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# Integrative electrochemical and biological catalysis for the mild and efficient utilization of renewable electricity and carbon resources

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Chemical catalysis and biological catalysis both play important roles in producing various fuels, chemicals, and materials conventionally. In view of renewable resources (biomass and CO<sub>2</sub>) utilization, combining both chemical and biological catalysis would create revolutionary routes that are more sustainable and efficient for the processing of these resources. Considering the electricity is usually a main form of renewable energy, electrocatalysis also plays an important role. Therefore, the integrative electrochemical and biological catalysis for the simultaneous utilization of renewable energy and resources is attracting significant attention. In this review, such integrative processes and methods are summarized, discussed in depth and two integration modes are distinguished based on the use of electroactive/non-electroactive microorganisms. The intermediates mediated consecutive synthesis from CO<sub>2</sub> or biomass to specific chemicals is shown to play a pivotal role, such as the H<sub>2</sub> enhanced microbial electrosynthesis (MES), CO or formate mediated longer carbon chain products synthesis. Accordingly, the synthesis efficiency was improved significantly following the collaborative design of abiotic and biological catalysts, as well as the route innovation. For example, acetate productivity of 1330 g m<sup>-2</sup> day<sup>-1</sup> in MES and low cost of 45 g kWh<sup>-1</sup> for producing butanol and hexanol could be achieved, which shows great potential for industrial application. The integrative electrochemical and biological catalysis can convert CO<sub>2</sub> or biomass feedstocks to a wide product distribution from C1 to C6+, and even large molecules such as sugars, lipid, starch, etc. This article exhibits the importance of integrative electrochemical and biological catalysis for efficient utilization of renewable carbon resources, the manners to integrate two different processes and some reflections for future research.

## 1. Introduction

Sustainable development of the society is one of the most pressing goals currently which is well exemplified by the 17 sustainable development goals (SDGs) from United Nations.<sup>1</sup> Minimizing the disruptions brought about by climate change and shifting to renewable energy are important measures to achieve some of the SDGs. The carbon dioxide (CO<sub>2</sub>) and biomass are generally regarded as renewable resources, due to their low cost and large-scale availability.<sup>2-4</sup> They can be converted to various carbon-containing chemicals and fuels to partially replace traditional fossil resources produced compounds.<sup>5-7</sup> Like oil refining and coal chemical industry, the conversion processing of CO<sub>2</sub> and biomass to appropriate products need feasible and advanced technologies as well as high energy efficiency. Compared to well developed and widely used thermochemical and heterogeneous catalytic processing technology, the mild and highly efficient technologies are desirable, because of the CO<sub>2</sub> inertness and polymerization of biomass. Biocatalysis and electrocatalysis are both preferential choices for such conversions.

Currently, the renewable energy mostly provides a form of clean electricity, including the solar, wind, hydro, and nuclear, etc.<sup>8-10</sup> The large-scale deployment of these clean electricity is crucial for defossilising the global energy supply. However, the renewable electricity alone does not meet non-electric energy demands, such

as fuels for transportation and chemicals for industry. Therefore, converting and storing renewable electricity into suitable fuel or chemical molecules have been proposed, also known as “Power-to-X” approach.<sup>11-13</sup> The fusion of renewable energy and sustainable feedstocks (CO<sub>2</sub> and biomass) calls for new processes and technologies to manufacture carbon-based synthetic fuels and chemicals, thus innovating industrial production.

Typically, both biocatalysis and electrocatalysis are mild and efficient routes to convert CO<sub>2</sub> and biomass to targeted products. They are generally operated at low temperatures (<100 °C) without large amount of gaseous pollutant emissions as is the case with traditional thermochemical processes.<sup>14, 15</sup> Similarly, the commercialization of biocatalytic or electrocatalytic reaction rely on the high reaction rate (expressed as conversion, yield, turnover frequency (TOF), etc.) and low energy consumption, namely technical and economic feasibility. The abiotic electrocatalytic reaction generally have high reaction rate because of the linear relationship of applied potential on the reaction activation energy.<sup>16</sup> Therefore, it can achieve equivalent level of product space-time yield (such as STY ~ 1.0 kg·L<sup>-1</sup>·h<sup>-1</sup>) as traditional thermal catalytic process.<sup>17</sup> However, for CO<sub>2</sub> electroreduction reaction, a very difficult question is to obtain high carbon number products due to the multi-protons and electrons coupling at the same time.<sup>18</sup> Multi-carbon product from CO<sub>2</sub> electroreduction will consume several-fold electric energy than C1 products, which results in ultrahigh costs.<sup>19</sup> For electrocatalytic upgrading of biomass derived compounds, the limited solubility in electrolyte and slow reaction kinetics usually hinders large scale electrolytic synthesis.<sup>20</sup> In comparison, besides the mild synthetic conditions, biocatalysis also has the characteristics of diverse transformation pathways and rich product types. It can

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synthesize many functional organic compounds such as higher alcohols, organic acids, polyols, and so on, from CO<sub>2</sub> or biomass. However, the synthesis rate and productivity of microbial fermentation processes are generally lower than those of chemical processes with a typical level  $\sim 0.1\text{--}3\text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$ .<sup>21</sup> The special bioelectrochemical synthesis also presents similar production level or much lower, such as microbial electrosynthesis (MES), reducing CO<sub>2</sub> to produce acetate.<sup>22</sup>

In this context, the combination of electrochemical and biological catalysis provides novel ways for enhancing synthetic efficiency and simultaneous utilization of renewable energy and resources.<sup>23</sup> Although numerous relevant reviews and study papers have been presented on the topic of combining chemo- and biocatalysis,<sup>24–29</sup> particularly in organic synthesis,<sup>30–33</sup> the summary and application on the specific coupling of electrocatalysis are rather limited.<sup>34–38</sup> A possible reason is the lack of academic and recognized concepts on the integrative electrochemical and biological catalysis. The bioelectrochemical systems (BESs) and abiotic electrocatalysis have been extensively studied, independently. The BESs, particularly microbial electrosynthesis (MES), is an overlapping concept with electro-fermentation (EF) and electrobiorefinery sometimes.<sup>39</sup>

Schroeder et al discussed the terminology and classification of microbial electrochemistry and technology.<sup>40</sup> They discussed classification of technologies for integrating electrochemistry and microbiology and believed that BESs should include all processes depending on bioelectrochemistry. However, it does not include abiotic electrocatalysis. Therefore, taking individual BESs or EF as an integrative electrochemical and biological catalysis is disputed, because the existence and facilitation of abiotic electrocatalysis in the system is not clearly identified and disclosed. The electrodes used in BESs are generally inert conductive materials without evident catalytic ability, such as graphite, carbon felt, stainless steel, etc. but the determination of the catalytic role of the electrode remains tricky. For a definite reaction and product, the decrease of overpotential, increase of reaction rate and selectivity could be good indicators for detecting abiotic catalysis on electrode. Enough attention should be paid to this catalytic effect for understanding the integrative electrochemical and biological catalysis.

This review focuses on the productivity performance and improvement for various integration of electrochemical and biological catalytic processes. The intermediates mediated coupling synthesis is summarized and addressed thoroughly. The idea is to gauge the distance of these new technologies to industrialization, as well as identify the room for technology and performance advancement. The combination of biocatalyst with heterogeneous chemical catalysis (non-electrocatalysis) will be excluded and not discussed, although they also present promising route but are out of the scope here.<sup>24, 41–44</sup>

## 2. Overview of the integrative electro- and biocatalysis

### 2.1 Renewable resources

The traditional carbon containing fuels and chemicals strongly rely on fossil materials, for example, oil, coal and natural gas. (Fig. 1). From a long-term perspective, they are non-renewable and will eventually deplete. The refining of these fossil resources to various fuels and chemicals has been mature, but serious environmental pollution and a large amount of greenhouse gas emissions are always associated with the processes. To address the sustainable development in future, alternative resources such as CO<sub>2</sub> and biomass are getting more attention. Due to the following common features, CO<sub>2</sub> and biomass can meet the demand for zero or negative carbon fuels and chemicals.

To begin with, their availability is huge in scale to meet the heavy demand as alternative feedstock. Every year, more than 20 billion metric tons CO<sub>2</sub> are discharged and about 100 billion tons of biomass is produced in the world (half in ocean and the other half on land). These are much higher than the consumption of coal and petroleum worldwide. Secondly, the use of CO<sub>2</sub> and biomass can realize closed loop of carbon cycle, which is renewable and sustainable development in the true sense.<sup>45–47</sup> Finally, it is well known that the simple CO<sub>2</sub> and functionalized biomass are suitable as feedstocks for biological and electrochemical transformation.<sup>48, 49</sup> The previous industrial fermentation processes also witnesses this status.<sup>50</sup>

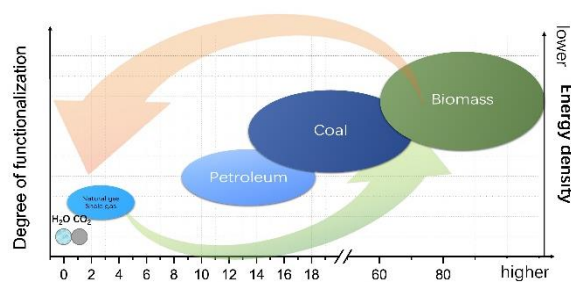


Fig. 1. The illustration of main carbon-based resources

As Fig. 1 shows, the component of petroleum has medium carbon number and low degree of functionalization (with abundant saturated aliphatic hydrocarbon), which makes it easy to be processed and refined relatively, while coal has higher carbon number and polymerization. The destructive processing methods are widely applied, such as dry distillation, gasification, etc. for chemicals production. Comparatively, biomass is plant-based material which has broader composition and nature. Typically, it includes starch, protein, vegetable oil and fat, lignocellulose, hemicellulose, etc. The energy density of biomass is much lower than petroleum and coal (7000–9000 kcal/kg) as well as natural gas (11600 kcal/kg). To convert to refined liquid fuels and functional chemicals is more important for biomass utilization, due to its high degree of functionalization and polymerization. Compared to fossil resources, biomass and its derivatives are more suitable for biological synthesis due to the characteristics of bio-feedstocks and bacterial growth environment, such as being water-soluble, non-toxic and with bioaffinity. The

electrochemical conversion or upgrading of biomass derivatives are common techniques and frequently applied.<sup>51-53</sup>

CO<sub>2</sub> being an inert and chemically stable gas, the energy input for CO<sub>2</sub> conversion is tremendous which not only supplies reaction demand (bond breaking), but also brings energy into the product. Therefore, the reductant for CO<sub>2</sub> reduction must be a kind of energy carrier (e.g. H<sub>2</sub>) or energy form (e.g. electricity). These attributes of CO<sub>2</sub> as feedstock makes electrocatalysis and biocatalysis as well as their integration as a promising approach for efficient activation and conversion to desired fuels and chemicals.<sup>54-56</sup>

## 2.2 Renewable electricity

The renewable and sustainable energy is booming in the last decades.<sup>57</sup> Global photovoltaic power generation has grown from about 5 GW in 2005 to an approximately 509.3 GW in 2018.<sup>58</sup> Taking China as an example, the world's largest photovoltaic (PV) market is formed with a PV installation capacity of higher than 200 GW in 2019. The total installed capacity of 1200GW including wind and solar was set by the 2030.<sup>59</sup> This stimulates the fast development of electrochemical engineering and technologies based on renewable electricity. The integration of photovoltaic cell – water electrolysis system has been an interesting R&D topic from early time.<sup>60-62</sup> The photovoltaic coupling electrolytic facility comprised of a PV panel and two proton exchange membrane electrolyzers arranged in order was assembled and achieved 30% of solar-to-hydrogen (STH) efficiency in 48 h, which is the highest value in the hydrogen evolution reaction research up to now.<sup>63</sup> In the meantime, the integration of photovoltaic cell - CO<sub>2</sub> electrolysis system also began to be widely studied.<sup>64</sup> The photocatalytic reduction of CO<sub>2</sub> to CO and O<sub>2</sub> on a bifunctional catalyst, SnO<sub>2</sub> on CuO nanowires (all earth-abundant elements), has been achieved at an efficiency of 13.4%,<sup>65</sup> as well as other cutting-edge solar-to-CO efficiencies of 15.6%<sup>66</sup> and 15.9%.<sup>67</sup>

The advantages and progresses of integrative photovoltaic-electrolysis system are also reflected on the decreasing cost of solar photovoltaics, the simplified routes for applying voltage or current to the electrolytic cell, and further thermal integration of PV and electrolysis modules to improve energy efficiency.<sup>68</sup> While the abiotic photocatalytic and photoelectrochemical techniques direct integration of photoelectric conversion and catalytic reactions, their efficiencies are still very low and their application is greatly limited.<sup>62</sup> However, abiotic photo- and/or electro- materials coupling biocatalyst hybrid system seems more interesting and provides newer opportunity for efficient CO<sub>2</sub> fixation to value-added chemicals.<sup>69, 70</sup> It requires the innovative design of photosensitive materials and active microorganism. The relative merits to other methods such as electroactive bacteria on electrode (microbial electrosynthesis) need careful comparison and analysis. However,

the wide implement of renewable electric energy is the precondition and foundation to large-scale deployment of electrocatalytic synthesis and integrative electro- and bio- catalysis processes. As a parallel research field, the prospect of renewable electricity is very optimistic in future.

