



Green horizons: how plant synthetic biology can enable space exploration and drive on Earth sustainability

Matthew Fox Morgan^{1,2,1}, Jonathan Diab^{1,2,*},
 Matthew Gilliam^{1,2} and Jenny C Mortimer^{1,2,3}

As humanity looks towards expanding activity from low Earth orbit to the Moon and beyond, resource use efficiency and self-sustainability will be critical to ensuring success in the long term. Furthermore, solutions developed for the stringent requirements of space will be equally valuable in meeting sustainability goals here on Earth. Advances in synthetic biology allow us to harness the complex metabolism of life to produce the materials we need *in situ*. Translating those lessons learned from microbial systems to more carbon-efficient photosynthetic organisms is an area of growing interest. Plants can be engineered to sustainably meet a range of needs, from fuels to materials and medicines.

Addresses

¹ School of Agriculture, Food and Wine & Waite Research Institute, University of Adelaide, Glen Osmond, SA 5064, Australia

² ARC Centre of Excellence in Plants for Space, Australia

³ Joint BioEnergy Institute, CA, USA

Corresponding authors: Gilliam, Matthew

(matthew.gilliam@adelaide.edu.au),

Mortimer, Jenny C (jenny.mortimer@adelaide.edu.au)

* These authors contributed equally.

Current Opinion in Biotechnology 2024, 86:103069

This review comes from a themed issue on **Energy Biotechnology**

Edited by **Thomas Eng, Michelle Omalley and Sudeep Agarwala**

Available online xxxx

<https://doi.org/10.1016/j.copbio.2024.103069>

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Introduction

Humans for the first time have made a serious commitment to establishing a long-term presence in space beyond low Earth orbit (LEO). Separate efforts are underway to establish permanent lunar habitats, led by both The United States' National Aeronautics and Space Administration (Artemis) and the Chinese Space Agency (International Lunar Research Station), while India recently became the first country to land a spacecraft at the Moon's south pole, an attractive site for a future Moon base [1]. These are intended to support future crewed missions to Mars [1].

In space, the efficient use of resources will be critical, especially in the context of lunar and Martian settlements, where resupply from Earth is both prohibitively expensive and impractically lengthy. Reliable processes that allow astronauts to live self-sustainably in the harsh conditions of space are required. The needs of human explorers are myriad, from food and building materials to fuels and pharmaceuticals. It is vital to produce these sustainably, on-demand and *in situ*. Equally important is the flexibility of production systems in accommodating the breadth of compounds required. Plants, a foundational life source on Earth, have been proposed as pivotal to these efforts [2–4].

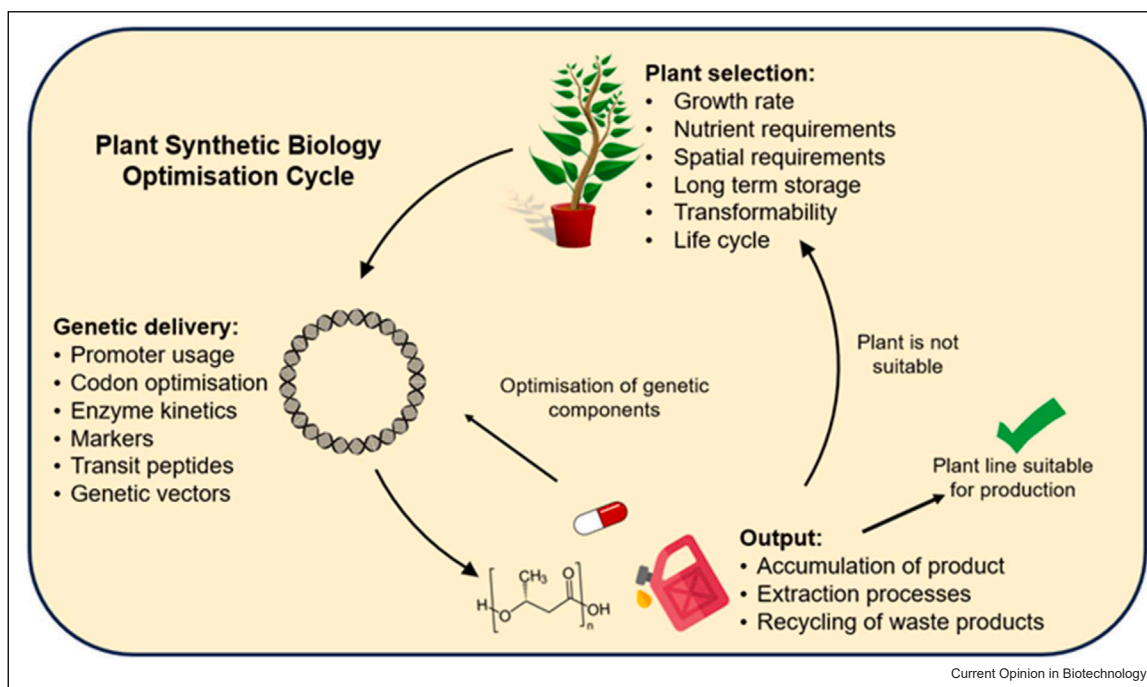
Plants are photosynthetic autotrophs that use CO₂, water, light and ~15 nutrient elements to produce a wide range of compounds. New technologies, such as synthetic biology and gene editing, can broaden and tune this capacity, creating novel on-demand biomanufacturing systems that are fit-for-purpose for space exploration and/or for improving sustainable production on Earth (Figure 1). Beyond acting as production systems, plants provide other benefits, such as oxygen synthesis, waste and water recycling, and deliver positive impacts on the psychological well-being of inhabitants [5]. Plant seeds can also be stored at ambient temperatures for many years.

