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Physical Biology of the Materials−Microorganism Interface

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ABSTRACT: Future solar-to-chemical production will rely upon a deep understanding of the material−microorganism interface. Hybrid technologies, which combine inorganic semiconductor light harvesters with biological catalysis to transform light, air, and water into chemicals, already demonstrate a wide product scope and energy efficiencies surpassing that of natural photosynthesis. But optimization to economic competitiveness and fundamental curiosity beg for answers to two basic questions: (1) how do materials transfer energy and charge to microorganisms, and (2) how do we design for bio- and chemocompatibility between these seemingly unnatural partners? This Perspective highlights the state-of-the-art and outlines future research paths to inform the cadre of spectroscopists, electrochemists, bioinorganic chemists, material scientists, and biologists who will ultimately solve these mysteries.

INTRODUCTION

How do natural living systems respond to the unnatural products of materials science? Such questions drive scientists working at the fuzzy border between biology and chemistry. Motivated by fundamental curiosity and applications in medicine, well-trod research has uncovered the ability for nanomaterials to electrically probe and stimulate the function of neurons,[1,2] to inhibit pathogenic microbes,[3] and deliver therapeutic treatments.[4]

But a new purpose of the materials-cell interface has emerged: to drive energy harvesting and chemical synthesis. As the dominance of petrochemicals fades, and plant biomass feedstocks, riddled with their own intrinsic limitations, struggle to compete economically,[5,6] a few hybrid systems that combine inorganic light harvesting materials and microbial biosynthesis have populated the literature.[7−10] In a typical design, a (photo)electrode or inorganic photosensitizer provides bioavailable reducing equivalents (e.g., electrical current, H_2, small-molecule mediators, etc.) derived from solar energy to microbes. These reducing equivalents enter native or engineered metabolic pathways to drive the enzymatic reduction of CO_2, N_2, H_2O, and simple inorganic salts to higher value products such as organic acids, polymers, fuels, pharmaceuticals, proteins, and whole cells in a form of semi-artificial photosynthesis. While many powerful combinations of material and microbe have surfaced, the nature of their interaction and guiding principles behind their optimization remain on the vista of exploration.

This Perspective explores two crucial research challenges of the materials−microorganism interface: (1) elucidating the nature of electron transfer between inorganic materials and biological systems, and (2) biocompatible materials and "chemocompatible" microorganisms (Figure 1). A survey of recent hybrid systems will guide this exploration before enumerating materials and techniques to probe this interface.

MATERIAL−MICROORGANISM ELECTRON TRANSFER

The materials−microorganism interface creates an excellent opportunity to design efficient solar-to-chemical conversion systems.[11] An efficient CO_2-fixing solar-to-chemical device requires (1) high-efficiency solar energy capture and (2) selective catalytic reactions with low kinetic barriers.[12] Solid-state materials, including inorganic semiconductors and nanomaterials,[13] have excellent optoelectronic properties for charge transport and solar-to-electricity conversion; in nature, non-photosynthetic microbes possess efficient CO_2-fixing biochemical pathways to yield select products through bioengineering.[14] Combining the benefits of materials and microorganisms, i.e., semiconductor-driven biochemistry to fix CO_2, simultaneously satisfies both criteria to produce devices with efficiencies exceeding natural photosynthesis that yield complex products not attainable via traditional abiotic systems.[8]

Two general modes of electron transfer between material and microorganism have been explored: mediated and un-mediated. In mediated systems, a soluble redox shuttle electrochemically regenerated at the electrode−solution interface provides

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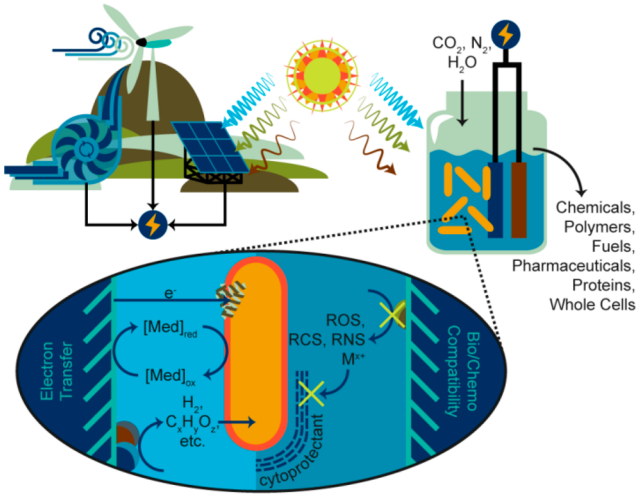

