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The coming wave of confluent biosynthetic, bioinformational and bioengineering technologies

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Isak S. Pretorius[1], Thomas A. Dixon[1], Michael Boers[2], Ian T. Paulsen[1] & Daniel L. Johnson[1]

Information and energy flows form the basis of all economic activity, with advanced *technologies* underpinning both. Profound uncertainties caused by geostrategic forces have accelerated a trillion-dollar race for technological superiority. The result is an onrush of "technovation" at the nexus of synthetic biotechnologies, information technologies, nanotechnologies and engineering technologies. This article explores recent breakthroughs in integrating chip technologies and synthetic bioinformational engineering. It investigates prospects of biomolecules as carriers of stored digital data, synthetic cells-on-a-chip, and hybrid semiconductors and next-generation artificial intelligence processors. Consilience—unity of knowledge—redefines possibilities emerging from the living interface of biologically-inspired engineering and engineering-enabled biology.

The confluence of frontier technologies

Time is a constant flowing stream carrying humanity forward into encounters with reality. Just as we cannot stop time, we cannot stop our movement down this ever-accelerating stream, and we cannot avoid these encounters; we can only approach and channel the stream's currents and waves in the best possible way[1–3]. This metaphor rings true in uncertain times when we realise that the encounters awaiting us will be radically different from anything we have experienced thus far in our lifetimes.

We live in times of multiple turbulent streams of transformative technologies flowing together to move us to new realities. However, we cannot just go with the flow without understanding and anticipating future directions of confluent technologies in today's fast-paced and contested world characterised by uncertainty, turbulence, novelty and ambiguity. Macroeconomic and geostrategic forces, alongside the rise of future-shaping technologies—such as artificial intelligence (AI), machine learning, quantum computing, nanoengineering, and CRISPR DNA editing—are shaping our collective outlook in profound ways. The implications of these forces are broad and varied, presenting us with extremely dangerous risks to mitigate, as well as tremendous opportunities to seize[4]. In this unpredictable environment, flexible futures thought-leaders inform us that there is significant value in framing and reframing potential contexts and scenarios to enable re-perception of possibilities, and, in turn, clarify strategic choices and identify more and better options[5].

A continuous cycle of prospective sensemaking of dynamic scenarios and global megatrends offers an opportunity to re-direct our research agenda in the multifaceted domain of BioInnovation. By shifting our focus toward fundamental understanding of society's biggest challenges and opportunities, we become more responsive to current and future applied needs at levels of both problem selection and conceptual/experimental design. For example, how can we, as researchers, respond to the fact that flows of information and energy underpin all economic activity, and that chokehold critical technologies —caught up in the maelstrom of geopolitical and economic rivalries— support both of these enterprises (www.pwc.co.uk/megatrends)? The race for technological dominance is inextricably intertwined with evolving and challenging geopolitics in a fast-fracturing and changing world order (www.dni.gov/nic/globaltrends; www.crreports.congress.gov). These rivalries are accelerating a trillion-dollar race for technological

[1]ARC Centre of Excellence in Synthetic Biology, Macquarie University, Sydney, Australia. [2]Silicon Platforms Laboratory, Macquarie University, Sydney, NSW, Australia. e-mail: sakkie.pretorius@mq.edu.au

superiority on multiple fronts, and therein lie disguised research opportunities[6]. These geostrategic contests for the core elements of technology supremacy—such as talent, knowledge, skills and markets—have spurred an onrush of technovation at the intersection of synthetic biotechnologies (BioTech), information technologies (InfoTech), nanotechnologies (NanoTech) and engineering technologies (EngTech) (Fig. 1).

Biological systems are highly optimised platforms that harness, contour and guide global flows of information and energy. Recent advances in chip technologies (ChipTech), and connectomics, synthetic genomics and bioinformational engineering offer prospects for the design and development of nucleic-acid-based biomolecules as biochip carriers of stored digital data for memory applications in future hybrid semiconductors and next-generation AI processors[7–9]. Such research and development (R&D) aspirations are based on the notion that synthetic DNA or RNA with proper encoding could meet some of the world's ever-growing data storage and computational demands. Future biomolecular information systems, living electronics and biochips could see orders-of-magnitude leaps in long-term storage capabilities of chemically-stable data with the potential to surpass the projected gains from electronic, magnetic and optical technologies based on inorganic semiconductors.

