

Boise State University

ScholarWorks

Materials Science and Engineering Faculty
Publications and Presentations

Department of Materials Science and
Engineering

3-2019

Roadmap on Biological Pathways for Electronic Nanofabrication and Materials

Reza M. Zadegan
Boise State University

This is an author-created, un-copyedited version of an article published in *Nano Futures*. IOP Publishing Ltd is not responsible for any errors or omissions in this version of the manuscript or any version derived from it. The Version of Record is available online at [10.1088/2399-1984/aaf7d5](https://doi.org/10.1088/2399-1984/aaf7d5)

Roadmap on Biological Pathways for Electronic Nanofabrication and Materials

Mark Bathe

Department of Biological Engineering
Massachusetts Institute of Technology
Cambridge, Massachusetts

Linda A. Chrisey

Department of Defense
Office of Naval Research
Arlington, Virginia

Daniel J. C. Herr

Nanoscience Department
The Joint School of Nanoscience and
Nanoengineering
The University of North Carolina at Greensboro
Greensboro, North Carolina

Qinghuang Lin*

IBM T.J. Watson Research Center
Yorktown Heights, New York
qinghuang.lin@gmail.com

Adam T. Woolley

Department of Chemistry and Biochemistry
Brigham Young University
Provo, UT

Reza M. Zadegan

Micron School of Materials Science & Engineering
Boise State University
Boise, Idaho

Victor V. Zhirnov*

Semiconductor Research Corp.
Durham, North Carolina
Victor.Zhirnov@src.org

(Authors are listed in alphabetical order.)

Abstract

Conventional microchip fabrication is energy and resource intensive. Thus, the discovery of new manufacturing approaches that reduce these expenditures would be highly beneficial to the semiconductor industry. In comparison, living systems construct complex nanometer-scale structures with high yields and low energy utilization. Combining the capabilities of living systems with synthetic DNA-/protein-based self-assembly may offer intriguing potential for revolutionizing the synthesis of complex sub-10 nm information processing architectures. The successful discovery of new biologically based paradigms would not only help extend the current semiconductor technology roadmap, but also offer additional potential growth areas in biology, medicine, agriculture and sustainability for the semiconductor industry. This article summarizes discussions surrounding key emerging technologies explored at 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.

1. Introduction

The semiconductor industry has established the aggressive goal of continuing the scaling of Moore's Law by targeting feature sizes below 10 nm. The breadth and number of technological challenges faced by the industry, if it is to achieve this objective, is formidable, and unquestionably/undoubtedly requires revolutionary new materials and nanofabrication approaches. This article presents a summary of discussion points and conclusions reached at 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 convened from government, industry, and academia to examine the roles that their sponsored and internal research programs might play in addressing current challenges faced by the industry. These experts provided diverse perspectives on challenges and opportunities in utilizing biology to attain cost-effective fabrication pathways and materials for structures, devices, and systems for next-generation sensing, computing, data storage, and communication systems.

Section 2 of this article examines technological requirements for nanoelectronics fabrication. The Semiconductor Industry has developed unique tools and has accumulated extensive expertise and know-how in subtractive nanofabrication of complex structures and devices, with semiconductor devices from the 10nm-technology-node currently in mass production, and even a 7nm-technology-node in sight. However, the capital cost of a semiconductor fabrication facility has also increased exponentially, reaching as high as \$14 B per fab in 2015. Moreover, numerous technical challenges remain to be solved for the high quality and low-cost fabrication of future generations of semiconductor devices, including implementing nanoscale architectures with low defect levels, overcoming hard physical limits of photolithography, and implementing scalable metrology with nanometer resolution. Thus, discovery of new manufacturing approaches that either limit or significantly reduce escalating expenditures would be of major benefit to the industry.

Section 3 provides an assessment of several bio-molecular nanopatterning technologies that may be able to replace or supplement existing electronic fabrication processes. In particular, biomolecules including DNA, RNA, and proteins provide a programmable mechanism for the development of a wide variety of shapes and structures for diverse functions. The unique capabilities of biomolecules alone or in combination with current top-down fabrication technology offer intriguing possibilities for the implementation of entirely new fabrication paradigms. As radically new devices and system architectures emerge, there may be significant synergy with biologically based self-assembly fabrication techniques. A near-term challenge for bio-molecular nanofabrication is defect density reduction and synthesis scale-up with a dramatic reduction in cost.

Section 4 reviews several approaches to enabling sustainable high-volume production of 2D and 3D parts for sub-20nm fabrication, such as sustainable processing methods using DNA and other biopolymers. Engineered microorganisms can also be used to produce a range of important chemicals and materials for semiconductor processes with desired chemical composition, morphology, 3D structures and properties.

Electronic devices are typically three-dimensional structures composed of different materials whose properties and interfaces determine overall device performance. A new materials base may be needed for future electronic hardware, which would be biocompatible and support sustainability through recycling, bio-degradability, aqueous, and production at room temperature. Section 5 focuses on biological materials that have interesting opto/electronic/mechanical properties, which might be used in emerging devices and systems.

The Workshop on Biological Pathways for Electronic Nanofabrication and Materials sought to establish a 10-year vision for biologically based manufacturing for existing, as well as alternative, electronics. Potential items for a Roadmap are summarized in the conclusions section.

Key Contributors: This team gratefully acknowledges the contributions by all Workshop participants, especially the Workshop presenters, listed below, whose vision and insight is laying the convergent foundation for new generations of information processing technology:

Mostafa Bedewy (U Pittsburgh), Christopher Bettinger (Carnegie Melon U), James Boedicker (U S. California), Gregg Gallatin (Applied Math Solutions), Sharon Glotzer (U Michigan), Thomas LaBean (NC State U), Derek Lovley (U Massachusetts), Haitao Liu (U Pittsburgh), Hareem Maune (IBM), Fiorenzo Omenetto (Tufts U), Marco Rolandi (UC Santa Barbara), Paul Rothemund (CALTECH), Gregory Rorrer (Oregon State U), Thorsten Schmidt (TU Dresden), Rebecca Schulman (Johns Hopkins U), Scott Sills (Micron Technology), Raluca Tiron (LETI), and Hao Yan (Arizona State U).

2. Challenges with Future Nanofabrication Technologies

The semiconductor industry has been very successful in the last few decades at producing smaller, faster, and cheaper semiconductor devices at a pace of about 18 to 24 months per generation. It has grown to be an enormous industry with an annual revenue of over 340 billion US dollars in 2017. The advances in semiconductor technologies has fundamentally altered the way people work, communicate, do business, receive healthcare, and interact with one other.

Nanofabrication: State-of-the-Art and Current Challenges

Modern semiconductor devices consist of three types of materials: electrical conductors, semiconductors and insulators. These multilayer devices are fabricated via the deposition of these three types of materials, followed by patterning with photolithography and reactive ion etching in an ultra-clean factory called a “fab”.

The success of the semiconductor industry in the last six decades has been fueled by continuous down scaling of semiconductor devices to offer smaller, faster and cheaper electronic products that now enable the “Internet of Things” and ubiquitous devices such as mobile phones and fully integrated personal hand-held devices such as the iPhone. This device scaling has been made possible by optical lithography with reduced optical wavelength of the light source, improved optics and imaging materials, continuous innovation in manufacturing approach, and larger wafer sizes. Indeed, lithography has consistently delivered about 35% cost reduction per transistor for every new generation of IC products until the state-of-the-art 193nm immersion lithography hit a practical limit of about 40 nm half pitch with a single exposure.

This practical limit of 193nm immersion lithography has been surpassed using an innovative patterning process called “multiple patterning”, in which dense patterns are decomposed into sparser patterns, and patterned multiple times, to ultimately form the desired dense synthetic pattern. The most advanced chip in mass-production contains billions of transistors per chip, and with critical feature sizes down to 14 nm. They are fabricated using a 193 nm immersion double-patterning process.

Several other lithography technologies are being considered for future generations of semiconductor manufacturing. They include extreme ultraviolet (EUV) lithography with a wavelength of the light source of 13.4 nm, directed self-assembly (DSA) lithography with diblock copolymers, and electron beam lithography. Current estimated patterning capabilities, challenges and possible solutions to these challenges are listed in Table 1.

Table 1: Current estimated patterning capabilities, challenges and possible solutions to these challenges.

Technology Option	Resolution (Half pitch, nm)	Overlay (nm)	Challenges	Potential Solutions
193 nm Optical Lithography, Double Patterning *	20	3.0	Cost, placement error	Additive selective deposition, Self-patterning
Extreme UV (EUV) Lithography	~15	3.5	Source power, cost, resist resolution & LER, extendibility beyond 5 nm node	High power source, High NA EUV optics, Non-CAR resist
Directed self-assembly (DSA)	~ 20	N/A	Design rules, resolution, defects, pattern quality	High-Chi block copolymers
E-beam Direct Write Lithography	~20	N/A	Resolution, productivity	N/A

* 193nm immersion self-aligned double patterning, CAR = Chemically amplified resist, LER = Line edge roughness, NA= Numerical aperture

Higher resolution capabilities of each of these patterning technologies have been demonstrated in research laboratories. Another promising patterning technology, nanoimprint lithography, has been shown to resolve astonishingly small features. It has, however, been mostly developed for possible applications in the hard disc and memory industries.

A snapshot of current capabilities of the state-of-the-art 193 nm immersion lithographic tools is presented in Fig. 1¹.

- Exposure Rate: (300 mm diameter wafers) ~ 175+ wafers per hour (24/7)
 - Alignment Time + Exposure Time ~ 20 seconds + 20 seconds = 40 seconds
- Feature Sizes ~ 10 - 20 nm (or less)
- Feature Edge Placement < 2 nm (Controlled...not random)
- Number of features generated per exposure ~ 10^{14}
- At most 1 defect per wafer per exposure... *usually 0 defects per exposure*
- Tool Life ~ 7 years with >95 % "uptime" (availability)
- Amortized Tool Cost per Exposure ~ \$10!

Fig. 1. Capabilities of modern lithographic tools¹

However, optical lithography faces many challenges due to fundamental physics limitations in the nanometer regime, with the immediate economic consequence of increased cost (Fig. 2).

While the general public is familiar with the remarkable achievements of the semiconductor industry, the economic bottlenecks of semiconductor manufacturing that exist currently are not fully appreciated. The capital cost of a semiconductor fab has increased exponentially over time², exceeding \$14 Billion in 2015³ (Fig. 2).

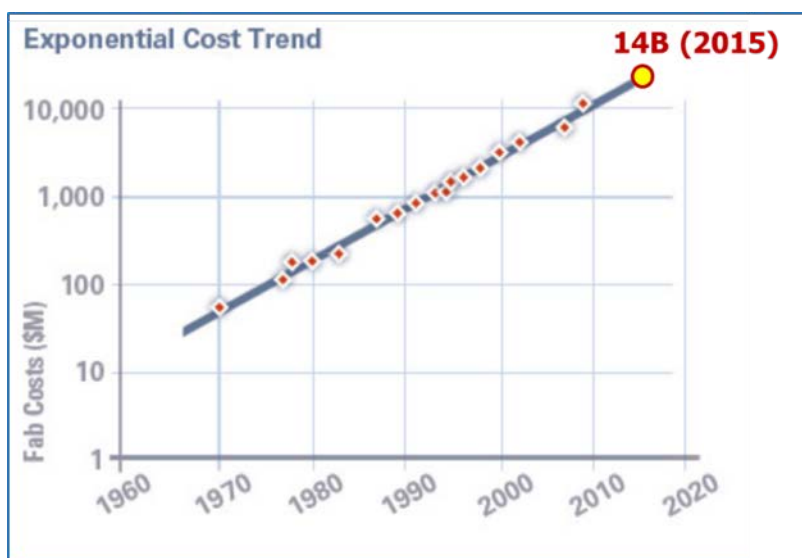


Fig. 2. Cost of semiconductor nanomanufacturing⁴

The fundamental economic driver of the semiconductor industry in the last 30 years has been to decrease of the cost per transistor in an integrated circuit. Recent indications suggest that it will be difficult to maintain the historical cost-per-transistor reduction trend in the future¹ (Fig. 3).

