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Towards the Future of Space Bioprocess Engineering

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ABSTRACT

Inspired by new measurements and imagery from the Perseverance mission, there is reinvigorated public interest in a crewed mission to Mars in the 2040s. To realize such a mission, we must work to solve multiple science and engineering challenges as described by NASA's Space Technology Grand Challenges (STGCs) for expanding human presence in space, centered around advancing technologies to support the nutritional, medical, and incidental material requirements that will sustain astronauts against the harsh conditions of interplanetary transit and habitation on the surface of an inhospitable alien world. Advanced biotechnologies that support flexible biomanufacturing from *in situ* resources can provide a mass, power, and volume advantage compared to traditional physicochemical strategies. However, critical bottlenecks remain that must be overcome to make Mars biomanufacturing practical and robust. Here we begin with a brief review of the recently codified field of Space Bioprocess Engineering (SBE) — the multidisciplinary approach for the design, realization, and technical management of a biologically-driven system in a space mission context — and we outline the concept of "Hilbert-like" problems that may shape the field in the future. We then describe a number of categories for such problems and expand on a number of preliminary Mission Design and Modeling problems that underpin SBE, in the fields of mission architecture formation and value benchmarking. We end by enumerating a list of problems and challenges across Mission Design and Modeling (MDM), *In Situ* Resource Utilization (ISRU), *In Situ* Manufacturing (ISM), Food and Pharmaceutical Synthesis (FPS), and Sustainability and Loop Closure (SLC). The Space Bioprocess Engineering problems provided here are based on an effort by the Center for the Utilization of Biological Engineering in Space (CUBES, https://cubes.space/). We recognize that more feedback is needed to better define the envelope and specifics of SBE challenges for the field, and we provide a link to a set of questions here: https://forms.gle/YKtuPU9MXZ3mi7gE6.

1 Introduction

Speaking at the *International Congress of Mathematicians* in Paris at the dawn of the 20th century[1], David Hilbert presented 10 problems ranging across mathematical subdisciplines to a coterie of eager mathematicians. Eventually, the list grew to 23[2] (or 24[3] if you want to get technical) problems and was published in translation in the *Bulletin of the American Mathematical Society*. They evolved to represent the pillars of his field, and long after his death and a century later, the unresolved problems still offer an opportunity for shaping the future of mathematics.

> *"Who of us would not be glad to lift the veil behind which the future lies hidden; to cast a glance at the next advances of our science and at the secrets of its development during future centuries? What particular goals will there be towards which the leading mathematical spirits of coming generations will strive? What new methods and new facts in the wide and rich field of mathematical thought will the new centuries disclose?"*[4]

We find ourselves at the nexus from which the dream of human space exploration may be realized – or at a time when the challenges of reaching skyward may prove too great. There are significant challenges, spanning a wide range of disciplines and bleeding beyond the scientific[5] and technical[6] to the political[7, 8], economic[9, 10], and societal[11, 12] spheres. Despite this expansive problem scope, much of the path forward will be driven by the design, construction, and deployment of space technologies within classes outlined by the NASA's Space Technology Mission Directorate's (STMD) Space Technology Grand Challenges (STGCs) by [13]

1. Expand human presence in space, via:
    (a) Economical Space Access
    (b) Space Health and Medicine
    (c) Telepresence in Space
    (d) Space Colonization
2. Manage in-space resources, via:

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   (a) Affordable Abundant Power
   (b) Space Way Station
   (c) Space Debris Hazard Mitigation
   (d) Near-Earth Object Detection and Mitigation

3. Enable transformational space exploration and scientific discovery, via:
   (a) Efficient In-Space Transportation
   (b) High-Mass Planetary Surface Access
   (c) All-Access Mobility
   (d) Surviving Extreme Space Environments
   (e) New Tools of Discovery

There is new and (in some cases, renewed) interest in applying biotechnological solutions within the space-context. To cite out own experience, over the past five years, the Center for the Utilization of Biological Engineering in Space (CUBES, https://cubes.space/) has road-mapped technological development that could support biomanufacturing for deep space exploration by realizing the mass, power, and volume advantages that biotechnology may have over traditional abiotic approaches[14, 15, 16, 17]. Over the past 5 years, CUBES has made technical progress in the development of biologically-based *in situ* resource utilization platforms[18, 19, 20, 21], in plant and microbial engineering to realize food and pharmaceuticals for astronauts[22, 23, 24, 25], in the manufacturing and shaping of biopolymers[26, 27, 28], and in the preliminary systems analyses that contour future mission targets[22, 17]. Most recently, this preliminary body of research has been codified into the nascent field of Space Bioprocess Engineering (SBE)[29]. Here, like Hilbert, we propose to formalize a list of open questions scoped within the SBE field.