Other biological systems have been proposed for space biomanufacturing, including microalgae, cyanobacteria [8] and heterotrophic bacteria [9,10]. Each will likely play a role, as advanced habitats on planetary surfaces will require an integrated ecosystem containing many classes of organism, for example, as outlined in Ref. [11]. A great deal of thought has been given to the production of food in space, as reviewed in Ref. [12]; here, we focus on the current progress in plants as biomanufacturing systems, and in particular how they can be harnessed for the provision of three example classes of products: biofuels, bioplastics and pharmaceuticals. We further propose that the lens of space can frame resource-innovative efforts for improving the sustainability of resource production on Earth.

Biofuels

Biofuels are defined as fuels derived from living matter. Plant biomass is the most common biofuel feedstock, and this is converted by chemical and/or microbiological

Figure 1



When planning and optimising the production of valuable biomolecules via metabolic engineering, various components of the expression and production system can be tuned, depending upon compound and purpose. At the start of the cycle, the choice of plant is critical. For proof-of-concept, a model plant (*Arabidopsis thaliana* or *Nicotiana* spp.) is often used [6]. When scaling up, plants need to fit specific requirements — transformability (stable or transient), growth rates, life cycle and nutrient requirements. For example, *Lemnaceae* spp. are being explored for large-scale biomanufacturing due to their fast growth rates and clonal reproduction [7]. Optimal product yield may be a compromise between compound concentration in the plant and its impact on plant growth. Genetic optimisation considerations for this include whether synthesis can be constitutive or inducible, requires compartmentalisation of products in specific organelles or tissues, transformants can be confirmed using herbicidal selection and/or visual markers and needs to produce specific isoforms to aid downstream processing and efficient extraction. If these optimisations are not sufficient, the choice of plant or other organism will need to be reconsidered.

means into the final product. The simplest and most widespread biofuel, sugarcane (sucrose) or corn (starch)-derived ethanol, is used either as an additive for gasoline or directly as a fuel for certain specialised engines, with the global market estimated to be ~US \$91B in 2022 with a predicted compound annual growth rate of 11.1% [13]. While these biofuels are renewable, their reliance on feedstocks that are otherwise human food sources reduces their sustainability. Use of whole-plant biomass (i.e. the cell wall) is more challenging, as the carbon is found in the more complex chemical forms of polysaccharides and lignin. It therefore requires extensive physical, chemical and/or biological deconstruction. However, the United States alone estimates that 1B tonne of plant biomass could be diverted into biofuel production without significant impact on food production or requiring new land to be brought into cultivation [14].

Application of synthetic biology will be critical to optimising the biofuel production pipeline, from feedstock to final fuel [15,16]. For example, altering plant cell wall

composition to simplify its deconstruction in the biorefinery has been a major target for research globally. However, cell wall composition is related to function, and altering it can have deleterious effects on plant growth. In particular, the water-conducting cells of the xylem and phloem are very sensitive to changes in wall strength, and collapse of these cells leads to plant dwarfing. One successful approach was to alter cell wall composition only in the stem fibre cells by using cell-specific promoters. This led to a 74% increase in sugar release, with no change in plant growth or stem strength [17]. Additional mid- to high-value compounds, such as nylon precursors, can be synthesised *in planta* as additional product streams, making the combined economics more feasible, as explored in Ref. [16].