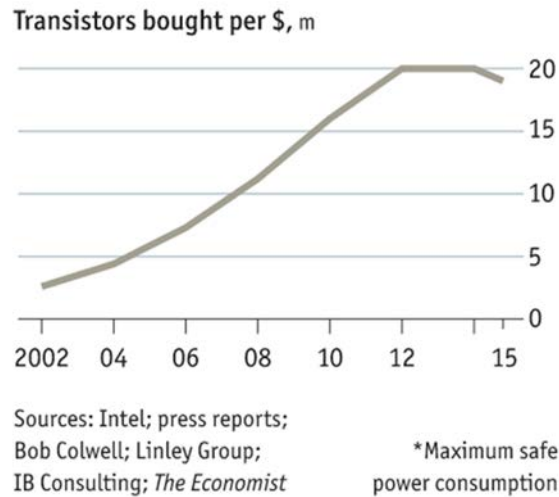


Fig. 3. Transistors that can be bought per dollar at different chip generations¹.

As a consequence, the semiconductor industry is currently exploring various new manufacturing technologies that could reduce cost and expenditure of resources for chip fabrication, including novel polymeric, biological, and biomimetic routes to electronics nanofabrication. Since it appeared in the 2007 International Technology Roadmap for Semiconductors (ITRS) as a potential patterning solution, the semiconductor industry continues to evaluate relatively simple forms of directed block copolymer self-assembly, as a resist, for advanced chip fabrication⁵.

Because living systems create complex 3D structures with high yields and low energy utilization, a key focus is to explore how biological principles might be applied to develop a revolutionary low-cost, high-yield nanofabrication technology. While Nature uses holistic processes of self-organization and self-assembly, programmable self-assembly of complex sub-10 nm semiconductor structures is currently beyond our reach.

Directed Block Copolymer Self-Assembly

Di-block copolymers, where the two polymer blocks are linked together by a covalent bond at the junction, exhibit a remarkable ability to self-organize (self-assembly) into a morphology of distinct patterns, depending on the chemical interactions between the two blocks and the volume fraction of each block. When directed by a lithography pre-pattern, these block copolymers exhibit potential as smart resists for sub-lithographic patterning, and there are ongoing efforts to demonstrate the feasibility of integrating the self-assembly (bottom-up) methods into semiconductor fabrication processes (Fig. 4⁶).

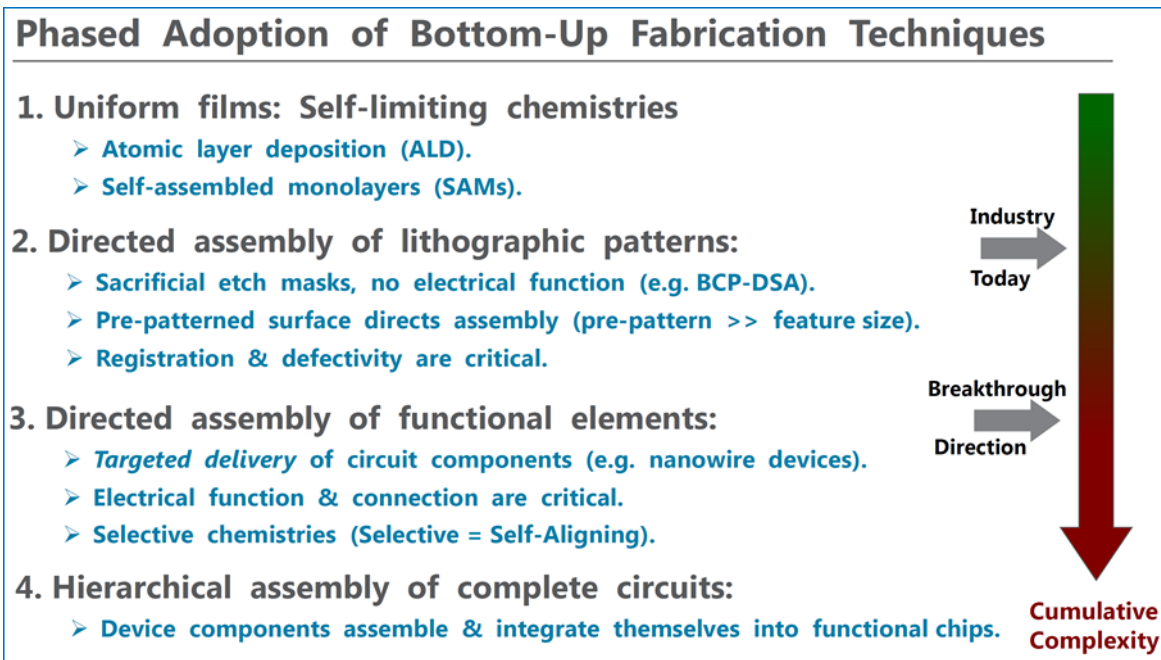


Fig. 4. A prototypical roadmap for phased adaption of bottom-up fabrication techniques⁶.

While sub-10 nm periodic structures made by DSA have been demonstrated, significant improvement is required in local critical dimension uniformity. The critical challenge for DSA is *defectivity*, as structural defects in DSA patterns are thermodynamically allowed. Minimizing DSA defects requires molecular degrees of freedom to control the configurational space: in other words, ‘smarter molecules’ are needed, e.g., nucleic acids and others used in biology. At this point, there are no quantitative assessments of self-assembly that characterize the informational content delivered to the material structure. Another unexplored direction, which is beyond current industrial R&D is directed self-assembly of functional circuit components.

Theoretical Drivers for Innovation in Nanofabrication

From an information theory standpoint, manufacturing is increasing material information content⁷, and as such is analogous to computation. Fig. 5 compares examples of subtractive (top down semiconductor fabrication) and additive (bottom up programmed self-assembly of a complex 3D biological system) processes as a form of information transfer. A corresponding metric for nanomanufacturing can be defined as the product of energy (e.g., energy of fabrication per atom), time (e.g., time needed to define position of one atom in the materials system), and ‘waste’ (e.g., a function of entropy, the total number of atoms participating in the process, but not becoming part of the resulting materials system, etc.), as shown in Fig. 6. The product of energy and time is inspired by the least action principle of physics, where many physical systems operate in a manner to minimize this product, whose time integral is known as the action⁸. The ‘waste’ resulting from fabrication is included in the metric to reflect the importance of the cost-efficiency of the manufacturing process.

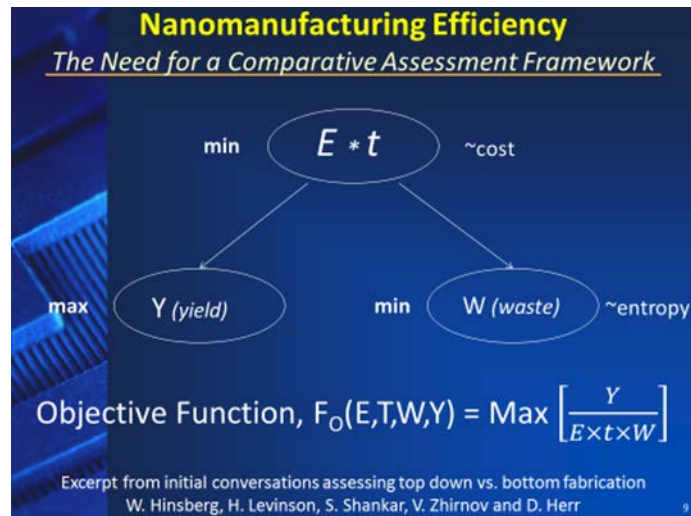


Fig. 5. A possible metric for nanomanufacturing efficiency⁹

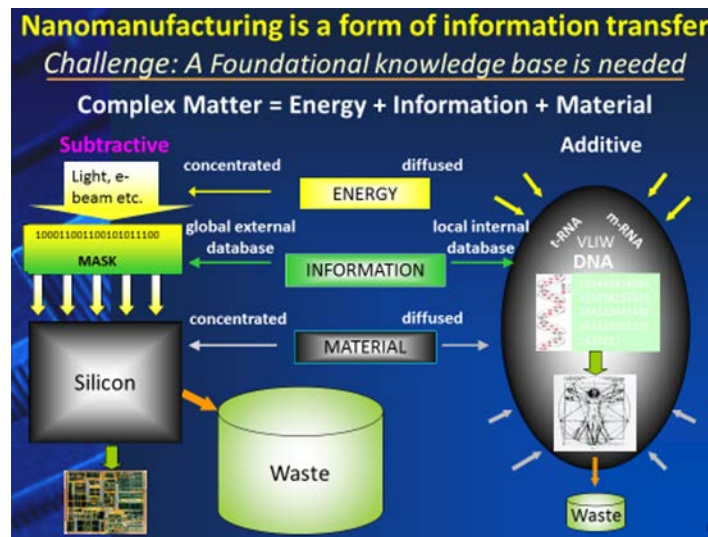


Fig. 6. Nanomanufacturing as a form of information transfer: Subtractive vs. additive⁹

An important theoretical task is to investigate the information sources and channels that convey the assembly instructions for self-organization of matter into complex structures and to quantify associated energy and waste costs.

To summarize, several technical and economic issues have been highlighted in this section:

The escalating capital expenditures and process costs in traditional semiconductor fabrication are unsustainable and therefore susceptible to disruptive innovation. Biological pathways, such as DNA/protein-based self-assembly, offer tantalizing possibilities for revolutionizing the fabrication of complex sub-10 nm information processing architectures.

However, integration of these disruptive biological nanofabrication processes into high-volume manufacturing is expected to face significant barriers due to substantial investments in the traditional fabrication infrastructure and associated inertia that will resist change in the semiconductor industry. One possible solution is a hybrid approach where the biological pathway is adopted to augment the capabilities of traditional fabrication processes.

One key advantage of the biological pathway is for application in “fault-tolerant” / “defect-tolerant” information storage and processing systems. A summary of the discussion on fault/defect-tolerant aspects of bionanofabrication is as follows:

- In electronics, a defect corresponds to a difference between an intended and actual structure. All current lithographic processes are imperfect, as reflected in e.g. line-edge roughness, the loss of pattern fidelity between layout and patterned wafer, etc. Correspondingly, a fault reflects a functional variance from desired behavior. A specific defect, depending on its size, type and location, may or may not cause an acute functional fault. For information processing systems, each technology node defines a set of acceptable defect attributes/levels that qualify the manufacturing processes as defect intolerant. Also, for a given system, a functional fault may or may not lead to functional errors or system failure, depending upon application and architectural considerations.
- For biological systems, one could argue that biofabrication is considerably more defect intolerant than current semiconductor manufacturing. For example, a 0.5 nm defect might be tolerable in the projected 2017 DRAM (22 nm) and MPU (18 nm) minimum half pitch structures. However, the change in one nucleic acid base, which is ~0.3 nm long, from adenine to thymine is responsible for the expression of human sickle cell anemia. The difference is in the set of acceptable defect attributes for each fabrication technology and application.
- For scaled wafer processing, it remains unclear whether some form of “bottom-up” self-assembly will achieve the low level of defectivity, cost effectively, in a high-volume manufacturing environment. Unlike the enzyme-controlled replication and adaptive error correction of DNA in living systems, a finished integrated circuit is a static set of structures.
- From this point of view, it seems there are two possible options that could enable a “bio” approach to be favorable:
 - Change the way chips are designed so that they are defect tolerant.
 - Find an application for the “bio” approach, other than patterning, in the semiconductor industry (or elsewhere), that is resistant to defects or even requires disorder.
- As biologically-enabled semiconductor R&D program initiatives evolve, it might be useful to develop a matrix that highlights the convergence between specific design and manufacturing-induced defect attributes, for various fabrication modes, e.g., top-down, DSA, etc.; and the set of tolerable defect attributes, e.g., size, shape, location, composition, molecular structure, etc., for the desired application, etc.

