

2018 Semiconductor Synthetic Biology Roadmap

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Editor's Note

I am delighted to introduce the 1st Edition of the SemiSynBio Roadmap, a collective work by many dedicated contributors from industry, academia and government. It can be argued that innovation explosions often occur at the intersection of scientific disciplines, and Semiconductor Synthetic Biology or SemiSynBio is an excellent example of this. The objective of this Roadmap is to serve as a vehicle to realize the transformative potential of the new technology emerging at the interface between semiconductors and synthetic biology. The SemiSynBio Roadmap is intended to catalyze both interest in and rapid technological advances that provide new capabilities that benefit humankind.

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Acronym Definitions

2D	Two-Dimensional	HSM	Hybrid-State Machine
3D	Three-Dimensional	MFC	Microbial Fuel Cell
AI	Artificial Intelligence	MIST	Molecular Information Storage
ARO	Army Research Office	NAM	Nucleic Acid Memory
BEM	Bioelectronic Medicine	NIST	National Institute of Standards and Technology
BDA	Bio-Design Automation	NSF	National Science Foundation
CAD	Computer-Aided Design	ONR	Office of Naval Research
CMOS	Complementary Metal-Oxide-Semiconductor	R&D	Research And Development
EDA	Electronic Design Automatin	REXCOM	Roadmap Executive Committee
DMSO	Dimethyl Sulfoxide	RF	Radio-Frequency
DNA	Deoxyribonucleic Acid	RNA	Ribonucleic Acid
DoD	Department of Defence	SEMISYNBIO	Semiconductor Syntetic Biology
EB	Exabyte	SDA	Software Design Automation
Gb	Gigabit	SNR	Signal-to-Noise Ratio
GB	Gigabyte	SRAM	Static Random-Access Memory
GP	Genome Project	SRC	Semiconductor Research Corporation
IARPA	Intelligence Advanced Research Projects Activity	TB	Terabyte
IDC	International Data Corporation	THF	Tetrahydrofuran
ISS	Intelligent Sensor System	TWG	Technical Working Group
IT	Information Technology	ZB	Zettabyte
HDD	Hard Disk Drive		

Introduction

Semiconductors enable the information technology infrastructure that we rely on for all aspects of our daily lives, including financial, transportation, energy, healthcare, education, communication and entertainment systems and services. The remarkable trend described by Moore’s Law has driven increases in performance and function, while decreasing costs. Today, the semiconductor industry is facing fundamental physical limits and punishing increases in technology development and manufacturing costs. In order to realize the benefits of the internet of things and “big data”, new approaches to collecting, sharing, analyzing and storing data and information are required. One such approach lies at the intersection of synthetic biology and semiconductor technology—the new field of Semiconductor Synthetic Biology, or SemiSynBio.

SemiSynBio aims to take advantage of the significant energy efficiency and information processing advantages that biological systems have over the best foreseeable equivalent silicon-based systems. SemiSynBio may fundamentally redefine semiconductor design and manufacture, unleashing forces of creative destruction and giving rise to industries that bear little resemblance to that which we know today. To fuel such an industry, not only is technical innovation required but equally important development of the future workforce. These advances build upon breakthroughs in DNA synthesis and characterization, electronic design automation, nanoscale manufacturing, and understanding of biological processes for energy efficient information processing.

In order to realize the transformative potential of the new technology emerging at the interface between semiconductors and synthetic biology, an industry-led consortium—SemiSynBio was formed in 2015. The SemiSynBio consortium includes stakeholders from all parts of the value chain and include semiconductor manufacturers, biotech and pharmaceutical companies, IT industry, software providers, and EDA and BDA companies. The consortium also includes universities and government agencies. The long-term goals of SemiSynBio Consortium are to advance the emerging SemiSynBio technology through industry-led precompetitive research and development. A critical activity for the consortium has been the development of a SemiSynBio Technology Roadmap. The Roadmap contains an overview of the status of the research in SemiSynBio, describes salient outcomes to date, and outlines research challenges that can now be foreseen. This Roadmap is intended to serve

as a planning tool that connects the societal trends and challenges facing a product or industry with the technologies needed to address them. It is also intended to help guide the future investments in this emerging field.

The SemiSynBio Roadmap identifies technology targets/goals in the following five technical areas:

1. DNA-based Massive Information Storage.
2. Energy Efficient, Small Scale Cell-Based and Cell-inspired Information Systems.
3. Intelligent Sensor Systems and Cell/Semiconductor Interfaces.
4. Electronic-Biological System Design Automation.
5. Biological pathways for semiconductor fabrication and integration.

To develop a comprehensive Technology Roadmap for SemiSynBio, joint efforts of experts from different disciplines have been employed: biology, chemistry, computer science, electrical engineering, materials science, medicine, physics, and semiconductor technology.

The SemiSynBio Technology Roadmap addresses a 20-year timeframe, embracing both current and projected needs. It serves as a guide for university researchers who will train the entrepreneurs, engineers and scientists who will lead the creation of this new industry. It is expected that many startups emerge from the research to commercialize these new approaches.

Chapter I

DNA-based Massive Information Storage

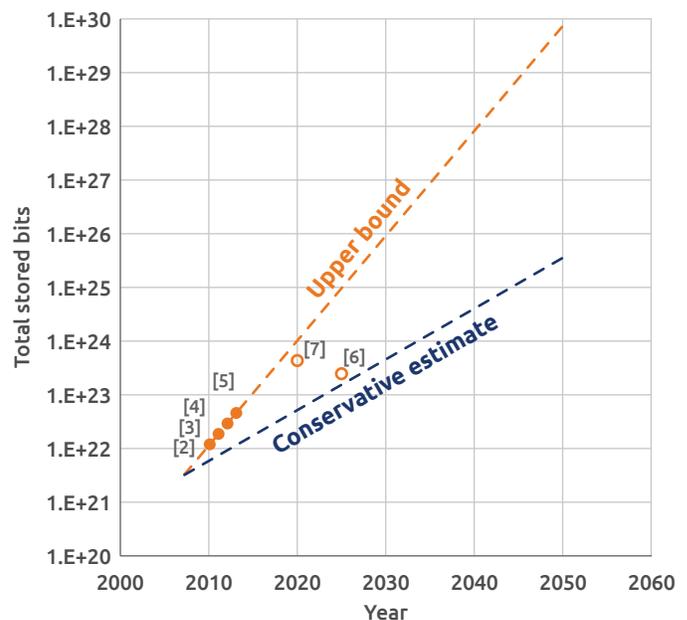
1. Introduction

Information has been the social-economic growth engine of civilization since the very beginning, and information production correlates with social well-being and economic growth. Currently, the production and use of information has been grown exponentially, and by 2040 the estimates for the worldwide amount of stored data are between 10^{24} and 10^{28} bits as shown in **Figure 1.1** (these estimates are based on research by Hilbert and Lopez [1]. The data points are taken from the International Data Corporation (IDC) reports [2]–[6] and the work by Xu [7].

Today, the world is creating data at a much faster rate than storage technologies can handle. There is a risk that within 10-15 years, buying exponentially more storage capacity will become prohibitively expensive (and potentially impossible due to limited materials supply, e.g. silicon wafers). Currently, there are three main paradigms for data storage (**Figure 1.2**): i) Optical, ii) Magnetic (HDD & Tape), and iii) Solid-State (e.g. Flash). Their feature sizes are already close to the physical limits of scaling and further improvement in storage density can be achieved only through 3D integration. However, even in the case of an extreme 3D packing the potential for improvement is limited. Therefore, the world is facing a serious data storage problem that cannot be resolved by current technologies.

In the search for potential solutions to this problem, multiple studies have used DNA and other synthetic polymers, to explore the use of sequence-controlled polymers as the basis for molecular information storage technologies (MIST).

Figure 1.1: Estimated and projected global memory demand—including a conservative estimate and an upper bound



[2] J. Gantz and D. Reinsel, "The Digital Universe Decade – Are You Ready?" *International Data Corporation Report* (May 2010).

[3] J. Gantz and D. Reinsel, "Extracting Value from Chaos". *International Data Corporation Report* (June 2011).

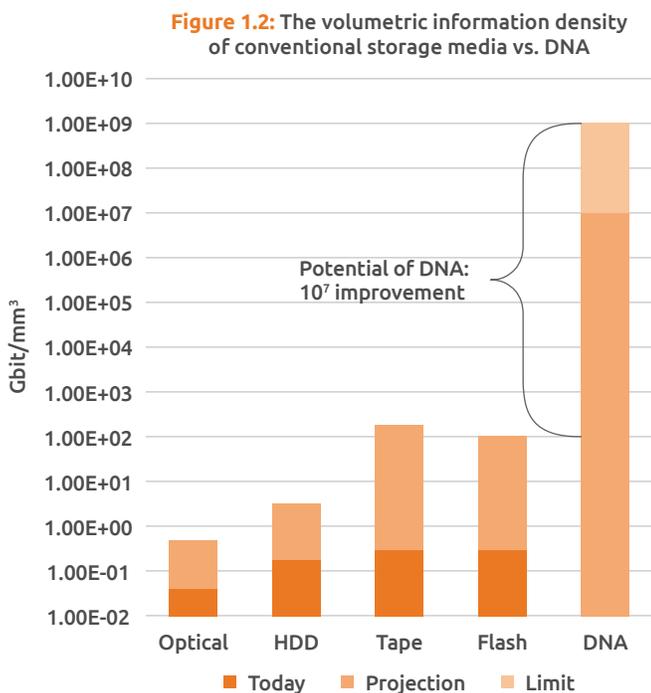
[4] J. Gantz and D. Reinsel, "The Digital Universe in 2020: Big Data, Bigger Digital Shadows, and Biggest Growth in the Far East". *International Data Corporation Report* (December 2012).

[5] V. Turner and J. F. Gantz, "The Digital Universe of Opportunities: Rich Data and the Increasing Value of the Internet of Things", *International Data Corporation Report* (April 2014).

[6] D. Reinsel, J. Gantz, and J. Rydning, "Data Age 2025: The Evolution of Data to Life-Critical." *International Data Corporation Report* 2017.

[7] Z-W. Xu, "Cloud-Sea Computing Systems: Towards thousand-fold improvement in performance per Watt for the coming Zettabyte Era", *J. Computer Sci and Technol.* 29 (2014) 177-181

Molecular media offers far greater potential for scaling exponentially, e.g. 10^7 above the best expectations for flash or magnetic storage (Figure 1.2). DNA can store information stably at room temperature for hundreds of years with zero power requirements, making it an excellent candidate for large-scale archival storage [8].



During 2016 and 2017, Intelligence Advanced Research Projects Activity (IARPA) and the Semiconductor Research Corporation (SRC) organized two workshops that assembled international stakeholders from academia and the biotech, semiconductor and information technology industries to roadmap clear and achievable engineering optimizations that would be necessary to develop scalable MIST systems. In 2018, IARPA announced a MIST program that seeks to put this roadmap into practice by assembling a multidisciplinary community around the shared goal of developing compact and scalable molecular information storage technologies to support real-world “big data” use cases [1]. This roadmap is consistent with the goals of the MIST program. It is expected that both small & medium-sized enterprises as well as large companies will participate in MIST developments.

2. Key challenges

A number of recent studies have shown that DNA can support scalable, random-access and error-free information storage [9]–[15]. Current DNA storage workflows take weeks to write and then read data due to reliance on life sciences technologies that were not designed for use in the same system. The current workflows are too slow and costly to support exascale archival data storage. Solving this problem will require: (i) Substantial reductions in the cost of DNA synthesis and sequencing, and (ii) Deployment of these technologies in a fully automated end-to-end workflow.

In summary, the two major categories of technical challenges include:

- Physical Media: Improving scale, speed, and cost of synthesis and sequencing technologies.
- Operating System: Creating scalable indexing, random access and search capabilities.

Information has been the social-economic growth engine of civilization since the very beginning, and information production correlates with social well-being and economic growth.

3. Key Technical Areas

3.1. Storage

The 2019-2022 goal of this technical area is to demonstrate a fully automated storage system capable of writing information to the polymer media with a high throughput, low cost, and writing accuracy that enable subsequent random access and error-free decoding of files. Possible storage media include, but are not limited to, DNA, peptides, or synthetic polymers. The projected storage capacity trend for MIST is shown in Figure 1.3.

