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Present and future of synthetic cell development

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Scientists are captivated by the prospect of creating a fully synthetic cell, offering the potential to revolutionize biology, medicine and biotechnology. In this Viewpoint, a panel of experts discusses the definitions of a synthetic cell and highlights current achievements, challenges and future opportunities of building such systems.

How would you define a synthetic cell? What elements or components are essential? What are the minimal properties of such a system?

Petra Schwille: Strictly speaking, a synthetic cell should be the person-made mimicry of a biological cell and, thus, the smallest unit of life. Yet, even the smallest units of life that we find on our planet today are still incredibly complex. Therefore, we first need to define the 'essence' of a cell that may be easier to build; here, different stakeholders will consider different components as essential. Biotechnologists, who use cells primarily as production platforms, will ask for a synthetic cell to be capable of producing something; doctors may ask for cell-like systems that could be used to interact with, or even replace, cells in our bodies; and biophysicists and other quantitative scientists would like to see synthetic cells with a dramatically reduced complexity as compared to natural ones, hoping that they could potentially define something like a 'hydrogen atom of biology' — the absolute minimal system that could be called alive. However, when can a system be called alive? This seems to be an even harder question than the one for a synthetic cell. Life appears to be an ongoing, never-ending and never-stopping cascade of biochemical reactions, which keep changing their form and composition upon the constant consumption of energy but never come to a complete halt and — importantly — also never seem to appear from scratch. However, at some point far back in time, at the mysterious 'origin of life', this cascade of biochemical reactions did in fact start from scratch, with molecules and environments that we have no real knowledge of. If it happened once, we should in principle be able to revisit this process. Regardless of the many different theories on the origin of life, we can probably agree on three major ingredients of all living cells today: (1) a selective and transformable boundary; (2) a metabolism that supports growth and homeostasis; and (3) an information carrier that defines the identity of the system and that would be accessible to Darwinian evolution, which occurs through division and self-replication.

Kate Adamala: A synthetic cell could be any life-like system that has emergent properties. There is no good definition of synthetic cell or of life in general. I use a definition borrowed from Justice Stewart: I know it, when I see it. To make it 'synthetic', it should not come directly from LUCA (last universal common ancestor of all life on Earth), and to make it a 'cell' it should be compartmentalized — those are the minimal requirements for any system that falls into this category.

To be alive, a synthetic cell should be capable of undergoing Darwinian evolution, with many possible biochemistries that could provide that ability. As long as there is some genetic polymer that can accumulate mutations, coupled with a selectable phenotype, evolution is possible. It does not have to be the exact DNA, RNA and protein system known from our life. To achieve life and evolution, the cell needs to replicate and not necessarily self-replicate. Any cell with a mechanism to make copies of the genome, grow the cell and split it into offspring could undergo evolution. Many undeniably living organisms do not self-replicate (even us, needing two people and some planning to make little humans). A very simple synthetic cell could require extensive help in making new cells, for example, some chemical trigger or mechanical push. Synthetic cells do not need many biosynthesis pathways. A synthetic cell could get away with being a perfect heterotroph, receiving all building blocks from the environment. It should have breakdown and regeneration pathways though, otherwise, metabolism would be unsustainable.

Yuval Elani: Maximalists believe we should not label something a 'synthetic cell' until it is autonomous and 'living' (whatever that means), while minimalists think any mimicry of cellular features qualifies. Some consider simple cell-sized compartments encapsulating biomolecules as synthetic cells. Many in vitro systems used by biologists over many decades would meet these criteria, as would complex drug-delivery systems. Everyone's definition varies. I sit in between but lean towards the minimalists. To me, a synthetic cell combines biomolecular elements with the goal of mimicking or recapitulating processes found in living systems or exhibiting 'behaviours' we associate with life.

Marileen Dogterom: There are many different answers possible to this question depending on how ambitious one is in getting close to mimicking real life in all its complexity (and beauty). For the purpose of our national Dutch programme Building a Synthetic Cell (BaSyC), we have decided to aim for a synthetic cell based on natural DNA and protein-like components that is able to autonomously grow and divide. This means it has to contain 'modules' for metabolic processes such as energy production and growth (for example, ATP and lipid synthesis), information transfer (for example, DNA replication and protein expression), and division (gene segregation and membrane fission) (see, for example, ref. 1). This leaves out components that one might also argue to be essential for (minimal) life: the ability to evolve, move and communicate.