3. Bio-Molecular Nanopatterning: Controlling Sub-20nm Structures

Precision in registration of components is a key challenge in chemistry and materials science of surfaces. In biological systems, macromolecules such as DNA, RNA, proteins, lipids, and carbohydrates provide the necessary programmability to control the location, orientation, and geometry of molecular components. These molecules provide modular on-demand precision that, via controlled interactions, construct the infrastructure of entire cells, organs and tissues. Leveraging the programmability of biomolecular self-assembly, particularly nucleic acids and proteins, the semiconductor industry might be able to inexpensively create patterns with the sub-20 nm structural resolution that it is striving for. In this section we discuss state of the art methods for deposition of artificial biological parts, nucleation and growth of large arrays, and registration and alignment of nanostructures.

DNA Origami Deposition, Registration, Alignment, and Pattern Transfer

Scaffolded DNA origami is a method in which a long single-stranded DNA is designed to fold into geometrically defined nanoscale structures with the help of short, accessory ‘staple’ oligonucleotides. Using this method, almost any desired shape and structure can be made on the 1-200nm scale, although there are several limitations. The unique addressability, modularity, and precision of DNA nanostructures, and the ease of DNA modification with chemical and optical materials during synthesis offer potentially nanometer-scale patterning abilities. Moreover, parallel production of massive amounts of DNA origami (~ 100 billion or more copies) at high chemistry-scale yields (greater than 90%) can be performed within 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. (Fig. 7). Rothmund's group showed the robustness of this method when they positioned molecular emitters in photonic crystal cavities and were able to monitor the local density of each component and their orientation.

However, a concern is the fact that to date the application of DNA origami in semiconductor patterning has been limited as the structures, and their precise positioning and registration, are usually error-prone. Some stakeholders believed there is not enough motivation (lack of applicable platforms for DNA origami) for the integration of DNA origami with the semiconductor industry at the moment, and that the features of DNA origami-semiconductor

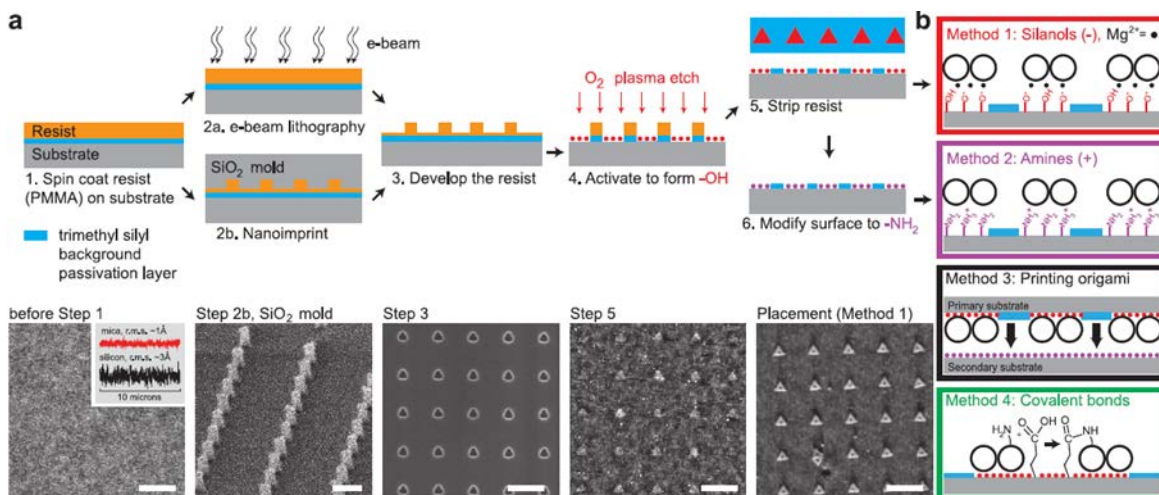


Fig. 7. DNA origami registration and immobilization on patterned surfaces. (a) Steps in patterning of triangular binding sites on an SiO₂ substrate via e-beam lithography, (b) Methods of origami registration on the patterned surfaces¹⁰.

interfaces which are road-mappable –such as producing arbitrary and complex patterns, scaling, and defect metrology – are not critically hard to solve (Fig. 8). The contributing community may need to focus on how to take advantage of the defects in the method rather than focusing on reducing defect rates. However, this approach was also questioned by some of the participants, since minimal scientific effort and research investment has been devoted to defect reduction using traditional (chemical modifications) and non-traditional (photo-crosslinking, etc.) means. This is particularly true when compared with the scale of investment devoted, for example, to polymer synthesis and metal forming and casting. Nonetheless, the current state of the art for DNA origami is to produce large-scale, precisely addressable patterns for controlling nanophotonic devices. These might be used to produce on-demand single photon light sources for quantum cryptography, communication and computation.

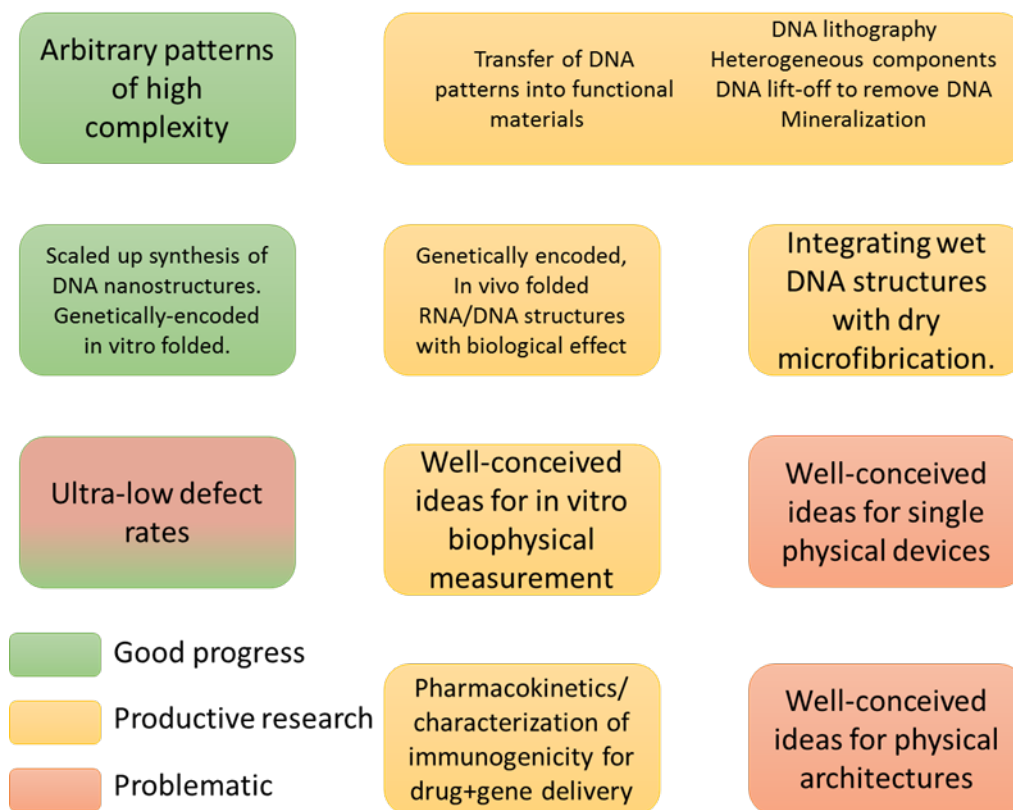


Fig 8. Flowchart of DNA origami-semiconductor interactions. Green boxes indicate the achieved goals, yellow is indicative of areas that are being pursued but still need more progress, and red indicates areas of research and implementation that are or could be problematic for the integration of DNA origami with semiconductor material¹¹.

Complex DNA Nanostructure Construction

Recent efforts have been directed towards developing top-down design software that enables the fast and autonomous design of 2D and 3D nanoscale objects of arbitrary structure and size that can be used for applications within and beyond biology^{12,13,14}. Production of DNA nanostructures at an industrial scale requires new, inexpensive synthesis approaches since current chemical DNA synthesis methods for oligonucleotide synthesis are costly. A reported application of a helper phage system from Bradbury et al.¹⁵ introduced the biological technology needed to scale-up sequence- and length-specific scaffold for low-cost bacterial production of scaffolded DNA origami, with non-chemically-modified staples being produced using an innovative DNAzyme approach¹⁶. Because current DNA nanostructure synthesis via thermally controlled self-assembly is energetically expensive, new methods that require minimum energy, e.g. isothermal self-assembly, should be further explored. Recent work from Bathe's lab has resulted in a fully automated, top-down CAD software that enables autonomous sequence design needed for arbitrary 3D scaffolded DNA origami objects (Fig. 9)¹². Production of ssDNA scaffolds of arbitrary length and sequence within the 1-5kb scale needed for these objects was presented together with high-resolution single-particle cryo-electron microscopy data demonstrating high structural fidelity in synthesized objects. Bathe's lab is extending this automated, top-down design approach to include arbitrary 2D and 3D geometries with increased rigidity of DNA-based edges. Low-cost cellular production of single-stranded DNA is being used together with alternative scaffold routing design approaches to eliminate the use of staple strands. Isothermal, high-quality, near-defect-free synthesis strategies are also under development.

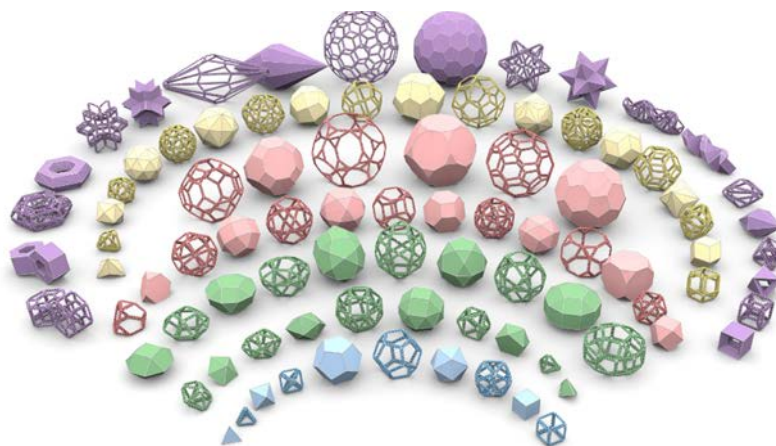


Fig. 9. DNA can be used to produce various complex 3D nanostructures¹²
(Figure courtesy Digizyme, Inc.)

Pattern Transfer from DNA Templates to SiO₂

Another important issue to be addressed is pattern transfer from DNA templates to inorganic materials¹⁷. One successful example has been demonstrated by the Liu group, where they've taken advantage of HF chemistry to transfer patterns created with DNA molecules, as shown in Fig. 10. HF etching is a water-dependent process that can be used to etch silicon dioxide surfaces for a negative tone nanoimprinting method. Both negative and positive etching of SiO₂ surfaces were demonstrated successfully. Using atomic-layer deposition, silicon or titanium surfaces were precisely patterned with nanometer scale resolution. One might assume that DNA is fragile, and that exposure to various chemical and physical conditions might affect the integrity of DNA structures, which would not bode well for its utility for the semiconductor industry. However, the Liu group reported that DNA can tolerate select harsh processing conditions such as heat treatments of up to 200°C for 10 minutes or being immersed in various organic solvents for 24 hours.

