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Biomanufacturing for Space-Exploration – What to Take and When to Make

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Abstract

As renewed interest in human space-exploration intensifies, a coherent and modernized strategy for mission-design and planning has become increasingly crucial. Biotechnology has emerged as a promising approach to increase mission resilience, flexibility, and efficiency by virtue of its ability to efficiently utilize in situ resources and reclaim resources from waste streams. Since its infancy during the Apollo years, biotechnology, and specifically biomanufacturing, have witnessed significant expansions of scope and scale. Here we outline four primary mission classes, on Luna and Mars, that drive a staged and accretive biomanufacturing strategy. Each class requires a unique approach to integrate biomanufacturing into the existing mission architecture and so faces unique challenges in technology development.These challenges stem directly from the resources available in a given mission class—the degree to which feedstocks are derived from cargo and *in situ* resources—and the degree to which loop-closure is necessary. We see that as mission duration and distance from Earth increase, the benefits of specialized sustainable biomanufacturing processes increases. Here we present a strategic approach, guided by technoeconomics, to development, testing, and deployment of these technologies serves to nucleate the larger effort of supporting a sustained human presence in space. The processes needed for each scenario spans the technical breadth of synthetic biology to design engineering, from sophisticated genetic tailoring of chassis-organisms to building scalable, automated, easily operable bioreactors and processing systems. As space-related technology development often does, these advancements are likely to have profound implications for the creation of a stable, resilient bioeconomy on Earth.

Keywords: in-space biomanufacturing, space synthetic biology, space bioprocess engineering, biological life-support systems, *in situ* resource utilization, circular economy

Abbreviations: CONOPS: concept-of-operations; ISM: *in situ* manufacturing; ISRU: *in situ* resource utilization; LC: loop-closure; SNOPs: sulfur, nitrogen, oxygen, phosphorus; TRL: Technology Readiness Level; TEA: Techno-Economic Analysis.

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Introduction and Background

With reinvigorated curiosity and enthusiasm for space-exploration and increasingly complex campaigns, humanity prepares to return to the Moon en route to Mars[1–3]. Efforts to modernize mission architectures[4]—combinations of inter-linked system elements that synergize to realize mission goals[5]—will need to leverage an array of enabling technologies including biomanufacturing towards the realization of such grand visions[6–9]. Microbial biomanufacturing has the potential to provide integrated solutions for remote or austere locations, especially where supply chains for consumable and durable goods cannot operate reliably[10,11]. Complementary to, but distinguished from merely remediative and extractive microbial functions, such as biomining[12,13], off-world biomanufacturing corresponds to any deployable system that leverages biology as the primary driver in generating mission-critical inventory items of increased complexity, i.e., the *de novo* synthesis of components for the formulation of food, pharmaceuticals, and materials[14–20]. When integrated effectively into mission architectures, bio-based processes will significantly de-risk crewed operations through increased autonomy, sustainability, and resilience, freeing up valuable payload capacity[21].

Key to the efficacy of biotechnology as a support of human space-exploration is its efficiency in using *in situ* resources (*in situ* resource utilization, ISRU) and the ability to utilize waste streams from other mission elements and recycle its own products (loop-closure LC)[22–24]. As missions expand, progressive advancement and wider implementation of *in situ* (bio)manufacturing (ISM/bio-ISM) will lead to greater independence, enabling more complex mission-designs with extended goals, and may eventually enable a self-sufficient human presence across the solar system. Biomanufacturing is appropriate for that purpose, because high-volume resources, like fixed carbon and nitrogen (as well as as well as low-volume, but critical resources such as minerals) can be produced and recovered in compact autonomous systems that are analogous to Earth's biogeochemical cycles[14–20,25]. Biochemistry also provides access to a plethora of organic compounds, often at unrivaled purity and selectivity, many of which are not accessible by other means[26,27].

Biologically-driven ISM in support of space-exploration becomes more significant the deeper humans venture into space: As the support of supply chains becomes increasingly challenging the further humans travel, ISM is most feasible in locations where resources are available, accessible and abundant, such as the Moon and even more so Mars (Figure 1). The advantages and drawbacks of biotic and abiotic approaches for ISM, in particular for life-support but also auxiliary functions for extended human operations beyond Earth-orbit, have previously been discussed at length[7,10,28,29] (qualitatively summarized in Table S4), but an actionable roadmap for deploying biomanufacturing-based systems within upcoming campaigns has yet to be formulated. Here, we discuss the applicability of biologically driven ISRU and LC in different off-world cases and present a qualitative techno-economic analysis (TEA) to assess different space-travel scenarios. Pursuant, we lay out paths for readying bio-based technologies for inclusion into mission-design and deployment, to enable the next phase of roadmapping for crewed missions into deep-space.