## 2.3 Product aspect

Multiple chemicals and materials can be produced by CO<sub>2</sub> and biomass feedstocks. The high value-added products of long carbon chain and rich functionalization were more expected first, such as higher alcohols, fatty acid, etc. However, the productivity to specific product is also important when considering the economic feasibility. Here the products are introduced according to the carbon number, obtained by bioelectrochemical systems or integrative abiotic and biological catalysis.

(1) **C<sub>1</sub> product**, including CO, formate, methanol, methane, etc. These products are mainly synthesized from abiotic or enzymatic electrocatalytic reduction of CO<sub>2</sub>.<sup>56, 71-73</sup> Most of them are bulk chemicals industrially, produced or obtained from fossil resources with quite low cost. However, the CO and formate are the most readily available product by abiotic electrocatalytic two-electron reduction of CO<sub>2</sub>.<sup>73, 74</sup> which presents obvious technical and economic feasibility and a bright future<sup>19</sup>. It shows more advantages when considering net CO<sub>2</sub> emission in the production process.<sup>75, 76</sup>

(2) **C<sub>2</sub> product**, mainly including acetate and ethanol. They are produced from microbial electrosynthesis (MES) from CO<sub>2</sub>,<sup>22</sup> a few abiotic electrocatalytic reduction of CO<sub>2</sub>.<sup>77, 78</sup> coupling electrocatalytic reduction of CO<sub>2</sub> to CO with CO gas fermentation<sup>79</sup> and unbalanced fermentations of glycerol.<sup>80, 81</sup> Although acetate and ethanol are more useful chemicals and/or fuels, they are also bulk chemicals too in industry. Alternative large scale industrial production from CO<sub>2</sub> by electro- and bio- based methods is meaningful but challenging.<sup>22</sup>

(3) **C<sub>3</sub> ~ C<sub>6</sub> product**, these products are more interesting because they link commodity chemicals and specialty chemicals, even they themselves as such are used widely. CO<sub>2</sub> and biomass can both be the starting materials to electrochemically synthesize C<sub>3</sub> ~ C<sub>6</sub> products, such as lactate (C<sub>3</sub>H<sub>6</sub>O<sub>3</sub>)<sup>82</sup> and butyric acid (C<sub>4</sub>OOH)<sup>83</sup> from glucose, butanol (C<sub>4</sub>OH), hexanol (C<sub>6</sub>OH) or hexanoate (C<sub>6</sub>OOH) from CO<sub>2</sub>-derived syngas fermentation,<sup>79</sup> isobutyric, butyric, caproic acids, and their alcohols from MES of CO<sub>2</sub>.<sup>84</sup> It is worth mentioning that direct abiotic electroreduction of CO<sub>2</sub> alone is not able to produce these products due to requirement of multiple electrons and protons coupling reaction.<sup>85</sup> The integrative (electro)biocatalysis via approaches such as electrofermentation is thus significantly desirable.

(4) **Other longer chains or large molecules products**, such as starch, lipid, sugars, etc. The examples include lipid from electro-fermentation of glucose, xylose, arabinose and glycerol,<sup>86</sup> coupling electrocatalytic reduction of CO<sub>2</sub> to acetate with acetate fermentation to glucose,<sup>87</sup> chemoenzymatic starch synthesis from CO<sub>2</sub> etc.<sup>88</sup> This is more likely artificial photosynthesis from CO<sub>2</sub> and H<sub>2</sub>O to specific biomass product. Interesting examples also include production of polyamides<sup>89</sup> or polyesters<sup>90</sup> from sugar, by combining metabolic engineering and electrocatalysis.

#### 2.4 Technical aspects

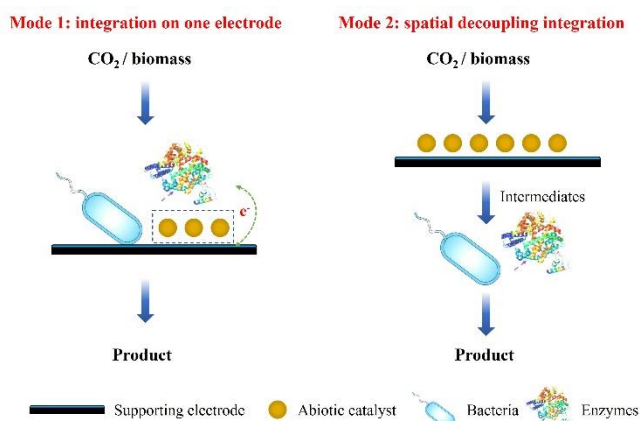
Efficient conversion of renewable energy and resources, as well as to selectively obtain the desired products, are both technical questions to be solved. Before introducing the integrative conversion of CO<sub>2</sub> and biomass, we first compare inorganic catalysts and biocatalysts in electroreduction of CO<sub>2</sub> reaction. After clarifying the difference and relation between abiotic and biocatalysis techniques, the methods and manners to perform integrative reaction for CO<sub>2</sub> and biomass conversion are analysed accordingly. As can be seen from **Table 1**, the CO<sub>2</sub> electrochemical reduction to specific product can be catalysed by both abiotic catalysts, usually inorganic materials, and biocatalysts. The biocatalysts include various enzymes and bacteria. All types of catalyst have similarities such as electroactivity and necessary supporting electrodes, which typically consist of carbon cloth, carbon felt, graphite, etc. But typical working potential and reaction productivity of abiotic catalysts and biocatalysts have obvious discrepancies. The abiotic catalysts need higher overpotential (-0.4 ~ -2.5 V vs. RHE) and present much higher productivity of 10 ~ 1000 g·L<sup>-1</sup>·h<sup>-1</sup>, in comparison to enzymatic or cell-based synthesis (0 ~ -0.6 V vs. RHE and 0.1 ~ 1 g·L<sup>-1</sup>·h<sup>-1</sup>). These differences are because of intrinsic characteristics of each catalyst. The abiotic catalysts are normally inorganic materials which are much stable under harsh conditions including high applied overpotential. While biocatalysts require milder conditions but much lower productivity and high potential usually inhibit cell growth and even lead to cell death.<sup>91</sup> Moreover, cell-based synthesis is capable of producing higher carbon products, such as acetate, ethanol, isobutyric, butyric, caproic acids, etc. The biocatalysis such as enzymatic synthesis has been regarded as comparable to inorganic electrocatalysis. For instance, the [NiFe] center in structure of AvH2ase was anchored at a pyrolytic graphite 'edge' electrode, which can catalyse hydrogen oxidation at similar rates with Pt catalyst but lower poisoning sensitivity to CO.<sup>92</sup> Heller et al. reported that a four-electron ORR biocatalyst was more active than Pt electrode in a biofuel cell working at 0.88 V.<sup>93</sup> MES also has the advantage of production intensity, with maximal butanol production density of 1121 tonnes.<sup>94</sup> However, it is still difficult to reach equivalent reaction rate between electro- and bio- catalysis. Biological synthesis needs larger electrode area and bigger reactor volume to achieve similar production scale<sup>95</sup>.

**Table 1.** Three kinds of catalyst on electrode for CO<sub>2</sub> electro-reduction

Catalyst		Biocatalyst
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	Abiotic catalyst	Enzymes	Bacteria
Examples	M-N-C single atomic catalyst; Sn, In, Bi based oxides or sulfides; etc.	Formate dehydrogenase; CO dehydrogenase; Formaldehyde dehydrogenase; etc.	<i>Sporomusa ovata</i> ; <i>Clostridium acetium</i> ; <i>Clostridium ljungdahlii</i> ; <i>Moorella thermoacetica</i> etc.
Supporting electrode	Carbon cloth, carbon felt, graphite, etc.		
Typical working potential /V vs. RHE	-0.4 ~ -2.5	0 ~ -0.6	-0.1 ~ -0.5
Products	CO, formate, methanol, methane, ethylene, ethanol, acetic acid	CO, formate, etc.	Methane, acetic acid, ethanol, isobutyric, butyric, caproic acids, etc.
Typical productivity / g·L <sup>-1</sup> ·h <sup>-1</sup>	10~1000	0.1~1	0.1~1
Features	High potential and high productivity, simple products	High selectivity, low overpotential	Low overpotential, multi-carbon products

The integrative electrochemical and biological catalysis is easily confused with many concepts, such as bioelectrochemistry, microbial electrosynthesis, electro-fermentation, etc. After surveying the literature, we believe that it is reasonable to divide the coupling system into two modes (**Fig. 2**). In Mode 1, the abiotic and bio- catalysts are designed on one the same electrode, where the biocatalysts are mostly electroactive bacteria or enzymes. The abiotic catalyst is optional and not necessary, although it is highly desired in the concept of integrative electrochemical and biological catalysis in this article. This mode includes all above contents of bioelectrochemistry, microbial electrosynthesis, electro-fermentation.<sup>96,97</sup> It relies on the application of special electroactive bacteria or enzymes on the electrode. In mode 2, the abiotic catalysis and biological catalysis are spatial decoupling in respective reactor. The sequential reactions that happen in the same electrolyzer, based on respective abiotic catalytic and biologically catalytic reactions, can also be regarded in this mode. The characteristics are that the electroactive microorganisms are not necessary and reaction intermediates are always mandatory.



**Fig. 2** The illustration of integrative electrocatalysis and biological synthesis with two modes

### 3. Integrative electrochemical and biological catalysis

#### 3.1 Coupling bio(photo)electro- catalysis

This section introduces above integration Mode I, where electroactive bacteria or enzymes are essential. It includes enzymatic electrocatalysis, whole cell based microbial electrosynthesis and electro-fermentation, as well as photo-electronic induced biosynthesis. The design of abiotic electrocatalyst and electroactive enzymes or bacteria are encouraged to consider and carry out simultaneously. Some exciting results have been achieved, such as the coupling of hydrogen evolution catalyst with electroactive bacteria in MES. However, the research is still relatively young and there is a large room for developing such integrative systems on electrode.

##### 3.1.1 Enzymatic electrocatalysis

Comparatively, enzymatic electrocatalytic synthesis has advantages of super reaction selectivity, good endurance and tolerance of co-solvents, and clearly known reaction mechanism, while whole cell based electrosynthesis does not need costly purified enzymes or necessary exogenous cofactors to facilitate a biological reaction and production.<sup>97</sup> Thus, different reaction activity and characteristics are presented in constructing an integrative catalytic system for enzymatic electrosynthesis and cellular electrosynthesis.

