Engineering Microbial Consortia for Industrial Production

Joseph T. Meyerowitz - prepared for SPRIN-D via the Big if True Science Programme – 10 December 2025

The Opportunity

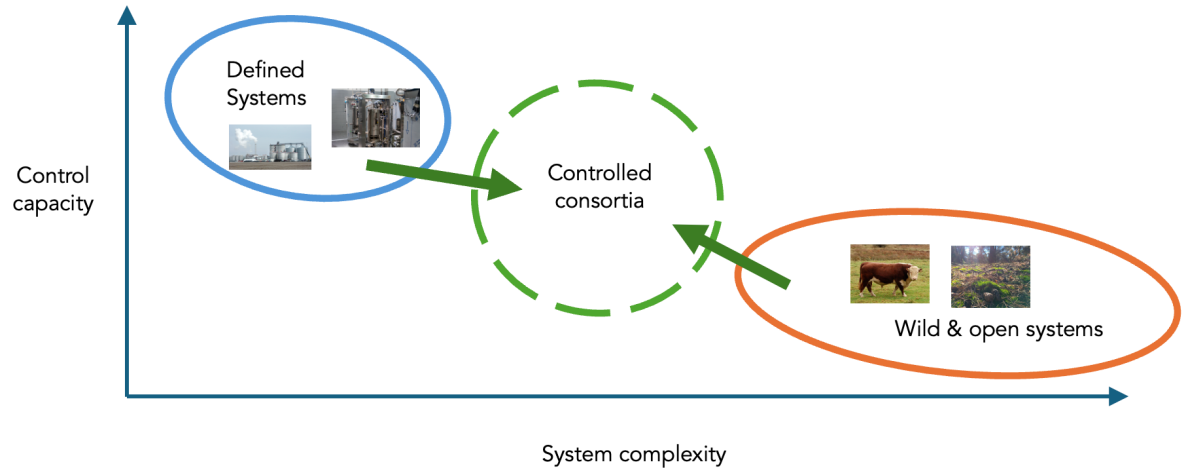
New approaches to industrial biotechnology are needed to enable the next generation of sophisticated biochemical syntheses, high-volume bio-based commodity chemicals based on non-sugar feedstocks, and "living" biotic products. The global bioeconomy generates roughly €4 trillion in annual economic output, with projections suggesting €30 trillion by mid-century [1].

For complex biosynthesis, each individual chemical step in a single engineered microbe can lower the yield of the product, limiting current processes to short biosynthetic pathways. For commodity chemicals, the use of sugar as a feedstock prevents biology from reaching cost parity with petrochemical processes. Emerging "living" products such as microbial soil amendments, nitrifying aquaculture starters, and self-healing concretes are starting to show how biotic materials can create value in entirely new application domains. To reach the full potential of industrial biotechnology, we need to surpass the limits inherent to our current approaches.

Precision fermentation, which dominates pharmaceutical and fine chemical production, achieves predictability through isolation. These systems provide repeatable production processes by minimising variability in feedstocks such as purified sugars, tight control of environmental variables such as temperature, pH, oxygen, and nutrient supply, and maintaining sterility. This reliance on isolation comes at a high cost, requiring expensive fixed infrastructure such as large steel bioreactors, sterilisation systems, feedstock purification, and process regulation.

Microbial consortia perform industrial processes today such as biogas production, composting, and wastewater treatment. Naturally occurring consortia process organic matter and fix nitrogen in soil, break down waste in anaerobic digesters, and transform raw ingredients into fermented foods. These systems are robust, operate at enormous scale, and require far less expensive infrastructure. They are limited, however, in the range of tasks they can perform. If a natural microbial consortium has been discovered that performs a needed task already, then it can be applied where it is needed. Steering a microbial consortium to perform a new task or intended chemical function requires engineering approaches that are not yet proven at industrial scale.

Predictive control of microbial consortia can unlock future opportunities in industrial biotechnology. Microbial consortia, composed of communities of multiple species of microorganisms in a common ecosystem, work in concert to perform complex chemical transformations. Their symbiotic, or cross-feeding, relationships allow for co-operative specialisation and division of metabolic labour within the community. With predictive control, microbial consortia can be intentionally designed or steered to function reliably in open, non-sterile conditions for a new purpose.