Off-world Biomanufacturing Approaches

Concepts-of-Operations: Differentiating ISM-Modes

Given that biomanufacturing is uniquely suited to play significant roles in the specific realms of food, materials, and therapeutics, a key challenge in realizing its potential rests in the availability and abundance of feedstocks that are mobilizable by microbes—provided through logistic resupply (directly or from re- and up-cycling of mission products) or obtained from *in situ* resources. This abundance depends on the destination and mission class and leads to a qualitative discrimination of cases as shown in Figure 1a. The *in situ* resources that may provide useful feedstocks to drive biomanufacturing processes on the Moon and Mars are broken down in Figure 1b, which aids in comparing mission profiles. For each case, different concepts-of-operations (CONOPS) are applicable—these CONOPS conform to specific inventory needs as they relate to mission- and crew-requirements and depend on the resources availability for ISM. The environmental context informs the specification of feedstocks and processing pipelines (LC or ISRU), as shown in Figure 1c.

Each case comprises a unique set of inventory elements; such elements may include infrastructure components (e.g., habitat assemblies and furnishing, functional hardware/appliances as well as scientific equipment and tools), transported as either pre-deployment cargo or with the crew. These elements are used to assemble the larger integrated habitation and life-support systems as well as (bio-)ISM-based LC or ISRU systems and infrastructure related to mission-objectives[30]. While all such cases are distinct in terms of operations[31], they serve as exemplars to better understand biomanufacturing strategies in relationship to mission elements that might provide resources, crew count/needs, and logistical constraints.

Implementation of Bio-ISM Dependent on Off-World Case

Case 1 (Moon, stable logistics) considers Artemis-like Lunar operations[1], specifically short stay missions for small numbers of astronauts carrying out tight scientific and technical explorations and tests. Because of the short times and logistic accessibility, crew-needs for food, medicine and materials can be provided through carry-along and resupply from Earth[32,33], rather than relying on the more complex, risky and time-intensive technologies of biomanufacturing. Also, due to the dearth of *in situ* resources on the Moon (Figure 1b)[34], the scale of biomanufacturing will be constrained by the supply chain and capability for recycling these elements[35]. However, because of the well-supported environment, it is an ideal location to prove and improve technologies for biomanufacturing in space by testing automated and scaling operation of critical bioreactor systems for different bioprocess types (e.g., electro- and photo-autotrophic (gas) bioreactors for lithoautotrophic and/or saprotrophic fermentation of macronutrients[36]), all of which are likely to have physiological and operational challenges in a low-gravity, resource-poor environment[37–39]. To this end, systems that have achieved a Technology Readiness Level[40,41] (TRL) of 5 are well suited to be implemented and evaluated. While these systems currently exist in isolation or partially integrated in laboratory and industrial contexts, building automated end-to-end, compact systems (advancement past TRL 7) will be a key requirement for case 1, so as to meaningfully scale to future, more constrained mission architectures.

Case 2 (Moon, disrupted logistics) considers advanced Lunar operation capabilities when extensive infrastructure has been deployed on the Moon. To increase the time for operations between resupply (and defending against unexpected resupply disruption), storage facilities will be increased and biomanufacturing become more attractive. Given the paucity of feedstock raw materials on the Moon, which do not provide the central resources necessary for bio-ISM (Figure 1b)[34], hyper-efficient use of stored supplies and efficient use of other available mission products and waste-streams via LC must be engineered. Derivatization of packaging materials, such as biodegradable plastics, and minimal processing systems for black and grey water could provide significant augmentations to expected feedstock and extend the operational times of biomanufacturing systems in the event of scheduled or unplanned disruption of the supply chain[8]. Under extreme conditions, being able to switch

