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Electrocatalytic CO_2 reduction coupled with biocatalysis for high-value products

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The rising concentration of carbon dioxide (CO_2) has created an urgent need for technologies that can both mitigate emissions and supply sustainable carbon feedstocks. Electrocatalytic carbon dioxide reduction utilizes renewable electricity to convert CO_2 into C_1–C_3 products at high rates under mild conditions, but it remains challenging to produce longer-chain molecules with high selectivity and efficiency. Biocatalytic systems are notable for forging C–C bonds and assembling complex products. However, most organisms fix CO_2 inefficiently and purely biological routes are constrained by thermodynamics and enzyme kinetics. This review examines how integrating electrocatalysis and biocatalysis in cascade systems combines the strengths of both approaches. We discuss the historical development and motivation for these hybrids, summarize recent progress in electrocatalytic CO_2/CO conversion to C_1–C_3 intermediates, and outline biocatalytic strategies that extend short-chain feedstocks to higher-value C_n products. We further examine challenges in catalyst stability, pathway and strain engineering, and process scale-up, and propose directions for advancing electro-biosynthetic manufacturing. Together, these developments point toward a circular carbon economy in which CO_2 becomes a practical starting point for complex carbon-based products.

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1 Introduction

The conversion of carbon dioxide (CO_2) into value-added chemicals is both a major challenge and an important opportunity for sustainable technologies. CO_2 is an abundant but low-energy carbon source, and its utilization could help mitigate greenhouse gas emissions while providing renewable feedstocks for fuels, materials, and food

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ingredients.[1–3] In nature, photosynthetic organisms fix CO_2 into biomass. However, this route is constrained by slow enzyme kinetics and low efficiency, which is typically well below 1%.[4] Conventional industrial routes for CO_2 utilization, such as thermocatalytic hydrogenation exemplified by Fischer–Tropsch synthesis of hydrocarbons from CO/H_2, operate at high temperatures and pressures and often yield broad, poorly defined product mixtures.[5,6] Over the past decade, electrocatalytic CO_2 reduction (CO_2RR) has emerged as a promising alternative that uses renewable electricity to convert CO_2 under relatively mild conditions. Electrocatalytic systems can generate C_1 and C_2 products, such as carbon monoxide, formate, methane, ethylene, ethanol, and acetic acid at high reaction rates.[7–9] However, as the desired carbon chain length increases (for example, C_3–C_5 products), purely electrocatalytic approaches face significant limitations in both selectivity and overall efficiency.[10–12]

In contrast, biocatalytic processes such as microbial fermentation and multienzyme cascades are highly effective at converting simple carbon sources into complex and high-value products, with precise control over structure and stereochemistry.[13,14] Cells and enzymes can form C–C bonds and generate long-chain or highly chiral molecules that are often difficult to obtain through conventional electrocatalytic synthetic methods. However, most organisms cannot fix CO_2 at high rates, because CO_2 is thermodynamically stable and key CO_2-fixing enzymes such as RuBisCO and formate dehydrogenases have intrinsically low activities.[15,16] Many natural CO_2 fixation pathways operate near equilibrium and have slow turnover rates, which limits the efficiency of purely biological CO_2 conversion.[17–19]

This contrast points to a clear strategy: integrating electrocatalysis and biocatalysis in a sequence of orchestrated chemoenzymatic cascades (Fig. 1). In such hybrid systems, an electrocatalytic module first reduces CO_2 to simple C_1–C_3 intermediates, which are subsequently elongated and assembled into larger, higher-value products by biocatalysis. In this configuration, the high driving force and rapid kinetics of electrochemical conversion are harnessed while the selectivity and synthetic versatility of biological catalysis are maintained. As a result, integrated electro-biocatalytic schemes are attracting increasing attention as routes to convert waste CO_2, under renewable energy input, into fuels, chemicals and even food products.

Many existing reviews discuss electrocatalytic CO_2/CO reduction and the biotransformation of C_1–C_3 substrates in depth, but fewer offer a fully integrated, system-level perspective on electro-biocatalytic cascades. Here, we provide a system-level synthesis that explicitly connects electrocatalysis with downstream biocatalysis through the lens of intermediate selection, interface compatibility, and coupling constraints. We distinguish the biocatalytic stage into two complementary modules—cell-free enzyme cascades and metabolic engineering-based bio-conversion—and clarify how each interfaces with electrocatalytic outputs. We begin by placing the field in its historical context and outlining the motivation for coupling electrocatalytic and biocatalytic platforms, with particular emphasis on the conceptual and practical advantages of cascade architectures. We then discuss the current state of electrocatalytic CO_2 reduction, focusing on recent progress in catalyst development, reactor engineering and performance metrics. Next, we discuss

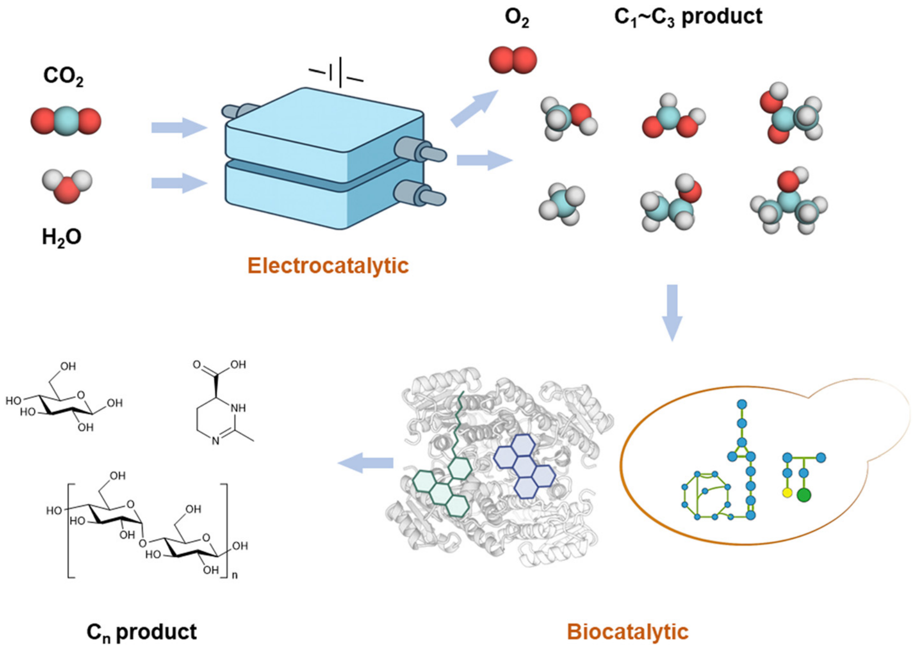

Fig. 1 Electrocatalytic–biocatalytic cascade system for CO_2 conversion. First, the electrocatalytic reactor converts CO_2 into C_1–C_3 intermediates such as CO, formate, methanol or acetate. These intermediates are then further upgraded by enzymatic or whole-cell biocatalysis into more complex C_n products, achieving carbon-chain elongation.

biocatalytic strategies for carbon chain elongation, including *in vitro* enzyme cascades and microbial metabolic engineering, and examine how these systems use C_1 and C_2 feedstocks. Representative case studies of integrated electro-biocatalytic systems are presented to illustrate the conversion of CO_2 into high-value products, ranging from fuels and bulk chemicals to biopolymers and food ingredients, and to highlight the design and optimization principles that govern each module. Finally, we identify key challenges at the interface between electrocatalysis and biocatalysis and propose directions for future research.

2 Background and early developments in CO_2 conversion

Using CO_2 as a carbon feedstock has long been viewed as a key goal on the path to carbon neutrality. Traditional strategies include high-temperature thermochemical processes, such as reforming and Fischer–Tropsch synthesis, and biological CO_2 fixation through natural photosynthesis or microbial fermentation driven by hydrogen or other energy sources.[1,20–23] However, these routes either demand intensive energy input or suffer from low efficiencies. Research on electrocatalytic CO_2 reduction (CO_2RR) has a long history and has undergone continuous development and refinement (Fig. 2). Early studies date back to the nineteenth century, when CO_2 was reduced to CO at Zn cathodes. Interest increased in the 1980s, after the oil crises of the 1970s, when systematic work on Cu, Zn and lead electrodes identified formate as a dominant product. Based on these results, CO_2RR was recognized by the end of the 20th century as a promising way to convert CO_2 into high-value products, ideally from renewable sources, under ambient conditions. Collectively, this work marked the beginning of systematic metal and alloy systems development for CO_2RR. Pioneering work by Hori and collaborators in the 1980s and 1990s further showed that Cu electrodes can reduce CO_2 to multi-carbon products such as ethylene and ethanol, although only at modest yields. In contrast, metals such as Au and Ag mainly produce CO, and metals such as Sn tend to form formate.[24–26] These studies clarified the fundamental reaction pathways and established the unique ability of Cu to promote C–C bond formation. By the 2010s, advances in catalyst design and cell architecture had significantly increased reaction rates and selectivity, bringing CO_2RR much closer to practical application.[27–30] For example, gas diffusion electrode (GDE) reactors have enabled current densities that are orders of magnitude higher than those in conventional H cells by alleviating limitations in CO_2 mass transfer.[31]

