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Space Synthetic Biology: A Paradigm for Sustainability on Earth and Beyond

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ABSTRACT

National space agencies and private entities aim to establish outposts on the Moon and Mars before the second half of the century. This goal requires new technology paradigms that must be readied now for implementation in mission architecture. Here we present the case that synthetic biology is one such enabling technology that will work in synergy with a growing bioeconomy to solve a broad array of challenges facing humans on- and off-Earth, as they establish a foothold on the Moon in the post-Artemis years and continue to the exploration and eventual habitation of Mars. We propose a phased integration of synthetic biology into Space missions over time and identify critical dual-use breakthroughs that will expand the impact of synthetic biology on both Space missions and the Terrestrial bioeconomy. Finally, we highlight actions by national space agencies and the private sector that will be critical in the coming years to harness the potential of synthetic biology for establishing a sustainable human presence off-Earth.

Keywords: synthetic biology, space biotechnology, human spaceflight, sustainable space exploration, dual-use technologies, circular bioeconomy

INTRODUCTION TO SPACE SYNTHETIC BIOLOGY: WHY NOW?

Synthetic biology (SynBio) is the application of engineering principles to biology for the design and construction of units or systems with new functions. Propelled by the ever accelerating advances in integrating life and computer science, from bioinformatics to deep learning to artificial intelligence, SynBio is poised to deliver breakthrough technologies that play a pivotal role in the emergence of a new bio-based economy. This bioeconomy is expected to redefine aspects of the energy, materials, food, and pharma sectors, related to but not limited to areas such as safety, security, and sustainability.

Given a projected global annual impact of USD 2–4 trillion by 2040,[1,2] the U.S. government has taken several actions to secure the position of the USA as a major stakeholder in bioindustrial manufacturing. Consortia of national laboratories such as Agile BioFoundry, funded by the U.S. Department of Energy, serve to "operate as a distributed biofoundry in collaboration with industry and academia."[3] Federally sponsored manufacturing innovation institutes such as the bioindustrial manufacturing and design ecosystem (BioMADE), which is sponsored by the U.S. Department of Defense, have been formed to spawn a "sustainable, domestic end-to-end bioindustrial manufacturing ecosystem."[4] White House Executive Order 14081[5] announced a "whole-of-government approach to advance biotechnology and

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biomanufacturing towards innovative solutions in health, climate change, energy, food security, agriculture, supply chain resilience, and national and economic security." Given the wide range of industry verticals that could be affected by an expanding bioeconomy, "Bold Goals" have been defined for U.S.-based biotechnology and biomanufacturing,[3] substantiating EO 14081.

A sustainable biochemical industry is seen as a foundation of an eventual circular economy, transforming the life cycle of commodities with regular demand and high turnover, both on Earth and in space.[6] Hence, in addition to driving the bioeconomy, SynBio-based solutions are relevant to the current United Nations Sustainable Development Goals,[7,8] with potentially major economic and social benefits worldwide.[9–12]

The bioeconomy will also extend into the new Space Age[13] as SynBio has several unique advantages with regard to Space versus Terrestrial applications (examples are discussed below). First, SynBio has the potential to solve upmass constraints on missions, thus increasing mission capabilities.[14] Second, there are no indigenous manufacturing industries or jobs off-Earth that would be disrupted by designing systems and processes that are inherently sustainable. Third, the potential for establishing new jobs and new economies through SynBio in Space is attractive for investing in the Space-specific education, functionalities, and markets that tie back to the Terrestrial bioeconomy.[15]

Perhaps most importantly, SynBio will also be key to addressing the recommendations of the National Academies' 2023 Decadal Survey on Biological and Physical Sciences (BPS) Research in Space that will empower humans to live and travel in Space,[16] as we argue below.

