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THE STANFORD EMERGING TECHNOLOGY REVIEW 2023

A Report on Ten Key Technologies and Their Policy Implications

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BIOTECHNOLOGY AND SYNTHETIC BIOLOGY

KEY TAKEAWAYS

- Biotechnology is burgeoning, contributing around 5 percent to US GDP with a historical doubling time of about seven years.
- Synthetic biology is third-generation biotechnology, complementing domestication and breeding (the first generation) and gene editing (the second generation).
- The United States is struggling to grasp the scale of the bio-opportunity, the strategic ramifications unique to network-enabled biotechnologies, and the possibilities and perils of distributed biomanufacturing.

Overview

Biotechnology depends on molecular and cellular methods to realize breakthrough products or services.[1] As representative examples, the Stanford biotechnology community in 2023 pioneered the bioengineering of skin microbes to combat skin cancer,[2] realized industrial-scale translation for yeast-based brewing of essential medicines,[3] and achieved full resolution imaging of precursor synthetic cells, setting the stage for a "life race" akin to last century's space race.[4]

Biotechnology-based products and services are already deployed at scale, having impacts equaling or exceeding those of more mature technologies due to the intrinsic power of biology. Yet leaders of one Fortune 100 company noted that biotechnology today is like a "snowflake on the tip of an iceberg."[5] Stated differently, most of biotechnology hasn't been imagined yet. This dual

reality (i.e., *applications* enabled via immature and still-emerging *methods*) creates the potential for confusion or bad decisions.

The ancient Greek word *sunthesis* means "composition" or "a putting together." Synthetic biology thus focuses on fundamental methods that improve the composition and putting together of living systems, primarily at the molecular to cellular scales but increasingly at the tissue and microbial population levels. Building on genetic engineering, synthetic biology is not limited to genes as found in nature but whatever can be engineered and composed for specific purposes (e.g., an enzyme evolved by humans to catalyze carbon-silicon bonds).[6] Just as airplanes and rockets enabled humans to overcome some constraints of land and gravity, synthetic biology enables humans to develop living organisms beyond the constraints of lineage, such as petunias that emit light (i.e., nightlights that need watering instead of an electrical outlet).[7]

A 2020 National Academies report valued the US bioeconomy at about 5 percent of GDP, or more than $950 billion.[8] A 2020 McKinsey report identified four hundred synthetic biology projects currently in the R&D pipeline, estimating such innovations could add $4 trillion in direct economic impacts over the next ten to twenty years.[9] This projected pace of bioeconomic doubling over the next seven or so years tracks the historical record.[10] Biotech venture capital funding was $29.7 billion in 2022, the second-highest year on record, following the record $38.7 billion invested in 2021.[11]

Estimates of niche and still nascent synthetic biology markets vary widely, from $37 billion by 2028 to $100 billion by 2030.[12] A conservative estimate by the Congressional Research Service reported that US government research funding for synthetic biology increased from about $29 million in fiscal year 2008 to nearly $161 million in fiscal year 2022. Many first-generation synthetic biology companies have struggled or worse, suggesting that some ideas need revisiting or more support and that translation efforts would benefit from smarter strategies.[13]

In principle, anything that can be encoded in DNA could be grown when and where needed. In other words, biology can be regarded as the ultimate distributed manufacturing. For this reason, some have called for biology to be recognized as a *general-purpose technology* akin to computing, triggering associated calls for strategy and leadership.[14] As one representative far-reaching vision, in 2018, the Semiconductor Research Corporation outlined an ambitious twenty-year synthetic biology road map with its ultimate goal being to enable bottom-up construction of microprocessors.[15]

A Synthetic Biology Primer

DNA is both physical hereditary material and a digital code of life. DNA can be represented abstractly as four bases (A, C, T, and G). Particular sequences (i.e., orderings) of bases encode different living functions including biomolecules. Cells consist of encoded molecules and realize different behaviors and functions by producing the various molecules at the appropriate time and place.

DNA sequencing and synthesis are two fundamental technologies underlying synthetic biology. Sequencers are machines that read the precise series of As, Cs, Ts, and Gs encoding genetic information, while synthesizers write user-specified sequences of As, Cs, Ts, and Gs. The cost of sequencing a human genome has fallen from $10,000 to $600 in the last decade,[16] while the cost of gene synthesis has dropped a hundredfold from 2005 to 2015.

