Visioning synthetic futures for yeast research within the context of current global techno-political trends

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Abstract

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Yeast [wiley]

PERSPECTIVE ARTICLE

Synthetic Biology

Visioning synthetic futures for yeast research within the context of current global techno-political trends

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Abstract

Yeast research is entering into a new period of scholarship, with new scientific tools, new questions to ask, and new issues to consider. The politics of emerging and critical technology can no longer be separated from the pursuit of basic science in fields, such as synthetic biology and engineering biology. Given the intensifying

race for technological leadership, yeast research is likely to attract significant investment from government, and that it offers huge opportunities to the curious minded from a basic research standpoint. This article provides an overview of new directions in yeast research, and places these trends in their geopolitical context. At the highest level, yeast research is situated within the ongoing convergence of the life sciences with the information sciences. This convergent effect is most strongly pronounced in areas of AI-enabled tools for the life sciences, and the creation of synthetic genomes, minimal genomes, pan-genomes, neochromosomes and metagenomes using computer assisted design tools and methodologies. Synthetic yeast futures encompass basic and applied science questions that will be of intense interest to government and non-government funding sources. It is essential for the yeast research community to map and understand the context of their research in order to ensure their collaborations turn global challenges into research opportunities.

Keywords: Minimal genome; supernumerary neochromosome; metagenome, pan-genome; synthetic genome; synthetic communities; *Saccharomyces cerevisiae* , Yeast 2.0

1 ? FROM SPIKE PROTEINS TO SPIKING PRICES AND A PERMACRISIS

The first three years of this decade put the world to the test. From a devastating global pandemic, collapsing supply chains, extreme weather patterns, and intensifying geopolitical tensions to outright war, soaring energy and food prices, escalating debt, inflation and a looming global recession (Figure 1), today's world is faced with a 'permacrisis'–an extended period of significant instability and insecurity (Vanhercke et al., 2022). Assumptions of a rules-based world order that held for decades–that agreed red lines of nuclear weapons won't be crossed, that international borders should be inviolable, that geopolitical rivalries won't weaponise critical supply chains or choke free trade, that inflation will stay low, and that the lights will stay on–have all been shaken to the core (www.economist.com/the-world-ahead; Gyngell, 2017). The 'peace dividend' nations enjoyed since the end of the cold war–releasing huge amounts of funds from defence to spend on other societal needs–is ending. Within the context of current rising geopolitical competition, the world is once again equipping itself for future geopolitical challenges between rivals (Khan et al., 2022).

The world has changed and continues to change, and so with this change does the technology that continues to shape our world into the future. The development of critical technologies, such as synthetic biology and the way we conduct frontier-shifting and future-shaping synthetic yeast research, will too be influenced by geopolitics. Examples include research into biofuels (Georgianna and Mayfield, 2012), which will be influenced by the reliability of global supply chains, and the necessity for unfettered access to advanced technologies, which are deemed critical to nations' economic prosperity, security and sovereignty.

One branch of science that has sparked interest, hope, and disputation among researchers, governments, policymakers, regulators and commentators is synthetic biology (Kitney, 2021). Looking beyond the bounds of this developing field into its wider geopolitical context, the intersection of science, technology and policy with changing great power dynamics has amplified existing fragilities in the international system. This fragility is fracturing globalization along political lines, producing more tension, more competition and increased fragmentation. It is not the first time that science has encountered this trend in international relations (Lieber, 2019), and for yeast research, with its long and storied history, it is not the first time that the community of scholars and practitioners has needed to respond to changed political winds. The question many are asking in the scientific community is: how will international collaboration continue given the current international context? This a complex question given that investment in research and development (R&D) is increasing at a rapid rate, driven by both new philanthropic investors and their funding priorities, but also by government competition and their political priorities. Technological competition is all but baked into the global economy for the next decade (Lewis, 2018). It is likely that these increased R&D investments would deliver unintended beneficial technological developments for synthetic biology and yeast researchers.

How can synthetic yeast research and yeast researchers ride this wave? Yeast remains one of the most versatile and resilient hosts for traditional and novel industrial use cases. Just as yeast must be part of the solution to, for example, viticulture and winemaking in the face of climate change, so must yeast be part of the solution to scaling biomanufacturing globally (Naseri, 2023). As the bioethanol, baking, brewing, distilling and

winemaking industries, along with the agricultural economies of ancient history relied on yeast (Pretorius et al., 2012), so too will the emerging bioeconomy find its backbone in this simple, single-celled fungus. While the global environment appears to be increasingly competitive, increasingly fractious, and far more dynamic– this is a source of optimism for yeast research and only serves to highlight the ongoing contributions the yeast community can meaningfully make to human progress. However, to take full advantage of the global macro changes, the yeast research community needs to fully capitalize on the tools and methodologies of synthetic biology and other related fields (EBRC, 2019). This must begin with the yeast community having a good answer for why anyone, government, corporate or philanthropist, should invest in synthetic biology-based yeast research at all.

2 ? THE BIGGER THE CHALLENEGES, THE BIGGER THE OPPORTUNITIES

Defence Advanced Research Project Agency (DARPA) style investments, often called moonshots, have been known to fast-track innovation and technological development (Weiss, 2014). This style of funding succeeds because it is multidisciplinary, it provides a degree of funding certainty based on the successful meeting of project milestones, while also providing a graceful pathway for unsuccessful projects to unwind. It is the *fail fast* mentality applied to ideas that combine high risks with high rewards. If synthetic yeast research can pivot both to a more multidisciplinary field of inquiry while also attuning itself to the *grand challenges* driving present day funding priorities, then the field will thrive in the new global environment.