T-Y Dora Tang: Although there are many potential definitions, in my lab, we are inspired by Erwin Schrödinger — he defined life as being in an out-of-equilibrium state. We used this framework to build synthetic cellular systems with sustained out-of-equilibrium behaviour as a proxy for life. Biology is well equipped to do this by utilizing the intrinsic complexity of the cell. However, minimal systems that lack molecular complexity tend to reach an equilibrium state. In our lab, we are inspired by biological systems and aim to incorporate the essential features of reactions, compartments and communication into synthetic cellular systems to establish sustained out-of-equilibrium behaviour. Of these three, the primary feature is the compartment, which

can contain and segregate reactions whilst coordinating population-level behaviour by molecular diffusion.

Masahiro Takinoue: The most characteristic properties of living systems that separate them from non-living matter are the functions that autonomously process information and convert matter or energy to another type of matter, energy or work to maintain their dynamic systems, which can arise only from non-equilibrium open chemical systems. Schrödinger and von Neumann have already discussed the importance of non-equilibrium and information in living systems[2]. From such a physical point of view, my definition of synthetic cells is non-equilibrium open compartments that can autonomously process information and generate matter, energy or work by chemical reactions. The compartment boundary does not have to be a strict boundary such as a lipid bilayer; it can be a looser boundary such as that in coacervate droplets[3]. In addition, matter or energy conversion is called metabolism in biological terms.

Ultimate synthetic cells are expected to have many properties as natural living cells have such as sensing and processing information, environmental responses, metabolism, autonomous locomotion, intercellular communication, adaptation, growth, self-replication and evolvability. However, for engineering purposes, synthetic cells are not required to have all those properties when they are designed to perform a specific task such as biomedical or health-care tool development, material synthesis, addressing environmental, agricultural or food problems, and understanding the physical origins of life. As minimal systems, synthetic cells must be equipped with the properties of (1) sensing and processing information; (2) conversion of matter or energy into valuable information, chemicals, or actions; and (3) programmability of molecules, structures and reaction networks.

Where are we at the moment with creating synthetic cells? What are the systems that we can reproducibly reconstitute, and which areas need further development?

PS: It is not easy to define 'where we are' because the field is so diverse and many groups have perfected their own particular approaches towards the reconstitution of usually only one or few particular cellular features such as pattern formation, signalling, a minimal metabolism, cell division or genome replication. It is probably easier to summarize the enabling technologies or assays that are used and shared by many groups around the world. There are several methods and techniques that I consider particularly useful and widespread. One is the use of giant unilamellar vesicles as compartments or 'protocells', which represent a very faithful mimicry of cellular membranes, and which can meanwhile be produced with high fidelity and reproducibility. Their charm lies mainly in their large sizes suitable for light microscopy, and their functional compatibility with membrane-associated or integral membrane proteins. Likewise, microfluidically produced emulsion droplets have become very popular as compartments for solution-based processes, in particular for assays that may involve screening or large sample variations. With regard to the production of defined functional proteins, cell-free protein expression by PURE or other TXTL systems has become very popular as it can be easily integrated into emulsion droplets, and lately also into vesicles. Finally, DNA or RNA origami shows some promise with regard to designing new biological functions for synthetic cells without the need for tedious protein reconstitution. An area that still needs a lot of development and better integration into the community is, in my eyes, metabolism design. So far, our systems are still very strongly tied to the 'traditional' energy currencies, such as NTPs and pH or ion gradients, which are very powerful but seriously restrict the design of functional molecular units as building blocks of synthetic cells.

YE: It is still early days, and we are currently in the 'tick box' phase of the endeavour. One by one, researchers are recapitulating fundamental features of living systems. They either stay faithful to biology, reconstituting these features using native machinery, or they explore alternative non-biological mechanisms. This includes aspects such as metabolism, energy generation, motility or signalling.

Some areas are more developed than others. Generally, bioproduction, metabolism, sensing and information processing can be achieved by leveraging the significant advancements in classical synthetic biology from past decades. This involves using tools such as DNA gene circuits and cell-free protein expression systems and applying them in the context of synthetic cells.

However, membrane-based processes present greater challenges. This includes processes such as continuous growth and division cycles (essential for inheritance and evolution) and those that rely on intricate transmembrane machinery (for example, directional motility using flagella or controlled secretion of biomolecular species). Regenerating molecular building blocks (aiming for a universal constructor) is a formidable challenge but remarkable progress is being made[4]. The next phase involves integrating individual modules, with the ultimate goal of constructing a holistic, autonomous cell mimic that could be deemed 'living'. We are quite some way away from achieving this.