On the biocatalysis side, the concept of microbial electrosynthesis began to emerge around 2010. Several groups reported that acetogenic bacteria growing on cathodes could directly accept electrons, or hydrogen generated *in situ*, and reduce CO_2 to acetate and other small organic molecules.[32–34] This direct coupling of electrical current to living cells showed that bio-based CO_2 reduction is feasible, but precise control of the process and achievement of high rates remains challenging. Indirect coupling through soluble intermediates emerged in 2012, when Li *et al.* reported an integrated electro-microbial process that converted CO_2 into liquid fuels using a two-step strategy.[35] In that study, CO_2 was first reduced electrochemically to formate, and an engineered strain of *Ralstonia eutropha*, a natural autotroph,

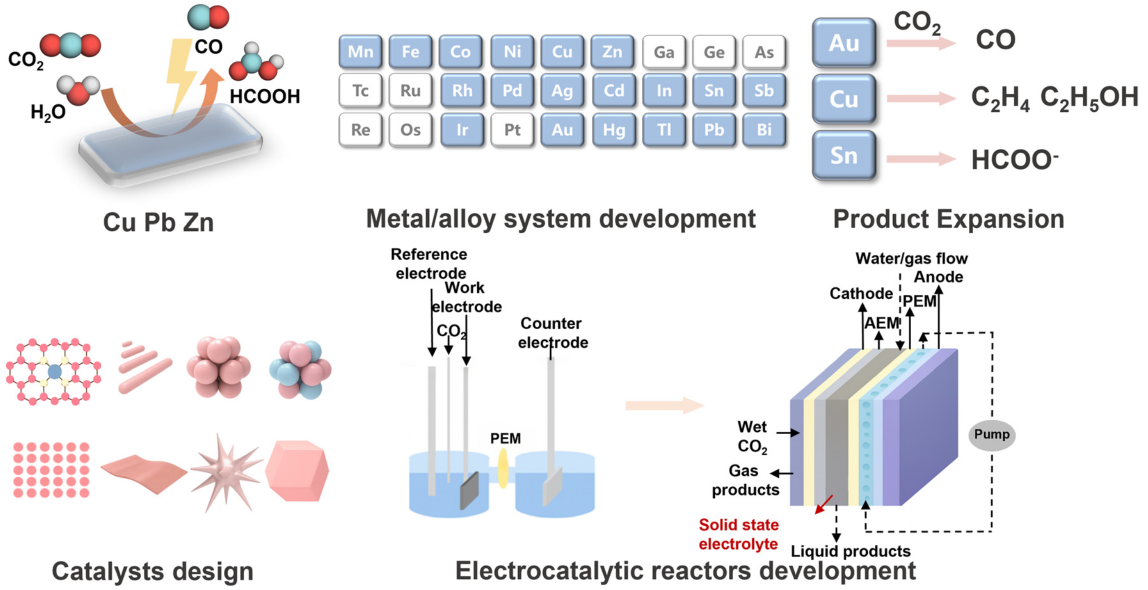

Fig. 2 Recent developments in electrochemical CO_2 reduction, including the development of metal/alloy catalyst systems, expansion of product selectivity, innovations in catalyst design, and the evolution of reactor configurations from simple H-cells to high-performance membrane and solid-state electrolyzers.

was then used to produce isobutanol and 3-methyl-1-butanol. The strain was engineered with a synthetic isobutanol biosynthetic pathway, thereby enabling electrical energy to be stored in liquid fuel molecules. Formate served as a clean energy carrier that circumvented the handling and solubility challenges associated with gaseous hydrogen in fermentation, while the biocatalyst directed carbon into a specific, high-energy-density fuel. This work provided a clear proof of concept that combining an electrolyzer with a bioreactor can help offset the limitations of each unit. The success of Li *et al.* stimulated many subsequent efforts to integrate electrocatalysis with fermentation.[35] Given the close interplay between microbial and enzymatic systems, electro-enzymatic CO_2 reduction emerged around the same time and largely in parallel with microbial electrosynthesis.[36] In 2014, Srikanth *et al.* presented an approach for electrochemical CO_2 reduction to formate catalyzed by formate dehydrogenase immobilized on an electrode.[37] Besides CO_2 reduction, NADH is regenerated in the electrochemical system at the same time. Also, Cai *et al.* have realized the potential of integrating enzymes with electrocatalysis. In their work, they show the electrochemical addressing of dehydrogenase enzymes without the requirement of any cofactor. In this electro-enzymatic system, CO_2 is reduced to ethylene (C_2H_4) and propene (C_3H_6) by a single VFe nitrogenase.[38]

Over the 2010s, many studies employed electrochemically produced small molecules as substrates for microbial production of ethanol, butanol, fatty acids, and bioplastics.[35,39–42] Multi-enzymatic cascade reaction provides a new avenue for C–C coupling directly from CO_2 under mild conditions.[43] A representative example of electro-driven, C–C coupling from CO_2 *in vitro* is the four-enzyme cascade developed for ethylene glycol (EG) synthesis. In this design, formate dehydrogenase (PaFDH) and formaldehyde dehydrogenase (BmFADH) generate C_1 intermediates from CO_2, which are then coupled *via* glycolaldehyde synthase (PpGALS) to form a C_2 backbone, followed by alcohol dehydrogenase (GoADH) to yield EG. To continuously supply reducing equivalents under mild conditions, the authors integrated a rhodium-based electrochemical NADH-regeneration electrode, achieving a Faradaic efficiency of 82.9% at ~0.6 V (*vs.* Ag/AgCl) and an NADH productivity of 0.737 mM h^{-1}.[36] These efforts fit into a broader vision of artificial photosynthesis, in which human-engineered systems aim to match and even exceed the efficiency of natural photosynthesis by separating the light-harvesting step from carbon fixation. Rather than relying on chlorophyll, these schemes employ photovoltaic devices or electrocatalysts for the light-harvesting stage, and microbes or isolated enzymes for the biosynthetic stage.[44,45] A representative example of artificial photosynthesis was reported by Hann *et al.*[46] Their team designed a spatially separated, solar-driven process to convert CO_2 into food. The electrochemical module first fixes CO_2 into a simple carbon substrate and then supplies this intermediate to cultures of photosynthetic algae or other microorganisms, which in turn produce starch and edible biomass. In both early and recent studies, inorganic catalysts are used for CO_2 activation, whereas biological systems provide flexible and selective product formation. Over time, the scope of the field has expanded from formate-based systems to those employing multiple intermediates, and from fuel alcohols to a broad range of products, including polymers, pharmaceuticals, and food ingredients.[47–49] The following sections review recent examples of each component of this tandem strategy and the current state of their integration.

2.1 Electrocatalytic conversion of CO_2 to C_1–C_3 compounds

CO_2RR proceeds through a sequence of coupled proton and electron transfer steps at the electrode surface, which progressively convert CO_2 into more reduced carbon-containing products. The associated reaction network is highly complex (Fig. 3). The number of electrons and protons transferred determines whether CO_2 is converted into a two-electron product, a six-electron product or a twelve-electron product.[50–53] Each major product class follows a distinct pathway with its own characteristic surface-bound intermediates. Faradaic efficiency (FE) is a key metric for evaluating electrocatalytic performance and is influenced by the catalyst type, operating potential, current density, reactor configuration and mass-transport conditions.

CO is typically generated *via* a two-electron reduction pathway. CO_2 first adsorbs on the catalyst and forms a **COOH* intermediate, and then loses an oxygen atom to produce CO. The rate-limiting step is often the formation of **COOH* and the subsequent desorption of CO. Catalysts such as Au and Ag bind the **COOH* strongly enough to form it but weakly enough to release CO, which makes them highly selective for CO.[54,55] As a result, FE above 90% on Ag and Au are common, particularly in flow reactors.[56,57] Formate/formic acid is another two-electron product that forms *via* a different intermediate, *HCOO**. *HCOO** is a bidentate species in which both oxygen atoms bind to the catalyst surface. Metals such as tin (Sn), bismuth (Bi), indium (In) and lead (Pb) are known to favour this pathway.[58–61] In optimized systems, formate selectivities are achieved above 90%. Moreover, its direct generation in the liquid phase, typically as a dissolved anion, facilitates coupling to downstream biological processes.[57] From an industrial perspective, formate and formic acid are currently among the most practical products, with some continuous flow systems delivering high current densities together with overall energy efficiencies >50%.[62] Methane and methanol are also C_1 products that form through a multi-electron reduction pathway.[52,63,64] Methane formation proceeds *via* surface-bound **COOH*, **CO* and **COH*, whereas CH_3OH likely follows a route involving **COOH* or dissolved hydrocarbon-like species.[65–67] Transition-metal catalysts such as cobalt phthalocyanines have also been tuned to