Figure 1. Schematic of materials−microorganism interfaces in solar-to-chemical technologies. Combinations of biosynthetic microbes (e.g., CO_2-reducing bacteria) with electrodes or inorganic photosensitizers provide synthetically versatile routes to a wide range of products derived from water and air, powered by renewable energy. Questions surrounding the mechanism of electron transfer and the nature of bio- and chemocompatibility between microbe and material remain fertile grounds for deeper investigation.

reducing equivalents to microbes.[8,9,15] Oxidation of these reducing equivalents in turn reduces $NAD(P)^+$ to NAD(P)H, the universal biological electron donor, which also produces ATP, the biological energy "currency". The most efficient systems employ a H_2-generating electrocatalyst paired in tandem with a H_2-oxidizing or CO_2- or N_2-reducing bacterium.[8,9,16] These easily implemented systems boast up to ∼10% solar-to-biomass energy efficiency,[8] an order of magnitude more efficient than typical plant-based photosynthesis.[17] This work exploits decades of research into understanding and optimizing the H_2 evolution reaction (HER).[18] On the biological end, this mechanism takes advantage of the robust, native autotrophic metabolism of a wide variety of microorganisms, leading to facile CO_2 fixation to small molecules,[19,20] materials,[21] proteins, and biomass.[8,9] Alternative redox mediators, such as formate,[15,22] viologens, and phenazines,[23] show promise as well.

The apparently unmediated electron-transfer pathway that requires no explicit exogenous redox shuttle[24,25] stimulates scientifically more intriguing questions on the nature of the direct transfer from cathode to cell. From a handful of model systems, probed through electrochemical and spectroscopic techniques, proposed mechanisms have begun to emerge.

Conductive Electrodes. In the earliest material−microorganism hybrids, electrogenic (electricity producing) bacteria cultured on simple conductive electrodes generated electricity from organics as microbial fuel cells (MFCs)[26,27] and electrotrophic (electricity consuming) bacteria synthesized chemicals from CO_2 from solar-derived electricity.[24] Several species of electrogenic bacteria rely upon the auto-secretion of redox shuttles, typically flavins or quinones, in a form of indirect charge transport. Electrochemical techniques, vibrational and electronic absorption spectroscopy, have identified key mediator species.[28] Conductive filaments, composed of

