

## Digitally-driven Bio Innovation Convergence in the Bioeconomy: a U.S. Perspective

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21<sup>st</sup> Century innovation and the rapidly growing bioeconomy increasingly will be driven by the convergence of the life sciences, digital tools and data, and engineering. For simplicity, I will call this paradigmatic shift Digitally-driven Bio Innovation Convergence, or “DBIC.”

Cutting-edge R&D and disruptive innovation based on DBIC already are beginning to reshape business model strategies, develop new products and services at industrial scale, replace or disrupt traditional markets and supply chains, and attract significant new investments and collaborations.

Nowhere is the broad impact of DBIC likely to be greater than through the exponential growth of synthetic biology or engineering biology. Advances in our ability to read, write, transform, and debug DNA have made genetic engineering a transformational technology with broad business applications across multiple markets.

It involves using Digital Bio technologies both to engineer or re-design living organisms for novel or enhanced functions and, over time, to design and construct useful new bio-based parts, materials, and organisms that could open the door to making and marketing new products that cannot be made at scale today. DNA synthesis made possible by Digital Bio, for example, enables the *de novo* generation of genetic sequences that specifically program cells for any of a wide range of purposes.

As noted in a recent U.S. National Academies report, “synthetic biology [or engineering biology] collectively refers to concepts, approaches, and tools that enable

the modification or creation of biological organisms.” Synthetic biology not only builds on a robust Digital Bio tools revolution, including genetic circuits and digitally redesigned genomes, but it also provides business with new general purpose Digital Bio technology platforms for multi-use applications that often break down traditional disciplines, supply chains, and business sector boundaries.

This relatively new field represents a truly international enterprise with global scope as more than 40 countries now have synthetic biology national strategies or comprehensive bio-innovation initiatives that include them. The United Kingdom and China, for example, not only regard synthetic biology, enabled by DBIC, as one the most critical technologies for next-generation economic growth and societal well being in their countries but also have developed comprehensive synthetic biology national strategies.

This article, however, focuses on DBIC and synthetic biology in the United States. In particular, it examines why synthetic biology and DBIC have become so important to U.S. strategic thinking about innovation and the bioeconomy, and what is driving the rapid confluence of the bioeconomy, synthetic biology/engineering biology, and DBIC in the United States.

### 1. Setting the Context

The Digital Bio revolution enabling the bioeconomy is based on the confluence and self-reinforcing interaction of at least seven key drivers and paradigm shifts. They, in

turn, are reshaping Digital Bio R&D, business strategies, and investments in the United States. For simplicity, this article summarizes these seven key drivers under the following headline categories: (1) Digital Bio Convergence as the new Paradigm; (2) the Digitalization of Biology and Life Sciences as an Information Technology; (3) the Industrialization of Biology; (4) Making Biology Easier to Engineer and More Predictive; (5) DBIC as a Tools Revolution; (6) “Cell as Factory”: Biology as a Next-Generation Manufacturing Platform that Leverages Biology as Technology; and (7) Accelerating Investments and Innovating Disruptive DBIC Business Models.

These advances are based largely on our increasing technological capacity to link the biological world with the digital one, and to accelerate the move from today’s design-build-learn iterations to tomorrow’s truly predictive biology that can be digitally simulated, and reliably designed and constructed. The U.S. National Academy of Sciences and others have concluded that the 21<sup>st</sup> Century will be the era of biology, a century of grand synthesis driving new innovation and the bioeconomy.

Bio-based markets enabled by DBIC already are significant in the United States – representing more than 2.5% of gross domestic product in 2014, or more than \$350 billion in economic activity. The full range of U.S. bio-based economic activity is estimated to have been more than \$1.5 trillion in 2012, or nearly 10% of U.S. GDP.

But the biggest market opportunities remain ahead. Estimates are that the bioeconomy as a percentage of U.S. GDP likely will more than double by 2025. And many believe this is too conservative. Recent estimates suggest that the value of the DBIC biology stack may approach 20-25% of U.S. economic value in the next 25 years.

As a result, the U.S. foresees broad applications of emerging DBIC tools and technologies and core synthetic biology platforms for multiple uses in new bio-based materials, products and services; new markets for Digital Bio enabling tools, platforms, and services; next-generation advanced manufacturing platforms; DBIC-oriented Big Data, AI, and data analytics; and new bio-based applications in traditional digital markets such as semiconductors,

computing, or massive storage.

## 2.1 Digital Bio Convergence as the New Paradigm

Solutions to complex and multi-faceted societal and scientific challenges increasingly depend on research and innovation at the intersection of multiple disciplines that go beyond interdisciplinary approaches to create new, integrated modes of thought. The emerging American consensus is that DBIC captures at least two new dimensions. First, as an MIT faculty study concluded, it involves “the merging of distinct technologies, processing disciplines, or devices into a unified whole that creates a host of new pathways and [market] opportunities.”

