitive to very low concentrations of redox-active molecules. The use of voltammetry however limits the frequency of measurements and the response time of the overall device. In contrast, signal transduction using direct electron transfer can be monitored using chronoamperometry (current vs. time) but requires metabolic flux that is sufficiently high to generate detectable currents. Chronoamperometry allows for real-time recording of signalling outputs allowing for rapid analyte detection. Building out miniature platforms that are compatible with both signal modalities will enable the use of living electronic sensors to monitor chemicals that can be deployed into the environment and human body.

Logic processor

In addition to functioning as sensors for single stimuli, more advanced genetic circuits have been introduced into bacteria enabling them to perform Boolean logical operations (Brophy & Voigt, 2014). The ability to encode multiple, layered DNA-based logic gates in populations of cells allows them to function analogous to electronic logic processing circuits including half adder (Wong et al., 2015), multiplexer (Sexton & Tabor, 2020), demultiplexer (Sexton & Tabor, 2020), artificial neural network (Sarkar, Bonnerjee, et al., 2021), maze-solving (Sarkar, Chakraborty, et al., 2021) and digital display (Shin et al., 2020) circuits. Often, these circuits utilized fluorescent proteins as outputs, but being able to couple these biological logic processing functions directly with electronic signals could enable biohybrid computing architectures (Sarkar, Bonnerjee, et al., 2021; Sarkar, Chakraborty, et al., 2021; Sexton & Tabor, 2020; Shin et al., 2020; Wong et al., 2015). Some work has been done implementing logic gate operations to control electronic signals. This allows cells to digitally respond to multiple stimuli for control of electronic signal production. To date, AND (Hu et al., 2015; Ueki et al., 2016), Buffer (Dundas et al., 2020) and NOT (Dundas et al., 2020) gates have been implemented to control electronic signals from living cells. There is great promise for further engineering of bacteria in living electronics to perform these more complex layered DNA-based logic processing operations outlined above that can be directly integrated into electrical circuits.

Bioactuator

In addition to using cells as sensors and logic-processing units, the ability to interface living cells with electrical devices opens the door to controlling the behaviours of cells using electrical stimuli, through what is called 'electrogenetics' (Mansouri & Fussenegger, 2022; Weber et al., 2009). This was first illustrated in 2009 by Fussenegger and colleagues when they showed it was possible to control gene expression in mammalian cells by modulating an electrical signal (Weber et al., 2009). In their system, the electrochemical oxidation of ethanol to acetaldehyde was used to induce gene expression from an acetaldehyde-responsive transcriptional promoter. By controlling the expression of the human placental secreted alkaline phosphatase (SEAP) and using a photodiode to monitor the production of a colorimetric indicator of phosphatase activity they showed that cells functioned as electronic current integrators that report on the total charge driven into the system using either direct or alternating currents. Additionally, cells could be engineered into frequency generators by introducing this electrogenetic system in cardiomyocytes to control expression of human bone morphogenetic protein 2 (BMP-2) which tunes the frequency of cellular contractions (Weber et al., 2009).

In Tschirhart et al., 2017, Tschirhart, Bentley and colleagues extended electrogenetics to microbes using redox signalling to trigger gene expression in *E. coli* (Tschirhart et al., 2017). This system is based on electrochemical control of the redox state of ferro/ferri-cyanide which in turn controls the oxidation state of pyocyanin, a redox-active molecule that when oxidized induces gene expression from an oxidative-stress promoter, P_{soxS} (Tschirhart et al., 2017). Similar to the mammalian cell example, this system enabled *E. coli* cells to function as electronic current integrators yielding gene expression that was dependent on the total charge extracted from the system by oxidation of

ferrocyanide at the electrode. This system was used for electronic control of fluorescent protein expression, cell motility and cell-to-cell communication (Tschirhart et al., 2017). Subsequently, electrode-controlled transcription was extended to genes not directly under the control of P_{soxS} by using this system to drive expression of guide RNAs used for targeting CRISPR-based activation (dCas9-ω) or inhibition (dCas9), which enabled genome-scale electronic control over gene expression (Bhokisham et al., 2020). The P_{soxS} promoter has been recently engineered to have a higher dynamic range, drive transcription in a single direction, and was tested with a diversity of redox-active molecules (Lawrence et al., 2022).

