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Opinion

Microbial Electrosynthesis: Where Do We Go from Here?

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The valorization of CO_2 to valuable products via microbial electrosynthesis (MES) is a technology transcending the disciplines of microbiology, (electro)chemistry, and engineering, bringing opportunities and challenges. As the field looks to the future, further emphasis is expected to be placed on engineering efficient reactors for biocatalysts, to thrive and overcome factors which may be limiting performance. Meanwhile, ample opportunities exist to take the lessons learned in traditional and adjacent electrochemical fields to shortcut learning curves. As the technology transitions into the next decade, research into robust and adaptable biocatalysts will then be necessary as reactors shape into larger and more efficient configurations, as well as presenting more extreme temperature, salinity, and pressure conditions.

Highlights

In the past decade, research in the field of microbial electrosynthesis (MES) has been driven forward by the development of cathode materials, electroactive bacteria or microbiome enrichment, and productivity improvements.

As the close of three complete funding cycles for the field is reached, recent reviews have sought to refocus emphasis to the eventual application of MES; a means of measurably reducing CO_2 waste via the formation of valuable products.

Using present knowledge of bioelectrochemistry, and by learning lessons from adjacent fields, it becomes apparent that the simplest gains in performance are likely to come from advancements in the reactor rather than the biocatalysts. Varying the reactor and operating conditions of the system, however, require adapting these biocatalysts.

Should We Continue Past Research Efforts?

The production of chemicals and fuels using CO_2 and renewable energy as feedstocks is a key aspect in achieving a sustainable society [1]. As CO_2 is the most oxidized form of carbon however, substantial energy is required to convert the inert molecule into a useful product. One of the research avenues being investigated for CO_2 conversion is **bioelectrochemistry** (see Glossary), which allows for the production of more complex chemical compounds than purely electrochemical methods. The technology is rooted in the ability for microorganisms to take up electrons from solid-state electrodes, use them within their metabolism to convert CO_2, and excrete a reduced chemical as an electron sink [2,3]. This electricity-driven microbial conversion of CO_2 is called **microbial electrosynthesis (MES)**[4]. Figure 1 depicts the six main products formed in MES to date, alongside their current main industrial production methods (depicted in red). To date, 75% of all MES studies have reported solely acetate production, with a greater diversification of the product spectrum occurring only within the past few years [5].

Over the past decade, since the original proof-of-concept [6], the focus of the MES research community has mainly been on developing cathode materials, enriching microbial catalysts and **electroactive microorganisms**, increasing productivity and selectivity, and shedding light on fundamental **extracellular electron transfer (EET)** mechanisms and microbial functions (with the relative research emphasis depicted visually in Figure 2A). These steps have been vital to uncover further microorganisms and **microbiomes,** as well as demonstrating reasonable productivities. Together, these fundamental and applied advancements have continued to motivate the technology as a means of large-scale CO_2 conversion. Looking forward to the next decade of MES, how will the field shift focus to accomplish the envisioned goal of replacing existing fossil-fuel production routes for these carbon-containing compounds? The following mainly focuses on **biofilm**-driven MES. Others have extensively discussed systems built around microorganisms in suspensions [7].

In a recent article, Prévoteau and colleagues outlined in-depth the figures of merit envisioned to make MES a reality [8]. Further, Jourdin and coworkers recently provided a techno-economic

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analysis illustrating the combined cost and performance barriers to a profitable demonstration of MES [9]. Here, a different perspective is taken and the following question is asked: what are the barriers currently limiting MES, and how can this field shift its everyday research to overcome these limitations in the next ten years?

Upon unpacking this question, it becomes apparent that many of the improvements in performance that are easily accessible are non-biological in nature, such as minimizing anode–cathode spacing and increasing salinity/temperature. These improvements have yet to be seriously considered as a way to improve the performance and commercial outlook of MES, which was the motivation for the writing of this opinion piece, providing a more in-depth perspective. Specifically, it needs to be considered that the vast majority of changes which can be made in reactor design, provide conditions that are unsuitable for current biocatalysts and cathode systems developed in the past decade. The remainder of this opinion will then discuss how the biocatalysts and reactors in MES systems will need to evolve, as there is a shift to more commercially-representative conditions.

Microbe–Cathode Attachment and Structuring

As the interaction between microbial catalysts and the electron-providing cathode is the central component of MES, discussing their relationship is essential as the field seeks to move to higher current densities and efficiencies. Importantly, how can both the structure of the biocatalyst and electrode be modified to overcome limitations in both cellular and geometric electron transfer rates.

To date, both pure and mixed microbial consortium have been successfully used in MES [10,11], and a variety of electron transfer processes from the cathode surface to the biocatalyst have been demonstrated or hypothesized, including direct electron transfer [6,11] and mediated electron transfer mechanisms. In CO_2 to acetate conversion for example, H_2 has been shown to act as electron mediator, whether the H_2 species originated electrochemically [12,13] or was biologically-induced [14]. In alcohol and longer-chain carboxylate production, both EET mechanisms and microbial functions in complex microbiomes must be investigated further [15–20]. Regardless of the exact method of electron transfer, it is accepted that the cathode and biocatalyst should be in close proximity to one another to facilitate this transfer, and the number of microbes should be high to increase the overall geometric rate of CO_2 conversion. This combination of needs has led many researchers to pursue the formation of a thick biofilm on the surface of the cathode [5].