Second, it involves the formation of the web of partnerships involved in supporting such scientific investigations and enabling the resulting advances to be translated into new forms of innovation and new bio-based products and services. In many cases, it changes fundamentally the questions we now can ask and the answers to them, including business models and value chains, corporate strategies, and workforce deployment.

## 2.2 The Digitalization of Biology and Life Sciences as an Information Technology

Biological systems and the digital world increasingly are interchangeable, interconvertible, and interoperable. Synthetic biology’s increasing ability to move back and forth between the “1”s and 0’s” of the digital world that has powered ICT’s for more than 50 years and the ACTG genetic letters of the biological one increasingly powers the bioeconomy. By digitizing living organisms, we now can send the “program” for an organism over the Internet and recreate or construct it anywhere around the world.

In many ways, we finally are realizing that biology should be viewed as a complex information science. It also is an increasingly automated enterprise that relies on cutting-edge digital technologies, artificial intelligence, machine learning, and data analytics.

The key point is that we increasingly can make living organisms programmable. This allows innovative companies to link biological systems with the digital and

cyber-physical world as we use the logic of ones and zeroes not only to understand life but also to design new products and services.

### 2.3 The Industrialization of Biology

The lab to market push for DBIC and synthetic biology is accelerating and poised for rapid growth as they move out of university research centers and national labs into a broad portfolio of commercial applications at scale. An important part of the lab-to-market trend is the Industrialization of Biology, or the “biologizing” of industries and services. The goal is to create commercially competitive products and services at scale based on DBIC and engineering biology that can serve as a foundation for the bioeconomy, more sustainable economic growth, and smart society solutions.

For example, the National Academy of Sciences Board on Life Sciences convened a national task force of experts to examine the Industrialization of Biology. Our initial study focused on the industrialization of biology to accelerate the advanced manufacturing of chemicals largely for four reasons – the size of the markets for high-value and high-volume chemicals, the beneficial societal impacts that could be achieved (including the replacement of fossil fuel sources), the readiness of business to move in this direction, and the timeliness of new technological advances that enable it.

In the course of our study, we found that \$4 trillion of products are made by chemical transformations globally but that only about 5-7% of the potentially “addressable markets” have been addressed biologically. In addition, as our report noted, this industrialization of biology also “will lead to more complex chemical structures and composite nanomaterials, which require precise control over dozens of genes.”

In the course of our study, we developed a technological and organizational roadmap for the industrialization of biology in advanced chemicals. We concluded that, within 10 years, biological synthesis and engineering can be on a par with, or superior to, chemical synthesis and engineering for chemical manufacturing covering at least 50% of all

to chemical transformations – i.e., potentially \$2 trillion in addressable markets for expanding the bioeconomy and replacing the oil barrel.

### 2.4 Making Biology Easier to Engineer and More Predictive

At the heart of many emerging DBIC and synthetic biology strategies is the concept of “making biology easier to engineer” and trying to make biology truly predictive, replicable, and re-usable. This, however, requires combining engineering principles and mindsets such as abstraction, modularity, standardization, and iterative design-build-test-learn cycles with digital technologies and electrical engineering insights adapted to the life sciences and biomedicine.

The underlying concept of modularity and abstraction, for example, is that complex problems can be broken down into smaller or more modular technical challenges or problem sets. As a result, complex or novel bio products based on biological parts, chassis, or assemblies now can be constructed by analyzing, modeling, testing and building new genetic circuits, parts, chassis, and subsystems.

Standardization is another prerequisite. One only needs to look at the engineering of Roman Empire roads or aqueducts, at the role of standardized tools, such as the Whitworth screw, in enabling the industrial revolution in the 19<sup>th</sup> Century or, more recently, the standardized interoperability of ICTs to recognize the power of standardization and metrology.

As a result, American companies are deeply engaged in developing new approaches to measurement for commercial applications in synthetic biology. This includes commonly accepted measurements for the effect of biological context and evolutionary dynamics, standards to enable exchanges, reuse, rules for common assembly, common reference points, reproducibility, and shared data and open innovation models for new collaborations.

### 2.5 DBIC as a Tools Revolution

In many ways, DBIC and synthetic biology represent a tools revolution propelled by “exponentials”. Each tool

in the DBIC toolkit – whether sequencing, synthesis, high throughput manipulations of biomolecules, AI/machine learning analytical tools, genome engineering tools, bio-CAD software, or highly automated processors – can be considered an “exponential” because it is accelerating faster than the pace of Moore’s Law and providing far greater functionality at ever reduced costs. As important as each tool is individually, the real power and transformational impact likely will come from the synergies achieved by combining these “exponentials” or “mixing and matching” them.