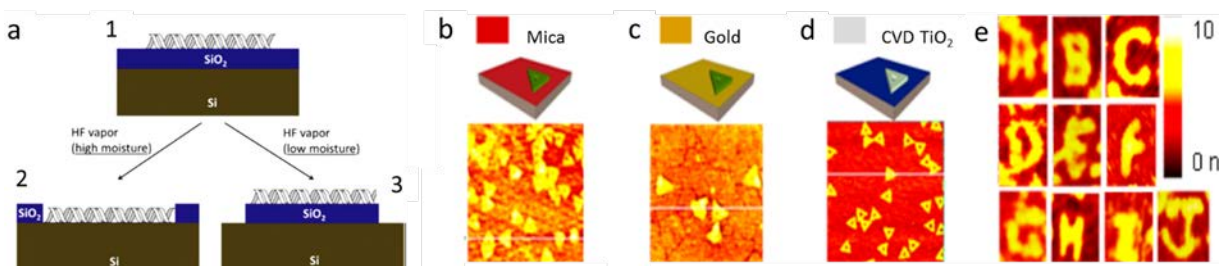


Fig. 10. Pattern transfer (a) Illustration of pattern transfer from DNA to SiO₂. (1) DNA deposited on the SiO₂ surface. (2) Negative tone pattern transfer to SiO₂. (3) Positive tone pattern transfer to SiO₂. AFM analysis of various shape and size pattern transfer from DNA to SiO₂. (b-d) Cartoon representations (top) and AFM images (bottom) of positive-tone triangular patterns on various surfaces. (e) High-resolution AFM images of some positive-tone SiO₂ printed letters¹⁸.

DNA Origami Mask for Sub-Ten-Nanometer Lithography

DNA nanotechnology shows promise for advanced lithography due to its ability to define nanometer scale features¹⁹. DNA can be used as a lithographic mask, and recently a 9×14 nm² hole pattern transfer from DNA origami into a SiO₂ layer with sub-10-nm resolution using anhydrous HF vapor in a dedicated semiconductor industry etching machine has been demonstrated (Fig. 11²⁰). The resulting SiO₂ pattern maintained fidelity to the DNA origami structure within a process time ranging from 30 to 60 s at an etching rate of 0.2 nm/s. 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. Nevertheless, challenges such as registration control as well as achieving high yields and high precision assembly are prerequisite for their wide adoption in the future. A systematic study to assess these challenges should be implemented.

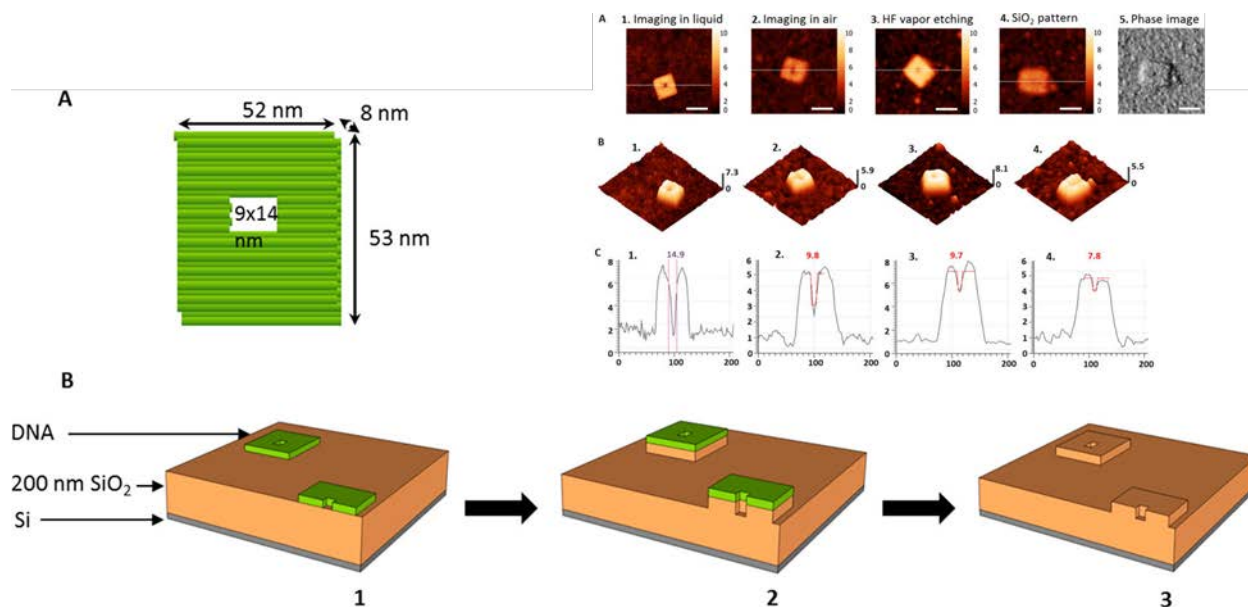


Fig. 11. Pattern transfer from DNA origami into SiO₂: (A) 3D DNA origami structure with 8 nm thickness. (B) 1. DNA origami are adsorbed on a Si substrate containing 200 nm of hydroxyl-terminated SiO₂. 2. Substrate is dried and then undergoes an HF vapor etching allowing the pattern transfer from DNA origami to SiO₂. 3. DNA mask is removed from the substrate to reveal the SiO₂ patterns.²⁰

Casting Inorganic Molecules, Metallization of DNA, and Hybrid Systems

Another example of a DNA nanostructure application is for inorganic material templating (Fig. 12)^{21,22}. Researchers have been able to develop methods that lead to the assembly of precise and geometrically defined inorganic 3D nanoparticles. Future directions may focus on mesoscale structure constructions, reducing the cost of assembled materials and autonomous defect repair mechanisms. After assembly of the DNA nanostructures, metal particles can be cast and grown inside the 3D DNA nanostructures, where they adopt the geometry defined by the nanostructure.

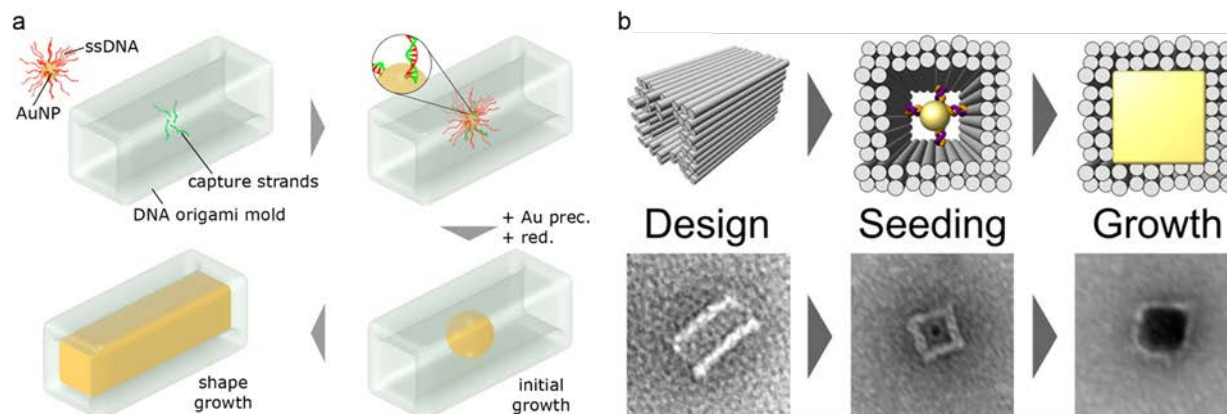


Fig. 12. DNA structures are being used to cast geometrically predefined inorganic particles²¹.

The DNA nanostructure community has a 10-year vision of constructing a hybrid, fully functional transistor, and 20-year vision of constructing 3D transistors using DNA materials. Issues that need to be addressed include cost reduction of DNA synthesis, achieving yields that exceed 90%, increasing dimensions to the micrometer scale and integration

of DNA with metals and other electronic materials. Woolley *et al.* have demonstrated construction of DNA-metal conjugates at the nanoscale²³. Plating of gold lines onto DNA origami by this group is illustrated in Fig. 13. Systematic tweaking of reaction conditions –varying magnesium ion concentration, hybridization time, ratio of nanoparticles to DNA origami, and freshness of nanoparticles– was important for optimal deposition of metal particles onto DNA nanostructures.

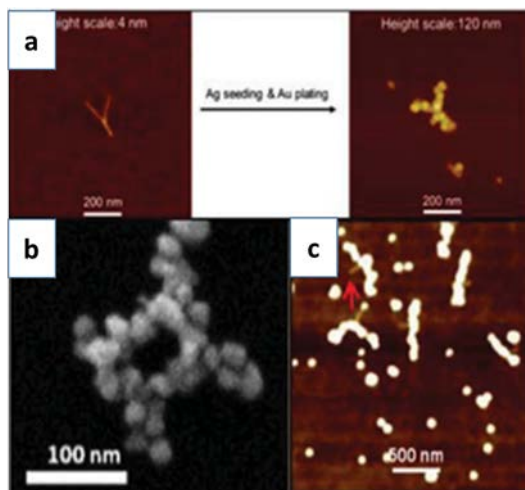


Fig. 13. Metallization of DNA origami (a) AFM images of a branched DNA origami structure before and after metallization²⁴; (b) SEM image of a palladium-seeded, gold-plated DNA origami structure²⁵; (c) AFM image of selective metallization along thin DNA origami structures²³.

Another example of hybrid materials is the DNA-guided assembly of carbon nanotubes into 2D and 3D complex structures that could have semiconductor related applications (Fig. 14). The challenges for such a system include: quality of assemblies, impurities, aggregation of materials, physical stability of the structures, quality of directionality and placement, and uniformity of assembled structures. However, the DNA nanostructure community believes that this research has provided processes that could be used for other materials and systems.

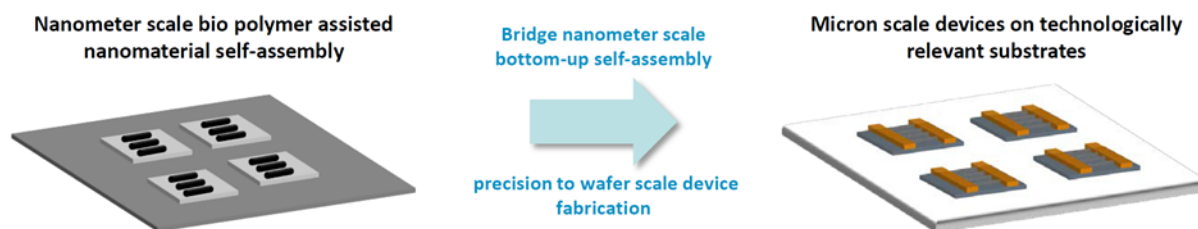


Fig. 14. A scheme to scale the DNA mediated self-assembly process and viably integrate it into conventional device fabrication methodologies²⁶.

Protein Based Nanofabrication

Proteins and amino acids are among the promising nano-manufacturing building blocks. For example, Jerala's group produced a tetrahedral structure that self-assembled from a polypeptide chain of 12 concatenated coil-forming segments and flexible peptide hinges (Fig. 15a)²⁷. Other efforts to design and produce protein-based nanostructures include the Baker group's 2D protein array that self-assembled through noncovalent protein-protein interactions²⁸. This method resulted in extended arrays at the micrometer-scale. Moreover, the structures were produced both in tubes and inside live cells; the latter provides a potentially inexpensive route to mass production. Other examples include work by Ohno and Inoue who demonstrated that RNA-protein complexes could be used to produce simple nanostructures with feature sizes of ~15 nm, as shown in Fig. 15b²⁹. However, the field of protein nanostructure manufacturing is still immature, where the design principles are not fully understood, programming and

computational tools are not universally applicable, the control of structure stability as well as performance is still challenging, and production of geometrically well-defined complex and large artificial proteins is not feasible at this time. Hence, our knowledge and ability to control protein assembly is limited compared to DNA assembly. However, a currently feasible pathway is the use of naturally occurring proteins that spontaneously self-assemble, such as those that form viral capsids. Capitalizing on recent progress in industrial biotechnology in food processing, cosmetics, and textiles, the path to commercialization of cost-effective protein-based nanomanufacturing can be accelerated.