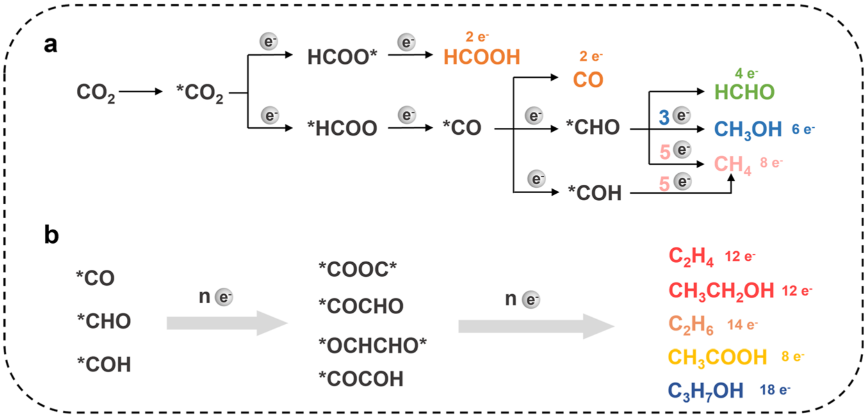

Fig. 3 The typical conversion routes and key intermediates for C_1–C_3. (a) The typical conversion routes and key intermediates for C_1 products; (b) the typical conversion routes and key intermediates for C_{2+} products. Species marked with an asterisk indicate short-lived/unstable precursors formed en route to stable C_1–C_3 intermediates.

methanol, although with low yields.[52,68,69] Achieving high selectivity for methanol is challenging due to competition from the hydrogen evolution reaction and the behaviour of key intermediates, which either bind too strongly and poison the surface or are further reduced to methane. In addition, maintaining the stability of the catalysts used for methanol production remains another challenge.

Cu is unique among pure metals in its ability to promote C–C bond formation, giving products such as ethylene, ethanol and even small amounts of *n*-propanol.[70–74] Formation of multi-carbon products generally begins with adsorbed **CO* or **COH* on the surface, followed by coupling between two CO-derived intermediates. If CO binds too weakly, it desorbs before C–C coupling can occur, whereas if it binds too strongly, it poisons the surface. The intermediate affinity of Cu for CO is widely believed to underlie its ability to deliver appreciable yields of C_2 products. Research has shown that the presence of mixed oxidation states of Cu, such as Cu^0 and Cu^+, and the presence of high index facets and grain boundaries can enhance C_{2+} formation by stabilizing key intermediates.[75] The most advanced Cu-based catalysts reported so far achieve about 50–90% combined FE for C_{2+} products. But these C_{2+} products are typically obtained as mixtures of ethylene, ethanol, acetate and related species, so the selectivity for any single product remains modest.[76,77] Controlling the distribution of multi-carbon products and selectively favouring one target remains difficult because the underlying reaction network contains many competing branching pathways.

A key performance metric for electrocatalysis is the overall energy efficiency (EE), defined as the fraction of electrical energy input that is stored in the chemical products. Recent progress in catalyst development and reactor engineering has substantially increased overall EE.[78–81] CO and formate can reach >50%, whereas multi-carbon products usually remain at 20–60% because their formation requires higher overpotentials and competes more strongly with side reactions. To make CO_2 electrolysis economically viable, efficiencies must be further increased by reducing voltage losses and enhancing product selectivity.

For the reactor, the field has evolved beyond simple H-type cells, in which two chambers are separated by a membrane, to continuous flow systems that handle gaseous CO_2 more effectively. Flow cells equipped with gas diffusion electrodes (GDEs) deliver CO_2 directly to the catalyst interface and can sustain high reaction rates,[82] for example, fluorine-modified Cu GDE achieved a C_{2+} (mainly ethylene and ethanol) formation rate exceeding 4.0 mmol h^{-1} cm^{-2}, with 80% FE.[83] In such devices, current densities of hundreds mA cm^{-2}, relevant to industrial operation, are routinely achieved, in contrast to the few mA cm^{-2} typically obtained in H-cells. One major challenge is the management of the liquid electrolyte, since flooding of the GDEs can block gas transport. Hydrophobic treatments such as polytetrafluoroethylene (PTFE) coatings are commonly used to extend GDEs' lifetimes. Existing studies have shown that periodically recoating the GDE with PTFE enables stable CO_2 electrolysis at 600 mA cm^{-2} for about 5200 hours, corresponding to more than 7 months of continuous operation.[84–86] Such durability is encouraging for scale up, as it suggests that degradation modes such as electrode flooding and catalyst deactivation can be mitigated through engineering strategies. Another important development is the membrane electrode assembly (MEA) configuration, similar to that used in fuel cells, in which humidified CO_2 gas is supplied directly to the catalyst layer without a liquid catholyte.[85,86] MEA reduces diffusion resistance and eliminates the need to dissolve CO_2, thereby reaching higher current and efficiency. However, these systems require careful water management and typically an ion-exchange membrane to conduct ions. Recently, solid-state electrolyte reactors have attracted increasing attention. In these systems, ionic charge such as H^+ or $HCOO^-$ is transported through a solid polymer or inorganic conductor, and the products can be collected as an almost pure liquid stream without mixing with electrolyte salts.[87,88] Xia and co-workers demonstrated a solid-state cell that continuously converted CO_2 into a 12 M formic acid solution, close to neat formic acid.[88] Likewise, Zheng and co-workers used a porous solid electrolyte reactor to produce purified acetic acid. Their configuration employed thick anion exchange membranes to conduct hydroxide and suppress crossover, achieving ~97 wt% pure acetic acid directly from the electrochemical cell.[89] This is a significant advance for integration with bioprocesses, since it eliminates the need for costly downstream separation of the product from supporting electrolytes. Together, these reactors and process innovations provide a much more favourable platform for CO_2 electrolysis, but the achievable rates and product distributions are still governed by the properties of the catalyst surface.

In parallel with these engineering advances, the search for more active and selective electrocatalysts has intensified. Beyond the conventional metals described above, current work focuses on alloys, nanostructured copper and well-defined molecular systems.[26,90] For example, single-atom catalysts (SACs) have shown exceptional activity for some reactions. Zheng *et al.* employed a Ni-based single-atom catalyst on a nitrogen-doped carbon (Ni–N–C) to convert CO_2 to CO with nearly 100% efficiency,[89] and then used CO to drive acetate formation on a Cu catalyst. Nano-structuring Cu to create grain boundary-rich surfaces has also been reported to enhance acetate production, reaching 52% FE for acetate in CO reduction.[75] Studies have also shown that oxide-derived Cu obtained by pretreating Cu_2O favours C_2 products such as ethylene and ethanol by maintaining a dynamic mixture of Cu^+/Cu^0 surface sites during operation. Bimetallic catalysts such as Cu–Ag and Cu–Sn aim to combine complementary functions, for example, using Ag domains to generate CO *in situ* on a Cu surface and thereby facilitate C–C coupling.[91,92] For example, a Cu–Ag GDE has been reported to allow the distribution of C_1, C_2 and even C_3 products to be tuned by adjusting the surface composition.[93]

One of the most challenging product classes under ambient CO_2/CO electroreduction conditions is still C_{3+}. Early reports showed only trace FE for *n*-propanol, allyl alcohol and related C_3 products on modified Cu electrodes, and sub-percent yields for C_4 species such as *n*-butane or 1-butanol.[75,94] Recent studies have improved the performance, with systems now reaching C_{3+} FE of ~56%.[95,96] These advances demonstrate that selective C_{3+} formation is indeed feasible, although broadly extending such high efficiencies across different systems remains challenging. As the carbon chain length of the target molecule increases, achieving its efficient synthesis by electrocatalysis becomes increasingly challenging.[97–99]

To push beyond this limitation, some researchers have taken inspiration from thermocatalysis.[100] For example, Cao *et al.* employed Ru nanoparticles for electrocatalytic CO reduction under elevated temperature and elevated pressure, essentially creating an electrochemical analogue of Fischer–Tropsch synthesis.[101] In that work, hydrocarbons up to C_{21} were produced, with a 32% FE for C_{5+} products. Although this strategy yields long-chain hydrocarbons, it relies on conditions far from ambient and on a specialised high-pressure cell, which blurs the boundary between electrochemical and thermochemical catalysis. Under mild aqueous electrolysis conditions, extending product distributions much beyond C_2 or C_3 appears to be intrinsically constrained by sluggish kinetics and competition from side reactions. This is where handing off the task to biocatalysis becomes attractive.

In summary, electrocatalysis can now generate a range of C_1–C_3 building blocks from CO_2/CO. CO and formate can be produced with high EE values, while ethanol, acetate and ethylene can be obtained in appreciable yields. Advances in reactor design have also enabled these processes to operate at industrially relevant current densities with improved stability. In some cases, they can run continuously for thousands of hours. However, the selectivity challenge intensifies for each additional carbon added electrochemically. The cascade strategies address this limitation by ending the electrosynthetic step at an optimal intermediate, such as formate or acetate, which can be produced in a relatively clean form, and then using biological systems to perform the downstream C–C bond-forming steps with high fidelity.