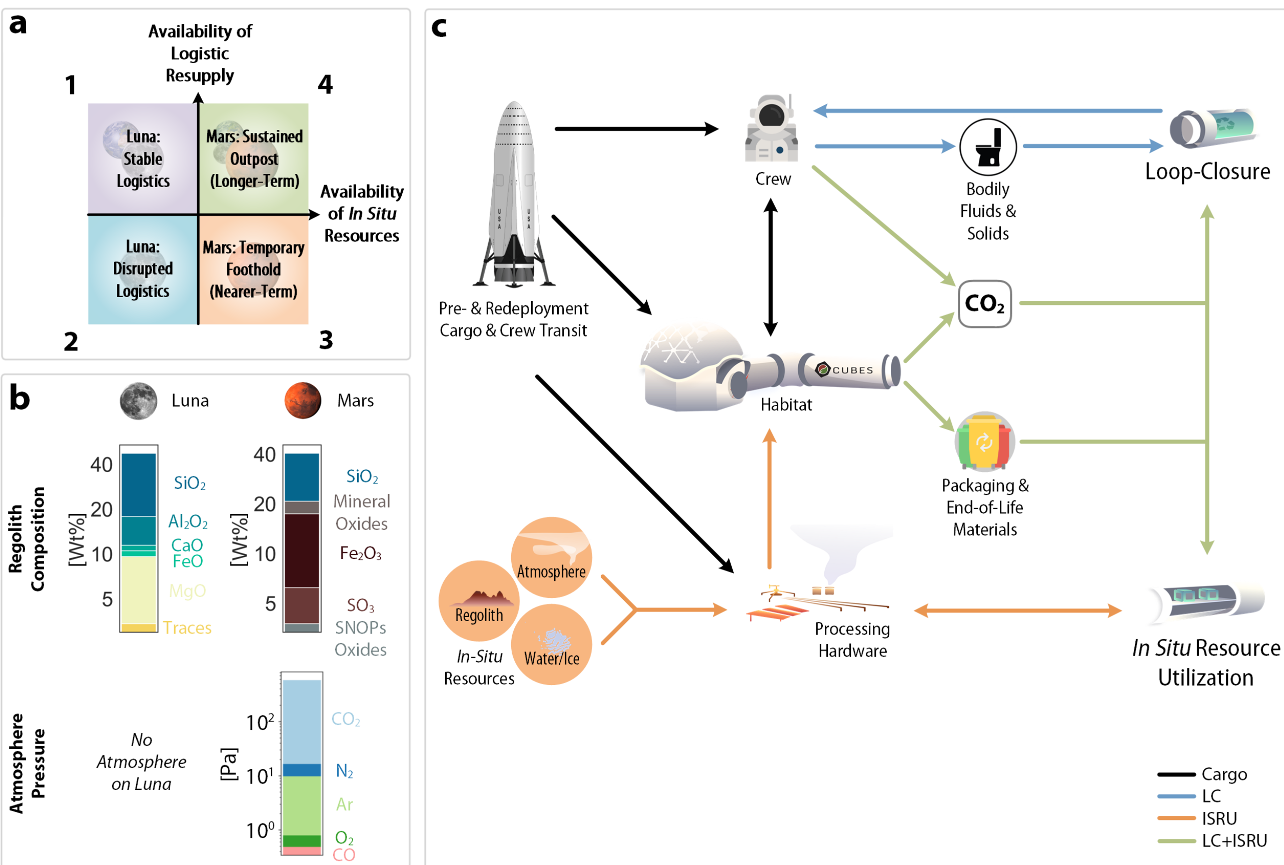

Figure 1. Approaches to *in situ* biomanufacturing dependent on off-world cases. The context-specific off-world cases 1-4 are defined in **a**, mapped as quadrants on qualitative spectra for the availability of *in situ* resources and logistic resupply. The surface-accessible *in situ* resources for the Moon and Mars are compared in **b** in form of gases and solids, broken down into elemental compositions (SNOPs: sulfur, nitrogen, oxygen, phosphorus). Biomanufacturing concepts-of-operations (CONOPS), outlined in **c**, are color-coded for the operational mode: outgoing from initial cargo (black lines), CONOPS can rely on either loop-closure (LC, blue lines), *in situ* resource utilization (ISRU, orange lines), or both (LC+ISRU, green lines).

biomanufacturing operations from, for example, complex vegetable foods to faster and less resource-intense production of simple cellular foods becomes paramount to defray risk. These challenges require innovations in new alternative feedstock engineering in organisms; co-design of mission materials for biological consumption; development of basic waste-processing systems; and flexible re-configurable infrastructures for production to respond to changing resource conditions. Applicable technologies comprise systems that have been tested in the relevant environments and brought to TRL over 7 within operations of Case 1, and are ready for implementation into mission architecture.

Case 3 (Mars, rudimentary logistics) considers basic biomanufacturing systems deployed on Mars with poor logistic resupply due to increased interplanetary distance but with greater availability of *in situ* resources compared to the Moon. While mission-design is still characterized by small crews on round-trips, resource constraints carry different weight. Given the extent and degree of the unknowns involved, these missions are ideally designed to maximize safety and stability by preparing for diverse contingencies. Providing those redundancies is exceedingly challenging due to the remoteness of Mars[31]. Hence, meaningful bio-ISM is necessary—with substantial scaling of the systems brought to TRL 8 to 9 in cases 1 and 2. While a portion of the food, therapeutics and materials will still derive from cargo, significant ISRU of regolith, water, and atmosphere must be implemented in addition to LC, to ensure mission flexibility and resilience. For food, nutritional completeness and palatability, together with customization of texture, flavor, and format will be of central importance. To further safeguard crew-health, essential therapeutics that cannot be included in cargo due to restrictions such as shelf-life, are within scope. For maximum fidelity of mission operations, a range of multi-purpose (thermoplastic) materials is useful for additive manufacturing—demand scales in correlation with mission duration with a greater factor than for food or pharmaceuticals. Enabling technologies include: modular fermentations and bioprocesses at scale, optimized genetically engineered microbial strains to efficiently produce intermediates (i.e., ingredients, agents, crude polymer), and formulation/processing systems to assemble the final products (i.e., meals, drugs, manufactured items)[10].