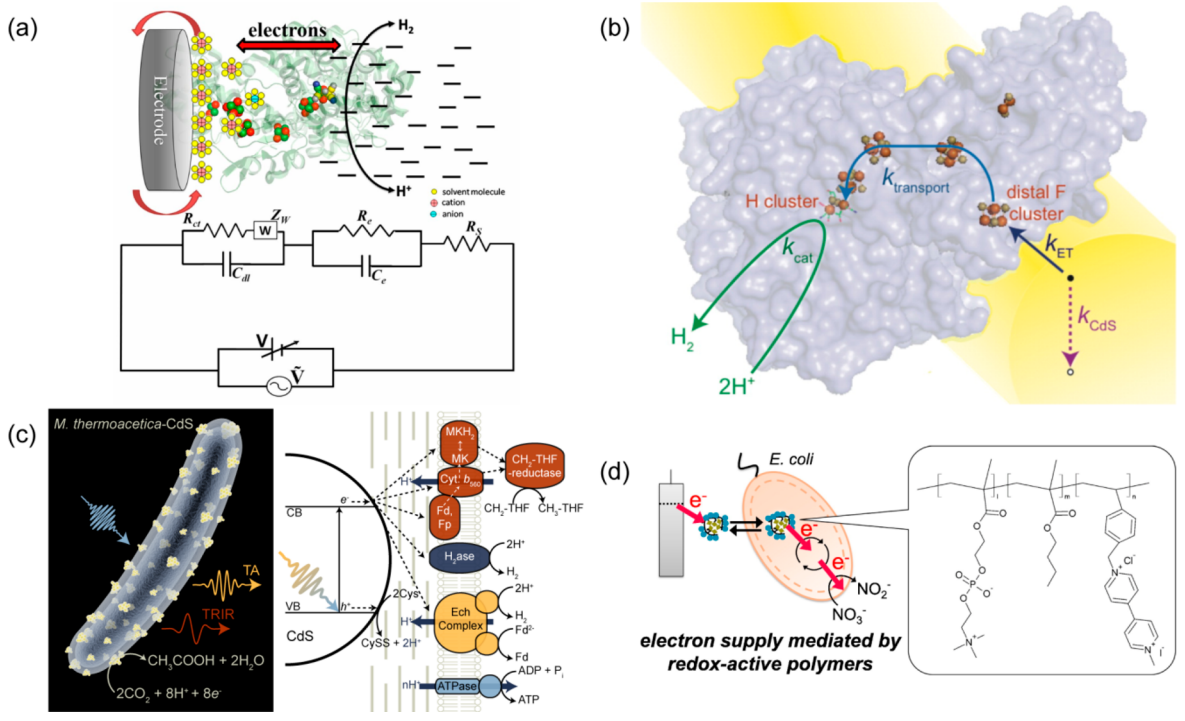

Figure 2. Material−microbe interfaces to facilitate and probe biotic−abiotic charge transfer. (a) Immobilized enzyme−electrode electrochemical impedance spectroscopy (EIS) yields an equivalent circuit to describe electron-transfer behavior. Reprinted with permission from ref 40. Copyright 2017 National Academy of Sciences. (b) Enzyme−semiconductor spectroscopic studies reveal kinetics of photogenerated electron transfer. Reprinted with permission from ref 49. Copyright 2014 American Chemical Society. (c) Whole cell−semiconductor spectroscopy extends these insights to reveal mechanistic details for more complex bacterial systems. Reprinted with permission from ref 50. Copyright 2016 National Academy of Sciences. (d) Whole cell−polymer systems open up a new pathway for electron transfer as well as new chemical probes for mechanistic study. Reprinted with permission from ref 59. Copyright 2016 Elsevier B.V.

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aromatic amino acids and/or cytochrome-containing membrane extensions, directly link oxidizing anodes to microbial respiratory metabolism.[29] The unique spectroscopic signature of the cytochromes implicated in direct microbial respiratory electron transport chains has enabled their study through bulk and surface enhanced techniques.[30−33] Complementary electrochemical studies have also lent credence to this membrane−cytochrome mechanism.[34,35] This behavior, however, seems somewhat specialized to a few genera of bacteria like *Shewanella* and *Geobacter*, dependent on the display of these membrane associated redox active proteins.[36] While a significant body of work has emerged surrounding the anodic direct electron-transfer mechanism, particularly the nature of the conductive filaments (or microbial nanowires) deep debate over the exact interpretation of these results continues.[37,38]

The reverse direction of direct electron transfer, from cathode to bacterium to enable CO_2 reduction, holds greater current mystery. While speculation that reversing the respiration of MFC bacteria such as *S. oneidensis* could reduce CO_2,[39] such predictions have not borne out. Rather, a completely different group of electrotrophic bacteria seem to engage in an electron-transfer pathway completely separate from their MFC analogues. The first of these devices, sometimes termed microbial electrosynthesis cells (MEC), employed the autotrophic bacterium *Sporomusa ovata* and other acetogens that routinely combine H_2 and CO_2 to produce acetate as a metabolic waste product.[24,25] Electrochemical analysis of whole cells of *S. ovata* on conductive electrodes yielded the first insights into the electron-transfer mechanism.[10] Tafel slope analysis of *S. ovata* on Si nanowire array electrodes showed two distinct Tafel slopes for Si-*S. ovata* hybrid electrodes and bare Si nanowires.[10] These results seemed to indicate a different electron-transfer mechanism in the presence of these bacteria, leading to the conclusion that simple abiotic H_2 production at the cathode followed by biological H_2 oxidation could not fully explain the electrotrophy of *S. ovata*. More advanced electrochemical techniques, such as electrochemical impedance spectroscopy (EIS) on simpler enzyme-based systems yield key mechanistic information (Figure 2a);[40] extending such methodology to studies of the materials−microorganism interface represents a logical next step. Thus began serious investigation into more definitive evidence of direct electron transfer.

Semiconductors. Semiconductors, in either bulk or nanoparticulate form, provide photogenerated reducing equivalents, enabling the spectroscopic study of their charge-transfer mechanism. As electrotrophic bacteria normally enter their CO_2-reducing metabolism through H_2 oxidation, a sensible mechanism for charge transfer would invoke surface-bound hydrogenases (H_2ases), and similar redox proteins like ferredoxin.[41−43] Exemplary work by researchers based in the National Renewable Energy Laboratory, University of Colorado, Boulder, and Utah State University provided evidence of direct charge transfer between semiconductor CdSe or CdS nanoparticles and purified H_2ases, among other redox enzymes, within *in vitro* systems (Figure 2b).[44−47] This photosensitized HER platform not only demonstrated a new material−biology interface, but also utilized the spectroscopic properties of quantum dots and the H_2ase active site to follow mechanistic charge-transfer kinetics. These suspension based systems allow transmission of light through a sample, unlike the opaque electrodes of previous hybrid designs, facilitating their direct study by conventional spectroscopic techniques.