For example, American companies are collaborating with each other, as well as with universities and government labs, to develop and commercialize DBIC foundational tools in three principal areas. The first focuses on DBIC methods and technologies such as DNA synthesis and assembly, genome scale engineering tools, and analytical tools for metabolic and regulatory networks that mediate biological functions.

The second covers the development of DBIC platforms for synthetic biology. It involves companies working on: biological design principles; genetically tractable organisms or chassis; minimal cells and *in vitro* systems; tools for plant systems and various microorganisms; and biocontainment mechanisms.

Finally, some of the most extensive efforts take advantage of digital advances and insights from electrical engineering by adapting them to DBIC and engineering biology. In particular, this focuses on new computational tools, bioinformatics resources, predictive modeling and simulation capabilities, bio-CAD and other types of software, and data analytics for synthetic biology.

## 2.6 “Cell as Factory”: Biology as a Next-generation Manufacturing Platform that Leverages Biology as Technology

The United States increasingly sees the “killer apps” for engineering biology and the Digital Bio revolution as next-generation advanced manufacturing and knowledge-intensive services. In this new bioeconomy production paradigm, as Neri Oxman from the MIT Media Lab has

commented: “The biological world is displacing the machine as a general world of design.”

This includes leveraging biology as technology. We increasingly can design and construct genetic pathways, networks and systems to harness the powerful synthetic and functional capabilities already found in biology. As Tim Gardner, an American synthetic biology executive commented: “There’s almost no physical problem that hasn’t been solved by a biological system.”

It also encompasses the concept of the “cell as factory.” This includes: combining genes and functions in new and useful ways (but not necessarily as evolution would dictate); doing things in nature more efficiently; the “cell as factory” where microbes perform tasks nature never intended; designing and constructing useful biological parts, components and circuits; and reprogramming genomes.

As my colleague David Rejeski has noted, this new cyber-biological-physical production paradigm is “digitally interconnected, increasingly automated, flexible and cost-effective.” It enables highly distributed production, sophisticated customization and flexibility, and accelerating cycle times for rapid design-build-test-learn iterations.

This new bio-based production ecosystem:

- makes possible new production systems, especially distributed manufacturing and customized production – often with the ability to produce in small or large volumes, far greater sustainability, and greater efficiency of both mass production and custom design and production;
- helps drive innovation, productivity, and, the new markets for “solutions-based” enterprise and new market opportunities responding to societal challenges in areas like health, nutrition, the environment, and energy;
- produces goods, services, and data that minimize the use of resources while maintaining or improving costs and performance at commercially competitive scales; and
- is based on new multi-functional platforms and multi-directional DBIC tools.

An increasing number of synthetic biology manufacturing

strategies and business models are based on decoupling design from fabrication and manufacturing. They seek to replicate the dramatic advances in the semiconductor industry made possible by decoupling design from fabrication.

Second, we already are seeing the “de-verticalization” of supply and value chains. Much as traditional vertically integrated computer companies such as IBM, DEC, NCR, and Honeywell Bull were overtaken by newer, more agile, and more innovative entrants that reshaped ICT value chains, the same is beginning to occur in the Digital Bio revolution. The traditional, vertically integrated models of large chemical, biopharmaceutical, and agrifood companies are being challenged by, or at least complemented by, the development of new DBIC and synthetic biology smart specialization strategies at different places along the value chain and the adoption of innovative disaggregation strategies.

Third, as Jason Kelly, the CEO of Gingko Bioworks has noted: “As we get better at designing biology, we’ll use it to make everything, disrupting sectors that the traditional tech industry hasn’t been able to access.”

## 2.7 Accelerating U.S. Investments and Innovating Disruptive Business Models

American synthetic biology/engineering biology, driven by DBIC and disruptive new business models, increasingly is viewed as a significant investable opportunity. It is attracting increased investment attention and funding from the full spectrum of American private sectors investors – venture capitalists, corporate venture funds, internal corporate R&D allocations, venture philanthropists and impact investors.

According to SynBioBeta, more than US\$1.7 billion was invested in new U.S. synthetic biology ventures related to DBIC in 2017 and, this year, investments in various American engineering biology start-ups are on track to exceed US\$3 billion, an increase of about 60% in one year.

In the last four years, more than 400 new synthetic biology/engineering biology SMEs have been created in the United States. Their business models are diverse and

include companies in differentiated market sectors such as genome synthesis, Digital Bio software, aquaculture, next-generation drugs and diagnostics, protein engineering, DBIC tools and automation, food and agriculture, organism engineering, and new biomaterials.