The yeast research community can best accelerate funding bodies' awareness of the prospects and importance of synthetic yeast research by better aligning with other critical technologies that have funding certainty (Figure 2). One example is quantum technologies, including quantum sensing and computing. The emerging field of quantum biology–once a theoretical domain peopled by physicists predominantly concerned with whether biology included non-trivial quantum effects–is now emerging as a frontier of technological development (Lambert et al., 2013; Cao et al., 2020). Government investment in quantum computing is all but assured across the next decade due to the potential for quantum computers to break existing encryptions standards (NASEM, 2019). Although it may seem like there is no room for yeast research to align with quantum computing, it should be emphasised that one of the dominant areas of early application for quantum computing has indeed been in the life sciences, with key applications in drug discovery and design (Cao, Romero and Aspuru-Guzik, 2018; Blunt et al., 2022). As quantum computers increase in complexity and scale their ability to model larger systems will rapidly improve. It would not be a conceptual leap to envision how the yeast research community could benefit by joining with the quantum sensing and computing community to share both basic and applied research goals.

Similarly, the well-entrenched area of artificial intelligence (AI) all but has funding certainty from government and the corporate sector, while also being characterised by industrial and geopolitical competition. Both AlphaFold and ESMFold have shown that intractable biological problems, such as predicting protein folding, can be largely solved *in silico* via classical computing approaches (Jumper et al., 2021; Lin et al., 2023). Predicting protein folding was long touted as a problem that quantum computing was going to solve, yet it was classically-trained AI that solved this problem. This highlights the need for the yeast research community to have a quantum-classical mindset that takes advantage of methodological advances being produced on both sides of the ledger. The life sciences and the information sciences have long been intertwined, arguably the greatest amplifier of the life sciences since the 1980s has been the accelerations in computation power often attributed to *Moore's Law* . Yet, it is the inspirational interplay of quantum physics and classical biology that has often produced the most disruptive advances with the discovery of DNA being the key example of what can be produced when both communities collaborate and draw inspiration from one another.

The key benefit that the yeast research community can bring to a collaboration with researchers in quantum computing, quantum biology or artificial intelligence is a fundamental understanding of applied practical problems that will move the needle on *grand challenges*across a range of different economic sectors. It has never been more important to understand and optimise fermentation methodologies for a changing environment and a changing climate (EBRC, 2022). It has never been more important to improve the scale and speed at which medical countermeasures, vaccines and pharmaceuticals can be developed–and this

includes the parallel need to develop low-technology production protocols for advanced medical technologies. Many rural areas around the world have bakeries, breweries, wineries and other types of bioreactors (i.e. fermentation infrastructure) that, if repurposed using yeast as a chassis organism, could revitalize this infrastructure as the advanced biomanufacturing technology of tomorrow (Walker and Pretorius, 2018). Understanding and optimising this kind of biomanufacturing based on a yeast platform begins with basic research questions that benefit from both the quantum and classical information sciences. The challenge for the yeast research community now is to future-proof itself against political headwinds, environmental change, and technological advances. That future-proofing begins with multidisciplinary collaboration and consilience.

3 ? Bioinformational versus Biophysical Engineering

The development of synthetic artemisinin has often been used as a case study of what can be achieved in the field of synthetic biology (Paddon and Keasling, 2014). However, in truth, it should actually be thought of as a case study in what can be achieved when yeast is harnessed at its true potential as a model organism. Synthetic artemisinin stands as an historical example of biophysical engineering–a refactoring of a yeast's metabolic networks to achieve a physical material objective. Biophysical engineering in yeast platforms has vastly matured since 2013. High-throughput approaches to combinatorial design (Naseri and Koffas, 2020), massive parallel combinatorial testing (Kehe, 2020) and the accompanying bioinformatics have fundamentally changed the speed and scale with which a biological design space can be explored (Dixon et al., 2021a,b). This is no longer news.

What is news is the next wave of research objectives that will each benefit from being trialled and optimised within a yeast platform. This is the realm of bioinformational engineering, where instead of engineering yeast to achieve physical material objectives, the objectives are information–that is, using the bio-compute infrastructure of a yeast colony to sense, surveil and report on the molecular environment. Although the traditionally conservative fermented beverage industries, such as the wine industry (Jagtap et al., 2017; Pretorius, 2000, 2016, 2017a,b; Pretorius and Bauer, 2002; Pretorius and Høj, 2005), may resist the use of engineered yeast, it is less likely to be politically impossible for yeast-based biosensing to be deployed from farm-to-table for monitoring and improving product quality (Eriksson et al., 2020).

Similarly, as the world continues to experience politically-driven supply chain shortages across the semiconductor industry (Miller, 2022), it is going to become increasingly advantageous to devolve computing power to yeast platforms when those platforms operate as the advanced sensing nodes in a precision agriculture or precision medicine network. Just as yeast research is essential today for its contribution to enhancing the organism's biophysical output across many varied industrial applications, so it remains highly likely that yeast will be integrated into the cyber-biological compute infrastructure of the coming decades (Botstein and Fink, 2011). In this, the yeast research community has much to learn from the early days of the quantum computing industry. Quantum computers are co-processes to classical computers, they are not going to replace classical computers altogether. Similarly, there is a once in a generation opportunity to create an entirely new industrial application for yeast, that as bioinformation co-processes that can integrate with classical and quantum-classical computer architectures (Zhirnov, 2018).

Basic science questions abound in a research trajectory that seeks an end point of integrating yeast biosignals with classical computing. Such questions range from electron shuttling and bioelectrochemical signal parsing, through to quorum sensing and intercellular communication in multi-species single-cell consortia. The opportunities to continue to do basic yeast science are vast when the work is framed in relation to government and funder political priorities, and integrated via multidisciplinary collaboration with government-supported critical technology domains. For yeast research, this opportunity is easier to take advantage of than in most scientific disciplines. There has not been a more exciting time to be in the field.