Space exploration is highly reliant on vast quantities of energy-dense fuel. Despite an enormous reduction in cost in recent years, launching from Earth to reach LEO still requires ~US \$1500–30 000 per kg of payload [18]. As the number of global launches increases through commercial and nation-state space providers, the carbon

footprint of such launches becomes significant. In addition, conventional rocket fuels produce soot, depositing it into the upper layers of the Earth's atmosphere. Bio-fuels have not been considered a priority for space technology, but there are signs that this is changing. For example, Orbex, a UK-startup company, has been testing biopropane as a propellant for suborbital rockets (a by-product of biodiesel production) [19].

Proof-of-principle work has shown engineered microbes can produce higher-energy biofuels suited for rockets. For example, engineered *Streptomyces*, using glucose as a carbon source, were able to produce polycyclopropanated fatty acid methyl esters (POP-FAMES) [20]. POP-FAMES have greater projected energy density than petroleum-derived products, such as Jet-A and RP-1, and are challenging to produce through organic synthesis. This demonstrates the potential for biofuels to not only replace fossil-derived fuels like-for-like, but to improve upon them. Scaled production will require significant further optimisation [16]. Given the large volume of fuels required at specific, and often remote, locations for rocket launch, there is the opportunity to explore whether year-round optimised biomass production in vertical farms co-located with microbial fuel manufacturing could be done at sufficient scale and costs to meet needs.

Off Earth, *in situ* production of biofuels is more conceptual still. Yet, the challenge of shipping propellant and oxygen is recognised as unfeasible, and *in situ* resource utilisation (ISRU) is an active area of research. Biotechnology-driven (bio)-ISRU has been proposed, in which biology (and often synthetic biology) is used to efficiently extract and generate an array of resources. For example, the use of cyanobacteria and *Escherichia coli* to produce 2,3-butanediol (2,3-BDO) in a Martian context has been proposed, with the added advantage of generating more than 20 tonnes of excess oxygen [21], whereas microbial mining can be harnessed to extract resources such as iron [22]. The addition of plants to the system is a clear next step in expanding bio-ISRU possibilities, particularly as biomass will be a by-product of other *in planta* production, such as the bioplastics and biopharmaceuticals described below.

Bioplastics

Plastics are among the most versatile of today's construction materials. They can be extruded, moulded and pressed into nearly any shape imaginable, and their physical traits can be tuned to a broad range of criteria. Their chemical structure is extremely stable, resisting degradation by both biotic and abiotic processes, and lending the polymer an excellent strength-to-weight ratio. These materials are employed across almost every sector of human activity, from packaging and textiles to

construction and consumer products. Plastics are deeply integrated into our way of life, and this trend is unlikely to change as humanity expands off our planet.

However, plastics have two major issues that remain unsolved. Their chemically inert nature means that microplastics can end up as persistent environmental contaminants [23]. In the context of space, this resistance to degradation means that the valuable elements of which they are composed are not easily reclaimed for reuse. Plastics are typically derived from petroleum, which is limited on Earth and entirely non-existent in space.

As reviewed by Rosenboom et al. (2022), and in the references therein, several biopolymer alternatives to petroleum plastics exist [24], and *in planta* biomanufacturing is an efficient means of their production. Traditional plastics such as polyethylene and polyethylene terephthalate have been produced in microbial systems, substituting the need for a petroleum feedstock with glucose [25]. Harnessing the ability of plants to photosynthesise may allow for a further reduction of input costs. However, the final molecules are chemically identical, and therefore will also suffer from the same issues with persistence in the environment and difficulties with recycling.

Plastics that biodegrade, yet possess the required functional properties, are thus in demand. Polylactic acid (PLA) is a plastic alternative made from plant starch and is currently manufactured at-scale for use in additive manufacturing, or 3D printing, applications. 3D printing technology facilitates self-sufficiency, and has been validated several times aboard the International Space Station (ISS) [26]. PLA, however, is a brittle material with a high degree of gas and moisture permeability [27]. This limits its use cases, ruling out some high-volume sectors such as films and packaging.