1.1 *Space Bioprocess Engineering*

We define Space Bioprocess Engineering (SBE) as the intersection of *systems engineering* and *biological engineering*.

At NASA[30], *Systems engineering* is defined as a methodical, multi-disciplinary approach for the design, realization, technical management, operations, and retirement of a system. A “system” is the combination of elements that function together to produce the capability required to meet a need. The elements include all hardware, software, equipment, facilities, personnel, processes, and procedures needed for this purpose; that is, all things required to produce system-level results. The results include system-level qualities, properties, characteristics, functions, behavior, and performance. The value added by the system as a whole, beyond that contributed independently by the parts, is primarily created by the relationship among the parts; that is, how they are interconnected[31].

Biological engineering is an emerging discipline that encompasses engineering theory and practice connected to and derived from the science of biology, just as mechanical engineering and electrical engineering are rooted in physics and chemical engineering in chemistry. Topical areas include, but are not limited to, synthetic biology and cellular design; biomolecular, cellular and tissue engineering; bioproduction and metabolic engineering biosensors; ecological and environmental engineering; and biological engineering education and the biodesign process[32]. Biological engineering employs knowledge and expertise from a number of pure and applied sciences such as mass and heat transfer, kinetics, biocatalysts, biomechanics, bioinformatics, separation and purification processes, bioreactor design, surface science, fluid mechanics, thermodynamics, and polymer science[33].

Given those subdisciplines, **we therefore define SBE as the methodical, multi-disciplinary approach for the design, realization, technical management, operations, and retirement of a biologically-driven system in a space mission context.** Example of recent efforts in SBE, include systems to support the nutritional, medical, and incidental material requirements that will sustain astronauts against the harsh conditions of interplanetary transit and habitation offworld[29, 17]. SBE combines synthetic biology and bioprocess engineering under extreme conditions to enable and sustain a biological presence in space. The primary sub-fields of SBE are currently (but not limited to)[29, 17]:

1. **Mission Design and Modeling (MDM)**: The aim of MDM is to optimally allocate and utilize Space resources, to tightly integrate and automate internal processes, and to satisfactorily achieve performance per mission specifications.

2. ***In Situ* Resource Utilization (ISRU)**: The aim of ISRU is to harness available *in situ* resources and human/mission wastes and transform them into useful feedstocks for utilization by downstream processes.

3. ***In Situ* Manufacturing (ISM)**: The aim of ISM is generally to produce propellants, biopolymers and other materials, and (bio)chemicals from media and feedstocks and to use generated materials to achieve mission goals such in research or to build infrastructure for the mission itself.

4. **Food and Pharmaceutical Synthesis (FPS)**: The aim of FPS is to leverage plant and microbial engineering to provide food and pharmaceuticals for astronauts.

5. **Sustainability, Loop Closure and Containment (SLC)**: The aim of SLC is to minimize mission resource utilization and waste production while maximizing use of these streams for regenerating life-support functions, biomanufacturing and food and pharmaceutical production. Since it is deeply integrated with optimal use of resources and loop closure, issues of biocontainment and safety are also included here.

Given the areas of SBE above Space Operation presents very specific challenges to the common operation of biotechnological industry. The most obvious differences are:

1. the logistical isolation of any operation and the massive expense of launching and storing large quantities of feedstocks and infrastructural materials;

2. the extreme constraints on the amounts and types of local resources that can be accessed to build and maintain infrastructure and transform into products of interest;

3. the attendant needs for extreme efficiency, reliability, and autonomous operation so that a limited human population is protected and not overwhelmed with operating the system;

4. the requirements for closed-loop, regenerative, and contained designs to maximize efficiency of resource utilization while protecting and improving the environment in which the plant operates;