Time-resolved pump−probe spectroscopy has yielded a wealth of information regarding kinetics and mechanisms at the semiconductor−molecule interface.[48] Over the past few years, pump−probe transient absorption (TA) and time-resolved infrared (TRIR) spectroscopy observed charge-transfer kinetics in these enzyme−semiconductor model systems.[44,47,49]

Such seminal studies inspired an investigation into a more complex whole-cell system of the acetogenic, electrotrophic bacterium, *Moorella thermoacetica*, photosensitized with self-generated membrane-bound CdS quantum dots.[7,50] This hybrid material−microorganism system demonstrated high efficiency for the photosynthetic reduction of CO_2 to acetate, yet clues to its inner workings and its connection to the contrived enzyme−semiconductor systems remained largely unknown. To probe photogenerated charge pathways and obtain a hint of the entry point of charge/energy carriers into the acetate producing Wood−Ljungdahl pathway, investigators conducted TA and TRIR spectroscopic analysis in conjunction with CO_2 reduction activity assays (Figure 2c). Over long time scales (24 h), increasing *M. thermoacetica*−CdS H_2ase activity correlated with an increase in photochemical acetate production. TA experiments revealed that H_2ase-rich hybrids also featured shorter band edge bleach lifetimes of their CdS sensitizers compared to H_2ase-free and CdS-only controls. The whole of the data suggested that H_2 efficiently generated from CdS photogenerated electrons via proximal H_2ase enters the Wood−Ljungdahl pathway as normal to reduce CO_2 to acetate. Researchers also observed, however, evidence of a second, non-H_2ase-mediated pathway that requires further characterization. This work implies that direct injection of reducing equivalents into the CO_2-reducing metabolism may not kinetically outcompete the (bio)chemical generation of molecular redox shuttles like H_2 as evidenced by the integration of semiconducting light absorbers with enzymes through soluble redox mediators[51,52] and in mediated systems as discussed previously.[8,9] Yet, the intriguing nature of the ambiguous second, non-H_2ase-mediated pathway bears further investigation, and exploration of non-acetogen hybrids may yield yet more charge-transfer mechanisms for comparison. Work by Stanford researchers demonstrated that electron transfer in methanogenic archaea occurs through excretion of extracellular H_2ases that catalyze H_2 production on electrode surfaces. Such a mechanism presents a facile way to reconcile ongoing whole-cell and purified enzyme investigations.[42]

Polymers. A more universal approach to material−cell charge transfer presents a Holy Grail challenge of biology and chemistry. Eukaryotes, such as yeast, mammalian cells, plants, and fungi, do not robustly oxidize H_2 nor do they appear to engage in natural electrotrophy. Current bacterial electrotrophs cannot replace eukaryotes for the production of pharmaceuticals such as therapeutic proteins,[53] and as a high-value direct food source. Additionally, electrotrophy has not been observed in the workhorses of synthetic biology, (e.g., *E. coli* and *B. subtilis*), and engineering electroactivity remains challenging.[54]

A few intriguing approaches to electrifying biology invoke electrochemically active polymeric structures. Due to their diverse and facile chemical functionality, polymers, carbon nanotubes, and oligomeric macromolecules offer a range of tunable materials with similar length scales as biological proteins. In the field of MFCs, the Bazan group has pioneered the use of conjugated oligoelectrolytes that intercalate into the cell membrane of bacteria to provide a conductive conduit

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across the bacterial membrane.[55] Similarly, Johansson et al. have developed conductive polymer–alkyl ammonium complexes that merge with phospholipid membranes to increase the transmembrane conductivity of frog eggs.[56] In a similar vein, Berggren and collaborators have demonstrated the ability to impregnate plants with conducting polymers by taking advantage of the uptake and transport of the plant's native vasculature.[57] Researchers at the University of Tokyo have made many co-polymer derivatives based on phospholipids polymerized with redox active shuttles such as ferrocene or methylviologen (Figure 2d).[58,59] These amphiphilic vesicle aggregates permeate into the cell and deliver reducing equivalents. All these approaches should work with any phospholipid membrane, and may expand the scope of cell–material electron transfer.

Work by the Strano group has set the frontline of the use of polymer-functionalized carbon nanotubes as cell penetrable photosensitizers.[60] The uptake of polymers and nanomaterials into the plant vasculature and across the cell membrane adds intracellular photosensitizers to augment photosynthesis. The ability to spectroscopically probe carbon nanotubes in a manner similar to semiconductor quantum dots also provides a convenient route to better understanding the nature of the cell–material interface.