A thick and thriving external biofilm alone, however, is insufficient to meet the eventual required **current density** for MES applications, often discussed to be above 50–100 mA cm^{-2} [8,9]. Using a 2D electrode structure as a basis, Claassens and colleagues completed a comprehensive review of microbial growth parameters associated with different feedstock and assimilation pathways, including acetogens using H_2/CO_2 [7]. In this work, it was calculated that with a high electron consumption rate of 100 µmol s^{-1} $gDCW^{-1}$ (dry cell weight), a 100 µm thick biofilm, and a density of bacteria of 0.5 gDCW cm^{-3}, a maximum current density of only *circa* 50 mA cm^{-2} could be achieved in MES. Such an analysis assesses the limitations of electron transfer rates of biocatalysts from the perspective of functional biofilm thickness/density and the rate of microbial electron consumption. It is then clear that the net quantity of the biocatalyst must be increased through other means such as using 3D or fibrous electrodes, which 70% of MES studies have now utilized (Figure 2B).

Extending the back-of-the-envelope calculations from Claassens and coworkers to 3D structures (see supplemental information online for calculation details), one can start to determine what microbial-cathode structures would be required to meet specific geometric current densities and begin assessing the trade-offs that may exist from this approach. Here a 1.2 cm thick

Glossary

Biocathode: use of microorganisms in the cathode compartment of a bioelectrochemical system, that are capable of taking up electrons (directly or indirectly) from the cathode.
Bioelectrochemistry: broad term that encompasses the use of microorganisms and/or enzymes in electrochemical systems, to donate to or accept electrons from an electrode.
Biofilm: one or several layers of microorganisms that stick to each other and often also to a solid surface (e.g., an electrode).
Current density: the amount of electric current flowing per unit area (or volume) of a material (e.g., electrode, membrane, or reactor).
Electroactive microorganisms: microorganisms able to exchange electrons with an electrode, (i.e., either donate electrons to an anode, or accept electrons from a cathode).
Extracellular electron transfer (EET): mechanisms by which some microorganisms exchange intracellular electrons with an extracellular electron donor/acceptor, including naturally occurring metal compounds and artificial electrodes, across the cell membrane.
Extremophiles: microorganisms that grow in environments that are hostile to most forms of life.
Halophiles: microorganisms that grow in high salt concentrations.
Microbial electrosynthesis (MES): electricity-driven process in which microorganisms take up electrons from the cathode and reduce carbon wastes such as $CO_2$to chemicals.
Microbiome: microorganisms in a particular environment (e.g., in a biocathode biofilm).
Ohmic drop: internal resistances that occur due to the resistance of both the flux of electrons through the electrode materials, and the flux of ions in electrolyte solution and separator membrane.

