Building a Synthetic Cell Together

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Synthetic cells (SynCells) are artificial constructs designed to mimic cellular functions, offering insights into fundamental biology, as well as promising impact in the fields of medicine, biotechnology, and bioengineering. Achieving a functional SynCell from the bottom up, i.e. by assembling it from molecular components, requires a global collaboration to overcome the many challenges of engineering and assembling life-like modules while addressing biosafety, equity, and ethical concerns in order to guide responsible innovation. Here, we highlight major scientific hurdles, such as the integration of functional modules by ensuring compatibility across diverse synthetic subsystems, and we propose strategies to advance the field.

Building a SynCell from molecular components is a staggering aim that involves a broad range of scientific challenges. However, the field is still in an explorative phase, and the approach and even the ultimate goal are not unanimously agreed upon[1]. Building SynCells from the ground up is a highly multidisciplinary undertaking requiring international collaborations. To this end, 36 senior scientists and 12 promising junior researchers from all around the globe gathered in Shenzhen, China, in October 2024, for the inaugural ‘SynCell Global Summit’. For the first time, this meeting brought together scientists from SynCell communities in Africa, Asia, Australia, Europe and the US. The attendees engaged in extensive discussions on challenging ideas, debated the limitations of the current approaches and worked towards establishing a consensus on the future direction of SynCell research. Researchers presented their initiatives, biofoundries, and funding programs, collectively striving to shape a unified vision for advancing the field. This article provides a brief overview of the outcomes of the summit on SynCell state-of-the-art research, major scientific challenges, and proposes synergistic efforts for the advancement of the field.

The bottom-up approach to SynCells: many benefits

There are diverse motivations for building a SynCell. For some, the drive stems from understanding, in a simplified context, the intricate processes found in living cells[2] and from probing origins-of-life theories[3]. Others view SynCells as minimal and well controllable biomimetic systems with augmented chemistries and functions for applications in therapeutics[4], energy production[5], and biomanufacturing[6]. Notably, the SynCell community is inspired by the possibility of creating a living system, characterized by the ability

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to self-reproduce and evolve, from non-living building blocks. If so, the minimal conditions to "reboot" cellular life can test our fundamental understanding of life and its basic unit, the cell.

The term "SynCell" is often used for engineered cell-sized systems capable of performing life-like functions, such as information processing, motility, growth and division, signaling, or metabolism (Fig. 1a)[7]. Alternatively, it can be defined as a physicochemical system that sustains itself and replicates in an environment capable of open-ended evolution (Fig. 1b)[8]. The first definition emphasizes a modular approach to reconstituting all the biological features, excluding replication and evolution, while the second definition emphasizes the ability of a fully interoperable SynCell to replicate and evolve, which is key in addressing the fundamental evolution of life.

Given the multidisciplinary challenge of building SynCells and their far-reaching potential impact, it is critical to promote global collaborations while striking a balance between exploration and unification of modules. The field will benefit from exploring different approaches, rather than be divided by definitions.

Current achievements in SynCell research

SynCells are far less complex than biological cells, however to date, only a few cellular functions have been reconstructed outside of the cellular context with much work still needed to achieve fully integrated systems[7]. Their exact nature (i.e., structure and function) varies greatly from SynCell to SynCell and is dictated by which life-like property is reconstructed, and in turn, which structural chassis has been chosen to facilitate it. However, key properties of living cells often involve compartmentalization and the coupling of genotype and phenotype through information processing. Therefore, the bottom-up approach to mimicking cellular functions typically comprises the use of molecular building blocks such as membranes, genetic material, and proteins. For example, taking inspiration from cell membranes, phospholipids to create lipid vesicles are widely used as an approach to creating SynCell structural chassis[9]. Other explored approaches include emulsion droplets[10], liquid-liquid phase separated systems[11], proteinosomes[12], or hydrogels[13].

Moreover, an essential cornerstone of cellular function is the coupling of genotype with phenotype. To this end, the assembly of transcription-translation (TX-TL) systems has been widely explored, either based on cellular extracts or reconstructed from purified components[14,15], and then further integrated with compartmentalization to achieve SynCells programmed to communicate[16], as well as interact with living cells[17].

Furthermore, efforts in creating SynCells stretch beyond compartmentalization and information processing and include the engineering of systems capable other life-like features, such as self-powering[18,19], self-propelling[20,21], as well as partially regenerating their own components[22].

Building blocks used in the assembly of SynCells reach beyond those found in nature. The option to explore non-natural components in the design of SynCells, such as polymerosomes[23] or nanoparticles[24], is one of the benefits synthetic systems hold over their biological counterparts, as these approaches have the potential to expand the functional capabilities of SynCells beyond those found in nature.