Outlook. Looking ahead, characterizing these charge-transfer pathways remains the primary target of physical biologists in this field. Time-resolved spectroscopic techniques can uncover a wealth of information not accessible with the standard methods employed in the biochemistry and microbiology community (Figure 3). Unambiguous assignment of spectroscopic signatures to specific processes remains the largest hurdle. The desire to study complex whole-cell systems, composed of several spectroscopically overlapping processes, complicates this endeavor. Site-specific protein tagging via conjugated antibodies routine in immunochemistry may play a role: following photoexcitation of a photoactive chemical/material probe, changes in the unique spectroscopic handle of the tag can monitor the charge-induced reduction or conformational change of a tagged biological moiety (Figure 3a,b). Fluorescent tags, in conjunction with super-resolution microscopy will also endow spatial resolution to charge- and energy-transfer processes within material–microorganism systems.[61] These methods yield fluorophore-by-fluorophore fluorescence spectra, bolstering the depth of information gleaned from such techniques. The move toward molecular and polymer based materials systems as discussed previously may also allow direct probing of the fluorescence of the electron-transfer material itself. High spatio-temporally resolved techniques developed for the study of neurons may also be applied to provide a greater level of detail.[62] Furthermore, element-specific techniques such as time-resolved X-ray absorption spectroscopy (XAS) may come into play to visualize oxidation state and local environment changes around an element-unique active site of specific metallo-enzymes.[63,64] However, such techniques have typically been applied to isolated proteins. Modifying such techniques to study *in vivo*, aqueous, whole-cell systems at biologically relevant conditions presents a significant challenge.

Advanced spectroscopic techniques that make use of localized phenomena may also overcome specificity issues in whole cells systems. Attenuated total reflectance (ATR) techniques invoke an evanescent wave that only probes phenomena within micrometer, or closer, proximity of the ATR crystal.[32,65] Such tools, combined with technologies like

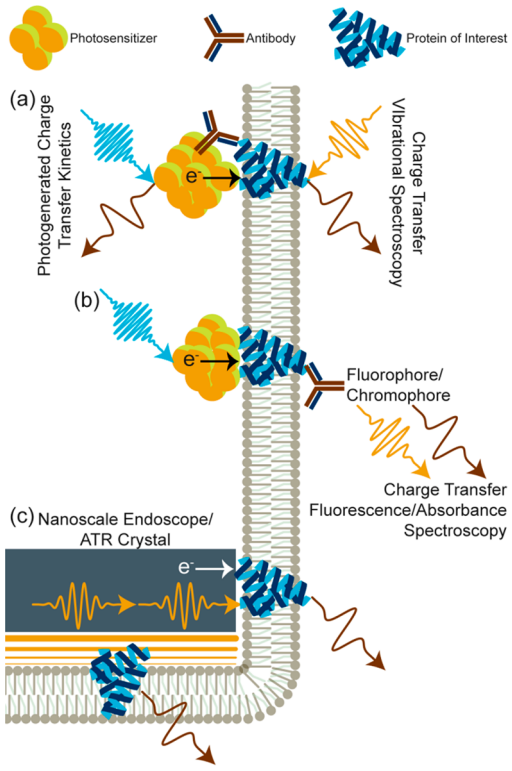

Figure 3. Prospective experimental spectroscopic techniques to investigate electron-transfer mechanisms. Antibody conjugation may allow association of specific proteins with photosensitizing agents (e.g., semiconductor nanoparticles). Protein specific mechanisms could be deduced by (a) observing photogenerated electron lifetimes (e.g., via transient absorption spectroscopy) of the photosensitizing material coupled to monitoring changes in vibrational spectra of the receiving protein. Alternatively, (b) charge transfer from the photosensitizer to a protein-conjugated fluorophore or chromophore, coupled with super-resolution microscopy, could lead to spatiotemporally resolved mechanistic information. (c) Nanoscale tools, like nanowire endoscopes and optical guides, could similarly probe local regions for material–microbe electron-transfer mechanisms.

nanoscopic endoscopes,[66] could provide significant site-specific information (Figure 3c). Plasmonic probes have bolstered the field of biology, as both a probing mechanism and a surface-enhanced technique.[67] Site- and surface-specific information can be obtained through selective uptake of plasmonic particles or even through the application of *in vivo* tip-enhanced Raman spectroscopy.[68] While many of these tools have been applied to *in vitro* systems and isolated proteins, their application in whole cell techniques to study complex *in vivo* systems represents the forefront of exciting new research in the field of physical biology.

BIOCOMPATIBILITY AND CHEMOCOMPATIBILITY

A great challenge of the materials and physical biology field seeks compatibility between living systems and relatively alien materials. This endeavor has called for the discovery and design of biocompatible materials free of toxic and inhibitory chemicals, as well as augmenting microorganisms to resist the high stresses of industrial chemical processes by increasing their "chemocompatibility".