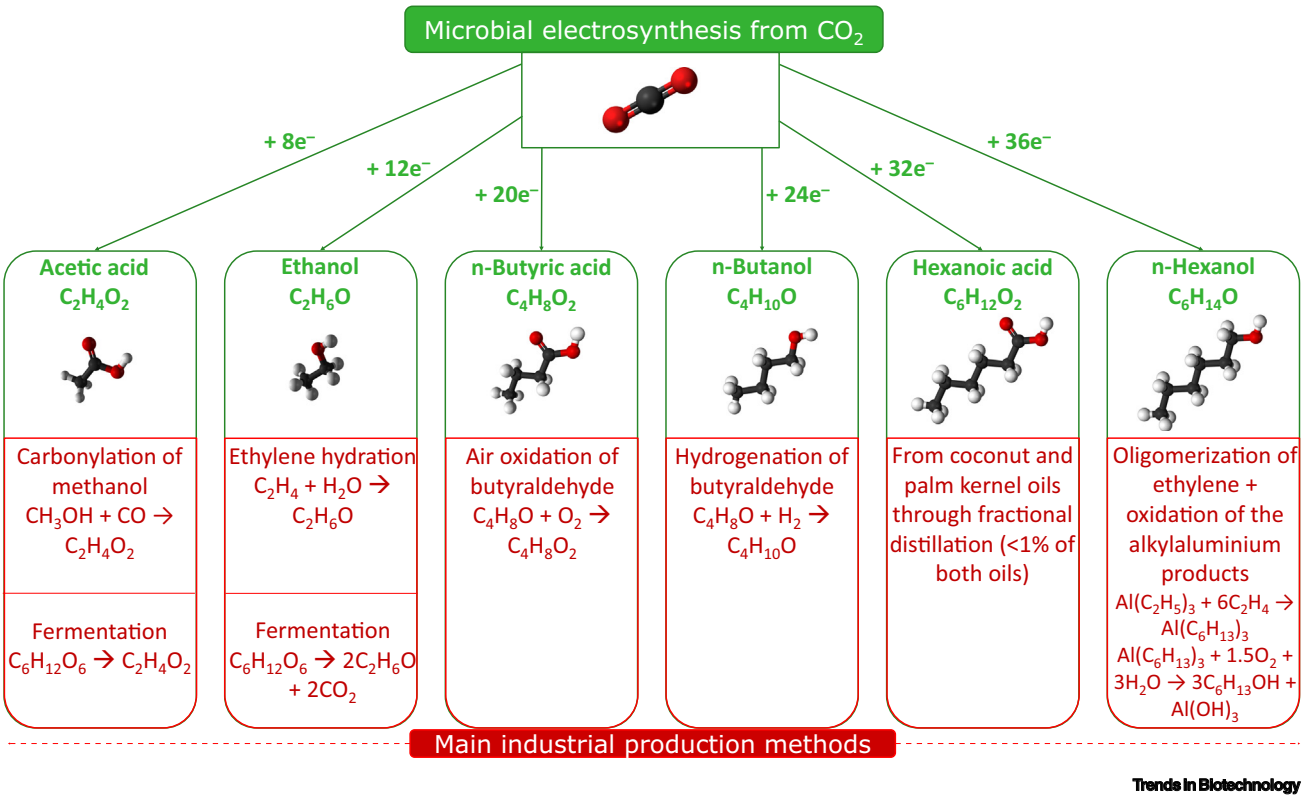

Figure 1. Overview of the Main Products Formed from Microbial Electrosynthesis (MES) From CO_2, Along With the Main Industrial Methods to Manufacture These Products. The main industrial production processes are primarily fossil fuel based, and most of them require high temperature and/or high pressure. MES from CO_2 and renewable electricity could be an alternative pathway to such fossil fuel-based processes.

carbon felt (fibrous) electrode is taken as a representative base case, which has previously been shown experimentally to reach an MES current density of – 17.5 mA cm^{-2} for an estimated external biofilm thickness of 400 μm [16]. For such a 3D electrode, biofilms can exist

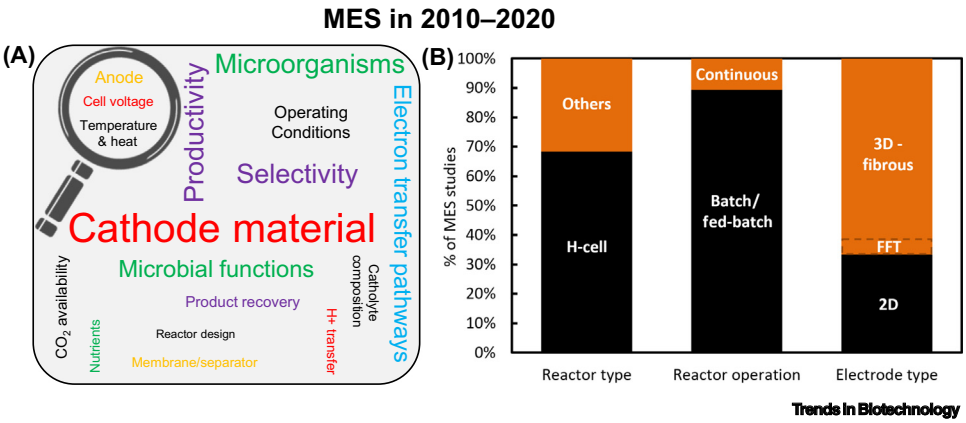

Figure 2. Microbial Electrosynthesis in the Past 10 Years. (A) Relative importance of the research effort spent on individual component and aspect of microbial electrosynthesis (MES) in the first decade of the technology (see Table S1 in the supplemental information online for quantitative distribution and references used). (B) Distribution of the type of reactor design, reactor operation, and electrode used in MES research to date (see in Table S2 in the supplemental information online for the references used). Abbreviation: FFT, forced flow through systems.

both on the exterior planar surface, as well as on the internal fibers of the thick carbon electrode (Figure 3A). Assuming similar activity parameters as Claassens and colleagues, Figure 3B–C shows the maximally achievable current density from a purely metabolic perspective, for different internal and external biofilm thicknesses. It can be seen already that with a 2 µm-thick inner biofilm, a current density ranging from – 750 to – 1100 mA cm^{-2} can in theory be reached (Figure 3B), which is far beyond that reached in the experimental results to date. These results also show that the inner biofilm thickness is more influential than the external biofilm thickness. Such findings are logical as the inner electrode surface area is orders of magnitude higher than the outer surface area (Figure 3C). Lastly, Figure 3D shows the impact of the porosity and total surface area per unit volume of 3D and fibrous electrodes, on the theoretically achievable current density. Even with a fairly open porosity which reduces the electrode area available to biofilms, sufficiently high current densities are metabolically attainable given appropriate microbial attachment and biofilm coverage.