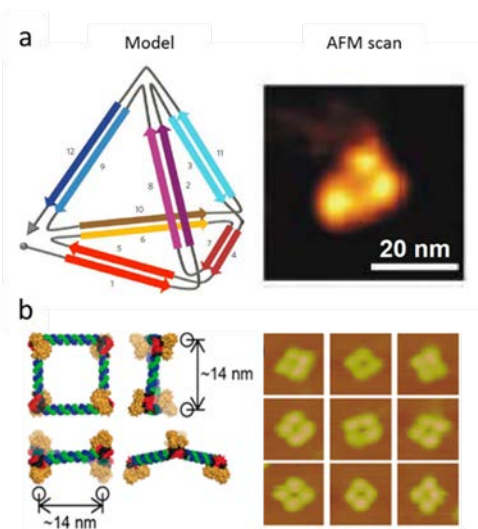


Fig. 15. Examples of synthetic protein based nanostructures. (a) Schematic and AFM image of 3D structure of synthetic protein²⁷, (b) Three-dimensional models and AFM image of square shaped RNA-protein complex²⁹.

To summarize, the following topics have been highlighted in this section:

Directed self-assembly using biomolecules like DNA or proteins is a powerful tool for patterning applications. Directed DNA or protein self-assembly could be adopted in three ways: (1) serve as a sacrificial layer and/or as etch mask; (2) to precisely place functional components in 3D space; (3) to template the organization of organic or inorganic materials into 2D or 3D structures.

Opportunities for future research include (but are not limited to): scalability, yield, feature size, resolution, object orientation, defect concentration, and domain size. Moreover, surface chemistry, deposition conditions, and nucleation and growth of the patterning materials should be carefully studied and benchmarked for the semiconductor industry.

4. Biological Nanofabrication and Cellular Factories

Today the viability of Moore's Law has come into question, and the profitability of the semiconductor fabrication industry may be preserved by expanding into other types of markets such as devices for the internet of things (IoT). For example, wearable or ingestible physiological monitoring or diagnostic devices offer an additional consumer industry for electronic devices, which may also have a significant societal impact. The semiconductor industry may be able to maintain or expand its profit base, by identifying new applications for, and strategies to inexpensively produce, large quantities of sub-20nm structures and devices. The aim of this section is to introduce methods that enable sustainable high-volume production of 2D and 3D components for sub-20nm fabrication that may inform the semiconductor or IoT industry (Fig. 16). Methods that were discussed included processing methods using DNA or other biopolymers, and utilization of microorganisms – such as diatoms, viruses, and bacteria – to produce chemicals and materials for semiconductor processes.



Fig. 16. Structural DNA nanotechnology design and applications³⁰.

DNA-Actuated Enzyme Nanoreactors

The combination of spatially addressable DNA nanostructures with enzyme-DNA conjugation chemistry offers great opportunities for engineering artificial multi-enzyme complexes. Enzyme subunits were precisely positioned on DNA origami using DNA-protein covalent linking (Fig. 17)^{31,32}. As a result of the enzymes being in close proximity, the system provides the substrate channeling effect that leads to higher enzyme activities. One example is a multi-enzyme system assembled on a flat DNA origami where a swinging arm facilitated hydride transfer between two dehydrogenase enzymes. Similarly, in another example, the DNA nanostructure was used to regulate two enzyme pathways by controlling the substrate channeling. Enzymes have also been caged in 3D DNA origami, which resulted in increased substrate turnover (Fig. 17d) and also reduced the rate of their degradation by proteinases. In a previous section of this report (Fig. 15b), research by Ohno and Inoue was described in which RNA was used to guide protein assembly²⁹. For fabrication approaches analogous to this, incorporating enzymes that can modify nucleic acids and/or proteins may expand the functionalities that can be attained.

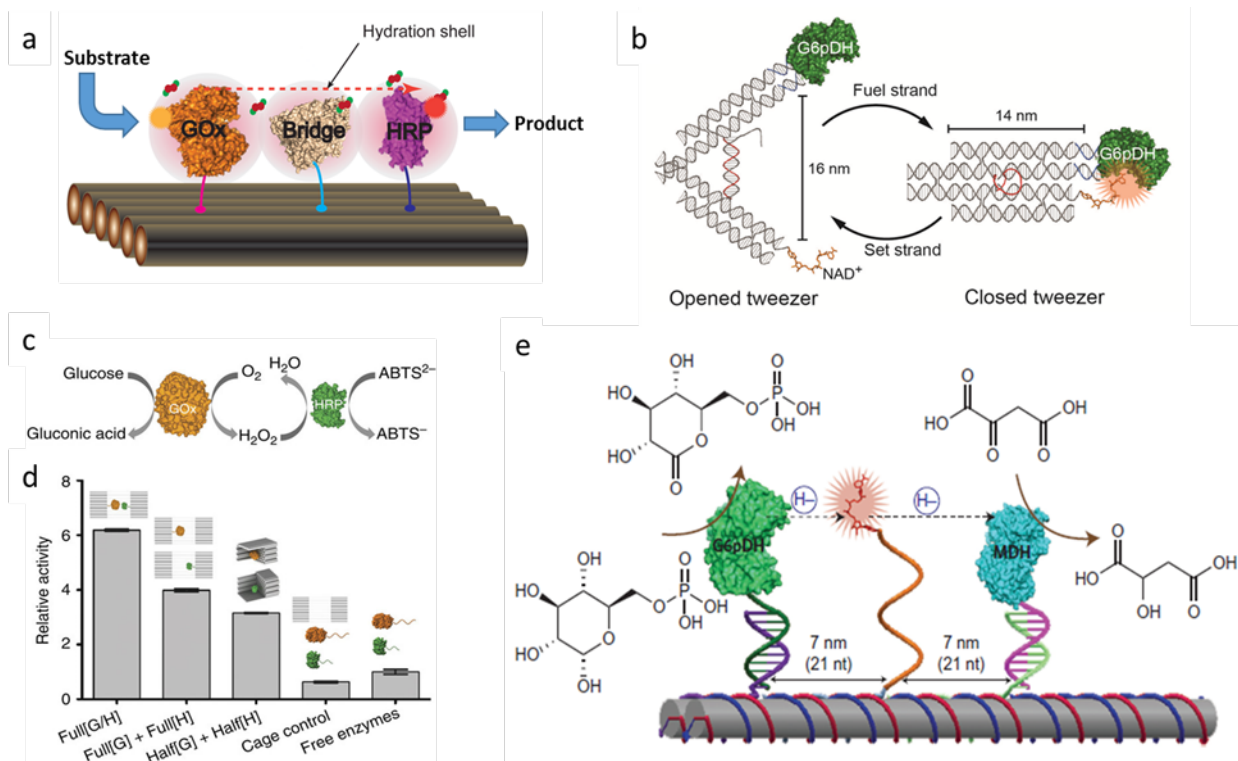


Fig. 17. Examples of reaction rate improvement by the aid of DNA nanostructures. (a) Engineering of a protein bridge to facilitate surface-limited diffusion. (b) A DNA device-actuated enzyme reaction that regulates enzyme switching between on/off phases. (c) The coupled reaction used in this study. (d) Increase of relative activity of the enzymes when they are caged in the DNA origami box. (e) The swinging arm in between the two enzymes provides restricted diffusion of NAD1/NADH between two dehydrogenases^{31,32}.

Multi-Domain Nanostructure Manufacturing with Error Correction

Designing self-assembly processes that create structures with a particular function and geometry, is of great interest, as this would enable the scientific and industrial community to program desired outputs without the need to achieve complete order within large-scale assemblies. Large-scale assembly of molecules in defined periodic or aperiodic order and orientation could benefit many fields such as semiconductor photonics, photocatalytic systems, and structural biology. For example, for micron-scale self-assembly, the quality and the yield of large DNA origami and DNA nanostructure assemblies depend on the structural and biophysical properties of reactive elements or building blocks (Fig 18)^{33, 34}. Improved understanding of these properties could be exploited to enable autonomous repair of defects in higher-order assemblies. Attention should be paid to the thermodynamics and kinetics of this meso-scale self-assembly process that often increase the defect rates (Fig. 19)³⁵.

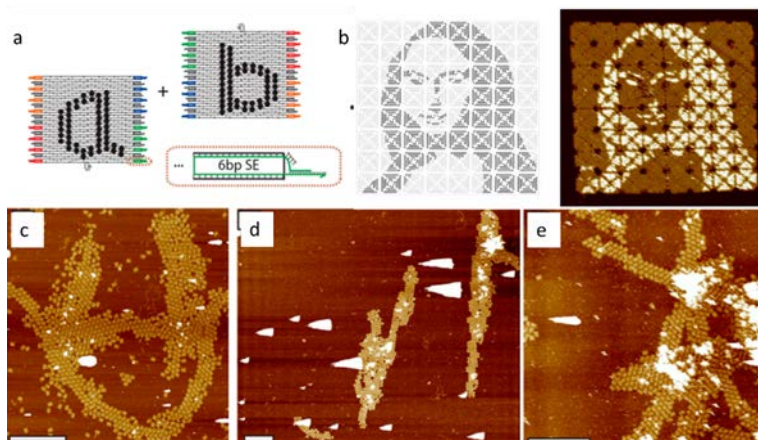


Fig. 18. Examples of higher-order DNA origami assembly. (a) Schematic representation of the building block and the pathways to multi domain DNA origami patches³³; (b) Highly addressable multi-domain DNA origami construction, using individually modified and addressable DNA origami building blocks³⁴ (c-e) AFM images of the assembled and organized DNA origamis³³.

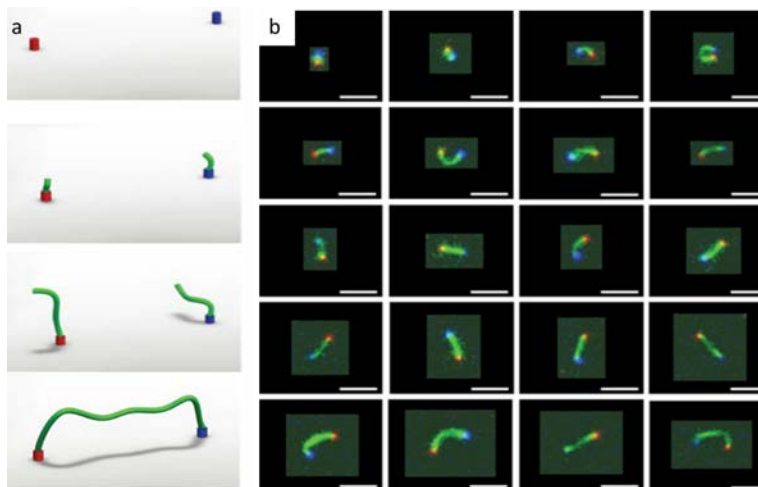


Fig. 19. Examples of adaptive DNA origami assembly. (a) Schematic of addressed polymerization of DNA nanostructures from DNA tile building blocks in multiple steps, and (b) the actual process was monitored and polymerization was confirmed by imaging techniques³⁵.

DNA Structures as Templates for Photonics

Plasmonic waveguides are typically produced by electron-beam lithography, which is a slow, non-scalable, and expensive method. DNA origami offers a scalable, bottom-up method to construct waveguides of plasmonically active metal nanoparticles. In these plasmonic waveguides, the position and the arrangement of each of the nanoparticles on a structure is of paramount importance to produce functional devices. Through a systematic study, Schmidt's team has examined the effect of ionic strength, stoichiometric ratio, oligonucleotide linker chemistry, and assembly kinetics on the quality of the resultant waveguide devices. They have developed and optimized a protocol for construction of plasmonic devices that results in a placement yield of up to 98.7% (Fig. 20)³⁶.

