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Commentary

Light-Independent Biological Conversion of CO₂

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A growing concern of 21st-century humanity is the continuing rise of atmospheric CO₂ levels from expanded use of fossil fuels for heat and power generation. Each day that CO₂ levels rise, humanity treads further into the uncharted waters of a changing climate and ecosystem. Mitigating carbon emissions is only a transitory solution to

relieving uncertainty in the future environmental impacts. To be able to control atmospheric CO₂ levels, capabilities to net remove CO₂—in other words, “negative emissions” technologies—are a must. Various carbon capture, utilization, and storage (CCUS) approaches are underway to remedy the imbalance between CO₂ generation and absorption. Strategies to convert CO₂ into value-added products are particularly appealing because of potential environmental and economic benefits.

In practice, achieving CO₂ utilization profitably is a grand challenge. Effective CO₂ utilization strategies must be able to stand the test of time. Recent US oil prices have been hovering around \$30–\$40 per barrel, and as states went into lockdown due to coronavirus disease 2019 (COVID-19), the price turned negative for the first time in history, albeit briefly. A business that converts CO₂ into fuel to sell it would struggle to survive in today's world of cheap oil. Likewise, few things are of lasting value, and thus a stable CO₂ removal program demands a flexible product lineup. What are the key features of enduring technologies that can weather geopolitical and economic turbulence? In addition to high concentration, purity, scalability, and productivity, a diversifiable product repertoire is needed.

Biological conversion of CO₂ may fit the bill. Most of us naturally associate biological CO₂ conversion with photosynthesis in plants and algae. While engineering photosynthetic hosts to convert CO₂ into high-value products is sensible, dependence on sunlight limits its tractability and scalability. The productivity of photosynthesis is proportional to the surface area exposed to sunlight, a capricious source of energy in many regions. Furthermore, the maximum efficiency of solar energy conversion by photosynthesis is ~5%, while typical solar

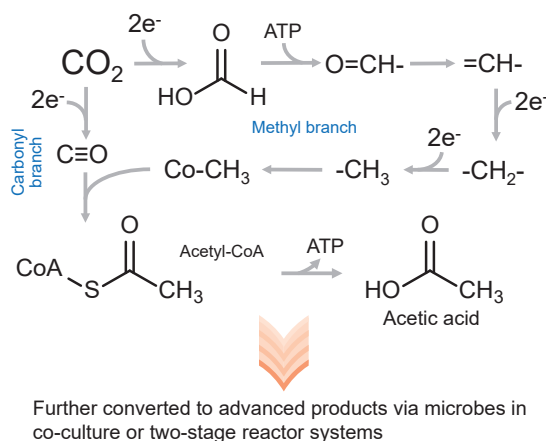
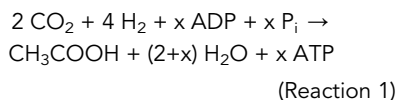


Figure 1. Non-photosynthetic CO₂ Conversion

The reductive acetyl-CoA pathway, also known as the Wood-Ljungdahl pathway (WLP), converts two CO₂ molecules, via the methyl and the carbonyl branches, into one acetic acid. The one-carbon units in the methyl branch are bound to and carried by tetrahydrofolate (not depicted). The CO₂-derived acetic acid can be fed to other microbes for synthesis of more advanced products.

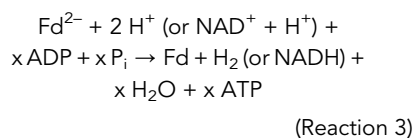
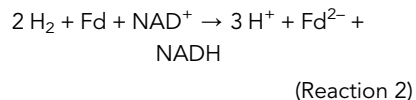
panel efficiency reaches ~20%. These shortcomings may be overcome if the Calvin cycle—the light-independent metabolic pathway in which CO₂ is assimilated by the famous enzyme Rubisco—is introduced into non-photosynthetic organisms and driven by chemical energy instead of light.¹

Perhaps less familiar to most is a biological yet non-photosynthetic CO₂ reduction mechanism: the reductive acetyl-CoA pathway, also known as the Wood-Ljungdahl pathway (WLP). Acetogenic microbes (e.g., *A. woodii*, *C. ljungdahlii*, and *M. thermoacetica*) can reduce two CO₂ molecules, via the carbonyl and methyl branches of this pathway, to make one acetic acid (Figure 1).² Unlike plants and algae, these acetogens do not depend on sunlight; they can instead derive energy from H₂ (Reaction 1).