Polyhydroxyalkanoates (PHAs) are a highly customisable class of bioplastics originally discovered in bacteria, and produced industrially using these microbial systems [28]. PHAs have a wide range of applications, from flexible, transparent films to rigid thermoplastics [29–31]. Microbial routes are well-established, but require expensive, carbon-rich substrates to achieve high yields. Autotrophic photosynthetic systems could be more energy-efficient production platforms; accordingly, PHA production has been engineered in a variety of plants, such as tobacco, switchgrass and sugarcane [32–36]. However, significant work in yield optimisation and organism health remains to be done in these systems. Synthetic biology solutions may aim at regulating gene expression to certain times, cell compartments or in response to specific triggers. Host plant choice may also be a route for success, by selecting a chassis robust enough to handle the additional demands.

A major hurdle for the adoption of bioplastics on Earth is a higher price point as compared with petroleum plastics, which is ultimately derived from the cost of production. The intrinsic need for ISRU in space largely negates the economic advantage of petroleum on Earth, but energy usage remains a concern in either context. Plants as synthetic biology platforms are ripe with the possibility for reducing input requirements by leveraging more efficient photosynthetic metabolism.

Another factor to consider is recyclability. All plastics degrade over repeated cycles of melting and reforming, not to mention the energy costs associated with depolymerisation. Next-generation polymers, such as polydiketoenamine (PDK), have been developed, which can be recovered under ambient conditions using a strong acid, even in mixed waste streams. Monomers can then be reused without loss of performance [37]. However, the initial cost of new material remains high [38]. PDK has recently been produced using biologically derived triacetic acid lactone, which relies on bacterial fermentation of plant biomass [39]. Going a step further and using plants as the primary production platform could potentially help to lower those input requirements, making the use of PDK more viable in the resource-constrained environment of space, and to improve their economics for Earth. Plants as a major source of these sorts of biomaterials will need to be price-competitive over microbes and fossil fuels, and progress is already being made in this direction [40,41].

Pharmaceuticals

Plants have historically been the main source of human medicines, but more recently, industry has taken advantage of the scale and quality that comes with organic chemical synthesis. In an effort to return to more renewable systems, the concept of 'molecular pharming' was proposed, that is, the genetic engineering of organisms for the production of pharmaceuticals. Recent successes, such as the production of recombinant insulin and a variety of other proteins in yeast and bacteria [42], highlight the potential for flexible biological factories to drive the predicted synthetic biology-led biomanufacturing revolution [43]. Biological systems house a more complex and flexible molecular machinery for the creation of small-molecule and protein-based therapies with more simple input materials than chemical synthesis. Work thus far is largely conducted on microbes with the complexity of heterologously produced chemicals increasing, for example, paracetamol in *E. coli* [44].

A return to plants for medication, facilitated by the biomanufacturing revolution, building on the discoveries in microbial synthetic biology, could be the future of pharmaceutical production. Plants, as a production platform for pharmaceuticals, have multiple benefits over microbial systems, including autotrophy, scalability,

tissue and cellular compartments for compartmentalising compounds, similar protein glycosylation to animals and the capacity to act as a direct vector for pharmaceutical delivery. Plants are capable of producing complex pharmaceuticals such as vaccines, monoclonal antibodies and polypeptide hormones [45,46]. For example, ZMapp, the experimental biopharmaceutical (monoclonal antibody cocktail) used to treat Ebola, was produced in *Nicotiana benthamiana* [47]. More recently, COVID-19 vaccines produced in *N. benthamiana* with phase-3 trials produced high levels of vaccine efficacy [6,48]. Plants as the new factories for pharmaceuticals could make the industry more sustainable by carbon offsetting production through photosynthesis and recycling plant waste into biofuels. Additionally, with parallel advancements in vertical farming, these pharmaceutical-producing crops do not need to compete with food crops for arable land.

In regard to space, medication is not used sparsely — astronauts on the ISS consume ~20 medications per week [49]. Unfortunately, medicine degrades over time, and current evidence shows that drugs may degrade faster in space [50,51]. Hence, with resupply missions untenable, the sustainable *in situ* production of pharmaceuticals is a significant hurdle to overcome. The pharmaceuticals that are transported to the ISS include those required for prevention or treatment of conditions that are not unusual amongst human populations [52]. However, astronauts face medical complications related to the unique environment of space, and as long-duration missions become longer and more common, so does the risk to the astronaut. These health risks include space-induced anaemia [53], microgravity-caused bone [54,55] and muscle loss [56,57] and increased cancer risks [58–60]. Hence, there needs to be a reconfiguring of the pharmaceutical cargo to sustain a human presence in space.