5. adapting the bioprocess design from organisms to production systems to require the minimal environmental conditioning (e.g. temperature, pressures, radiation protection) for optimal operation so they cost less and have less risk for sustained operation in space;

6. infrastructural designs ranging from nimble personalized bioengineering and bioproduction for 'novel' agents on demand as unexpected needs are discovered to large-scale bioproduction of materials or foods as demands for support of larger infrastructural projects or human populations arise;

7. long-term storage and management of feedstocks and products in harsh conditions where shelf-life is expected to be reduced due to extreme environmental stressors like radiation, temperature variation, pressure differentials, and gravitation changes;

8. finally, deciding when a biotechnological approach is superior to an abiotic approach or 'delivery from earth' requires accurate systems models coupled with technoeconomic analyses that support rational and effective decision making at all stages of the mission.

Many of the above present exceptionally difficult engineering and social challenges that mostly require will and resources to overcome. Others of these require scientific breakthroughs, for example, in the tools for biomolecular and cellular engineering including new innovations in the design of cellular, organismal and community functions, stress responses, resilience and safety; and in design and operation of complex, interconnected bioprocesses under extreme uncertainty since testing under full operational conditions will be very limited and more.

These require solving fundamental scientific and technological bottlenecks which together with the engineering challenges would likely not be economically feasible to address for earth-based industry but, if solved, would have great impact on our terrestrial economy and operations.

2 SBE Problem Structure

> *"A mathematical theory is not to be considered complete until you have made it so clear that you can explain it to the first man whom you meet on the street." This clearness and ease of comprehension, here insisted on for a mathematical theory, I should still more demand for a mathematical problem if it is to be perfect; for what is clear and easily comprehended attracts, the complicated repels us. Moreover a mathematical problem should be difficult in order to entice us, yet not completely inaccessible, lest it mock at our efforts. It should be to us a guide post on the many paths to hidden truths, and ultimately a reminder of our pleasure in the successful solution"[4].*

Ultimately, SBE seeks to ensure that a particular biotechnology provides a benefit that exceeds its cost on a mission and, if possible, a benefit that exceeds its cost on Earth. A common thread of all SBE problems begins with the need for formal and quantifiable specification of missions in terms of a set of interdependent, temporally ordered technological operations.Any mission leveraging biotechnology may require new or differently emphasized cost-benefit metrics that acknowledge the specific challenges in SBE itself (and its component fields such as chemical engineering, synthetic biology, bioprocess engineering). The challenges facing SBE, then, are to clearly define these operations and the need gaps necessary to their effective implementation, as well as the barriers to their development.

Here, we attempt to outline how to formulate, at a high, level these key operations to motivate communities to work on them as Hilbert problems were motivating to mathematicians. We set forth a structure in which there is a problem statement/motivation, a specification, a termination criteria (when are we done), and a statement of its general importance for SBE. We start with two very high-level examples that, while not specific to SBE, are prerequisites for being able to value and set boundaries for other technologies:

1. Determining how to rigorously specify a mission to enable comparative technoeconomic analyses of different technological implementations to meet concrete mission goals and,
2. Defining quantifiable metrics beyond meeting core technical specifications that properly capture other systems and society-level desiderata that are often ignored but have, we argue, high relevance to mission success and SBE approaches.

3 MDM Problem #1: Formal Mission Architecture Specification

3.1 *Problem Motivation*

The definition and specification of a particular mission or interlinked set of missions to space is likely to be an evolving target and may involve several communicating stakeholders ranging from national space agencies, industrial partners, university laboratories, policy groups and politicians. Communication should ideally be high and different proposals should be easy to communicate, compare and quantify. Development of an open, standard, computable framework for specification and quantification of missions is critical to meet this goal as is a validated, acceptable database of mission elements- their composition, costs, and models of operation.

For example, consider the complexities of a human exploration mission to Mars. There are two major classes of such mission: shorter-term , opposition class missions of approximately 30 days of surface operations, and longer-term conjunction class missions of around 500 days of operation[34]. These will have very different cost-benefit analyses for technologies to support crew operations for food, medicine and materials[35]. In the former case, it is likely that bring-along supplies will be the best solution and in the latter case, that SBE biomanfacturing could become more attractive. However, within and across these mission types, to effectively know when and which biotechnologies will be most suitable we need to be able to to represent and calculate the cost and benefit of each technological selection. This means being able to specify for each stage of the mission how technologies get packed, launched, maintained when non-operational, unpacked, deployed, operated, then broken down and returned and how these elements put constraints on other mission operations. Design of the formal language, modeling framework, and development of the validated data with which to support its application is a class of grand challenge all its own.