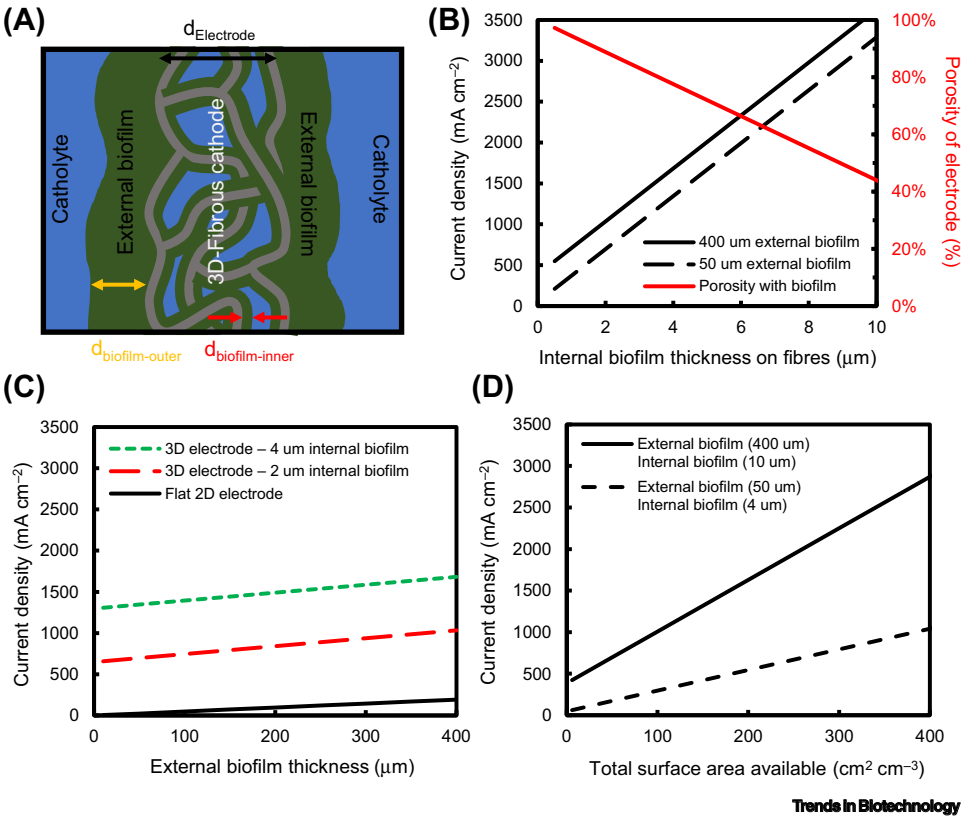

Figure 3. Impact of Biofilm Thicknesses on Metabolically Attainable Current Densities in 3D/Fibrous Electrodes. (A) Schematic representation of the three important dimensions/thicknesses that must be considered when discussing biofilm coverage on 3D/fibrous electrodes. The analysis uses a 1.2 cm thick carbon felt (560 cm^2 cm^{-3}) as a base case. Calculations are performed for prescribed internal and external biofilm thicknesses as described in [16]. (B) Plot of maximum available geometric current density as a function of internal biofilm thickness for two different external thicknesses. Also shown is the porosity as a function of increased internal biofilm thickness. (C) Comparative maximum geometric current density available for a 3D electrode with different external biofilm thicknesses. (D) Effect of the total surface area available for biofilm development on current density. Absolute cathodic current densities are normalized to projected surface area. The calculations from Claassens and colleagues [8] were applied here to 3D/fibrous electrodes, with a microbial electron consumption rate of 100 µmol s^{-1} $gDCW^{-1}$ and a density of bacteria of 0.5 gDCW cm^{-3} (see the supplemental information online for the detailed calculations).

Since it is known that biofilms have been shown to be present throughout the entirety of such 3D fibrous structures [16], the results here indicate that factors other than maximum metabolic rates are limiting geometric MES rates in these systems. In our view two distinctive research avenues deserve our interest in order to understand and realize greater activity of 3D MES systems. One direction takes a more biological approach and focuses on homogeneous biofilm growth strategies in thicker 3D structures, while another seeks to improve the system from a purely electrochemical reactor design perspective, considering factors such as mass transport and current distribution. The following section expands the views on these themes. In both cases, methods to determine the kinetic rates on both a cellular (i.e., biomass-specific) and geometric level, would be a valuable metric for interpreting these advancements, and to assess whether there are intrinsic limitations of the MES microorganisms, which impact their metabolic rates from the values suggested by Claassens and colleagues (100 μmol s^{-1} $gDCW^{-1}$).

Reactor Design and Multiscale Modeling as a Key Enabler of the Technology

The preceding section addressed the limitations of MES activity from a metabolic perspective, using the dimensions of the electrode and biofilm as primary factors in determining limiting rates. In reality, as the dimensions of the electrode and the overall quantity of bacteria are increased, so too are limitations reached, which requires the invocation of reactor design concepts to ensure productivity.