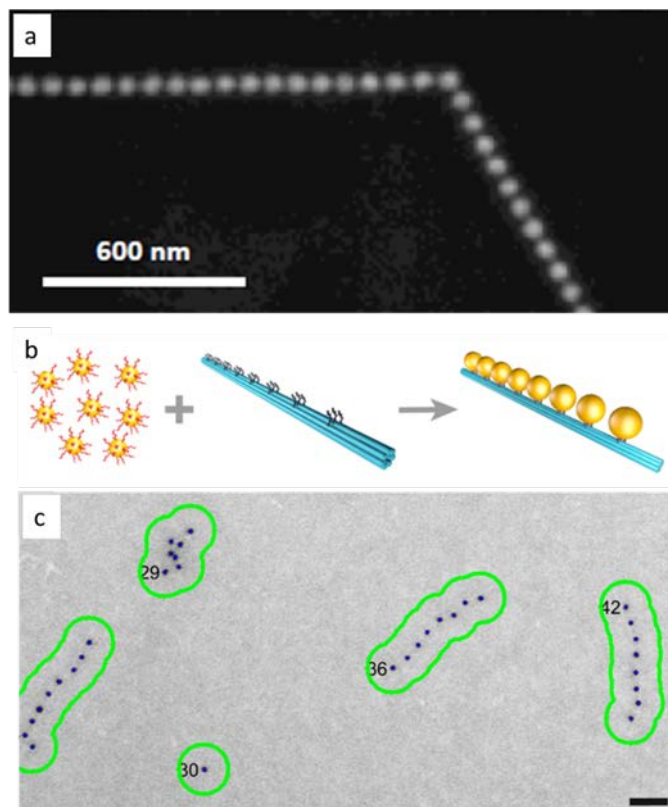


Fig. 20. Waveguide assembly. (a) Scanning electron microscopy of a plasmonic waveguide, fabricated using electron beam lithography. The gold dots are ~ 50 nm in diameter and spaced by ~ 75 nm³⁷. (b) Schematic of the design of the waveguide structure, where functionalized nanoparticles will attach to the tube DNA origami³⁶. (c) Representative SEM image of a non-optimized assembly reaction.

Cellular Factories

Cells are currently employed to massively produce many organic materials (e.g., polymers, pharmaceuticals) typically under aqueous and ambient conditions, and this approach may be applicable to inorganic or hybrid materials. As such, microorganisms have significant potential to biosynthesize metal oxide semiconductors and functional polymers with well-defined nanostructure. One important feature of this cellular factory approach is a sustainable and environmentally friendly platform for the biogenic production of nanobiomaterials using sustainable inputs, including naturally abundant inorganic materials such as carbon dioxide and sunlight. One example is the production of biogenic nanomaterials from diatoms (Fig. 21). These 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 consume soluble silicon and make silicon shells that have patterns of 1-100 nanometers. By changing the feeding material (e.g. exchanging silicon with germanium or titanium) to the diatom cells, Rorrer's team have produced metabolically inserted semiconductor nanophases into the structure of the diatom shells. Immense potential exists to harness the unique biosynthetic capacities of microscopic marine organisms for nanotechnology applications.

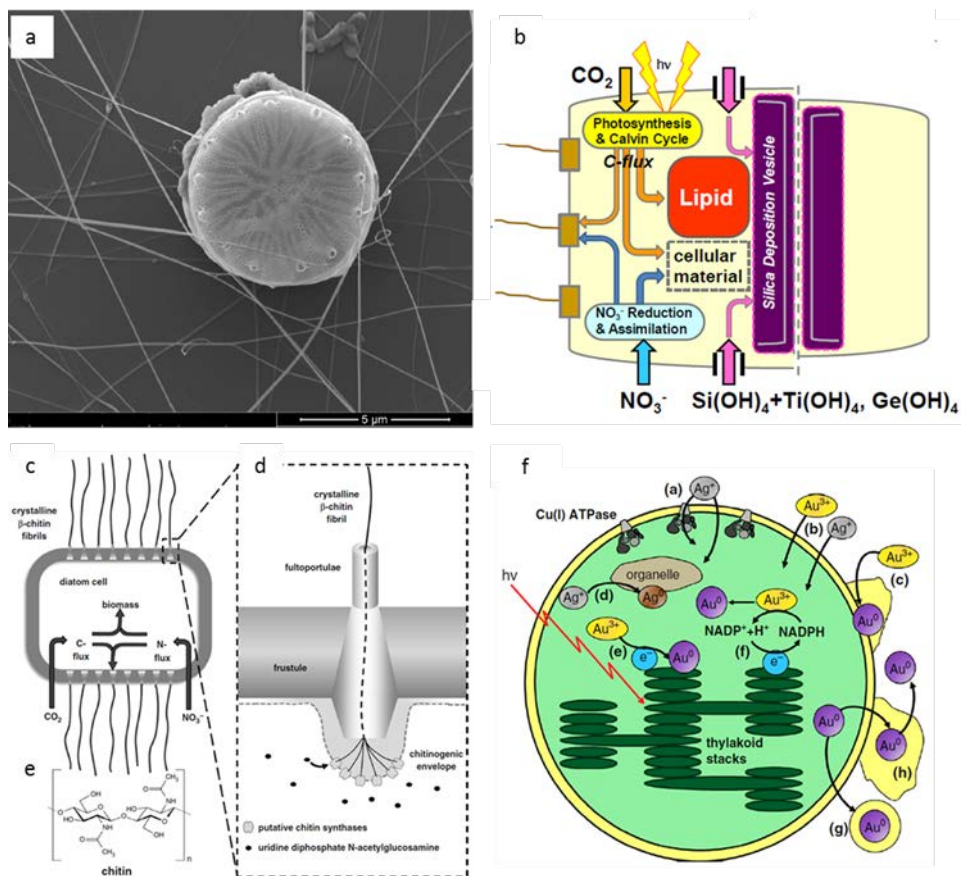


Fig. 21. The production of crystalline β -chitin fibrils from diatom cell culture. (a) SEM image of the marine diatom *Cyclotella*. (b) Diatom photosynthetic cell factory. Produced nanostructured metal oxides could be used for semiconductor and optoelectronic applications, Lipids could be used as biofuels, and chitin nanofibers could be utilized for biomedical and advanced material applications. (c) Under silicon starvation the cell continues to take up CO_2 and NO_3^- . (d) Polymerization of chitin fibrils from monomer units. (e) The chitin repeat unit. (f) The proposed mechanisms of metal cation uptake and transformation into metallic nanoparticles³⁸.

To enable the production of useful nanomaterials *in vivo* it is important to understand the cellular and genetic pathways that are involved in the regulation and production of natural biogenic materials (Fig. 22). With this understanding we may be able to tailor living systems to produce desired nanomaterials, with non-natural compositions or geometries³⁹. For example, when evolving novel reductases to process new materials, it is critical to understand natural bacterial reduction pathways, enzymatic effects on nanostructure properties, influence of the host and neighboring cells on the formation of materials, and desired properties of the target nanomaterial. Biology offers the unique opportunity to combinatorially explore billions of genetic variants to gain understanding of cellular and sub-cellular architectures and structures and how these influence the synthesis, organization, regulation and packaging of nanomaterials.

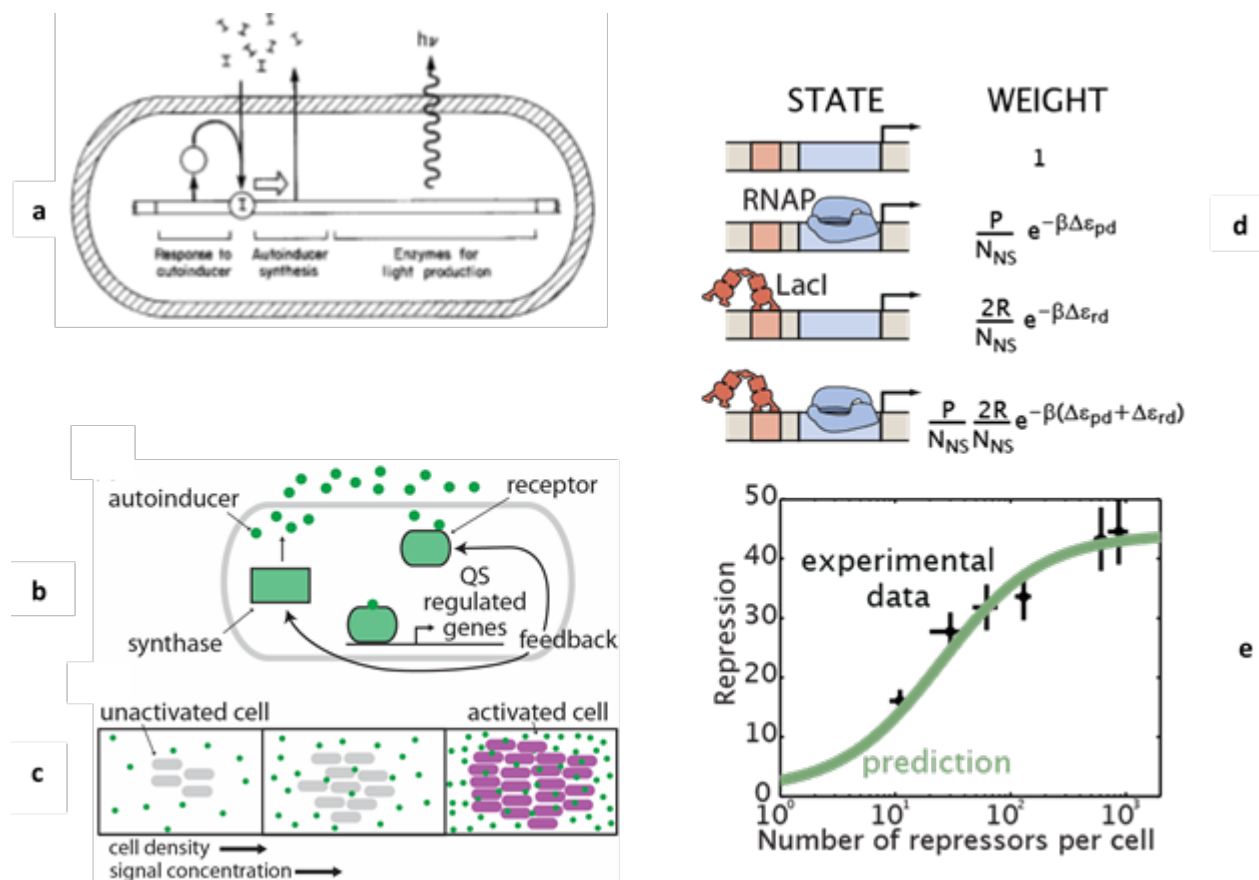


Fig. 22. Model of auto-induction in cells: a) The response to auto-inducer is encoded in the genes that results in the synthesis of a long chain aldehyde needed for light emission (Reproduced from ⁴⁰). b) The basic quorum sensing system includes a synthase that makes the autoinducer and a receptor that binds the autoinducer. A bound receptor is activated to regulate the expression of quorum sensing controlled genes⁴¹. c) As cell density increases, the concentration of the autoinducer increases. When the autoinducer concentration exceeds a threshold, receptors become activated and the cells in the population express quorum sensing regulated genes⁴¹. (d & e) Predictive input-output functions of gene regulation⁴².