4 ? SYNTHETIC YEAST FUTURES

This section presents a summary of emerging trends and how these rapidly-expanding bioinformational and biophysical engineering technologies might enable development in a variety of newer concepts, including

synthetic yeast genomes, synthetic model systems (Figure 3), and, in the long run, the creation of a synthetic cell with which new understandings of biological complexities could be achieved (Dixon et al., 2020; Dixon and Pretorius, 2020). These new frontiers include the construction of fully synthetic yeast genomes (Pretorius and Boeke, 2018); synthetic minimal genomes (Xu et al., 2023); supernumerary neochromosomes (Kutyna et al., 2022; Schindler and Walker et al., 2023); synthetic metagenomes (Belda et al., 2021) ; synthetic yeast communities (Walker and Pretorius 2022); synthetic specialists yeasts (Dixon et al., 2021a,b; Lee et al., 2016; Llorente et al., 2022;); and new-to-nature synthetic cells (Frischmon et al., 2021). Box 1 provides definitions for the rapidly expanding synthetic yeast research landscape.

These conceptual model genomes, systems and cells are all inspired by the complexity inherent to natural biological systems, yet implemented through rational design undertaken by synthetic biologists. Most are at varying stages of development with plenty of technological pitfalls to be overcome. Naturally, these futuristic concepts will be subject to review and improvement as new data and technologies become available. Although these revolutionary ideas may very well not progress beyond the boundaries of a laboratory, their implementation will lead to better and more practical developments with which researchers could uncover some of the hitherto mysterious aspects of yeast resilience, fermentation performance, flavour biosynthesis, and ecological interactions (van Wyk et al., 2018).

4.1 ? Synthetic yeast genomes

A key early advantage in synthetic yeast genome design was enabled by *Saccharomyces cerevisiae* 's well-curated and regularly updated genome sequence (Cherry et al., 2012). This in turn enabled synthetic genome designers the ability to rapidly derive value and understanding by implementing a 'build-to-understand' approach through the construction of a synthetic yeast genome. The starting material of this synthetic yeast genome was founded on the haploid laboratory strain, *S. cerevisiae* S288c and associated 'BY' lineage, with the end goal to ultimately design and chemically synthesize a modified version (Richardson et al., 2017).

At the beginning of the previous decade, the availability of this well-characterised reference genome sparked the idea of swapping the natural genome of *S. cerevisiae* S288c with a redesigned and chemically synthesized version without compromising the physiological fitness of the original host strain (Dymond et al., 2011). In 2019, the work of an international *Synthetic Yeast Genome* (Yeast 2.0 or Sc2.0) consortium culminated in the announcement of the first draft synthetic set of the 16 linear chromosomes of the 'BY' lineage (Pretorius, 2020). However, since the 2019 announcement, several of these draft chromosomes still needed to be corrected for growth defects. With the exception of one chromosome, the 'debugging' is now complete and the publications are currently under review. It is anticipated that the sequential consolidation of synthetic chromosomes into a single cell will accelerate progress toward the ultimate Sc2.0 strain, which will ultimately contain a radically altered genome. This includes streamlining and stabilising (removal of transposons, non-essential introns; and the relocation of all tRNA genes onto a separate, supernumerary tRNA neochromosome), addition of standardised telomeres, a 'freed-up' TGA stop codon, PCR-Tags recognition labels and multiple LoxPsym sites (Richardson et al., 2017).

4.2 ? Synthetic minimal genomes

Synthetic genome minimalization efforts seek to overcome the limitations of genetic redundancy inherent to several billion years of natural evolution. This includes uncovering the minimal number of genes required for cell viability. Notable past efforts include the construction of the bacterium, *Mycoplasma mycoides,* which unexpectedly revealed many genes with unknown function that were essential for life (Hutchison et al., 2016). By reducing complexity and improving engineerability through the removal of unnecessary genetic elements, a streamlined minimalised genome will enable opportunities in both basic and applied research, with the latter enabling the creation of novel platform chassis of use in industrial biotechnology. Such advantages include an increased predictability in rational design, freeing-up unnecessary genetic components for increased biosynthetic capacity, improved genome stability through the removal of repetitive genetic elements and generating fundamental insights into genome function for future genome synthesis (Xu et al., 2023).

Additional research value can be derived through the implementation of biosecurity layers built into organism design. By removing all genetic material that does not support the laboratory- or bioreactor-based growth of the organism, the fitness of the organism in natural and wild environments is notably reduced (Torres et al., 2016). This significantly lowers the risk of unintentional releases of engineered organisms into the wild, an important trait for all industrial organisms to have when the world is on the cusp of rolling out next-generation fermentation infrastructure across regional areas that are proximate to feedstocks, but also proximate to natural and agricultural environments. Combined with research into other biosecurity techniques, such as kill switches (Moe-Behrens et al., 2013), this provides the researcher with a toolkit of biosecurity methodologies for layering over any given biological design.

Both 'top-down' and 'bottom-up' represent the fundamental two approaches to minimal genome design. 'Top-down' refers to the reduction of existing gene content, and 'bottom-up' describes the application of whole genome synthesis and design through *de novo* DNA synthesis. Notably, these two approaches can be combined into one chassis, with the Yeast 2.0 project minimalizing existing genome content by removing transposable elements and implementing one of the more important method discoveries to arise out of the Yeast 2.0 project, the SCRaMbLE technique (Shen et al., 2016, 2019; Wu et al., 2018). SCRaMbLE can generate significant diversity in minimal genome structure, order, and content, or even alter the composition of essential gene variance within those designs (Xu et al., 2023). This is due to genomic deletion being the most commonly occurring SCRaMbLE-related event, leading to a near-infinite number of variable minimal genomes. However, a key challenge in this area is ensuring cell viability after deployment of SCRaMbLE, with a significant proportion of the cells dying following induction. This is an area of active research and the overall promise of standardising a minimal genome chassis for industrial biodesign will both complement *in silico* design through improved understanding of minimal content while ensuring biosecurity features are engineered in from the start.