One of the clearest challenges of operating 3D MES electrode structures is ensuring that ample CO_2, protons, and nutrients, can be provided to all layers of microbes within the electrode, such that desired growth and reaction rates of each individual microorganism throughout the entirety of the 3D electrode can be sustained. An exterior biofilm with thicknesses on the order of 400 μm, for example, is likely to run into diffusion limitations of reactants from the bulk electrolyte to the biofilm closest to the electrode. Conversely, electrons (or electron carriers) transferred from the electrode may deplete prior to reaching the exterior biofilm surface, and product and hydroxide (OH^-) build-up could result in reduced stability or intrinsic productivity. Both aspects will hurt productivity per cell due to nonideal transport. Ensuring ample transport is even more complex for biofilm on the interior surfaces of thicker fibrous structures, particularly if fluid flow is constrained to only one side of the electrode, as is common in flow-by systems (~95% of current MES studies as shown in Figure 2B). In cases where the electrolyte is forced to flow through the porous electrode matrix, higher current densities and improved biofilm coverage have been demonstrated versus H-type reactors with magnetic stirring [5]. While MES research to date has not placed substantial emphasis on reactor design concepts to improve mass transport (Figure 2A) [16,21–23], small modifications to the reactor itself can allow for improved geometric metabolic output.

A separate transport consideration in 3D electrode structures is the ionic transport between the anode and cathode. As discussed by Prévoteau and coworkers, the **ohmic drop** within the electrolyte will constitute a significant portion of the operating cell voltage [8]. For fixed voltage operation, the portion of the anode and cathode closest to one another will then have the greatest electrochemical activity, as the ohmic drop will be the lowest. A consequence of thicker electrodes, is increased ohmic drops deeper in the electrode structure, which effectively results in reduced potentials and current densities on the back of the electrode [24] independent of CO_2/nutrient transport. Under extremely high metabolic rates, 2D electrodes are actually preferred. From an ionic perspective, the need for a dispersed biological system is contradicted by an ideal 2D reactor design, implying that a compromised electrode thickness must be found. As a quick reference, (see Figure S1 in the supplemental information online) highlights how the maximum possible current density varies for different electrode thicknesses, if only the metabolic rate is limiting.

From the previous transport arguments, a strong motivation for greater mass transfer, fluid dynamics, and cell geometry modeling in MES reactors can be seen, which can then be validated using experiments. Up to now, computational modeling of MES at all relevant scales (i.e., from μm to m-scale), has been underexplored, and is necessary to achieve breakthrough understanding of the process-limiting steps, and for rational design and scale-up. To our knowledge, only Gadkari, Kazemi, and colleagues, modeled the (inter)-dependence of some operating parameters [25], and current density and biofilm thickness on substrate concentration [26], while Enzmann and co-workers modeled some design parameters from their bubble column reactor [21]. Salimijazi and colleagues also very recently modeled the theoretical interdependence between electrical-to-fuel efficiency, and biofilm resistivity and thickness [27]. While only a 2D system was modeled, they concluded that as the biofilm resistivity increases, its thickness must decrease and its geometric area increase, in order to maintain a given efficiency. However, following their conclusion, a 3D or fibrous electrode would allow to maintain thin, low-resistivity, biofilm throughout the whole cathode, and thus may allow the maintenance of high energy efficiency at a reasonable reactor footprint. Ideally, a cheap commercial material with appropriate thickness, porosity, and other important physical–chemical properties [2,5,28] can be used as a cathode. Otherwise, innovative synthesis methods could be explored such as, for example, 3D-printed materials that fulfil the characteristics discussed earlier. It should be noted that higher energy efficiency could be targeted upon replacing the energy-intensive water oxidation anodic reaction (Box 1).

In brief, both mass and ion transport will dictate the optimal electrode design of an MES system, providing a trade-off for different parameters. These considerations are separate from many of the fundamental concepts studied in the field today, but are required more and more as microbial productivity continues to increase.

Temperature, Salinity, and Pressure: Turning the Knob

In MES a number of different operating conditions have been investigated, such as the effect of pH [29,30], applied cathode potential [31], applied current [32], or continuous supply of nutrients [16,20]. The effect of feeding CO_2 as gas or as bicarbonate salt [33,34], and of intermittent power supply, have also been examined [35]. Going forward, it is expected that changing the intrinsic properties of the system (i.e., temperature, salinity, and pressure), may lead to substantial gains in the viability of MES systems (Figure 4A). Here we discuss how increasing each of these parameters can be found to be advantageous, and how adaptions to current microbes are needed to enact these benefits.