Enzymes are recognized as very active electrocatalysts for redox reactions on electrodes including both anodes and cathodes, which can catalyse electrochemical reactions that are difficult to occur (even with the well-developed abiotic catalysts) and need a high applied potential to reach a feasible reaction rate.<sup>98</sup> Bioinspired redox catalysts could provide a condition to lower activation energies, accelerate electron and proton transfers, adjust the formation and stability of important intermediates, and regulate redox thermodynamics. Therefore, the enzymatic redox

electrocatalysis has always been an active area with potential application in fuel cells, sensors and synthesis based on interface electrochemical reaction.

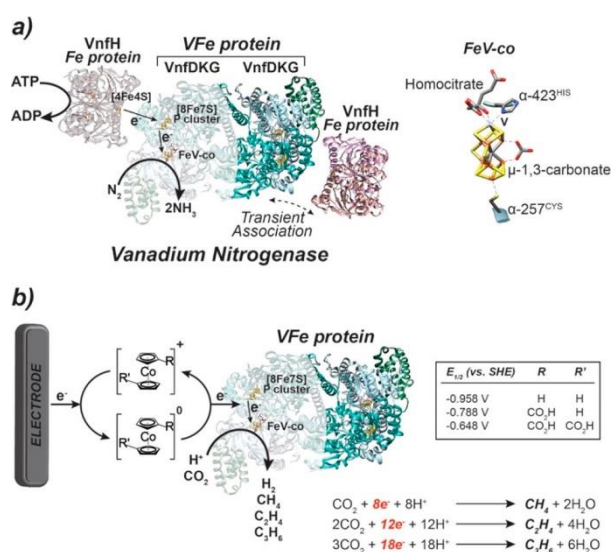
However, due to the stereoscopic macromolecular structure, the deposited enzyme on electrodes brings the first intractable electron transfer issue between them. Generally, two pathways of electron transfer play important roles, one is direct electron transfer (DET) and the other is mediated electron transfer (MET). DET route is more attractive due to the simple system configuration and operation. Kenji Kano observed the DET on D-Fructose dehydrogenase (FDH). The catalytic oxidation peak of D-fructose was observed on the FDH decorated electrode without electrons' mediators in the enzyme kinetic study, even the current density is as high as  $10 \text{ mA cm}^{-2}$ . The heme c site in the enzymes was supposed to be mediator for direct electron transfer from FDH to electrode. The dynamic delivery of D-fructose to Ketjen black-modified anodes was totally unobstructed.<sup>99</sup> Besides, many other redox enzymes, such as hydrogenases,<sup>100, 101</sup> CO Dehydrogenase, have also been proven to have the ability to exchange electron with electrode.<sup>102</sup> It has been recognized that the heterogeneous electron transfer lead to an optimal space between a cofactor (electron donor) and an electrode (electron acceptor) to achieve a fast transfer rate, which should be less than  $2 \text{ nm}$  ( $20 \text{ \AA}$ ).<sup>103</sup> Carole Baffert et al used peptidic coupling to construct covalent bonding between FeFe hydrogenases and carbon electrodes, which realized DET<sup>104</sup>. The surface patch of lysine residues efficiently favours fast and direct electron transfer, not affecting the enzyme activity. The lysine amino acid residues could also provide covalent attachment of enzymes on electrode and play the role, including immobilized proteins molecules via lysine group or anthracene decorated electrode to enhance enzymes' DET.<sup>105</sup>

Fast electron transfer has significant impact on reaction rate. In addition, the electrode applied potential decides the energy efficiency of the system. Lower overpotential means less electric energy input and high efficiency. The enzymatic electrolysis exhibits overall lower overpotential than abiotic electrocatalytic reaction. For example, the formate dehydrogenase can reduce  $\text{CO}_2$  into formic acid at cathodic potential of  $-0.8 \text{ V vs. Ag/AgCl}$  ( $-0.19 \text{ V vs. RHE}$ ),<sup>106</sup> which is near to the theoretical potential for electrocatalytic reduction of  $\text{CO}_2$  to formic acid ( $-0.20 \text{ V vs. RHE}$ ).<sup>56</sup> The enzymatic catalysed fast interconversions on electrode between  $\text{CO}_2$  and its reduced counterpart, such as CO or formate, are quick indicators of low reaction overpotential. Armstrong reported that Ch Ni-CODH immobilized on a graphite electrode showed super electrocatalytic performance for CO oxidation and  $\text{CO}_2$  reduction simultaneously, realizing fast and effective electrochemical  $\text{CO}_2/\text{CO}$  mutual transformation by above CO dehydrogenase, which proved the theoretical  $\text{C}_1$  gas bioelectrochemical use with low overpotential.<sup>107</sup> Moreover, mutual transformation of formate and  $\text{CO}_2$  was also

discovered.<sup>108</sup> A redox polymer containing cobaltocene can help to immobilize Mo-FDH on carbonaceous electrode surface. At the same time, it could also enhance electron transfer to Mo-FDH at a low potential.<sup>109</sup> CO<sub>2</sub> could be reduced on this bioelectrode to produce formate at a moderate cathodic voltage of 0.66 V vs. SHE (~ -0.25 V vs. RHE). A high Faradaic efficiency of 99% was obtained.

As stated above, the supporting electrode for enzymes is normally inert material, such as graphite, the study on combination of a chemical catalyst with enzymes to exert a synergistic action is rare. Recently, Zhang and Ji realized the electroenzymatic reduction of CO<sub>2</sub> to methanol and reach 0.742 mM production. The multiple enzymes were in-situ encapsulated into ZIF-8, a kind of metal-organic framework, which played a key role and showed obvious superiority to free enzymes. The final methanol production rate reached 822 μmol g<sup>-1</sup> h<sup>-1</sup>.<sup>110</sup> The gas diffusion electrodes (GDE) are widely used in proton-exchanged membrane fuel cell<sup>111</sup> and electrochemical reduction reaction of CO<sub>2</sub>,<sup>112</sup> which can eliminate the limitation of CO<sub>2</sub> dissolution in electrolyte<sup>113</sup>. Inspired by GDE configuration, a W-containing formate dehydrogenase, which was derived from *Desulfovibrio vulgaris* Hildenborough, was wired in a low-potential organic polymer, showing an experimental potential of about -0.39 V vs. SHE. The electrodes exhibited excellent stability that enabled long-time operation of electrocatalytic formation of formate from CO<sub>2</sub>.<sup>114</sup>

The electrochemical reduction of CO<sub>2</sub> to C<sub>2+</sub> products like hydrocarbons by electro-enzymes is of great interest. However, to synthesize hydrocarbons by CO<sub>2</sub> is much challenging which needs multiple hydrogenation steps, electron transfers and C-C coupling reactions. Cai et al constructed a bioelectrocatalytic process by vanadium nitrogenase from *Azotobacter vinelandii*, which realized CO<sub>2</sub> electroreduction to multi-carbon products, such as ethylene (C<sub>2</sub>H<sub>4</sub>) and propene (C<sub>3</sub>H<sub>6</sub>) (Fig. 3). The bioelectrochemical system was independent of ATP-hydrolysis and the electrons can be transferred by some cobaltocenium derivatives.<sup>115</sup>



**Fig. 3.** (a) Crystal structure of vanadium nitrogenase and FeV-co from *Azotobacter vinelandii*. (b) Bioelectrocatalytic turnover of VFe nitrogenase mediated by derivatives of cobaltocene/cobaltocenium. Reproduced with permission.<sup>115</sup> Copyright 2018, American Chemical Society.

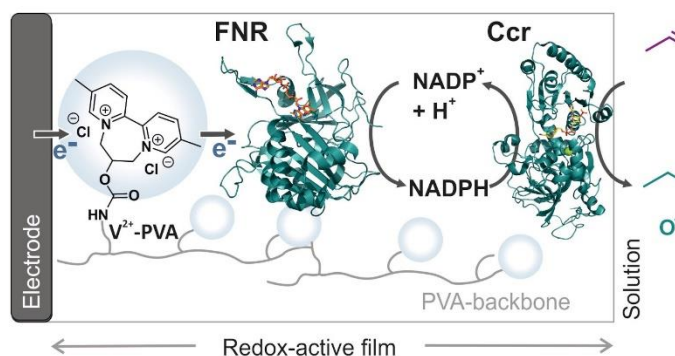
In general, the electrochemical reactions are redox reactions involving electronic gain and loss (transfer) among reactant, electrode and various reaction intermediates. Coincidentally, the oxidoreductases are the most important and extensively studied enzymes. To implement their inherent catalytic function, these oxidoreductases generally need the assistance of additional coenzymes or cofactors. Among many cofactors, NADH is the most important because about 80% of oxidoreductases need NADH. They attach to the enzymes and join in various redox reactions concerning electrons (e<sup>-</sup>) and protons (H<sup>+</sup>) transfer with outside. However, the fast and efficient regeneration of NADH is necessary due to its instable and expensive characteristics. The regeneration of NADH has various methods, such as chemical, electrochemical, photochemical and enzymatic method, etc. This has been an issue of widespread concern and a lot of excellent reviews and articles have summarized the study and progress on the topic.<sup>116-118</sup> Electrochemical approach to regenerate NADH is more welcome because it can be easily controlled and achieve high efficiency by regulating the potential precisely. This was also well reviewed recently.<sup>119</sup> Besides electrified cathode acts as electron donor, photogenerated electrons can also implement the regeneration of NADH effectively. It provides the chance of combining photoelectrocatalyst and active enzymes. Furfural (FAL) is a widely available biomass platform compound. The hydrogenation of FAL to value-added furfuryl alcohol (FOL) was realized by hybrid enzymatic catalysis by using a photoelectric material and an alcohol dehydrogenase (ADH), driven by visible light (Fig. 4). The QDs/g-C<sub>3</sub>N<sub>4</sub> nanosheet as photocatalyst produces an NADH yield of 95.7% in equilibrium.<sup>120</sup> It should be kept in mind that the photochemical regeneration of NADH is essentially regenerating NADH by photogenerated electrons. Thus, appropriate electron potential is crucial to efficient reduction of NADH (-315 mV vs. NHE).



**Fig. 4.** Photobiocatalytic hydrogenation of FAL into FOL. Reproduced with permission.<sup>120</sup> Copyright 2020, American Chemical Society.

As mentioned above, the multi-carbon products from CO<sub>2</sub> are always interesting. Besides direct C-C bond coupling synthesis, the addition of CO<sub>2</sub> into organic molecules through carboxylation

reaction is also attractive. a ferredoxin NADP<sup>+</sup> reductase and crotonyl-CoA carboxylase/reductase was co-immobilized on a processed hydrogel. Thus, the NADPH can be recycled to synthesize (2S)-ethylmalonyl-CoA stereo-selectively (Fig. 5). Faradaic efficiency reached 92.6% at a productivity of 1.6  $\mu\text{mol cm}^{-2} \text{h}^{-1}$ .<sup>121</sup>



**Fig. 5.** Bioelectrocatalytic C@C bond formation by reductive carboxylation. Reproduced with permission.<sup>121</sup> Copyright 2021, Wiley.

Thus, the enzyme based bioelectrocatalytic systems are efficient in converting CO<sub>2</sub> or biomass materials. However, the combination of abiotic catalyst with the system is extremely rare. The photocatalyst incorporation is a specific example and needs deep exploration. Overall, the enzymatic electrocatalysis mostly suffers from rather low productivity level ( $\sim \mu\text{mol h}^{-1} \text{cm}^{-2}$ ). The integration of enzymatic electrocatalysis with abiotic electrocatalysis is challenging but brings opportunity to improve enzymatic electrocatalytic synthesis from CO<sub>2</sub> and biomass.