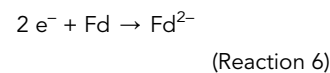
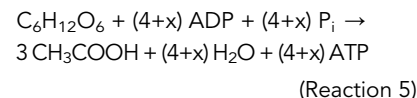
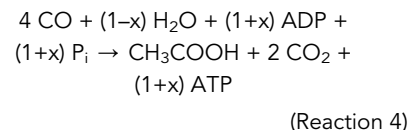


x varies between 0 and 1 depending on organisms and conditions because ATP is generated by chemiosmosis (the transport of H⁺ or Na⁺ down their electrochemical gradients).

As the WLP includes thermodynamically challenging steps, cells use an energy-efficient means of transferring electrons, termed electron bifurcation.³ An example is the hydrogenase enzyme that transfers electrons from H₂ to two electron carriers (Reaction 2): (1) ferredoxin (Fd), an iron-sulfur protein family with more negative reduction potential to overcome the reduction energy barrier and (2) NAD⁺, with less negative reduction potential to limit wasting free energy. Some electron transfer steps involving transmembrane proteins (e.g., Ech and Rnf complexes) are linked to creating an electrochemical gradient by pumping out H⁺ (or Na⁺ in *A. woodii*) across the cytoplasmic membrane. ATP synthase then uses the proton motive force, the flow of H⁺ back into the cytoplasm, to drive ATP synthesis (Reaction 3).



Acetogens can extract usable energy from various sources: gases (Reactions 1 and 4), organic molecules (Reaction 5), and electricity (Reactions 3 and 6).



This versatility in energy utilization allows CO₂ conversion via mixotrophic fermentation⁴ (e.g., simultaneously using Reactions 1, 4, and 5) and microbial electrosynthesis⁵ (i.e., using Reactions 3 and 6 to obtain reducing power and ATP to convert CO₂ and sustain necessary cellular functions).

An inevitable challenge associated with biological CO₂ conversion is that typical bioprocesses are slow and must be sped up. This complication arises because cells require energy in two forms, reducing power and ATP, in balance. For acetogens, which are obligate anaerobes unable to use aerobic respiration with its associated potent oxidizing agent O₂, converting redox potential to ATP is a challenging task (Reaction 3). ATP is not only required for maintenance of essential cellular functions for survival, but it also drives otherwise thermodynamically unfavorable reactions by hydrolyzing its high-energy phosphoanhydride bond for biosynthesis. Therefore, metabolic engineers must ensure that (1) minimum cellular ATP requirement is met and (2) cells have ATP and reducing power in the right stoichiometry for desired product synthesis. If these are achieved, carbon yield and productivity can be greatly accelerated (e.g., each gram of acetogenic *M. thermoacetica* cells can

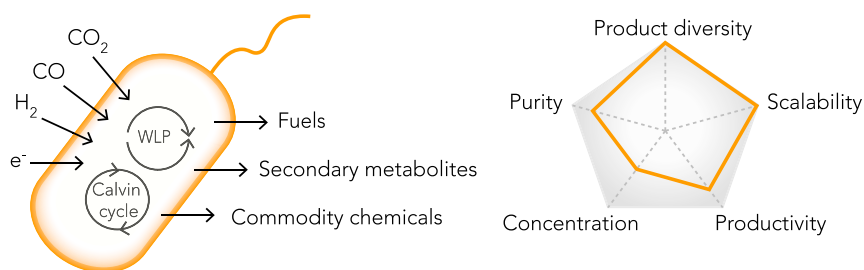


Figure 2. The Strengths of Light-Independent Biological CO₂ Utilization

CO₂ can be converted into diverse products via the WLP and the Calvin cycle. Product diversity and scalability are the strengths of light-independent biological CO₂ utilization.

reduce 56 g of CO₂ per day, ~50 times as fast as photosynthetic cells).⁶

How is non-photosynthetic CO₂ utilization beneficial? One major benefit is that, in addition to having a relatively high specific productivity, this approach scales up volumetrically, not areally, due to its independence from sunlight (Figure 2). Furthermore, while the product of CO₂ assimilation, acetic acid, does not itself have a high market value, it can support both microbial cell division and biosynthesis of more valuable molecules. When provided as a substrate to other microbes, acetic acid derived from CO₂ may yield various biomolecules including fatty acids, polyketides, and isoprenoids.

The depth of potential bioproduct diversity from CO₂, with the advancement of synthetic biology and diverse genetic materials found in the kingdoms of life, is nearly unfathomable. Converting CO₂ into secondary metabolites—via co-culture or two-stage reactor systems—is an exciting opportunity because of their antimicrobial, anti-inflammatory, antioxidant, and other diverse biological activities. Since the discovery of penicillin, antibiotics have been among the best-known microbial secondary metabolites, which are non-essential for cell growth but useful in coping with environmental stressors and facilitating symbiosis. Secondary metabolites encompass alkaloids, aromatic compounds, isoprenoids, oligosaccharides, nonribosomal peptides, and polyketides, which are of use in pharma-

ceutical, cosmetic, food, agricultural, and chemical industries as drugs, UV filters, plant growth regulators, insecticides, etc. This market diversity is a hedge against future volatility—for example, as a way to make up for low profitability of biojet fuel and biodiesel in a world of cheap oil.