2.2 Biocatalytic carbon chain elongation from C_1/C_2 to C_n products

Biological systems are adept at C–C bond formation and complex molecular synthesis, as illustrated by the diversity of natural metabolites ranging from sugars and fatty acids to polyketides.[102,103] Currently, two broad biocatalytic platforms can be employed, including multi-enzyme cascades *in vitro* and engineered microorganisms operating *in vivo*. Each offers distinct advantages. Cell-free enzymatic systems offer a defined environment free of cellular regulation, allowing the use of non-natural pathways and potentially higher fluxes. Microbial systems benefit from self-replication, long-term stability and the broad catalytic repertoire of living metabolism.

2.2.1 *In vitro* multi-enzyme cascade synthesis. In an *in vitro* multi-enzyme cascade, a series of enzymes is combined in a one-pot or sequential reactor. By linking multiple enzymatic reactions, one can construct synthetic pathways that do not exist in nature. A straightforward example is the enzymatic reduction of CO_2 to methanol. This can be achieved with a three-dehydrogenase cascade: formate dehydrogenase (FDH) reduces CO_2 to formate, formaldehyde dehydrogenase (FaldDH) converts formate to formaldehyde, and alcohol dehydrogenase (ADH) reduces formaldehyde to methanol.[104] The second is thermodynamically uphill and tends to be the rate-limiting step, because formaldehyde is higher in energy than formate. Discovering or engineering a highly active FaldDH is an ongoing challenge. Turning to C_3 products, a

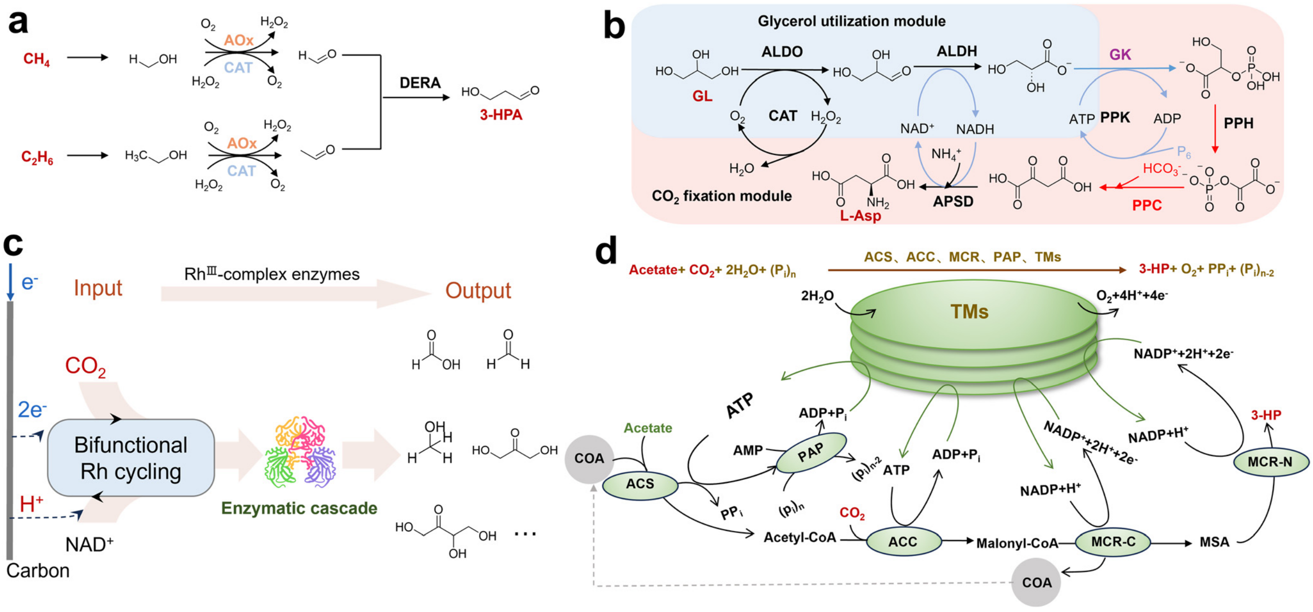

Fig. 4 Synthesis *via* multi-enzyme cascades. (a) Multi-enzyme conversion of C_1/C_2 alcohols to 3-HPA. Methanol and ethanol are first oxidized by alcohol oxidase to formaldehyde and acetaldehyde, respectively. The resulting C_1/C_2 aldehydes are then condensed to 3-HPA by a C_1/C_2 carboligase (DERA), while the hydrogen peroxide formed during alcohol oxidation is decomposed by catalase. Reprinted with permission from ref. 107. Copyright 2025, American Chemical Society; (b) *in vitro* pathway for L-aspartate (L-Asp) production, comprising a glycerol utilization module coupled to a CO_2 fixation module. Reprinted with permission from ref. 110. Copyright 2025, Elsevier; (c) bifunctional Rh(III) complex-driven CO_2 reduction and NADH regeneration enabling direct bio-electrosynthesis of C_{2+} products. The metal complex $[Cp^*Rh(bpy)Cl]^{2+}$ (Rh(III) complex, $[Rh(III)–H_2O]^{2+}$) simultaneously catalyzes electrochemical CO_2 reduction to formate and the reduction of NAD^+ to NADH. Formate is subsequently upgraded to methanol (C_1), dihydroxyacetone (C_3) and L-erythrulose (C_4) *via* tandem enzymatic cascades ACS–ACDH–ADH, ACS–ACDH–FLS and ACS–ACDH–FLS–FSA^{A129S}. Reprinted with permission from ref. 118. Copyright 2024, American Chemical Society; (d) light-powered *in vitro* synthetic enzymatic biosystem (*iv*SEB) for 3-HP production from acetate and CO_2. The cascade involves ACS, ACC, MCR-C, MCR-N, PAP, AMP and MSA to achieve stepwise conversion of acetate to 3-HP. Reprinted with permission from ref. 119. Copyright 2024, American Chemical Society.

landmark was the synthesis of dihydroxyacetone (DHA) from CO_2 in a multi-enzyme system comprising FDH, FaldDH and formolase (FLS).[105] FLS forms a C–C bond by linking C_1 formaldehyde units, a synthetic transformation with no direct counterpart in natural metabolism.[106] By immobilizing these enzymes on a hydrogen-bonded organic framework, researchers achieved a 1.8-fold higher yield of DHA.[105] This study illustrates how artificial enzyme cascades can extend beyond the capabilities of natural pathways. Another creative cascade involved converting different C_1/C_2 units. Seo *et al.* designed a pathway in which methanol and ethanol are converted into 3-hydroxypropionaldehyde (3-HPA) (Fig. 4a).[107] They designed the three-enzyme system where a novel soluble alcohol oxidase (AOx) converts methanol to formaldehyde and ethanol to acetaldehyde in one step, and then the 2-deoxyribose-5-phosphate aldolase (DERA) catalyzes the C–C bond formation between formaldehyde and acetaldehyde to 3-HPA. A catalase (CAT)-based H_2O_2 scavenging module was integrated, doubling 3-HPA production. Under the optimal conditions, the system produced 18.3 mM 3-HPA, showing how mixing different small alcohols can produce a larger product *via* cascade design.

The power of computation and enzyme engineering has greatly expanded the realm of possible cascades. Researchers use pathway design algorithms to identify theoretical routes for target molecules, then assemble and optimize these pathways with available enzymes or engineered ones.[108,109] A prime example is the recently reported artificial biosynthesis pathway, which converts CO_2 and glycerol to L-aspartate in one pot using eight enzymes and produces 18.6 mM aspartate within 2 h (Fig. 4b).[110] In another case, Ding *et al.* obtained lactic acid titers of 2.2–2.8 g L^{-1} from 100 mM methanol by carefully optimizing enzyme loadings and cofactor supply.[111] These studies demonstrate that with the appropriate enzyme catalysts, C_1 substrates can be channelled into central metabolites and organic acids.

