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Perspectives on biorefineries in microbial production of fuels and chemicals

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Microbes drive our complex biosphere by regulating the global ecosystem through cycling elements and energy. Humankind has barely begun leveraging this biotransformation capacity to impact global economies and ecologies. Advances in genetic engineering, molecular analysis, metabolic flux modeling, microbial consortia/biome mapping and engineering, cell-free bioproduction, artificial intelligence/machine learning and the ever expanding -omics frontiers have set the stage for paradigm changes to how humankind produces, uses, transforms, and recycles carbon and energy through microbes. Harnessing this enormous potential could drive a global bioeconomy and manage carbon at a planetary level but requires understanding and application at a grand scale across a broad range of science and engineering disciplines. The penultimate manifestation of these advances is the “bio-refinery”, which is often referenced, but is a long way from being fully developed as a global carbon management platform. Broadening the feed stocks, processing operations, and product portfolio to a sequential cascade optimizing the conversion as a whole instead of limited outputs could greatly advance deployment and stability of a bioeconomy.

KEYWORDS

bio-refinery, bioconversion, biofuels, bio-products, carbon management, bioeconomy, industrial microbiology

Introduction

The “bio-refinery” is envisioned as “biomass in - products out” via a sequence of mechanical, thermochemical, and biological processes (Takkellapati et al., 2018) (Figure 1A) over a range of feed stocks and products. Setting aside grain/sugar feed stocks, lignocellulosic inputs dominate this landscape, often limited to one or a few closely related materials. Residual carbon represents an untapped resource for additional products or carbon sequestration. Proposed dedicated bio-refineries include starch (Koutinas et al., 2007; Laufer, 2019; Parchami et al., 2021; Marzo-Gago et al., 2022; He et al., 2023), sugarcane (Pereira et al., 2021; Valladares-Diestra et al., 2021; Deeba et al., 2022; Fernando