T-YDT: There is exciting progress in the synthetic cell community where our ability to reproducibly reconstitute biological function is becoming more advanced. The measure for

The contributors

Kate Adamala: is a biochemist engineering synthetic cells. Her research aims to understand the chemical principles of biology, using artificial cells to create new tools for bioengineering, drug development and basic research. Kate is a co-founder of the synthetic cell therapeutics startup Synlife, and coordinator of the international Build-a-Cell synthetic cell community.

Marileen Dogterom: is a biophysicist and professor of bionanoscience at Delft University of Technology. Her interests include biophysics of the cytoskeleton and building minimal cytoskeletal systems for synthetic cells. She leads the Dutch consortium on Building Synthetic Cells and is one of the founding members of the European Synthetic Cell Initiative.

Yuval Elani: is co-director of the fabriCELL Centre at Imperial College London. He is a biotechnologist who leads a group working on bioinspired engineering approaches for new synthetic cell therapies, delivery vehicles, vaccines, AgriTech tools and cellular models. His research spans synthetic biology, biohybrid engineering, microfluidics and chemical biology.

Petra Schwille: is biophysicist and director of the Cellular and Molecular Biophysics Department at the Max Planck Institute of Biochemistry in Martinsried, Germany. Her research is concerned with the question what the smallest living system could look like, and how to construct it from the bottom-up.

Masahiro Takinoue: is a biophysicist and a professor in the Department of Computer Science at Tokyo Institute of Technology, focusing on soft matter physics, molecular computing and DNA nanotechnology for artificial cell construction. Recent interest in his laboratory involves the design of DNA-based and RNA-based phase separation droplets for artificial cells and organelles.

T-Y Dora Tang: is a professor of synthetic biology at the University of Saarland (and partner group at the MPI-CBG). Her interdisciplinary research contributes to artificial cell synthesis, unravelling the origin of cellular life and using synthetic cells as models for modern biological systems.

reproducibility is a method that can be replicated between laboratories. Given that, the most successfully reconstituted system in the field is the incorporation of cell-free transcription and translation within a synthetic cellular chassis. This brings the central dogma of molecular biology (information flow from DNA to protein) within a compartment that is a key feature of biological cells. This provides a foundational platform to incorporate other features into synthetic cellular platforms, including replication and metabolism. In our lab, we have made progress in the incorporation of reactions within a variety of membrane-bound and membrane-free compartments. We and others have shown the ability to drive communication by molecular diffusion between compartments within a population. However, to date, we have not realized the ability to integrate the features of reactions, compartments and communication to sustain out-of-equilibrium behaviour. We have recently been awarded an ERC consolidator grant that focuses on solving this problem. We plan to integrate a bottom-up synthetic biology approach with biophysics to define how physico-chemical parameters of reactions, compartments and communication by molecular diffusion can tune out-of-equilibrium behaviour. Doing this will provide us with a set of design rules to rationally build 'living' synthetic cellular systems from scratch.

MT: Non-equilibrium chemical reactions have been reproducibly reconstituted in compartments such as lipid bilayer vesicles, water-in-oil droplets, liquid–liquid phase-separated droplets, polymer coacervates and gels. In addition, synthetic cells equipped with a few characteristic functions, such as material synthesis, information processing, spatiotemporal pattern formation, environmental response, autonomous movement and adaptation, have already been reported. Furthermore, organizing multiple synthetic cells to mimic tissues or intercellular communication is reproducible. In other words, basic technologies for producing synthetic cells with minimal properties have already been reproducibly achieved. However, the challenges of growth, self-replication, evolution and autonomous control of synthetic cell populations and the realization of higher-order functions through multistep cooperative reactions are still in the early stages, and further development is needed in these areas. In addition, although the development of synthetic cells is currently focused on the aspects of chemical reactions, it is necessary to elucidate and reproduce cellular phenomena emerging from coordinating multistep chemical reactions with physical phenomena, such as molecular crowding effects, coacervation, phase transition, wetting and viscoelastic complex flow, in cell-sized soft matter. Revealing such phenomena will promote the construction of more sophisticated functions for synthetic cells such as information processing and growth, deformation or division based on huge, dynamic cellular structures like genomes and organelles as conducted by natural cells. Here, our DNA droplet technology[5] may help development.