Conversely, natural building blocks can also be utilized in non-canonical ways. For example, the modularity of DNA or RNA has been used outside the context of information storage to create DNA-based[25], or RNA-based[26] cytoskeletons, as well as to establish collective behaviors[27] or even to design programmable genetic networks that allow synthetic cells to sense environmental changes, and respond dynamically[28].

While a plethora of life-like modules have been so far engineered, and further exploration is encouraged, challenges discussed in the followings need to be tackled in order to advance the field.

Building a SynCell is an integration challenge

Many tasks must be accomplished to cooperatively develop a SynCell. This cooperation and compatibility-driven approach can focus our efforts towards achieving a common ultimate goal of creating a "living" system capable of self-reproducing and undergoing evolution. For this, three major scientific challenges were discussed during the summit. First, to develop functional SynCell modules that are essential for life to fully recapitulate cellular behaviors. This requires developing techniques that allow reproducible, modular and integrable designs of SynCells in order to favor compatibility for subsequent integration. Second, to overcome existing incompatibilities between diverse chemical/synthetic sub-systems developed by many groups with diverse expertise, which hampers our capacity to integrate such modules into a single system to allow the emergence of more complex life-like systems. Additionally, when aiming at building a SynCell, the complexity of combining and integrating components in an interoperable and functional way scales exponentially with module numbers. Third,

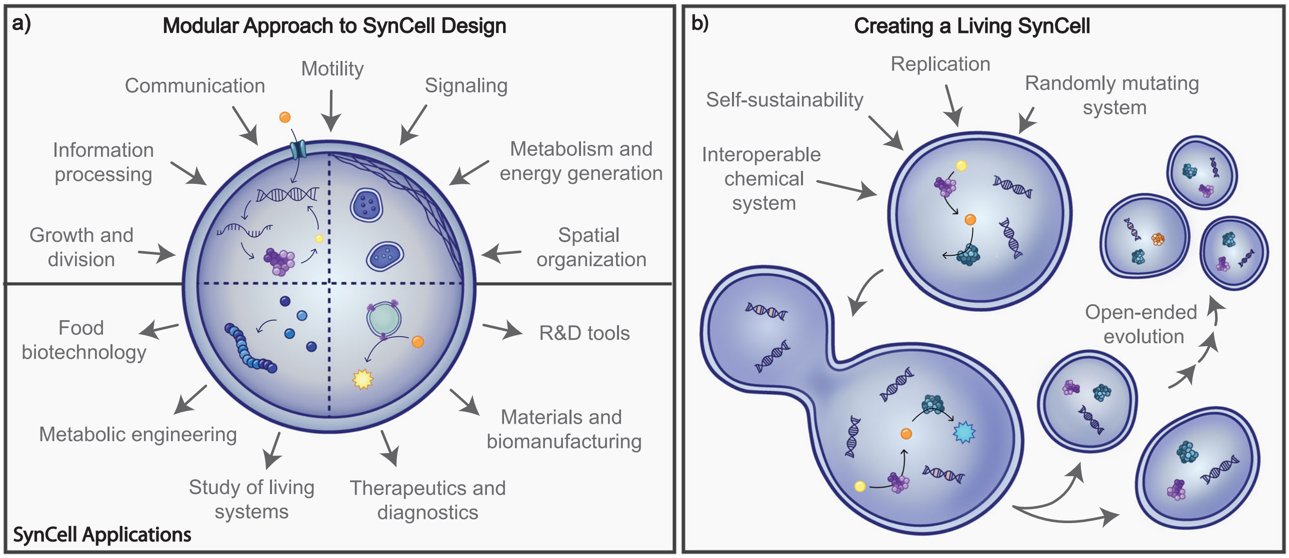

Fig. 1 | Synthetic Cells. a Modular approach to SynCells with structural and functional modules represented (top) and main applications of SynCells (bottom). **b** Key functional characteristics for the realization of living SynCells.

Table 1 | SynCell modules

Modules	Main achievements	Current challenges
Growth	Ribosome biogenesis[29,30] Protein synthesis[22,30,33] Lipid synthesis[31] Replication of genomic DNA[32] tRNA synthesis[65]	Doubling of cellular components
Autonomous division	Contractile ring formation[34,35] Abscission[36]	Synthetic divisome
Metabolism and transportation	Metabolic networks providing energy[37,38] Metabolic networks providing building blocks[39] Integration of metabolism and gene expression[40]	Programmable degradation of damaged macromolecules, recycling of metabolic intermediates as well as end-products.Transmembrane transport of molecular fuels/wastes.
Minimal synthetic genome	Chemical synthesis of a minimal bacterial genome to support cell growth[45]	Improved understanding of minimal genome to facilitate core functions of life.
Spatial organization	The use of various structural chassis; coacervates[46], emulsion droplets[47], hydrogels[48], lipid vesicles[49], polymersomes[50], multi-compartment liposomes[51] and phase separation[66]	Better understand and control spatial coordination. Integrating different modules in a spatially ordered manner.