4.3 ? Synthetic yeast neochromosomes

Neochromosomes represent a new concept of designer biological structure that exists both in abstraction, and in addition, to their natural chromosomal complement. In contrast to existing synthetic chromosomes of the Yeast 2.0 project, neochromosomes are generally not based on any natural template and, as such, *in silico* bio-design approaches play a central role due to their *de novo* nature. Furthermore, in contrast to classical synthetic biology approaches that view DNA as a 'code' to be written, these bio-design efforts extent to treating neochromosomes as a physical entity and therefore require approaches more closely resembling structural engineering performed at the molecular scale. The point-like nature of *S. cerevisiae*centromeres and the great power of homologous recombination also render yeast the perfect host. Notable recent advances have demonstrated their application in the systematic refactoring of genetic components (Postma et al., 2021) , the introduction of novel characteristics (Kutyna et al., 2022) and can be used to construct human biosynthetic pathways (Agmon et al., 2020).

Neochromosomes present novel opportunities and advantages to rapidly scale DNA synthesis. In their circular form, these entities can be readily extracted and chemically transformed into a new host chassis at will (Noskov et al., 2011), facilitating the direct transfer of large amounts of genetic information between host biological systems. Subsequently, these chromosomal circles can be converted into functional linear chromosomes by introducing synthetic telomere seed sequences using the telomerator system (Mitchell and Boeke, 2014).

The radical re-engineering approaches of the Sc2.0 consortium have enabled the removal and relocation of all 275 tRNA genes onto a dedicated 'tRNA neochromosome' (Schindler and Walker et al., 2022). This project has led to unique insights into tRNA, cell and chromosomal biology that would not have been possible through 'traditional' approaches. Following synthetic chromosome consolidation into one host cell, it's anticipated that the tRNA neochromosome will provide new insights into host-cell tRNA supply and demand through an orthogonal SCRaMbLE system based on the *Dre-rox* recombination. Thus, the tRNA neochromosome will provide novel insights into cell stress and industrial biotechnology and improve our understanding of minimal genome dynamics once the two SCRaMbLE systems are activated.

4.4 ? Synthetic pan-genomes

Large-scale sequencing studies have unravelled the fundamentals of genetic diversity leading to the concept of a pan-genome (Peter et al., 2018). Similar to minimal genomes, pan-genomes seek industrial workhorse applications by stretching the bounds of what genetic substrates can encode within a functional organism. The laboratory strain S288C, and future minimal genome derivatives, are ultimately restricted in their application and lack many of the genotypic features found in industrial strains that define their utility in niche environments (Warringer et al., 2011). In this context, encoding pan-genomic functionality onto a defined neochromosome will complement the objectives of a minimal genome. For example, additional phenotypic plasticity was added to the Sc2.0 substrate through the pan-genomic bolt-on of a 17^{th} neochromosome (Kutyna et al., 2022). In this example, not only does a potential minimal genome gain from the rationalisation of the Sc2.0 chassis as an engineering platform, but the neo-chromosome provides a mechanism to selectively reintroduce naturally occurring wild-type genomic diversity in an abstracted manner. This approach can be used to drive differential carbon source use but would also be amenable to modifying or modulating many of the minimal genomic attributes of the Sc2.0 platform.

The pan-genomic approach to biodesign has also been shown to integrate well with the SCRaMbLE methodology. This provides the researcher with two techniques, one probabilistically random and one based on active human choices. When both techniques are integrated, they provide a way to combinatorially build large phenotypic diversity from a singular starter platform. SCRaMbLE introduces the large opportunity space to work in concert with the genetic diversity of a defined neo-chromosome, thus directing phenotypic diversity towards user-defined evolutionary outcomes and attributes.

Finally, although these concepts represent good examples of 'top-down' and 'bottom-up' approaches to engineering yeast for industrial biotechnology, exploring these methods in concert with microbial community dynamics represents a largely untouched and exciting research opportunity.

4.5 ? Synthetic yeast communities

To predictably engineer fully-synthetic yeast communities that are often highly complex, it is first necessary to study existing complex systems (Conacher et al., 2021) or to undertake stepping-stone research into consortia dynamics, such as that of semi-synthetic microbial communities (Walker and Pretorius, 2022). That is, characterising yeast communities that include both natural and engineered organisms to better understand how these interactions might be optimised. There are an enormous number of potential applications in industry. The fermentation industries, including beverages such as wine and beer, but also precision fermentation, are good examples where advances will translate into economic outcomes. For example, studying functionality of semi-synthetic interactions may lead to a greater understanding of resource sharing, leading to improved compartmentalisation of function and greater efficiencies at scale (Tsoi et al., 2018).

In the context of synthetic yeast communities, there are themes of work that need further investigation. For example, these include intercellular communication between singular and multiple species, co-dependency dynamics and how these can be optimised or controlled as part of a cell consortia engineering strategy, and temporal control such that long-term stability can be achieved in cell consortia dynamics but also such that systemic resilience can be engineered into the overall consortia.

The challenges inherent in synthetic yeast communities elevates the concepts of a pan-genome and minimal genome to a higher level of abstraction. Despite these challenges, exploratory research in this area remain largely untapped and ripe for the development of 'new science', with the potential for untapped applications in the coming decades. For instance, minimising a given consortia to a suite of minimal genomes and then exploring their dynamics in relation to one wild type offer an initial starting point. Similarly, exploring the interaction of multiple pan-genome models built on the Sc2.0 platform with differing neochromosomal diversity is another angle. Now is a very exciting time for synthetic yeast research, with each new discovery offering another layer of engineering to combine in search of novelty and industrial utility.

4.6 ? Synthetic yeast for biosensing

Communication with the biological world and the digital represent the next frontier of synthetic yeast futures. The deployment of yeast for industrial biosensing has applications across multiple sectors – from beverages to fermentation-based biomanufacturing (Dixon et al., 2021a,b). An industrial workflow that can be automated at the cellular level will reduce the level of process touchpoints (human or autonomous), and is therefore highly likely to result in more resilient and less error prone engineering loop (Williams et al., 2016, 2017). Self-regulating bioindustrial systems may benefit from cellular-level (or enzyme-level in a free cell system) biosensing solutions (Avalos, 2022; Wahid et al., 2023; Yu, Lei and Nie, 2022). These types of solutions offload sensing and computational needs from adjunct monitoring equipment to the actual living system responsible for the biomanufacturing or fermentation process.