### 3.1.2 Microbial electrosynthesis

The microbial electrosynthesis (MES) based on BESs generally refers to the electroreduction of CO<sub>2</sub> to organic products, such as acetate and ethanol, on a biocathode by using electroactive strains. This concept has been well introduced by Rabaey and Rozendal<sup>94, 122</sup> and experimentally demonstrated by Nevin and Lovley at 2010.<sup>123</sup> Then it became a hot area and was intensively studied over the past decade. As stated above, the whole cell synthesis has cost-effective and robust attributes compared to enzymes.<sup>97</sup> For the moment, the endeavour to improve MES efficiency and product yield can be understood from three aspects, namely microorganism optimization, electrode material modification, and abiotic electrocatalyst integration (regulate MES by generating intermediates). Therefore, it has a close relation with integrative design of electro- and biocatalysis.

Firstly, pure and mixed bacteria are both studied in MES. *Sporomusa ovata* is the most widely adopted species.<sup>123</sup> It can intake

electrons from electrode and CO<sub>2</sub> gas dissolved in culture medium to synthesize acetate efficiently.<sup>124</sup> Comparative study on mixed and pure strains for CO<sub>2</sub> reduction was carried out by Bajracharya et al and the results showed that the mixed strains could produce acetate at productivity of 1.3 mM d<sup>-1</sup>, with small amount of CH<sub>4</sub> and H<sub>2</sub> when operating at -1.1 V vs. Ag/AgCl. The *Clostridium ljungdahlii* strain produced 2.4 mM d<sup>-1</sup> of acetate yield at -0.9 V vs. Ag/AgCl, showing notable superiority.<sup>125</sup> The *C. ljungdahlii* also exhibited long-term operation stability. Biomass growth and product accumulation for CO<sub>2</sub> electro-reduction has been completed with a highest acetate producing rate of 400 mg L<sup>-1</sup> catholyte d<sup>-1</sup> at -1.0 V (vs. Ag/AgCl) in more than 300 days.<sup>126</sup>

Undoubtedly, enhancing extracellular electron transfer among electrodes and various cultures is an important criterion to improve efficiency, which needs to carefully disclose the heterogeneous electron transfer mechanisms.<sup>127, 128</sup> Uptaking electrons to the cell seems to be limited by the microorganisms themselves.<sup>22</sup> Even the mechanism that conducts electron transfer in transmembrane, such as c-type cytochromes, microbial nanowires,<sup>129</sup> membrane attached Fe-S proteins, oxidoreductase and periplasmic enzymes for gram-positive bacteria,<sup>96</sup> the improvement of intrinsic electron transfer rate is a subject of much discussion.<sup>130</sup> Currently, a lack of mechanistic understanding and intrinsic improvement in the means of extracellular electron transfer limits the development of MES into an industrial bioproduction process.<sup>129</sup>

Secondly, the electrode is the carrier and supporter of electroactive bacteria. It also has attributes of conductivity and even abiotic catalytic activity. Therefore, the material composition, structure, and modification of (bio)cathode play important role in enhancing MES productivity. Jourdin et al used a kind of highly free reticulated vitreous carbon (RVC) electrodes with 0.6 mm diameter of macropores and got a highly available surface area for biofilm attachment and fast mass transfer among the electrolyte, the electrode and microbial surface simultaneously. The acetate was produced with a productivity of 1330 g m<sup>-2</sup> day<sup>-1</sup> at -1.1 V vs. SHE, with a current density of 200 A m<sup>-2</sup>.<sup>131</sup> Including this RVC and another EPD-3D (electrophoretic deposition of CNTs), they have summarized their research on purposely designed electrode materials for improving MES in a review article.<sup>132</sup> Lovley developed several strategies to modify cathode materials and improve MES, including grafted by chitosan and cyanuric chloride, modification with 3-aminopropyltriethoxysilane, treating carbon cloth with gold, palladium, or nickel nanoparticles. By these manners, the acetate production rates was increased by 3-7 fold than untreated cathode.<sup>133</sup> Sharma et al. elaborated the material properties to be used as ideal electrode designing in MES and proposed an activated carbon-based VITO CORE<sup>®</sup> electrode to be with such properties<sup>134</sup>.



Thirdly, the mediator in the electrolyte can help to enhance electron transfer dramatically. Besides the artificially added or self-secreted mediators,<sup>135-137</sup> the in-situ generated intermediates are more interesting to strengthen electron and mass transfer thus to improve MES, for example, H<sub>2</sub> or formate species. This is principally feasible, particularly having been verified by the enhancement of H<sub>2</sub> mediated MES.<sup>138</sup> Another example is hydrogenases and formate dehydrogenases released by methanogens and acetogens and in-situ deposited on electrode could produce hydrogen and formate when potential of only -0.6 V is exerted, explaining the fast electron uptaking rate in the absence of direct transfer in the MES system.<sup>139</sup>

The idea of integrated electrochemical system by inorganic and bio-catalysts (mixed bacteria system) has been elucidated, which is actually designing abiotic catalysts on electrode to purposely produce intermediates, such as CO, HCOO<sup>-</sup> and H<sub>2</sub>, to increase extracellular electron transfer and CO<sub>2</sub> uptake rate (Fig. 6).<sup>140</sup> Firstly, CO and HCOO<sup>-</sup> can be ingested into some microorganisms' cell as carbon resource, making multi carbon sources. The assumption is technically feasible, because formate has been demonstrated to be a more effective source of the methyl group than CO<sub>2</sub> in synthesis of acetate by *Clostridium thermoaceticum*.<sup>141</sup> The synthesis of acetate and ethanol by CO/H<sub>2</sub> gas fermentation is also feasible, even mature.<sup>142-144</sup> Secondly, HCOO<sup>-</sup> and H<sub>2</sub> can carry electrons through reversible redox reactions, intensifying the indirect electron transfer.<sup>145, 146</sup> Some abiotic H<sub>2</sub> evolution catalysts were also found to enhance MES by in-situ H<sub>2</sub> production experimentally.<sup>147, 148</sup>

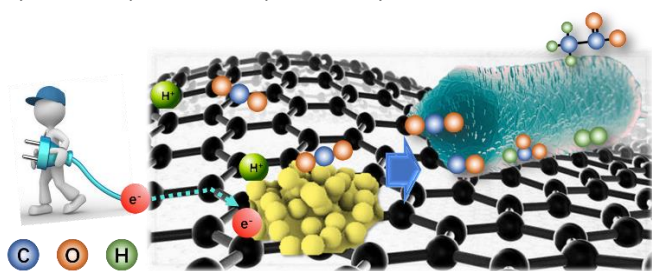
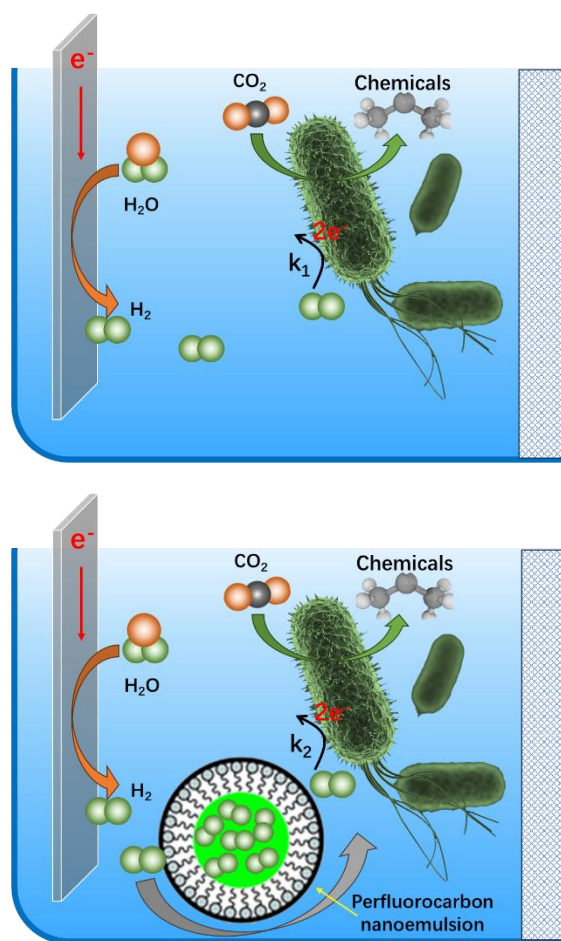


Fig. 6. Scheme of chemical-bio-catalyst integration for CO<sub>2</sub>RR on electrode. Redrawn with permission.<sup>140</sup> Copyright 2019, Wiley.

H<sub>2</sub> has a limited dissolution in aqueous solution. To solve this problem, a biocompatible perfluorocarbon (PFC) nanoemulsion was designed to be a H<sub>2</sub> carrier to improve the MES performance. H<sub>2</sub> was in-situ produced on a stainless-steel electrode decorated with Co-P alloy catalyst. The results showed that an 6.4 g L<sup>-1</sup> of acetate titre with productivity of 1.6 g L<sup>-1</sup> day<sup>-1</sup> and 100% Faradaic efficiency was achieved by using the acetogen *S. ovata* system.<sup>149</sup> As shown in the Fig. 7, Scenario 1, H<sub>2</sub> gas generated by traditional electrochemical catalysts, playing the role of reducing equivalent to microbes, has limited solubility in water ([H<sub>2</sub>]<sub>1</sub>). The limited mass transfer of H<sub>2</sub> from the electrode to microbial cells restrains the rate of CO<sub>2</sub> fixation and acetate productivity. In scenario 2, PFC nanoemulsions was applied as the H<sub>2</sub> carrier to increase the transfer of reductant. Thus, the H<sub>2</sub> concentration ([H<sub>2</sub>]<sub>2</sub>) was increased, together with the improvement

of migration rate ( $k_2$ ). The CO<sub>2</sub> reduction rate was increased dramatically up to 190%.



**Two factors:  $[H_2]_1 < [H_2]_2$ ;  $k_1 < k_2$**

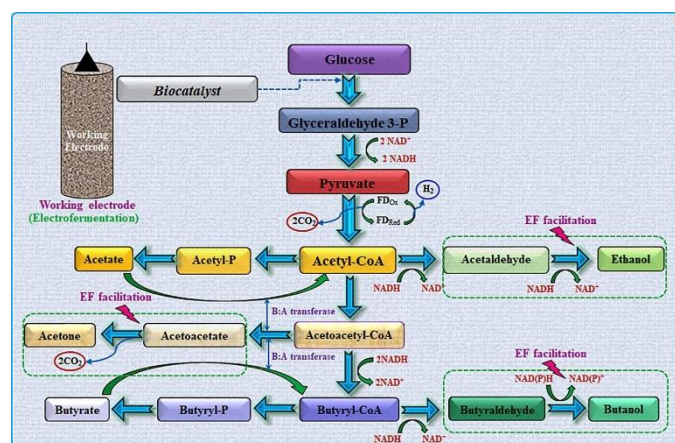
Fig. 7. Schematic of perfluorocarbon nanoemulsion enhancing H<sub>2</sub> transfer and CO<sub>2</sub> reduction rate. Redrawn with permission.<sup>149</sup> Copyright 2019, Springer Nature.

Acetate is the most reported primary products in MES, other products with less selectivity and productivity include methane,<sup>150</sup> ethanol,<sup>151</sup> butyrate,<sup>152</sup> 2-oxobutyrate,<sup>153</sup> and even poly-b-hydroxybutyrate by a H<sub>2</sub> evolution catalyst coupling a H<sub>2</sub> oxidizing autotroph, *Cupriavidus necator* H16.<sup>154</sup> The synthesis of higher carbon products involves multi-electrons transfer, which address the synergistic interaction between energy and electron transport, such as NAD(P)<sup>+</sup>/NAD(P)H, FAD<sup>+</sup>/FADH<sub>2</sub>, Cytochromes C<sup>(ox/ed)</sup>, Ubiquinone/Ubiquinol, and so on. Krömer et al summarized progress of electron transfer and proposed a mechanical method to estimate the effect of different transfer manners on the energy metabolism, which will benefit to understand and optimize BESS.<sup>135</sup> Additionally, deep participation of electrode abiotic catalyst into the extracellular electron transfer is encouraged to consider simultaneously.