The age of engineering biology is here, but there is little to no understanding of how, for example, biointelligence systems will integrate with the global biome or human-engineered systems. Fundamental research questions at the interface of synthetic biology and semiconductors will have to be addressed in the first instance. This will require, amongst other things, the development of computational and experimental models of biomolecular and cellular-based systems. Sustainable biomaterials for novel bio-nano hybrid architectures and circuits will have to be designed to test the limits of transient electronics. These will be essential prerequisites before hybrid biology-based semiconductor electronic systems with information storage functionalities can be fabricated and piloted. Only then would it be possible to commence scaling-up and integration of hybrid synthetic bio-electronic storage systems (www.src.org; National Science Foundation's *SemiSynBio-III* program). Before any practical application, advanced manufacturing techniques will have to be refined in semiconductor foundries and biofoundaries of the future.

As researchers survey emerging capabilities across the proliferating multiscalar disciplines of synthetic biology and bioinformational engineering to assess the likely impact they might have on future semiconductor technologies, spin-off technologies and other applications will become available for rapid adoption. These InfoTech-BioTech-ChipTech-EngTech driven innovations will enable a diverse range of enterprises to take advantage of the latest core advances, develop worldwide applications in niche areas, and contribute to opening up the chokehold global supply chains. Companies with a long-term focus, cutting-edge R&D capabilities, ample resources, and global reach will especially benefit from technological advances (www.dni.gov/nic/globaltrends; www.src.org).

The intersecting biosynthetic, bioinformational engineering and bioelectronic technologies span applications from new drug discovery and production of synthetic fuels and solar panels, to organs-on-a-chip diagnostics, growing novel resilient materials structures, through to the manufacture of biocomputing systems, biosensors and biological machines. This is the emerging world of hybrid biological-semiconductor electronic systems. We define bioinformational engineering as the engineering of biological substrates for collecting, communicating and transforming information contained in biological systems into digital information contained in opto-electronic systems[10]. We define semiconductor synthetic biology, or semisynbio, as synthetic biology research directed towards the understanding, design, and engineering of biological systems for energy efficient information processing and aligned nanoscale manufacturing objectives[11]. Hybrid synthetic bio-electronic systems are forecast to have a wide range of applications, including soft robotics biosensing; parallel diagnostics for waterways, blood markers, and the gastro-intestinal tract; and the actuation of living matter at the cellular, tissue and organism levels through engineered sensing and logic functions[12].

Throughout history, with guidance of sound ethical and regulatory principles [i.e., careful consideration of political, economic, social, technological, legal and environmental (PESTLE) factors; Fig. 2], consilient future-focussed explorations of this nature resulted in unforeseen applications that have benefitted both people and

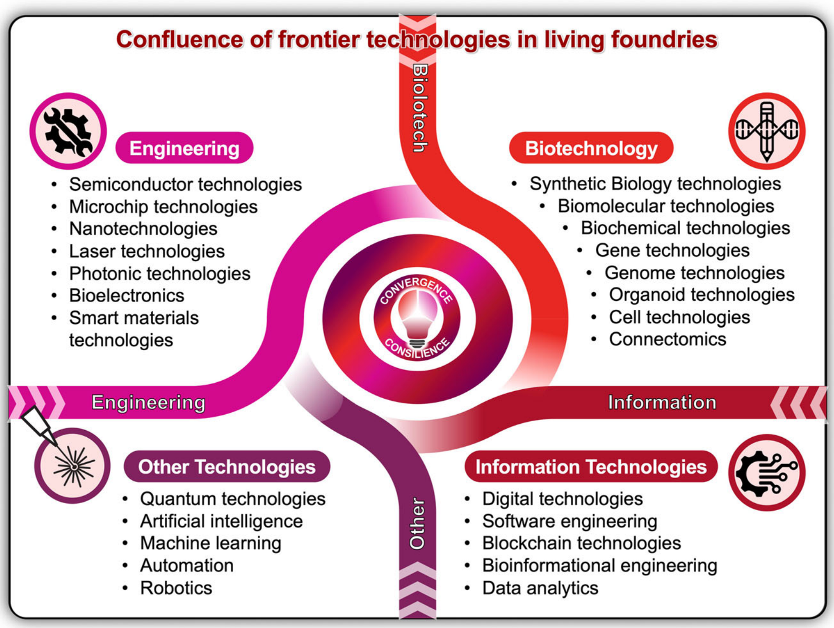

Fig. 1 | Converging critical technologies are driving much of the flows of information and energy, which underpin the world's economic performance. The intersection and integration of advanced biological, physical, information and engineering technologies form the basis of 'Technovation' and 'Bioinnovation'.