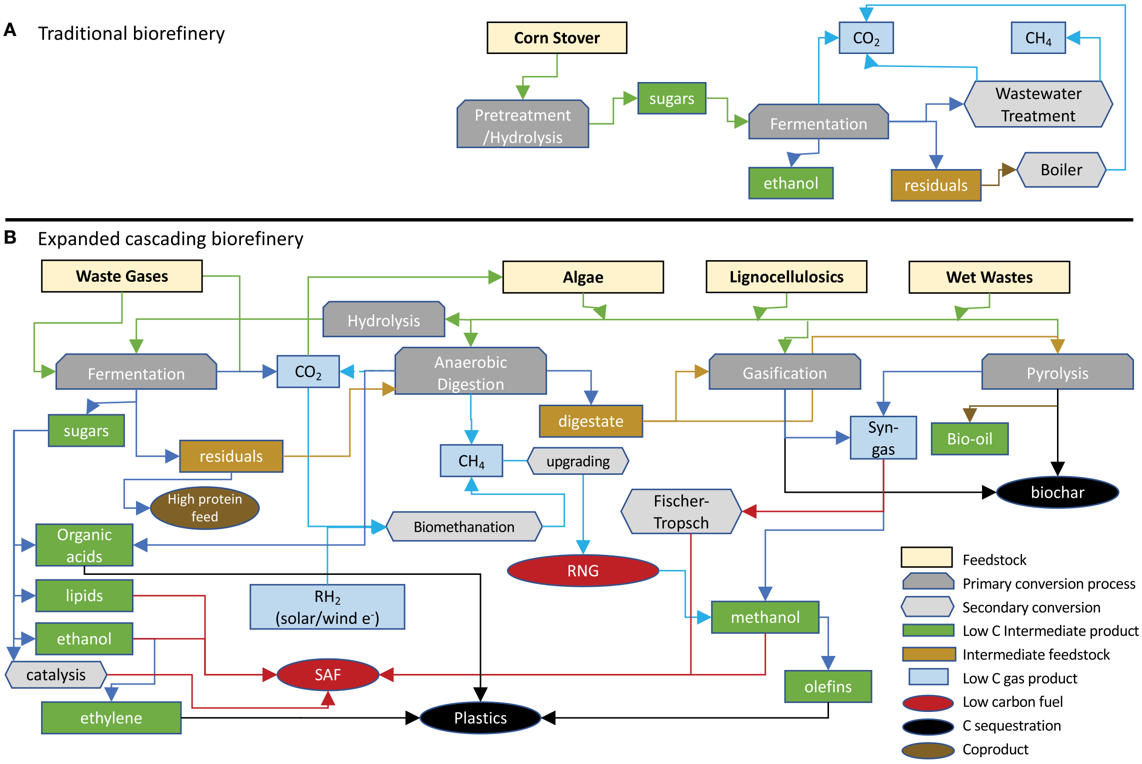

FIGURE 1
(A) Typical bio-refinery process scheme where limited feed stocks are transformed by a linear process into limited bio-products. (B) Expanded bio-refinery concept using multiple conversion processes to transform a range of feed stocks into an array of bio-products and sequestering untransformed carbon. RNG, Renewable Natural Gas; SAF, Sustainable Aviation Fuel.

Herrera Adarme et al., 2022), or wheat straw to ethanol (Kaparaju et al., 2009), lignocellulosics to BDO (Huang et al., 2013; Li et al., 2014; Forte et al., 2016; Hazeena et al., 2020; Rehman et al., 2021), waste gases to ethanol (Arslan et al., 2019; De Tissera et al., 2019; Liu et al., 2022; Tharak and Mohan, 2022), trees to paper pulp (Huang et al., 2010; Hundt et al., 2014; Gottumukkala et al., 2016), wet waste to biogas and fertilizer (Bhaskar et al., 2016; Dahiya et al., 2018; Ge et al., 2018; Desmond-Le Quemener et al., 2019), biomass to hydrocarbon fuels (Davis et al., 2020; Klein et al., 2021), and biomass to biochar, bio-oil, or syngas (Wang et al., 2013; Sarkar et al., 2015; Yuan and Macquarrie, 2015; Hong et al., 2017; De Bhowmick et al., 2019a; De Tissera et al., 2019; Sun et al., 2020). “Niche” platforms have been proposed for specific feed stocks, conversion processes, and products. Usmani et al. published a review of lignocellulosic bio-refineries in 2021 (Usmani et al., 2021)and the IEA published a limited bio-refinery status in 2022, not including the US or Canada among others (Annevelink et al., 2022), which included “extended” pulp/paper, anaerobic digestion, or sugar/starch-based bio-refineries and only nine convert lignocellulosics to ethanol, most with mixed product streams. Feed-stocks for the remaining are variable and include wood processing waste, wet wastes, pulp and paper waste, used/primary vegetable oils/animal fats, textile waste, seed/starch based, grasses/ag crops/residues, and MSW/other wastes. Table 1 is a compilation of selected lignocellulose/waste-based bio-refineries compiled from several websites (Ethanol biorefinery locations; Biorefineries in Europe; Global biorefinery status report 2022; Facilities).

Lignocellulosic bio-refineries transforming the energy landscape through renewable fuels has had numerous social, political, and technical obstacles. Food vs. fuel, land-use, and carbon emissions have been used as arguments against biomass conversion. And while lack of incentives and credits are implied, failure points are mainly technical, i.e. conversion of recalcitrant plant polysaccharides to sugars (Yogalakshmi et al., 2023). Lignin is a problem as is crystalline cellulose and the heterogeneity of hemicelluloses, requiring complex processing and expensive enzymes. Dozens of pretreatments have been tested and generally failed, many due to focusing too tightly on a single product and devaluing the remainder (Yogalakshmi et al., 2023). Fibrous or woody structure requires energy to overcome and collection and transport impose additional costs and supply issues (Saini et al., 2020). Feedstock complexity leads to process design, construction, and operational complexity, other points of failure (Saini et al., 2020). A few examples speak to the primary causes. Dirty feed stocks wreaked havoc at Beta-Renewables and Poet’s Project Liberty had feed stock feeding and pretreatment issues. KiOR failed to scale their facility correctly and low production could not maintain operational capacity while the ADM/Metabolix bioplastic venture failed due to uncertainties in design, production, and market adoption (Saini et al., 2020). Complexity failed INEOS’ Indian

TABLE 1 Snapshot of global lignocellulose/waste-based bio-refineries operating at the time of this article's development.