From an economic perspective, the cost of goods sold (COGS) and product prices determine which CO₂ utilization strategies are worthwhile. The cost of CO₂ varies considerably depending on the proximity of CO₂ capture plants to CO₂ generating plants. Direct air capture currently costs ~\$700 to remove one metric ton of CO₂,⁷ but the cost would be substantially lower if more concentrated CO₂ is captured at the source before being released into the atmosphere. For example, the flue gases from coal and natural gas power plants, as well as ethanol plants, would provide “cheap” CO₂ if directly passed on to CO₂ utilization plants. Subsequently, CO₂ conversion should be carried out in cost-effective processes.

Bioprocesses offer cost-effective solutions, especially for synthesis of large or complex molecules. That is because the catalysts—which in non-biological processes, are often a major expense—are cells that self-replicate rapidly. Furthermore, cells can be genetically modified to be equipped with various biosynthetic pathways without additional capital expenditure. This in turn provides bioprocesses with the benefit of relatively

low facility-dependent costs such as depreciation and amortization (the direct fixed capital of a plant with a 500 m³ bioreactor capacity, which can remove ~200 metric tons of CO₂ per day, is ~\$200 million). Instead of relying on traditional batch-culture systems, utilizing continuous bioprocessing may lower operating expenditure and COGS.

Other important determinants of unit production costs via non-photosynthetic bioprocesses are the cost of energy (electricity and H₂) and the cost incurred by downstream processing—which comprises as much as 80% of manufacturing costs and depends on product concentration and purity, as well as production scale. Today, electrical energy is generally more cost effective than H₂. In California, the retail energy prices are ~\$0.05/MJ for electricity (~\$0.20/kWh) and ~\$0.12/MJ for H₂ (using 120 MJ/kg, lower heating value). H₂ is ~\$14/kg at a hydrogen fueling station, although H₂ production by electrolysis would cost ~\$11/kg with some additional costs expected due to pressurization and distribution. In some regions, however, renewable H₂ price may be as low as ~\$3.50/kg.⁸ H₂ is even cheaper (as low as \$1/kg) from large-scale fossil hydrogen supply. While not ideal, even H₂ derived from methane could still enable net CO₂ removal. Via steam methane reforming and water-gas shift reaction, each methane produces one CO₂ and four H₂, which can be used to convert two CO₂ into one acetic acid, a starting substrate for any biomolecule. As these processes require heating and cooling, the actual net CO₂ that can be reduced via the WLP per methane would be lower (~0.1 net CO₂ removed per CH₄). Of course, the full CO₂ utilization potential is realized when the energy requirement is through clean zero-emission sources.

Despite these energy prices, producing high-value chemicals may render non-photosynthetic bioprocesses economically viable, while producing lower-value