### 3.1.3 Electro-fermentation

The traditional fermentation refers to the chemical breakdown of a substance (mostly organics) by bacteria, yeasts, or other microorganisms with or without oxygen. Glycolysis is a common stage that all organisms must go through for glucose catabolism. The whole reaction process of glycolysis is carried out in the cytoplasm. Like MES process, electro-fermentation (EF) is also whole cell-based reaction on electrode. If the MES can be regarded for CO<sub>2</sub> electroreduction, EF technology can be deemed for biomass derived feedstocks conversion. Although this is not a strict definition and assignment. The concept of MES has not been unified into a consensus. Harnisch et al have presented a concise overview on technical and economic evaluation of electro-biosynthesis.<sup>39</sup> Taking an example of sucrose fermentation to produce lysine and considering electricity prices, a market potential was demonstrated as cost savings could be anticipated with necessary high yields.<sup>155</sup> Therefore, electro-fermentation is quite applicative and important for biomass materials conversion. The typical biomass derived feedstocks include glucose from starch, glycerol from biodiesel or oils and fats industry, even more common lignocellulose. The EF conversion of glucose is introduced firstly.

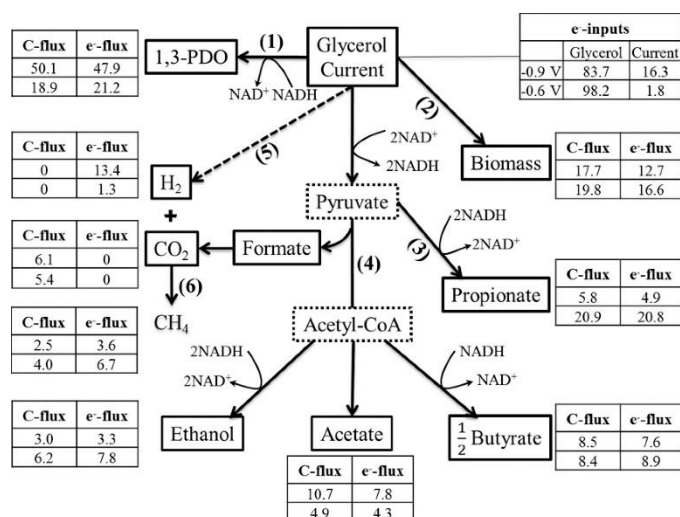
Bioelectrochemical system provide the chance of direct electron flow enter or exit the electroactive cells. Thus, the metabolism in the biosynthesis may be regulated and facilitated<sup>156</sup>. In a study of EF of glucose without mediators by *C. acetobutylicum*, the solvent yield could be increased in the batch fermentation when using a poised electrode. The titre of acetone-butanol-ethanol production was increased from 0.141 g/L to 0.202 g/L. The improvement was ascribed to the enhanced rate of butyrate consumption induced under the specific fermentation conditions, which could increase butanol and acetone yield through EF facilitation as illustrated in Fig. 8<sup>157</sup>.



**Fig. 8.** The metabolism pathways in electro-fermentation of glucose. Reproduced with permission.<sup>156</sup> Copyright 2021, Elsevier.

Carboxylic acid product is more common in fermentation bioproduction. Kondo studied lactate production from glucose electro-fermentation by using *Corynebacterium glutamicum*. The lactate yield of around 1.62 at potential of -0.6 V (vs. Ag/AgCl) was higher than that in control experiment (1.10 without potential) by a bioelectrochemical method. The anthraquinone 2,6-disulfonate (AQDs) was used as electron mediator to control potential, showing that reduction of applied potential is useful to facilitate lactate yield.<sup>82</sup> Under two mixed microbial cultures, glucose conversion to butyric acid was improved with electro-fermentation and redox mediators.<sup>83</sup> Without these mediators (Neutral Red or AQDS), the increase of butyric acid yield was mainly ascribed to those simultaneous fermentation products, such as acetic acid, ethanol, under EF condition at -700 mV vs. SHE. Plant derived lipids by fermentation attracts researcher's interests. The oleaginous yeast *Rhodospiridium toruloides* demonstrated ability to lipid production with electro-fermentation in a broad potential. The cathodic EF (CEF) and anodic EF (AEF) were both constructed and studied. They both have positive effects on lipid yield, which increased from 37% to 50% in the ratio facilitated by Neutral Red mediator.<sup>86</sup>

The biodiesel industry flourish in the past years where glycerol is produced as a by-product with 10% biodiesel yield. A large-scale renewable glycerol stimulates people to develop technology for upgrading to other value-added products. Keller et al studied a mixed culture for glycerol fermentation on the electrode with current as additional driving force. A titration and off-gas analysis (TOGA) sensor was applied for research carbon and electron flows for glycerol metabolism in the reaction.<sup>158</sup> As shown in Fig. 9, four main metabolic routes were determined: (1) production of 1,3-PDO by glycerol hydrogenation; (2) biomass generation; (3) redox neutral and ATP favourable for propionate fermentation from glycerol; (4) Pyruvate decarboxylation to acetyl coenzyme A, followed by acetic acid, ethanol and butyric acid metabolism. It deserves to notice that the electrochemical H<sub>2</sub> evolution (route 5) play important role, particularly in formic acid formation at -0.9 V. Additionally, formic acid can act as the electron shuttle between interspecies in these glycerol-fed BESs, since the standard electrode potentials of H<sub>2</sub>/H<sup>+</sup> and formate/CO<sub>2</sub> are close to each other (-0.414 V vs. -0.432 V). This discovery is quite consistent with above discussion in mediated MES process. Particularly, two sources of hydrogen are found as current, namely electrochemical hydrogen production (route 4) and fermentative hydrogen production (route 5), illustrating the superiority of integrative abiotic and biocatalysis.



**Fig. 9.** Carbon and electron flux tree in glycerol electro-fermentation. Reproduced with permission.<sup>158</sup> Copyright 2021, American Chemical Society.

Gescher and co-workers performed glycerol fermentation in BESs by using *Escherichia coli* and observed the heterologous electron transfer pathway and their interaction with electrode. The new electronic transmission chain impels *E. coli* reprogram from glycerol fermentation. The redox dye, methylene blue, also enhanced electron transfer to carbon electrode.<sup>81</sup>

Besides glucose easily digested by bacteria, lignocellulosic materials are more widely available and meaningful for conversion. Reguera et al. studied lignocellulosic substrates into ethanol using bacterium *Cellulomonas uda* on anodic electro-fermentation. Strain GR52 played the role of integrating oxidation of lactate to the electrode reduction at +240 mV vs. Ag/AgCl in the reactor. EF process is supposed to greatly enhance the microbial ability to their original metabolic capability towards industrial fermentation.<sup>159</sup>

To sum up, these EF examples exhibit the advantages in enhancing and regulating traditional fermentation process. Returning to our topic in this article, the existence of abiotic catalysis is unknown due to the lack of study and discussion in these systems, such as oxidation or reduction of fermentation intermediates. The use of inert conductive electrode (carbon or graphite) also does not support the occurrence of abiotic catalytic reaction. However, the abiotic electrocatalytic oxidation or hydrogenation reaction on electrode is expectable because of the diverse metabolites. The key issues include polarized potential matching, electrocatalyst poisoning, product selectivity control, and so on. More investigation and purposely designed experiments are urgently needed in future.

### 3.1.4 Abiotic photoactive materials coupling biocatalyst

Photo-electro-bio techniques together have been recognized as efficient pathways for converting renewable energy to chemicals, which are widely applied for CO<sub>2</sub> conversion.<sup>54,160</sup> Although they are not typical concept of electrocatalyst coupling biocatalyst, photogenerated electron transfer from semiconductor nanoparticles

to microbial cells or active enzymes is also key factors to influence system's efficiency.<sup>161</sup> This is homologous to electrode as electron donor in two aspects.

First, the semiconductor materials can integrate with both enzymes and cells, respectively.<sup>70</sup> Hydrogenase-CdTe nanocrystal hybrids have been controllably assembled and used for solar hydrogen production, which was studied earlier by Brown et al.<sup>162,163</sup> The photogenerated electrons can straight transfer to H<sub>2</sub>ase enzyme from nanocatalyst surface, providing more chance to integrate them. Armstrong et al firstly reported the photocatalytic reduction of CO<sub>2</sub> to CO by an enzyme and TiO<sub>2</sub> nanoparticle composite. The thermodynamically favourable two-electron pathway was found by using visible light.<sup>164</sup> Later, they also tried ZnO, SrTiO<sub>3</sub> semiconductors and propose a strategy of using 'linking' molecules (polymyxin B sulfate, glutamic acid), which created a tight binding between TiO<sub>2</sub> surface and D-cluster of CODH, enhancing their electron transfer each to other and thus improving the coupling system's activity.<sup>165</sup>

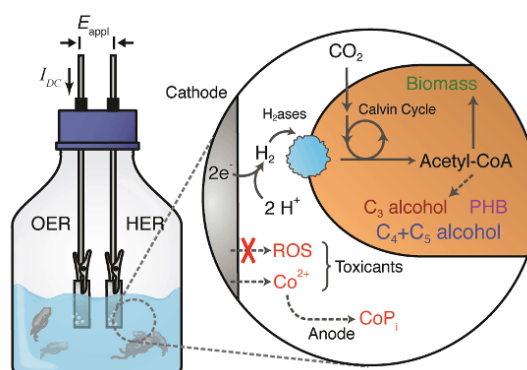
Yang and co-workers have done many pioneering and excellent works in this type of artificial photosynthesis, particularly on the hybrids of inorganic semiconductors with microbial cells. A light-absorbing Si nanowire arrays - bacteria (*S. ovata*) hybrid was constructed for unassisted solar CO<sub>2</sub> fixation to useful chemicals or fuels, such as n-butanol, poly hydroxy butyrate (PHB), and isoprene-like products.<sup>166</sup> Then they combined another inorganic semiconductors (CdS) for light harvesting with high specificity and low cost biocatalyst, a microorganism insensitive to light, *Moorella thermoacetica*. Its self-photosensitization with attached CdS nanocrystals realized efficient photocatalytic reduction of CO<sub>2</sub> to acetic acid.<sup>167</sup> The photosensitized nanoparticles have a closer contact with the cells, enabling more efficient electron transfer than Si nanowire arrays. A cost-effective photocatalyst sheet also demonstrated the same function for CO<sub>2</sub> reduction to acetic acid by acetogenic culture, *S. ovata*, with 0.7% of solar energy utilization efficiency.<sup>168</sup>

The similar system could be expanded to variable combinations. Guo and Joshi developed a hybrid platform including a photocatalyst InP and genetically modified *Saccharomyces cerevisiae*, a leading bacterium. Differently, the InP produced photoelectrons to regenerate cofactors for relating to oxidation-reduction. The separation of biosynthesis and cofactor regeneration steps promoted the carbon neutralization and energy-saving production of shikimic acid.<sup>169</sup> Furthermore, an integrated system composed of CO<sub>2</sub>- and N<sub>2</sub>- fixing bacterium *Xanthobacter autotrophicus* and light-harvesting CdTe quantum dots exhibited ability to fix CO<sub>2</sub> and N<sub>2</sub> simultaneously, with quantum efficiencies of 47.2% and 7.1%, respectively. The charge-transfer kinetics were accelerated when interfacing microbe to semiconductor nanoparticles.<sup>170</sup>

Second, similar intermediates mediated biosynthesis also plays important role in the hybrid system. In Yang's research mentioned

above on *M. thermoacetica* and cadmium sulfide hybrid system, two feasible ways contribute to redox equivalents ([H]) yielding, namely, in vitro and direct electron transport into the cell. The [H] is delivered and joined Wood-Ljungdahl metabolic pathway to convert CO<sub>2</sub> to acetate.<sup>167</sup> The H<sub>2</sub> intermediate deduced synthesis was also disclosed by conventional spectroscopic method. The study from Yang and co-workers showed that electron transport to H<sub>2</sub>ase can generate H<sub>2</sub> as a transfer mediator. The high quantum efficiency and a long-time scales (24 h) ensure acetic acid production by a direct energy-transducing enzymatic pathway at a short time scale (3 h). A high concentration of extra(intra)cellular H<sub>2</sub> accumulates in hybrid inorganic-biological organisms and facilitates high photosynthetic rates in this solar-to-chemical system.<sup>171</sup> The results definitely demonstrate the useful H<sub>2</sub> mediation in photo-electrocatalytic conversion.