Figure 1.3: MIST storage capacity growth projection

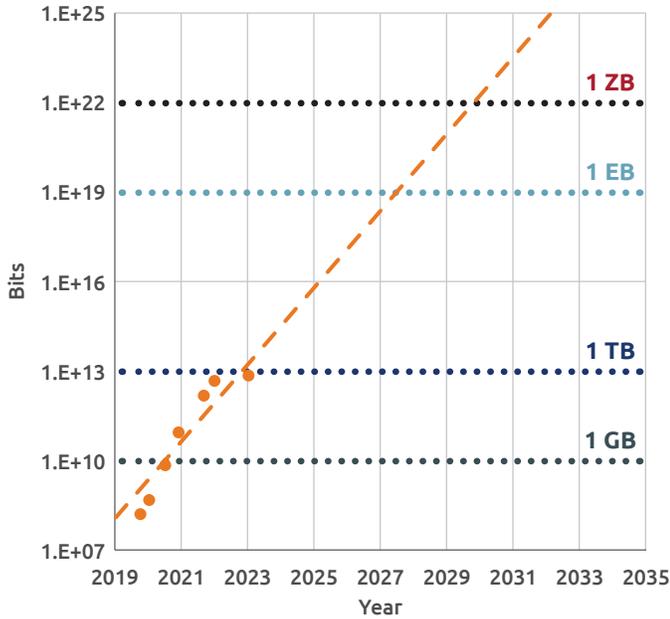
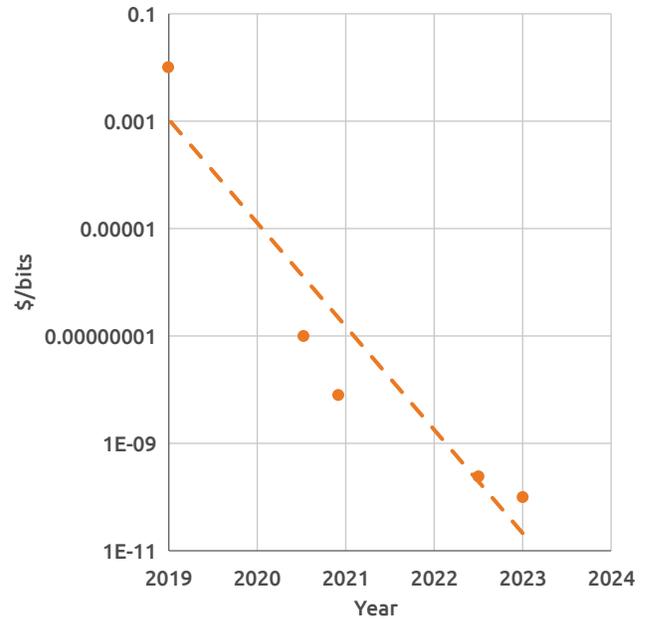


Figure 1.4: MIST DNA synthesis cost targets



Methods for writing data to polymers include, but are not limited to, *de novo* chemical synthesis, *de novo* enzymatic synthesis, or selective editing of existing sequences (for a detailed discussion see the SemiSynBio Roadmap reports [16] and [17]). Important considerations for development are resource requirements to write each decodable bit of information, maximum write error rate, maximum write throughput for decodable data, total storage capacity, longevity of stored data, and compatibility with available retrieval approaches.

A dramatic reduction in cost of DNA synthesis or synthetic polymers is mandatory for practical MIST systems. Technical approaches for the cost reduction are discussed in [17].

Figure 1.4 displays DNA synthesis cost targets as formulated in the MIST program [18].

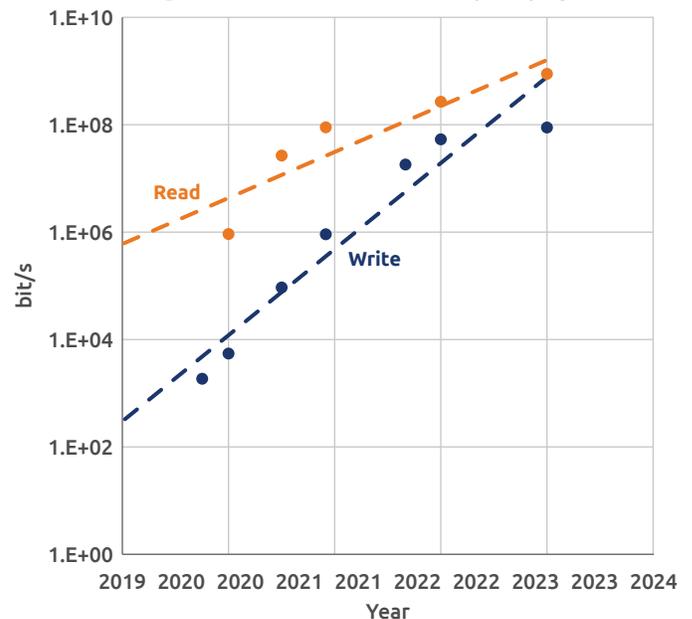
3.2. Retrieval

The 2019-2022 goal of this technical area is to demonstrate a fully automated device capable of reading information stored in the polymer media with high throughput, low cost, and read accuracy sufficient to enable random access and error-free decoding.

Methods for reading data from polymers include, but are not limited to, Sequencing By Synthesis, Single Molecule RealTime Sequencing, Nanopore Sequencing or Mass

Spectrometry. Important considerations for development are resource requirements to read each decodable bit of information, bit depth, maximum read error rate, maximum read throughput for decodable data, time to first byte after a read request, and compatibility with available write approaches. The MIST write and read speed projections are shown in Figure 1.5.

Figure 1.5: MIST Write and Read speed projection



3.3. Operating System

The 2019-2022 goal of this technical area is to demonstrate an operating system that coordinates scalable and efficient bulk write/read and random access workflows. The targets for the operating system development are shown in **Table 1.1**.

Important considerations for operating system development include: i) resource requirements for file addressing and encoding with molecular media, ii) performance of algorithms for physically organizing media by file type or other properties, iii) specific resource requirements for error correction and random access of files, and iv) overall resource requirements for reconstruction of files.

Table 1.1: Targets for MIST operating system development

2019	<ul style="list-style-type: none"> Development of a simulator of molecular storage and retrieval devices
2020	<ul style="list-style-type: none"> Demonstrated robustness to anticipated failure modes of storage and retrieval devices; Demonstrated indexing, addressing, decoding and random access capabilities that plausibly scale into the exabyte regime.
2021	<ul style="list-style-type: none"> Operating system capabilities are further improved, refined, and optimized for practical applications; Tools development for extreme compression and approximate reconstruction of multimedia data.
2022	<ul style="list-style-type: none"> Support for content-addressable memory, or pattern-based search over the content of a molecular archive; Support for security access control, such as the ability to dynamically set unique policies per asset and/or per user.

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Chapter 2

Energy Efficient, Small Scale Cell-Based and Cell-Inspired Information Systems

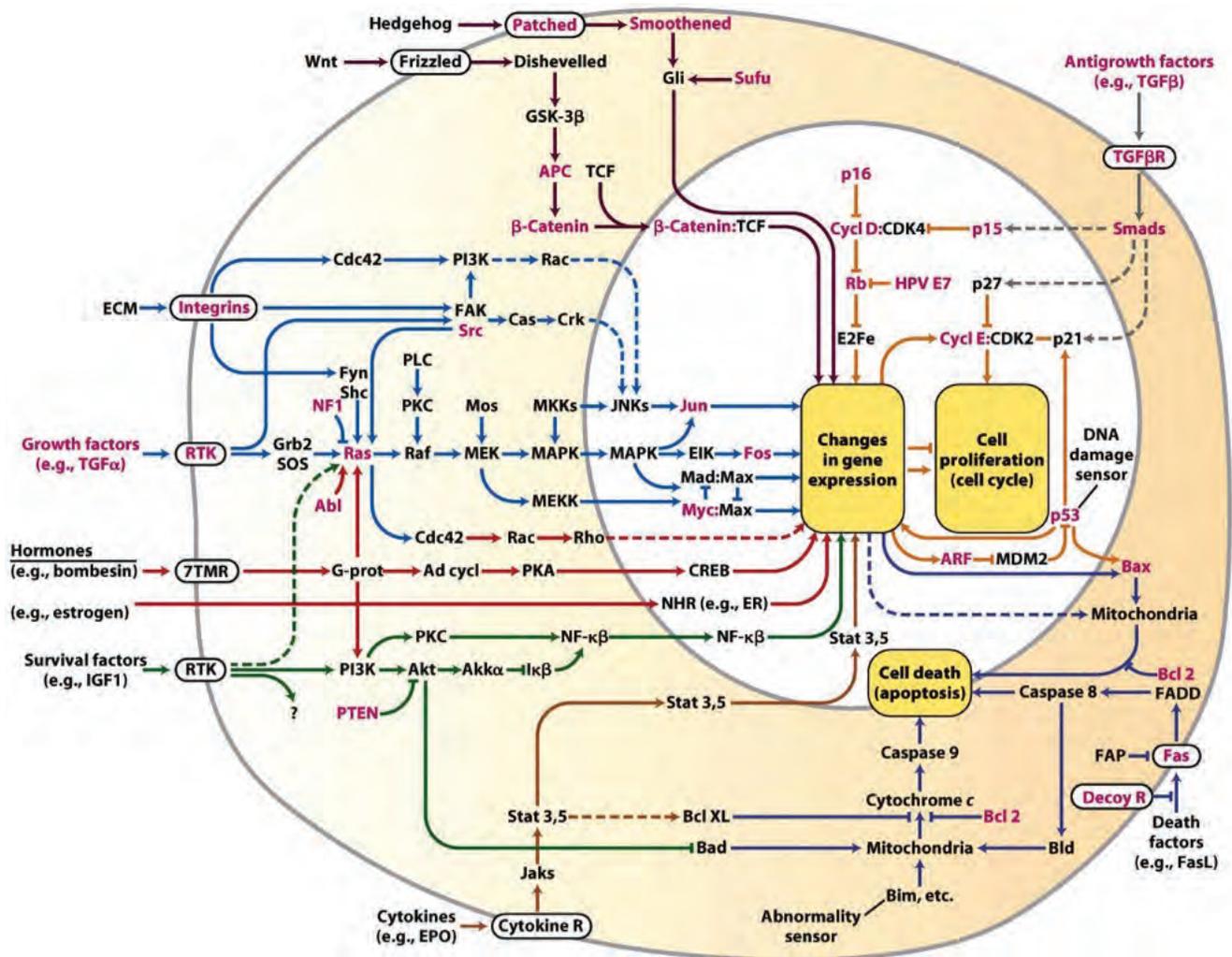
1. Introduction

Recently, there has been an increasing interest in hybrid biological-semiconductor platforms that can leverage both natural/synthetic biological processes and semiconductor technologies. In these hybrid platforms, living cells and tissue can function as a “Biological Front-End” layer with the cellular biochemical processes, while the underlying semiconductor platforms can form a “Semiconductor Back-End.” Seamless organic/inorganic signal processing can potentially realize self-regulated operations between “Biological Front-End” and “Semiconductor Back-End,” which may enable fine-grained controls of cellular physiological environment. It is important to note that the impact of hybrid cell-electronics systems goes well beyond cell biology, since it will also serve as a pivotal technology to improve human health, wellness, and ability. For example, the recent fast growing areas of ‘electroceuticals’/bioelectronic medicine or brain-machine interfaces rely on judicious design of cell-electronics interfaces to ensure the designated electrical signals are sent into the specific cells in a controlled fashion [1].

The hybrid biology-semiconductor systems can be employed in a broad spectrum of critical applications with groundbreaking scientific and economic impacts. Leveraging the built-in or synthetically programmed cellular machineries and their interactions with semiconductor platforms, these hybrid systems will potentially offer unprecedented capabilities far beyond conventional electronics-only devices. Examples of application include i) fast and high-throughput chemical screening for drug discovery, ii) diagnosis and therapy planning for personalized medicine, iii) detecting chemical and biological agents for defense and environmental needs, and iv) novel microscopic biological actuators or robots.