Improvements in DNA sequencing methods were jump-started and driven initially by government support for the initial human genome sequencing project. This public investment was sufficient to kick-start significant downstream market opportunities that

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have since driven ongoing innovation and improvement. There has been no equivalent public support for improving DNA synthesis. Improvements in DNA synthesis have been sporadic and dependent on private capital, and the cost of commercially available gene-length DNA synthesis services has not improved significantly in the last six years.[17]

SARS-CoV-2's arrival in Switzerland in February 2020 illustrates the powerful potential of DNA sequencing and synthesis together, combined with the information transmission capabilities of the internet. Before the pandemic could naturally arrive, a researcher in China sequenced the virus's genome, uploaded a digital file representing that genome to the internet, from which a Swiss researcher downloaded the information, ordered the DNA, reconstructed the genome, and infected cells in the laboratory, accomplishing all this twelve days before the actual pandemic arrived over the Italian border.[18]

This example suggests that the "superpower" of the internet—the ability to rapidly move information—might usefully and ultimately recombine with the superpower of biology, namely the ability to grow and assemble complex objects locally. Stated differently, a DNA synthesizer is a "1-D printer," but the polymer it prints (i.e., DNA) in turn programs biomolecules that construct and assemble 3-D objects with atomic precision. DNA sequencers and synthesizers connected to the internet could thus routinely allow researchers to move viruses around the world faster than a pandemic can spread. Developed wisely, such capabilities could lead to biodefense and public health systems operating at light speed. Ignored or mismanaged, such capabilities could result in widespread access to bioterror capacities or worse.

Along with DNA reading and writing, synthetic biology is slowly advancing our ability to coordinate the composition of living systems. One line of work seeks to enable coordination of labor via reliable reuse of materials, measurements, and models. Example projects include developing standards for quantifying gene expression levels inside cells,[19] akin to how telegraph engineers long ago struggled to make and maintain communication systems using copper wire prior to the invention of the Ohm as a common unit of resistance.[20] Such fundamental research enabling coordination of labor allows many more to learn about, safely participate as citizens of, and benefit from the world of emerging biotechnologies and enables experts to realize products of increasing complexity more quickly. Such foundational research is almost entirely unsupported domestically at present but is increasingly a topic of discussion for international standards-setting bodies.

More ambitious projects seek to learn to construct artificial (or synthetic) cells entirely from scratch.[21] While there are many applications of such cells, the fundamental motivation is to make routine the engineering of living systems. For context, no natural cell used in any biotechnology process is fully understood. All natural cells require a significant number of essential genes whose encoded functions remain entirely unknown. Thus, contemporary biotechnology workflows remain Edisonian (i.e., tinker and test). By learning to construct cells from scratch, synthetic biologists are seeking to architect an operating system for life at its most fundamental level.

Key Developments

Synthetic Biology Applications

Being able to engineer and thus to modify existing cellular functions, synthetic biology has been able to make contributions to:

- **Medicine** DNA and RNA synthesis underlie all mRNA vaccines, including those for COVID-19. Synthetic biology also enables more sophisticated engineering of cell-based diagnostics and therapies, from bioengineered immune cells to microbiomes.[22]

- **Agriculture** Synthetic biology has been used to cultivate drought-resilient agricultural crops, enhance food security with indoor farming, offer plant- or cell-based meat cultivation, and improve food safety through easier tracing of contaminated products.

- **Manufacturing** Synthetic biology enables cells to be programmed as efficient, sustainable factories for medicinal drugs, fuels, and other useful substances.[23] One estimate expects "as much as 60 percent of the physical inputs to the global economy could, in principle, be produced biologically."[24]

- **Sustainability** Synthetic biology enables carbon-neutral and carbon-negative manufacturing. Developments in electrobiosynthesis (i.e., growing biomass from CO_2 and electricity)[25] and mycological manufacturing[26] are particularly compelling. Direct and indirect impacts of synthetic biology on biodiversity and conservation biology are gaining increasing attention.[27]

Artificial Intelligence in Synthetic Biology

In recent years, we have also seen computational methods enabled by artificial intelligence (AI) realize significant advances in predicting the three-dimensional shapes of proteins (one important class of biomolecules) from DNA sequence information. The specific shapes of proteins determine their function in the body.