To summarize, potentially fruitful future research directions are: (1) hybrid fabrication where integration of bio and traditional assembly leads to development of new tools and infrastructure; (2) investigation into the tradeoffs of hybrid fabrication and systems, for example, benefits of self-assembling biomaterials/structures (such as economic, sustainable, aqueous and ambient processing) and attendant materials defects of biological processes or bio-semi hybrid systems; (3) the development of scalable biosystems that involve communities of organisms for temporally and/or spatially controlled production of multiple or composite materials; (4) use of organisms as factories for synthesis, patterning, testing, and repair of existing useful organic and inorganic materials. For example, biosilica could be used as a natural, renewable source for silicon, or organisms like diatoms could be used for 3D hierarchical inorganic material synthesis and organization.

Recommendations include: (1) both the biology and the semiconductor communities should start to identify and adopt common objectives, languages, and milestones. In particular, a common language would encourage collaboration that leverages the strengths across communities; (2) These communities need to identify applications that benefit from tolerance of disorder and adaptive repair, or can leverage biomolecular components as active quality checking and control agents; (3) The community needs to produce minimal cells – minimal architectural and structural requirements for achieving a desired functionality – that integrate a solution from simple raw materials to achieve devices of arbitrary complexity and functionality. This will provide green, sustainable, and inexpensive materials for diverse applications – including electronics – to be developed over the next 15-20 years.

5. Biomaterials for Electronics

A new materials base may be needed for future electronics hardware. While most of today's electronics use silicon, this may not be a sustainable approach. If, for example, billions of sensor nodes are realized as a part of the Internet of Things, many sensor nodes will have short lives and/or are disposable. We need to be thinking about more sustainable materials, for example carbon-based systems that can be recycled or reused. The potential role for alternative materials (polymers, paper, etc.) also needs to be explored. It may also be possible to utilize silicon formed by natural bio-silica systems like diatoms and glass sponges. The focus of this section is on emerging biological compounds or structures that have interesting optical/electronic/magnetic/mechanical properties.

Engineering Assembly for Complex 3D Colloidal Architectures

Researchers are actively seeking materials capable of properties and behaviors that enable new technologies⁴³. Bottom-up design techniques, such as self-assembly, provide a promising method for synthesizing precisely engineered materials. Particles and their assemblies are poised to become the 'atoms' and 'molecules' of tomorrow's materials if they can be successfully assembled into useful structures. Enormous design space is available to modern colloidal matter, where colloid nanoparticle shape and interactions may be manipulated to span a nearly infinite range of possibilities⁴⁴.

A statistical thermodynamic framework can form the basis for "*digital alchemy*" – a new computational building-block design⁴⁵. This framework allows one to directly probe the thermodynamic response of a system to a change in the attributes of its building blocks, such as shape of nanoparticles or particle-to-particle interactions. Such a statistical thermodynamic framework allows investigation on self-assembly for any materials, any shape, at all length scales and study on programmability, and reconfigurability of nanoparticle self-assembly.

New "elements" can be synthesized as "patchy" nanoparticles through hybridization by DNA or proteins. Anisotropic shape and interactions through chemical "patchiness" are powerful tools for engineering the assembly of particular targeted structures. For example, semiconductor CdTe nanoparticles interact with cytochrome C proteins to self assemble in spherical supraparticles – stable, self-limited terminal assemblies with a narrow size distribution. Such self-limiting behavior originates from the competition between electrostatic repulsion and non-covalent attractive interactions. These supraparticles exhibit photoenzymatic activity and could be used in artificial photosynthesis systems harnessing sunlight to drive chemical reactions⁴⁶.

Inspired by *pluripotent* stem cells, which are capable of differentiating into multiple biological tissues, Mirkin's team at Northwestern University introduced the concept of a transmutable nanoparticle—a building block with different possible binding characteristics that can be selectively activated or deactivated, and then used to generate discrete forms of complex crystalline matter⁴⁷. Using DNA-based hairpin ligands, transmutable nanoparticles were formed, that can be assembled in different material structures (Fig. 23).

Programming for Pluripotency

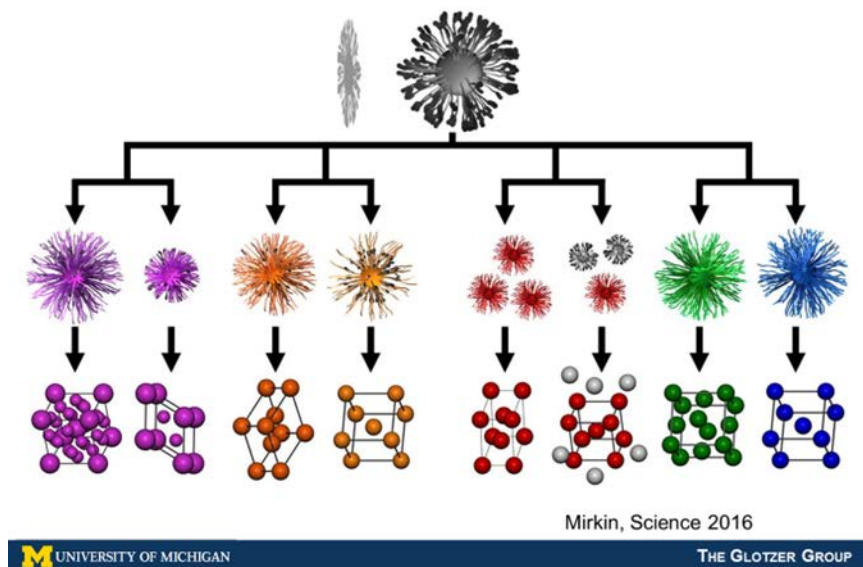
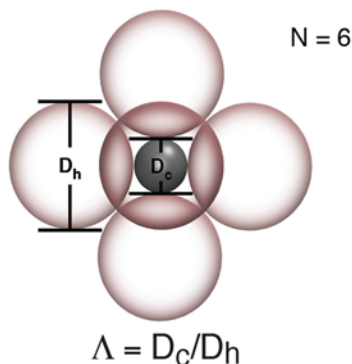


Fig. 23. Structural complexity with DNA programmed assembly of nanoparticles⁴⁷.

Systems of colloidal nanoparticles have a potential to form high-density computing elements termed digital colloids (Fig. 24)⁴⁸. For example, reconfigurable clusters made of N colloidal particles have the capacity to store an amount of information that increases as $O(N \ln(N))$. This information can be written, saved, and erased. Experimentally, an $N = 4$ reconfigurable cluster was assembled from chemically synthesized colloidal building blocks. Its equilibrium dynamics were monitored and state switching was observed. This cluster can store one bit of information, and represents the simplest digital colloid. Such a system could be used in emerging unconventional information processing, such as “wet computing”.

A terabyte in a tablespoon.



N	Point Group of Spherical Code	Rotational Symmetry	Storable States
4	T_d	12	2
5	C_{4v}	4	30
6	O_h	24	30
7	C_{3v}	3	1,680
8	D_{4d}	4	10,080
9	D_{3h}	18	20,160
10	C_{2h}	2	1,814,400
11	C_{5v}	5	7,983,360
12	I_h	60	7,983,360

Fig. 24. Digital colloids as high information density elements⁴³.

Constructing Novel Materials with DNA

DNA has been recognized as a useful building material in the field of nanotechnology⁴⁹. Its miniature scale, geometric properties, and molecular recognition capacity make DNA an appealing candidate for the construction of novel nanomaterials⁵⁰. DNA can be used as smart glue to create a variety of two- and three-dimensional nanoarchitectures.

An interesting approach is the assembly of stochastic 3D networks of carbon nanotubes that interconnect deterministic nanodevices, e.g. nanoparticles with nonlinear behavior (Fig. 25)⁴⁹. It is proposed that similar systems could be used in emerging unconventional information processing, such as “*reservoir computing*”. Recently van der Wiel’s team at the University of Twente demonstrated experimentally that a disordered network of nanoparticles (acting as strongly nonlinear single-electron transistors) can be configured in situ into any of the two-input Boolean logic gates by tuning six static control voltages⁵¹.

Bacterial Electronic Materials

Cells are 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 surroundings⁵². 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 pili⁵³. Typical length of the conductive pili is 10-50 μm, diameter 1.5-3 nm, and measured conductivities range 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 demonstrated⁵⁴. A possibility of genetic modifications for new properties of the e-pili materials is envisioned.

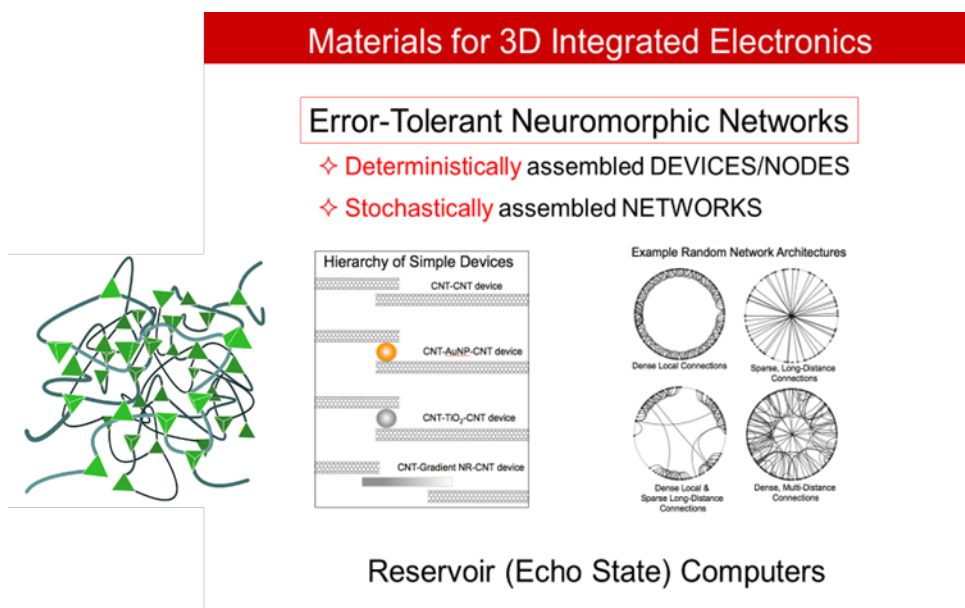


Fig. 25. Illustration to assembly of stochastic 3D networks interconnecting deterministic nanodevices⁴⁹.

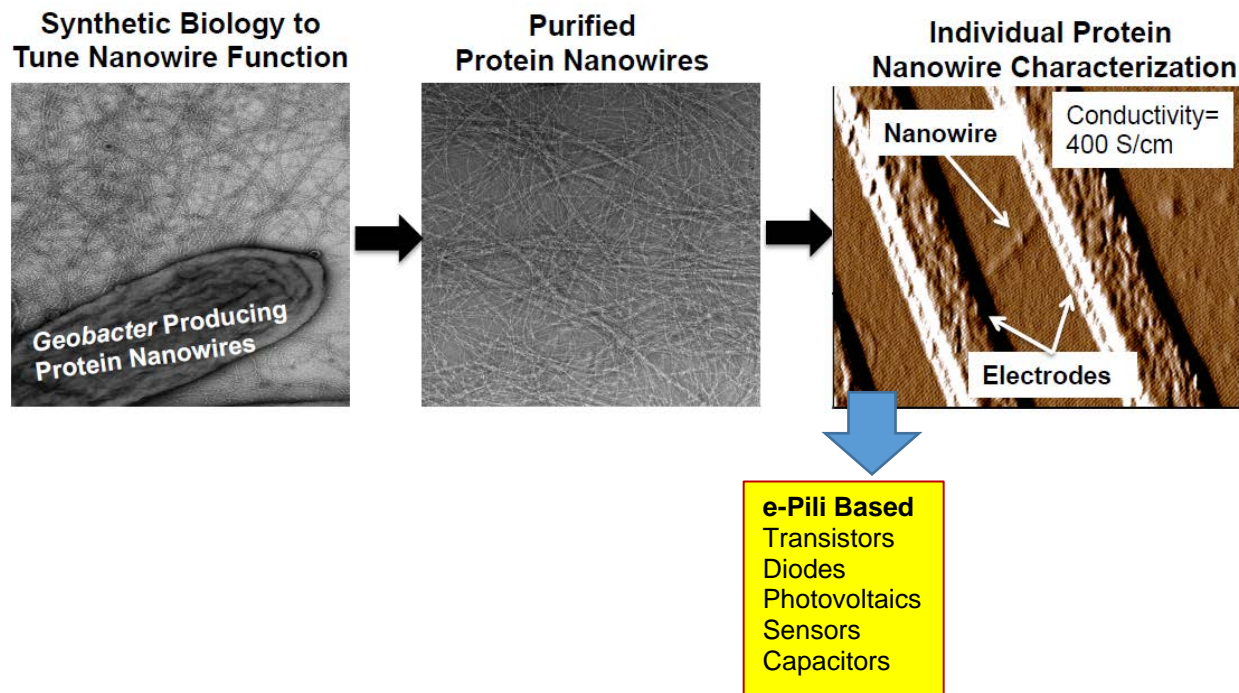


Fig. 26. Bacterial nanowires for electronic applications⁵².