Two current approaches to industrial biology. (Left) Defined systems achieve control through isolation, but at high capital cost. (Right) Wild systems operate at large scales with minimal infrastructure, but offer limited programmability. This proposal focuses on the middle: predictive control of microbial consortia that combine robustness with targeted function.

In the past years, laboratory-scale demonstrations have shown substantial improvements in our ability to predictively control microbial consortia for new functions. Both synthetic consortia composed of microbial members developed and chosen in the lab, and domesticated consortia enriched from a natural source, have provided recent first-of-a-kind examples of robust production of valuable molecules [2–6].

Consortia-based manufacturing can treat biological complexity as an asset rather than a liability, combining the advantages of defined, closed biotechnology with the advantages of open, wild biotechnology. High-throughput methods for experimentation, data collection, and modelling together provide structured datasets for artificial intelligence (AI) and machine learning approaches to predict community behaviour for the first time. Data-informed control and actuation are now possible for active control of the metabolic state of whole microbial communities.

This degree of control over microbial consortia advances industrial biotechnology along multiple lines. Tolerance to contamination, adaptability to varied non-sugar feedstocks, and robustness to changing environments could enable petrol-competitive bio-based commodity chemical production that resembles agriculture more than pharmaceutical production. Multi-strain and multi-species fermentations can access new chemistry inaccessible to current single-strain synthetic biology, enabling production of previously inaccessible pharmaceutical and fine chemical compounds. New living materials can be engineered to provide enduring function in increasingly complex and stringent environments.

By building on Europe's strengths in environmental biotechnology, microbial ecology, and sustainable manufacturing, this proposed SPRIN-D challenge will accelerate a growing strategic capability in bio-based chemical production.

The State of the Art

Two converging research directions are bringing controlled consortia within reach.

First-of-a-kind demonstrations now show that engineered systems can add robustness to new metabolic production processes. The key insight is metabolic interdependence: if microbial strains form obligate partnerships where each organism’s survival depends on the other, they can support each other and evolve to avoid destabilising competition. In 2022, Li and colleagues showed that engineering strains to exchange multiple essential nutrients creates self-regulating partnerships that maintain stable composition without external intervention [2].

In parallel, Aulakh and colleagues developed syntrophic yeast pairs where one organism's metabolic output becomes another's required input; their 2023 study demonstrated that such pairs achieve stable coexistence and improve production yields compared to single-strain approaches [3]. By 2025, Chen and colleagues had extended this platform to split a biosynthetic pathway of over 40 steps across two yeast strains, showing that certain high value plant-derived lignans could be produced for the first time [4]. This progression from stability principles to complex biosynthesis demonstrates rapid maturation.

Parallel advances show that natural communities can be steered towards new functions without sacrificing robustness. In 2019, de Smit and colleagues showed that adjusting pH and substrate composition in an open bioreactor could direct a mixed community to produce n-valerate with high selectivity [5]. In 2024, Castagnoli and colleagues demonstrated that aeration control alone could steer a mixed culture fed on organic waste toward accumulation of polyhydroxybutyrate (PHB), a biodegradable plastic precursor, without sterility, defined inoculum, or genetic engineering [6]. Environmental parameters can serve as control levers when informed by sufficient data about community dynamics.

New approaches to community control beyond environmental control and genetic engineering are emerging. Bacterial viruses can selectively shift community composition in intentional ways, knocking down susceptible bacteria while leaving other community members intact [7]. Quorum-sensing systems have been engineered to provide multiple orthogonal communication channels, enabling coordinated gene expression across distinct populations in co-culture [8]. Some of these tools remain at earlier stages of development; combined with environmental control, they could expand the toolkit for data-driven predictive control across a wide range of uses.

The gap between current laboratory demonstrations and commercial deployment is substantial. Applying syntrophic designs to a new production target, or identifying the right environmental lever for a new community, still requires

considerable research and development effort. In terms of Technology Readiness Levels, none of these new approaches to predictive control of microbial consortia have been scaled up to demonstrate industrial utility yet. A SPRIN-D challenge funding the operational development of the underlying tools, and the commercial applications which rely on them, can provide the competitive and collaborative environment for success in this direction.