Traditionally, determining protein shapes required the use of expensive experimental methods such as X-ray crystallography. However, in 2022, researchers used AI to predict the structures of more than two hundred million proteins from some one million species directly from their DNA sequence information, representing nearly every known protein on the planet.[28] About 35 percent of the predictions have been found to be as good as experimentally determined structures and perhaps an additional 45 percent are interesting enough to guide research. Similar methods are being developed to predict RNA structures.[29] Note, however, that structure alone may be insufficient to predict the function (i.e., the actual physical or biochemical behavior of the resulting biomolecule).[30] The success of such computational methods often depends on large sets of training data obtained (thus far) via decades of experimentation by far-flung research communities.

AI-based approaches are also being developed to aid in the design of genetic constructs.[31] Imagine a ChatGPT-like capacity enabling natural language requests that result in DNA-sequence designs for functional biomolecular systems. For example, "Hey Siri, get me a plasmid that will make *E. coli* smell like bananas when growing and wintergreen when dormant" could soon result in a well-designed DNA construct for synthesis.

Physics in Synthetic Biology

Computational methods in biology also depend on the validity of our mathematical representations of the physics of living systems. Such representations are well established for structural biology (i.e., how atoms are organized to comprise proteins and nucleic acids) but are less mature for cellular-scale

systems (i.e., how molecules are organized to compose cells).[32] The application of colloidal hydrodynamic modeling to cellular-scale systems has recently enabled rational design of cellular-scale systems.[33]

Over the Horizon

Impact of Synthetic Biology

Future applications of synthetic biology may include:[34]

- Biomanufacturing of chemicals, solvents, detergents, reagents, plastics, electronic films, fabrics, polymers, agricultural products such as feedstock, crop protection solutions, food additives, fragrances, and flavors[35]
- Synthetic fuels that are energy dense enough for transportation produced by recycling carbon from sources such as cellulosic feed stocks, crops that make oil, and agriculture and municipal wastes[36]
- Nutrient-dense, drought-resistant crops that improve food and water security[37]
- Concrete that fixes carbon while curing and construction materials embedded with biomolecular functions that "heal" cracks[38]
- Biologically active paint that prevents biofouling of ship hulls or reduces pipeline corrosion[39]
- Biomining of critical minerals and bioengineered materials produced locally, contributing to more efficient, robust, and secure supply chains[40]
- A global biosecurity infrastructure that rapidly detects the emergence of pathogens anywhere on Earth and enables the rapid manufacturing of tailored vaccines, testing equipment, rapid therapeutics, and other treatments at the source of the outbreak within days[41]

Challenges of Innovation and Implementation

STRATEGIC VISION

Most discussions of and investment in biotechnology are understandably motivated by and focused on applications of biotechnology. However, from a governance and strategy perspective, advances in underlying methods that change what biotechnologies are possible are where strategies take root, where leverage begins, and where a strategic vision is most needed. US federal policy seeks to advance synthetic biology and biotechnology more broadly. Several building blocks are in place, including the following:

- The congressionally mandated National Engineering Biology Research and Development Initiative was established by Public Law 117-167, Section 10402—commonly known as the CHIPS Act of 2022.
- The National Biotechnology and Biomanufacturing Initiative was launched under Executive Order 14081 of September 2022.[42] It seeks whole-of-government action to increase domestic biomanufacturing capability, expand market opportunities for bio-based products, drive R&D, streamline regulation, and improve biosafety and biosecurity.[43]
- National Security Memorandum 15, "Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security" (NSM 15), signed in October 2022, establishes as a goal that the United States must "fundamentally transform its capabilities to protect our Nation from biological threats and advance pandemic preparedness and health security more broadly for the world."
- A report from the President's Council of Advisors on Science and Technology (PCAST), *Biomanufacturing to Advance the Bioeconomy*, was submitted to the president in December 2022 and is discussed below.[44]

Other proposals have gone further than the vision laid out in current federal policy. For example, the Special Competitive Studies Project calls for biotechnology moon shots to advance the underlying science and technology behind construction of fully synthetic cells; the alignment of incentives for biotechnology commercialization such as the local biomanufacture of medicines; and the building-out of infrastructure to support the biotechnology enterprise, including research and manufacturing facilities, data management policies, a skilled workforce, and international cooperation with likeminded nations.[45]

The National Academies of Sciences, Engineering, and Medicine reported that the United States has pioneered advancements in biotechnology. But their report, along with reports from others, also noted the emergence of significant competitors, China and Europe in particular, and therefore that any US lead cannot be taken for granted.[46]