Case 4 (Mars, developed logistics) envisages a fully developed and integrated biomanufactory where essential logistic resupply is enabled by interplanetary networks and deep-space outposts[42–44], combined with extensive ISRU and LC. Specifically, this case would entail sustained human operations on Mars on the verge of permanent settlement. The extensive infrastructure that must be deployed for this kind of mission-design enables production of complete and diverse foods with a spectrum of forms and nutrition, a holistic range of therapeutics, and different bulk as well as specialty materials (plastics, metals, composites) that allow not only the maintenance but also expansion of infrastructure, semi- or fully autonomously. Biomanufacturing technologies and auxiliary infrastructure need to be fully developed and matured to readily deploy tailored microbial cell factories that can potentially be engineered on-demand as the need arises. To this end, even the accommodation of a "space biofoundry" (i.e., automated infrastructure for engineering and analytics of biological systems[45]) in the mission architecture is within scope. Eventually, this will also entail the ISM of specialty chemicals and reagents like e.g., phosphoramidites for DNA synthesis, supporting on-site bioengineering[46], in addition to the total inventories of foods, therapeutics and materials.

Off-World Mission-Scenarios and Bio-Available Inventories

CONOPS for ISM—the flow of resources and integration of LC with ISRU—not only differ for the four considered off-world cases, but are dependent on and influenced by mission-design scenario. To assess the potential impact that biomanufacturing can have on mission-design more quantitatively, five distinct but comparable scenarios were established as per Figure 2a. The outlined scenarios were designed with the objective of greatest comparability among destinations (Moon or Mars), and are agnostic of the cases previously described in Figure 1 (which served to aide in grouping mission architectures by location and biomanufacturing strategies). Scenarios 'A' and 'B' correspond to single sorties to the Moon and Mars, respectively, using standard surface operation duration[8]. Meanwhile, scenarios 'C' to 'E' consider 5,400 days of surface operations either as multi-sortie campaigns (scenarios 'C' and 'D') or in a single sortie (scenario 'E'). Using NASA's 'Advanced Life Support Sizing Analysis Tool' (ALSSAT)[52], an analysis of cargo inventory broken down for each scenario and compared by means of Equivalent Systems Mass (ESM, see BOX)[47] was conducted (see SI for details on data aggregation). The bar-charts in Figure 2 decompose the scenario-cost by means of ESM, differentiated by components (mass, power, cooling, volume, crew-time; 2b), system elements (waste, food, water, air, thermal; 2c) and material composition (structural metal, plastic, water, biomass, electronics, etc; 2d), serving as *prima facie* estimates for mission-expense.

This preliminary TEA provides a primary step towards drawing a relationship from the availability of cargo resources to potential inventory elements that lend themselves to biomanufacturing. Apart from highlighting that longer duration Mars journeys have the highest ESM effort, the analysis also provides insight into inventory differences, which has implications for applicability of ISM among the scenarios. Figure 2b shows that across all scenarios the primary cost in terms of ESM will be mass itself, followed by volume. The biomanufactory schema breakdown in Figure 1 is supported by the data in Figure 2c, which shows that ESM for scenarios 'A' and 'C' (Moon) are dominated by air systems (∼30% and 26%, respectively) while scenarios 'B' ,'D' and 'E' (Mars) are dominated by food systems (∼38%, 38% and 59%, respectively). Given the resources associated with each location, more air system supplies are required on the Moon, which does not lend itself to carbon dioxide