Yang and Changa applied  $\alpha$ -nickel sulfide as a HERcatalyst, which is earth-abundant and highly biocompatible, to couple a biocatalyst *Methanosarcina barkeri* for CO<sub>2</sub> reduction to CH<sub>4</sub>. Faradaic efficiency of product was achieved as high as 86% in 7 days.<sup>69</sup> In this integrated system, the H<sub>2</sub> production and microbial CO<sub>2</sub> reduction is carried out separately, but they happened at the same cathodic compartment of electrolytic cell. The planktonic biological fermentation has advantages than biofilm on electrode growth in three-dimensional space. There is another interesting example using H<sub>2</sub> as energy intermediate. In the same reactor, H<sub>2</sub> is oxidized by hydrogenases and powers *R. eutropha* to absorb CO<sub>2</sub> through Calvin-Benson-Basham cycle to secrete various organic chemicals, such as C<sub>3</sub>~C<sub>5</sub> alcohols, PHB, etc (Fig. 10). In this integrative abiotic catalytic water splitting and biocatalytic carbon fixing system, water is split by Co-P alloy catalysts into molecular H<sub>2</sub> through hydrogen evolution reaction (HER) at relatively low voltages. Then CO<sub>2</sub> of low concentration is converted to chemicals and fuels by *R. eutropha* with above H<sub>2</sub> as reducing equivalent. It should be noted that the presence of O<sub>2</sub> produced by oxygen evolution reaction (OER) in water splitting has no obvious negative effects on the biosynthesis. An energy efficiency of ~50% and energy consumption of 180 grams of CO<sub>2</sub> per kW of electricity were achieved at last. The overall energy efficiency of ~10%, surpassing natural photosynthesis, is expected when connecting to an existing photovoltaic system.<sup>172</sup>



**Fig. 10** Schematic illustration of integrative CO<sub>2</sub> fixation with in-situ water splitting produced H<sub>2</sub> by *R. eutropha* BESs. Reproduced with permission.<sup>172</sup> Copyright 2021, Science AAAS.

Charge transfer between inorganic materials and biological systems is one of the eternal topics. Mediated and un-mediated electron transfer are two common pathways. From traditional conductive electrode to semiconductors, the electron-transfer mechanism is highly desired to be discovered. The rich porous structure provide additional choice due to its diversity and convenience, especially for eukaryotes with irreversible application at present<sup>136</sup>. Along with important biocompatibility nanomaterials with cells, the size matching between them is also a crucial factor. This can be concluded from promotional effect of gold nanoclusters (~2 nm),<sup>173</sup> core-shell quantum dot (2~4 nm),<sup>174</sup> Si nanowires (~1  $\mu$ m),<sup>175</sup> CdS (5~10 nm),<sup>176</sup> which ensure the energy harvesting efficiency and competitiveness with natural photosynthesis.<sup>177</sup>

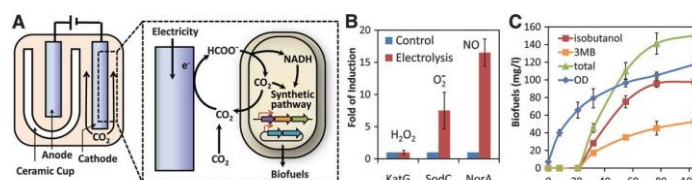
### 3.2 Spatial decoupling electro- and bio- catalysis: free combination

The concept of electrobiorefinery stresses the alliance of electro- and bio- catalysis. Integrating microbial and electrochemical conversions allows developing and exploitation of new technologies for the storage of electricity to sustainable chemicals<sup>39</sup>. Sequential or tandem electro- and bio- catalysis in respective reactor can avoid mutual restriction of reaction rate and reaction conditions, as well as retain respective advantages of electro- and bio- catalytic reactions. It overcomes the shortage of limited number of electroactive organisms. The tandem reactions have been well studied in organic synthesis with tighter domino or cascade reaction modes even in one-pot.<sup>178</sup> This arouses researchers to develop sequential coupling electro- and bio- catalytic reactions to seek higher reaction rate and energy efficiency, as well as products' level and values. As a future trend, people began to understand a spatial decoupling strategy is an effective solution mismatch between the electrochemical and biological components in classical bioelectrochemical CO<sub>2</sub> fixation.<sup>179</sup> A widely reported approach is to use the product of electroreduction of CO<sub>2</sub> as substrate that is further converted to chemicals by microbial fermentation. The most used intermediate

products include formate, CO (or syngas) and acetate, etc. Conversely, the electrochemical conversion of biosynthetic intermediate products from CO<sub>2</sub> or biomass is also surely feasible.

### 3.2.1 Formate mediated coupling synthesis

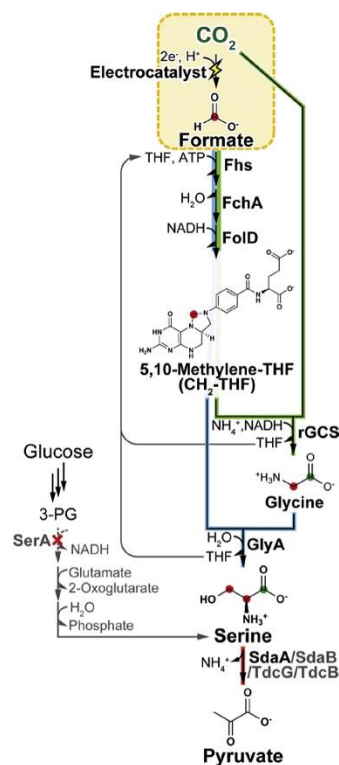
Firstly, methylotrophic microorganisms can consume methane, methanol, formate and other methylated substrates as unique sources of carbon and energy, which provide the foundation of formate mediated coupling reaction.<sup>180</sup> James provides the first integrative electrocatalysis and bio-catalysis system to convert CO<sub>2</sub> to higher alcohols<sup>91</sup>. Formic acid was used as energy carrier and intermediate which can be produced by abiotic electroreduction of CO<sub>2</sub> efficiently. At the same time, *R. eutropha* H16 (now known as *Cupriavidus necator*) was used as the cell factory while isobutanol and 3-methyl-1-butanol (3MB) were produced as the target products. First, In and Pt metal were used as cathode and anode respectively, which were inserted into the nutrient solution saturated with CO<sub>2</sub>, to produce formate (Fig. 11, A). The *Ralstonia* stopped growth if electric current passed, but cell growth resumed when the current removed. They also disclosed some mechanisms that in plasmid under electrolysis, *sodC* and *norA* promoters rather than *katG* promoter induced the expression of *β*-galactosidase (Fig. 11, B). Furthermore, a porous ceramic was used to cover the anode, a toxicity problem, namely the stress response and inhibited growth in *Ralstonia* cells triggered by O<sub>2</sub><sup>-</sup> and NO, was circumvented (Fig. 11, A). Thus, the well work of *Ralstonia* bacterium brings a yield of over 140 mg/L biofuels, by a integrative system for electroreduction of CO<sub>2</sub> (Fig. 11, C).



**Fig. 11.** An integrated electrocatalytic and biological reduction of CO<sub>2</sub> to alcohols. (A) tandem production of electroreduction of CO<sub>2</sub> to formate and biocatalytic conversion of formate to isobutanol and 3MB by the engineered *R. eutropha*. (B) a reporter gene driven by promoters that respond to reactive oxygen and nitrogen species. (C) Engineered *R. eutropha* LH74D exhibited good growth and biofuels production in an integrated process. Reproduced with permission.<sup>91</sup> Copyright 2012, Science AAAS.

Using formate as an intermediate, Kondo realized a coupling system of electrocatalysis and biological catalysis to reduce CO<sub>2</sub> to pyruvate by using a general and friendly organism, *E. coli*.<sup>181</sup> On the whole, two formate and one CO<sub>2</sub> molecules are converted into one pyruvate molecular following glycine and L-serine pathways. In details (Fig. 12), CO<sub>2</sub> was firstly converted to formate catalysed by an indium sheet at -1.2 ~ -2.0 V (vs. Ag/AgCl). Formate is then assimilated by reductive glycine pathway, which is comprised of 3 modules to synthesize pyruvate at last. (1) Formate and CO<sub>2</sub> combine through a reversal of glycine cleavage system to produce glycine. (2)

Formate is converted to CH<sub>2</sub>-THF through Wood-Ljungdahl pathway and binds with glycine produced in module 1 by the Serine-Glycine cycle enzyme GlyA to synthesize L-serine. (3) At last, deamination of serine to pyruvate happens irreversibly. This work demonstrated that integrated electro-biological catalytic process in *E. coli* can fix carbon and involving the electro-products into core metabolism, suggesting the great potential of coupling catalysis for utilization of renewable electricity and CO<sub>2</sub>/biomass resources.



**Fig. 12** Electro-biochemical CO<sub>2</sub> conversion to pyruvate through formate. Reproduced with permission.<sup>181</sup> Copyright 2018, Elsevier.

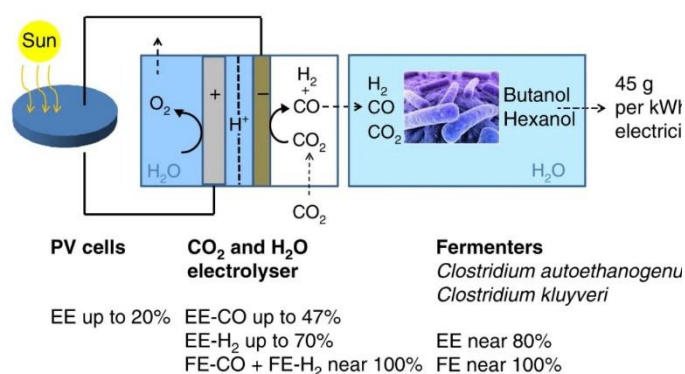
Although many methylotrophic organisms can grow on formate as a sole carbon, electron and energy source, they are generally less suitable for bulk cultivation and industrial needs. Thus, Bar-Even et al investigated the engineering of industrial model bacterium *E. coli* and used for formatotrophic growth. Various computational methods were presented and applied for comparison various pathways that may support formatotrophic growth. The popular formatotrophic pathway is the electrons derived from the oxidation of formate to CO<sub>2</sub> are used to support autotrophic growth. However, the pathway is more interesting that some formate molecules are used to generate energy and reducing power to assimilate some other formate molecules into central metabolism.<sup>182</sup> These results provide strong foundations of formate mediated biological synthesis coupling from CO<sub>2</sub> electrocatalytic reduction to reach real bioproduction.