Name	Country	Feedstock	Output
OCEANIA			
Mackay Renewable Biocommodities Pilot Plant	Australia	lignocellulosics	Bioethanol
Ethtec, Hunter Pilot Biorefinery	Australia	Lignocellulosic material (sugar cane bagasse, crop stubbles and forest material)	Ethanol and xylitol
Northern Oil Advanced Biofuels	Australia	Sugar cane bagasse and prickly acacia. In the future: sawmill waste, tyres, plastics, food waste, biosolids	Biofuels (bio-crude)
EUROPE			
AustroCel Biorefinery -	Austria	Cellulose waste	Bioethanol
AGRANA Biorefinery	Austria	Wheat, maize	Bioethanol, animal feed, CO2
Lignovations - TU Wien	Austria	Woody residual biomass	Colloidal lignin particles
AustroCel Biorefinery	Austria	Cellulose waste	Bioethanol
Cellulonix Kajaani	Finland	forest residues	Bioethanol
Futurol	France	Multifeedstock	Ethanol, chemicals
Brensbach/Biowert	Germany	Grass and Silage	Energy, material and chemical products
UPM Leuna	Germany	Wood	material and chemical products
Cellulac Ltd	Ireland	Lignocellulosic	lactic acid ethyl acetate.
Cellulac Ltd. Commercial	Ireland	Lignocellulosic materials	High enantiopurity lactic acid and ethyl acetate.
Biochemtex-Crescentino	Italy	Lignocellulosic biomass	Bioethanol
Versalis Biorefinery	Italy	Hardwood, ag residues	Bioethanol, Lignin
Zambezi process	Netherlands	Wood (Non-food biomass)	Chemicals: high-purity glucose and lignin
BioMCN	Netherlands	municipal waste	Biomethanol
Neste Biorefinery	Netherlands	Waste residues	Fuels and chemicals
ChemCell Ethanol	Norway	sulfite spent liquor	ethanol
Clariant Romania	Romania	agricultural residues	ethanol
Domsjö Fabriker	Sweden	Forestry raw material	Cellulose, lignin, bioethanol and Biogas
Södra Mönsterås Liquid Forest^{TM}	Sweden	Wood chip	Biomethanol
SCA Obbola–Umeå	Sweden	Black liquor	liquid biofuels and chemicals
Novamont-Terni,	Sweden	Local agricultural crops.	Bio-lubricant and bioplastics
Biochemtex-Crescentino	Sweden	Lignocellulosic biomass	Bioethanol
SOUTH AMERICA			
GranBio	Brazil	Cellulosic Bagasse/straw	Bioethanol
Raizen Energia	Brazil	Cellulosic Bagasse/straw	Bioethanol
NORTH AMERICA			
Tembec Chemical Group	Canada	spent sulphite liquor feedstock	Bioethanol
Iogen Corporation	Canada	lignocellulosics	Bioethanol
Parallel Products	US (CA)	Waste Sugars/Alcohol	Bioethanol
Pelican Acquisition LLC	US (CA)	Corn/Sorghum/Cellulosic Biomass	Bioethanol

(Continued)