3.2 *Problem Specification*

The goal here is to develop a formal language for mathematical representation of complex missions such that new mission scenarios, operational elements, and technologies can be placed within a common framework and detailed from the abstract class level to precise technological specification that enables for modeling, optimization and comparison of different scenarios algorithmically.

1. Define a framework for defining any abstract mission architecture and the corresponding specification requirements of a specific mission instance.
   (a) Define an abstract mission architecture.
   (b) Define a mission instance.
2. Given an abstract mission architecture, define a general algorithm for specifying a benchmark mission instance.
   (a) Define a benchmark mission instance.
   (b) Demonstrate that the evaluation of a benchmark mission in terms of the performance metric (cost) can provide a worst-case scenario for mission comparisons.
   (c) Demonstrate the mathematical framework for automated benchmarking such that its use in the community can be adopted in tool development and as a potential comparator for developing mission architectures and technology platforms. We note here that such tools must be augmented with a clear and

formal ontologized way of representing mission elements, their compositions, their operational models and assumptions, and variables from which costs and benefits are derived.

3.3 *Termination Criteria*

Termination of a formal mission architecture specification is achieved by proof that multiple teams with competing technology can represent and compare the operations and costs of their different mission designs on a fair basis using a common platform accessible to all teams so results may be shared, checked, and extended. To date this has been partly realized in systems such as the ALSSAT[36, 37, 38] or HabNet[39] but these are difficult to extend. We have proposed to build on their foundation with an entirely new tool called echusOverlook[40] to address making the specification and its reduction to practice in technoeconomic modeling frameworks adherent to FAIR (Findable, Accessible, Interoperable, Reusable) principles[41]. The design and construction of such a software tool to addresses these MDM problems as a means and method for evaluating mission architecture across a myriad of metrics common to Environmental Control and Life Support System (ECLSS)[42] serves as an instantiating and termination criteria.

4 **MDM Problem #2: SBE Metrics and Cost Benefit Analysis**

4.1 *Problem Motivation*

As a field, mission design has existed long before Space Bioprocess Engineering, powered by the safety and cost demands of a given mission, but it has never formalized its offerings towards science, exploration, and policy stakeholders. Given a formal framework for defining mission architecture, it becomes necessary to ensure that a mission's benefits exceed its associated costs. This requires establishing accepted genres of value that proposed architecture can deliver, criteria to measure them, and mathematical avenues to line them up for full cost-benefit analyses.

The challenge is to represent a mission through its logistical operation supported by the technologies to accomplish the mission goals in a format with sufficient resolution and concreteness to allow its incorporation into one or more types of formal comparative technoeconomic analysis. However, current analyses of this sort to date have largely been focused on very fundamental costs that a technology can meet, given simple specification for its function — constraints such as volume, mass, power/physical resource requirements, astronaut time, etc. There is work even to define each of these costs formally so that they can be calculated over a multistage mission and compared across different technology composition and mission architectures[43].

However, we argue that there is opportunity to improve and extend these metrics for aspects that are especially, though not solely, relevant to biotechnologies. Metrics that capture aspects that make a technology more operable and maintainable such as complexity and modularity; or aspects that address environmental impact such as waste recapture, containment and resource regeneration; or metrics that capture mission resilience like operational risk, sustained operation without logistical resupply, and autonomous operation with crew intervention. Metrics could also include allied benefits such as impact of successful development on Earth economy, the environment, and social equity.

Formal design of these metrics to meet mission and larger societal goals with sufficient mathematical rigor could be a boon to trade-off analysis and the assessment of reference mission architecture.