Living cells implement complex computations on continuous environmental signals, which involves both analog and digital information processing [2]. Many synthetic cellular computing systems have recently been demonstrated [3, 4]. Deeper understanding of the principles of cellular information processing can also enable new generations of cell-inspired semiconductor architectures. Possible alternate computing models include analog approximate and stochastic computing. “Cytomorphic” chips can offer a fast, high-throughput simulation-and-modeling tool for living cells [5].

Figure 2.1: Information processing plays a central role in enabling the functionality of biological systems [11]



National Science Foundation (NSF), Army Research Office (ARO) and Semiconductor Research Corporation (SRC) organized two workshops that assembled international stakeholders from academia and biotech, semiconductor and information technology industries to roadmap targets that would be necessary to develop practical hybrid biological-semiconductor systems [6, 7]. In 2018, NSF and SRC have launched a Semiconductor Synthetic Biology (SemiSynBio) program that seeks to put this roadmap into practice by assembling a multidisciplinary community around the shared goal of developing compact and scalable hybrid biological-semiconductor technologies [8]. This roadmap is consistent with the goals of the SemiSynBio program. It is expected that both small and medium-sized enterprises as well as large companies will participate in the development of the cell-based and cell-inspired information systems.

2. Key challenges

Three major technical challenges include:

- Lack of significantly deep understanding of complex biological systems
- Boundaries and limitations of the bio-computational potential are still not clearly defined
- Hybrid Bio-Semi computing systems currently lack a well-defined interface between biological and electronic layers

3. Key Technical Areas

3.1. Cell-electronics systems for computation

It is becoming increasingly clear that information processing plays a central role in enabling the functionality of biological systems, and it has been shown that cell biochemical reactions (Figure 2.1) perform information processing at energy efficiencies that are a several orders of magnitude lower than the most advanced semiconductor nanotechnologies can achieve. This is accomplished concurrently with a very high information throughput [9]. For example, a 1 μm *E. coli* cell performs computations using nanoscale DNA-protein ‘devices’, with approximately $10 k_b T$ of energy per operation and a power consumption of $\sim 10^{-13}$ W [10]. Therefore, living cells represent alternative models of functional systems that operate efficiently and effectively with component sizes that are on the scale of fractions of a nanometer.

Hybrid cell-electronics systems could enable extremely low-energy and high-performance analog and digital computing. Table 2.1 presents example roadmap targets for cell-electronics systems.

A prominent target of application is a wearable or implantable cellular control systems with artificial electronic cells and actual biological cells that will be used for predictive pathway cures in disease treatment. A possible first port of entry is point-of-care biomedical computing architectures.

Table 2.1: Roadmap targets for cell-electronics systems

2023	<ul style="list-style-type: none"> • Biomedical and security applications of the synthetic cell-electronic systems • Increased understanding of computational potential and nature of biological systems
2028	<ul style="list-style-type: none"> • Neural computation understood well for at least some brain areas or functions. • Some commercial biologically-inspired computing systems • Biological principles exploited for order-of-magnitude reduction in energy budget required for information processing
2033	<ul style="list-style-type: none"> • Application-specific biologically-inspired computing systems become readily available
2038	<ul style="list-style-type: none"> • Computational devices based on neurons commonly used for specialized applications enabled by form factor and power consumption

Connecting the biological matter with electronics is a critical element of such hybrid systems. In current practice an optical interface is overwhelmingly used, which puts severe limitations on a system’s size, functionality and performance. Creating reliable electrical, two-way communication channels should be a short-term research priority. Optical and electrical communication channels can coexist concurrently in a bio-electronic system, analogously with the wireless vs. wired concurrency. Optical interface is ‘wireless’ and does not require direct proximity. However, it has limitations on bandwidth, signal propagation, spatial resolution, etc. On

Figure 2.2: ‘Cognitive’ chip using biological neurons on silicon by Koniku Inc.

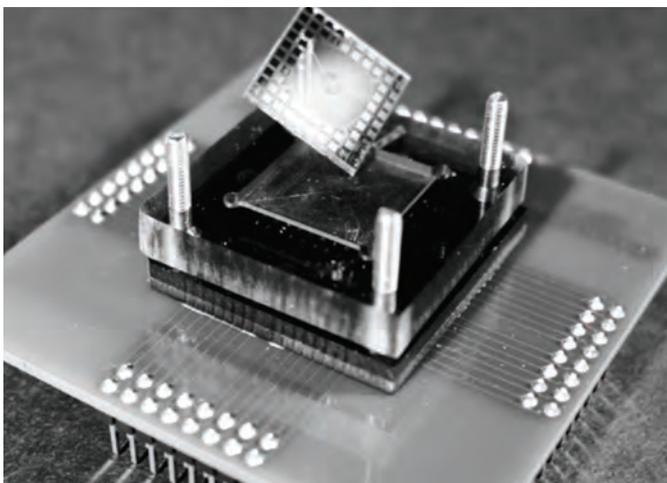
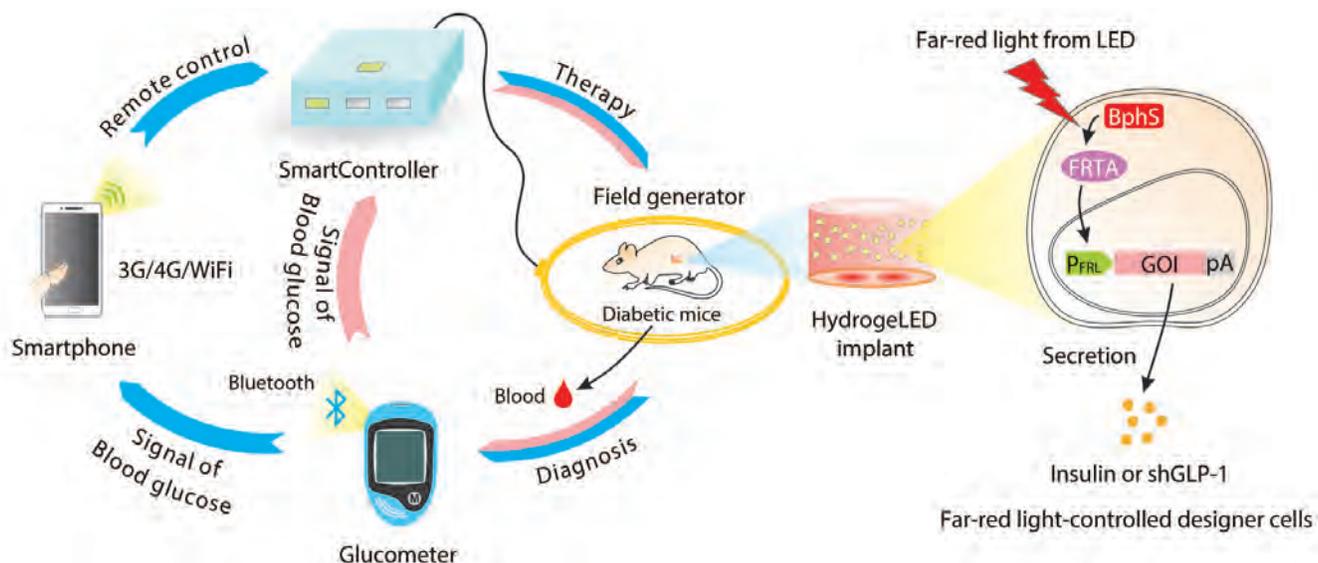


Image Credits: Koniku



Figure 2.3: Smartphone controlled therapeutic implant with optogenetically engineered cells connected to a smartphone for control of the glucose homeostasis in diabetic mice [13].



the other hand, electrical connection allows for better sensitivity and precision, smaller energy consumption, compact system size, etc. However, it requires a close proximity between biological and electrical components, which is often difficult to accomplish.

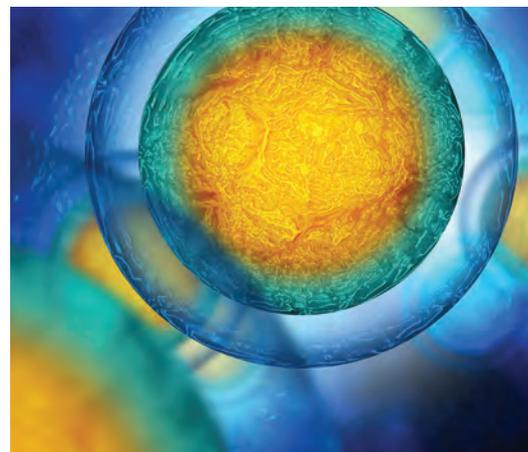
One recent demonstration of the cell-based electronic systems is a 'cognitive' chip made by Koniku Inc. that uses biological neurons on silicon shown in [Figure 2.2](#) [12].

[Figure 2.3](#) depicts how a glucose homeostasis in diabetic mice can be controlled with optogenetically engineered cells connected to a smartphone [12].

3.2. Analog/Hybrid State Machine Representations of Fundamental Bio-molecular Circuits

Based on the similarities between the electronics and chemistry, it is possible to map circuits between electronic and biological domains in a rigorous fashion and design electronic chips for accelerated modeling of cellular processes [14, 15].

A fast, high-throughput simulation-and-modeling tool for living cells is critical for synthetic biology applications and for understanding the molecular mechanisms of human diseases. However, modeling and simulation of biochemical reaction networks in living cells that involve small molecules, DNA, RNA, and proteins is very challenging, in part due to very high computational demand. For example, even for a relatively simple



The hybrid biology-semiconductor systems can be employed in a broad spectrum of critical applications with groundbreaking scientific and economic impacts.

Table 2.2: Roadmap targets for cytomorphic electronics systems

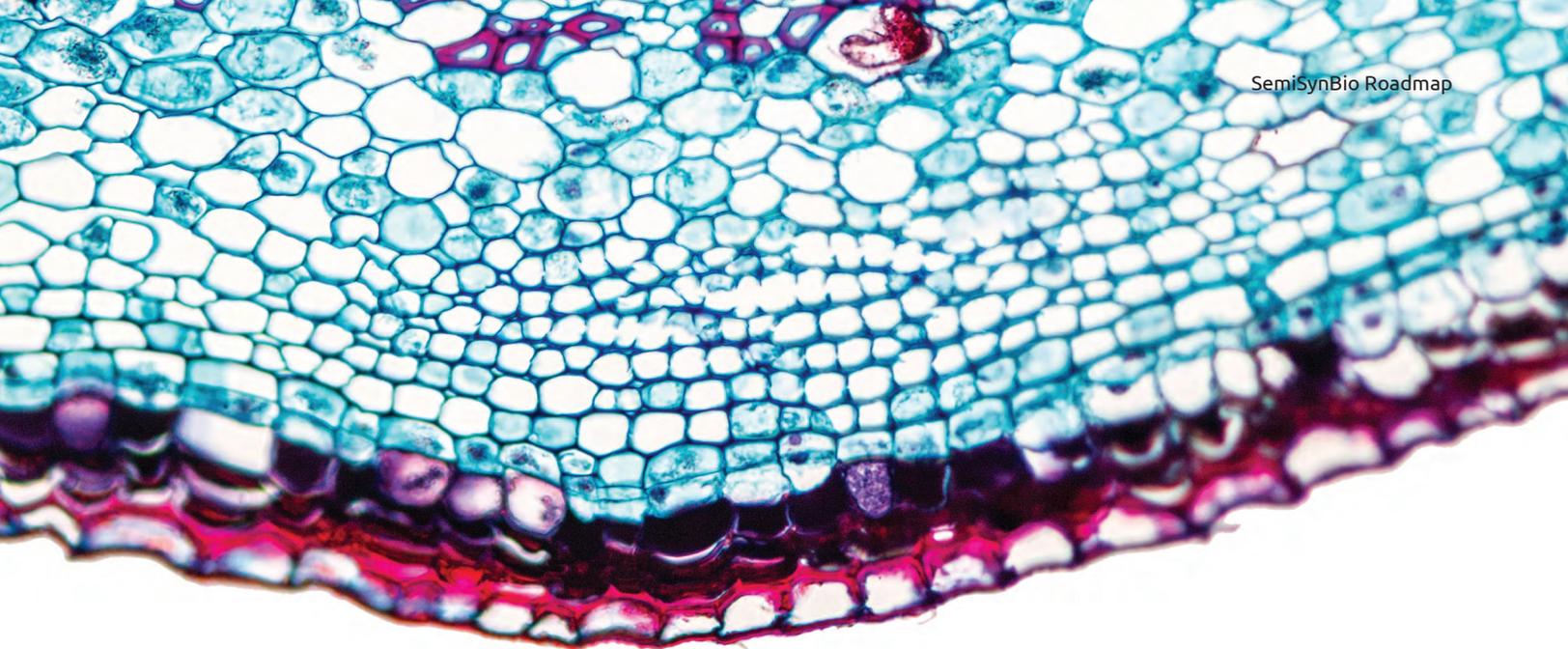
2023	<ul style="list-style-type: none"> • 10-state variable analog feedback dynamical system with specified constraints on energy, part count, molecular copy number, speed, precision, context invariance, operation over a wide dynamic range of input molecular concentration. • 20-component vector molecular pattern recognition and control
2028	<ul style="list-style-type: none"> • 30 state variable analog feedback circuits. The precision of nonlinear, stochastic, feedback semiconductor circuit design is merged with a biological circuit design via the cytomorphic mapping. • Simulation of a 12-year stochastic computation with 4500 state variables in ~10 minutes on a cytomorphic computer.
2033	<ul style="list-style-type: none"> • Application-specific biologically-inspired computing systems become readily available. • Use of cytomorphic computers for predictive pathway medication in healthcare and synthetic biology.
2038	<ul style="list-style-type: none"> • Novel hybrid-state machine architectures to solve 10,000-state-variable NP-complete problems efficiently • Highly stochastic 100 to 1000 molecule per-state-variable (and high burst-noise factor) biological and electronic computing systems that are fault-tolerant and that solve problems that are highly inefficient on a deterministic computer.