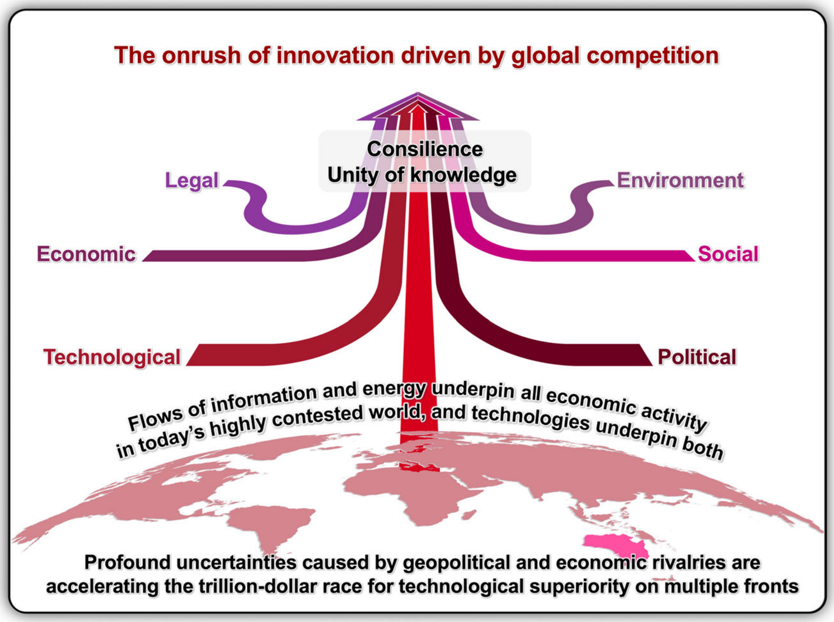

Fig. 2 | PESTLE analysis is rooted in the principle of consilience, the concordance of evidence and unity of knowledge. Geostrategic political, economic, social, technological, legal and environmental (PESTLE) forces are accelerating the race of which country holds sway over critical technologies, especially those at the nexus of synthetic biotechnologies (BioTech), information technologies (InfoTech), nanotechnologies (NanoTech), engineering technologies (EngTech), and semiconductor chip technologies (ChipTech). Consilience—the convergence of evidence from diverse, independent sources—underpins robust PESTLE analyses and strategic and dynamic decision making in the multifaceted domain of these confluent 'Bioinnovation' technologies.

planet[13,14]. This article embraces the concept of consilience—the unity of knowledge and the principle that evidence from independent, unrelated sources can converge on strong conclusions. We also look beyond the current horizon and synthesise a link between what we know now and what could be.

Advancing AI-driven semiconductor technologies chip by chip

Integrated circuits are the primary electronic devices used in compute, communication, storage and sensing applications (Fig. 3). All these applications are undergoing rapid innovation with each new generation of technology, supporting higher performance systems and permitting specialisation of design and material to targeted applications, mostly driven by the data centre, consumer, communications and automotive markets (www.crreports.congress.gov)[15,16].

Much of the global effort in search of technological superiority, and commercial and national competitive advantage is focussed on improvements to existing materials and technology platforms. Extraction of more performance per unit area (leading edge is 3 nm at present, tracking to <1 nm in coming years, noting that the node names have been detached from the physical transistor size for several years now, but an increasing density of transistors has still to be achieved by using the vertical domain) has been the dominant focus over time[11]. More recently, advances in design, engineering and packaging, e.g., to create more three-dimensional (3D) structures and units on chips, are helping to improve performance. Increasingly, improved performance is also being generated through the integration of classical chip technology with broader tools such as photonics, quantum and artificial intelligence, both at the chip itself and through the software used to control chip performance and extract its output. However, recent performance gains have come at a significant increase in both expense and power consumption requirements.

Moore's law held for >50 years, although the once-linear curve has flattened slightly in recent years, leading some to suggest Moore's Law is dead. Over time, experts in the field have periodically questioned if further progress can be made given the fundamental laws of physics. Thus far, each time an apparent limit is reached, a solution is found and progress continues, albeit at a slower pace of late. Such improvements, however, are becoming prohibitively expensive, and it is not yet apparent how to overcome the physical limitation of producing a physical wire thinner than the thickness of an atom[16].