4.2 *Problem Specification*

The primary goal is to develop the methods for best metricizing the full set of risks, costs, and benefits of proposed mission architectures. To produce a consolidated series of factors for optimizing a cost-benefit model, we need to establish the metrics worth developing. The innovation we are proposing here it to extend standard metrics beyond meeting core technical specifications of each mission element to include systems levels metrics, metrics of maintainability and upgradability; metrics that account for risk; and metrics that include other benefits such as the possible dual-use of the technology to solve problems on earth or the follow-on impact of scientific discovery. Decision makers may ultimately use different subsets of these but the ability to formally specify such metrics compatible with the technoeconomic framework proposed above is critical and these themselves should be FAIR. What follows are some of the need gaps and possible futures to this effort.

1. Formalize SBE performance metrics for the criteria of sustainability, autonomy, supportability, recyclability, and modularity[29]. Such SBE performance metrics serve as novel means for evaluating the costs of SBE-driven campaigns. Initial examples might include:
    (a) *Modularity*: to assess the agility of a system in responding to product changeovers and demand variations to maximize flexible biomanufacturing – de-risking on-demand biological production.
    (b) *Recyclability*: to assess the extent to which wastes and byproducts can be recycled and

bioprocesses can be reused/repaired to minimize overall consumable requirements – de-risking circular bioprocessing.

   (c) *Supportability*: to assess system self-sufficiency to maximize self-reliance and minimize logistic resupply requirements from Earth – de-risking unplanned mission extension.
   (d) *Autonomy*: to assess the extent to which optimal system performance can be realized under unknown and transient offworld conditions, as well as potential system faults/-failures, with minimal human intervention to maximize the system resilience – de-risking robust and fault-tolerant biomanufacturing.
   (e) *Sustainability*: to assess the flow of environmental assets to minimize environmental footprint and maximize resource efficiency – further de-risking the potential for negative impacts to planetary protection.

2. Formalize Scientific & Technical Value, Exploration Value, and Stakeholder Value as novel means for evaluating the benefits of SBE-driven campaigns.

   (a) *Scientific & Technical Value*: Scientific & Technical Value is a proposed benefit to measure the scientific and technological progress achieved by a mission. With a reference mission architecture that can simulate possible landing site, habitat setups, astronaut schedules, and equipment manifests with some detail, a metric capturing experimental progress, and the demonstration of technology could be established. While a given technology/operation on a mission may prove fundamentally expensive compared to others, if this particular element advances new technological approaches with high follow-on value within or beyond the mission scope (e.g. it has a quantifiable future return on investment by making future needs cheaper for example) or if it provides the capability to achieve scientific outcomes not available otherwise, both these softer 'returns' should be captured when comparing different mission plans. Even when such values are uncertain, capturing them parametrically so it can be seen how they impact choice formally would be useful and comparative frameworks that allow capture of this uncertain return-on-investment would be valuable. Missions that give opportunities to mature critical technologies or make critical discoveries obviously have more intrinsic value that those that don't. But there are tradeoffs between expense and these future returns that need formal capture. A scale demo unit of a future technology like MOXIE[44, 45], tested *in situ* can reveal key features and needs, which could make future versions more effective, or streamline development. A rise in technology readiness level (TRL)[46] across technology elements can reflect development and testing that enables future improvements when deployed. Possible proxies for this metric include the number of experiment instruments deployed, experiments conducted, or technology readiness level (TRL)[46] gain across technology elements.
   (b) *Exploration Value*: As noted above, a more expensive mission design may lead to new knowledge of sufficient future value to defray the cost. Exploration has both its own value in the human knowledge base, and to the success of future Martian campaigns: locations for bases, water and resource deposits, and safe travel routes explored by one mission could reduce cost and risk for future missions, an aspect of a mission's offerings that could be captured mathematically. There has been work in the literature examining exploration logistics: exploration vehicle options[47], rover performance[48], surface exploration budgeting as an optimization problem[49], but there has been no consolidated metric for campaign exploration value. Possible proxies to conduct analysis include total exploration area, outposts built/discovered, samples collected, and sample mass. The elements of the metric would prioritize exploration findings and ground covered, versus only the purely scientific and technical elements from the previous benefit metric.
   (c) *Stakeholder Value*: Space exploration can offer different societal dividends, but as an analytical exercise mapping them, stakeholder interests can be conflicting and complex. Stakeholder theory for space exploration has been well-defined in the literature, with some analyses focusing on the larger goals of human exploration[50, 51], others on the definition of stakeholder interests[52, 53, 54], and others on exploration architecture returns[55, 56, 57]. This call is for an expansion of some of this work into a sin-

gle metric for measuring stakeholder value at the architectural level. Space for innovation exists for a measurement at the mission level of economic return-on-investment; societal co-benefits in education, diversity, equity, and inclusion[29]; and technologies that may provide dual-use extensibility on Earth. Other aspects such as campaign sustainability could be attractive as a way to lower costs and risk for future missions using the same infrastructure, and as a way to hedge against astronomical threats.