cell, such as *E.coli*, the stochastic Gillespie simulation of the molecular networks would involve $\sim 10^{14}$ biochemical reactions and thus, is nearly impossible to completely simulate [5]. For another example, even simple 6-state-variable (S-V) stochastic simulations can take hours. In contrast, complex nonlinear, stochastic, analog circuits are realized that contain over 30,000 state variables inside cells [11].

“Cytomorphic” analog and hybrid analog–digital architectures (termed as hybrid-state machines - HSM) [9] are useful for describing computations in cells that are in the development or cell cycle pathways. These machines provide a methodology for gene–protein networks to be computed in a sequential analog fashion. HSMs also provide a good framework for describing spiking neuronal computation. The principles of cytomorphic computing can further be applied to pattern recognition, learning, inference, etc. **Table 2.2** presents example roadmap targets for cytomorphic electronics systems over the course of the next 20 years.

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Chapter 3

Intelligent Sensor Systems and Cell/Semiconductor Interfaces

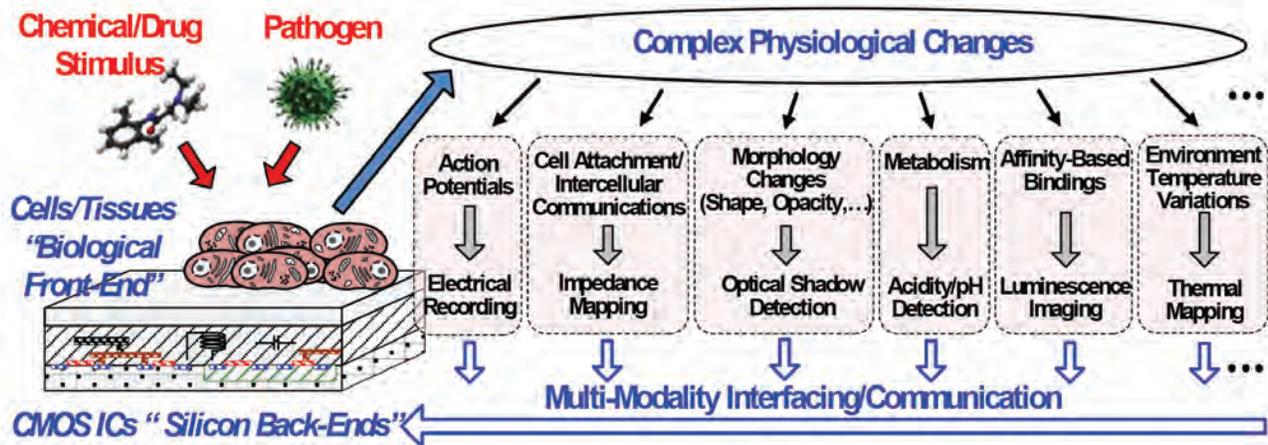
1. Introduction

Cells are viewed as the smallest building blocks of life that constitute all living organisms. Typical cell sizes highly depend on the cell types, with range from 100 μm (e.g., human egg), to 8-10 μm (e.g., human red blood cells), and down to 1-2 μm (e.g., *E. coli* bacteria). Despite their small size, cells are highly complex systems with numerous molecules operating concurrently in hundreds of pathways that are carefully regulated to maintain cell phenotypes and proper cellular functionalities.

Understanding cells and leveraging their built-in or synthetic functionalities will have a tremendous economic impact. From the economic perspective, the cell biology directly impacts multiple large-volume and fast-growing markets in healthcare and pharmaceutical industries, such as cell-based assays dominated by drug discovery/testing (\$18.3B by 2020 [1]), stem-cell development (\$170.1B by 2020 [2]), and medicine (\$67.5B by 2020 [3]). Cells offer a wide variety of natural or synthetic functionalities, such as sensing, actuation, synthesis, signal processing, energy generation etc. Furthermore, cells can also serve as an organic and highly versatile interface to the external environment.

Cells offer a wide variety of natural or synthetic functionalities, such as sensing, actuation, synthesis, signal processing, energy generation etc.

Figure 3.1: Multi-modal interfacing with cells is essential to capture complex cellular physiological changes and achieve holistic cellular characterization [4].



Living cells integrated with complementary metal-oxide-semiconductor (CMOS) technology in a hybrid bio-semiconductor system (Figure 3.1) have demonstrated a high sensitivity and specificity at low operating energy. In addition, integration of biological or biologically-inspired systems may offer alternative methods for providing energy to power the device. Self-powered, on-chip Intelligent Sensor Systems (ISS) that integrate biological sensing functions and energy generation with inorganic information storage and computation capabilities enable a broad spectrum of critical applications with great scientific, economical, and societal impacts. Leveraging the synthetically programmed cellular machineries and their interactions with semiconductor platforms, these hybrid systems will potentially offer unprecedented capabilities far beyond conventional electronics-only devices.

For example, advances in this field could stimulate developments of self-powered ISSs that integrate biological sensing functions and energy generation with inorganic information/computation capabilities that would enable diverse new applications such as i) fast and high-throughput chemical screening for drug discovery, ii) diagnosis and therapy planning for personalized medicine, iii) detecting chemical and biological agents for defense and environmental needs, and iv) novel microscopic biological actuators or robots.

National Science Foundation (NSF), Army Research Office (ARO) and Semiconductor Research Corporation (SRC) organized a workshop that assembled international

stakeholders from academia and biotech as well as semiconductor and information technology industries to roadmap clear and achievable engineering optimizations that would be necessary to develop a reliable multi-modal bi-directional cell-semiconductor interfaces and Intelligent Sensor Systems [4]. It is expected that both small & medium-sized enterprises and large companies will participate in the development of ISS.

2. Key challenges

- Scalability issues (e.g. size-dependent bandwidth-SNR trade-off for electrical modalities, yield and cost of packaging, etc.)
- Maintaining long-term cell viability on semiconductor substrate
- Ultra-low-power circuit interface to *in vitro* or *in vivo* cell sensors [5]

3. Key Technical Areas

3.1. Hybrid cell-electronics systems for next-generation sensing, actuation

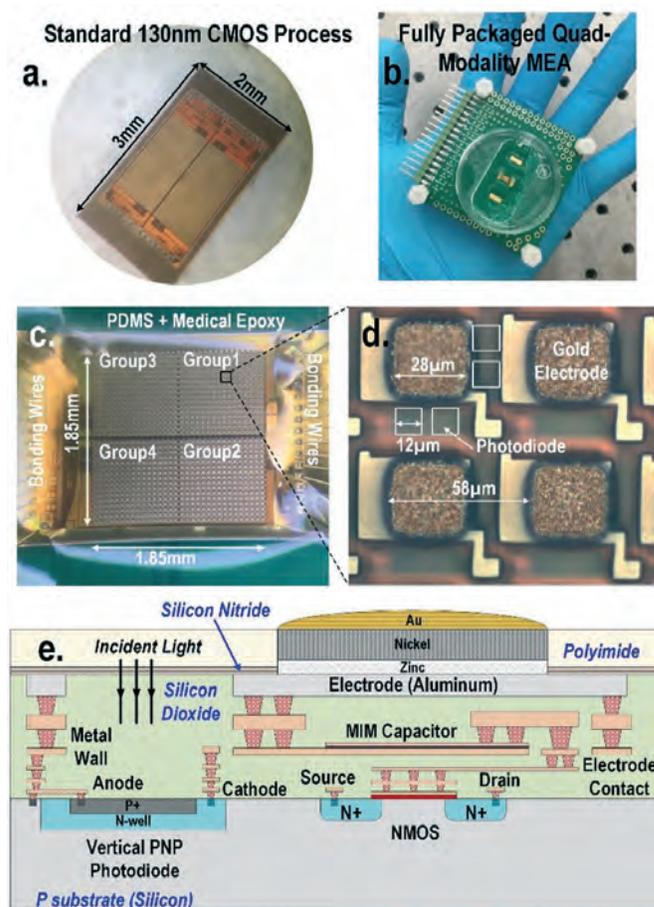
Multi-modal interfacing to cells is essential to capture the complex cell physiological changes, modulate cellular functionalities and enable holistic characterization and understanding of cells (Figure 3.1). Typical cellular processes of interest include cellular potential, cell-surface attachment, cell morphology, metabolism and molecular markers.

Table 3.1: Roadmap targets for hybrid cell-electronics systems for next-generation sensing

2023	<ul style="list-style-type: none"> Two-way real-time communications (sensing/actuation) with mammalian single-cell (~10μm) spatial resolution for both extracellular and intracellular interfacing Cell/semiconductor platforms with joint multi-modalities in electrical and optical domains Understanding fundamental scaling limits of cell-electronics systems for different modalities Energy harvesting from <i>in vivo</i> environment with nW-μW power for implantable individual ISS and weeks' operation time First market-ready ISSs based on biological tissues
2028	<ul style="list-style-type: none"> Two-way real-time communications (sensing/actuation) with sub-cellular (<2~5μm) spatial resolution for both extracellular and intracellular interfacing Cell/semiconductor platforms with joint multi-modalities in electrical, optical, and chemical domains Energy harvesting from <i>in vivo</i> environment with μW-mW power for implantable ISS networks and months' operation time Autonomous ISSs based on hybrid of biological tissues, nano-electronics, and AI
2033	<ul style="list-style-type: none"> Cell/semiconductor platforms with joint multi-modalities in electrical, optical, chemical, and thermal domains Genetic modifications to expand possible sensing or actuation modalities Completely self-contained self-powered autonomous ISSs based on hybrid of biological tissues, nano-electronics, and AI
2038	<ul style="list-style-type: none"> Cell/semiconductor platforms with joint multi-modalities in electrical, optical, chemical, thermal, and mechanical domains First market-ready completely self-contained self-powered autonomous ISSs based on hybrid of biological tissues, nano-electronics, and AI

Furthermore, useful cellular actuation modalities include electrical voltage/current, electrochemical reactions, thermal, mechanical, and optical processes. In principle, semiconductor technologies can support cellular interfacing with different modalities. In addition, the potential large-volume and high-growth market related to cell biology also matches well with the economics of the semiconductor industry that relies on mass production of silicon chips and scaling economics. Therefore, it is envisioned that semiconductor technologies (e.g., CMOS) can greatly benefit the study of cell biology and biotechnologies, while the latter also offer promising new markets that could potentially support the continuous growth of semiconductor industry in the "post-Moore" era. The targets for the hybrid cell-electronics systems for next-generation sensing are shown in [Table 3.1](#).