The tools and techniques required for engineering autonomous biosensor-based control loops into yeast constructs are advancing but continue to require dedicated pre-commercial problem solving at the level of basic and applied research questions. One of the key problems continues to be engineering ligand-binding domains and standardising biosensor architectures (Leonard and Whitehead, 2022; Pham et al., 2022). Yeast is the perfect organism to prototype industrial solutions to this problem set due to the model organism *S. cerevisiae's*principal usage in commercial scale biotechnology worldwide. Plug-and-play biosensor architectures built for *S. cerevisiae* can capture a large market that will favour first movers. To do this, however, will require solving the two fundamental problems at play in biosensor research: the lack of detection domains for every conceivable target molecule and the lack of a standardised architecture. If these problems are not amendable to a singular solution, then research will need to focus on standardising protocols of biosensor deployment, rather than the architecture itself. For example, a commercial biosensor design would need to begin with a rational process for proof-of-concept using Fluorescence Resonance Energy Transfer pairs or glucose dehydrogenase electron transfer (Zhang et al., 2019; Stolarczyket et al., 2020). Alternatively, tuneable, modular and orthogonal G-protein-coupled receptors (GPCRs) (Shaw et al., 2019) represent promising targets for plug-and-play systems. That same process would then need to link the biosensor pathway into an autonomous internal pathway optimising a commercial objective such as increasing product yield or quality.

4.7 ? Synthetic yeast for long-range space travel

In few areas of application will this approach of exploring the final biological frontier be more apparent than in space. To support human viability, future production of food, chemicals and materials in space will almost certainly be based on the deployment of synthetic organisms (Berliner et al., 2021; Montague et al., 2012, Santomartino et al., 2023), of which yeast will play a major role (Llorente et al., 2022). No other technology can promise such low weight at launch, with the ability to use end-point resources for building biomass and product yield in a dried product. Simply put, microorganisms require fewer inputs, double their biomass faster and can be engineered more effectively at the end-point in comparison to abiotic alternatives. Space travel not only offers, but requires an entirely new arena of application for engineering biology.

Engineered yeast will be essential to nutritional diversity in space, ensuring that a range of tastes, flavours, aromas (van Wyk et al., 2018) and colours negate the risk of dietary fatigue. Altered carbon source utilisation will be essential to wholly circularise waste management on any resource-isolated extraterrestrial destination (Espinosa et al., 2020, Bell et al., 2022). As yeast research and technology matures, it may be feasible within a few decades to produce a 'colony starter kit' consisting of a consortia of engineered yeast with pan-genomic diversity through carefully selected neo-chromosomes layered over minimal genome architectures. Such a starter kit would provide the new colony maximal diversity of functionality within a small volume, together with the inputs required to engineer their biologics for the nuances of their end point location and user requirements. Until such time, research geared towards such an objective will have multiple end-users on Earth in the burgeoning industrial biomanufacturing sector. It is important to note, however, the key differences and difficulties between growing an organism in space compared to earth (Santomartino et al., 2023). For example, a key area of research necessary to enable these types of applications may involve hardening yeast chassis to cosmic and solar sources of radiation. This area of investigation is likely to have implications for human habitation in space and may intersect with ongoing advances in cancer research.

4.8 ? Synthetic cells as a multipurpose platform

The above rapidly advancing areas of yeast research and synthetic biology are both a necessary step towards the building of a fully synthetic cell (Figure 5), and also a model of international consortium collaboration geared towards the achievement of moonshot 'learning by building' life sciences goals (Frischmon et al., 2021). The SynCell2020/21 conference is a good example of the nascent synthetic cell community preparing for a multi-decade research program that will require international collaborative links spanning the globe. SynCell2023 in Minneapolis will continue to advance this agenda bringing together the core organisations that have developed this vision: the Max Planck Institute of Medical Research, Delft University of Technology, the University of Minnesota and the University of New Mexico.

Fundamental research in yeast is central to setting the boundaries of what is known about cellular life and what can be imagined about its future potential in fully synthetic systems (Stano, 2021, 2022). In this context, technologies and developments derived from advances in minimal genomes, neochromosomes and synthetic yeast genomes encompassing global collaborative efforts will be shared with these 'bigger picture' projects and ultimately contribute to a wider consortium focusing on a model-agnostic platform.

The visions of developing synthetic cells includes concepts such as*pocket factories* , but the core element of the project is a*bottom-up* development and integration of complete cellular function with near-complete understanding and predictable outcomes. This contrasts with the current *top-down* engineering protocols for cellular and free-cell based biodesign. The catch, of course, is that even *bottom-up* research focusing on the fundamentals of life is necessarily bounded by contemporary understandings of how the mechanisms of life interact and achieve objective-directed functionality. The field of chemical-based artificial intelligence is one example of how this SynCell research can lead to novel lines of inquiry (Gentili and Stano, 2022).

5 ? RESPONSIBLE INNOVATION

Both the future of yeast research and the synthetic cell movement have wholly engaged with the discourse of responsible research and innovation. Not only has this covered biosafety, bio-ethics, biosecurity and the emerging world of cyberbiosecurity (McLennan, 2018; Peccoud et al., 2018), but it now must contemplate and develop new models of international engagement and collaboration that hedge emerging themes of geopolitical risk (Dixon, 2021). The future of biology is full of basic research questions that can only be achieved through international collaborative consortia (Hillson et al., 2019). For example, mega-projects that require modular approaches to decade-long initiatives such as developing a synthetic cell. These kinds of projects are well suited to scientific diplomacy objectives that keep communication lines open between nations that might be competing in other economic, cultural and political domains.