### 3.2.2 CO or syngas mediated coupling synthesis

The previous study indicates that CO or syngas (CO+H<sub>2</sub>) is also useful intermediates to drive the integration of electro- and bio-

catalysis. Schmid coupled a CO<sub>2</sub> electrolyser to a fermentation module, realizing butanol and hexanol synthesis from CO<sub>2</sub> with high carbon utilization and selectivity through syngas intermediate product. A GDE immobilized with Ag catalyst was used for electroreduction of CO<sub>2</sub> to syngas, which was then fermented to final alcohol products (Fig. 13).<sup>79</sup>

In this mode, the respective reactor and reaction conditions can be optimized separately to reach the highest energy efficiency (EE) and Faradic efficiency (FE). Thus, overall an optimal yield and efficiency are obtained. For CO<sub>2</sub> electrolysis to syngas, the reaction run for 1,200 hours at 300 mA cm<sup>-2</sup> and the overall energy efficiency is greater than 20%. This resulting syngas mixture (CO:H<sub>2</sub> ratio of 2:1) flowed into a fermenter with 0.5 L of strain of *C. autoethanogenum*, in which acetate and ethanol were synthesized by fermentation of CO, H<sub>2</sub> and CO<sub>2</sub>. The biotransformation continued for 50 h, the ethanol was produced from the syngas mixture. In another experiment, the flow cell of CO<sub>2</sub> reduction was operated at 150 mA cm<sup>-2</sup> to produce a syngas mixture with composition of 10% CO, 60% H<sub>2</sub> and 30% CO<sub>2</sub> and a stable volume of flow. After the similar syngas fermentation to acetate and ethanol by the same culture, additional inoculation with *C. kluyveri* cells was carried out, butyrate and hexanoate can be synthesized from acetate and ethanol to by *C. kluyveri* and then butanol and hexanol were synthesized by *C. autoethanogenum*. The right combination of electrocatalysis and biocatalysts provides many new routes to produce a variety of renewable chemicals from CO<sub>2</sub> and water. Additional microorganisms combining with *C. autoethanogenum*, such as *Pelobacter propionicus* for propionate and acetate production, oleaginous yeast for lipids production, provides more and flexible integrations of electro- and bio- catalysis processes.

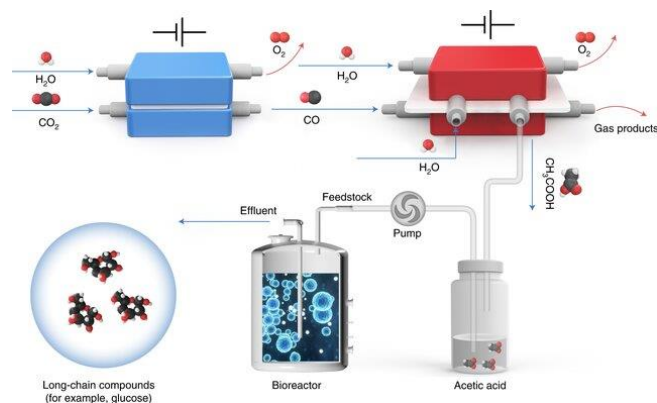


**Fig. 13** Illustrated scheme of artificial photosynthesis of 1-butanol and 1-hexanol from CO<sub>2</sub> and H<sub>2</sub>O by appropriate combining electrocatalysis and biocatalysts. Reproduced with permission.<sup>79</sup> Copyright 2018, Springer Nature.

### 3.2.3 Acetate mediated coupling synthesis

Acetate is an important carbon source for microorganism, which can be directly catalysed to acetyl coenzyme A (Acetyl-CoA) as a synthetic precursor of many bulk and fine chemicals. Afore mentioned Si nanowire arrays - bacteria hybrid system is using acetate as intermediate, which is produced in MES like process, to further synthesize n-butanol and PHB.<sup>166</sup> This approach is also developed to accomplish space exploration missions by providing life-support materials, with updated productivity of 10.4 mmol acetate L<sup>-1</sup> day<sup>-1</sup> by *S. ovata* and 12.54 mg PHB L<sup>-1</sup> hour<sup>-1</sup> by *Cupriavidus basilensis*.<sup>183</sup>

An inspiring result of converting CO<sub>2</sub> into energy-intensive macromolecular compounds such as glucose was reported recently by Zeng, Yu and Xia.<sup>87</sup> CO<sub>2</sub> was firstly electrolyzed to acetate through two steps (Fig. 14): (1) CO<sub>2</sub> was converted into CO in a MEA electrolyzer by a Ni-N-C single atomic catalyst (with Faradic efficiency of 100% and current density of 154 mA cm<sup>-2</sup>); (2) CO electroreduction to acetate by step-defected Cu catalyst (Faradic efficiency of 43% and current density of 200 mA cm<sup>-2</sup>). The obtained acetic acid was then bio transformed to glucose through genetically engineered *S. cerevisiae*. An average glucose titre of 1.81 g l<sup>-1</sup> was achieved with a productivity of 0.226 g L<sup>-1</sup> day<sup>-1</sup>. The genetical engineering operation of deleting hexokinase genes and overexpression of glucose-1-phosphatase contributed to improve performance significantly. Moreover, they also proved that the coupling method has a wide application and can be expanded to synthesize other useful compounds besides glucose. For example, a heterologous fatty acid metabolic pathway in yeast was reconstructed, including metabolic recombination and directional evolution, which realized in vitro production of free fatty acids (C<sub>8</sub> ~ C<sub>18</sub> chain) from above CO<sub>2</sub> electroreduction derived acetic acid by the engineered strain LXJ015 in a similar systematic design.

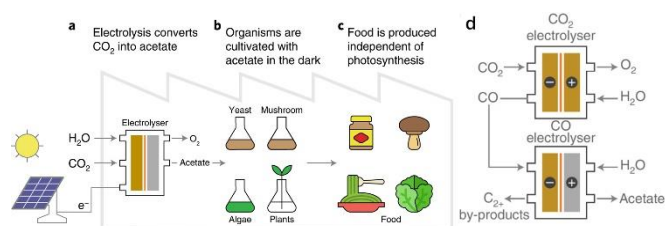


**Fig. 14** Schematic illustration of the in vitro artificial sugar synthesis combining electrocatalysis and biological catalysis. Reproduced with permission.<sup>87</sup> Copyright 2022, Springer Nature.

The acetate mediated synthesis from CO<sub>2</sub> have even expanded to food production recently.<sup>184</sup> As illustrated in Fig. 15 (a-c), the system can make food independent of photosynthesis by using CO<sub>2</sub>, H<sub>2</sub>O and solar energy, mainly including (a) CO<sub>2</sub> and H<sub>2</sub>O were converted into O<sub>2</sub> and acetate by using photovoltaic electricity. (b) *Chlamydomonas*, *S. cerevisiae*, mushroom producing fungi and various vascular crops were grown using the electro synthesized acetate. (c) The organisms fostered with acetate synthesized from CO<sub>2</sub> were processed to various food products. Therefore, to improve selectivity and productivity of acetate by CO<sub>2</sub> electroreduction in the first step is highly desired. For this purpose, a sequential connected electrolyzers were applied to reduce CO<sub>2</sub> to CO and then reduce CO to acetate (Fig. 15, d), quite similar to above work by Zeng, Yu and Xia.

First, a photosynthetic alga *Chlamydomonas* (*C. reinhardtii*) was grown on electrogenerated acetate heterotrophically in the dark. *Chlamydomonas* can produce food products such as starch, protein and lipid. The result indicated that 1 g acetate can produce 0.28 g algae and almost 99% of acetate was consumed. Thus, the acetate mediated synthesis of natural organisms by combining CO<sub>2</sub> electrolysis and heterotrophically growth may replace traditional photosynthesis.

As is well known, the nutritional yeast *S. cerevisiae* can make food production such as breads and beverages. Electrogenerated acetate effluent can support yeast growth with a turnout 0.19 g-yeast /g-acetate, much higher than the yield grown without acetate or glucose. Similarly, as a food and high-protein meat analogue, fungal mycelium (mushroom) could also be cultivated by acetate fermentation, which is the only carbon and energy source. Additionally, some oyster growth showed potential independence of photosynthetic carbon and energy. Therefore, widespread adoption of this integrative electrocatalysis and biological approach with inexhaustible solar energy allow to produce more food or animal feed with the limited agricultural lands.



**Fig. 15** A combined electrochemical–biological system to produce food from CO<sub>2</sub>. (a) Electrocatalytic conversion of CO<sub>2</sub> to acetate. (b) Organisms cultivation with acetate in dark. (c) Food production without photosynthesis. (d) A two-step consecutive electrochemical process for reducing CO<sub>2</sub> into acetate. Reproduced with permission.<sup>184</sup> Copyright 2022, Springer Nature.

Acetic acid could also be produced by traditional biological fermentation of gas sources, such as CO<sub>2</sub> and CO or H<sub>2</sub> (CO and H<sub>2</sub> can be produced by electrolysis of CO<sub>2</sub> and H<sub>2</sub>O) or their selected

mixture, with anaerobic acetogen *M. thermoacetica* and an engineered oleaginous yeast, *Yarrowia lipolytica*, in a two-stage bioreactor system, respectively. Eventually the system directly yields C<sub>16</sub>-C<sub>18</sub> triacylglycerides from syngas with a titre of 18 g/L and productivity of 0.19 g·L<sup>-1</sup>·h<sup>-1</sup>, the lipid content reaches 36%.<sup>185</sup> Acetate as an intermediate could also be converted to caproate and caprylate with 8.17 and 0.32 g l<sup>-1</sup> biologically, using mixed microbial communities dominated by relatives of *C. kluyveri*.<sup>186</sup>

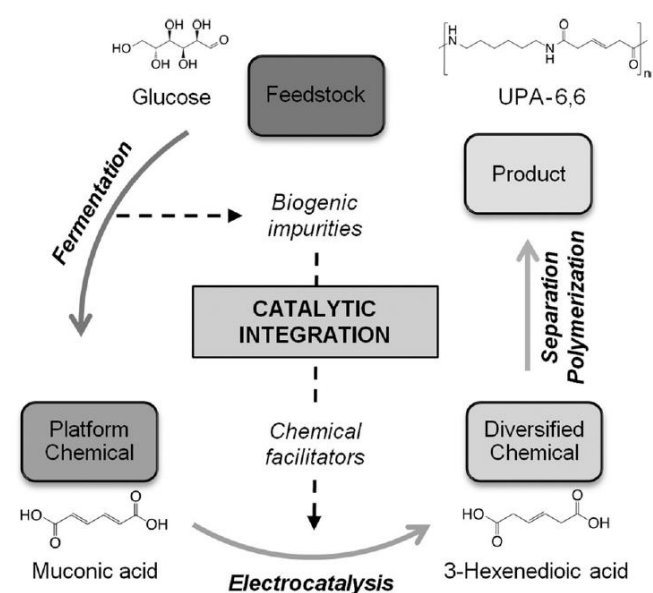
### 3.2.4 Other spatial decoupling electro- and bio- catalytic synthesis

Recently, a cell-free chemoenzymatic synthesis of starch from CO<sub>2</sub> was reported, in which chemically-synthesized methanol was used as starting material of next enzymatic synthesis, showing a chemical-biochemical hybrid conversion attribute.<sup>88</sup> CO<sub>2</sub> was firstly converted to methanol with H<sub>2</sub> by a heterogeneous hydrogenation reaction. Although it is a thermocatalytic reaction, electrocatalytic reduction of CO<sub>2</sub> can also produce methanol efficiently,<sup>187</sup> leading to the potential of integrating electro- and bio- catalysis. The anabolic pathway in artificial starch includes 11 core reactions, developing by computational pathway design. The modular assembly and protein engineering optimization were also carried out for three key enzymes. Overall, the conversion rate reached 22 nmol CO<sub>2</sub> min<sup>-1</sup> mg<sup>-1</sup> catalyst, much higher than starch production in corn planting, opening the way of chemical and biological hybrid synthesis of starch.