The synthetic biology toolbox for microbial electrogenetics is rapidly expanding. Another oxidative stress promoter, P_{oxyR}, has also been leveraged for electrogenetics (Stephens et al., 2021; Terrell et al., 2021). Rather than relying on the introduction of an exogenous mediator to electrically connect cells to an electrode, instead systems using P_{oxyR} rely on the electrochemical production of hydrogen peroxide at the surface of electrodes under aerobic conditions. Hydrogen peroxide activates gene expression from P_{oxyR} but is quickly enzymatically consumed by the cells. This results in heterogeneous gene expression when cells are in planktonic conditions, but results in homogenous expression in the electrode-localized cells (Terrell et al., 2021). To extend these electrical signals to the planktonic cells, P_{oxyR} was used to control the production of acyl-homoserine lactone enabling cell-to-cell chemical communication generating a biological local area network (BioLAN) (Terrell et al., 2021). BioLAN was used to control the activity of two different strains: a 'verifier' strain that produces electrical signals to verify the input and an 'actuator' strain that excretes a fluorescent protein and granulocyte macrophage colony-stimulating factor, a therapeutic protein (Terrell et al., 2021). In a similar illustration, planktonic 'relay' cells used P_{oxyR} to respond to electronic signals and control the growth rate of 'controller' cells changing the relative composition of the community (Stephens et al., 2021). This illustrated that electrogenetics coupled to cell-to-cell signalling can enable the electronic control of a population of diverse strains. Additionally, there are active efforts to enable electrogenetics in natively electroactive bacteria to also enable closed circuit actuation-verification (Hirose et al., 2019).

An alternative to using redox-mediated communication between electrodes and cells to control biological systems, ionic signals that are endogenously produced in some bacterial biofilms can be used to control microbial behaviour (Prindle et al., 2015). Similar to how neurons electrically communicate, some bacteria have evolved to respond to stimuli by using ion channels to control the local concentration of ions in their environment. These ions can serve as electrical signals that propagate through the biofilm community (Larkin et al., 2018; Prindle et al., 2015) and to recruit other diverse microbes to form multispecies biofilms (Humphries et al., 2017). Electrodes have been used to exogenously control the concentration of such ionic signals which resulted in control over membrane potential and the transcriptomic differentiation of motile and biofilm cells near the electrode (Comerci et al., 2022). It remains to be seen how portable such ionic signalling systems are in other microbial hosts that do not natively respond to such ionic signals. Regardless, ionic signalling is an exciting avenue to further explore for using electrical stimuli to control biological behaviour.

In addition to controlling gene expression, the metabolic activity of cells can be controlled using external electrodes. While not a major focus of this review as they have been extensively reviewed elsewhere (Rabaey & Rozendal, 2010; Schievano et al., 2016), electrosynthesis and electrofermentation have been a major focus of efforts in the electromicrobiology field and are both quintessential examples of bioactuation by using electrodes to tune the metabolic profile of both native and engineered cells. In the case of electrosynthesis, cells are grown in the presence of cathodes that provide electrons for the reduction of CO_2 into more reduced (e.g. formate, methane) and longer-chain organic molecules (e.g. acetate, butyrate). In the case of electrofermentation, cells are grown in the presence of an anode to facilitate the recycling of intracellular reduced cofactors resulting in shifts in the fermentative products generated and allowing for unbalanced fermentation pathways (Askitosari et al., 2019; Bursac et al., 2017; Förster et al., 2017; Tejedor-Sanz et al., 2022; TerAvest et al., 2014). Recently, there has also been an interest in both electrosynthesis and electrofermentation to control microbial-based food production (Tejedor-Sanz et al., 2022; Wise et al., 2022). The extensive use of microbes in both chemical and food production makes this particular type of electrical bioactuation particularly exciting.

The ability to use electrical stimuli to control the genetic and metabolic states of microbial cells holds great potential as a tool for synthetic biology. The development of generalizable strategies for controlling the behaviour of cells using electrical stimuli will open avenues to new biohybrid devices. Electrical bioactuation systems in microbes utilize promoters that are natively used to respond to stress signals including oxidative stress and starvation and incidentally control the global transcriptome of the cell. Strategies for using electrical stimuli-responsive promoters that are orthogonal to cell stress response systems and do not consequently alter the global transcriptome of the cell would be useful to develop.

Information storage

DNA is the primary information storage medium of living organisms and is an attractive energy efficient and

high-density data medium for long-term archival data storage applications. One challenge with using DNA storage is the requirement for in vitro synthesis (column- or array-based) and sequencing of DNA (Sanger-, short-read-, long-read or nanopore-based). While the price of DNA synthesis and sequencing has dropped precipitously over the past two decades, the price of DNA storage remains 7–8 orders of magnitude higher than conventional tape-based archival storage (Ceze et al., 2019). One approach to solving this cost challenge would be for living cells to synthesize DNA. Digital-to-biological data storage has been implemented in living bacterial populations using an engineered redox-sensitive CRISPR system (Yim et al., 2021). This technology enables digital data to be directly encoded into the genomes of living cells by using electrical signals to change concentrations of redox molecules (ferricyanide and phenazine methosulfate) that control the activity of Cas1-Cas2 spacer acquisition machinery. While this is a powerful illustration of using genomic DNA as an electronically writable data storage system, it ultimately requires extraction and in vitro sequencing of the DNA. Developing systems for cells to electronically report on the state of information stored in DNA could close this loop leading to living data storage and retrieval systems.