A Global Forum on Synthetic Biology has been proposed as a mechanism for bringing together the global leadership of synthetic biology to ensure responsible research and innovation continues to occur within meaningful international collaborations (Dixon et al., 2022). The proposed Forum has seven thematic objectives: (i) sharing information as a network hub—benefits, risks, practical steps and lessons, and leveraging scarce financial resources; (ii) developing agreed technical consensus/guidance documents for use by policymakers and regulators that do not prejudge different policy and political decisions; (iii) linking synthetic biology practitioners more closely with multilateral policymakers and international fora; (iv) facilitating increased global collaborations and co-ordination, including initiatives for addressing societal grand challenges or better integrating synthetic biology with ongoing global efforts such as the UN's *Sustainable Development Goals* (SDGs) (French, 2019); (v) helping to 'de-risk' synthetic biology, including security, governance, and finance/investment; (vi) better integrating synthetic biology with broader initiatives around the bioeconomy, sustainability, and bio-based production; and (vii) developing systemic responses to issues of diversity and inclusion in synthetic biology. Ensuring internationally engaged and collaborative approaches to these objectives both advances and future proofs yeast research at the highest levels internationally.

6 ? Conclusion

Every challenge presents an opportunity, and with a world filled with more challenges, there too lie wider fields of opportunity. Yeast research appears to be reaching an inflection point on the crosswinds of cyber-biological convergence. Research on synthetic yeast can be used to enable minimal genomes, which when use

in concert with pan-genomes and neochromosomes creates new frontiers for experimental exploration. None of these advances, however, have eventuated outside the context of global politics and the grand challenges all of humanity faces. Multi-decade trends continue to shape yeast research, and to be shaped by that same research. The same trends that produced Moore's Law are now exponentially advancing the rate of technological change in the life sciences.

The challenge for the yeast research community (and the opportunity) is to responsibly advance the future of industrial biotechnology within the current context of techno-politics and great power competition. The tools and techniques of science diplomacy are being dusted off and re-honed so that they are properly shaped for the post-pandemic world. There is much that the yeast research community can be optimistic about, and the limit to what can be achieved continues to be set by the boundaries of our imagination.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Figure Legends

FIGURE 1 Current global political, economic, demographic, environmental and technological future-shaping structural forces are driving an extended period of significant uncertainty, insecurity and instability in today's unsettled world. Although this 'permacrisis' of disharmony, fragmentation, disequilibrium, contestation and need for continual adaptation brings daunting challenges at multiple fronts, it too also might reveal great unexpected potential opportunities for technological developments and breakthroughs that could advance synthetic yeast research and human development over the next few decades.

FIGURE 2 The convergence of synthetic biology technologies (e.g. DNA reading, writing and editing) engineering, computational and informational technology is revolutionising life sciences, including yeast research. Transformative breakthroughs that have the potential to shift frontiers in yeast research are likely to be catalyzed by the age-old principle of consilience–scientific advances and evidence from unrelated specialized fields is a powerful dynamo for the acceleration of progress and solutions to grand challenges.

FIGURE 3 The fast-expanding repertoire of biodesign tools are moving the barriers beyond the frontiers of yeast research. These novel concepts include the construction of fully synthetic yeast genomes, minimal genomes; supernumerary pan-genome neochromosomes; synthetic metagenomes; and synthetic yeast communities, synthetic yeast biosensors and even specialized synthetic yeast strains to augment the supply of fermented food during long-range space travel. These concepts are at varying stages of development with plenty of technological pitfalls to overcome before such model synthetic model strains and systems would illuminate some of the yeasts' genetic blind spots and ill-understood aspects of yeast resilience and fermentation performance.

FIGURE 4 The futuristic concept of building a fully synthetic cell as a multipurpose platform is at a very early stage of development. The 'learning by building' approach taken by yeast researchers is central to the construction of a synthetic cell from scratch.

FIGURE 5 The 'compass of responsible innovation' guides researchers involved in frontier science toward a process aimed at creativity, opportunities and innovation for science that are socially desirable and conducted in the wider public interest.

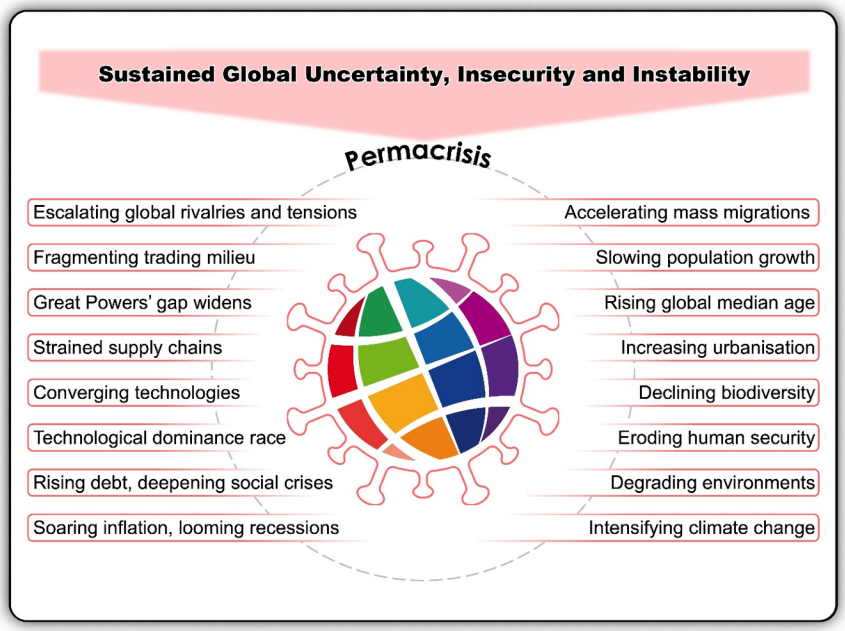

FIGURE 1 Current global political, economic, demographic, environmental and technological future-shaping structural forces are driving an extended period of significant uncertainty, insecurity and instability in today's unsettled world. Although this 'permacrisis' of disharmony, fragmentation, disequilibrium, contestation and need for continual adaptation brings daunting challenges at multiple fronts, it too also might reveal great unexpected potential opportunities for technological developments and breakthroughs that could advance synthetic yeast research and human development over the next few decades.