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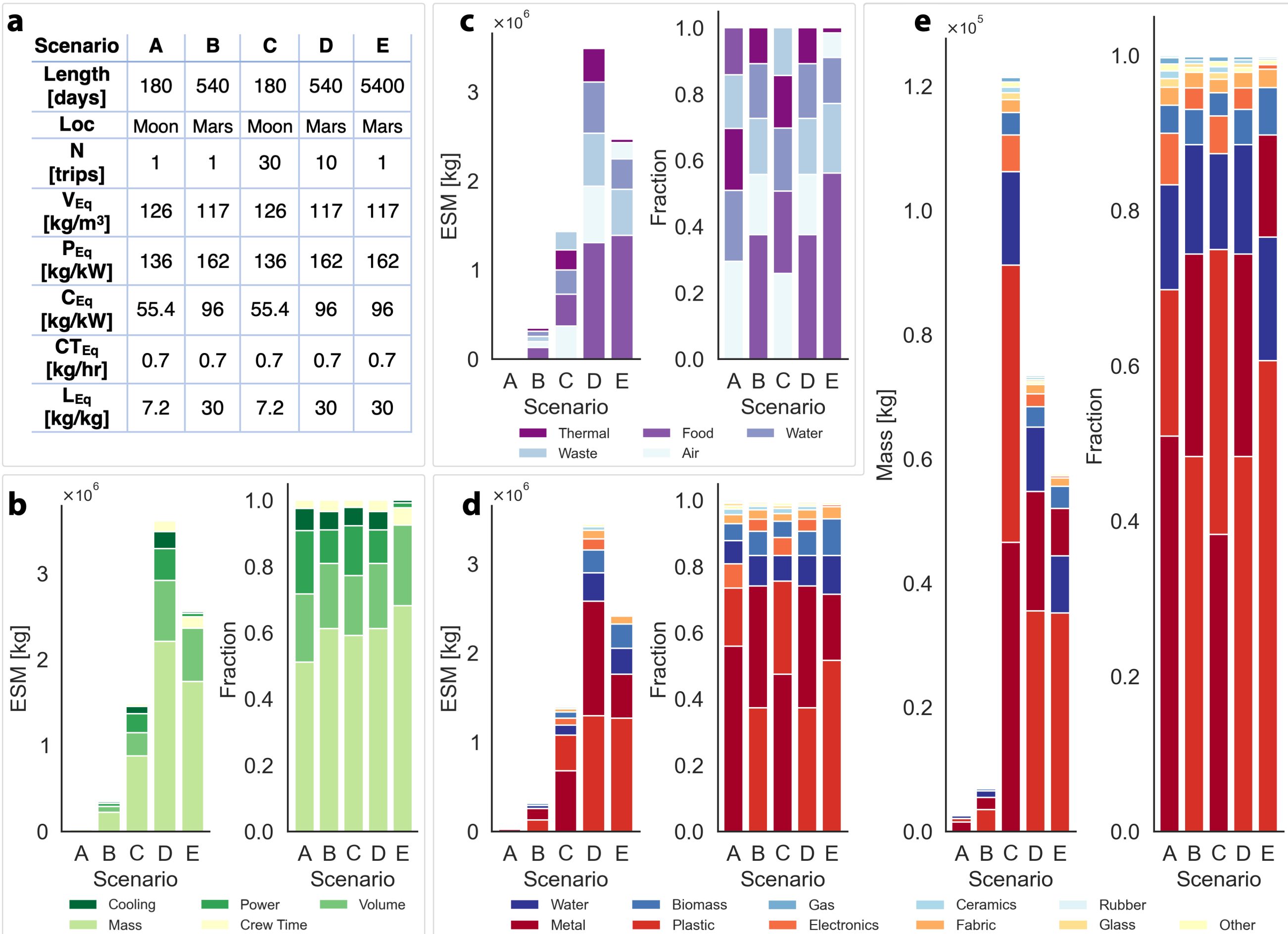

Scenario	A	B	C	D	E
Length [days]	180	540	180	540	5400
Loc	Moon	Mars	Moon	Mars	Mars
N [trips]	1	1	30	10	1
V_{Eq} [kg/m³]	126	117	126	117	117
P_{Eq} [kg/kW]	136	162	136	162	162
C_{Eq} [kg/kW]	55.4	96	55.4	96	96
CT_{Eq} [kg/hr]	0.7	0.7	0.7	0.7	0.7
L_{Eq} [kg/kg]	7.2	30	7.2	30	30

Figure 2. Breakdown of inventory elements dependent on mission scenario. Panel **a** provides an overview of parameters for exemplar mission-design scenarios: 'A' and 'B' correspond to single sorties (N) to the Moon and Mars respectively using standard surface operation duration[8], while 'C' and 'D' correspond to multi-sortie campaigns with the same 5,400 days of total surface operation as in 'E'. These parameters can be used to calculate the ESM cost and include equivalency factors for Volume (V_{eq}), Power (P_{eq}), Cooling (C_{eq}), Crew-Time (CT_{eq}), and Location (L_{eq}). Panels **b** – **e** visualize the inventory breakdown by component (**b**), system element (**c**), and material composition (**d** & **e**), respectively: the bar-charts in panels **b** – **d** show the breakdown in ESM units (on the left, in mass [kg]), and the fractional breakdown of each scenario (on the right, unit-less). The bar-charts in panel **e** visualize the absolute (left, in mass [kg]) and fractional (right, unit-less) inventory breakdown of material composition. ESM = Equivalent Systems Mass[47] – for more information see the BOX, as well as the SI.

fixation technologies as on Mars. In all scenarios the primary costs will be structural metals, plastics, water, and biomass. Most notably, Figure 2c shows that both, the mass and ESM for each scenario, is dominated by cargo composed of metal and plastics. Unfortunately, structural metal is likely to remain unsuitable for biomanufacturing for the foreseeable future. While biomanufacturing is usually conceived towards food production or therapeutics for sustaining astronauts, we note that plastic represents ∼17% of mass in shorter duration scenarios 'A' and 'B' and from ∼36% up to 60% in longer duration scenarios 'C', 'D' and 'E'. This supports the emphasis on ISM of these materials with increasing mission-duration. Further, with an estimated ∼12% to 16% of the total cargo-mass being water, the associated systems contribute ∼15% to 20% of total ESM (Figure 2c). Because the mass contribution from water is higher for scenarios 'A' and 'B', any biomanufacturing strategy employed should be geared towards water recovery and reuse.