MD: As a field[6], we have managed to engineer and reconstitute many elementary modules, including DNA replication, lipid synthesis, protein expression, ATP synthesis, minimal cytoskeletal systems for DNA segregation, membrane containers, modules for physical deformation of these membrane containers, and minimal regulatory networks such as clocks. However, what is missing for the moment is the ability to integrate these modules, including the spatial-temporal regulation of such an integrated system. In many cases, experimental conditions are optimized for one module, which does not necessarily provide optimal conditions for other modules. An example is (membrane) container size, which is preferentially small (up to several 100 s of nanometres) for metabolic processes but much larger (several tens of micrometres) for (cytoskeletal) systems that help segregate DNA or drive cell division.

KA: We have reconstituted most but not all elements of central metabolism and cell physiology[7]. We are pretty good at making compartments. We have good energy regeneration, genome replication and protein expression systems. However, there is room for improvement in nearly all of those systems. We need to diversify energy sources, engineer higher-efficiency DNA replication systems and find a way to control stoichiometry in gene expression. The least developed area is the reconstitution of cell division and the associated cytoskeleton mechanics. We have mechanical and chemical means of dividing the cell but no division in response to cell cycle events. We also need a way to organize the internal components for even partitioning during division. To drive this field forward, we need to pay more attention to the standardization of methods and to safety regulations. The reproducibility of many crucial protocols is now rather poor, with hands-on training required to pass on knowledge of published protocols. The safety and security considerations of this emerging field need to be considered by regulatory agencies across the globe, developing new frameworks that will cover work with organisms from non-natural lineages. One of the biggest achievements of our field is the growth of a very collaborative international community. We are training students, pursuing foundational research and developing applications across geographical boundaries.

Reconstituting cellular elements using bottom-up biology is very valuable in revealing principles of how cells are built and function. However, what are the limitations of bottom-up biology as an approach for creating synthetic cells? What alternative approaches could be explored?

KA: There are two main approaches in our field: bottom-up (making a cell from non-living components) and top-down (simplifying existing living cells). Neither of those approaches has yet yielded a complete living synthetic cell. Bottom-up biology results in systems that are very close but not yet over the threshold to life. Top-down resulted in the simplest known living cells that are still somewhat a black box, with many essential genes of unknown function. I do not think that we need a radically different alternative approach. The field is making great progress, quickly bringing us closer to fully chemically defined living cells. I believe that, by keeping up this rate of progress, we will reach the goal of fully chemically defined artificial life before the end of this decade.

MD: In principle, there are no limitations to bottom-up approaches except for the large number of experimental conditions that needs to be explored for optimizing the (integration of) multiple functional modules. To help guide this exploration, it is very useful to pursue parallel top-down approaches where the function of artificially designed or reconstructed modules can be tested in functional cells with minimal genomes.

YE: If you are interested in using synthetic cells to glean insights into how cells function, a major limitation is the inherent simplification associated with all models. The more you simplify a model, the less accurately it represents the real thing, diminishing the reliability of your insights.

If you are interested in their use for applications, a key limitation is adhering strictly to the pathways that biology already employs when replicating biological behaviours. For example, when looking to engineer photosynthesis, one could default to the mechanisms observed in thylakoids. Yet, there might be other viable methods that are not currently recognized in biology. Can we do things differently by using entirely abiotic building blocks or by constructing biological machines that current cells lack, for example, through DNA nanotechnology[8], protein engineering, or unnatural amino acids or nucleic acids?

Another strategy, rather than building up complexity, involves starting with living cells and systematically knocking down redundant genes and pathways to yield cells composed only of their essential components, effectively creating a minimal cell. This method has been successful, but it is mostly executed on a genetic level, which can sometimes limit molecular-level insights that are more readily available with bottom-up approaches.

Recent advancements in the field have been marked by the emergence of biohybrid and cellular bionics philosophies[9], which involve hybrid systems marrying engineered living cells with synthetic cell subsystems formed from the bottom up. From a foundational biology standpoint, such hybrids may offer unique insights, shedding light on how systems and subsystems interact. It may also give us the best of both worlds when it comes to applications, allowing us to combine the power of evolved biological systems with the advantages associated with synthetic cellular systems.