What are the major challenges to human long-duration Space travel and settlement across the solar system? The 2020 NASA Space Technology Taxonomy identifies distinct challenges,[17] such as radiation and physiological adaptation to lower gravity. Although SynBio conceivably *could* be applicable in nearly all of these areas, we must consider whether it *should*. Although there are strong arguments for using existing systems that are proven to support humans off-planet, extended missions will need to address additional payload constraints, particularly limits to the mass launched into Space (upmass) and the shelf-life of the cargo.[18] Critically, reliability and resilience as well as redundancy and flexibility will be key to mission success and crew safety, given the increasing fragility of supply chains when advancing into deep Space. These considerations motivate our focus here on three NASA technology taxonomy areas in particular: TX06 (human health, life support, and habitation systems), TX07 (exploration destination systems), and TX12 (materials, structures, mechanical systems, and manufacturing). SynBio is also relevant to recurring tenets of NASA's Moon to Mars objectives, including: RT-1, International Collaboration; RT-2, Industry Collaboration; RT-3, Crew Return; RT-5, Maintainability, and Reuse.[19]

THE POWER OF BIOTECHNOLOGY TO OVERCOME UPMASS CONSTRAINTS

Imagine a manufacturing technology that is self-replicating and self-repairing, modular, reprogrammable, and exceedingly flexible in terms of the input. It can create fine chemicals and polymers with monomeric precision, is remarkably resilient, and can be stabilized simply by dewatering, with a shelf-life at room temperature on the order of years to centuries.[20] That technology is life.

Biotechnology has the power to solve many of the upmass constraints of Space travel by enabling the reuse of resources and basic feedstocks that are available en route (through so-called "loop closure") and/or at destination (through "*in situ* resource utilization" (ISRU)). In the former case, the feedstock can be derived through the recycling of waste streams derived from supplies that have been transported from Earth such as food and packaging. In contrast, ISRU takes advantage of feedstocks that are available in significant, accessible quantities on-site, such as H_2O, atmospheric CO_2 and N_2, and minerals, in the case of Mars.[18,21–23] On Earth, advanced manufacturing approaches that leverage these resources usually require bulky (heavy) and sophisticated hardware and infrastructure such as chemical reactors, rectification columns, and cleanrooms, as well as costly and potentially environmentally damaging inputs such as fossil fuels, rare earths, and noble metals. But there is no more precise nanotechnologist and molecular factory than a living cell.[24] For example, several biochemical mechanisms exist for fixing CO_2 and N_2; metals are bound to various biomolecules with precision, potentially paving the way for extraction and separation of ore as well as spent electronics.[25,26]

Further, many supplies of regular use,[18,27,28] such as food and pharmaceuticals but also materials, lack the long-term stability required for a nominal $\sim$2.5-year roundtrip Mars mission (conjunction class).[29] Thus, a "take" strategy must be supplemented with "make" strategies to enable sustainable exploration.[18,27,28] Examples of such supplies include food[30] as well as pharmaceuticals—especially peptide-based biologics that support crew health, such as human growth hormone (hGH)—and have shelf-lives of much less than a year, even with refrigeration.[31] An on-site, on-demand "astropharmacy" based on the transgenic SynBio production of such pharmaceuticals may be part of the solution,[32–34] supplementing abiotic approaches.[35] Importantly, such technologies have dual applications on Earth, particularly for austere locations with unreliable supply chains or when needs are restricted to a small number of people, such as orphan drugs.[36] Further, Space Biotechnology could include self-renewing recycling and manufacturing systems (biorefineries) for materials, as well as power plants, sensors, and diagnostics.[14]

The major challenge to harnessing the power of biology in support of Space activities pertains to the fact that Terrestrial life evolved on Earth. Natural biological organisms and their underlying biochemistries have evolved for survival and competitive advantage on Earth, rather than being optimized for one specific task. Thus, most organisms taken out of their natural ecological niche and possibly even off-planet should and perhaps must be adapted (evolved or engineered) to the altered conditions (such as higher radiation and lower gravity). SynBio provides the means to tailor organisms or ecosystems for specific off-planet needs.[37,38] This strategy may reduce the engineering required for designing and operating bioprocesses in Space, thus decreasing mass and power requirements while delivering robust and potentially flexible mission capabilities. For example, a microbial cell factory that has already been modified on Earth for a particular biomanufacturing task may only require additional genetic engineering to withstand the higher radiation levels of Space.[39] Alternatively, a species must be cultivated in a controlled environment closer to its Terrestrial environment, which has the benefit of relying on well-studied systems that do not need significant further modifications. In either case, planetary protection concerns need to be considered to avoid contamination of potential research targets for astrobiology.[14,36,40,41]

FROM EARTH TO SPACE: PHASED INTEGRATION OF SYNTHETIC BIOLOGY

Harnessing the power of SynBio in support of human exploration and settlement of the Moon and Mars requires the coordination of two rapidly moving fields: (1) the planning and implementation of space-exploration programs, and (2) the advancement of SynBio and its applications.[40] Replacing existing abiotic technologies with potentially superior but less flight-tested biological solutions introduces risk until proven by design-build-test-learn (DBTL) cycles designed to increase the technology readiness level (TRL) of the biotic solutions. Ideally, such technologies will drop into the existing mission architecture, minimizing the extent of changes required and disruption to other systems, thus enabling rapid deployment.