Taking a bigger picture perspective[11,16], far less attention has been directed to completely new forms of technology that might one day achieve compute or storage performance attributes beyond even that contemplated by an optimistic extrapolation of Moore's Law, or at least allow for future performance improvements in current platforms if the laws of physics prevent further miniaturisation.

As scientific disciplines collaborate and incorporate the best elements of each other, opportunities will emerge for disruptive approaches capable of offering a compelling alternative and/or addition to existing CMOS / IC approaches[11].

In particular, the broad discipline of biology is increasingly driven by engineering thinking, for example through the DNA write capabilities now available in synthetic biology to build whole new chromosomes and genomes, and refine organisms to enable improved performance or novel attributes, including those not readily found or known to exist in nature[17,18].

Semiconductor applications across compute, communication, storage and sensing will all be enhanced through integration with biological systems. This may take the form of biosensors, biointerfaces (e.g., brain—computer interfaces), bio-integration [e.g., brain—on—chip, nucleic acid nanotechnology (NAN) storage], bioinspiration (e.g., neuromorphic compute), and tantalisingly, even compute functions and information storage itself[19]. For example, unlike current semiconductor chips, biological brains, which evolved over many millennia, do not separate analysis, processing, learning and memory. Reproducing them in silicon seems like a good idea – biomimicry and digital biology. The recent FlyWire-related publications of a fruitfly's connectome—a 3D map of *Drosophila melanogaster*'s 139,255 neurons and the 54.5 million synaptic

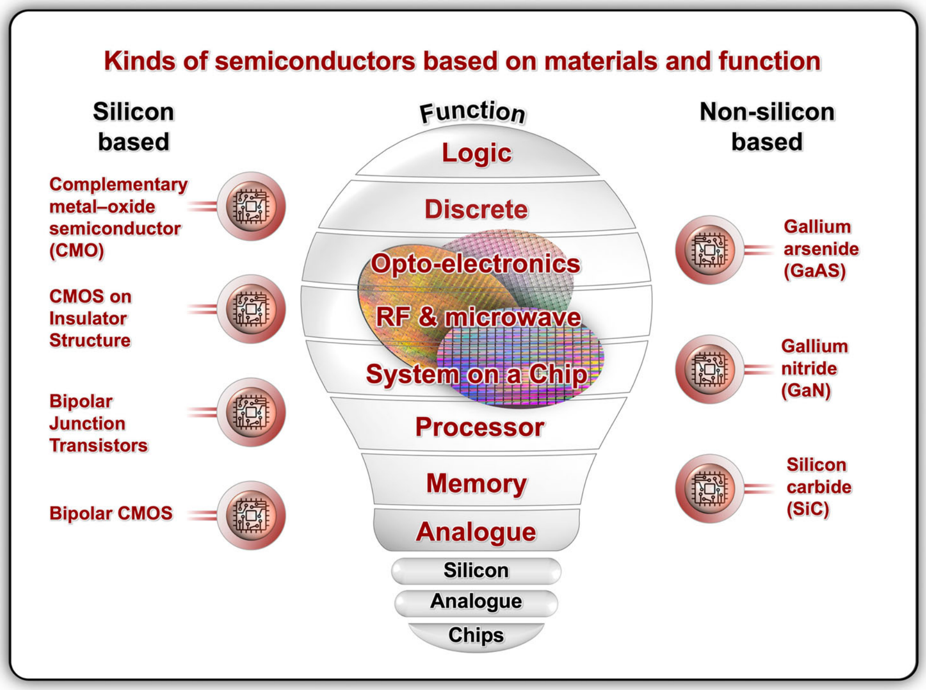

Fig. 3 | Classification of the types of chips and semiconductors. Semiconductors can be classified by function, and by the technology and material used. By function, semiconductors can broadly be grouped as (i) Analogue (simple analogue devices, amplifiers, linear regulators); (ii) Memory (many different types, volatile/non-volatile; (iii) Processor (CPU, GPU, etc); (iv) System on Chip (Processor + analogue + RF); (v) Radio Frequency and Microwave (power amplifiers, low noise amplifiers, etc); (vi) Opto-electronics (LED, laser diode, etc); (vii) Discrete (transistors, diodes, etc); and (viii) Logic (simple logic gates, NAND/NOR, up to large FPGAs). By technology and material used, semiconductors can be broadly grouped as silicone based (CMOS, CMOS-on-SOI, Bipolar, BiCMOS), and non-silicon based (GaAs, GaN, SiC).