Physical Interfaces. One of the initial challenges of material biocompatibility centers on promoting positive physical interactions between material and microorganism.

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This goal draws stark contrast to efforts in biomaterials development of anti-microbial surfaces for use in medical devices to inhibit pathogenic microorganisms.[3] Instead, solar-to-chemical hybrid systems require pro-microbial surfaces to encourage the stable integration of electrode and microbe.

Encouraging the attachment of electroactive microbes to electrodes has been achieved through two main mechanisms: (1) surface functionalization and (2) nanostructuring. Progressive work by Lovley and Zhang has screened a number of materials to impart a positive surface charge to cathodes to adhere negatively charged bacteria.[69] Increasing volumetric surface area with nanomaterials like carbon nanotubes have also increased current density by allowing more bacteria−electrode attachment sites.[70]

Insight into the assembly of biofilms onto electrodes offers a further means of controlling physical interfaces. Using nanostructures to investigate and control the initial formation of bacterial biofilms, thick mats of bacteria and extracellular biopolymers that naturally form on surfaces, have deepened our understanding of bacteria, enabling us to model their initial behavior as classical colloidal particles.[71,72] In recognition of this, an intriguing idea employs electrophoretic deposition to actively steer the formation of bacterial biofilms onto electrodes.[73] Finally, embracing and exploiting the biological signaling pathways that steer biofilm formation, and investigating emergent ways in which materials might control such cues,[74] represents a highly intriguing research direction.

Metal Toxicity. While toxic side products rarely appear in biological reactions, the same cannot necessarily be said of chemical reactions (Figure 4a−c). Any metal based catalyst inherently incurs the incidental dissolution and accumulation of toxic metal ions. While cofactors such as vitamin B_{12} require Co^{2+}, high concentrations of this metal kill cells.[8] This poses a challenge for the Bionic Leaf, pioneered by Nocera and Silver, that employs a Co−P-alloyed HER cathode.[8] Accumulation of Co^{2+} inhibits the growth of the CO_2-reducing bacterium, *Cupriavidus necator* (previously known as *Ralstonia eutropha*). Pairing the Co−P cathode with a CoPi oxygen-evolving anode suppresses the soluble Co^{2+} concentration through a self-healing, redeposition feature of CoPi (Figure 4a,e).[75] This pair forms a biocompatible electrode system that promotes bacterial growth and pushes the solar-to-biomass efficiency to ∼10%. Introduction of new electrode materials will require examination of the potential for metal leaching. Future work must consider not only equilibrium stability of metal systems, as often predicted by Pourbaix diagrams, but also the kinetic stability under catalytic regimes (Figure 4e).[76] Precision analytical and inorganic chemistry may lead the way in characterizing and engineering the biocompatibility of metal and mixed metal electrocatalysts from across the periodic table.

Biological responses to metal toxicity may also promote the chemocompatibility of organisms. Many bacteria possess an innate resistance to toxic metal elements, such as Hg, Pb and Cd.[77,78] This feature of *M. thermoacetica* produces self-photosensitizing CdS nanoparticles from otherwise toxic Cd^{2+}.[7] In the case of low level leaching of Cd^{2+} back into solution during photocatalysis, *M. thermoacetica* can reprecipitate it back into CdS to detoxify provided a suitable sulfur source. Similarly, many electrochemically interesting bacteria precipitate metal nanoparticles and metal oxides as a natural response,[79] creating a unique synergy between materials and these chemocompatible microbes. Future research should explore this space, looking to uncover the diversity of bacterial