TABLE 1 Continued

Name	Country	Feedstock	Output
AVAPCO	US (GA)	Multiple lignocellulosics	Bioethanol, sugars, nanocellulose
Quad County Corn Processors	US (IA)	Corn/Cellulosic Biomass	Bioethanol
POET Biorefining - Shell Rock LLC	US (IA)	Corn/Cellulosic Biomass	Bioethanol
POET Biorefining - Iowa Falls LLC	US (IA)	Corn/Cellulosic Biomass	Bioethanol
NewEnergyBlue LLC	US (IA)	Cellulosic Biomass	Bioethanol
Louis Dreyfus Grand Junction LLC	US (IA)	Corn/Cellulosic Biomass	Bioethanol
PureField Ingredients LLC	US (KS)	Corn/Sorghum/Cellulosic Biomass	Bioethanol
ELEMENT LLC	US (KS)	Corn/Sorghum/Cellulosic Biomass	Bioethanol
Parallel Products	US (KY)	Waste Sugars/Alcohol	Bioethanol
Red River BioRefinery LLC	US (ND)	Waste Sugars/Starch	Bioethanol
VERBIO North America Corp.	US (NV)	Corn/Cellulosic Biomass	Bioethanol
Dynamic Recycling LLC	US (TN)	Waste Sugars/Alcohol	Bioethanol
Ace Ethanol LLC	US (WI)	Corn/Cellulosic Biomass	Bioethanol
ASIA			
COFCO Zhaodong Co. COFCO Demo	China	Lignocellulosic	Bioethanol
Beijing Shougang LanzaTech New Energy Technology Co., Ltd	China	waste gasses	ethanol
Longlive Bio-technology Co. Ltd.	China	Lignocellulosic	Bioethanol
Shandong Zesheng Biotech Co.	China	Lignocellulosic	Bioethanol
Jilin Fuel Alcohol	China	Lignocellulosic	Bioethanol
Anhui BBCA Biochemical	China	Corn Stover	Bioethanol
Henan Tianguan Group Henan 2	China	Lignocellulosic	Bioethanol
DINS Sakai Co.,Ltd.	Japan	Construction waste	Bioethanol
PraJ industries	India	Cellulosic Bagasse/straw	Bioethanol
Indian Oil RD 2G cellulosic	India	Cellulosic Bagasse/straw	Bioethanol
Indian Glycol & DBT-ICT Mumbai	India	Cellulosic Bagasse/straw	Bioethanol
Assam Bio Refinery (ABRPL)	India	Cellulosic Bagasse/straw	Bioethanol
Indian Oil Corporation 3G plant	India	waste gasses	ethanol

River facility with blame being put on wet wood, hydrogen cyanide production, and a range of equipment and power failures. (Investigation: INEOS failed despite $129 million in taxpayer subsidies) Basically, lab-based processes and TEA/LCA models failed at demonstration or commercial scale.

Dedicated bio-refineries based on localized feed stocks and targeted bio-products and continued advancement of all biological aspects of conversion are essential. However, a new paradigm valorizing carbon capture, mitigation, management, and sequestration is emerging; flexible bio-refineries using expanded feed stocks, cascading conversion technologies, and a portfolio of bio-products and sequestered carbon (Figure 1B). Carbon management as income provides flexibility in processing, obviating the constraint for high specific yields as subsequent processes can take partially converted residuals into a new production stream. Branching and cascading processes can trade decreased yield for increased throughput, lower capital and operating costs, and feed stock and product flexibility to fit local or changing markets while increasing overall carbon conversion yield through the inclusion of carbon sequestration.

A broader range of feed stocks and wider product portfolio, requires synergy and co-development in numerous areas and disciplines to optimize the overall system. This will include biology and biochemistry, chemical and mechanical engineering, thermochemical processing, chemical catalysis, techno-economic and life cycle analyses, and even other renewable energy sources to supply low-carbon power and electrons. A “true” bio-refinery will operate much like a petro- refinery; where feed stock is converted into an array of bio-products using multiple technologies optimized holistically. This concept has had limited effort to date, primarily exploration of gaseous feed stocks and the use of algae to capture CO_2 and serve as a feed stock or production system (Subhadra and Grinson, 2011; Morais et al., 2015; Butti and Mohan, 2017; Kassim and Meng, 2017; Wiesberg et al., 2017; De Bhowmick et al., 2019b; North, 2019; Yadav et al., 2019; Banerjee et al., 2021), however various social and political pressures to valorize carbon management and sequestration will undoubtedly lead to higher interest in more extensive carbon utilization.

While BioEnergy with Carbon Capture and Sequestration (BECCS) is still uncertain (Jones and Albanito, 2020), technologies such as pyrolysis to form biochar waste carbon to concrete, plastics, and other durable materials (Arehart et al., 2021) could be a simpler option for carbon management (Lefebvre et al., 2020; Papageorgiou et al., 2021). The global bioeconomy is poised to emerge and impact planetary carbon reduction, but needed underlying science and engineering is just being developed.