connections between them—offer an important step in this direction[20–23]. Connectomics will enable researchers to study neural circuitry in biological brains in their entirety, and the learnings will, amongst other things, be applied to build more efficient electronic brains. As AI models made connectomics possible, it would be poetic if connectomics could, in turn, help develop better AI models and next-generation chips and AI processors over the coming years. These divergent threads of current research all find form in the pursuit of models of life, and ultimately, the unification of task-specific, abstraction-specific, and organism-specific models that enable high throughput robust in silico design. Doing digital biology requires biological training data, and that, in turn, requires new tools and methodologies for exporting biological data from biological substrates into digital systems. This is an inherently messy multi-disciplinary domain of big science. In this perspective we attempt to identify diverse, convergent and parallel fields of research and practice that are accelerating innovation in the life sciences due to their implications for information processing.

Blurring the line between biology-inspired engineering and engineering-enabled biology

Synthetic biology is an interdisciplinary field that integrates engineering concepts with molecular sciences to design and create novel tailored microbes for bespoke applications[10,14,24] (Fig. 4). Synthetic biology is a platform technology that has the power to profoundly impact diverse sectors including energy, commodity and specialty chemicals, materials, bioremediation, mining, agriculture and food production (www.roadmap.ebrc.org). Engineered microbes, such as yeast, can be used in precision fermentation to produce a diverse range of high value products using biomass, waste or industrial gases as feedstocks[25–27].

One of the exciting possibilities for synthetic biology is its convergence with artificial intelligence/ machine learning (AI/ML), and electronic integrated chip technologies. Early work in this realm has demonstrated that living cells can be used for computation. A full range of Boolean logic gates have been constructed by engineering a NOR logic gate in the bacterium *Escherichia coli* and wiring inputs or outputs to nearby cells using quorum sensing[28]. Genetic programs within a single cell have been built by layering multiple transcriptional AND gates in *E. coli*[29]. While electronic technology has reached a high level of standardization, there are only a limited number of standardized, orthogonal genetic logic gates developed by synthetic biology.

DNA is being developed as a long data storage solution, due to its capacity for high density information storage and its long-term stability[30,31]. Initial feasibility was demonstrated with the synthesis of DNA of encoded information and retrieval via DNA sequencing[32,33]. Most recently, a DNA store and compute device has been developed that can store 10 terabytes of data per mg on a DNA/colloidal cellulose acetate substrate, which has a projected half-life of 6000 years at 4 °C. Data could be retrieved non-destructively by RNA transcription and subsequent nanopore sequencing of the RNA[7,34]. An alternative approach for encoding digital data in DNA is to use epigenetic methylation of the DNA as a binary code, where the presence of a methyl group corresponds to a 1, and the absence to a 0[9].

Cells can sense and respond to a tremendous diversity of signals, this includes not only concentrations to a diverse range of chemicals, but also light, electricity, magnetism, pH and temperature. Protein switches can interconvert these various signals, for instance coupling detection of chemicals, such as methotrexate with the emission of electrons[35]. Protein switches that interconvert chemical and electronic signals could for instance be used as biosensors that output electronic