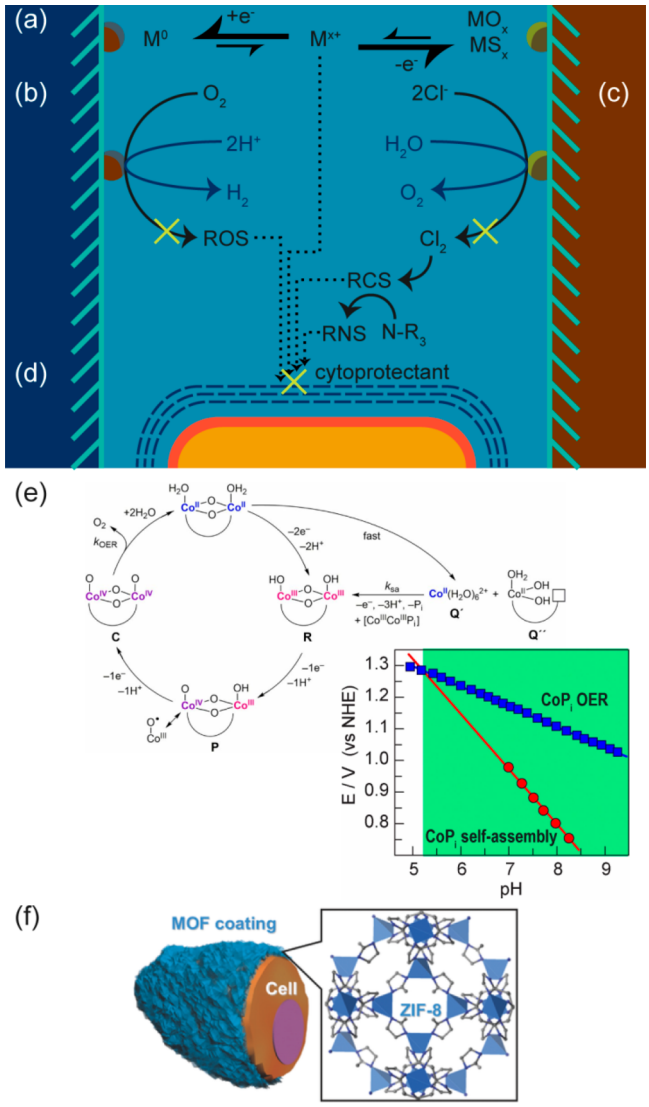

Figure 4. Challenges and materials solutions to bio- and chemo-compatibility. (a) Reductive and oxidative redeposition of toxic metals minimizes extracellular concentrations. (b) Selective catalysts inhibit the cathodic production of reactive oxygen species (ROS). (c) Selective catalysts inhibit the anodic production of Cl_2 and other reactive chlorine species (RCS), which may subsequently react with amines to produce chloramines and other reactive nitrogen species (RNS). In the absence of biocompatible catalysts, encapsulation of microbes in cytoprotectant such as metal−organic frameworks (MOFs) physically shield the cells from these toxic species (d). (e) Careful selection of Co-based O_2-evolving materials promote self-healing under catalytic conditions. Reprinted with permission from ref 76. Copyright 2017 National Academy of Sciences. (f) MOF coating of cells provides cytoprotective properties. Reprinted from ref 90. Copyright 2016 Wiley-VCH.

responses to metals encountered in solar-energy applications. A number of different approaches have demonstrated the power of screening and selection techniques, such as screening oligopeptide sequences for their binding affinity to different semiconductor crystal faces.[80,81] Such peptides promote the nucleation of inorganic nanomaterials, allowing a semi-rational approach to materials biosynthesis. Directed evolution of natural enzymes to incorporate new ligand environments, new metal active sites, and an expanded substrate scope similarly opens up new biological routes to materials chemistry

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as it has already done for synthetic organic chemistry.[82] Discovery, directed evolution, and biological engineering hold great promise for ensuring the facile integration of microbes and toxic metals.

Reactive Oxygen, Chlorine, and Nitrogen Species. In addition to leaching reactions, electrodes may also catalyze the production of inhibitory side products such as reactive oxygen, chlorine, and nitrogen species (ROS, RCS, and RNS, respectively) (Figure 4b,c). On one hand, abiotic electrocatalysts generally avoid the production of singlet oxygen, $^1O_2$, commonly produced by chlorophyll in natural photosynthesis. However, in the earliest iterations of the bionic leaf design, the production of ROS from the partial reduction of O_2 at the cathode to H_2O_2, $O_2^{\bullet-}$, and $OH^{\bullet}$, inhibited the growth of cells in electrochemical devices.[15,83] Again, while this feature may be useful for anti-microbial sterilization technologies, it poses a significant problem for solar-to-chemical performance. An engineering solution calls for applying a grossly high overpotential to the electrode to force the desired reaction (e.g., H_2 evolution) to kinetically outcompete ROS production at the great expense of energy efficiency. Liu et al. have developed a Co−P alloy HER cathode that selectively suppresses ROS generation, a significant advantage that both increases microbial growth rates, and lowers the required overpotential.[8] How this material suppresses ROS, and whether its design principles may guide future development of low ROS-producing cathodes opens up a new subfield of biocompatible electrode design.

Looking ahead, similar challenges with the production of RCS and RNS at the anode remain to be fully explored (Figure 4c). In addition to O_2 evolution, the anode may oxidize Cl^- to Cl_2 and OCl^-, also known as bleach, routinely used to sterilize and kill microorganisms. To get around the production of this inhibitory RCS, current designs either physically separate the anode and bacteria through an ion exchange membrane, or employ a Cl^- free electrolyte.[8,10] Such designs face a barrier to economic competitiveness due to the significant material cost, high solution resistance of the membrane, and expense of Cl^- removal from natural water sources. Rather, materials chemists ought to search for RCS-suppressing anodes that maintain the high O_2 evolution activity of current catalysts. These challenges become even more crucial as researchers look to utilize nitrogenous, environmentally derived media/electrolytes, such as wastewater, where the RCS react with nitrogen to produce long-lived chloramines and other RNS.[84] On the chemocompatibility side, studies of biological responses and mechanisms to resist ROS, RCS, and RNS continue.