Modern water electrolyzers and fuel cells typically operate at higher temperatures for several reasons. First, as these devices operate with efficiencies <70%, substantial heat is generated during operation, which raises the temperature naturally. Secondly, temperatures up to 100°C result in a rise in electrochemical activity of heterogeneous catalysts (via an Arrhenius relationship), and a large increase in electrolyte conductivity, both of which lower cell potentials. For example, the electrolyte conductivity for NaCl is shown to increase by several factors from 25°C to 90°C as shown in Figure 4B and for Na_2HPO_4 in Figure S2 (see the supplemental information online). The challenge for MES in taking advantage of higher temperatures, however, is that organics formation in MES has only been demonstrated in mesophilic bacteria, with metabolic activity constrained to 15–45°C. If thermophilic microbial cultures could be acclimated to operate under higher temperatures, however, then device efficiency could be increased purely by a change in system properties (Figure S3 in the supplemental information online). Such culturing is not without precedent, as demonstrated by microbial fuel cells (MFCs) operating under thermophilic conditions (>45°C), with benefits including higher microbial activity, better (soluble) substrate solubility, higher mass transfer rates, and lowered risk of contamination [36–40]. Recently, Reiner and colleagues

Box 1. Alternatives to Anodic Water Oxidation May Prove Favorable

To date, the focus of microbial electrosynthesis (MES) development has been on the **biocathode**, with water oxidation performed at the anode largely for convenience. Attempts have been made to couple the biocathode with a biological anode [54], though additional effort is required to make this configuration technically and economically viable [9]. Now that biocathodes and production are better understood after a decade of research, it is worthwhile to begin pairing MES with a more energetically and economically favorable anodic reactions.

The water-oxidizing electrode of the cell not only represents the main cost contribution of MES, amounting to 59% of the total capital expense (CAPEX), but requires substantial overpotentials [9]. As adjacent research fields have recently sped up the development of anodic catalysts for the oxidation of organics, these advancements can be incorporated into MES systems in the near future [55]. Table I lists a nonexhaustive list of four promising anodic reactions for the oxidation of glycerol and glucose, together with the Gibbs free energy of the overall reaction, and the resulting cell voltage under different pH conditions.

Several important conclusions can be made from Table I when considering replacing water oxidation. First, oxidizing glycerol or glucose requires lower cell voltages than water oxidation. Second, the proposed organic reactions favor high pH environments, which is in contrast to the current acidic anolytes used in MES studies. And third, positive E_{cell} values are in theory achievable when coupling electro-oxidation of glycerol or glucose at pH 14 to a biocathode at pH 7, given a suitable means of separating the two pH electrolytes (e.g., bipolar membranes).

From an economical perspective, alternative anodic reactions provide the potential to make a second valuable product. This promise, however, is not without additional constraints. For example, it needs to be ensured that the market of the anodic product pairs well with the cathode product in terms of location, global production (tons/year), feedstock availability, and cost. Further, if the goal of MES is to replace substantial portions of waste CO_2, then the anodic product market size must also be substantial. Detailed life cycle and techno-economic assessments should then drive the choice of the anodic feedstock.

For now, water oxidation will continue to persist due to its ease of operation for investigating biocathodes. Water is abundant, pH operation can be flexible, and current densities are easy to match with the cathode. As the field moves forward, so too does the possibility of replacing the anode as a promising development for commercializing MES technology.

Table I. Theoretical Gibbs Free Energy of Reaction and Cell Voltage for the Cathodic Microbial Electroreduction of CO_2 to Hexanoate ($6CO_2 + 32H^+ + 32e^- \rightarrow C_6H_{12}O_2 + 10H_2O$), Coupled to Anodic O_2 Evolution, or Glycerol and Glucose Electro-Oxidation, at Different pH Conditions

Possible anode reactions	Possible overall reactions	Std. conditions (pH 0, 298K)		Anode pH 1 – cathode pH 7		Anode pH 14 – cathode pH 7	
		ΔG^0_r (kJ mol^{-1})	E^0_{cell} (V)	ΔG_r (kJ mol^{-1})	E_{cell} (V)	ΔG_r (kJ mol^{-1})	E_{cell} (V)
Water → oxygen $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$	$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_2 + 8O_2$	3453.48	–1.12	4549.36	–1.41	2174.96	–0.70
Glycerol → glyceraldehyde $C_3H_8O_3 \rightarrow C_3H_6O_3 + 2H^+ + 2e^-$	$6CO_2 + 16C_3H_8O_3 \rightarrow C_6H_{12}O_2 + 16C_3H_6O_3 + 10H_2O$	896.68	–0.29	1992.56	–0.65	–381.84	0.12
Glycerol → lactic acid $C_3H_8O_3 \rightarrow C_3H_6O_3 + 2H^+ + 2e^-$	$6CO_2 + 16C_3H_8O_3 \rightarrow C_6H_{12}O_2 + 16C_3H_6O_3 + 10H_2O$	426.28	–0.14	1522.16	–0.49	–852.24	0.28
Glycerol → formic acid $C_3H_8O_3 + 3H_2O \rightarrow 3CH_2O_2 + 8H^+ + 8e^-$	$6CO_2 + 4C_3H_8O_3 + 2H_2O \rightarrow C_6H_{12}O_2 + 12CH_2O_2$	82.36	–0.03	1178.24	–0.38	–1196.16	0.38
Glucose → gluconic acid $C_6H_{12}O_6 + 1H_2O \rightarrow C_6H_{12}O_7 + 2H^+ + 2e^-$	$6CO_2 + 16C_6H_{12}O_6 + 6H_2O \rightarrow C_6H_{12}O_2 + 16C_6H_{12}O_7$	–562.52	0.18	533.36	–0.17	–1841.04	0.60

successfully enriched the first thermoacidophilic electroautotrophic community from a natural hydrothermal environment, that not only operated at 60°C, but also at pH 3.5 for the conversion of CO_2 to polyhydroxybutyrate [41]. *Moorella thermoacetica* and *Moorella thermoautotrophica* were also tested at temperatures up to 70°C [42].