T-YDT: Bottom-up biology can be valuable in revealing principles of how cells are built and function, and the reconstitution of biological elements is one part of that. However, creating synthetic cells is not restricted to cellular reconstitution but also takes advantage of the integration of non-biological parts into synthetic cells, which broadens the scope of materials and molecules that can be used. One of the challenges of bottom-up biology is to generate living systems from a minimal number of parts. Biological systems use complexity to enable the singular but intricate function of supporting life, and this molecular complexity is missing in minimal systems built from the bottom up.

To address the grand challenge of creating synthetic cells, complementary approaches would open new opportunities. In conjunction with the design and construction of synthetic cells, biophysical analysis would provide a quantitative description of synthetic cells. Further, quantitative approaches can also provide a gateway to theoretical modelling, which can be used to generate predictions for how minimal systems might behave. Further, in silico-modelled cells can be extremely powerful in mapping and dissecting the minimal requirements of a 'living' system.

MT: At present, it is necessary to create synthetic cells using existing or engineered proteins (especially synthesizing enzymes and motor proteins) when we implement complex functions into the synthetic cells. Regarding a completely bottom-up approach, there are limitations in the design and synthesis of functional proteins, although protein design and long-chain peptide synthesis will be possible in the future. Mimicking such protein functions with nucleic acid nanotechnology has been successful in that direction. Still, the spectrum of molecular functions provided by the nucleic acid nanotechnological tools is narrower and the specificity and efficiency of their molecular reactions are inevitably lower than those of proteins. Another approach is the creation of dynamic systems comparable to living systems by fully chemically synthetic molecules, which can overcome many difficulties caused by biomolecules such as instability and strong dependence on pH and temperature. Combining synthetic cells with electronic and microfluidic devices will not only provide means for external control of synthetic cells but will also allow exploration of alternative approaches to achieving non-equilibrium behaviours and complex information processing.

PS: The beauty of bottom-up biology is, at the same time, its main limitation. It would be nice if simpler systems functioned better and more controllably than complex ones but the opposite is true – if you will, that is exactly what drives evolution to higher complexity. Many of the physiological protein functions that we are attempting to implement in a minimal cell mimicry are not recapitulated in a cell-free environment, a fact that has always troubled biochemical reconstitution. The reasons may simply be missing environmental or interaction factors, but it also becomes increasingly evident that unambiguous assignments of cellular functions to single proteins are often not even possible and, rather, these functions are based on a whole cascade of heavily intertwined reactions. Yet, and that is the good news for minimal biologists, proteins may exhibit completely new and physiologically 'hidden' functions when reconstituted in synthetic systems to the point that they could replace other proteins, as we have recently shown with our work on pattern-forming bacterial proteins that can push vesicles like molecular motors do[10].

The ultimate goal of creating synthetic cells is to be able to use them for practical applications. In your view, how feasible is this goal and what advantages can be seen in fully synthetically assembled cells over bioengineered cellular systems?

MD: I think this goal will eventually be feasible, certainly if the ambition is limited to cell-like systems that are engineered to produce compounds that can be used for applications in, for example, food, medicine and biofuels. It is less certain that completely autonomous self-replicating systems could eventually be engineered that mimic the complexity of real cells. This would be most valuable for gaining basic insight into how real life works but not necessarily required for useful applications. The advantage of relatively 'simple' synthetic cells over bioengineered cellular systems is that the latter will be inherently 'multi-tasking' systems that are not necessarily optimized to (just) produce compounds in an efficient sustainable way but will also spend resources and energy on cellular processes that are unrelated to the production of desired compounds.

T-YDT: This goal is entirely feasible and there are labs that are actively working in this area. There are some advantages to synthetic cells over bioengineered cellular systems. For example, synthetic systems are tunable and programmable from a molecular level and they could be readily tailored with designed functionality. If synthetic cells could be designed to support metabolism, for example, they could be coupled to reactions, or living cells to trigger or rewire energy states. Furthermore, synthetic cells that sit close to an out-of-equilibrium state can be used as responsive therapeutics, which release a chemical upon receiving a cue from biological systems. Another exciting avenue would be to utilize synthetic cells within materials to tune properties and functions of the materials. The utilization of synthetic cellular systems to transform our daily lives with regards to energy and health remains a realizable and promising aspect of the field.

YE: Many in this research community (I am not among them) disagree with the assertion

that the primary value of synthetic cells lies in their practical applications. Instead, they view synthetic cells as tools to deepen our understanding of biology and the essence of living systems. Their perspective aligns more with how physicists perceive the study of the Big Bang. For them, exploring the intersection between the living and non-living is pivotal to comprehending the nature of life, independent of any direct applications.