Artificial intelligence and machine learning

This new holistic approach can be further enhanced with the use of advanced machine learning techniques and artificial intelligence developed in the past decade allowing the exploration of data sets from the benchtop scale to the bio-refinery scale and pushing the boundary for real-time predictive systems that are tailored for both microbes and feed stocks (Oruganti et al., 2023). These data driven approaches have proven to be a powerful tool in assisting design and understanding of biological production of fuels and chemicals. Already studied for optimizing algae growth as a feed stock (Oruganti et al., 2023), this approach can improve yield, product purity, analytics, and guide genetic engineering strategies (Yang et al., 2023) and enzyme engineering (Foroozandeh Shahraki et al., 2021). Reducing severity, time, Capex, and Opex and providing flexible product portfolios driven by prevailing markets are potential areas limited by the current model emphasizing high yields of limited products.

Feed-stocks

Starch, sugars, and lignocellulosics

Microbiology has been used for centuries to produce bio-products and biochemicals from various biomass feed stocks (Buchholz and Collins, 2013). Most well-known is alcoholic fermentation by yeast, whether for beverage or fuel. Additional yeasts and bacterial systems are being developed and production of industrial chemicals such organic acids are heavily based in fungal fermentation of sugars (Grewal and Kalra, 1995; Francisco et al., 2020; Xue et al., 2021; Shikina et al., 2022; Upton et al., 2022; Chib et al., 2023).

The U. S. Department of Energy focuses on lignocellulosic biomass crops such as hybrid poplar, switchgrass, miscanthus, and other grasses and fast-growing hardwoods (Feedstock technologies). Other lignocellulosics include agricultural residues such as corn stover, sugarcane bagasse, and wheat, oat, and rice straws, forestry thinnings, and wood processing residues. Proposed feed stocks include everything from municipal solid wastes and gases to algae. Any lignocellulosic biomass can be converted given the right process and market conditions and the myriad of proposed process technologies in "dedicated" bio-refineries are usually linear and focused on optimizing yield of one or a few products from a limited feed stock input.

Wet wastes and plastics

Food waste, manures, municipal solid waste, and sewage offer wide opportunities for conversion processes and products. As landfills increasingly reject organic wastes, alternative disposal routes are needed. Bio-refining is being proposed for many industrial food waste streams (Kumar et al., 2022) while sewage bio-solids are limited in traditional land-application for disposal (Collivignarelli et al., 2020). Expansion of municipal wastewater systems is often limited by urban sprawl so faster, more efficient options are needed (Jing et al., 2021). Manure is often concentrated by localized high volume ranching, farming, and processing operations. Some of these materials are used to generate biogas by anaerobic digestion, often in co-digestion with other ag residues, however residual digestate contains a large fraction of the original carbon and disposal is still problematic (Chiumenti et al., 2018).

Thermochemical treatment and land filling are the primary means of plastic disposal, however biological deconstruction for renewable plastic generation or other bio-products are being investigated (Bertocchini and Arias, 2023; Malik et al., 2023). Recycling and up-cycling plastics to biodegradable plastics bio-products are two approaches that can help restore the damage caused by this polymer (Kochanska et al., 2022; Morici et al., 2022). Plastics can serve as an excellent source of carbon for microbes, provided the bonds are hydrolysable. While microorganisms metabolize many natural recalcitrant compounds, they have not evolved to breaking down these recently developed man-made materials (Kim et al., 2022; Lim and Thian, 2022; Mat Yasin et al., 2022; Crystal Thew et al., 2023; Thew et al., 2023).