Many enzymatic reductions (FDH, ADH) require NAD(P)H as electron donors, and some ligase or kinase steps require ATP.[104,112,113] These cofactors are expensive and must be regenerated *in situ* for the process to be sustainable. Inexpensive phosphites can be oxidized to phosphates by adding enzymes such as phosphite dehydrogenase (PTDH), simultaneously reducing $NADP^+$ to NADPH.[104,105,112] Alternatively, NADH can be obtained directly at the electrode or through redox media (such as viologen or quinones) by electrochemical cofactor regeneration.[114–116] This effectively links an electrical energy input to drive the biochemistry, similar to how nature uses the photosynthetic electron transport chain to generate NADPH. Researchers have constructed bio-electrocatalytic cells in which one electrode continuously supplies NADH to an enzyme cascade. For example, Wu *et al.* employed an electrochemical system to sustain a reductive glycine pathway (rGlyP), producing 0.81 mM glycine from CO_2 and NH_3.[117] Li *et al.* developed a bifunctional Rh(III) complex that simultaneously catalyzed the reduction of CO_2 to formate and the electrochemical regeneration of NADH at the electrode (Fig. 4c).[118] Coupled with two downstream enzymes, this one-pot system produced dihydroxyacetone and L-erythrulose from CO_2. Although the yields were low (2.63 mM DHA and 1.93 mM erythrulose), this work demonstrated a practical all-in-one route: from electrical energy to a formate intermediate, then to enzymatic C–C coupling and ultimately to higher polyols. Photochemical regeneration of cofactors offers another attractive strategy.[119] By harnessing light, cofactor recycling can be driven by photoredox systems or by whole thylakoid membranes isolated from plants. Ning *et al.* used chloroplast thylakoid membranes to supply ATP and NADPH for the CO_2-to-3-hydroxypropionate (3-HP) pathway, achieving a 92% yield (Fig. 4d).[119] This approach integrates concepts from natural and artificial photosynthesis by using light-harvesting proteins to power a synthetic cycle. And several systems have eliminated specific cofactor requirements through pathway redesign. Liu *et al.* recently reported a chemoenzymatic route to synthesize amino acids and pyruvate from CO_2 and methanol without external NADH/NADPH or ATP.[120] Normally, the glycine to serine conversion requires the NAD-dependent protein. They replaced that step by using a chemical reducing agent, dithiothreitol (DTT), to keep the key enzyme in a reduced state, effectively substituting DTT for NADH in that step. With this innovation, they coupled methanol oxidation and CO_2 incorporation to produce glycine, which was then converted to serine and pyruvate, achieving titers in the g L^{-1} range for those products.

In summary, multi-enzyme cascades offer a modular and tunable platform for upgrading C_1–C_2 building blocks to larger products through protein engineering, pathway design, and use of chemical or electrochemical energy inputs. These cascades are a powerful complement to electrocatalysis. Enzymatic biocatalysis enables precise control, but it often relies on purified enzymes and externally supplied cofactors or recycling systems, leading to higher cost pressure during scale-up.[121] Scaling up these cascades and maintaining their efficiency outside the laboratory remains a significant challenge. Integrating them with electrochemical processes that provide a continuous driving force is one promising way to address this limitation.

2.2.2 Microbial routes for C_1/C_2 assimilation and product synthesis. Instead of relying on purified enzymes, one can use whole-cell catalysts, engineered microbes, to assimilate C_1/C_2 and convert them into target products. Whole-cell systems regenerate NAD(H)/NADP(H) intracellularly and are generally more cost-efficient and easier to scale, but offer less controllability and may be constrained by mass transfer and cellular physiology.[121] Many microorganisms naturally metabolize C_1 compounds. For example, methanotrophs oxidize methane, methylotrophs grow on methanol, and acetogens ferment CO_2 or CO to acetate.[122–124] However, these native pathways are often limited in rate and product range. Synthetic biology makes it possible to transplant or rewire metabolic routes so that industrially tractable hosts (such as *E. coli* or *Saccharomyces cerevisiae*) can utilize C_1/C_2 substrates to produce the desired chemicals.[125–128] Several studies have implemented rGlyP or variations in bacteria and yeast.[129–131] Yishai *et al.* demonstrated that *E. coli* can be engineered to fix formate *via* an introduced rGlyP.[131] When supplying external C_1 compounds to microbes, it is essential to consider how these substrates can be routed into central metabolism. Formate can be assimilated through the *Wood–Ljungdahl* pathway in native formate utilizers (such as *Clostridia*), or *via* the rGlyP or serine cycles in engineered hosts.[62] Native formatotrophs typically grow slowly and mainly produce acetate or re-oxidize formate, so researchers often turn to engineered fast-growing hosts. Tian *et al.* implemented this strategy by engineering the fast-growing bacterium *Vibrio natriegens* to co-utilize formate and glucose (Fig. 5a).[132] The resulting strain fixed formate into biomass and produced indigoidine, a blue pigment. By supplying both carbon sources, they obtained 29.0 g L^{-1} indigoidine in 72 hours while consuming 165.3 g L^{-1} formate. These results show that formate can contribute substantially to product carbon when metabolism is properly engineered and that co-feeding helps overcome the slow growth typically observed on formate alone. In another study, an oxygen-tolerant variant of rGlyP was expressed in the yeast *Komagataella phaffii* (also known as *Pichia pastoris*), enabling aerobic co-assimilation of CO_2, formate and methanol.[133] The engineered yeast was able to incorporate C_1 units from all three substrates, illustrating the potential for flexible C_1 feedstocks in a single organism.

Methanol is an attractive substrate for biotechnology. It is a liquid and energy-dense substrate that can be produced *via* syngas-based routes or electrochemical methods.[134–136] *Pichia pastoris* is widely used industrially for recombinant protein production on methanol-based feed.[133] Synthetic biology has enabled even non-methylotrophic organisms to utilize methanol by transplanting or imitating these pathways.[137,138] *E. coli* and *S. cerevisiae* have been engineered to co-consume methanol and sugars by expressing methanol dehydrogenases together with downstream assimilation enzymes, although robust growth on methanol as the sole carbon source remains difficult to achieve. In parallel, methylotrophic yeasts have been engineered to convert methanol into a variety of valuable chemicals. Zhao *et al.* reprogrammed *Pichia pastoris* to produce cordycepin, a nucleoside drug precursor, achieving titers of 1.55 g L^{-1} in shake flasks and 8.11 g L^{-1} in fed-batch fermentation (Fig. 5b).[139] Similarly, Niu *et al.* engineered *Pichia pastoris* to produce a complex plant secondary metabolite.[140] These examples show that methanol-fed bioproduction can reach

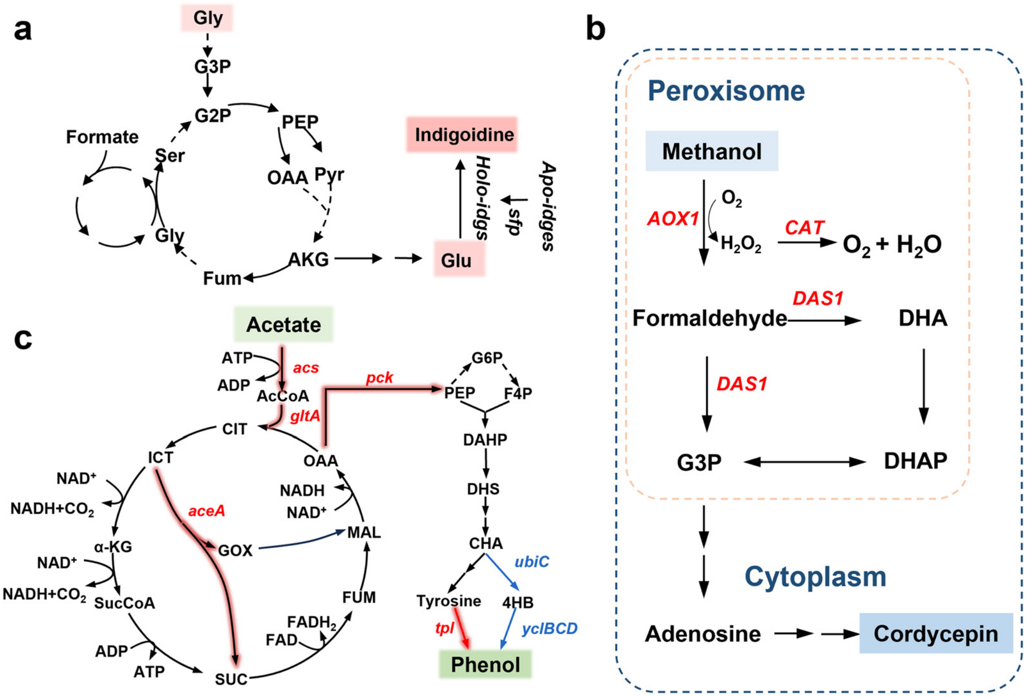

Fig. 5 Microbial routes to product formation. (a) Engineered biosynthetic pathway for the microbial production of indigoidine. Reprinted with permission from ref. 132. Copyright 2023, Springer Nature; (b) schematic of enhanced methanol assimilation in peroxisomes and the resulting changes in cordycepin yield achieved through enzyme fusion engineering. Reprinted with permission from ref. 139. Copyright 2023, Elsevier; (c) engineering of a microbial pathway for phenol production from acetate, illustrating the underlying genetic modification strategies. Reprinted with permission from ref. 143. Copyright 2025, American Chemical Society.

g L^{-1} levels for high-value products. A significant metabolic challenge is the toxicity of formaldehyde, a key intermediate in methanol metabolism. Cells must keep the formation and consumption of formaldehyde in a tight balance. When engineering methanol/formate-utilization pathways, it is therefore often necessary to increase downstream flux so that formaldehyde is rapidly converted into product to enhance detoxification and tolerance mechanisms to prevent its accumulation.