Highlights of main achievements and challenges

SynCell technologies need to be safeguarded against accidental and intentional misuse, to enable broad and responsible adoption. Below, we present a brief exploration of these main challenges, focusing on some of the critical SynCell modules and highlighting recent progress in the development of these (Table 1).

SynCell modules

Growth. De novo production and self-replication of all the essential components, e.g., ribosome biogenesis[29,30], lipid synthesis[31], and replication of (genomic) DNA[32], is required to keep SynCells self-sustaining[22,33] and replicable[30]. The current state-of-the-art is still far from achieving doubling of cellular components, and is therefore one of the biggest challenges in the SynCell effort, in which cell-free protein synthesis, either via cell extract[15], or purified components (e.g., PURE system)[14] will take a critical role. Indeed, reconstruction of all needed components, as well as maximizing both the protein synthesis capacity and controllability of cell-free gene expression, are key challenges. While the major components for replication, transcription, and translation have been identified through biochemical and molecular biology studies, achieving the implementation of a synthetic central dogma with an efficiency and controllability comparable or even superior to living systems remains a substantial challenge.

Autonomous division. Cell division is a biophysical process that requires the coordination of many proteins that often compose higher-order macromolecular assemblies to support large-scale mechanical deformation and rearrangement of the membrane. While certain elements have been realized, e.g., contractile ring formation[34,35] or final abscission[36], a controlled synthetic divisome has not yet been realized, calling for extensive biophysical characterizations towards better understanding and controllability of division in synthetic systems.

Metabolism and transportation. Energy supply, anabolism, and catabolism are pivotal and ubiquitous functions that keep living systems out of thermodynamic equilibrium. While metabolic networks providing energy[37,38] and building blocks[39] have been reconstituted in vitro as well as recently integrated with genetic modules[40] for SynCells, improvements in metabolic flux, efficiencies, as well as coupling with complementing pathways sharing essential metabolites are awaited. Developments in programmable degradation and efficient recycling systems for damaged macromolecules[41], metabolic intermediates[42], or end-products of metabolic pathways[43] together with the transport of molecular fuels/wastes across the membrane[44] would improve the stability and longevity of the entire system that currently are limited.

Minimal synthetic genome for a SynCell. As the top-down JCVI minimal cell projects demonstrated, chemical synthesis of a synthetic genome is doable[45]. Based on the size of this top-down minimized genome (473 genes), a synthetic genome synthetized from the bottom-up capable of encoding only essential features and their spatiotemporal control may need 200–500 genes. Nevertheless, our grasp of the architecture of a fully functional minimal genome is still minimal.

Spatial organization and initial conditions. The cellular interior is a highly orchestrated architecture of biomolecules within a micrometer-sized environment. It is a challenging mission to find the proper "initial" conditions to boot up a bottom-up SynCell. Currently, there is no blueprint guiding us in integrating different modules in a spatially ordered manner within a SynCell. Future work needs to focus on how to get a better understanding, control, and simplified view of spatial coordination to successfully boot up a SynCell. Coacervates[46], emulsion droplets[47], hydrogels[48], lipid vesicles[49], as well as polymersomes[50] are studied to assure out-of-equilibrium conditions and provide the genotype/phenotype coupling that is essential for an evolving system. However, their compatibility with other modules, standardization, reproducibility, and automation are pressing challenges for achieving SynCells. Other compartmentalization strategies, such as liquid-liquid phase-separation, could facilitate localizing and concentrating biomolecular components within the SynCell to tune biochemical reactions[51].

Integration and scalability

A defining characteristic of a living SynCell is the presence of a functional cell cycle, where processes such as DNA replication, segregation, cell growth, and division are seamlessly coordinated and tightly integrated. This ensures the SynCell can propagate and maintain its biological functions in a controlled and sustainable manner. As a building strategy, the modular approach that is so pervasive in engineering greatly inspires the current approaches in building a SynCell, giving rise to a vast catalog of key modules of cellular functions and SynCell chassis. A highlight of the summit was a discussion on how to integrate these disparate modules into a functioning whole[52,53]. Here are countless numbers of possible combinations and arrangements of essential building blocks in a single SynCell, and the parameter space is too large to explore. This is underscored by a lack of theoretical frameworks that predict the behaviors and robustness of reconstituted systems, especially when multiple modules are combined. Thus, it was proposed that efficient optimization systems, both experimentally and computationally, through machine learning approaches are highly desired to accelerate the parameter-sweeping processes. The implementation of efficient optimization systems are additionally paramount to ensure the scalability of SynCell production, which must be considered toward the implementation of SynCells as a practical, widely used technology[54].