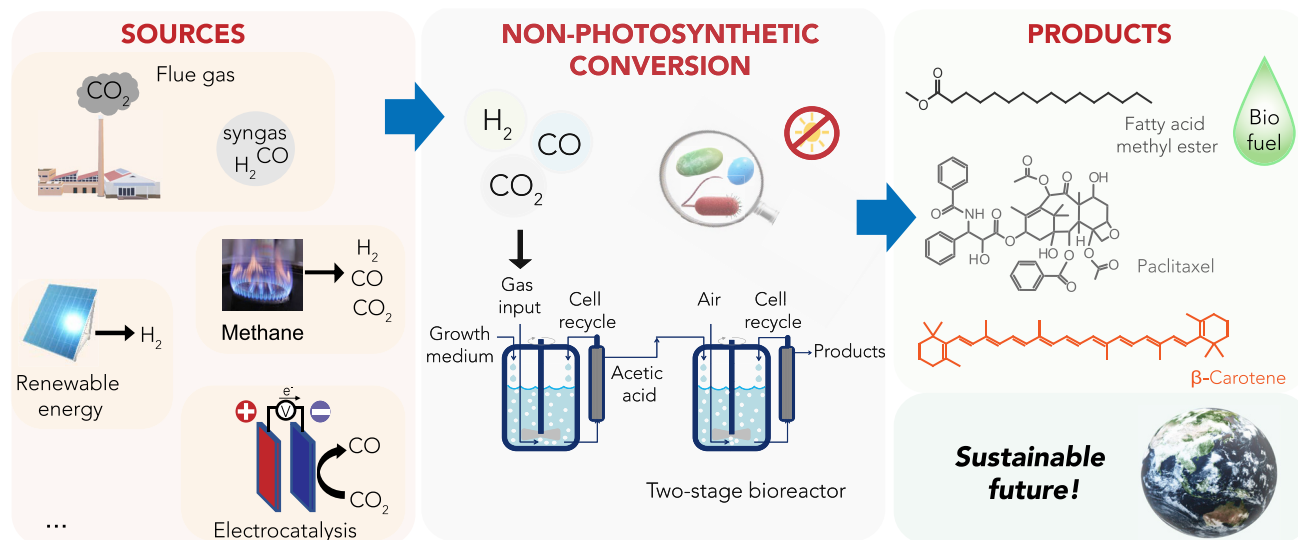


Figure 3. The Overall Schema for Non-photosynthetic CO₂ Utilization toward a Sustainable Future

Using various sources of energy and integrated biological-inorganic catalysis may optimize non-photosynthetic CO₂ conversion. Producing both high-margin products and high-volume products will ensure economic and global-scale CO₂ utilization.

products faces headwinds. Since H₂ delivers electrons directly to cellular molecules and contributes to biosynthesis stoichiometrically while Faraday efficiency in microbial electrosynthesis is not well established, here the focus will be on renewable H₂. Using H₂ at \$3.50/kg to convert CO₂ into acetic acid—one of the simplest products made by non-photosynthetic CO₂ conversion—corresponds to ~\$0.50 worth of H₂ to produce (without taking into consideration fermentation and purification costs) one kg of acetic acid whose market price is ~\$0.60/kg. The CO₂-derived acetic acid can be directly fed to other microbes for advanced product synthesis. The economic challenge lingers if producing, for example, biofuel, which requires combining several acetic acids, when producing one kg of biofuel costs >\$3, yet crude oil is ~\$0.25/kg (\$34/barrel). However, if the targets were β-carotene and paclitaxel, which respectively are ~\$1,000/kg and ~\$1,000,000/kg,⁹ the CO₂ conversion processes would make sense—but not without challenges. Besides the total addressable market being smaller than the fuels market, one key challenge to overcome in secondary metabolite production is low product

concentration. For instance, β-carotene, a tetraterpenoid with health benefits that is produced by engineered *Y. lipolytica* via the mevalonate pathway, currently reaches the titer of 6.5 g/L.¹⁰ Furthermore, the great diversity of chemical structures, reaction mechanisms, and genetic origins presents important hurdles for chemists and metabolic engineers. Discovering nature's chemical toolset would unlock more opportunities.¹¹ The advancement of modern genetic and analytical tools, as well as integrative omic approaches, would facilitate these efforts.

Economic and global-scale CO₂ utilization requires multidisciplinary teams of scientists and engineers. While the high specificity of enzymes—owed to discriminatory and stereospecific recognition of substrates—is a key ingredient for successful CO₂ utilization, the full potential of CO₂ utilization will only be realized by integrating biological and inorganic catalysis. The biochemical part of the team should strive to rapidly produce complex chemicals at high purity and concentration starting from acetic acid (past metabolic engineering efforts have

focused on utilizing mainly glucose). With the goal of integrating with the former, the abiological counterpart should strive to maximize gas and electron transfer rate to cells and efficiently purify the products. To maximize net CO₂ utilization, further research into securing low-carbon energy at a low cost is needed. Solving these challenges will allow CO₂-derived products to enter more markets (including the fuels market) more competitively.

These are not insurmountable challenges. Technological advances have been driving renewable energy costs lower. CO₂ utilization processes could perhaps use H₂ generated using the intermittent surplus energy in the electricity market. The unique strengths of biological and inorganic catalysis may be combined by using non-photosynthetic microbes that are amenable to integration with inorganic processes.¹² Formic acid and CO, which can be readily produced electrochemically and provide carbon and energy to microbes, would serve as good intermediary molecules. Furthermore, CO₂-derived products may be

strategically developed to utilize existing infrastructures (e.g., oil infrastructure for refining, distributing, and storing biofuels). Developing technologies to convert CO₂ into both high-margin products and high-volume products would ensure a positive global impact (Figure 3).

In the near future, it will be possible to kill two birds (attain environmental and economic benefits) with one stone. Until then, rigorous technoeconomic analysis and life cycle assessment should be carried out for any promising technologies. The processes should be designed to withstand the constant pressure for lower price. With their evolutionarily crafted efficiency, microbes that have once contributed to rendering our primordial planet habitable may help innovate solutions to rising CO₂.

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