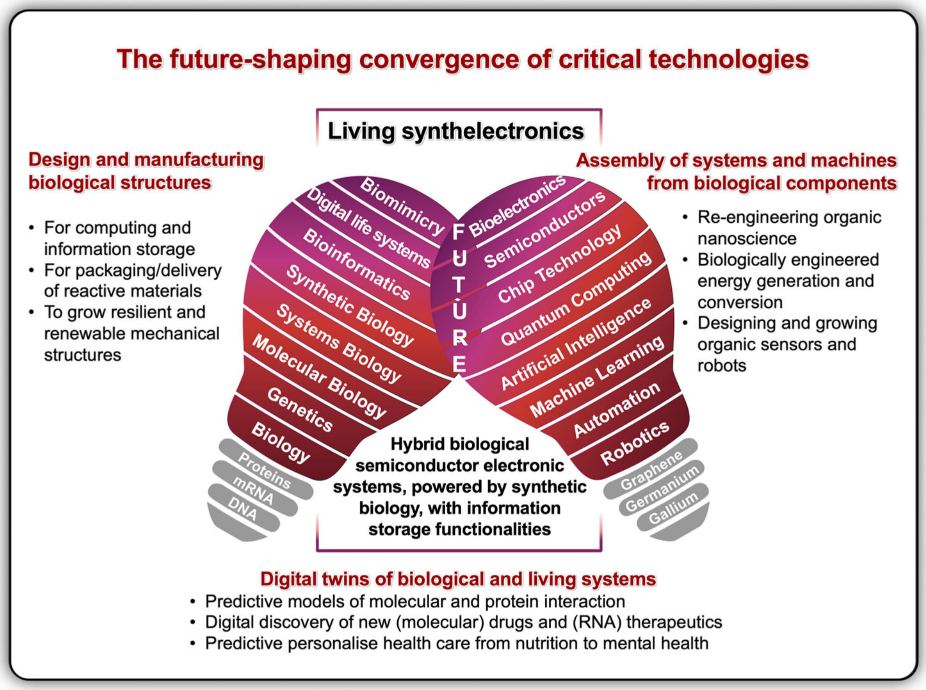

Fig. 4 | The confluence of biosynthetic, bioinformational and bioengineering technologies in 'living foundries' is redefining possibilities at the interface of biology-inspired engineering and engineering-enabled biology. For example, some of the 'big questions' in Agriculture, Health, Medicine, Environment, Data Storage and Defence could be addressed with living synthelectronics.

signatures for detection by digital devices or as electronic devices for controlling the metabolism of industrial microbes[36–40]. Light, magnetism or temperature could also be used as input signals in bioelectronic or 'cyborg' devices.

Another important confluence between digital and living systems is the development of organs-on-a-chip (OoC)[41]. These are multichannel 3D microfluidic cell cultures on an integrated circuit (chip) that simulates the activities, mechanics and physiological response of an organ. Put differently, these organs (or organoids) on a chip are OoC systems containing engineered or natural miniature tissues cultivated inside microfluidic chips to better mimic human physiology (and other functionalities). The most recent developments include lung, gut, skin, etc on a chip[42]. Combining advances in tissue engineering and microfabrication, OoC microfluidic devices have the potential to replace or reduce the use of animal models in chemotherapeutic drug testing and other biomedical research.

Recent years have seen exciting breakthroughs in the application of machine learning to protein structure prediction[43,44] and to protein design[45,46] culminating in the award of the 2024 Nobel Prize for Chemistry. The next frontier is the application of machine learning to metabolic pathway design. This opens up exciting possibilities to massively accelerate the iterative design, build, test, learn cycle of synthetic biology by combining machine learning-driven pathway and protein design with the automated engineering of new synthetic microbes using robotic platforms in biofoundries[10,14].

Finally, to paraphrase Craig Venter, 'we are now able to engineer cells, whose parent is a computer'[17]. Synthetic genomic technologies have enabled the design of a genome on a computer, followed by chemical synthesis of the genomic DNA, and replacement of the naturally occurring DNA of a cell with the new synthetic genome. This was first demonstrated with the synthetic genome of the bacterium *Mycoplasma mycoides*[17], and a subsequent minimal synthetic genome[47]. The Yeast 2.0 (Sc 2.0) consortium has built synthetic versions of each of the 16 chromosomes of the eukaryote *Saccharomyces cerevisiae* and is now working on consolidating them into a complete synthetic chromosome[18] and minimal genomes[40]. Both the *M. genitalium* and *Yeast 2.0* synthetic genome designs were modified versions of their native genomes. More recently, neochromosomes or new-to-nature chromosomes have been constructed based on highly novel designs[40,48,49]. Could the next step be a yeast cell on a chip?

Chipping away at biointelligence

A key provocation we wish to raise in this article is, what can biology do better than traditional computing? We acknowledge this is not a new provocation, but it is one that deserves revisiting. Biology is inherently well-adapted to the processing of analogue information in chemical, optical and electrical substrates, and much of this information lies beyond the molecular curtain of existing abiotic measurement. We believe the life sciences are driven by new approaches to measuring biological information, and that this is the driving force of semisynbio as an emergent field of research. It is a multi-faceted answer that most simply resolves to biology's superior ability to approach problem-oriented optimisation. After nearly a century of computer science trying to emulate actual intelligence, we have begun to see some domain-specific advances in artificial intelligence. Yet, we continue to grapple with the enormous energy and resource costs of the artificial intelligence endeavour. There are physical scaling limits for semiconductor design, physical energy limits for on-world abiotic computing, and physical bandwidth limits for information transfer via contemporary wired and wireless technologies. Biointelligence is our call to action to look beyond these scaling limits and to begin developing solutions that will leapfrog traditional alternatives, and the massive costs associated with increased performance and next-generation fabrication for traditional CMOS. It is through advancing the tools that collect, capture, translate, process and store biological information that we can push discovery in the life sciences forward. These tools have for decades interfaced digital systems with biology, and through innovation in semisynbio the rate of discovery will be accelerated again.