One recent demonstration of the cell-electronics systems is a quad-modality CMOS cellular interfacing array for label-free fully automated drug screening that enables multi-parametric cell profiling including cellular impedance characterization, optical detection, extracellular potential recording, and biphasic current stimulation ([Figure 3.2](#)) [6].

Figure 3.2: CMOS cellular interfacing array for label-free fully automated drug screening

In another example, an ingestible micro-bioelectronic device has been demonstrated that combines an engineered probiotic sensor bacteria (*E. coli* Nissle 1917) together with ultra-low-power integrated electronics to enable in-situ detection of gastrointestinal biomolecules associated with health or disease. Sensing of target biomarkers by the bacteria generates light, which is detected by photodetectors embedded in the electronics. These electrical signals are processed by an integrated bioluminescence detection circuit and are transmitted wirelessly to an external device [7].

3.2. Biocompatibility of Biological Front-End and Electronics Back-End

A critical component of cell-based Intelligent Sensor Systems are technologies to manipulate living cells and tissues and assemble them on a semiconductor surface. These technologies should potentially support high-throughput, scalability, and low-cost implementation/operation. A difficult challenge towards implementation of cell-semiconductor systems is maintaining cell viability on semiconductor substrate: Living cells will be integrated with CMOS technology to form a hybrid bio-semiconductor system, and keeping cells alive on silicon is a critical task for these systems. Fundamental and practical limits of enhancing the biocompatibility of semiconductor surfaces need to be studied. In addition, the long-term reliability of the electronic or semiconductor interfaces in the biologically relevant environment needs to be investigated, such as thin dielectrics with long-term robustness in cell culture medium, cell-matrix interface engineering, development of III-Nitride interfaces for sensing and cell studies, flexible and ultra-high density 3D heterogeneous packaging for biomedical applications, nano-biocomposites that contain living cells, etc. [4]. Further, long cell lifespan on semiconductor surfaces should be maintained in complex, unknown, and varying in-field environments to address various practical sensing and monitoring applications. The targets for the biocompatibility of biological front-end and electronics back-end are shown in [Table 3.2](#).

3.3. Energy generation by living cells/biological machineries

In many energy-constrained applications, such as implantable devices, it is highly desirable to harvest energy from the living organisms and the surrounding biological environments to

Table 3.2: Roadmap targets for biocompatibility of biological front-end and electronics back-end

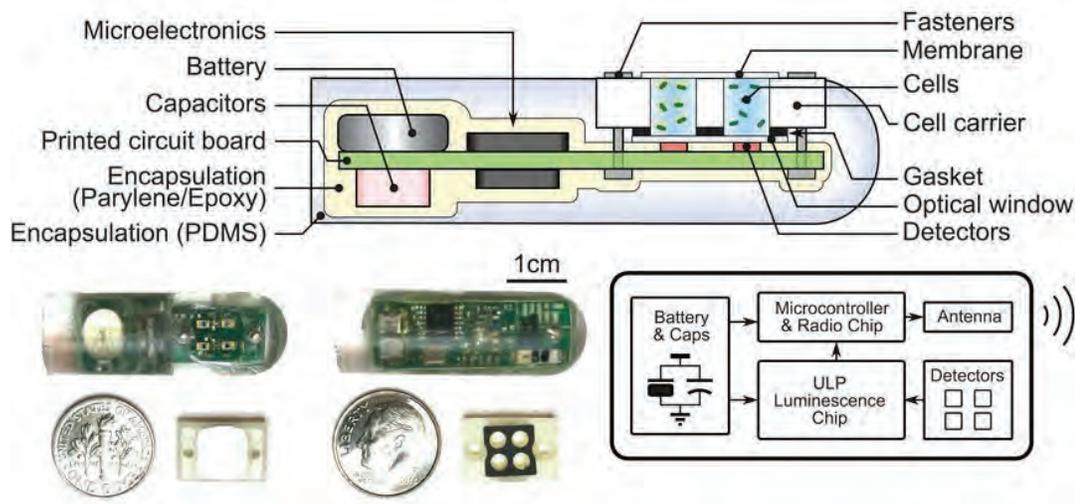
2023	<ul style="list-style-type: none"> • Typical cells lifespan in cell-electronics systems in lab-based environment—6 month • Understand the impact of surface material and geometry on cell viability
2028	<ul style="list-style-type: none"> • Typical cells lifespan in cell-electronics systems in lab-based environment—1 year • Typical cells lifespan in cell-electronics systems in in-field environment—3-6 months • Understand fundamental and practical limits on life time of cells on semiconductor surfaces
2033	<ul style="list-style-type: none"> • Typical cells lifespan in cell-electronics systems—5 years • Typical cells lifespan in cell-electronics systems in in-field environment—1-2 years • Genetic modifications to maximize cell's lifespan
2038	<ul style="list-style-type: none"> • Typical cells lifespan in cell-electronics systems—10 years • Typical cells lifespan in cell-electronics systems in in-field environment— >5 years

power the hybrid electronic systems. Microbial fuel cells (MFC) can convert chemical energy to electrical energy by the action of microorganisms. The microbial fuel cell technology offers sustainable solutions for distributed power systems, but the generation of practically usable power from small scale MFCs remains a major challenge for system scale up and application. By using synthetic biology techniques, engineered cells can substantially improve the performance of MFCs [8]. The targets for energy generation by living cells are shown in [Table 3.3](#).

Table 3.3: Roadmap for MFC using engineered cells

2023	<ul style="list-style-type: none"> • Sustainable power density 0.5 mW/cm²
2028	<ul style="list-style-type: none"> • Sustainable power density 1 mW/cm² • Miniature 3D MFC with volumetric power density 20 mW/cm³ • Understand fundamental and practical limits on MFC energy generation
2033	<ul style="list-style-type: none"> • Sustainable power density 1-5 mW/cm² • Miniature 3D MFC with volumetric power density 50 mW/cm³
2038	<ul style="list-style-type: none"> • Sustainable power density >5 mW/cm² • Miniature 3D MFC with volumetric power density 50-100 mW/cm³

Figure 3.3: Ingestible micro-bioelectronic device using engineered probiotic sensor bacteria [7]



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Chapter 4

Electronic-Biological System Design Automation

1. Introduction

Semiconductor information processing is providing tools and instrumentation for fundamental biological discovery and for medical applications while increasingly sophisticated software strategies provide the logical “glue” between instrumentation, samples and the data sets they produce. This chapter addresses the synergies between these three domains: the electronic, its software layer, and the biological.

Already, semiconductor technologies have directly enabled remarkable progress in sequencing technology, microscopy, and other types of instrumentation, but synthetic biology remains a small-scale, engineering field in its infancy due to the limited automation and large-scale integration in the build/test phases of the design cycle. As instrumentation miniaturizes and the demand for high-throughput characterization increases, semiconductors and electronic assembly technologies are well-suited to continue to scale into the biological domain as essential platforms. However, the incorporation of these technologies will further require a step-change in the way that we approach Software Design Automation (SDA) for Synthetic Biology. For synthetic

biology designs to be robust, trustworthy and economical, they should be verified and thus breakthroughs in biological programming languages and formal verification techniques for large-scale biological engineering are needed.

Currently, the biological design cycle is slow, expensive and laborious, and in most cases design is carried out empirically using a small number of parts without predictive modeling [1, 2, 3]. Despite the *ad hoc* synthetic biology demonstrating many impressive proof-of-concept circuits, full-scale computer-aided design tools will be needed for reliable design of larger and more complex systems [4]. Leveraging advanced electronic design automation (EDA) tools and concepts for complex design can enable a radical increase in the complexity of biological design automation (BDA) capabilities [5] (currently demonstrated are $\sim 10^4$ BDA designed equivalent ‘bits’ versus $\sim 10^9$ EDA ‘bits’).

This chapter is based on the results from the Workshop on the EDA/BDA Interaction Roadmap that was held on August 19-20, 2016 at Newcastle University, UK [6]. It is expected that both small and medium-sized enterprises as well as large companies will participate in electronic-biological system design automation.

2. Key challenges

There are several challenges that require additional research efforts to enable impactful thrusts in electronic-biological system technologies:

a) Collection, Organization and Validation of Experimental Data

- Characterization and novel abstractions for defining the biological programming languages require better-curated data than most experimentalists are currently gathering.
- Both business development and complexity management require development and adoption of standards and integration of disparate data sources.
- Experimental validation for designs needs to be incorporated as feedback into BDA tools and workflows.
- BDA needs clear and accessible spatio-temporal metrics and benchmarks for success.
- Formalization and capture of experimental protocols in a computer readable format.

b) System Level Design and Analysis

- Multi-scale modeling is needed, incorporating complex-systems understanding of self-organization, feedback, non-Markovian (memory) and emergent phenomena
- Design needs to support consideration of the full life-cycle, including deployment, maintenance, and disposal.
- There is a need for affordable “on the desktop” experimentation in the loop with design tools.
- Design conception to physical assembly workflows

3. Key Technical Areas

3.1. EDA-BDA Synergy

In contrast to modern Electronic Design Automation (EDA), the present Biological Design Automation (BDA) is much more fragmented and task-specific. The key limitations of BDA currently are the cost (in time and resources) of building and testing systems and the difficulty in accessing well-curated and relevant biological data. Some EDA tools have been or are being adapted for use in BDA [7]. In fact, lower-level genetic design

aspects of biological design have already drawn significantly from EDA [8]. However, most of the current approaches have drawn primarily on simple models of digital circuitry, and there is a need to move toward higher-level abstractions (i.e., free-energy landscape inspired automata that go beyond Turing machines) [9] that account for the spatio-temporal multi-scale and higher-order characteristics of biological systems.

It is insightful to compare the evolution of abstractions in semiconductors versus biology: In semiconductors, abstractions rose over time in stages, from the basic physical theory to isolation of regulatory components, then to circuits made of those elements, to standardized components for the modular assembly of circuits and finally, from standardized components to a progression of EDA tools for managing ever-increasing circuit complexity. For biological systems based on genetic expression, the basic underlying theory is well established, the components are identified and circuits can be constructed. Anticipating the BDA stage, many experimental tools have been constructed. The utility and application of these tools, however, is currently significantly impeded by the lack of a sufficient system of standardized components for modular construction of circuits. Until this precondition is fulfilled, it is unlikely that modular circuit construction will proceed to the level of complexity that is necessary to support and drive development of an effective ecosystem of high-level BDA tools.

There is already both sufficient task complexity and market to drive development of low-level BDA tools. For example, in converting from information to biology, BDA tools may be given a set of DNA sequences, then assist in the synthesis and assembly of those sequences, performing quality control on the products, and transforming those samples into the context where they will be evaluated (Figure 4.1). Also, BDA tools can assist in managing the execution of an experiment,

applying instruments to measure performance, and collating performance data for interpretation. The value of BDA in this context is in allowing engineers to focus more of their time and energy on the specification of the sequence (the “design” phase of a design-build-test loop), rather than the experimentation required for building and testing. Low-level BDA tools can also enable miniaturization and integration of the build and test processes, allowing more processes to be run much more cheaply and possibly at a faster rate. There is already a considerable amount of work in this field, both in the academic and corporate worlds, with a particular emphasis on development of flexible hardware platforms (e.g., robotics and microfluidics), and associated supporting software. A separate branch of development aims at “cloud labs” that would allow outsourcing of build and test efforts.

For high-level BDA, obtaining effective modular and standardized components requires maturation of a number of different supporting technologies. In order to support an effective “design kit” for synthetic biology (Figure 4.2), the following requirements need to be satisfied:

1. Fabrication must be sufficiently reliable to allow designs to be realized with cost-effective yield.
2. Models must be available to predict the behavior of designs with sufficient precision to guide choices between competing design options.
3. Simulation tools must be able to evaluate those models in reasonable time.
4. Characterization procedures must be able to capture the information needed for models.
5. Libraries of characterized devices must share a standard description of this information.