Challenge Structure

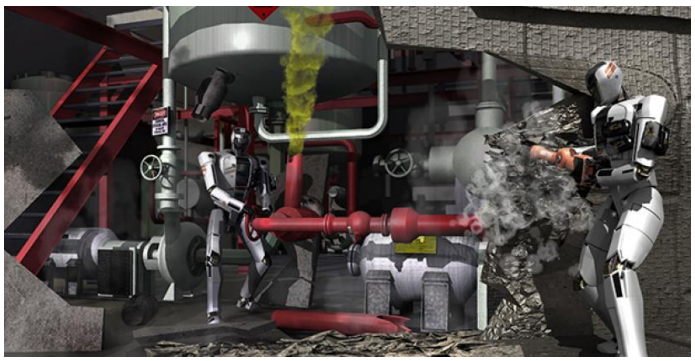
A challenge programme would need to close the gap between current laboratory prototypes and scaled-up industrial processes. With a view towards developing both the tools for predictive control of microbial consortia and the translational uses of microbial consortia, one potential approach is a two-track challenge with tools teams and applications teams.

Application teams would develop controlled consortia systems for products with genuine commercial potential. They would be evaluated by technical progress toward production goals and by the commercial viability of their target application, including the scale of the market they address and the clarity of their route from demonstration to deployment. Staged evaluation with down-selection between phases ensures that resources flow toward teams making genuine progress.

Many of the underlying tools for sensing, for actuation, for modelling, and for high-throughput experimentation are not application specific. Building a two-track challenge would allow for tools teams to compete with each other to provide value to the applications teams, while helping each application team avoid independently developing the same internal protocols and experimental pipelines.

Past high-risk, high-reward programmes have included one or more "systems integrator" teams to provide common infrastructure or services for the other teams. DARPA's 1000 Molecules component within the Living Foundries programme (2010–2019) ran parallel tracks for strain engineering teams and bioproduction infrastructure teams. By requiring collaboration and co-development of tools with production processes, the programme exceeded its goal of producing 1000 new molecules [9]. The DARPA Robotics Challenge (2012–2015) commissioned the Open Source Robotics Foundation to create a cloud-based simulator for a first Virtual Robotics Challenge, followed by engaging Boston Dynamics to build the Atlas robot as a common chassis; teams could request an Atlas robot as a starting point or build their own (see Inset) [10]. The DARPA Grand Challenges for autonomous vehicles (2004–2007) also designated a non-racing team to build the desert racetrack that the other teams used [11].

The DARPA Robotics Challenge (2012–2015) demonstrated how shared infrastructure can accelerate progress without constraining innovation. DARPA commissioned Boston Dynamics to build the Atlas humanoid robot as government-furnished equipment, offered to teams that lacked their own hardware. Seven teams received Atlas robots; others built custom platforms. Crucially, teams were not required to use the shared infrastructure, and the eventual winner (Team KAIST) competed with a self-designed robot.



The coupling between systems integrator and application teams was tight and iterative. After the 2013 Trials revealed limitations in untethered operation, DARPA funded Atlas upgrades that replaced roughly three-quarters of components before the 2015 Finals. Boston Dynamics engineers stationed at competition sites provided on-site support and incorporated team feedback into hardware revisions.

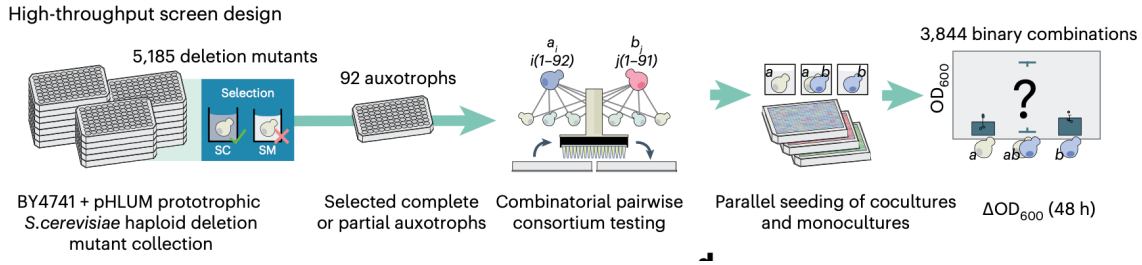
The phased structure allowed systems integrators to establish capability before application teams entered: a Virtual Robotics Challenge tested software in simulation, followed by physical Trials, then Finals with increased difficulty. This approach accelerated progress by years while maintaining competitive pressure and nurturing an enduring community of robotics researchers. *(image credit: https://www.darpa.mil/research/programs/darpa-robotics-challenge)*