The PCAST report mentioned above identified three challenges that must be addressed to ensure the United States maintains its leadership and fully exploits the benefits of the bioeconomy:

- The lack of an adequate US biomanufacturing capacity and workforce
- An outdated US regulatory process for many new bioproducts that can delay or stop their commercialization
- An integrated and overarching bioeconomy strategy to help guide federal agencies in managing the development and transfer of these biotechnologies toward social and economic advancements

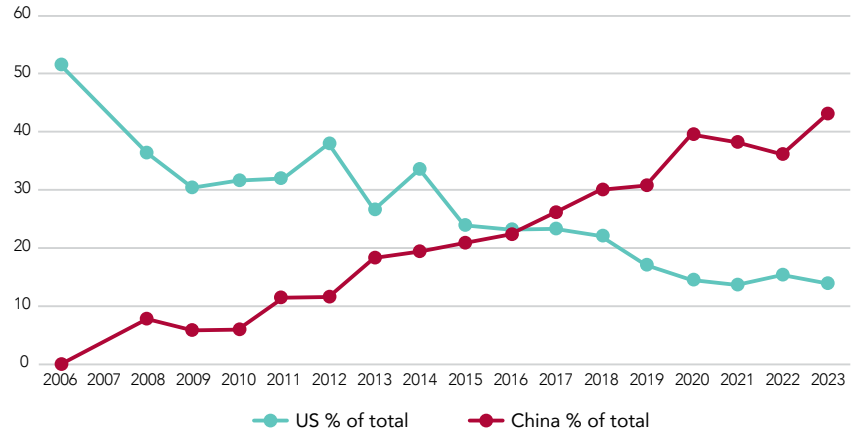
As an illustration of the first bullet above, consider the International Genetically Engineered Machines (iGEM) Competition, which involves teams from all over the world composed of self-funded students enrolled in high schools or institutions of higher learning, or from people working in community labs. The competition, which began at the Massachusetts Institute of Technology in 2003, gives each team a kit with a variety of genetic parts and asks them to use their own laboratories to create bioengineered organisms that address a local need or problem. About one hundred thousand students have participated in iGEM and many iGEM alumni are now leaders (e.g., the chair of the US Congress's National Security Commission on Emerging Biotechnology is an iGEM alum). In 2003, the competition had only American teams. But over the last decade, teams from China have outnumbered US teams by a factor of three, and in 2023 there were 175 teams from China compared to 56 from the United States (see figure 2.1). European teams have also been increasing their numbers.

STANDARDS SUPPORTING R&D AND TRANSLATION

One key early institution for synthetic biology was the Registry of Standard Biological Parts operated and funded by the iGEM Foundation, offering a collection of genetic parts used in the synthesis and assembly of new biological components, systems, and devices. The "standard" adjective in "Standard Biological Parts" means that any given part is compatible (to a limited degree) with other similarly standardized parts and can therefore be integrated into larger and more complex assemblies while still maintaining the compatibility format of the standard.[47] Users of the registry are encouraged, but not required, to contribute data and develop new parts to enhance the resource. Today, the Registry contains over twenty thousand parts.

This one physical assembly standard, however, is not enough. For example, biological data obtained in one laboratory needs to be usable across the entire synthetic biology community. Computational models of biological processes and organisms should be usable across the entire community to validate results. Such interoperability requirements

FIGURE 2.1 Percentage of iGEM teams from the US and China



Source: iGEM, Team List of iGEM Championship (data for 2008 through 2023); iGEM, Schools Partipating in iGEM 2006 (data for 2006).

often drive the need for standards that specify what data elements must be retained, what annotations need to be provided, and in what format they must be retained. These standards are necessary to ensure that biological data and computational models are usable across the entire community.

The effort to develop standards must include academia and actors from the private sector. The lines between research and specific applications are particularly fuzzy for synthetic biology in that private-sector firms support a substantial amount of research in the field. These firms include companies dedicated to exploring the commercial potential in synthetic biology, from start-ups to major pharmaceuticals, as well as firms that have historically been focused on information technology.

The US government could play a critical role in supporting technical standards underlying biotechnology. Traditionally, the US approach to standards development is more market driven than, for example, the European approach.[48] But given that the market is unlikely to develop standards that can support collaborative work in both academia and the private sector, a degree of government involvement in this enterprise would not be inconsistent with the intent expressed in the CHIPS Act of 2022 (discussed in chapter 8 on semiconductors) to support strategically important fields.