Figure 4.1: Low-level BDA focuses on automation of the transformations from information to biological matter and back, such as the tasks shown in this diagram [10]

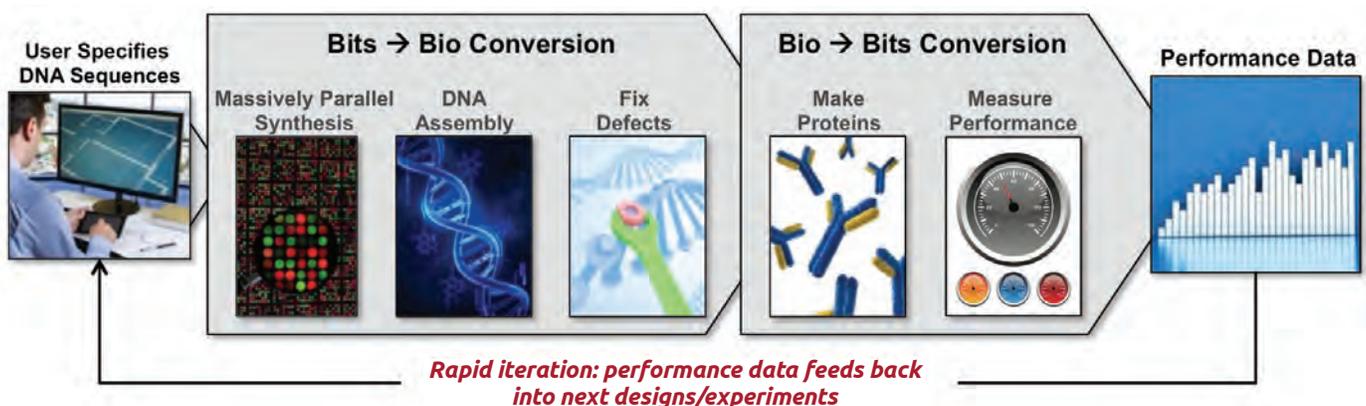
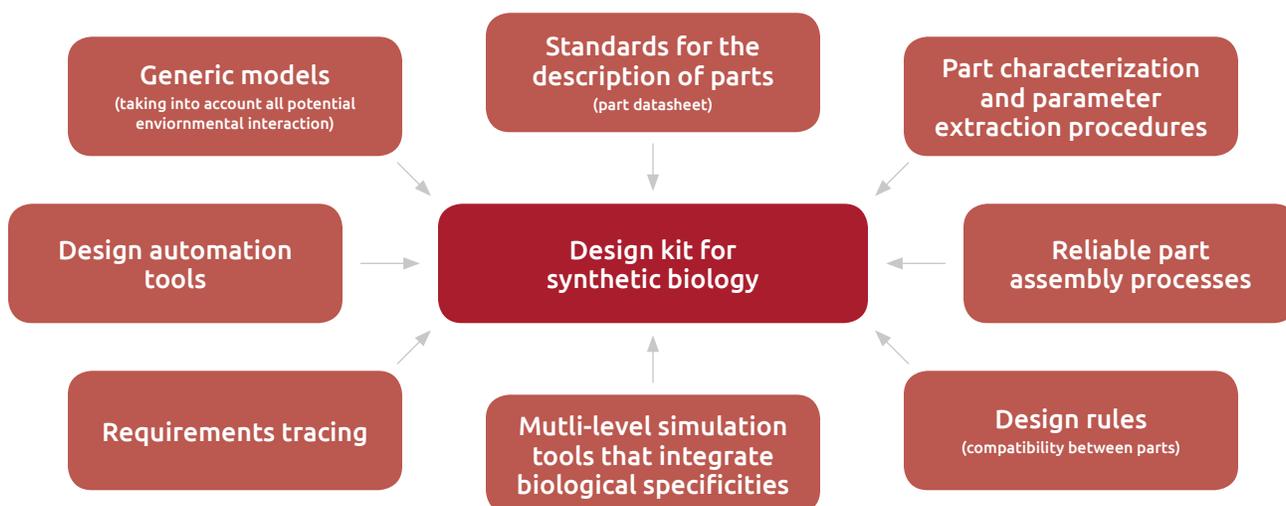


Figure 4.2: Supporting technologies needed for effective application of high-level BDA to organism engineering, adapted from [7].

6. Design rules must capture the intuitions of human experts for automatic application.

Only when all of these supporting technologies are available, can effective design tools be constructed to marshal them together into an effective “toolkit” for supporting biological engineering.

In some cases, there are specific opportunities for application of existing EDA tools. For example, it was shown that certain biological genetic regulatory network circuits can be mapped onto an equivalent electrical circuit description [11]. Once this mapping has been accomplished, existing EDA tools for analysis of electrical circuits can be directly applied, and their results translated back to the biological circuit in order to predict its properties [7].

In other cases, the restraints of biological engineering will impose challenges that the EDA tools are unlikely to be able to solve, requiring novel BDA-specific tools. This is already evident with many of the low-level BDA tools, which tend to be tightly linked with the biochemical models specific for biological processes and products. At higher levels of abstraction, it appears more likely that there will be more commonalities, driven by the universal and substrate-independent nature of information processing and control. The particular regions of that design trade-space that are emphasized, however, are likely to be different than are emphasized in much of EDA, e.g., involving more analog, hybrid, and uncertain elements.

Roadmap targets for EDA-BDA Synergy over the course of the next 20 years are summarized in **Table 4.1**.

3.2. Hybrid Semi/Bio technologies and Design Automation

Hybrid semi/bio technologies are suited for acceleration and scaling, especially DNA storage and bio/silicon devices such as instrumentation. The priority *technology development* areas identified by the SemiSynBio Roadmap committee are as follows:

Sequencing—Existing companies have been using and exploring semiconductors and computing, becoming more familiar with these technologies, but advanced integration is very limited. In particular, directly coupled chemistry/sensing and fluid technology has not scaled quickly. The value to semiconductor industry is becoming much more facile at working with DNA as a potential path to storage technologies.

Synthesis—Biotech companies are beginning to use silicon as a material, but with little of fabrication and integrated device expertise to incorporate active feedback and process control. Scaling of DNA synthesis (as was as other biopolymers) in cost and volume is progressing much slower than sequencing.

Lab automation (biochemistry, cell culture/assay, microscopy/instrumentation)—Adapting board/package and silicon to directly integrate with miniaturized microfluidics and optical systems appears ready for development. Commodity technologies are being utilized, but it is difficult for the

Table 4.1: Roadmap targets for EDA-BDA Synergy

2023	<ul style="list-style-type: none"> Widespread availability of effective and commercially viable BDA tools. Early tools are likely to also provide experimentalists with clear physical assembly plans. Standards for characterization and composition of biological components, backed by large databases of useful components that conform to those standards. Standard interfaces and tools that enable flexible workflows customized to lab and project needs. Effective sequence porting, optimization and tools applicable to the most common organisms and components. Widespread availability and integration of laboratory automation for key build and test workflow steps. Automation might be implemented either via local “black box devices” or via cloud/outsourcing. Integration of pathogen screening safety measures into key BDA tools. Effective exploitation of most EDA tools that are applicable to the BDA context. Formalized mechanisms to capture experimental protocols in software Routine BDA-assisted engineering of simple biological designs (< 10 functional units).
2028	<ul style="list-style-type: none"> Effective and commercially viable BDA tools based on analog and stochastic models. BDA workflows that enable complex designs largely without need for laboratory work, except for final verification and testing. Large numbers of “lab-less” biological engineers, similar to fabless electronics manufacturers. Mature informational and commercial ecosystem supplying biological components and modules at many levels of abstraction and complexity (by analogy to EDA, from “capacitor” to “op-amp” to “graphics card”). Widespread availability and integration of laboratory automation for all workflow steps. Integration of generalized threat assessment and management into BDA workflows. Routine BDA-assisted engineering of complex biological designs (up to 100 functional units).
2033	<ul style="list-style-type: none"> Effective and commercially viable integrated BDA/EDA workflows for hybrid bio-electronic systems. Laboratory automation displaces most of the manual experimental work.
2038	<ul style="list-style-type: none"> Mature BDA industry with segmentation of markets and separation of trades. Routine BDA-assisted engineering of biological designs at the scale of complex organisms (10^4 to 10^5 functional units)

biological community to access more advanced technologies, which have not been tailored to biological usages in high-volume manufacturing.

Adapting tools from EDA for hybrid semi/bio technologies design automation is straightforward, with fairly direct reuse of many classes of tools.

Table 4.2 presents roadmap targets for hybrid semi/bio technologies design automation over the course of the next 20 years.

3.3. Software Design Automation for Complex Biological and Electronic Issues

Understanding and engineering biological systems sets new goals and challenges for software engineering. There is a need for “bio-programming languages” and design representation standards that embrace multi-scale processes,

and for automated program synthesis tools to create software that meets specifications for complex biological-electronic systems. Current formal verification approaches are of limited use for biological systems due to the complex nature of both organisms and environment. Some of the drawbacks of current design and verification tools originate from the lack of accurate abstractions that can capture the spatio-temporal multi-scale characteristics of biological systems. Moreover, the abstractions, design and verification frameworks cannot quantify and explain the degree of emergence, self-organization, robustness and complexity we observe in nature [12]. Lower-level genetic design aspects are already benefiting from automation and from standards being the key to enabling abstraction, decoupling, and interchange. There is already a vast amount of available biological data that is barely usable at the moment. Semantics-mediated data integration may be an effective approach to integration, curation, and utilization.

Table 4.2: Roadmap targets for the hybrid semi/bio technologies design automation

2023	<ul style="list-style-type: none"> • Accessible microfluidics for most common assays. • Synthesis of the expertise of the biological and semiconductor communities, as well as experts in software development, to design hybrid bio/CMOS chips with applications in DNA synthesis, read/write nucleic acid-based memory. • Exploration of new biocompatible materials that can be readily integrated into the fabrication path. • Accessible software design of silicon-based microfluidic devices, similar in complexity to current FPGA or printed circuit board design.
2028	<ul style="list-style-type: none"> • Desktop laboratory-in-a-box systems. • Chip fabrication and realization of the designs developed in the 5 year vision. • Automatic conversion of a high-level description of a biochemical reaction or ongoing biochemical process into a customized device that can efficiently execute the reaction and/or process.
2033	<ul style="list-style-type: none"> • Affordable consumer laboratory-in-a-box.
2038	<ul style="list-style-type: none"> • Truly hybrid bioCMOS chips, combining biological and electronic logic. • Silicon-based DNA storage technology with CAD-designed fluidic subsystems.

Table 4.3 presents roadmap targets for software design automation over the course of the next 20 years.

Table 4.3: Roadmap targets for Software Design Automation for complex biological and electronic issues

2023	<ul style="list-style-type: none"> • Comprehensive spatio-temporal multi-scale models, on the scale of a complete bacterium up to a microbial community, integrated to support precision engineering. • Integration of all major human-curated biological databases into an effective federated resource to support biological design. • BDA tools based on asynchronous and stochastic computational abstractions.
2028	<ul style="list-style-type: none"> • Comprehensive models, on the scale of a complete eukaryotic cell, integrated to support precision engineering. • Automatic curation of biological databases • Biological engineering informational costs dominate lab work costs. • Biological engineering adopts agile software development practices such as test-driven development and continuous integration.
2033	<ul style="list-style-type: none"> • Comprehensive models, on the scale of a complex many-tissue eukaryotic organism, integrated to support precision engineering.
2038	<ul style="list-style-type: none"> • Agile development practices for biological engineering on same scale of complexity as agile software development.