CO and CH_4 are gaseous substrates that some microbes can utilize.[141,142] Their low solubility in water poses a practical challenge for bioreactor operation. To address this, innovative reactor designs are being developed to enhance gas–liquid mass transfer. Ma *et al.* constructed a hollow-fiber membrane bioreactor that efficiently delivers CH_4 to methanotrophic cultures, enabling high cell densities and single-cell protein production from methane with a yield of 1.36 g biomass per g methane and a protein content of 67% w/w.[142] Such designs could likewise facilitate CO utilization by providing a large surface area for gas exchange. Acetate and ethanol are liquid substrates that are broadly compatible with microbial metabolism. Acetate can be taken up and converted to acetyl-CoA, although high concentrations of acetic acid can become inhibitory by lowering the pH.[128,143–146] Ethanol is similarly converted to acetyl-CoA *via* alcohol dehydrogenase and acetaldehyde dehydrogenase in many organisms. Because of their simplicity in metabolism, a wide range of products can be made with appropriate metabolic engineering. Feng *et al.* engineered *E. coli* to produce phenol from acetate by introducing the tyrosine-to-phenol pathway (Fig. 5c).[143] Phenol is an aromatic chemical normally derived from petroleum, but here they achieved up to 2.01 g L^{-1} phenol using fed-batch culture with *in situ* extraction. And Qian *et al.* reassembled a plant flavonoid pathway in *Pichia pastoris*, enabling the yeast to convert simple carbon sources into 4′-deoxyflavones.[128] They engineered synthetic regulatory circuits to balance the pathway, achieving high-level production of baicalein. While that particular demonstration used glucose as the carbon source in the published work, the authors noted the host could also run on methanol, illustrating the potential to produce complex natural products from C_1 feeds in the future.

In all of these microbial systems, metabolic engineering is critical. It involves introducing new enzymes, deleting competing pathways and installing dynamic control circuits. In a representative study on acetate-to-flavone biosynthesis, the researchers divided the pathway into modules and used synthetic transcription factors to control each module, ensuring that precursors were supplied with appropriate ratios and timing for efficient synthesis.[128] Comparable levels of control are likely to be necessary when integrating unfamiliar feedstocks into hosts that do not naturally metabolize them. In electro-bio cascades, microbes act as versatile biocatalysts that take the relatively small set of molecules produced by

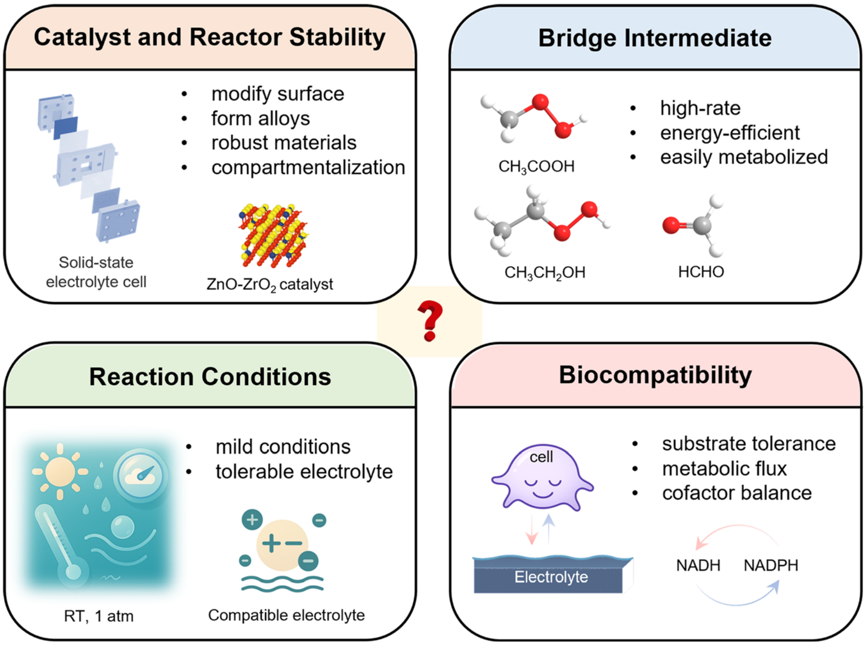

Fig. 6 Key factors of effective coupling for electro-biocatalysis cascade systems. Highlight the requirements on the catalyst and reactor stability, bridging intermediate, compatible reaction conditions, and overall biocompatibility.

electrolyzers and convert them into a wide variety of products through their metabolic networks.[147] They also enable chain elongation beyond C_3/C_4 *via* polymerization or iterative pathways, giving access to biopolymers and larger fuels that are difficult to obtain by electrocatalysis alone.[148–151] Recent work has shown that yeast can convert acetate into sugars and even starch polymers, and that bacteria can upgrade formate into C_4 products.[152,153]

3 Design of the coupled electro-biocatalysis cascade system

Integrating an electrochemical reactor with a bioprocess is non-trivial. The two systems have very different operational requirements, and direct interfacing can lead to mutual interference if not properly managed. Here, we outline key design considerations for effective coupling (Fig. 6) and then highlight illustrative case studies where these principles are applied.

3.1 Key factors for effective coupling

Choosing an appropriate bridging intermediate, the electrocatalytic product that feeds the biocatalytic step, is critical. Intermediate selection in electro-biocascades should be tailored to the target product and the downstream module, and should be made by jointly considering electrolyzer performance, interface compatibility, and biocatalytic assimilation requirements. This intermediate should be produced at a high rate and efficiency by the electrocatalytic module and be readily and selectively consumed by the biological module. Generally, liquid products are preferred over gaseous products (CO and H_2). From a technological maturity standpoint, CO_2RR to formate/formic acid is currently among the most industrially feasible routes, largely because it offers markedly higher selectivity and formation rates than C_{2+} products. By contrast, liquid products such as methanol, ethanol, and acetate have higher energy density and are more readily utilized as carbon feedstocks for downstream bioconversion, yet further improvements in their selectivity and yields remain necessary.

Catalyst and reactor stability are also critical. A typical fermentation might run for a few hours to several days.[132] Therefore, the electrocatalyst must be able to operate stably over comparable durations. Many laboratory-scale CO_2 reduction catalysts, particularly nanostructured materials, lose activity within tens of hours because of sintering, poisoning and carbonate formation in the electrolyte. For practical integrated systems, catalysts need to maintain high activity and selectivity over extended periods. Strategies to enhance stability include using more robust materials, modifying the catalyst surface, forming alloys, and continuously regenerating the active surface, for example, by applying potential pulses or adding ions that promote surface healing.[60,154–156]

In a single reactor where microbes and electrodes co-exist, the reaction conditions must suit both. This is challenging because many electrocatalysts perform best in strongly alkaline electrolytes such as KOH, whereas most cells require near-neutral pH and cannot tolerate highly alkaline media. Likewise, catalysts may depend on some metal ions but might be inhibited by others. Ca^{2+} and Mg^{2+}, common components of growth media, can precipitate on electrodes or even deactivate the catalyst. Conversely, the electric field and local high potentials near the electrode can harm delicate biological components or cause unwanted reactions of metabolites. Meanwhile, impurities introduced or generated in the electrolyte—such as metal ions leached from the electrodes and partially oxidized byproducts—may also inhibit enzyme activity or cell growth and disrupt the redox balance.[157,158] In one-pot configurations where the culture medium also serves as the electrolyte, these problems often arise. To avoid such cross-interference, researchers use compartmentalization, in which membranes separate the electrochemical chamber from the bioreactor and allow only the intermediate to pass, or temporal separation, in which the electrolyzer is run first and its product is then fed to the bioreactor.[46,89,151] This avoids direct exposure of cells to electrochemical conditions and allows each part to be optimized independently.

On the biological side, substrate tolerance and affinity are critical. Formate concentrations >100 g L^{-1} can inhibit many microorganisms due to acid stress and high ionic strength, high methanol levels are toxic to non-adapted cells, and acetate concentrations >10 g L^{-1} often slow bacterial growth. Enzymes also tend to exhibit poor tolerance to organic solvents. Advances in immobilization technologies have expanded the feasibility of electroenzymatic cascade catalysis. For example, co-immobilizing enzymes or cells on electrodes to construct bioelectrodes can effectively improve the compatibility between the electrochemical and biocatalytic modules.[159] Protein engineering to enhance robustness can therefore make enzyme cascades more resilient at higher substrate loadings. Alternatively, intermediates can be fed in a stepwise or fed-batch manner to keep their concentrations within a non-toxic window. Similarly, feeding intermediates at excessively low concentrations into a bioreactor can cause substantial volumetric dilution, limiting achievable product titers and increasing the energy demand for downstream separation. Efficient conversion of intermediates into products typically requires metabolic rewiring of the host. For example, transcriptional reprogramming and pathway engineering in *Saccharomyces cerevisiae* can enable strains to assimilate acetate and channel it into glucose biosynthesis.[89] In addition, metabolic engineering must secure efficient cofactor regeneration by coupling to auxiliary pathways or introducing transhydrogenases, so that assimilation and product formation proceed without stalling.[160]

3.2 Studies on electro-biocatalysis cascade systems

Biocatalytic conversion of CO_2 into value-added chemicals is an exciting research direction with the potential to transform biomanufacturing processes. Table 1 summarizes representative studies and key performance metrics in CO_2 electro-biocatalysis cascade systems. In general, these strategies first electrochemically reduce CO_2 to well-defined C_1–C_3 intermediates (*e.g.*, CO, formate, acetate/ethanol), which are subsequently upgraded *via* enzymatic catalysis or microbial metabolism through carbon-chain extension and functionalization, yielding more energy-dense, higher-carbon-number long-chain products.