4.3 *Termination Criteria*

The termination criteria would be an integrated framework for these larger implications of space ventures that could plug into formal technoeconomic mission-planning tools such the one, eO[40], that we are developing or other mission design software. A successful development of this analysis should demonstrate sufficient extensibility such that users can create new metrics and redesign aspects of value here, and democratize this new platform for scientists, engineers, and policymakers. New metrics would need to be validated against Earth-based bioprocessing at the systems level, and the resulting cost-benefit analysis should grant reasonable valuations using prior Apollo exploration missions and current Mars reference mission architecture. And though a menu may suffice, a full rendering of a weighted cost-benefit values may prove more informative.

4.4 *Problem Significance to SBE*

At the core of any formal comparative technoeconomic analysis of a space mission is the ability not just to model the 'effect' of choosing a particular architecture and implementation (e.g. a particular set of operations to get a crew to Mars to carry out a specific set of operations and return them home using a core set of specified technologies) but to be able to assess the cost and benefit of those particular choices. While practical costs (such as weights, power and resource use, operational load, etc.) are common and relatively easy to measure, other costs are more subtle (such as risk, maintainability). The value returned as noted above is also hard to assess. However, successful representation of these issues in a consistent computable, sharable, integrated mathematical format will great improve communication and comparison. When it is possible for different constituencies to apply different combinations of metrics and assess where they difference in their cost-benefit driven designs arise and why, this challenge has been successful and will properly capture the value of novel technological approaches like SBE.

5 Moving Forward

In moving forward, we provide an enumerated list of *prima facie* "Hilbert-like" problems scoped within Space Bioprocess Engineering in Table 1. At current, these problems are non-exhaustive and should be considered a work in progress. In presenting them in this proceeding, we aim to offer a glimpse at the means and methods that shape the SBE challenges. The Space Bioprocess Engineering problems provided here are based on an effort by the Center for the Utilization of Biological Engineering in Space (CUBES, https://cubes.space/). However, we recognize that more feedback is needed to better define the envelope and specifics of SBE challenges for the field as a whole. Thus, here we provide a link to a set of questions here: https://forms.gle/YKtuPU9MXZ3mi7gE6. We invite all interested to please fill out this brief survey and sign up for future updates! This form enables all interested parties to add the following elements for defining SBE problems.

1. **SBE category:** These categories (outlined above: MDM, ISRU, etc.) provide a simple categorical classification system for initially sorting problems into SBE themes.
2. **1-2 Sentence Description:** These descriptions essentially provide a minimal "abstract" for discussing the problem. In some sense, these descriptions also provide an analogue to Hilbert Problems such as "Solution to Fermat's Last Theorum" or "Proof of Riemann's Hypothesis."
3. **Full Problem Description:** An extended problem description provides a full accountancy for the defining a given SBE problem. The problem description will begin with a brief problem motivation which leads into a full description of the problem.
4. **Termination Criteria:** A description of what specifically is needed for the problem to be considered answered in full.
5. **Significance to SBE:** We will end each expanded problem description with a statement on the problem's significance to SBE.

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Authorship Contributions

All authors developed, wrote, and edited the manuscript.

Competing Interests

All authors declare that they have no conflicts of interest.