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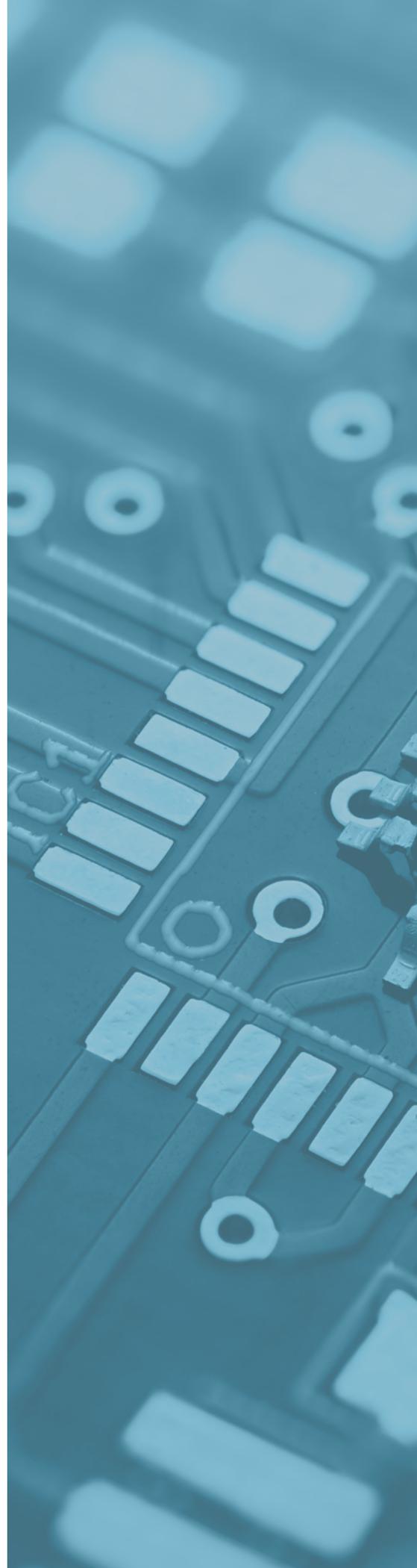
Chapter 5

Biological Pathways for Semiconductor Fabrication and Integration

1. Introduction

Semiconductor chip fabrication is very energy and resource intensive. Thus, the discovery of new manufacturing approaches that reduce these expenditures would be highly beneficial to the industry. In comparison, living systems fabricate complex nanometer-scale structures with high yield and low-energy utilization. For example, biological self-assembly occurs at a rate of $\sim 10^{18}$ molecules per second (at biological growth rates a 1 Gb chip could be built in about 5 seconds), and energy utilization of $\sim 10^{-17}$ J/molecule, which is 100x less than that of conventional subtractive manufacturing. Combining these capabilities of living systems with synthetic DNA- or protein-based self-assembly offers transformative potential for revolutionizing the synthesis of complex, sub-10 nm information processing architectures. Therefore, discovery of new paradigms of biology-based switches in biology, agriculture, and medicine, offer additional potential areas of major growth for the semiconductor industry.

For example, new manufacturing paradigms such as: i) the rapid three-dimensional, additive manufacturing with molecular and atomic precision, ii) bottom-up and self-directed processes, and iii) critical material interfaces may all provide a cost-effective path to the envisioned novel materials and architectures. Additionally, the convergence of semiconductor manufacturing and biology could offer new materials, processes and system designs for different classes of electronic products. These new manufacturing paradigms could enable cost effective manufacturing, to provide affordable solutions to industry and government customers, and stimulate innovation by small, medium and large businesses.



This chapter is based on the results from the Workshop on Biological Pathways for Electronic Nanofabrication and Materials that was held on November 16-17, 2016 at the IBM Almaden Research Center in San Jose, CA. In this workshop, specialists were convened from government, industry, and academia to examine the role of current research, either sponsored or conducted by them, might play in addressing some of the challenges faced by the industry. These experts provided perspectives on challenges and opportunities for utilizing biology to attain cost-effective fabrication pathways and materials for structures and devices to support future generations of sensing, computing, data storage and communication systems [1].

2. Key challenges

Several key challenges were outlined by the experts in the field:

- Achievement of nanometer resolution in biologically self-assembled systems
- Cost reduction of DNA synthesis
- Defect density reduction in DNA assembly
- Higher yields for biosynthesized materials and biological processes (>90%)
- Development of methods for self-assembly of complex sub-10 nm heterogeneous structures

3. Key Technical Areas

3.1. Bio-molecular nanofabrication

The focus of this technical area is on biomolecular-guided patterning and assembly for sub-20nm fabrication. Biomolecules such as DNA, RNA or proteins can provide a molecularly programmable mechanism for the development of a wide variety of structures and shapes. The unique capabilities of biomolecules in combination with the current top-down fabrication technology may enable new fabrication paradigms. A near-term challenge for bio-molecular nanofabrication is defect density reduction.

DNA nanotechnology shows promise for advanced lithography due to its ability to define nanometer-scale features. DNA can be used as a lithographic mask, and recently a hole pattern transfer from DNA origami into a SiO₂ layer with sub-10-nm resolution has been demonstrated [2]. The combination of a small-sized high-density pattern and the capacity to self-align versatile templates makes DNA-based lithography an intriguing candidate for next generation lithography [2, 3, 4], if the challenges such as registration control, achieving high yields, and high-precision assembly can be resolved. DNA can also be used to build conductive nanowires that could be implemented as potential nanoscale interconnects of both two-dimensional and three-dimensional geometries [5, 6]. **Figure 5.1** summarizes the results of fabrication of DNA-based metal nanowires over the years.

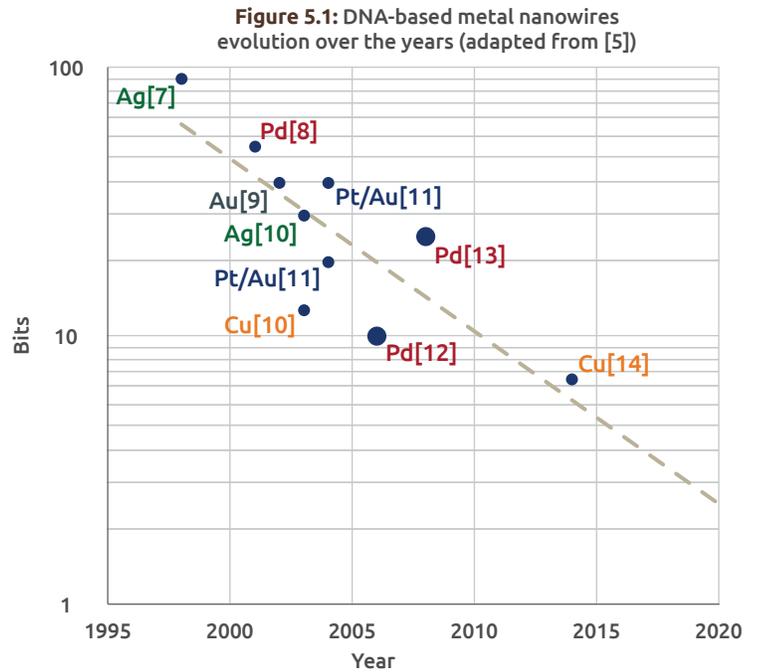
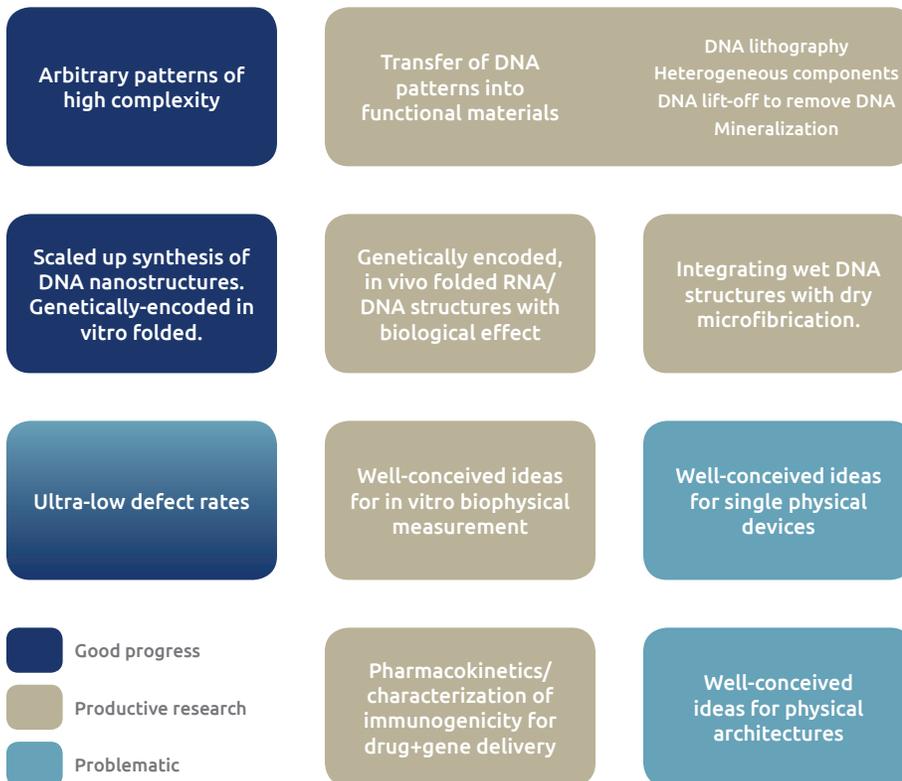


Figure 5.2: Flowchart of progress in DNA technology. Green boxes indicate the achieved goals, yellow is indicative of areas that are being pursued but still need more progress, and red indicates areas of research and implementation that are or could be problematic for the integration of DNA origami with semiconductor material. Adapted from [17].



Tremendous progress has been made in the last few years in producing arbitrary and complex patterns, scaling and defect reduction. The DNA origami method offers the unique addressability, modularity, and precision of DNA nanostructures, and the ease of DNA modification during synthesis with chemical and optical moieties offers many options for nanometer-scale patterning. Moreover, parallel production of massive amounts of DNA origami (~100 billion copies) at high yield (80-90%) can be performed in less than an hour. Current efforts in the field are focused towards precisely positioning a large number of chemically-diverse functional molecules on a lithographically-patterned chip. However, many issues remain to be resolved, including appropriate devices and architecture for taking advantage of DNA-based semiconductor fabrication (**Figure 5.2**). The current state-of-the-art technique of DNA origami is able to produce large-scale, precisely addressable patterns for controlling

Table 5.1: Roadmap targets for bio-molecular nanofabrication

2023	<ul style="list-style-type: none"> • Self-assembled 10 nm-scale metal-semiconductor junctions • Self-assembled 3D vertical nanowire transistor • Demonstrate ion channel devices with multiple functionalities such as photodetectors, diodes, transistors, etc.
2028	<ul style="list-style-type: none"> • Self-assembled, functional 5 nm-scale transistors • Controlled placement of arrays of 3D vertical nanowire transistors • Scalable production of single functional SRAM or multi-channel transistor by DNA-based 3D nano-manufacturing at 5 nm node • Demonstrate single ion channel devices with sub 10 nm features
2033	<ul style="list-style-type: none"> • Finalization of industry-compatible DNA 3D manufacturing process at 3nm node • Networks of ion-channel devices with neuronal computing capabilities
2038	<ul style="list-style-type: none"> • Self-assembling 3D computers and computational modules

nano-photonics devices [15]. Based on the demonstrated DNA-controlled self-assembly of different nanostructures, such approaches have the potential for making complex sub-10 nm semiconductor devices, such as transistors [16].

Recent efforts have also been directed towards developing CAD software that can enable fast and fully automated design of the 2D and 3D nanoscale objects of arbitrary structure and size [18]. Production of DNA structures at industrial scale requires novel, fast, and inexpensive synthesis methods. Also, current DNA nanostructure synthesis is energetically expensive, and methods that require minimum energy, e.g., isothermal self-assembly, should be investigated. Enzymatic or cellular low-cost single-stranded DNA synthesis approaches are being pursued. Isothermal, high-quality near-defect-free synthesis strategies are under development together with application to inorganic materials for long-term durability on the scale of hundreds to thousands of years.

Table 5.1 presents roadmap targets for biologically-derived nanostructures and materials for electronics over the course of the next 20 years.

3.2. Biologically-derived Nanostructures and Materials for Electronics

New methods need to be developed for sustainable high-volume production of nanoscale 2D and 3D parts, such as sustainable processing methods using DNA and other biopolymers. Engineered microorganisms (bacteria, viruses etc.) or cell-free

systems can also be used to produce a range of important chemicals, materials and structures for semiconductor processes and to self-assemble, pattern, organize, or repair organic polymers, inorganic materials, biopolymer materials, functional circuits, and/or electrical components.