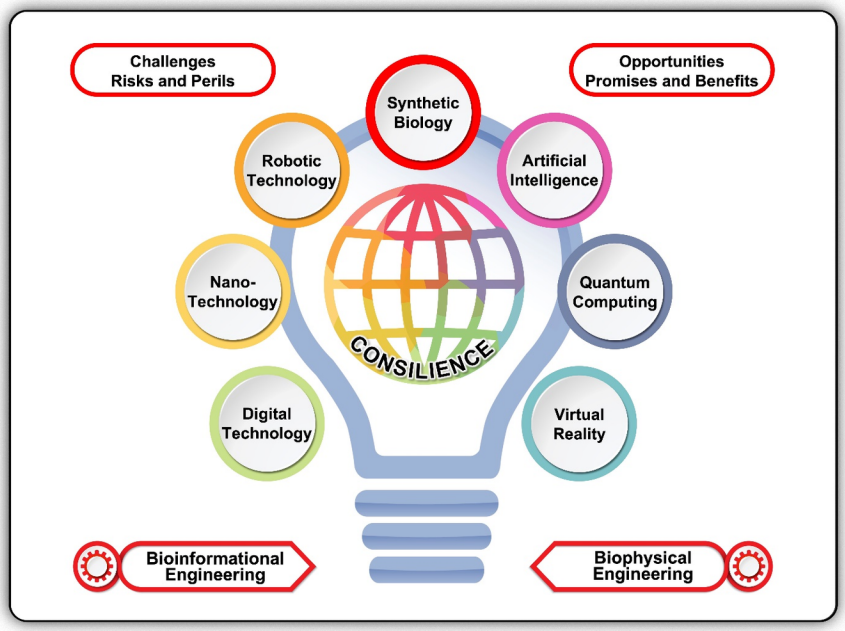

FIGURE 2 The convergence of synthetic biology technologies (e.g. DNA reading, writing and editing) engineering, computational and informational technology is revolutionising life sciences, including yeast research. Transformative breakthroughs that have the potential to shift frontiers in yeast research are likely to be catalyzed by the age-old principle of consilience–scientific advances and evidence from unrelated specialized fields is a powerful dynamo for the acceleration of progress and solutions to grand challenges.

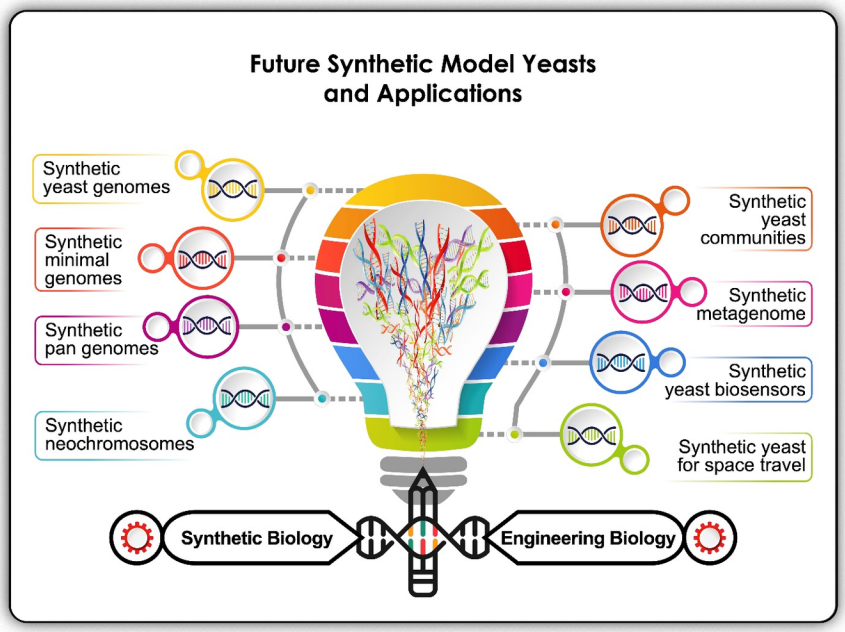

FIGURE 3 The fast-expanding repertoire of biodesign tools are moving the barriers beyond the frontiers of yeast research. These novel concepts include the construction of fully synthetic yeast genomes, minimal genomes; supernumerary pan-genome neochromosomes; synthetic metagenomes; and synthetic yeast communities, synthetic yeast biosensors and even specialized synthetic yeast strains to augment the supply of fermented food during long-range space travel. These concepts are at varying stages of development with plenty of technological pitfalls to overcome before such model synthetic model strains and systems would illuminate some of the yeasts' genetic blind spots and ill-understood aspects of yeast resilience and fermentation performance.