Sensing, reasoning, path finding, actuation, these are all capabilities for which biological systems have been highly optimised over 3.5 billion years. If we begin to look at cellular computing in the same way as we do quantum computing, the future of semisynbio becomes apparent[11]. Cellular computing, liquid computing, and DNA massive data storage are each co-processing modalities that can augment and amplify the capabilities of contemporary CMOS technology. The time and investment of 3.5 billion years of sunlight and evolutionary pathways is not something to be discarded lightly. Let's learn to work with some of the alternative intelligent architectures that the planet has to offer – biological systems.

We believe that there is real and enduring value in pursuing biological intelligence integrations. Biological signals are best collected by engineering biology and any system that interfaces with the chemical, electrochemical, thermogenic, optical, magnetic or gravitational world is probably going to benefit from integrated biological intelligence. Let's offload the sensing, processing and actuation of the biological world to biologically engineered systems[37] (Fig. 5). Synthetic biologists have often apologised for the messiness of the design-build-test-learn cycle. Yet it should be the other way around. How disappointing is it that no one can grow a semiconductor, yet a slime mould can undertake nearest neighbour computations that outmatch CMOS capabilities on a fraction of the energy load.

It is time to move beyond the Internet of Things (IoT) and to realise an Internet of Biological Things (IoBT). Rather than designing systems that are poor cousins of their biological equivalents, we should be thinking about how to interface with and network systems that are already optimised for life on Earth. At the end of the day, what do we actually use artificial intelligence for if not to mediate flows of information? Yet we have limited ourselves to digitally instantiated information and digitally structured data. There is a vast global biome of biological intelligence awaiting us if we choose to open our eyes and reimagine what computing can be[11,16].

This article is a call to action to reconsider how biological intelligence is grown/engineered, what it is used for, and how it is interfaced with the global abiotic information architecture that we have woven around human civilisation. It is a call to action on the future of chemical artificial intelligence engineered into DNA-RNA interactions, and an ask that the science-policy establishment begins to consider how life is a series of highly conserved systems optimised for solving analogue problems that stretch the current bounds of what traditional computing can efficiently achieve[13,50]. We believe the focus of the coming decades should be on integrating systems of biological intelligence with networks of artificial intelligence and developing the semisynbio chip technology that enables this integration. We don't know what this technology looks like now, and that should simply excite everyone.

Put simply, the World Wide Web could be connected to the Wood Wide Web. It is through maturing a process of nature co-design that we can push the boundaries of what intelligence is and how it is instantiated in biotic and abiotic substrates. This is the promise of semisynbio.

Leaning forward

The market capitalisation of chipmakers and semiconductor companies has skyrocketed over the past five years. For example, the leader in AI semiconductors, Nvidia, is now the most valuable company by market capitalisation in the world. While Nvidia's share price dropped initially in response to DeepSeek's R1 model release it has recovered ground and continues to be above six- and twelve-month price points. Market dynamics and political competition are inextricably intertwined when it comes to considerations of national computing power. In 1950, when Alan Turing wrote Computing Machinery and Intelligence, the most valuable companies in the world were General Electric, Standard Oil and AT&T. Then as now, the most valuable companies in the world are those that design and manufacture general purpose substrates for energy, information and intelligence. Our hypothesis is that fifty years from now the most valuable companies in the world will be designing and manufacturing semisynbio substrates that interface biointelligence with artificial intelligence for general purpose applications. These companies will design and deploy unified models of life