In addition to changing the temperature of the electrolyte, the electrolyte can also be made more concentrated. Doing so substantially increases the conductivity, and lowers the ohmic drop in the system (Figure 4C). This is not only necessary from a cell potential perspective [8], but a high electrolyte conductivity would reduce the current and potential distribution penalties described in thicker electrodes by lowering the ion transport penalty. The obvious challenge of operating at higher salt concentration, is the need to enrich halotolerant or halophilic MES microbial cultures that can withstand it [8]. **Halophiles** are classified as slight (0.3–0.8 M NaCl), moderate (0.8–3.4 M NaCl), and

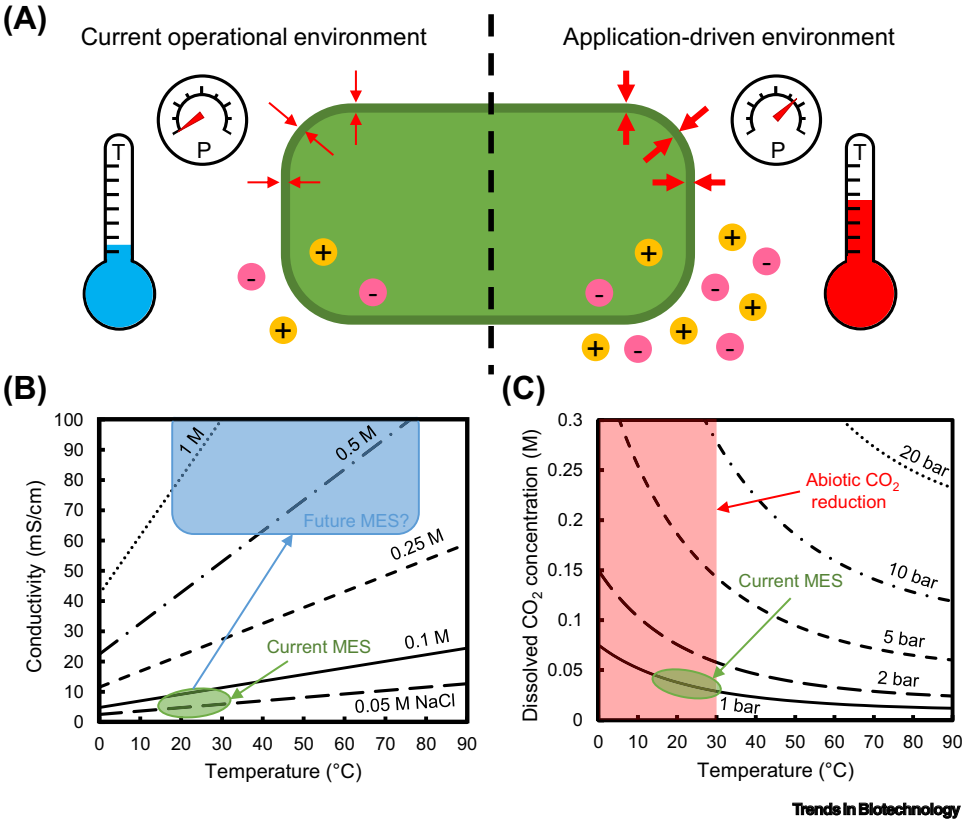

Figure 4. Turning the Knob on MES Intrinsic Properties. (A) Scheme representing the increase of three intrinsic properties of the system temperature, salt concentration, and pressure on a bacterial cell, from current operational environment to an application-driven environment. (B) Effect of temperature on the conductivity of a sodium chloride (NaCl) solution at different concentrations. (C) Effect of temperature on CO_2 solubility, at different pressure. These property relationship curves were adapted from available literature data (see Figures S4 and S5 in the supplemental information online). Abbreviation: MES, microbial electrosynthesis.

extreme (>3.4 M NaCl) halophiles [37,43]. Three main strategies can be employed towards enrichment of halophilic microorganisms for MES applications, such as applied in other biotechnologies: (i) adaptive laboratory evolution [44]; (ii) enrichment or isolation of microorganisms from extreme natural or anthropogenic environments [37,45,46]; or (iii) genetic engineering [8,40]. As an extra advantage, higher salt concentration may even induce biofilm formation, as shown for *Clostridium ljungdahlii* via NaCl addition [47]. Alqahtani and colleagues recently enriched a halophilic homoacetogen culture from a hypersaline deep Red sea brine pool [48]. Their culture was capable of reducing CO_2 to acetate at 3.5% NaCl, though at low current densities. Depending on the targets (current density and cell voltage) and the halotolerance of the microbial culture, increasing the temperature can allow for the electrolyte conductivity to increase while remaining within the 'operating' domain of the culture. The higher the salt concentration, the steeper the absolute increase of conductivity with temperature (Figure 4B).