BOX: Assessment of Economics, Feasibility and Risk of Mission-Architecture
In-space biomanufacturing systems will need to demonstrate superiority over traditional systems in supporting crewed space-missions. To this end, traditional mission-designs must be directly comparable to those augmented with biomanufacturing. One of the more widely used metric to quantify specific attributes of life-support systems is Equivalent Systems Mass (ESM)[47]. In brief, ESM allows mass, volume, power and crew-time to be converted into a single metric in kilograms-equivalent to predict the up-mass requirement[48]. ESM has become a standard metric also for comparing biomanufacturing systems[49,50], however, it cannot account for aspects such as risk, sustainability, recyclability, complexity, modularity, reliability, robustness, resilience, readiness, scalability, or safety.
As a complement to ESM, the concept of payback time (PBT)[51] has been developed to assess some of these criteria – PBT reflects cost, recyclability, and economic sustainability. Specifically, the PBT is useful in assessing ISRU options, as it allows comparison of the cost to launch and deploy (bio)manufacturing capabilities with the cost of a continuous resupply from Earth over time. Adding statistical risk assessments to the PBT can also help to quantify risk, safeguarding robust and reliable systems. For example, the concept could determine the statistical risk of landing on Mars, with the risk reduction of reduced number of landings on one side but a loss of the payloads carrying ISM hardware being more critical than failure of resupplying missions on the other side. The statistical value of those risk-factors must be carefully assessed based on previous missions, the general technology development roadmap, and the expected learning rates on those factors. Through reliable and generalizable analyses like these, the biomanufacturing approaches which are most vital can be meaningfully assessed.

Integrating Biomanufacturing with Mission-Architecture

Rational Coupling of Biological Systems and Resources

Selection of the specific feedstocks utilizable for different ISM purposes must be guided by critical consideration for recycling of resources at molecular and elemental level—any dead-end, non-recyclable stream will eventually require a resupply from Earth. For auxiliary functions (e.g., materials for additive manufacturing), production volume is more important than continuity and response time (as is critical in case of food and therapeutics), therefore requiring the adaptation of widely available resources (carbon dioxide and derivable single-carbon compounds or crude biomass), either directly (where available), or through (physico)chemical means (e.g., as secondary beneficiary of propellant production from *in situ* resources)[53]. Hence, the collective approach to more deeply developing synthetic biological tools for bio-ISM must begin with the feedstocks—sugars or other purified multi-carbon compounds (e.g., higher alcohols and fatty acids) will likely not be the prime substrates of biomanufacturing in space, but rather the products/intermediates in a manufacturing chain or loop that serves life-support (within LC elements such as regeneration of oxygen and waste reclamation)[54]. Critically, because in space savings on payload supersedes commercial relevance, adaptation of non-model microbes that save mass is much more valuable. The range of microbial taxa being proposed and investigated for in space-applications is, however, still narrow and often limited to the few model organisms (e.g., *E. coli* and *S. cerevisiae*) whose popularity in Earth-based applications is mostly rooted in legacy. Although a great deal of progress has been made to adapt these organisms to utilization of single-carbon feedstocks[55,56], they are still outclassed by organisms naturally capable of these functions[57,58]. Therefore, species with nutritional modes and metabolism uniquely suited to leverage resources available through LC and ISRU must be considered for development of ISM systems, basing their selection on application (feedstock/product pairing, scale, continuity, and responsiveness of the respective process) and scenario-specific criteria (environmental parameters)[36,59]. Specifically, organisms with the ability to assimilate single-carbon compounds alongside organics (mixotrophy) are most suitable. For this purpose, expansion of metabolic engineering efforts to create (synthetic) pathways that increase the carbon-efficiency of metabolism and/or allow the catabolism and subsequent up-cycling of non-natural feedstocks, like e.g., synthetic plastics, is also sensible[60,61]. To illustrate these considerations, a qualitative breakdown of possible production routes/flow of carbon through different biomanufacturing approaches for inventory items from case-dependent *in situ* resources is established in Figure 3.

Production of Materials for Manufacturing

For off-world ISM of materials and fabrication of mission objects a multitude of different approaches exist, many of which are still inhibited by the extent of initially required critical infrastructure[62,63]. Biomanufacturing has the potential to surmount this limitation, by supporting the fabrication of consumable and durable goods made of plastics[19,64,65], metals[66,67], and ceramics[68] (∼18% to 60%, ∼13% to 50%, and ∼1% of total mission ESM respectively, Figure 2d) with uses and sizes ranging from small replacement parts and functional tools to physical components of the life-supporting habitat[69,70].