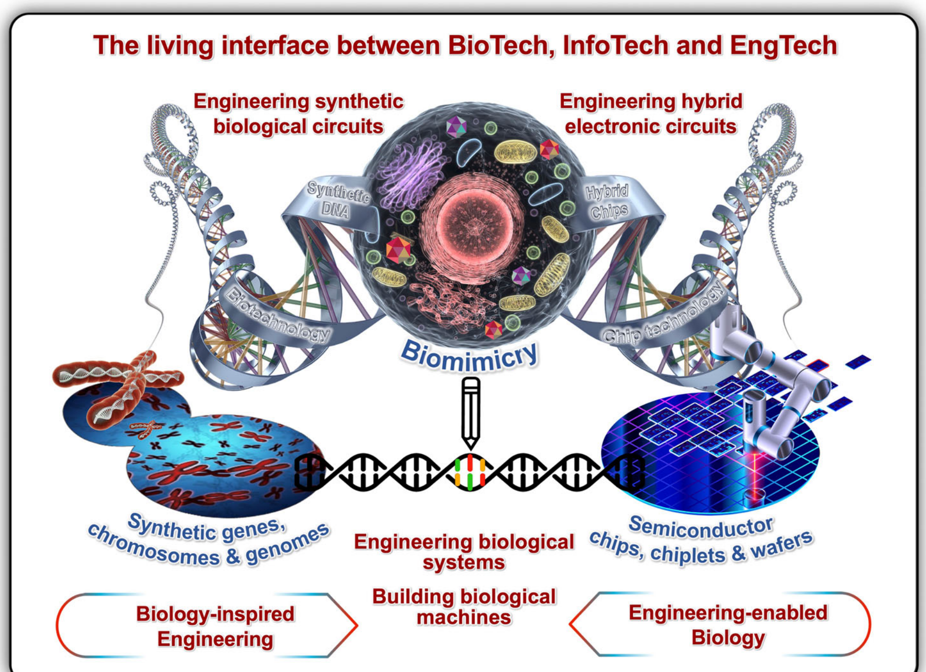

Fig. 5 | Hybrid biology-based semiconductor electronic systems are within the realm of possibility. Synthetic genomics (BioTech) and advanced AI-driven chip technologies (ChipTech) are expected to merge over the next decade and a half.

for whole-of-economy benefits, potentially enabling DNA writing based on user prompts, ecosystem modelling based on real-time biosensing, biosecurity risk ratings based on in silico challenge studies, and many other opportunities. Society's shared policy problems find their basis in biology. Responding to these problems is better enabled by interfacing our computational platforms with biological systems, and through doing so, undertaking biology-based computing. Semisynbio promises the platform tools that will enable this transformation in global sensing and compute infrastructure. Indeed, we anticipate that the timeline for new developments may be significantly accelerated due to great power technological rivalry, the associated supply chain decoupling in advanced technologies, and the looming onset of physical scaling limits for abiotic computing. New approaches to global information compute are needed within decades.

Gordon Moore chaired the Semiconductor Industry Association Technology Committee during the development of the 1992 Roadmap, which was updated in 1994 and subsequently distributed globally. These semiconductor roadmaps arguably formed the foundation for the continuation of Moore's Law through the 2000s because the global industry collectively understood its shared problem set. The semisynbio opportunity exists in a world almost thirty years prior to these groundbreaking roadmaps: technological readiness is low, feasibility is not well understood, and disparate market actors lack strong interconnection. There is fertile ground for new market entrants undertaking basic and fundamental research seeking completely new categories of information substrate technology[11,16]. This is the world of semisynbio and interdisciplinary research questions are abundant. We anticipate the development of new sensors, including quantum biological sensing paradigms[51], coupled with new modes of analogue and digital computation via electrical, chemical and optical means. Science begins and ends with measurement, we can only do science on that which we can measure. Semisynbio opens new opportunities to measure biological mechanisms previously inaccessible across difference scales of time and space. These measurement tools are prerequisites for building the basis of digital biology, and without sensing we cannot engineer new modes of computation, for example, wetware-as-a-service via digitally interfaced user-unique instances of trainable neural organoids as available from Cortical Labs in Australia.

This article helps to redefine what could be possible at the Info-Bio-Nano-Eng nexus, and the blurred line between biologically-inspired engineering and engineering-enabled biology. We believe it is possible to create tools that will enable in silico unified models of life that will fundamentally change the conduct of the life sciences with a similar if not greater impact to that of traditional computing. As the physical and biological worlds are set to integrate, almost all aspects of society and the economy stand to benefit, and the implications for global geopolitics will be profound.

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I.S.P. conceived, developed, and edited the manuscript. T.A.D., M.B., I.T.P., and D.L.J. contributed sections of the article and significantly helped with the refinement of the paper.

Competing interests

M.B. is the founder and Chief Executive of Atto Devices, and he is also an employee of Macquarie University. D.L.J is a Director of Atto Devices. The other authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Isak S. Pretorius.

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