I, on the other hand, think that they can, should and will be used for practical applications as micromachines exploiting the power of biological systems that can be programmed to act as therapeutic agents, sensors and bioremediation agents. In my view, we are closer to these applications than we think. There are startup companies already operating in this space.

A major advantage of these artificially assembled cells (as opposed to bioengineered cells) is derived from the fact that they are not alive. Many engineering challenges imposed by working with living systems do not apply. We are not constrained by the need to keep them 'alive', nor are we constrained by the use of natural building blocks. In principle, one can interface electronic, optic, plasmonic, inorganic and abiotic machinery into synthetic cells with relative ease, giving them capabilities that are difficult, if not impossible, to achieve with conventional cell engineering.

Equally important is the fact they cannot (yet) autonomously replicate, evolve, mutate or infect, nor are they considered genetically engineered organisms. There are therefore fewer of the regulatory, safety and public perception challenges that have hindered the progress of engineered cellular technologies with applications in the clinic and in the field.

KA: Many practical applications are already on the way. We (the royal we of the whole field, not my own lab) demonstrated how synthetic cells can make vaccines, therapeutic phages and even shrink tumours in mice[11]. Short-term biomedical applications include cancer and enzyme replacement therapies close to entering clinical trials. Synthetic cells can enable programmable, responsive therapeutics, compliant with the immune system of an individual and tailored to their specific needs[12].

Long term, the most impactful applications will take advantage of the programmability and robustness of synthetic cells, being able to tolerate unnatural or even toxic conditions. As our economies move away from using fossil fuels, finding ways to synthesize the raw materials, ideally with similar properties as petrochemicals, comes into focus. This would require expanding our ability to make toxic products at scale — an ideal application for a synthetic cell with designer metabolism.

MT: It would be relatively feasible to create synthetic cells involved in synthesizing specific materials such as those that convert light energy into chemical substances. Creating complex and sophisticated synthetic cells, such as immune cells that can move around, make decisions and heal our bodies, is not at the stage where they will be practically applied soon. However, progress is certainly on the way. Although the mRNA vaccines against COVID-19 do not have non-equilibrium dynamic functions inside, they might be regarded as the first 'proto' synthetic cells that have been applied to our bodies because they encapsulate artificial functional mRNAs (information) in lipid nanoparticles and can install mRNAs into our living cells, working to change the cells. These technologies could be extended to non-equilibrium dynamic synthetic cells as more sophisticated biomedical tools. I anticipate that creating such advanced cellular systems will be within our reach in 10 years (although not at the industrial or hospital levels).

Full programmability of synthetic cells is their most valuable advantage. As with drug-delivery systems, synthetic cells have industrial and medical advantages such as avoiding the problem of immunological rejection, being chemically synthesized in large quantities and cryopreserved, clearing ethical issues because no living cells are used, providing a method for non-biological mass synthesis of valuable drug proteins or materials even with cytotoxic properties, and no requirement to keep the 'living' state of cells. In addition, bottom-up construction of synthetic cells would allow their combination with electrical and digital technologies, creating new technologies such as the Internet of Bio-Nano Things[13].

PS: The use of synthetic cells in practical applications has already long begun, without the need of them being truly alive. In fact, the fastest progress over the last years has been made in the applied fields, where researchers have created synthetic cells that mimic only a particular aspect of cell biology, and instead are tailored to perform specific tasks, such as carbon fixation[14], or are used as therapeutics[15]. Moreover, there have been impressive breakthroughs with regard to the synthesis of complete bacterial genomes and even eukaryotic chromosomes[16,17], such that it is fair to say that, in principle, we have the ability to provide at least the functional information of biological cells in their entirety. Brought into the right biochemical environment, a fully synthetic genome may unfold all the functional features of a natural one. It may thus seem that we are already pretty close to synthesizing life. However, there are very strict conditions under which life may be run with a synthetic genome: only if we would be able to also assemble the receiving biochemical environment from scratch (for example, like a membrane container that holds all the metabolic ingredients) and to kick-start life by introducing the synthetic genome, could we rightly claim to have created a synthetic biological cell. To me, this seems still a pretty far goal, although it may be nearer than we think. In any case, I am sure that, in the meantime, we will see very exciting practical applications of 'not quite alive' cells, maybe even some that will help us dramatically in dealing with our everyday challenges in health, climate and environment.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

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