#	Sub-field	Minimal Problem Summary
1	MDM	Develop a formal language for mathematical representation of complex missions in a common object architecture– such that new mission scenarios, operational elements and technologies can be placed within a common framework and detailed from the abstract class level to specific technological specification– that enables for modeling, optimization and comparison of different scenarios algorithmically.
2	MDM	Given an abstract mission architecture, define a general algorithm for specification of a benchmark mission instance.
3	MDM	Given a specific mission instance, develop a framework for defining, evaluating, comparing, and optimizing a SSB-tailored performance metric for sustainability.
4	MDM	As a field, mission design has existed long before Space Bioprocess Engineering, powered by the safety and cost demands of a given mission, but it has never formalized the exploration and policy stakeholder offerings, nor the demands of its schedule and equipment on the health and comfort of its crew. How can we best metricize the full set of risks, costs, and benefits of a proposed mission architecture?
5	ISRU	DNA synthesis will be key to bits->atoms production of on-demand biosynthesized materials. How do we make an ISRU-based, energy/mass/time efficient DNA synthesizer of sufficient reliability? How do we recapitulate or replace phosphoramidite chemistries with biosynthesizable analogs?
6	ISM	Maximize the fraction of the biomanufactury which can made from materials synthesized by the biomanufactury itself and which can be easily recycled to feed itself when parts fail or wear out.
7	AHP	Develop a systems engineering plan for manufacturing radiation protection for humans, plants and microbes (including those in storage) that ranges from genetic engineering, to chemical treatment, to synthesis of radioprotectant materials for shielding, to reactor and factory designs that minimize radiation penentration for operations in flight and on planet.
8	ISM	Develop a scalable modular design for microbial bioreactors which allow for flexible interconnects of multiple reactor types through modular processing units so that the outs of one reactor bank can be processed and fed to the next in an automated and robust fashion and which use materials defined by the biomanufactory materials challenge. Ensure they meet the specifications of a modeling framework that allows off- and on-line process optimization as different numbers and types of units are interconnected. Design these so that they can be stored and automatically robotically assembled upon delivery pre-crew arrival.
9	ISRU	Develop a rapidly growing, quickly engineerable plant and microbial food substrate that can be processed into meat- and vegetable-like functional foods delivering different nutritional, taste, texture, odor and pharmaceutical service to astronauts.
10	SLC	Develop a set of optimized modular waste recycling units that process all form of biomanufactury, human and other compatible mission waste into feedstocks for the biomanfacturing system.
11	MDM	Given a set of of both plant and microbial growth reactors, and harvesting and processing systems, develop a method for the design of the smallest footprint plant that optimizes the operations of the reactors, respecting power, light, gas, liquid flow constraints and use/reuse of heat, expelled gases, etc. and ensures easy repair and accessibility to systems.
12	MDM	Develop a coherent framework for quantifying actuarial risks of technologies for which, in the models of the technological process, there is uncertainty in the knowledge of the parameters of the process, intrinsic variability in parameter values and in the normal operations of the technology, and for which there is a statistical rate of failure of elements of the technology. The risk should capture a quantitative measure of probability of delivering a specified performance or better as a function of time. This should be inferable from well-defined design of experiments on the technology and/or from first principles. A second framework should propagate this ‘unit operation’ level risk to the mission scale to be able to calculate the risk of failure of mission objectives up to and including total mission failure. This should be integratable into mission scenario comparison and optimization frameworks above.
13	SLC	Develop a zero-escape design of the biomanufactury such that the probability of contamination of landing location with any materials produced or recycled from the biomanufactury is as close to zero as possible.
14	SLC	For any waste that cannot be recycled, develop a methodology for conversion into materials for construction or other mission needs that do not leach any materials with biological signatures into the environment.
15	ISM	Design organisms ever-more adapted to the conditions of the deep space biomanufacturing plant that also reduce costs of inputs and conditioning.
16	ISRU	Optimize system for delivery of bacterial fixed N_2 and recovered N to plant growth for food and pharmaceutical production
17	ISM	Design and operate a halophilic bioreactor to optimize production of bioplastics that can be easily recovered via osmolysis
18	FPS	Recovery of earth-based genetic expression in microgravity settings to maximize recycling and the production of biofuel, biopolymers, and pharmaceuticals in both microbes and plants
19	FPS	Development of platform technologies for mRNA-based therapeutics/vaccine production, purification, formulation, and quality assurance/qualification that utilize reagents produced using photoautotrophic organisms, maximize ISRU, and minimize ESM.
20	MDM	Develop an adaptable, learning-based automation framework towards the safe and on-demand biomanufacturing in unknown, uncertain, and dynamic Martian environments with “astronaut-in-the-loop”. The goal is to construct a feedback loop that encompasses all processes which will be monitored using advanced machine learning and predictive control techniques.

Table 1: Table of Initial SBE Problems

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