The grand challenge associated with biological conversion of plastics is multidimensional. Bio-catalysts that crack tough chemical bonds in plastics are limited. Enzyme engineering needs to be applied to develop enzymes for individual plastic types. Bio-conversion research on plastics has primarily focused on PET metabolism and research on other plastics is quite rudimentary. Metagenomic approaches to identify novel organisms and enzymes with plastic degrading properties must be explored to determine naturally evolving bio-catalysts from plastic enriched microbiomes, such as the landfills and oceans. Furthermore, integrated microbial and chemical approaches to deconstruct and valorize plastic carbon to bio-products will be critical to a circular bioeconomy.

Algae

Micro- and macro-algae present a massive biological resource for sequestering carbon and have long been proposed as bio-refinery feed stocks and catalysts. Algae take up CO_2 directly and often have very high productivity rates. Algae's ability to use HCO_3^- directly enables 5-7-fold higher CO_2 absorption than wood (Jang et al., 2012) and biomass productivities nearly 4-fold higher than sugarcane (Adams et al., 2008). They can be grown without land or freshwater and do not compete for food production resources. In 2019, over 35 million tons of algae was harvested worldwide, with ~97% by aquaculture. Over 99.8% was macroalgae and 0.16% microalgae (Cai et al., 2021).

Microalgae are used to capture CO_2 and waste nutrients for production of bio-products and feed stock biomass. They have high neutral lipid concentrations (up to 70%), driving interest for biodiesel and biofuel production (Chisti, 2007; Sajjadi et al., 2018). Microalgae accumulate other storage compounds such as starch, which can serve for fermentative conversion to biofuels. The flexibility of growing microalgae in open ponds and enclosed photobioreactors under photoautotrophic, heterotrophic, or mixotrophic conditions make them an attractive system for bioproduct applications, though photobioreactors are generally considered too expensive and small scale for production of commodities such as biofuels.

Macroalgae (seaweeds) are starting to be recognized for applications such as waste-water treatments and natural fertilizer applications (Farghali et al., 2023). Their high carbohydrate content (over 60%), in comparison to less than 20% in microalgae (Jung et al., 2013; Jambo et al., 2016) and general lack of lignin and crystalline cellulose point towards easier biological conversion than lignocellulose, however harvest is a challenge. Their unusual polysaccharide chemistry and sometimes high protein content offer both challenges and opportunities. Alginates, carrageenan, fucoidan and laminarin found in the cell walls of macroalgae are recognized for their biological protective activities in humans, highlighting their pharmacological importance (Praveen et al., 2019). They serve as hydrocolloids or functional ingredients in the food industry. Pigments in the form of carotenoids and chlorophyll can serve as replacement for synthetic colors in the food industry (Biris-Dorhoi et al., 2020). The macroalgae industry can impact direct CO_2 removal efficiency by sequestering carbon in the form of biochar or via a bio-refinery approach (Farghali et al., 2023).

Most of the genetic engineering efforts have focused on microalgae, macroalgae are only starting to get some attention (Charrier et al., 2015; Cao et al., 2022). Significant efforts are underway to engineer microalgae for biofuel production, despite considerable scientific challenges resulting in several unsuccessful commercialization attempts. Nevertheless, the field of microalgal research has come a long way towards realizing the potential of these photosynthetic organisms. Genetic engineering in macroalgae is just developing, leaving a lot of scope to be explored. While microalgae must be engineered to improve robustness and productivity, large scale cultivation of macroalgae supported by genetic engineering efforts must be achieved for biofuel and specific bioproduct-based applications.

Cyanobacteria have properties similar to micro- and macro-algae and show promise as an environmentally friendly feed stock for production of fuels and plastics alternatives (Farrokh et al., 2019; Afreen et al., 2021). They are known to produce pigments applicable in the food and cosmetics industries, while also serving as food supplement themselves (Zahra et al., 2020). Interesting bioactivities of their metabolites have also been reported, suggesting clinical importance. With smaller genome sizes, challenges associated with improving productivity and product diversity for industrial scale deployment can be addressed effectively using synthetic biology approaches in comparison to the more-cumbersome higher algae.