For a microbial consortia challenge, systems integrators might provide capabilities analogous to the Atlas robot: shared infrastructure that application teams can use but are not required to adopt. With the common requirement that their tools and datasets be made available to application teams, one team might specialise in tools for synthetic

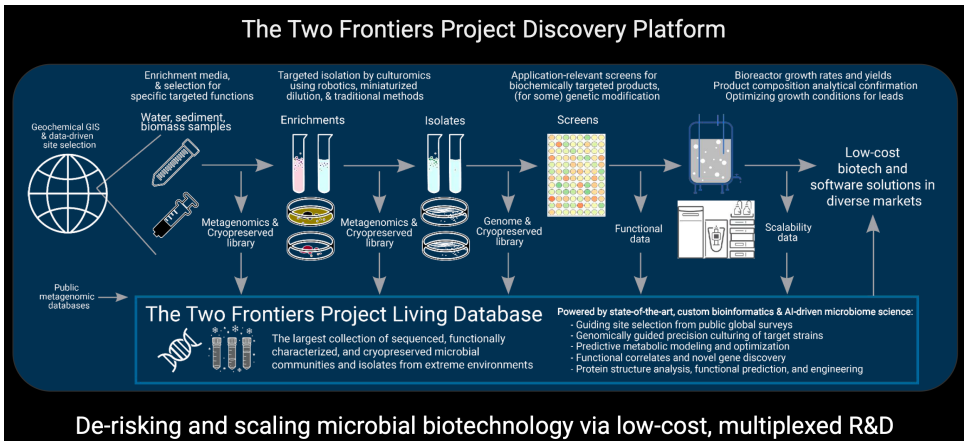
defined consortia, and another team might provide tools for natural and domesticated consortia. Common data standards for experimental results, techno-economic analyses, designs for actuators such as phage and quorum-sensing molecules, and other general purpose tools would be in scope for the small number of infrastructure providers competitively selected for the challenge. These infrastructure teams can be evaluated by adoption and utility, and themselves be subject to competition to provide demonstrable value to the application teams.

The goal of this two-track approach is to allow application teams to use their capital more efficiently. By encouraging valuable advances in general-purpose tools to develop in infrastructure teams, it aligns incentives for commercially viable microbial consortia development services to become broadly available outside of the challenge.

It may be advisable to stagger the start times for each track. By starting the tools track first, systems integrators would characterise representative consortia systems and publish open datasets on community composition and dynamics. When the call for application proposals opens, application teams would have access to validated methods and preliminary data, enabling stronger proposals and faster progress toward production goals.



Two potential approaches to high-throughput experimental pipelines for microbial consortia. (Top) A synthetic approach starts with defined strains and engineers stability through metabolic interdependence, offering precise control but requiring significant upfront characterisation *(image credit: Aulakh et al. 2023 [3])*. (Bottom) A natural consortia approach starts with environmental communities and selective enrichment, searching for existing microbial teams that provide the desired chemistry in an existing experimental, archival, and retrieval pipeline *(image credit: Two Frontiers Project / University of Palermo)*.



Vision and Impact

The long-term vision is to routinely use microbial systems that combine the robustness of natural ecosystems with the intentional function of engineered synthetic biology. In bio-based chemical production, the goal is infrastructure that resembles agriculture more than pharmaceutical production. Open or semi-open vessels would process locally available feedstocks, steered toward targeted products by data-driven intervention, operating at capital intensity similar to composting or wastewater treatment. These new processes for converting waste streams into valuable products will broadly enable a new kind of sustainable manufacturing.