Therefore, we envision a phased approach toward integration of SynBio in which missions during the 10-year horizon focus on "carry-along" and "drop-in" SynBio-based technologies that have a track record of success on Earth or in some cases in low Earth orbit (LEO). Within 5 years of the first Artemis astronauts setting foot on the Moon, "make it there" SynBio approaches with the greatest potential to be transformative for space missions (*e.g.*, by dramatically decreasing upmass) should be prioritized to deliver reliable applications within the 10–30 year horizon. Such prioritized SynBio approaches would include ones that tackle problems for which there are no abiotic approaches currently available, such as the shelf-life issue of pharmaceuticals described above. Ideally, these approaches will be highly automated and resilient, minimizing burdens on crew training and active time during a mission. The specific benefits of implementing such advanced support functions will depend on many factors that determine the concept of operations for a given mission scenario, which will be informed by explicit techno-economic analyses and backed by calculations of equivalent systems mass to validate biotechnological approaches for *in situ* manufacturing.[41] Potentially pivotal "stretch goals" for SynBio in Space should be defined and researched as soon as possible to enable proof-of-principle work and, if promising, the required DBTL cycles to raise their TRL to where they are robust and reliable solutions. Consistent with this latter approach, the 2023 Decadal Survey on BPS Research in Space recommended that NASA pursue a research campaign in Bioregenerative Life-Support Systems (BLiSS).[16]

We believe that SynBio will be key for both of these recommended research campaigns, which constitute science and engineering fundamental to life off-planet. When biological engineering at destinations like Mars becomes possible, an ecosystem of biomanufacturing facilities co-localized to spacecraft, -stations, or bases could underpin sustainable communities of people, delivering the food, air, water, and waste processing that will enable long-duration or even permanent human habitation off-Earth while protecting environments such as the surfaces of the Moon and Mars.

CRITICAL BREAKTHROUGHS WILL DELIVER DUAL-USE TECHNOLOGIES

All technologies, including SynBio, must become efficient, reliable, and flexible before they can become critical pieces of infrastructure that drive circular economies on Earth or in Space. We have identified critical breakthroughs that will enable the development of dual-use technologies, having the potential to benefit both Earth and Space (*Fig. 1*). Specifically, the successful application of SynBio in Space will require purposefully created reagents, chassis organisms, methods, and hardware with maximum fidelity for cross-platform application.

Molecular biology requires reagents that are manufactured and formulated to exceedingly high standards, while key

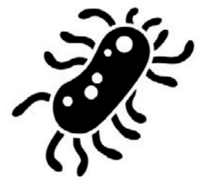
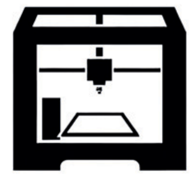
Critical breakthrough	Shelf-stable reagents for biological engineering	Development of robust chassis organisms	Hardware for agile small-batch biomanufacturing
			
Short-term benefit to Earth's bioeconomy 	Eliminate the need for chemical preservation and cold chain, enabling diagnostics and biomanufacturing in low-resource settings.	Improve ground biomanufacturing through development of robust extremotolerant chassis organisms.	Custom small-batch biomanufacturing for personalized medicine and materials for manufacturing.
Long-term benefit to Mars exploration 	Reduced hardware complexity and upmass, improved reliability.	Recycling / loop-closure (LC) and *in-situ* resource utilization (ISRU) with biomanufacturing under off-Earth conditions.	Improved mission resilience and flexibility using on-demand biomanufacturing.
Relationship to current NASA objectives	TX06. Human Health, Life Support and Habitation. Monitoring of environment and astronaut health. HBS-1. Understanding the effects of short- and long-duration exposure to off-Earth environments.	TX07. Infrastructure for ISRU and sustainability. AS-3, LI-7, and MI-4. Identify accessible resources for ISRU, demonstrate industrial-scale ISRU.	TX12. Materials and manufacturing. LI-4. Manufacturing and autonomous construction.