CO_2 and other gases

Bio-generated CO_2 from fermentation and CH_4/CO_2 from anaerobic digestion represent point-source concentrated feed stocks for carbon capture, cycling, and utilization. Bio-conversion routes can generate renewable natural gas and methanol as well as ethanol which can be further upgraded to jet fuel and other products. Microbial engineering to enhance this capture and conversion is only now beginning. Syngas is already used as a feed stock for biorefining with several pilot and demonstration plants currently operating (Dahmen et al., 2019; De Bhowmick et al., 2019b; De Tissera et al., 2019; Yadav et al., 2019). LanzaTech uses flue gas bioconversion for ethanol and other bio-products and subsequent upgrading to jet fuel using the LanzaJet process.

Bio-driven GHG mitigation is likely the only viable global-scale option in the near-term and bio-refineries are primed to contributed. Biology has been capturing CO_2 since the beginning of life at a planetary scale, the energy is sunlight, and biomass represents high-density carbon. The key will be balancing economical bio-products and sequestering the low-value carbon. In contrast, Direct Air Capture using adsorbants, desorption, and underground sequestration is too energy intensive. According to the International Energy Agency, DAC CO_2 requires between 6.5 and 10 GJ/t CO_2 or 1.8 to 2.7 MWh per ton (Budinis). In simple terms, sequestering 1 GT of CO_2 using DAC would require between 1800 and 2700 TWh, roughly half of the total U.S. output in 2021 of ~4000 TWh. The largest operating DAC facility, Climeworks ORCA plant in Iceland, sequesters 4000 MT/year, necessitating 250,000 similar plants to capture 1 GT CO_2/year.

Bio-catalysts

Biocatalysis forms the core of any circular bioeconomy, bio-refinery, or industrial biotechnology process. Biology's ability to rapidly catalyze biochemical reactions sequentially at low temperature and high specificity forms the basis of industrial biotechnology. Classical bio-catalysts such as microbes and enzymes have been used for centuries. More recently, immobilized cells and cell-free systems have gained attention as means to accomplish certain biochemical pathways without "wasting" carbon and energy maintaining viable cells. Regardless of form, bio-catalysts are fundamental to industrial production of biofuels, biochemicals, and bio-products.

Microbes

Bacteria, yeast, fungi, and other whole cell bio-catalysts dominate industrial microbiology in biofuel and biochemical production. Examples include fungal production of organic acids and lipids (Grewal and Kalra, 1995; Carvalho et al., 2019; Chib et al., 2023), alcohols and lipids in yeast (Olson et al., 2004; Hull et al., 2014; Cai et al., 2016a; Pendon et al., 2021), alcohols and biochemicals in bacteria (Cai et al., 2016b), lipids and carotenoids in microalgae (Lopes da Silva et al., 2019; Monte et al., 2020; Papachristou et al., 2021; Oh et al., 2022), and a myriad of other bio-products from a range of microbes. Advances in molecular biology have enabled rapid and targeted metabolic engineering for increased product rate and titer, biofunneling to increase yields, expanded substrate utilization, redox balancing, and other cellular redesigns. Cutting edge technologies such as high through-put sequencing and targeted genome modification tools have opened a Pandora's box of opportunities in microbial metabolic engineering. The dawn of the -omics age has extended these opportunities even further as metabolomics, proteomics, fluxomics, genomics, transcriptomics, lipidomics, and glycomics continue to increase our understanding of cellular metabolism and pathways. Metagenomics, epigenomics, microbiomics, and secretomics have led us to the edge of engineering and directing microbial consortia in specific and targeted manner. These data-intensive techniques are tailor-made for big data applications of artificial intelligence and machine learning and as this interface of biology and data science continues to expand, we expect leaps forward in our understanding and manipulation of these cellular processes.