Ethics, biosafety and security

Beyond the scientific challenges, ethical, biosafety, inequality, and other societal concerns were discussed during the summit. Some of the potential risks posed by SynCells are the possibility of disruption of ecosystems and risks to human health, if SynCells were to be injudiciously released into the environment. Another concern is the dual-use aspects of this technology, including accidental and intentional misuse. Recently highlighted concerns about specific types of SynCell technologies, such as Mirror Cells, bring urgency to those discussions[55]. The all-continent representation was key in nurturing exchanges on the importance of inclusive accessibility to SynCell research and its outcomes. The summit further explored safeguards for the foundational research and emerging applications of SynCells, utilizing both existing regulations, and discussing the need for novel safety mechanisms that can and should be hardwired into future SynCell designs. Furthermore, scientists should engage with the general public to ensure our efforts and current regulations are informed.

Paths to overcoming the current challenges

Technological developments offer exciting opportunities to tackle these challenges. On the one hand, with AI-aided protein design, the time has come to create de novo proteins for SynCells. For example, proteins that hold different cellular functions[56] and binders[57] suited for a wide variety of different compounds can now be designed, which enables us to build SynCells with wholly new elements instead of those borrowed from nature. On the other hand, biofoundries offer integrated 'design, build, test, learn (DBTL)' platforms, incorporating the techniques of bioinformatics, mathematical modeling, big data analysis, and artificial intelligence to design new enzymes[58], reaction networks[59], and pathways[60], as well as conducting automatic detection, sorting, and re-encapsulation in a fully continuous and autonomous way. Indeed, there is great potential in going beyond pure engineering design. Emphasis was put on moving towards directed evolution strategies for systems optimization and development. Finally, combining computational and evolutionary approaches can help us tackle the multiscale complexities of soft matter, biomolecules, and nonlinear dynamics.

During the summit, an AI-based automated DBTL evolutionary workflow was proposed to go through the aforementioned bottlenecks, starting with simple vesicle phenotypes and cell-free gene expression. The parameter space includes biochemical variables such as the genotype, molecular composition, pH, and temperature. This approach is a primitive form of AI machine learning, which offers a way to rapidly go through parameter space. The phenotype is characterized, which can give quick information closer to our objective function. Active learning algorithms are used to learn optimal parameters from the generated experimental conditions and suggest new experiments. A similar approach has already been adapted to optimize cell-free gene expression from mycoplasma JCVI lysate[61]. Collecting standard and quantitative AI-ready data across labs is the key to integration, which needs effective and reliable global cooperation.

Building open-access data repositories to facilitate the sharing of experimental protocols, data, and module blueprints will help promote the existence of universal module interfaces for off-the-shelf unification of individual modules[62].

SynCells have many potential applications

It is equally important to consider how SynCell can benefit human society. SynCells hold the promise of simplicity, programmability, and controllability, which are considered main advantages over natural cells, offering an alternative approach to challenges within biomedicine, metabolic engineering for sustainability, materials science, food biotechnology, and R&D tool development. Although potential applications of SynCells have been demonstrated in many areas, such as biomedical application[4,63,64] or biosensors[28], the community must in the short-term (5 or 10 years) provide proofs of concept for such benefits. The application-focused design approach starts by identifying a specific unmet need in our society and fabricating relatively simple SynCells with the prime aim of tackling this challenge using our current expertise and toolbox. In this regard, the need to consider critical technical bottlenecks that must be tackled to facilitate the future widespread use of SynCells is emphasized, including cost, stability, shelf life, and production throughput. Similar to major technological shifts in the past, the drive toward SynCells is poised to catalyze a wave of advancements across biotechnology, nanotechnology, and molecular engineering, leading to innovations, such as improved drug delivery systems, cell-free biosensors and novel biomaterials.

Outlook

There are good reasons to expect that it will be possible to build a living SynCell from nonliving components. The ability to build a living SynCell from nonliving components represents a paradigm shift in our understanding of life and our capacity to engineer it. It bridges the gap between living and nonliving matter, offering unprecedented opportunities to explore the boundaries of biology and harness its principles for innovative applications. This effort not only pushes the limits of science and technology but also inspires new ways of thinking about life itself. This comes with the responsibility to ensure biosafety, inclusiveness, and benefit to society. To this end, the community should initiate open and transparent dialog with the general public and listen to the concerns and what the audience expects from SynCell to widely benefit human society. SynCell research should be developed as an Open Science and engage researchers in reflecting on possible abuse of the knowledge created and make recommendations to policymakers about how SynCell research should be governed. There is a broad consensus among the SynCell community to promote such collaboration and communication. The next Global SynCell Summit is planned to take place in April 2026 in Delft, the Netherlands. This and related future meetings (e.g., the SynCell2025 meeting in September 2025 in Stanford, US) will help to continuously clarify and focus the goals and efforts of this exciting emerging field.

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Author contributions

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Competing interests

The authors declare no competing interests.

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