Li *et al.* integrated an electrocatalytic formate generator with an engineered *Ralstonia eutropha* strain that produced isobutanol and 3-methyl-1-butanol (Fig. 7a).[35] Powered by solar electricity, the electrolyzer generated formate at high yield. The bacterium was engineered with a heterologous pathway that redirected acetyl-CoA from CO_2 fixation into isobutanol and 3-methyl-1-butanol. The integrated system achieved an electrical-to-alcohol energy conversion efficiency of about 50%. Although product titers were still modest, on the order of a few g L^{-1}, and the setup was a batch proof of concept, the study demonstrated that electricity and CO_2 can be converted into liquid fuel in a single integrated process. Zheng *et al.* developed a synthetic pathway for glucose production from CO_2. They used a Ni single-atom catalyst in a membrane assembly to convert CO_2 to CO, and then a nanostructured Cu catalyst rich in grain boundaries to reduce CO to acetate, achieving ~52% FE.[89] To avoid salt contamination, they built a custom reactor, where acetate was formed as an acetic acid

Table 1 Representative studies and key performance metrics in CO_2 electro-biocatalysis cascade systems

Substrate	Intermediate	Products	Yield	Ref.
CO_2	CO	Butyrate ($C_4H_8O_2$)	2.1 mmol h^{-1}	161
		Butanol ($C_4H_{10}O$)	1.68 mmol h^{-1}	
		Hexanol ($C_6H_{14}O$)	0.8 mmol h^{-1}	
CO_2	Formate ($HCOO^-$)	Polyhydroxybutyrate (PHB) (C_{6+})	11.5 mg h^{-1}	151
CO_2	Formate ($HCOO^-$)	Poly(3-hydroxybutyrate) (C_{6+})	75.6 mg L^{-1} per day	162
CO_2	Formate ($HCOO^-$)	Mesaconate ($C_5H_6O_4$)	151.6 mg L^{-1} per day	163
		2*S*-Methylsuccinate ($C_5H_6O_4$)	220.2 mg L^{-1} per day	
CO_2	Formate ($HCOO^-$)	Isobutanol ($C_4H_{10}O$)	28 mg L^{-1} per day	35
CO_2	Acetate (CH_3COO^-)	Food or food products (C_n)	—	46
CO_2	Acetate (CH_3COO^-)	Glucose (C_6)	1.81 g L^{-1}	89
		Fatty acids (C_{6+})	~500 mg L^{-1}	
CO_2	Acetate (CH_3COO^-)	PHB (C_{6+})	118 mg L^{-1} per day	164
CO_2	Acetate (CH_3COO^-)	PHB (C_{6+})	153.3 mg L^{-1} per day	165
CO_2	Ethanol (CH_3CH_2OH)	Polyhydroxyalkanoates (PHA) (C_{6+})	566.2 mg L^{-1} per day	166
CO_2	Ethanol (CH_3CH_2OH)	Lactol (C_6)	712–752 mg L^{-1} per day	43

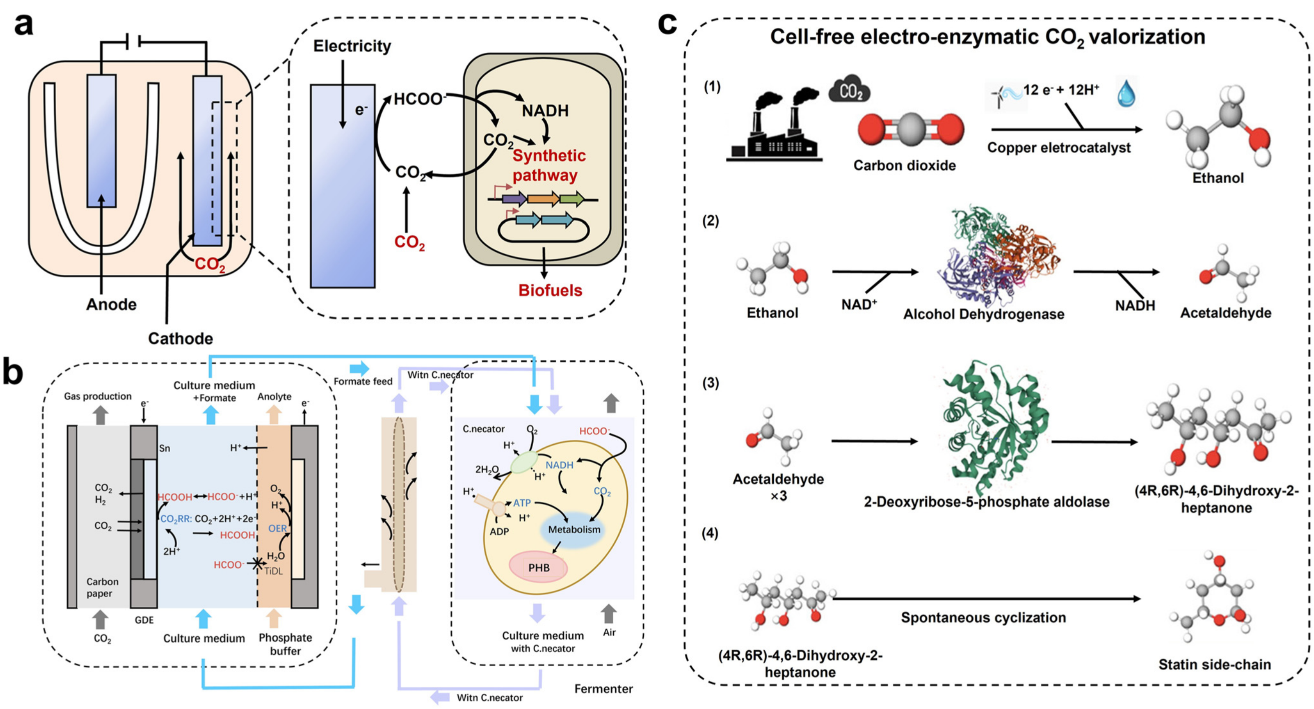

Fig. 7 Electro-biocatalytic synthesis. (a) An integrated electro-microbial process to convert CO_2 to higher alcohols. Electricity powered the electrochemical CO_2 reduction on the cathode to produce formate, which is converted to isobutanol and 3 MB by the engineered *R. eutropha*. Reprinted with permission from ref. 35. Copyright 2012, American Association for the Advancement of Science; (b) gaseous CO_2 is reduced to formate in the electrolyzer, and a single catholyte, formulated to be compatible with both electrochemical CO_2 reduction and microbial growth, is continuously circulated to a fermenter where cells transform formate into PHB. Reprinted with permission from ref. 151. Copyright 2012, National Academy of Sciences; (c) hybrid electro-enzymatic CO_2 valorization process. Waste CO_2 is electrochemically reduced to ethanol on a Cu electrocatalyst (1), and the ethanol is subsequently upgraded in a two-enzyme cascade: ADH (with NAD^+/NADH) oxidizes ethanol to acetaldehyde (2), and DERA catalyzes tandem aldol condensations to form cyclic statin-precursor molecules (3, 4). Reprinted with permission from ref. 43. Copyright 2022, American Chemical Society.

solution of about 97% purity. The acetate stream was continuously collected and fed to an engineered yeast *Saccharomyces cerevisiae* strain. With these modifications, the yeast grew on acetate and produced an average glucose titer of 1.81 g L^{-1}. The related engineered strain was further adapted to produce free fatty acids (C_8–C_{18}), reaching about 0.5 g L^{-1}. This study represented a breakthrough by demonstrating a carbon-negative route to sugars, producing them directly from CO_2 rather than from plants and without relying on photosynthesis. Initial glucose yields were low, but subsequent optimizations by the same research team and related groups significantly increased production to tens of grams per liter, far above the initial 1.8 g L^{-1}.[152] Together, these advances outline a compelling concept of a fully renewable sugar refinery in which CO_2 is converted, using only electricity and engineered microbes, into sugars and other biochemicals at industrially relevant concentrations.