In combination with additive manufacturing[71], bioplastics could make up the majority of high-turnover items with regular demand, while also providing for contingencies, i.e., non-anticipated servicing and repairs of incidental nature. Such polymeric constructs can be derived from basic (carbon) feedstocks in a more compact and integrated way in a one-step bioprocess than by chemical synthesis, especially in the case of comparatively (to Earth-based manufacturing industry) low-throughput products[7,10]. Furthermore, especially high-performance polymer-fibers such as for example aramids and arylates have a range of applications in space technology, including ballistic protection. The building blocks for these, or even final polymeric materials of equivalence, can be obtained through biomanufacturing[64,72]. Technologies for production of biomaterials, in particular bioplastics, from *in situ* resources like carbon dioxide are also immediately relevant to providing solutions for the most pressing challenges of humanity on Earth. This includes mitigation of greenhouse gas emissions through carbon-capture and carbon-neutrality (i.e., LC), as well as reduction of environmental pollution by non-biodegradable materials. Biomaterials production from inorganic carbon is therefore an enabling technology for the evolution of a circular economy and sustainable (bio)chemical industry on Earth[73].

Use of soil and rock (Figure 1b), while likely large by volume for surface operations as components of buildings and structures, has a limited number of applications due to the poor mechanical properties of regolith (e.g. low flexibility and plasticity)[74–76]. Nevertheless, autonomous 3D-printing of infrastructure relying on regolith and composites thereof with (thermoplastic) binding resins has been proposed and prototyped (also see SI)[77,78]. This requires significant up-mass of auxiliary equipment to allow for e.g., stripping and processing of topsoil, as well as the raw material for the binding resin. If, however, the binding agents (such as polyesters like polylactic acid) could also be derived or produced on-site from *in situ* resources, an additive manufacturing method may become immediately more feasible[79,80].

Another possibility to overcome the low versatility of raw regolith and leverage it as an *in situ* resource is to extract certain

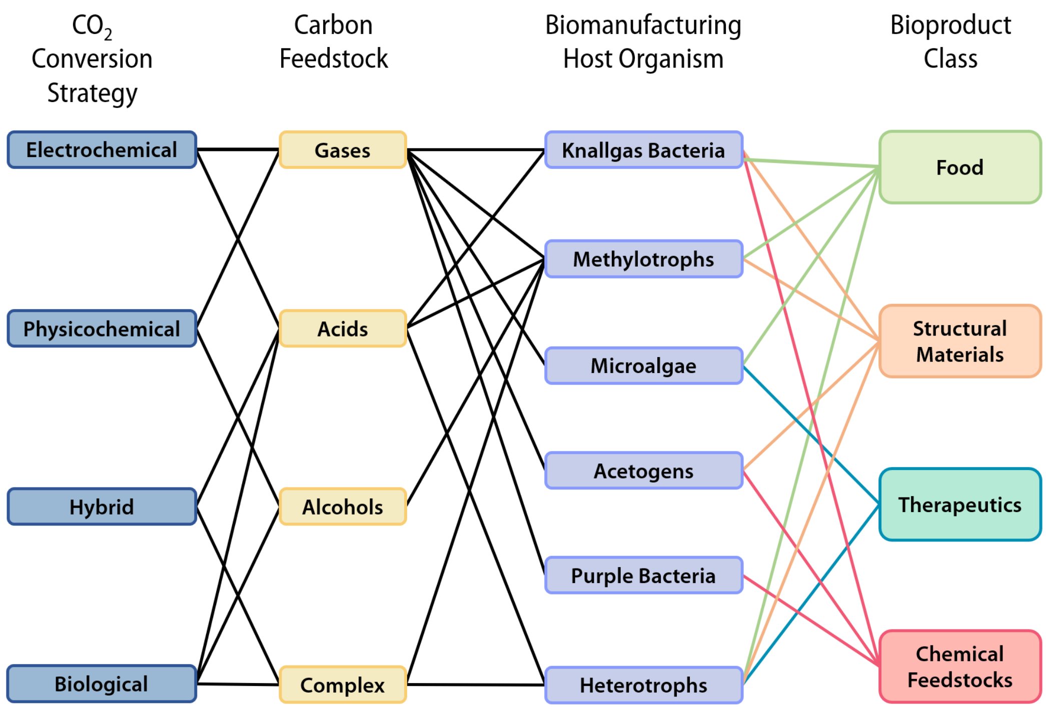

Figure 3. Breakdown of available routes for bioproduction of inventory elements from carbon dioxide—either as *in situ* or recovered resource. Connecting lines represent possible paths for carbon-compound conversion of intermediates to products. Usability of different feedstocks is tied to nutritional mode of the microbial host organism (more than one nutritional mode is possible for certain organisms). Classes of products are assigned to respective microbes in respect of their metabolism as well as not represented 'shadow-characteristics' of the chassis (e.g., aerobic/anaerobic, prokaryotic/eukaryotic, metabolic rate, robustness, etc.), rather than ability to (naturally) derive the respective compounds. While metabolic engineering theoretically allows almost any bio-available compound to be produced in any organism, the effort required for realization can be excessive. For example, oxygen-dependent pathways will hardly be functional in obligate anaerobes without extensive modifications. Likewise, correct folding of proteins with high post-translational modifications in prokaryotes is unlikely. Products may or may not comprise some of the initial feedstocks, hence consecutive runs through this chart to up-cycle carbon are conceivable.