Fig. 1. Critical dual-use breakthroughs of SynBio for Space. Pursuing critical technologies to advance SynBio in Space will benefit basic science, technology development, business, and ultimately daily life on and off Earth. These critical breakthroughs largely align with overarching research and development needs to fulfill the Bold Goals for U.S. Biotechnology and Biomanufacturing, (2) as well as the recommendations of the Decadal Survey on BPS Research in Space (9). LC, loop-closure; ISRU, *in situ* resource utilization; SynBio, Synthetic Biology.

components require cold storage to deliver even limited shelf-life. This limitation constrains the deployment of molecular biology on Space missions, where power for temperature control is at a premium and fresh reagents cannot be readily obtained (even "just" for resupply to LEO); holding times of payloads in anticipation of launch can be excessive. There is already movement toward adapting more robust and functional molecular biology for rugged conditions, for example by creating shelf-stable diagnostic tests that can be freeze-dried and rehydrated for use.[33] Further investing in the development of simple, robust reagents for molecular biology such as highly stable dried cell-free transcription/translation systems will accelerate the field by opening up new application areas in Space and on Earth, for example in remote and resource-constrained locations.

A second critical breakthrough is the development of Space-worthy chassis organisms. Today, we know of extremophiles that tolerate or thrive in many of the exotic conditions that are more like places elsewhere in the solar system than the rest of Earth's biosphere. Nevertheless, organisms that match the combined demands of a specific extraterrestrial environment are lacking. Harnessing the natural diversity of life on Earth to find or engineer microbes that are designed for use in specific unusual environments is a breakthrough critical for effective biomanufacturing—and not only in Space.[37] This task will involve applying the entire modern toolkit of SynBio bioprospecting,[23] adaptive evolution,[38,39] and genetic manipulation toward new Space-focused applications. On Earth, advancing the engineering of extremophilic organisms will enable industrial bioprocesses to operate under more extreme (non-natural) conditions—such as high pressure, temperature, or excess concentrations of chemicals (*e.g.,* solvents)—to optimize production (rate, titer, yield) and thereby reduce process costs. Longer-term, Space-worthy chassis organisms may one day be the backbone of *in situ* biomanufacturing on Mars. To this end, the 2023 Decadal Survey on BPS Research in Space[16] recommended that NASA increase investigations into the impacts of the Space environment on biological growth, reproduction, and evolution, fundamental scientific knowledge that will be key to sustainable SynBio with live organisms.

The lack of hardware for biomanufacturing in Space, under conditions of lower gravity and higher radiation than on Earth,[42] is a crucial bottleneck that presently limits the speed of progress in the field. Most notably absent is flight-tested hardware for DNA synthesis and manipulation where low gravity makes standard methods impossible. Bioprocessing in Space[42] is still in its infancy, with some basic techniques such as DNA sequencing, DNA amplification,[43] and gel electrophoresis[44] performed in Space; facilities such as the Wet Lab RNA SmartCycler[45] and a bioreactor (Multiple Orbital Bioreactor with Instrumentation and Automated Sampling (MOBIAS))[46] are already operational on the ISS. The ability to synthesize DNA remotely, and thus program biological instructions on demand, unlocks the full utility of SynBio as a highly flexible and programmable technology platform for manufacturing and sensing. A critical breakthrough for the field will be translating the existing capabilities of ground-based biofabs to Space,[47] allowing the rapid prototyping and building of any molecule. The existing infrastructure on the ISS has previously been sufficient to test SynBio capabilities, especially with an emphasis on miniaturization and automation, while accounting for lower gravitational forces (*e.g.*, the use of microfluidic rather than "test-tube" platforms[42]). As ISS is decommissioned, small satellites, commercial platforms for LEO, Gateway, and other upcoming *cis*-Lunar operations must provide opportunities for extended testing and translation of biofoundry components.

A suite of hardware for SynBio in Space may in the short term allow for rapid iteration on biomanufacturing protein-based biomaterials in LEO, or deployment of similar devices in low-resource environments, benefiting developing countries in particular. In the long term, it will enable on-demand synthesis of chemicals that were not or could not be brought along (for example to Mars), significantly improving the resilience and feasibility of future missions.