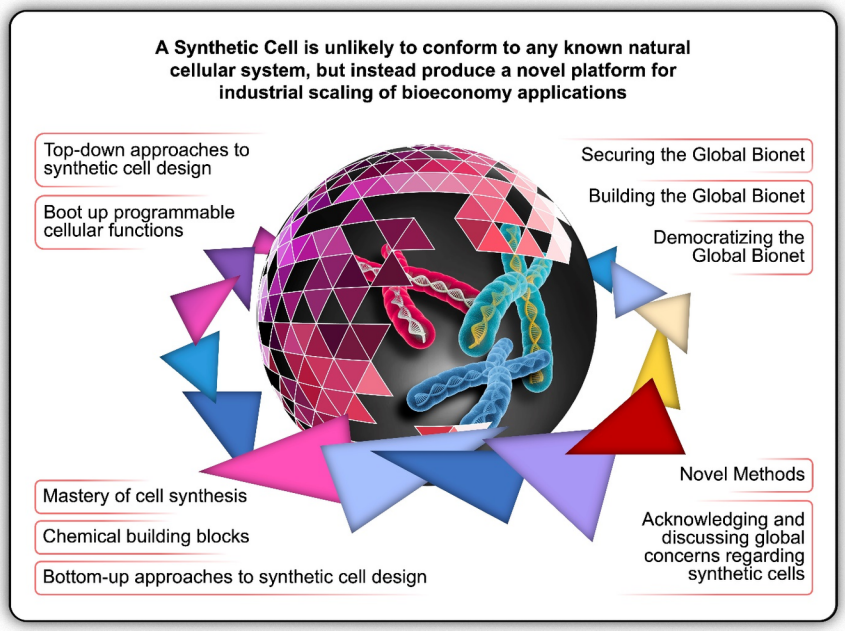

FIGURE 4 The futuristic concept of building a fully synthetic cell as a multipurpose platform is at a very early stage of development. The 'learning by building' approach taken by yeast researchers is central to the construction of a synthetic cell from scratch. The technical basis of the bionet is the ability to barcode, archive, and track artifacts as they move through the world, along with regularly updated standards and protocols for material exchange between researchers. While providing an intuitive way for scientists to store and share their material inventories, the bionet offers novel ways of organizing actions and information around biological subjects such as the synthetic cell project.

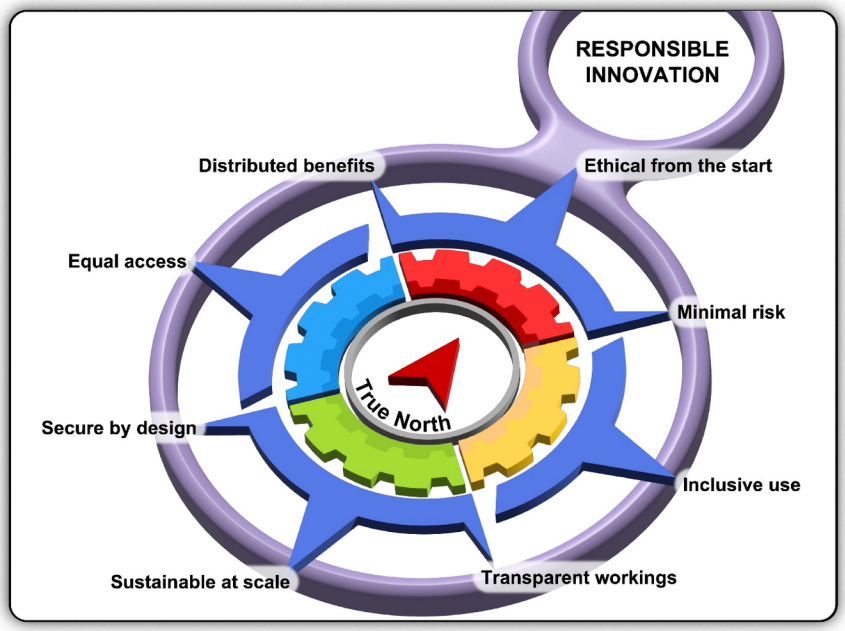

FIGURE 5 The 'compass of responsible innovation' guides researchers involved in frontier science toward a process aimed at creativity, opportunities and innovation for science that are socially desirable and conducted in the wider public interest.

Box 1: Defining the Synthetic Yeast Research Landscape

Synthetic Biology: The design and construction of new biological parts (genes), devices (gene networks) and modules (biosynthetic pathways), and the redesign of biological systems (cells and organisms) to achieve human objectives.

Biophysical Engineering: Synthetic Biology tools, techniques and methodologies that adapt engineering and design thinking to biological substrates in order to control and actuate the physical characteristics associated with that substrate. For example, chemical synthesis, feedstock refactoring and biomass optimisation.

Bioinformational Engineering: Synthetic Biology tools, techniques and methodologies that adapt engineering and design thinking to biological substrates in order to control and actuate the informational characteristics associated with that substrate. For example, optogenetics, biosensors and bioelectrochemistry.

Synthetic Yeast Genome: The use of Synthetic Biology to design and build a fully functional genome.

Synthetic Model System: An *in silico* model of a biological system that enables the rapid prototyping of engineering designs via a Computer Assisted Design tool. It may enable the user to work at different abstractions of a biological system. For example, genes, gene networks, biosynthetic pathways, or biological systems.

Synthetic Cell: An internationally collaborative research program that seeks to remove current biological unknowns and achieve an end state where biological functionality can be entirely designed via Computer Assisted Design and Synthetic Model System solutions.

Synthetic Minimal Genome: A design methodology that removes unnecessary genetic elements from natural or model organisms to optimise productive capacity for a target growth environment.

Synthetic Metagenome: A synthetic genome that encodes multi-species genetic information from a point-of-interest. For example, a synthetic yeast that contains the code for all naturally occurring yeast species at a given vineyard.

Supernumerary Neochromosome: An additional chromosome appended to a synthetic chromosome that contains pan-genomic information for optimising functionality towards a specific objective.

Synthetic Yeast Community: The design and construction of an engineered consortia involving defined or synthetic biological elements. This may be semi-synthetic (an engineered strain interacting with a natural biotic counterpart) or fully-synthetic (two or more engineered counterparts).

Synthetic Specialist Yeast: A synthetic yeast optimised for productive functionality in a target environment.

Pan-Genome: An assembled array of multiple genomic elements normally associated with an industrial or environmental site, for appending to a natural, synthetic or semi-synthetic organism's genome, to improve functionality and productivity of the engineered organism in the target environment.

New-to-Nature: A biological substrate of any level of biological abstraction that cannot be found to have occurred through the natural process of evolution on Earth.