In developing this concept for a SPRIN-D challenge, multiple nascent and existing commercial teams were consulted. Across projects in production of sustainable aviation fuel from brewery waste, construction materials from algal biofilms, biodegradable plastics from organic waste streams, and bioethanol from steel refining flue gases, a deep

roster of potential participants in a microbial consortia challenge is available. Each of these teams demonstrates the range of commercial opportunities where controlled consortia can succeed over existing approaches.

Europe operates over 20,000 biogas plants that use anaerobic digestion to convert agricultural waste into methane [12]. These facilities already contain robust microbial consortia operating on heterogeneous feedstocks at industrial scale. Based on some of the recent laboratory results, we can envision a new future for manufacturing. These existing consortia could be steered toward higher-value outputs such as medium-chain fatty acids or precursors for biodegradable plastics with minimal investment in new infrastructure beyond sensors, digital models, and controllers.

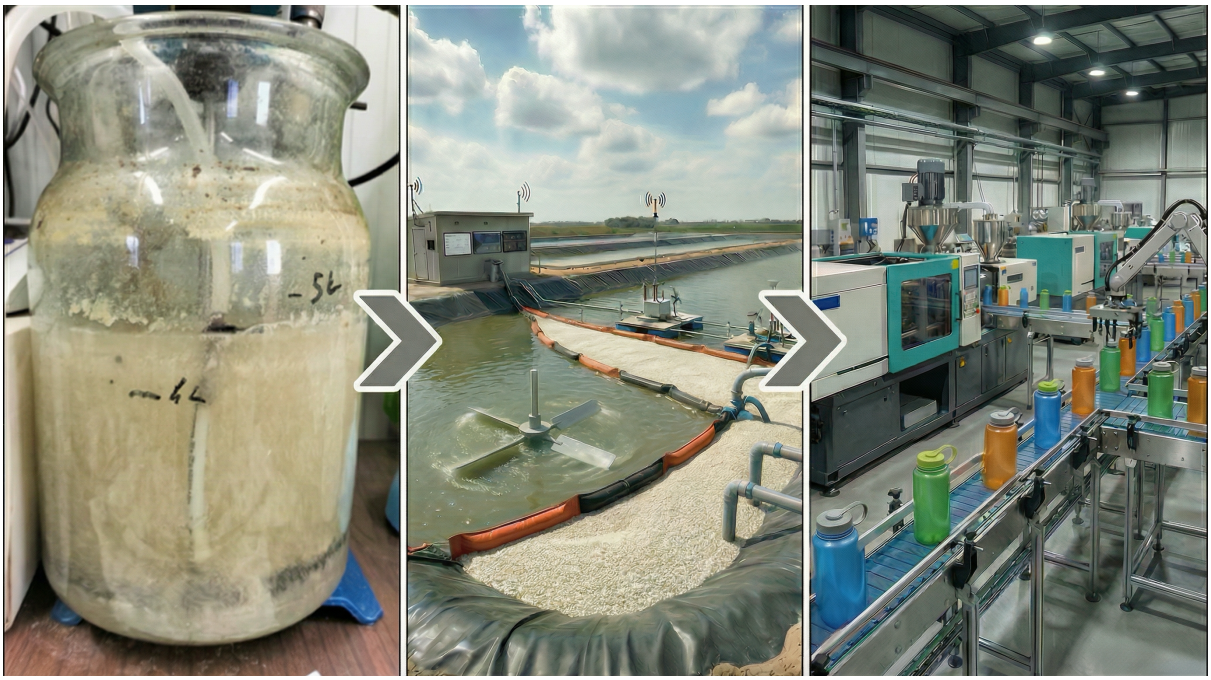


Illustration of a progression from today's laboratory-scale controlled consortium producing plastic to a future open-pit fermentation system and future plastic end-products (image credit – left panel, Castagnoli et al. 2024 [6]).

The path from laboratory demonstration to industrial reality is now clear. European research groups are already leading much of the foundational work described in this document. A coordinated effort to develop controlled consortia as a production platform will contribute to European goals for a circular bioeconomy and industrial resilience while reducing reliance on imported petrochemicals.

The tools exist in nascent form. The applications are within sight. A focused SPRIN-D challenge in predictive control of microbial consortia would enable the translation of new strategic manufacturing abilities for Europe and the world.

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