HOW TO GET THERE—A CALL TO ACTION

The bioeconomies of the USA and other countries will contribute to making reliable, cost-effective, and sustainable biomanufacturing a staple of life on Earth and in Space, driven by the private space sector and national (space) agencies alike.[12]

Fundamental improvements to the resource requirements, reliability, and scale of biomanufacturing are best addressed by the global bioeconomy.[2] Today, biomanufacturing processes often require expensive (and often unsustainable) feedstocks, are prone to variability in product quality, and are difficult to scale. Decreasing costs and improving the reliability of biomanufacturing is therefore essential. The global bioeconomy is collectively tackling these fundamentals by experimenting with new low-cost feedstocks derived from waste streams, creating low-cost purification strategies, developing processes that are more scalable, and engineering pathways to produce new products. For example, the USA has substantial renewable carbon resources that could support large-scale biomanufacturing efforts, which will likely incentivize investments into the development of the infrastructure required to leverage these resources.[48,49] The result will be a thriving bioeconomy that creates jobs and is reliable, cost-effective, and sustainable. In this article, we call for the expansion of this vision to encompass humanity's future off-Earth, positioning SynBio to address the recommendations of the National Academies as fundamental to human success in Space.[16]

Meanwhile, the private sector is well positioned to address many of the new hardware needs that come with the use of SynBio off-planet. Several companies have developed and are flight-testing cell-culture devices to conduct bioengineering and biomanufacturing in a microgravity environment.[12] Expanding this repertoire of devices, particularly through open-access frameworks, will benefit these for-profit companies as well as national space agencies. This public-private integration will be critical for expanding both the pool of contributors to key advances in Space and the set of stakeholders in a sustainable human future.

Due to the exceptional flexibility of this technology, it is challenging to isolate a single best first use case of SynBio in Space that extends further than technology demonstration; the first use case will be determined based on mission needs and associated quantitative analyses such as equivalent systems mass.[41] For example, is it better to ignore drugs that have a short shelf-life or make them fresh on demand? Most importantly, the multitude of national space agencies (*e.g.,* NASA, CSA, ESA, JAXA, CNSA, and ISRO) can uniquely and in combination contribute to advancing the field by putting biomanufacturing solutions through the rigorous flight-testing process, ensuring that these processes are ready for human missions.

CONCLUDING REMARKS AND VISIONARY OUTLOOK

The vast majority of humans are and likely will stay, on planet Earth for the foreseeable future. So what is to gain from advancing SynBio for Space applications? Simply put, SynBio has the potential to revolutionize manufacturing, healthcare, environmental remediation, energy dependence, and other problem spaces. Critically, on Earth, solutions to these issues are pursued through legacy approaches that may not meet the needs of future generations. Game-changing solutions often do not gain traction as there is no immediate economic advantage to replacing legacy solutions. Planning for Space empowers us to reimagine solutions to Terrestrial problems by focusing on a use case that either does not currently have a solution, or replacing the planned solution has little socioeconomic or geopolitical ramification. Further, these solutions must ultimately be closed-loop—where all inputs and outputs as well as their dynamic fluctuations are known and accounted for—thus providing a template for a circular economy at a global scale.

Vulnerabilities in bioeconomy supply chains were exposed during the COVID-19 pandemic. Off-planet, supply chains are limited and fragile. A Mars supply chain would be the ultimate onshoring effort. Given the wide spacing of launch windows for Mars (currently a 2-year cadence),[50] supply chains should be short, flexible, and resilient to unexpected events and geopolitics.

The Terrestrial SynBio ecosystem has other requirements, such as scalability, near-term profitability, and environmental and geopolitical concerns such as national laws and competing economic interests. A Space-based SynBio ecosystem allows the industry to bypass many of these impediments. The Space Industry provides an unusual opportunity in that there are specific needs that currently lack a fully established ecosystem; default plans such as the Mars Design Reference Architecture 5.0 are currently in place but are in flux and can be improved.[51] Further, given the global effort to wean ourselves from petrochemistry, new planetary bodies devoid of fossil fuels will force novel solutions without perturbing the legacy systems that exist on Earth. Thus, we firmly believe that aggressively pursuing SynBio for Space applications will not only solve urgent problems of human health, habitats, life support, and materials production for off-Earth applications but will ultimately deliver the game-changing solutions that will empower humans to thrive in the Anthropocene, wherever we call home.

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All authors contributed equally to the development, writing, and editing of the article.

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