The last property which can be increased to improve system performance is the electrolyte pressure, which can be utilized to enhance CO_2 availability. While it is still unclear how the growth and reaction kinetics of MES microbiomes are affected by soluble CO_2 concentration [i.e., at which minimum CO_2 concentration the maximum biomass specific substrate consumption rate (q_s^{max}), and max growth rate (μ^{max}) are achieved], the advent of thicker electrodes and geometric current

densities is expected to be a greater draw on available CO_2 in the system. Further, higher operating temperatures and salt concentrations have a large negative consequence on CO_2 solubility, as illustrated for temperature in Figure 4C. A simple approach is to increase the CO_2 partial pressure, as has been done in heterogeneous catalysts [49]. In general, microorganisms are resilient at increased pressure, such as demonstrated in other biotechnologies (e.g., anaerobic digestion) [50]. Independent of increasing CO_2 availability through pressure increases, reactor design strategies to increase CO_2 mass transfer to the biocatalysts that are scalable, and possibly stackable, must be investigated. For example, the use of gas diffusion electrodes [51], bubble column reactors [21], and conductive hollow fiber cathodes [23,52], were investigated to improve CO_2 transport to the biocatalysts, either for acetate or methane production. It was shown that increasing the CO_2 flushing rate at constant pressure improved faradaic efficiency, and electron and carbon selectivity towards butyrate and hexanoate, apparently via better mass transfer of CO_2 [17].

While varying electrolyte properties are an attractive route forward for MES, a careful concomitant control of the salinity, temperature, and pressure, is likely to play a key role in successful demonstration and scale up of high rate systems. Special attention to preventing growth of methanogens will be important, as in nature, the higher the salinity and the temperature, the more the archaea tend to thrive as compared with bacteria [37]. Moreover, a way to increase the salt concentration may be to increase the pH buffer concentration (Figure S2 in the supplemental information online). This strategy was deemed noneconomic for MFC application using wastewater streams for cheap electricity production [37]. However, for MES using a gaseous substrate and producing higher value chemicals, this strategy may prove economically feasible if the buffer is effectively and cheaply recycled. Using high buffer concentrations may also prove crucial for high current density and/or high-pressure systems, in which the pH is likely to shift away from the optimum growth pH.

Many similarities exist between MES and other electrochemical technologies. Research on some of the latter are more advanced (CO_2 electrolyzer), or are even industrially implemented already (e.g., fuel cell, water electrolyzer, and chlor-alkali processing). Therefore, inspirations and lessons from reactor design, scale-up, and stackability perspectives, as well as process and system design, and system management (heat management, power management, etc.) should be taken from them. For examples, computational modeling of mass transport phenomena and cell geometries could be adapted to MES [24,53].

Concluding Remarks

Considering all of these arguments, it is our opinion that a comprehensive technology system approach needs to be developed to improve the commercial viability of MES systems. Understanding and abating all rate and yield limiting steps, from microorganisms to reactor scale, concomitantly is nontrivial (see Outstanding Questions), and will require researchers from a variety of disciplines, such as microbiology, physics, (electro)chemistry, process engineering, and multiscale modeling. We argue that the non-biological developments are more easily attainable. Designing (with the help of computational modeling), and testing new (scalable) reactor and electrode geometry is probably the technological advancement that can be made the quickest, to significantly improve MES productivity and efficiency. The changes required will likely result in important additional demands on the microorganisms in the system. In the mid-term future, the genetic toolbox of homoacetogens and other microorganisms will expand and mature, leading to, for example, increased tolerance to harsher environments (e.g., temperature and salt) and/or to the production of a wider range of products from CO_2 by MES. The genetic engineering of microorganisms for MES applications remains the toughest challenge, while pure cultures have

Outstanding Questions

What is really limiting MES? Can a biofilm effectively sustain current densities in the order of 100 mA cm^{-2} and higher?

Can a general multi- and cross-scale model be built and used as a prediction tool for MES and as a tool for rational scale-up?

Can **extremophiles** be evolved in the laboratory or enriched from natural and/or anthropogenic environments to achieve high MES rates?

For reactor design, what inspiration can come from both large-scale fermentation reactors and large-scale electrochemical reactors? Should MES be scaled by volume or by number?

Is water oxidation the best anodic reaction for MES applications?

so far demonstrated lower productivities than microbiomes. In the meantime, MES should be demonstrated at higher technology readiness levels (TRLs) for the production of carboxylates and/or alcohols (C2–C6) to encourage further progress, either by adapting current microbiomes to application-driven environments, or enriching microbial catalysts from extreme natural or anthropogenic environments.

In parallel to biofilm-driven MES as discussed here, systems based on microorganisms in suspension deserve further attention. Whether suspended cultures are introduced within the electrochemical reactor itself, or within a fermenter coupled to an electrochemical reactor that produces an electron and/or carbon donor (e.g., CO, formic acid, or H_2) for microbial utilization. Flexibility in both reactor designs and processes will provide the greatest opportunity for both technological advancement and novel discoveries.

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