Cytoprotective Materials. In the absence of biocompatible electrodes, and difficulty of improving the biological robustness of microorganisms, an intermediate strategy to improve the chemocompatibility of microorganisms exists in encapsulation (Figure 4d). Semiconductor−microorganism hybrids, such as *M. thermoacetica*−CdS, may require the integration of ROS producing materials. While the conduction band and reduction potential of CdS suffices for biological CO_2 reduction, CdS cannot perform stable photocatalytic O_2 evolution.[85] As such, *M. thermoacetica*−CdS paired with TiO_2 for photoanodic water oxidation generates O_2 in tandem with CO_2 reduction.[86] However, TiO_2 generates toxic amounts of ROS[87] and requires potentially microbe-damagingly high photon flux.

The hardiest and most persistent microbes resist such stressors by forming spores: tough shells composed of proteinaceous material designed to protect the core genetic material of bacteria and fungi from an adverse battery of solvents, heat, desiccation, and other stressors.[88,89] Instead of a protein spore coat, material biologists may turn to ceramics, polymers, and MOFs to provide the same function with greater chemical tunability. Initial research exploring simpler enzyme−MOF hybrids demonstrated enhanced stability through physical immobilization, limiting denaturation, and restricted access of detrimental molecules through the pores of the MOF.[90,91] Work by the Tsung group has demonstrated the use of MOFs in protecting the functionality of enzymes through size exclusion.[92] Liang et al. report a MOF that crystallizes directly on the membrane of *Saccharomyces cerevisiae* under physiological conditions, paving the way for whole-cell work (Figure 4f).[93]

A bioinspired strategy taken from diatoms for cell preservation entails the synthesis of protective coatings made up of silica, silica−titania, and alternating polyelectrolyte polymers.[94−96] These mechanically stable, selectively permeable shells can degrade controllably and offer a functionalizable template.[97] However, protective coatings on individual cells may induce dormant states and restrict cellular replication as well as metabolic activity.[89,98]

Hydrogels, such as alginate, have housed cells as they allow for unencumbered proliferation.[99] Microorganisms replicate freely in alginate by creating microvoids—small pockets suitable for replication.[100] Furthermore, biocompatible fluidic methods can produce alginate microbeads to encapsulate multiple cells.[101] Mixing different cell types or controlling their local density may also control emergent community or quorum sensing properties. Opportunely, protective coatings can be synthesized directly onto the microbe-filled alginate microbead surface. This method has produced polydopamine/alginate core−shell microbeads that shield microorganisms from environmental stresses.[101] Direct cell surface polymerization has recently been reported by Niu et al. In this approach, a biocompatible radical polymerization process initiates directly on the cell surface, offering advantages over previous polymer-grafting approaches.[102]

Appropriately, a silica-based polymer has been demonstrated to preserve DNA from ROS.[103] The tetraethylorthosilicate-based polycondensation of the silica polymer directly onto the surface of the alginate microbead could similarly create an ROS-free interior. Appropriate titanium precursors could extend this method to include photocatalytic TiO_2, combining cytoprotection and light harvesting in a single technique.[104]

■ CONCLUSIONS AND OUTLOOK

A broad question on the nature of material−microorganism interaction began this Perspective, the answer to which now seems to be: sometimes they act harmoniously to accomplish great feats of solar-to-chemical synthesis, other times they inhibit each other to kill performance. The rather ambiguous nature of the answers that emerged well represents many of the unresolved questions of this field. Laudable work from chemists, biologists, materials scientists and engineers working to transform solar energy, air, and water into every product under the sun has drawn focus toward understanding the backbone of these hybrid systems: how charge (and by extension, energy) transfers from material to microorganism in a bio-/chemocompatible way. While the initial work relied upon adventurous scientists willing to bridge the gap between biology and materials chemistry, the future of these endeavors requires the aid of specialists in spectroscopy and microscopy

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to study the mechanisms of these systems, and clever electrochemists, catalyst designers, and materials biologists to overcome the incompatibilities of material and microorganism. Not only will such advances tamp down the known stumbling blocks to solar-to-chemical production, but they also poise the scientific community for the serendipitous discovery of new emergent properties born from combining living with non-living, natural with unnatural.

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