Enzymes

Enzymatic bioconversion of lignocellulosic biomass in the past 40 + years has evolved from relatively simple models of fungal cellulases such as Cel7A from *Trichoderma reesei (*Taylor et al., 2018), to a broader and more comprehensive understating of mesoscale deconstruction mechanisms employed by multifunctional bacterial enzymes such as CelA from *Caldicellulosiruptor bescii* (Brunecky et al., 2017), synthetic multifunctional cellulases (Brunecky et al., 2020), and megaDalton sized cellulosomal complexes utilized by CBP organisms like *Clostridium thermocellum* (Hirano et al., 2016). Moreover, the critical debranching roles of accessory enzymes acting on xylan and other hemicelluloses (Moon et al., 2011; Barr et al., 2012; Pryor et al., 2012; Lagaert et al., 2014; Cao et al., 2015; Goncalves et al., 2015; Hu et al., 2015; Laothanachareon et al., 2015; Sun et al., 2015; Yang et al., 2018; Ogunyewo et al., 2021) and the discovery of Lytic Polysaccharide Mono-Oxygenase enzymes have also been critical in the development of modern commercial cellulases (Agger et al., 2014; Muller et al., 2015; Bernardi et al., 2020; Cheng et al., 2020; Calderaro et al., 2021).

Two primary challenges will be understanding deconstruction of lignocellulosic materials by novel enzymes and enzyme classes and leveraging that understanding to develop advanced commercial enzymes. Future enzyme cocktails will apply these deconstruction strategies to minimally pretreated lignocellulosic feed stocks in a cost-effective manner. Facile, robust, and low-cost production of enzymes must be developed significantly beyond the current state of the art to be applicable at global commodity scale.

Cell-free systems

Bio-based fuels and chemicals rely on living microbial cells, presenting challenges in engineering and optimizing metabolic pathways for these compounds. Mass transfer and pathway optimization are constrained by cell membranes and intracellular processes (Lu, 2017; Wilding et al., 2018) and much of the carbon ends up in cell biomass, reducing overall carbon efficiency. A high carbon efficiency bioeconomy could benefit from a move toward highly efficient cell-free synthetic biology (Sheldon and Woodley, 2018; Wilding et al., 2018). Cell-free synthetic biology is an emerging interdisciplinary approach utilizing enzymes and cofactor components that are engineered and optimized without the use of living cells, allowing direct control of transcription, translation, and metabolism in an open environment (Lu, 2017).

The primary advantages of cell free enzyme systems are facile manipulation of substrate ratios, and careful adjustment of high energy flux ratios that are either difficult or impossible to control in microbial systems. Enzyme activity and temperature optima are tuned through careful enzyme selection. In contrast, living systems issues include metabolite competition, generation of side products, suboptimal enzyme ratios, and variable temperature optima for the cell (Bergquist et al., 2020) and devotes significant energy and effort in keeping itself alive and reproducing. Unfortunately, key problems for cell free systems remain, largely related to robust and facile protein expression, where post translational modifications are key. Recycling energy carriers such as NADH/NADPH or ATP is also an problem, however there are some approaches using whole cell lysates or redox balancing reactions (Ullah et al., 2016). Examples of possible reactions are too many to list, but two common substrates, glucose and glycerol can be utilized to produce a variety of products (Bergquist et al., 2020).

Discussion

We are on the cusp of a carbon-management-based global bioeconomy driven by reducing GHG levels, decarbonizing a wide range of industries, and equilibrating bioenergy and bio-products opportunities across geographical, cultural, economic, and social barriers. The bio-refinery will play a central role in this new paradigm and will function from niche to regional commodity scale. Feed-stocks and products will be extremely narrow or exceedingly broad based on local opportunities and the science and engineering needed will vary accordingly. The social, political, and economic factors will likely stay in flux for years, however the underlying need to solve global carbon levels will only continue to increase. Bio-based technologies offer the best and possibly only opportunity to achieve this planetary effort at scale and in the shortest time, but developing the myriad technologies needed to implement the solution will require constant and ongoing dissemination of results, collaborations across disciplines, and rigorous peer review to advance the bio-refinery to a meaningful level to solve rising carbon levels worldwide.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

SD: Overall concept and framework, principal writing for abstract, introduction, Feed-stocks (starch, sugars, LCs, wet wastes, CO_2 and gases), Biocatalysts (microbes), edited and contributed to other sections, handles references, final editing and submission. RB: Principal writing for enzymes and cell-free sections, general contributions to rest of article, JY: Principal writing for AI/ML and cell-free. VS: Principal writing for algae, plastics, and microbes sections, general contributions to rest of article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author SRD declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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