In addition to DNA, other biomolecules have been used to develop short-term rewritable memory systems. Charge stored in monolayers of the redox-active molecules such as ferredoxin (Yagati et al., 2009b) and azurin (Yagati et al., 2009a) has been used as rewritable memory bits. In such devices, bits are written by applying either oxidative or reductive potentials to shift the redox state of the electrode-attached redox-active molecules electrode between oxidized and reduced state, while open circuit potential measurements are used to read the state of the device. Similarly, the previously described chitosan-catechol capacitors have been used as memory devices for temporal integration of the production of mediators by bacteria and enzymes by storing charge in the catechol moieties (Wu et al., 2019; Wu, Kim, et al., 2020). Neuromorphic memristors have also been constructed using protein nanowires derived from *G. sulfurreducens* (Fu et al., 2020). In these devices, the nanowires catalyse the voltage-dependent reduction of Ag^{+} nanoparticles that form a conductive metal channel between electrodes resulting in changes in conductance. These changes in conductance function to temporally integrate charge flux from electrode pulses are experienced by the device (Fu et al., 2020).

In addition to biomolecules, cells can also function as memory-storing bits. The aforementioned biofilms that produce ionic electrical signals can store a history of their ionic signalling in their membrane potential (Yang et al., 2020). In this study, light is used to activate ionic signalling in discrete regions of a biofilm resulting in those cells becoming hyperpolarized (i.e. generating a high ionic potential across their cell membrane). This shift to a hyperpolarized state results in a phase shift relative to the remaining biofilm as they exhibit oscillatory ionic signalling behaviour (Prindle et al., 2015) and this anti-phase behaviour is maintained over several hours as a form of electrical memory. Since electrodes have been used to interact with biofilm ionic signalling (Comerci et al., 2022; Stratford et al., 2019), it is possible to envision exploiting this concept of electrical memory in a living electronic circuit.

Assembly of living electronic circuits

To leverage the diversity of living electronic components to build living electronic circuits, there is a need for methods to control the spatial arrangement of these components. A variety of strategies have been utilized to localize both biomolecules and cells onto electrode surfaces and non-conductive surfaces including chemical-conjugation, light-patterned adhesion and electrodeposition. Development of generalizable approaches that can be applied to the diversity of living electronic components that span a range of length scales will enable the arrangement of these components into living electronic circuits that can integrate the multitude of electrical properties outlined in the previous sections.

There have been extensive efforts for the immobilization of biomolecules onto electrode surfaces (Yates et al., 2018). Biomolecular components are often immobilized by making surface modifications to the electrode to introduce molecular handles that enable chemical-coupling of the biomolecule with the electrode (Yates et al., 2018). Proteins can be covalently bound to gold electrodes by selective introduction of the thiol-containing amino acid cysteine, which enables Au-S bond formation (Algov & Alfonta, 2022). Diverse electrode materials can be bound by using approaches from protein engineering and chemical biology to site-specifically introduce non-canonical amino acids that include chemical-handles specific for the material of interest (Algov & Alfonta, 2022). Similarly, polyhistidine tags have also been used to bind diverse materials by using functionalized Ni^{2+}-NTA as adapter molecules. For example, Ni^{2+}-NTA covalently linked to pyrene can be used to attach redox-active molecules to carbon-based electrodes (Sakamoto et al., 2019). In addition to chemical-conjugation approaches, DNA hybridization has been used to spatially localize and arrange multiple redox-active proteins on an electrode surface (Tepper, 2010). Recently, three-dimensional DNA nanostructures were utilized to selectively orient horse-heart cytochrome C on an electrode surface to facilitate electron transfer (Ge et al., 2019). These diverse approaches allow for the selective binding of redox-active molecules to electrode surfaces.

There have been a great deal of efforts to localize and enhance the formation of electroactive biofilms, which

have been reviewed elsewhere (Catania et al., 2021). Early efforts utilized chemically modified surfaces to selectively bind electroactive bacteria (Lienemann et al., 2018; Young et al., 2020). Synthetic biology has enabled genetic control over biofilm formation such as engineering the expression of adhesive cell surface proteins that enable the binding of specific materials. To enhance electrode colonization on specific metal surfaces, cells have been engineered to display extracellular matrix proteins fused to metal-binding peptides (Suo et al., 2020). Additionally, cells have been engineered to display DNA sequences that could hybridize with complementary sequences that have been selectively deposited onto surfaces (Furst et al., 2018).