Several anecdotal calculations suggest that larger established companies and corporate venture funds have invested an additional US\$2-3 billion, coupled with more than US\$1.5 billion in U.S. government research funding and at least US\$250 million from venture philanthropies and social entrepreneurs who believe that DBIC and engineering biology hold transformational promise for solving vexing challenges in health, conservation and ecology, environment, or food and nutrition that are aligned with their non-profit missions.

A striking feature of this new American investment wave is the breadth of innovative business models emerging and the scope of how many different companies and sectors are involved. Most initial business models and investments were centered on the potential of synthetic biology for creating biofuels and renewables, for attempting to harvest the sun’s energy with microorganisms, or for biopharmaceutical-related discoveries.

Many of these efforts continue with second-generation biofuels and a broader health portfolio that now includes new vaccines, pandemic preparedness, and new delivery mechanism. But most business models and investments have shifted away from the first generation investments. Many now involve a broad range of novel or more sustainable consumer products; agricultural applications and the development of novel foods; flavors, fragrances and cosmetics; bio-CAD and other Digital Bio software, and, especially, high-valued added chemicals and new materials for industrial uses.

Five promising U.S. synthetic biology start-ups based on DBIC underscore how companies are translating DBIC and synthetic biology into innovative business models with significant commercial value and follow-on investments. They already are reshaping the competitive landscape and creating new types of supply and value chains while attracting large new investments.

- Zymergen uses a sophisticated DBIC automation platform, AI, and machine learning to create biologically produced materials for a wide range of applications that require performance-enhanced materials.
- Gingko Bioworks engineers customized microbes for cultured ingredients in a variety of industries such as cosmetics and fragrances, flavors, and nutritional ingredients, as well as other applications. It uses a highly automated proprietary biofoundry and sophisticated DBIC tools for discovery, custom design, and construction.
- Twist Bioscience focuses on providing new tools through customized DNA synthesis, including high-density data storage. It is a new type of synthetic DNA service company that uses a DBIC platform for DNA production and also has an early stage DNA writing on silicon platform.
- Amyris, based on technology developed at Berkeley, was an early market entrant showing the promise of multi-use DBIC platforms for novel bio-production. It started with health applications, specifically a much lower cost and more efficient way to develop artemisinin for malaria drugs. But the same multi-use technology platform, however, also can be used to more sustainably produce farnesene for the production of tires or advanced biofuels for aviation and other transportation uses.
- Synthetic Genomics' business model centers on data that drives design. It has developed an integrated technology platform engineered to harness biology complexity through a combination of bioinformatics, biodiscovery, advanced automation for Digital Bio, and cell optimization. From this integration, it has developed advanced biological-to-digital converters for next-generation bio-production.

New and unexpected markets already are emerging. For example, recent National Academy of Sciences, BioBricks Foundation, and SynBioBeta conferences have highlighted how synthetic biology and DBIC can sustainably create and commercialize protein-rich animal products to meet global

and domestic demands for food and improved nutrition. A number of U.S. companies are developing novel agricultural and food products from cells and microbes, such as lab-grown meat and dairy products. Others are focused on next-generation aquaculture or the diversity of oceans for genetically engineering algae for new animal vaccines.

Two other significant American business trends merit attention. First, large new market opportunities exist for those companies that develop and commercialize Digital Bio tools. As many American history students learned from the California Gold Rush in the 19<sup>th</sup> Century, the companies that sold the picks, shovels, and supplies to the miners usually outperformed the high-risk prospectors looking for gold.

These market opportunities for developing DBIC tools and technologies have not gone unnoticed. Established life sciences tool providers such as Agilent, Illumina, and Thermo Fischer are investing heavily in the new DBIC space, as are large information technology product and service providers such as Microsoft Life Sciences, Google, and IBM.

Second, DBIC and synthetic biology in the United States are attracting significant interest, collaborations, and investments from “non-traditional” players outside more traditional biopharma, chemicals, or agrifood sectors. The engagement of companies as diverse as Lockheed Martin, Nike, Autodesk, IKEA, Amazon, Procter & Gamble all underscore the growing role of the bioeconomy, DBIC, and synthetic biology.

Finally, large future markets for DBIC loom, even in existing digital technologies. For example, semiconductors and massive storage represent significant new business opportunities based on DBIC and synthetic biology. The U.S. recently has launched a public-private partnership, SemiSynBio, to advance semiconductor synthetic biology for information processing and storage technologies. This may include: (1) cytomorphic-semiconductor circuit designs that apply lessons from cell biology to new chip architectures and vice versa; (2) bio-electric sensors, actuators and energy sources dedicated to enabling hybrid semiconductor-biological systems; and (3) molecular-precision additive fabrication that creates manufacturing processes at the mini-nanometer scale inspired by biology.