SUSTAINED R&D FUNDING

Although mRNA vaccines came into widespread public view in 2021, their history began some thirty years ago, with academia and industry both playing key roles in advancing the science.[49] These scientists improved the understanding of the mRNA pharmacology and made novel insights in immunology, laying the foundation for the next-generation mRNA vaccines. This history strongly suggests the need for "patient capital"—that is, investment in R&D that is sustained in times of ebb and flow in the pace of scientific advancement.

Also, from a competitiveness perspective, as the scope of bio-opportunities grows, the total amount

of funding for basic research and translation must also grow. All of about forty Stanford faculty interviewed for this chapter clearly highlighted the issue of limited funding for foundational biotechnology research; one recent Nobel laureate reported that over 90 percent of her research projects remain unfunded.

Policy, Legal, and Regulatory Concerns

ENVIRONMENTAL AND SAFETY RISKS

New organisms not found in nature raise concerns about how they will interact with natural and human environments. For example, engineered cells in the human body can lead to unanticipated adverse effects. Bioengineered organisms that escape into the environment and possibly disrupt local food webs or displace natural species have long been a concern. Importantly, synthetic biology itself offers the possibility of bioengineering organisms from scratch that are incapable of escaping or evolving.[50] Such examples highlight how political and cultural concerns need not wait to be expressed and addressed; governments could facilitate and underwrite more active realization of the public interests in emerging biotechnologies.

NATIONAL SECURITY, PANDEMIC PREPAREDNESS, AND PUBLIC SAFETY CONSIDERATIONS

As the science and technology of synthetic biology becomes increasingly available to state and nonstate actors, there are legitimate concerns that malicious actors will create organisms harmful to people or the environment. For example, polio, horsepox, SARS-CoV-2, and influenza have been synthesized from scratch in laboratories.

The US government does have an explicit policy for the oversight of research in the biological sciences, known as "dual use research of concern,"[51] focused on certain high-consequence pathogens and toxins. The policy is intended to preserve the benefits of such research while minimizing the risk of misuse of the knowledge, information, products, or technologies associated with it. Nevertheless, the policy covers only research funded or conducted by the US government, research involving one or more specified agents on a US government list, or one of several specific types of experiments. Moreover, despite growing concerns, such research is not per se illegal under international law (the Biological Weapons Convention) as long as it is consistent with the general-purpose criterion in Article I of the convention, leaving some to argue that education is the only way to significantly reduce the likelihood that such work will be conducted.[52]

GAPS IN REGULATORY REGIME

The PCAST report highlighted the inadequacies in the current regulatory process for approving biotech products. The current regulatory regime is the Coordinated Framework for the Regulation of Biotechnology, which splits biotech regulation among three different federal agencies, the Environmental Protection Agency (EPA), the US Department of Agriculture (USDA), and the Food and Drug Administration (FDA). The oversight is based on the end products' characteristics and unique features rather than on their production method.[53] However, some have voiced concern over whether the Coordinated Framework is sufficient given the increasingly complex, novel, and broad applications of synthetic biology that "go beyond contained industrial uses and traditional environmental release."[54]

ETHICAL CONSIDERATIONS

Different religious traditions may have different stances toward life and whether the engineering of new life forms violates any of their basic precepts. Often classified as potential nonphysical impacts, the effects of synthetic biology when considering these religious concerns are difficult to predict in advance.

In the words of a Wilson Center report on this topic, concerns about nonphysical impacts are primarily "concerns about the appropriate attitude to adopt toward ourselves and the rest of the natural world."[55] The report notes that these concerns involve "the possibility of harm to deeply held (if sometimes hard-to-articulate) views about what is right or good, including . . . the appropriate relationship of humans to themselves and the natural world." The report also notes that many people disagree about "whether a particular activity threatens these values, how we should reduce nonphysical harm, who should be responsible and what may be sacrificed along the way. . . . We do not always agree about what counts as a nonphysical harm, because we disagree about what is human well-being . . . [and this is because we embrace] different ethical frameworks."

In short, policymakers will have to be aware of and able to navigate issues and aspects of synthetic biology such as those described above if they are to help guide the development of the field and the increasing diversity of the resulting biotechnologies.

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