Beyond fuels and sugars, tandem electro-bio systems have also been applied to make polymeric materials directly from CO_2. Lim *et al.* integrated CO_2 electrolysis with fermentation to produce the biopolymer poly-3-hydroxybutyrate (PHB) (Fig. 7b).[151] In this system, a Sn-based GDE catalyst converted CO_2 to formate with high efficiency, and the formate-containing electrolyte was circulated through a bioreactor holding *Cupriavidus necator*. The researchers optimized a nutrient-containing phosphate-buffered catholyte so that it supported both efficient electrochemistry and robust bacterial growth. The bacteria accumulated PHB up to 83% of their dry cell weight, yielding 1.38 g of PHB in a small reactor with a 4 cm^2 electrode. The PHB content is comparable to that achieved in PHB processes fed with sugar. They also demonstrated continuous operation by continuously withdrawing broth rich in PHB and adding fresh cells. In this way, they maintained a steady state in which the electrolyzer supplied formate and the culture produced PHB for more than 17 days. This setup addresses two key integration issues. It directly couples electrolysis and fermentation through a circulating loop, and it can run continuously, which is important for scale-up. PHB is usually produced from plant-derived sugars, so directly making gram-level PHB from CO_2 in this study is a significant advance. Studies have shown that PHB productivity can reach up to 118 mg L^{-1} per day.[164] These results show that CO_2 electro-biosystems can produce materials, not just simple chemicals, at practically relevant scales, thereby providing a solid process foundation and strong prospects for renewable electricity-driven biomanufacturing of materials.

The healthcare sector is carbon intensive and urgently requires decarbonization. Jack and co-workers proposed and validated an end-to-end hybrid electrochemical-enzymatic route that upgrades waste CO_2 into high-value C_6 pharmaceutical precursors (Fig. 7c).[43] In this platform, a three-chamber electrolyzer equipped with a Cu-based GDE efficiently converts gaseous CO_2 to ethanol at a current density of 40–60 mA cm^{-2}, achieving a selectivity of 43–81 mol% and a production rate of 368–428 mg L^{-1} h^{-1}. The electrolytically produced ethanol is then separated, purified, and fed into an enzymatic reactor, where alcohol dehydrogenase (ADH) and 2-deoxyribose-5-phosphate aldolase (DERA) further construct C_6 statin-precursor molecules *via* an acetaldehyde intermediate, delivering overall yields of 29–35%. The process attains competitive C_6 lactol synthesis performance, with rates of 4.7–5.7 mM per day and titers of 712–752 mg L^{-1}, demonstrating the feasibility of electro-enzyme cascades for manufacturing high-value molecules. Given that the C_6 lactol product can be readily converted into statins, this work offers a new pathway for CO_2 valorization to pharmaceutical-value chemicals.

More recently, Chen *et al.* developed an "electro-biodiesel" platform to synthesize lipid (fatty acid) biodiesel precursors from CO_2.[167] They co-designed the catalyst and the microbe. The Zn–Cu catalyst was tailored to favour C_2 products. The genetically engineered *Rhodococcus jostii* strain can efficiently consume acetate and ethanol and store the carbon in the form of lipids. The resulting system reached a solar-to-lipid energy efficiency of 4.5%, greatly exceeding crop-based biodiesel in land use and energy efficiency. This work showcases a fully integrated design from catalyst to microorganism, where the catalyst is tuned to produce the C_2 intermediates preferred by the microbe and the microbe is tuned to efficiently assimilate the catalyst's product stream, yielding one of the most efficient CO_2 to fuel processes reported so far.

Taken together, these case studies employ different intermediates and operating modes, illustrating multiple integration strategies that couple electrocatalytic CO_2 reduction with biocatalysis to produce multi-carbon products. The overall performance of integrated electro-biocascade systems is jointly constrained by electrolyzer losses (*e.g.*, mass-transport limitations and overpotentials) and the ATP/NAD(P)H demands of downstream bioconversion. Thus, even when individual modules perform well, system-level energy and carbon efficiencies can remain limited. By contrast, conventional thermochemical CO_2 to methanol synthesis can achieve a thermal efficiency of 62%,[168] and traditional fermentation for PHB production could reach peak productivities of 1.73 g L^{-1} h^{-1},[169] which are substantially higher than those of most electro-biocascades. Because evaluation metrics and system boundaries differ, direct quantitative comparisons between these routes remain scarce. Nonetheless, recent demonstrations show rapid progress: CO_2 electrolysis coupled with gas fermentation has operated continuously for >1200 h at 300 mA cm^{-2} and achieved near-quantitative Faradaic utilization during higher-alcohol production.[161] Meanwhile, formate-mediated biohybrid platforms have also demonstrated stable electrolysis at ~120 mA cm^{-2}, highlighting the strong development potential of electro-biocascades.[151]

4 Challenges and future directions

Despite exciting progress, the field of CO_2 electro-biocatalytic conversion is still in its early stages. There are scientific and engineering challenges to address before these hybrid systems can be scaled up and widely implemented. Here we discuss key challenges and suggest directions for future research.

Improving overall energy efficiency

Despite substantial progress at the module level, overall efficiencies for converting CO_2 to products remain modest once all losses are taken into account. The overall energy efficiency of existing electricity-driven microbial electrosynthesis systems varies widely across reactor configurations and product pathways. Reported systems can reach efficiencies on the order of the teens to several tens of percent, yet further improvements are generally needed, particularly for end-to-end integrated operation and long-duration runs.[89,167,170] Future efforts must focus on lowering electrocatalytic overpotentials, sharpening product selectivity, minimizing side reactions and redesigning biological pathways to reduce ATP and NAD(P)H demand. Whole process models that couple electrolysis with cellular metabolism will be essential to identify dominant energy sinks and guide targeted optimization.

Scaling up and redesigning reactors

Moving from electrodes on the centimetre scale and bioreactors with volumes from milliliters to liters to industrial plants will amplify challenges in mixing, mass transfer, gas handling and product purification. Large area electrodes and high currents are already used in water electrolysis and in plants that convert CO_2 to CO, but maintaining high purity liquid products and managing large CO_2 and O_2 flows at industrial scale remain difficult.[171] Modular "scale-out" architectures, with many electro-bioreactors operated in parallel and co-located with cheap renewable power and CO_2 point sources, are likely to be a practical route to deployment.

Engineering biocatalysts and intermediate selection

On the biological side, a key goal is to build strains that consume C_1 and C_2 feeds rapidly and channel carbon into products at high titer, rate and yield. Strategies include adapting existing production strains that currently run on sugars, exploiting non-model organisms that natively fix CO_2 or C_1 substrate, and designing co-cultures that divide labor between substrate assimilation and product formation. Continued development of genetic tools for acetogens, methylotrophs and other specialist microbes will expand the design space for electro-biocatalytic cascade systems. In parallel, establishing target-oriented, quantitative criteria for selecting bridging C_1–C_3 intermediates (*e.g.*, achievable titer and stability, separation/transport penalties, and biocompatibility/assimilation constraints) is an important next step to guide the rational design of electro-bio cascades.

Integrating control, CO_2 sourcing and sustainability

Although electrocatalytic CO_2 reduction has shown promise for scale-up, achieving large-scale and stable industrial production remains challenging once it is cascade-coupled with biocatalysis, particularly in terms of long-term operational stability, mass-transport and impurity tolerance, and system-level energy efficiency and cost control. Robust operation of coupled systems will depend on dynamic control of the relative rates of electrolysis and bioconversion. These processes must also be coupled to realistic CO_2 sources (for example, flue gas or direct air capture streams) and validated through rigorous techno-economic analysis and life-cycle assessment to demonstrate climate benefits and cost competitiveness.[172,173] Future cascade research should be oriented toward industrial deployment by strengthening integrated technical-economic-application evaluation and optimization. And quantitatively evaluate the environmental benefits and economic costs to provide more intuitive data support. Utilizing waste or air-derived CO_2, alongside low-cost renewable energy sources, is one strategy that significantly improves economic efficiency.

In conclusion, electro-biocatalysis cascades represent a powerful synthesis paradigm for a sustainable future. Fast and modular energy input supplied by electrochemistry is coupled to the complex and carbon-efficient chemistry of biological systems. In recent years, striking proof-of-concept studies have been reported in which fuels, plastics and even food precursors are produced from CO_2 and renewable electricity. The field is evolving rapidly, with continuous improvements in catalysts, metabolic engineering strategies and integrated process designs. Advances in materials science will be needed to deliver stable, selective catalysts and practical reactor architectures. Progress in synthetic biology will be required to create robust cell factories and enzyme systems. Contributions from systems and process engineering will be essential to integrate and scale these hybrid platforms. Together, these efforts point toward a new industrial paradigm in which carbon waste becomes a valuable feedstock, powered by green energy, to yield the products society needs—from fuels and fertilizers to pharmaceuticals. Over the coming decade, both incremental improvements and step-change innovations, such as substantial gains in overall energy and carbon efficiency, are expected to further strengthen the technical and economic feasibility of this approach.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

This review article does not involve original data. All analyzed information is from published sources.

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