Additionally, a new material base is likely to be needed for future electronic hardware. While most of today's electronics use silicon, this may not be a sustainable or optimal approach of tomorrow, as billions of heterogeneous sensor nodes are realized as a part of the "Internet-of-Things", many of which have short lifetime and must be discarded. Novel materials that can be implemented in future electronic components and systems and that can support sustainability through recycling and bio-degradability are of interest.

Cells could be employed to massively produce organic and inorganic materials and 3D hierarchical structures, typically under aqueous and ambient conditions. For example, photosynthetic marine microorganisms have significant potential to biosynthesize metal oxide semiconductors and functional polymers with defined nanostructure, and can assemble these materials into hierarchical structures using sustainable inputs, including inorganic earth-abundant materials and sunlight. One example is the production of biogenic nanomaterials from diatoms [19]. This class of materials include crystalline β -chitin nano-fibrils, biosilica, and gold and silver nanoparticles. Employing living cells to produce nanomaterials reduces the cost and energy of production, resulting in green production of the materials. Diatoms integrate soluble silicon into silicon exoskeletons that have patterns of 1-100 nanometers. Immense potential exists to harness the unique biosynthetic capacities of microscopic marine organisms for nanotechnology applications. Recently, DNA origami methods have been used to template silica composite nanomaterials into a variety of geometries, suggesting biomolecular strategies may also prove useful [20].

Cells may be able to produce useful electrically conductive materials. For example, *pili*, which are a bacterial protein 'nanowire' present on the surface of *Geobacter* bacteria, can play a major role in long-range electron transport between the cell and its surroundings [21]. The conductivity of the pili can be increased by genetic modification, which results in conductive protein filaments 2000-fold more conductive than the wild-type pili [22]. Typical length of the conductive pili is 10-50 μm , diameter 1.5-3 nm, and measured conductivities from 0.4 to nearly 1000 S/cm. These microbial nanowires were found to be stable in a diversity of solvents (water, chloroform,

DMSO, THF, hexane), in vacuum, at high-temperature, and over wide pH ranges. Devices can be produced from individual pili (“e-pili”), e-pili networks, and by incorporation of e-pili into polymeric materials. A gating effect was observed in the microbial biofilm and a field-effect transistor function was demonstrated [23]. A possibility of genetic modifications for new properties of the e-pili materials is envisioned.

A difficult challenge for implantable/ingestible bioelectronic devices is that 90% of device mass consists of packaging material and an energy source. Biologically-derived silk materials offer favorable opportunities for implantable bioelectronic devices due to their biocompatibility and biodegradability properties [24]. Vanishing (transient) electronics are electronic systems that physically disappear into the surrounding environment in a benign way. A passivation strategy for transient electronic devices was introduced that consists of encapsulation in multiple pockets fabricated from silk fibroin. The silk pockets have been shown to be useful for controlled modulation of device lifetime. Other application examples include diffractive optics, photonic crystals, metamaterials, optical fibers, waveguides, lasers, transistors, reabsorbable or biodegradable electronics for medical devices [25], RF antennas, and fuel cells [26].

The idea of ‘edible’ batteries was also introduced as a strategy for future implantable/ingestible devices [27]. The ‘edible’ batteries fabricated from biologically-derived melanin were demonstrated to exhibit increased charge storage capacity compared to other materials and are rechargeable [28].

Table 5.2 presents roadmap targets for biologically-derived nanostructures and materials for electronics over the course of the next 20 years.

Table 5.2: Roadmap targets for biologically-derived nanostructures and materials for electronics

2023	<ul style="list-style-type: none"> • Microbially produced electronic nanomaterials or structures see first use in conventional fab (e.g., inorganic nanowires, quantum dots, biomolecule-templated metal nanoparticle ‘wires’, e-pili materials, protein ion channels) • Processes for seamless 3D integration of living tissue and electronics
2028	<ul style="list-style-type: none"> • Programmable biosynthesis of multi-functional material structures, e.g., conductive core ‘wires’ surrounded by insulator.
2033	<ul style="list-style-type: none"> • In silico designed, self-assembled nm-scale materials palette
2038	<ul style="list-style-type: none"> • 3D arrays of 3D DNA materials assemblies

4. Summary and Examples of Current Research

This chapter presented a roadmap vision for biologically based electronic manufacturing. Some examples, of disruptive innovations and trends include:

- Demonstrating 3D hierarchical functional components and systems with biological approaches
- Constructing electronic materials, e.g., wires, transistors, diodes, capacitors, etc. from protein filaments or other structural forms, e.g., layers, capsules.
- Integrating abiotic and biotic elements, in particular approaches to effectively integrate biologically-derived materials, e.g., silk or bacterial electronic materials with semiconductor devices.
- Designing for “fault-tolerant” and/or “defect-tolerant” application spaces.
- Developing scalable bio-systems that involve communities of organisms for temporally and/or spatially controlled production of multiple or composite materials. Organisms can be used as factories for synthesis, patterning, testing, and repair of existing useful organic and inorganic materials.

Table 5.3 presents roadmap targets for electronic applications of biologically-derived components over the course of the next 20 years.

Table 5.3: Roadmap targets for electronic applications of biologically derived components

2023	<ul style="list-style-type: none"> • Materials and structures that support electronic components of ingestible medical devices • Sensing and drug delivery applications
2028	<ul style="list-style-type: none"> • Bionic Ears” • Smart surgical devices
2033	<ul style="list-style-type: none"> • Ingestible robots
2038	<ul style="list-style-type: none"> • 3D arrays of Architectures approaching the scale of biological systems: 10²⁰ biomolecules working together, dynamic systems that can adapt to the environment, self-heal, and self-optimize f 3D DNA materials assemblies

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Chapter 6

Ongoing Impact of the SemiSynBio Roadmap

1. New Initiatives

1. NSF-SRC SemiSynBio Program: The National Science Foundation (NSF) and Semiconductor Research Corporation have formed an industry-government partnership to fund research on the SemiSynBio topics (the program started in August 2018). Objectives: To explore semiconductor synthetic biology for information processing and storage technologies and to foster integration of research and workforce development. Amount: \$4M per year over three years, \$12M total.

2. Idaho Global Entrepreneurial Mission Award: The SemiSynBio team at Boise State University received a \$2M Higher Education Research Council Idaho Global Entrepreneurial Mission award from the Idaho State Board of Education to establish a world-class Nucleic Acid Memory (NAM) Institute (announced in August 2018). Objective: In support of future industries, the Institute will bring together the necessary infrastructure, resources, and expertise needed to pioneer NAM technologies and to educate a future NAM workforce.

3. ONR MURI Program: The Office of Naval Research (ONR) Multi-disciplinary University Research Initiative (MURI) topic was developed with input from the SemiSynBio Roadmap Committee (project selection for funding completed in February 2018). Amount: approx. \$1.5M per year over five years, \$7.5M total. Objectives: To explore SynBio-enabled synthesis, sensing, and control of microbial or microbially-produced electronic materials, circuits, and components, etc.

4. IARPA MIST program: The Intelligence Advanced Research Projects Activity (IARPA) Molecular Information Storage (MIST) initiative was developed with programmatic support from the SemiSynBio Roadmap Committee (program announced February 2018, the program is expected to start January 2019). Objective: To develop deployable storage technologies that can eventually scale into the exabyte regime and beyond. Amount: undisclosed (4-year program).

2. Complementary Roadmaps

The work of the SemiSynBio Technical Working Group (TWG)#3 on Intelligent Sensor Systems / Cell-semiconductor interfaces and TWG#4 on Biological Design is being extended to include Bioelectronic Medicine (BEM). A supplementary Bioelectronic Medicine Roadmap has been developed that is intended to guide a new collaborative industry-government initiative. This will be the first collaboration between traditionally different industries consolidating biotechnological, pharmaceutical and semiconductor companies and government agencies.

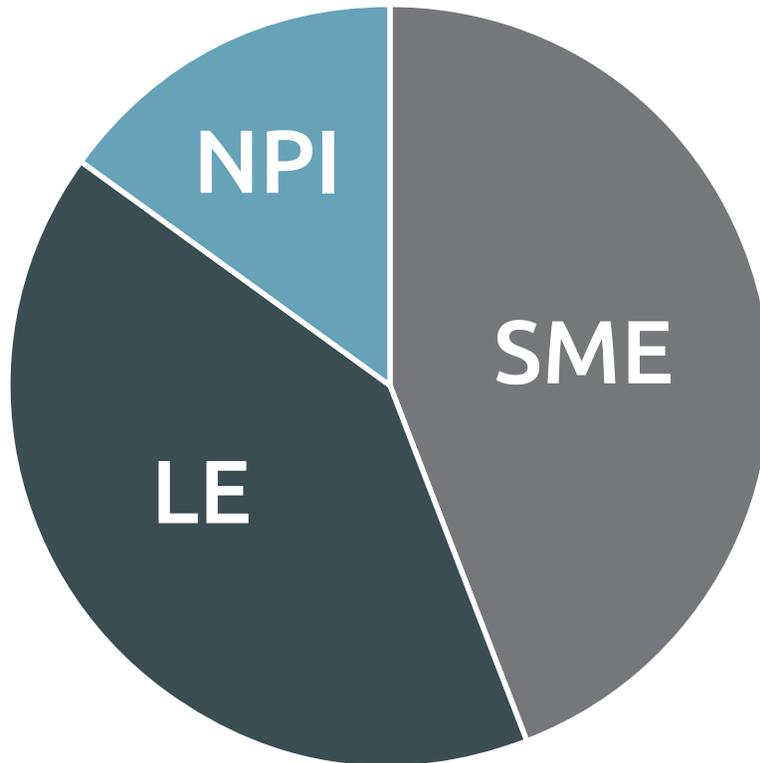
3. Collaboration with other consortia

Members of TWG#1 on DNA Memory and TWG#4 on Biological Design actively collaborate with the Genome Project—Write (also known as GP-Write): The GP-Write project was announced on 2 Jun 2016 as an extension of Genome Projects (aimed at reading genomes since 1984), now to include development of technologies for synthesis and testing of many genomes of microbes, plants and animals. The GP-Write project is now developing the GP-Write roadmap to track/project synthesis of large portions of many genomes aiming for medical advances.

4. Workforce Development

Several new research and development initiatives have been directly influenced and supported by the SemiSynBio Roadmap as stated in Section 1 of this Chapter. One of the strategic objectives of these initiatives is *to foster integration of research and workforce development*. SRC, a recipient of the National Medal of Technology, is a non-profit consortium of firms in semiconductor and related industries. As the premier technology research consortium for more than thirty years, SRC sponsors pre-competitive university research on behalf of its members. Having developed efficient tools and processes, SRC makes a critical contribution to the R&D activities. Since its inception, SRC has invested over \$2 billion in cutting-edge, pre-competitive university research, supporting over 10,000 students at more than 250 universities. Many of today's semiconductor industry leaders are former SRC supported students. Because its industry members are actively engaged in shaping the research program, providing oversight of and extracting value from SRC-funded research, SRC represents a particularly effective vehicle for technology transfer, commercialization, and workforce development.

Industrial Participantsⁱ



Small and Medium-Sized Enterprises (SME)ⁱⁱ

CatalogDNA (2), Cognit (1), GenoCAD (1), Gingko Bioworks (1), Koniku (1), OmniData (1), SynBioBeta (1), Turner Designs Hydrocarbon Instr. (1), Twist Biosciences (2).

Large Enterprises (LE)

Autodesk (1), IBM (1), Intel (2), GLOBALFOUNDRIES (1), Merck & Co (1), Micron Technology (1), Microsoft (3), Mentor Graphics (1), Raytheon (1).

Non-Profit Institutions (NPI)

SRC (4)

ⁱ The number in parentheses indicates the number of participating people from this organization

ⁱⁱ Definition of Enterprises by business size as given by <https://data.oecd.org/entrepreneur/enterprises-by-business-size.htm>

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