The expression or activity of adhesins has been placed under optogenetic control enabling biofilm lithography using light to pattern cells onto surfaces (Jin & Riedel-Kruse, 2018; Moser et al., 2019; Zhao et al., 2022). Recently, this approach was used to tune the conductance of electroactive biofilms by controlling biofilm dimensions using light (Zhao et al., 2022). While not used to pattern cells, optogenetic control over cyclic-di-GMP synthesis in *S. oneidensis* leads to increased electrode colonization and current production (Hu et al., 2017). Similar optogenetic approaches for controlling cyclic-di-GMP synthesis have been used to spatially pattern *P. aeruginosa*, another electroactive organism, indicating this could be an alternative strategy for light-patterning of conductive biofilms (Huang et al., 2018). Taking advantage of biofilm lithography and combining it with controllable cytochrome expression can lead to the living electronics equivalent of solid-state photolithography and dopant implantation for modulating material conductivity, techniques ubiquitous in semiconductor fabrication.

In addition to biofilm lithography, a range of electrobiofabrication approaches can be used to spatially pattern electroactive biofilms (Li et al., 2019). Dielectrophoretic deposition (DEP) has been used to spatially sort electroactive bacteria based on their cytochrome content which is related to the cell surface polarizability used to generate the electrokinetic forces that enable the deposition (Wang, Jones, et al., 2019). DEP also shows great promise for guiding the spatial arrangement of cells onto surfaces (Albrecht et al., 2006). Electrodeposition of multiple strains of electroactive bacteria in a single device can be achieved by spatial patterning of conductive polymers as individually addressable electrodes and selectively applying oxidative potentials to individual electrodes (Tseng et al., 2022). DEP and electrodeposition are two diverse approaches to control surface deposition of electroactive cells by using electric fields or electrode potential respectively. Such electrodeposition approaches could complement chemical-patterning and lithography.

Harnessing these biofilm patterning techniques ahead of biomineralization could be used for the controlled surface deposition of biogenic nanomaterials for various potential electronic device applications. Additionally, these techniques can be used to create hybrid biomaterials that can combine the unique properties of cells, such as sensing and self-assembly, and those of synthesized nanomaterials, such as photoactivity. Using biomineralization-capable electroactive microbes as the base for such biomaterials allows the biomaterial to be conductive without relying on the nanomaterials and it allows for materials to be natively synthesized, simplifying the engineered system. Thus, by combining the biomineralization capabilities of electroactive microbes, as well as with synthetic biology biofilm engineering strategies, novel biohybrid living electronic circuits can be developed.

CONCLUSION

Recent works in the fields of electromicrobiology, synthetic biology and bioelectronics have yielded a wealth of information about the electrical properties of cells and biomolecular components. It is an exciting time where rapid advances in knowledge and engineering of such components are enabling the integration of these biological entities with electrical devices to generate living electronics. It is encouraging to see the recent trend for reporting on the intrinsic parameters (e.g. conductivity and charge carrier mobility) of conductive biomolecules and multicellular networks. As knowledge in these areas continues to expand, it is important for the community to continue, whenever possible, to communicate these intrinsic properties so that they can be directly compared and evaluated across studies. Taking advantage of the natural and engineered sensing capabilities of these electroactive biomolecules and microbes has led to the development of new biosensors directly capable of providing an electronic readout. The development of bioactuator components for electrically controlling the behaviour of biomolecules and microbes is allowing for closed-loop biohybrid devices that electrically communicate enabling them to sense, compute and actuate in response. Additionally, the recent trends for controlling the assembly of biomolecules and cells hold great promise for integrating multiple disparate living electronic components into more complex electrical circuits with predictable and tuneable behaviours. By combining these assemblies with biofabricated metallic and semiconductor nanomaterials, living electronic systems with both solid-state and biological functionalities can be developed. The bodies of work discussed herein show the different avenues in which living electronic components can be constructed and characterized, highlighting the diverse specialities and points of view required to push the overall field forward. However, this then creates new space for these specialities and their resulting disparate developments to converge in

overcoming challenges and creating new technologies thought impossible when attempted separately. By combining the different facets of electromicrobiology, synthetic biology and bioelectronics, perhaps novel living electronics with improved biocompatibility, lower environmental footprints and hybrid biological and solid-state capabilities can be constructed.

AUTHOR CONTRIBUTIONS

Joshua T Atkinson: conceptualization (lead); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Marko S Chavez:** conceptualization (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (equal). **Christina M. Niman:** conceptualization (supporting); writing – original draft (supporting); writing – review and editing (equal). **Moh El-Naggar:** conceptualization (supporting); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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