As stated above, biomass is also alternative resource with carbon-neutral attributes. The sugars and starch have been widely used as biological manufacturing raw materials in conventional fermentation industry. While lignocellulosic biomass has an advantage by non-competing with human food. In the bioethanol production from lignocellulosic materials, delignification pre-treatment of wood is a widely concerned technological barrier.<sup>188</sup> A novel delignification approach of wheat straw was described by Ferro et al. It was mild and only 10 min required. The HOCl-containing water solution synthesized from diluted brines and activated electrochemically was quite environmentally friendly and harmless. Using the obtained holocellulose rich materials (approximately 36 % of the initial lignocellulose), a 68% bioethanol production was obtained in by fermentation of the enzyme-hydrolysed cellulose. It indicates the tolerance of adopted yeast (*C. tropicalis*) to the delignified medium that can simplify the integrative process avoiding separation and purification.<sup>189</sup> This is a good example of coupling electrochemistry with microbial fermentation to convert biomass resource. Metabolic engineering study is important to improve biotransformation efficiency and selectivity. Product-specific enzymes or entire metabolic pathways can be designed to transfer from rare or genetically intractable organisms to those easily engineered. By combining enzymes or pathways from different hosts into a single microorganism, the synthesis of specialty chemicals, bulk chemicals, and fuels can be realized intentionally.<sup>185</sup>

For converting biomass to bio-based polymer materials, combination of metabolic engineering and electrocatalysis was applied to produce polyamides from sugar.<sup>89</sup> As shown in Fig. 16, a

biocatalyst of engineered strain of *S. cerevisiae* firstly converted glucose to muconic acid and the fermentation titre achieved 559.5 mg L<sup>-1</sup>. The electrocatalytic hydrogenation of obtained muconic acid allowed further production of 3-hexenedioic acid with high yield (94%) without separation of impurities in fermentation broth. Finally, the unsaturated nylon-6,6 was synthesized by polymerization of bio-based 3-hexenedioic acid with hexamethylenediamine. Next, in another work, the possible obstacles of bio- and electro- integration in the same reactor was studied and analysed, such as impurities induced catalyst failure and Faradaic efficiency loss resulting from other reactions. The combination of biological and electrocatalysis in single reactor enable production of 3-hexenedioic acid from muconic acid with 100% efficiency and 94% productivity. A techno-economic analysis indicated a 3-hexenedioic acid cost of approximately only \$2.00 kg<sup>-1</sup> due to the direct fermentation without separation.<sup>90</sup>

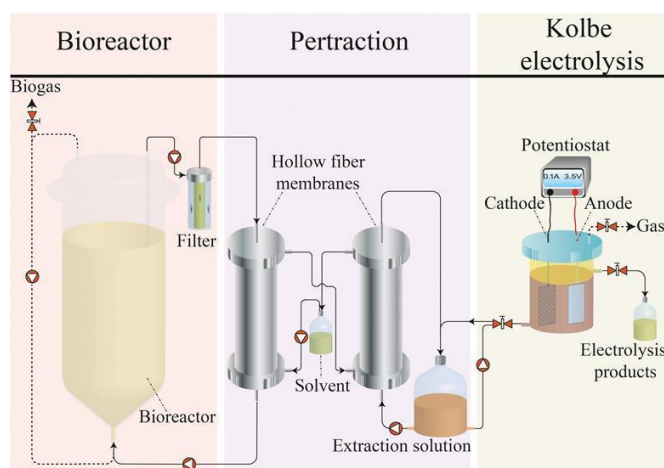


**Fig. 16** Cascade biological catalysis and electrocatalysis for transformation of glucose into UPA-6,6. Reproduced with permission.<sup>89</sup> Copyright 2016, Wiley.

A direct further catalytic conversion after fermentation can simplify the process by reducing the reactors and separation and purification unit of high energy consumption. This approach is also adopted by Palkovits et al, who performed a study on electrocatalytic conversion of itaconic acid, which was in the fermentation broth without separation, for producing methylsuccinic acid.<sup>190</sup> A thermochemical and electrochemical reduction reaction was carried out for a comparison. The results showed that the chemo-catalytic conversion of itaconic acid under Ru/C or RANEY® Ni catalysts was inhibited because of residual salts and glucose in the solution. In contrast, the electrochemical hydrogenation enabled benign conversion and achieved 99% faradaic efficiency. The integrative bio-

and electro- catalytic system without intermediate products' purification not only reduces process cost but also provides means to incorporate renewable electricity into biomass upgradation, belonging to green and clean technology.

Although the direct electrochemical upgrading of products in fermentation broth has its advantages, separation is still necessary in cases. A combined microbial fermentation and electrochemical reaction realizes yield of chemicals (alkanes) from biomass with the aid of electricity, where the carboxylic acids separation by pertraction.<sup>191</sup> As shown in **Fig. 17**, carboxylic acids are firstly produced in a bioreactor with anaerobic microbiomes. Various renewable biomass can be used as feedstocks, such as ethanol- or lactate-rich biobased substrates. The carboxylic acids were then recovered from broth by a pertraction method, which composed of two hollow fiber modules and included a forward extraction in an organic solvent and a back-extraction in an alkaline solution. Subsequently, the electrochemical reduction of carboxylic acids to alkanes with a Kolbe reaction. Because of different carbon chain number of carboxylic acids, different liquid alkanes from medium-chain carboxylic acids or lower alkanes and alcohols from short-chain carboxylic acids can be obtained. Remarkably, carboxylic acids with a six or more-carbon chain length could be efficiently transformed to liquid alkanes with low energy consumption of only 0.100 kWh mol<sup>-1</sup> carboxylic acid. It is worth to be noted that the reaction rate of electrochemical conversion of carboxylic acid is much higher than the carboxylic acid fermentation, allowing batch electrochemical reaction during electric peak.



**Fig. 17** Proposed process flow schemes. Step 1 - Fermentation to carboxylic acids; Step 2 - Pertraction to recover carboxylic acids from fermentation broth; Step 3 - Kolbe electrolysis to alkanes. Reproduced with permission.<sup>191</sup> Copyright 2017, The Royal Society of Chemistry.



#### 4. Challenges and opportunities for future integrative electro- and bio- catalysis

The integrative electro- and bio- catalysis has brought new opportunity to improve conversion efficiency and upgrade product level of renewable resources (CO<sub>2</sub> and biomass) by utilizing regenerative and clean electricity directly, which would develop novel catalytic system and lead to new manufacture process. It transcends the general range of bioelectrochemistry by integrating abiotic electrocatalytic materials. The microscopic reaction pathway on electrode or macroscopic process combination needs new understanding and optimization in the integrative design.

In integration mode 1 (Fig. 2, a), the interfacial extracellular electron transfer is the same challenge which needs precise elucidation of mechanism and useful enhancement strategy.<sup>192</sup> In the integrative system, more efforts are required on the control deposition of abiotic catalyst or other nanomaterials, as well as their mutual interaction with bacterium or enzymes on electrode. A complicated electron transfer network may exist and play crucial roles in synthetic reactions.

Another aspect is biological means, development of metabolism and synthetic biology. Metabolic engineering provides strategies and chances to construct new techniques, which includes genetic engineering of electron transfer pathways as well as product engineering metabolic synthesis. Thus, genetic engineering method gives possibilities to relieve the major obstacles of electron assimilating rates and product's productivity.<sup>193</sup> In the long run, synthetic biology development will make bioelectronics and engineering life materials a reality. The understanding of fundamental design rules on expressing components of extracellular electron transfer in cells or out of cells becomes more important.<sup>194</sup> Caroline et al demonstrates that electron transfer route from microorganism to inorganic catalyst can be created by a genetic cassette, and stresses the importance of size matching between microbe and electrode, the electron donors and acceptors vice versa.<sup>195</sup> Michaela A. et al designed an extracellular electron transfer route to connect electrode with the reduction reaction in the living cells in *Shewanella oneidensis* MR-1. The electrode electrons are transferred to the inner membrane quinone pool and then to NAD<sup>+</sup> in steps by the native Mtr proteins and NADH dehydrogenases, respectively. A light powered proton pump was designed to alleviate unfavourable reverse functioning of NADH dehydrogenases. Finally, acetoin could be reduced to 2,3-butanediol through a heterologous butanediol dehydrogenase.<sup>196</sup> Integrating microorganisms with photocatalysts into an artificial photosynthetic system for CO<sub>2</sub> fixation also face the same challenges and opportunities in regulating metabolic pathways precisely.<sup>197</sup>

To realize industrial production is the ultimate object of BESs. One significant challenge for BESs is to scale-up reactor towards industrial use and consequent system engineering problems. The major technical challenges for the industrial use of bioelectrochemical synthesis include an proper electrode surface

area ratio, biocompatible interfaces, low cost and long-term stability of bioelectrochemical reactors<sup>198</sup>. To step forward to commercialization of MES, electrode stack design and techno-economic assessment are also urgent needed.<sup>199, 200</sup> The traditional bacterial culture methods and various structure of bioreactors can facilitate culturing electroactive bacteria, assisted by necessary electrochemical control and process monitoring.<sup>201, 202</sup> Holtmann performed a reasonable reactor scale-up from 1 L to 50 L to produce methane by bioelectromethanogenesis. The experiments of pure bacterial fermentation with *Methanococcus maripaludis* were also successfully carried out.<sup>203, 204</sup>

For integration mode 2, it is not necessary to use electroactive microorganisms, the combination of abiotic catalysis with biological catalysis is much free and flexible. The CO, formate, acetate mediated synthesis has been proved to be effective and important in developing such integrative system, particularly for CO<sub>2</sub> conversion and utilization. Therefore, the respective CO<sub>2</sub> electro-reduction to CO, formate, methanol or acetate and subsequent bio fermentation of these intermediates can be studied and developed independently, such as the abiotic electrocatalyst design and genetically engineered bacterium. However, the process development and optimization need careful consideration of scale and operation matching. The reaction productivity to specific product determines the size and volume of reactor for both electrolysis and biological fermentation. That's the reason why need to improve productivity substantially by developing high-performance catalyst. According to the productivity level of abiotic electrocatalytic reaction and biocatalytic synthesis, the size of electrolyzer should be much smaller than a bioreactor to reach a scale match.

However, the biological fermentation has many mature technologies and processes, but the large-scale electrolysis for CO<sub>2</sub> and biomass derivatives conversion in industrial level still has many technical problems, such as CO<sub>2</sub> electroreduction based on GDE (gas diffusion electrode). The urgent technical barriers that need to be studied and solved include electrocatalyst stability, resistance of ion exchange membrane and carbonate anion (CO<sub>3</sub><sup>2-</sup>) permeation, etc.<sup>205, 206</sup> They may hinder the development of CO<sub>2</sub> electroreduction technology and the proposed electro- and bio- catalysis integration techniques. However, the fast development and significant progress on fundamental and applied research of CO<sub>2</sub>RR are being made currently.<sup>207</sup>

#### Conclusions

As typical renewable carbon resources, activation and conversion of CO<sub>2</sub> as well as biomass to value-added and renewable fuels and chemicals, replacing traditional fossil resources' origin, provides sustainable development opportunity for future. The new technology and processes are urgently required to realize the targets. The electrosynthesis is a green and environmentally friendly method, which connects utilization of renewable electricity (photo voltaic, wind, hydropower, etc.) and carbon resources (CO<sub>2</sub> and

biomass). The abiotic electrocatalytic reaction and bio(electro)chemical synthesis is both mild and efficient methods to meet above objectives. Furthermore, the integrative electrochemical and biological catalysis show more advantages to improve productivity and innovate synthetic processes. The integrative system is a complex concept, and two modes are distinguished based on the existence and use of electroactive microorganism. In mode 1, the abiotic and bio- catalyst have a close contact mostly on the same electrode. The electroactive bacteria or enzymes are core catalysts which determine the product selectivity and whole productivity. The promotional effect of coexisting abiotic catalyst lies in electrocatalytic production of H<sub>2</sub> or formate which enhances electron transfer and mediates reaction pathways. The improvement of electrode conductivity happens sometimes. Aiding of intermediate products is the essential content in mode 2, spatial decoupling integration. CO, methanol, formate, acetate are all important intermediates in coupling CO<sub>2</sub> electroreduction and biological fermentation to multi-carbon products. It is also very useful in biomass conversion through a proper intermediate sequential exchangeable electrocatalysis and biological catalysis. More and more examples and studies are appearing with extended area and applications.

### Author Contributions

LL: conceptualization, visualization, writing – original draft, and writing – review and editing. DP: writing – original draft, and writing – review and editing..

### Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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