Plant-produced therapeutics are being explored for use on astronauts, such as the human parathyroid hormone (PTH). PTH is a polypeptide hormone that promotes bone formation, and its supplementation is used therapeutically to treat osteoporosis [61,62]. Preliminary data suggest that microgravity reduces PTH production and is thus being looked at as a supplement for astronauts [63,64]. The peptide residue that is used for therapeutic treatment, PTH(1-36), has successfully been transiently expressed in *Nicotiana benthamiana* (tobacco) [65]. Similarly, insulin-like growth factor 1 (IGF-1), is another polypeptide hormone that has bone remodelling functions [66] with potential for the treatment of microgravity-caused bone loss [67,68]. IGF-1 has successfully been transgenically produced in rice calli (*Oryza sativa*) [69], in tobacco (*Nicotiana tabacum*) and lettuce (*Lactuca sativa*) [70].

These examples do not represent the extent of heterologous pharmaceutical production *in planta*, further

examples can be read in the review by Lee et al. (2023) and references therein [71]. However, they are important steps towards developing plant-based medical foundries for space and other remote locations. Studies in the future need to utilise plant production systems that are better suited for space, that is, whole plants that have low waste, fast growth rates, high stress tolerance and minimal input requirements [3]. Tuning the rate and location of production is also at a very early stage and would be essential for ensuring efficient and scalable processing. Additionally, traditional pharmaceuticals utilised by astronauts, such as sleeping aids, opiates and antibiotics, of which most are produced through synthetic chemistry, also need to be converted to and optimised for plant production systems.

Future perspectives

Over the last few decades, there has been an eruption of interest in synthetic biology, spurring the creation of new tools and techniques that have allowed an unprecedented level of control over biological systems. While many of these advances have been in microbial systems, translating those ideas over to plants may allow us to leverage the many useful traits they bring to the table, including a more efficient metabolism, ability to produce complex products and energy-rich tissues ready for downstream conversion. However, plant synthetic biology is relatively new compared with traditional synthesis platforms, which benefit from a long history of development, and the iterative development that underpins the synthetic biology experimental approach is limited by the longer life cycle of plants. Our understanding of plant systems will therefore need to deepen in order to disrupt currently entrenched production processes at-scale, and thus realise the potential sustainability advantages that plants offer [72,73]. It will be important to understand how gene x environment x management (G x E x M) can impact metabolic engineering efforts. Technological advances in other fields, such as vertical farming, can be incorporated, enabling researchers and producers to fix 'E' for optimal outputs. The development of programmable gene circuitry in plants offers the opportunity to tightly control when, where and how transcription is controlled [74]. Continuing advances in plant transformation open up a much wider range of plant chassis for use, with moss (*Physcomitrium patens*), liverworts (*Marchantia polymorpha*) and duckweed (*Lemnoideae spp*) examples of species being explored [7,75–77].

The profound need for efficiency in human space habitation lowers the barrier to entry for plant biomanufacturing and provides a rigorous testbed that will allow for the maturation of these nascent technologies. The harsh conditions of space necessitate innovation, and plant-based synthetic biology may well provide the platform to assist humans venturing further in the solar

system than ever before, as well as creating more sustainable production systems back on Earth.

CRedit authorship contribution statement

Matthew Morgan: Conceptualization, Writing – original draft. **Jonathan Diab:** Conceptualization, Writing – original draft. **Matthew Gilliam:** Conceptualization, Writing – review & editing. **Jenny C. Mortimer:** Conceptualization. Writing – original draft; Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

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

Acknowledgements

JD and MFM are funded through the Industrial Doctoral Training Centre. JD and JCM also acknowledge establishment funds awarded to JCM by the University of Adelaide. JD, MFM, MG, and JCM acknowledges the Australian Research Council Centre of Excellence funding: CE230100015. JCM also acknowledges that this work was conducted in part with support of the DOE Joint BioEnergy Institute (<http://www.jbei.org>) supported by the U.S. Department of Energy, Office of Science and Office of Biological and Environmental Research, through contract DE-AC02-05CH11231 between Lawrence Berkeley National Laboratory and the U.S. Department of Energy.

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