elements of interest for further processing and application. Performed with microorganisms, this process, known as bioleaching, is already being applied on Earth (e.g., for 20% to 30% of global copper production[81]). For space applications, three classes of resources are distinguished: (1) metals and minerals like iron and sulfur oxides[82,83], or silicates[84], all of which are common in various regolith types and can be extracted for construction purposes and other bulk applications[13]; (2) rare earth elements like lanthanides, scandium and yttrium, which can be extracted from specific regolith types[85]; (3) noble metals found in components of electronics brought from Earth (e.g., copper), which could be reused for new circuitry. While (1) and (2) are part of ISRU and (3) contributes to LC, all of these extraction processes can be combined and coupled with additive manufacturing for perpetual or on-demand ISM. For Earth, these technologies would further contribute to advancement of remediation techniques, contributing to the move towards a more sustainable and circular economy.

Paths to Realization of Emerging Technologies

Readying Microbial Production Systems for off-world Bio-ISM

While having gained significant traction over the last decade, the study of space biomanufacturing is still limited to small-scale microgravity experiments[86–88] (e.g., BioRock[89] or Rhodium Inflight Biomanufacturing[90]). More extensive R&D will be required to ready bio-ISM technologies for implementation in mission architectures, especially to scale and adapt synthetic biology and bioprocess engineering to the relevant (off-world) environments (specifically Moon and Mars)[21,91]. To this end, the development of microbial cell factories must go hand-in-hand with the development of appropriate hardware for in-space bio-ISM. Specifically, standardized but versatile bioreactor systems that are scalable, automatable and capable of providing the environmental conditions for handling and cultivation of microbes in different off-world scenarios are required, combined with autonomous data acquisition for process and hardware performance characterization to monitor production outcomes (scalable yield, titer, and rate, as well as controlled quality).

Integration of Research and Development with Public and Private Sectors

To evolve the technological readiness in the described areas requires scientists and engineers from various fields spanning biology, chemistry, physics, and engineering to work together to advance microbial cell factories and build cross-compatible and scalable processing systems within the confines and stressors of space[21]. Biomolecular, bioprocess, and biosystems engineering must be integrated with pre-processing of resources and downstream processing of products, and tied in with mission-support infrastructure and logistics. Coordination mission specialists are critical to deploy tests in space under different constraints (scenarios) and build long-term partnerships and understanding between the public and private sectors. Such groundwork requires long-lived multidisciplinary centers that are secure from volatility of markets and swings of political agendas to perform the large-scale, long-term science necessary to succeed. A dedicated space-based R&D Hub as an associated 'field-station' could greatly streamline and facilitate the advancement of fundamental technology that increases TRLs. Service providers would dedicate and manage resources both on the ISS (near-term) and next-generation space station(s) (mid-term). This pipeline would ensure testing, prototyping, and maturation of technologies in space with assigned, predictable launches, hardware and support.

Conclusion

The strategic application of biomanufacturing will de-risk and expand crewed space-exploration capabilities. The farther from Earth the more mission-critical biomanufacturing becomes – Lunar missions may be not sustained only supplemented with LC, recycling and repurposing of waste-streams, Mars missions will require ISRU. To take full advantage of mission supplies and *in situ* resources, advanced biomanufacturing technologies must be developed – given the austerity of the Moon and Mars, research efforts must be geared towards the most abundant resources to benefit future deep-space missions. Near-term Lunar missions will serve to build-out and stress-test LC technologies that will inform long-term ISM processes on Mars. Techno-economic analyses of mission scenarios direct the strategic development of hardware and can, as opposed to hardware, be readily implemented at trivial capital cost. Biomanufacturing technologies for both, LC as well as ISRU, have promise for dual-use applications on Earth for a circular-economy and in extreme or inaccessible environments.

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Authorship Contributions

NJHA and AJB conceived of the study and conceptualized the manuscript with help from SNN as a whitepaper for the '2023 Decadal Survey in Biological and Physical Sciences in Space' of the National Aeronautics and Space Administration (NASA), conducted by the National Academies of Sciences, Engineering, and Medicine (NASEM). AJB designed the concepts-of-operation with supported from NJHA and conducted the break-even analysis of mission-scenarios together with SZ, GLV and DH. NJHA composed the remaining sections (supported by SNN, BAEL, JES and KBC) and performed their integration. AJB, DH, and NJHA headed the graphics effort with assistance from SNN. LRD, CAC, SNN, and APA edited the manuscript.

Competing Interests

SNN is an employee of Circe Bioscience Inc., a biomanufacturing company with financial interest in the microbiological production of foods. All other authors declare no competing interests.

Data Availability

Source data are provided with this paper as per the SI.

Supplementary Information

Supplementary materials include: (1) document containing supporting information and a rendering of data used to produce Figure 2; (2) a Jupyter notebook for plotting the results using spreadsheets as input. The provided materials are sufficient for reproducing all results, additional data can be request from the corresponding authors.

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