Bioprotonic Devices

Inspired by biological information processing in living cells, concepts of fluid nanoelectronics/nanoionics are proposed that utilize ionic liquid media^{55,56,57}. In principle, such structures might be used to make devices scalable to ~1 nm or below.

Ionomers, which are polymers with ionic properties, offer a merger of solid-state and fluid nanoionics. These polymers are highly permeable to water and are good conductors of protons. Currently protons are the best choice as information carrier in nanoionic devices, because they have smallest mass among all ions, therefore allowing for highest speed at lowest energy. A ‘*protode*’ - quasi-solid-state protonic device structure - consists of a protonic source and drain made of palladium hydride (PdH) separated by a proton transport medium (an ionomer such as nafion) as shown in Fig. 27⁵⁸. Concepts for nanoprotic memory, logic and sensor devices were proposed. Fig 28 depicts a notional bioprotonic device that utilizes natural or engineered membrane protein channels to regulate proton flux⁵⁹.

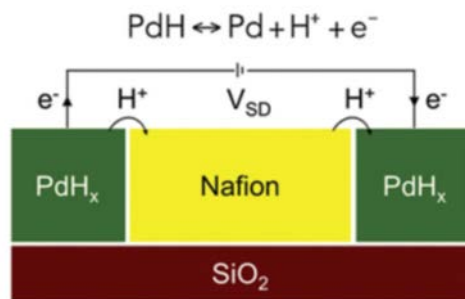


Fig. 27. Protode - a quasi-solid-state protonic device structure consisting of a protonic source and drain made of palladium hydride (PdH) separated by a proton transport medium^{55,58}.

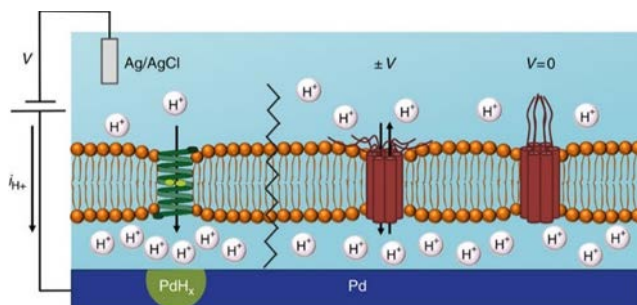


Fig. 28. Schematic depiction of the ion channel bioprotonic device^{55,59}.

Silk Protein Materials

Silk in its raw state consists of two main proteins, sericin and fibroin. New silk protein materials are prepared by removal of sericin from natural silk fibers, followed by water-based extraction and purification⁶⁰. The resulting water-based suspension of fibroin protein can be then transformed into different forms of silk materials driven by polymer self-assembly (Fig. 29). Examples of applications include nanostructured surfaces and volumes, diffractive optics, photonic crystals, metamaterials, optical fibers, waveguides, lasers, transistors, resorbable or biodegradable electronics for medical devices⁶¹, RF antennas, and fuel cells⁶². Different fabrication methods have been used to make functional silk structures, including nanoimprinting, UV- and e-beam lithography, and inkjet printing⁶³.

Silk materials offer favorable opportunities for implantable bioelectronic devices due to their biocompatibility and biodegradability properties. Vanishing or transient electronics are electronic systems that physically disappear into the surrounding environment in a benign way, at prescribed times and with well-defined rates. A passivation strategy for transient electronic devices was introduced that consists of encapsulation of devices in multiple pockets fabricated from silk fibroin. The silk pockets have been shown to be useful for controlled modulation of device lifetime. These interesting demonstrations of silk in electronics applications suggest that there might be roles for this, and other biopolymers (and biopolymer composites) in electronic devices.

Silk forms - examples



Fig. 29. Different forms of silk materials and application examples⁶⁰.

Materials for Ingestible Electronic Devices

There are many examples of ingestible electronic devices for applications that include biosensors for monitoring patient compliance, gastrointestinal endoscopy, “smart pills” for controlled drug release, etc. While the sophistication of the electronic parts in these implants has increased over recent years, there are many persistent challenges that may limit the application space of the ingestible and implantable device-based therapies. Two difficult challenges are that 90% of device mass consists of packaging material and an energy source (Fig. 30), and many state-of-the-art batteries are toxic⁶⁴. The idea of edible batteries was introduced as a strategy to overcome this challenge. Specifically, edible batteries fabricated from biologically-derived melanin were reported (melanin is a group of natural pigments produced by the oxidation of the amino acid tyrosine, followed by polymerization). Melanin was used as the anode material to form an aqueous Na⁺ battery that was non-toxic. Although performance of these melanin batteries is modest, they exhibit increased charge storage capacity compared to other materials and are rechargeable⁶⁵. Overall, the melanin pigments have potential to be viable materials to power edible electronic devices⁶⁶.

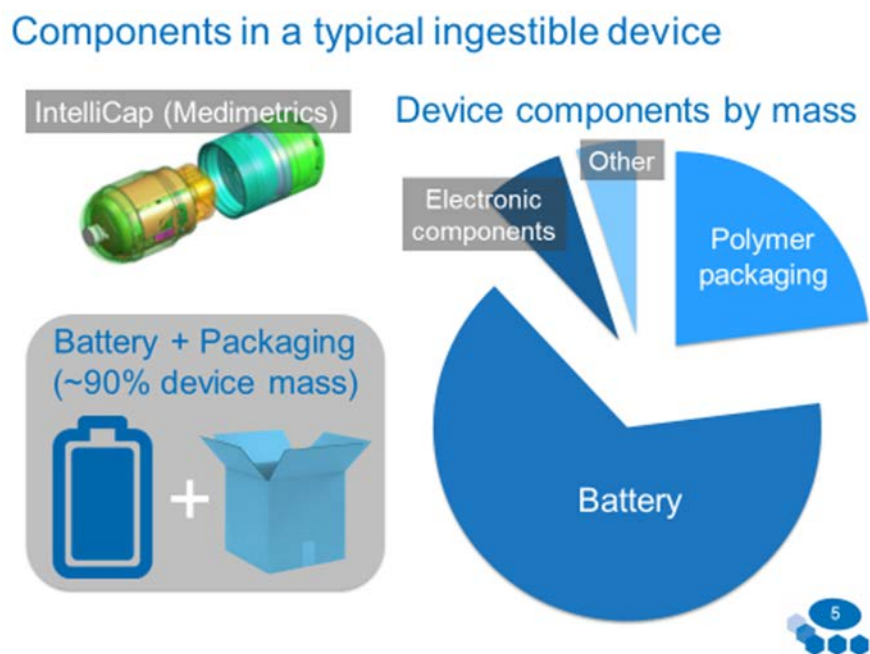


Fig. 30. Components in a typical ingestible device by mass⁶⁴

Mechanisms of Charge Transport in Biomolecular Nanostructures

Interfacing biomolecular materials and nanostructures with electronics is a critical consideration for hybrid bio-semiconductor systems. Electrical interfaces (i.e., electronic or ionic) are the most compatible with semiconductor subsystems, and interesting results have been presented on the studies of microbial electron exchange with external electronic devices⁶⁷. It should be noted that many natural cells have evolved an insulating envelope, which makes a direct exchange of electrons difficult. There are several modes of electron transfer between solid supports and cells such as i) electron donation from the cytochrome network to the solid substrate; (ii) transfer to redox-active electron shuttles; and (iii) long-distance electron transport via conductive bio-nanowires, such as e-pili⁶⁸. Potential mechanisms of charge transport through bio-nanowires range from fully incoherent hopping to fully coherent band transport (typical for metals and semiconductors)⁶⁹. However, the fundamental limits of electrical conductivity of bio-nanowires is still an open question. Moreover, charge transport processes at the bio-inorganic interface, e.g. between redox-active enzymes or proteins and electrodes, are still poorly understood at a microscopic level⁷⁰. Inorganic nanostructures, such as metal nanoparticles or carbon nanotubes were shown to be an effective way to improve bioelectronic charge transfer⁷¹. Recently genetically controlled conductive protein nanofibers have been demonstrated that will be useful for interfacing biotic and abiotic systems^{72,73}.

As was pointed out in⁶⁸, currently researchers are only ‘scratching the surface’ in terms of understanding cell-electrode interaction, and current models of extracellular electron transport are still debated. Understanding the charge transport through biomolecular materials and nanostructures as well as the transport properties at bio/metal contacts is a subject of active research; the readers can be referred e.g., to^{74,75} for recent perspectives.

To summarize, potentially fruitful future research directions are: (1) deeper understanding of the electronic/biological interfaces for specific applications; (2) approaches to effectively integrate biologically-derived materials with standard CMOS devices; (3) exploring construction of electronic materials (wires, transistors, diodes, capacitors, etc.) from protein filaments or other structural forms (e.g., layers, capsules); (4) creating processes for seamless integration between abiotic and biotic elements e.g., silk or bacterial electronic materials might be a useful part of the toolbox in interfacing electronics with biology; and (5) developing a validated library of modular genetic/protein ‘bioelectronic’ parts that can be used by others outside the field.

6. Conclusions

The Workshop on Biological Pathways for Electronic Nanofabrication and Materials sought to establish a 10-year vision for biologically based manufacturing, broadly defined, with sub-20nm resolution, at low-cost, with low energy utilization, and with tolerable defect rates for existing, as well as alternative, electronics. Potential items for a Roadmap include the development of a framework to compare different bio-based and biomimetic manufacturing approaches, and a plan to reconcile the very different philosophies of the semiconductor fabrication and the biotech/synthetic biology communities. Indeed, a common language needs to be developed that bridges the two communities. In fact, the semiconductor industry would greatly benefit from the properties the biotech/synthetic biology community can bring to bear, e.g., 3D architecture, low cost, low toxicity, etc. However, the integration of synthetic biology into mainstream semiconductor manufacturing would require considerable research funding from multiple federal and other agencies. The exceptionally large capital investment needed for new semiconductor fabrication facilities render the approach highly susceptible to disruptive innovations. Examples of disruptive innovations and trends discussed at the workshop include:

1. Demonstrating 3D hierarchical functional components and systems with biological approaches from the nm to μm scale.
2. Constructing electronic materials, e.g., wires, transistors, diodes, capacitors, etc. from protein filaments or other structural forms, e.g., layers, capsules.
3. Integrating abiotic and biotic elements, in particular approaches to effectively integrate biologically-derived materials (e.g., silk or bacterial electronic materials) with semiconductor devices.
4. Patterning with bioinspired directed self-assembly, e.g., using DNA or proteins as a sacrificial layer and/or etch mask. Also, organic or inorganic materials can be precisely organized on the DNA nanostructures to provide compartments with functionality. Important aspects of these technologies to be investigated include, but are not limited to: scalability, yield, feature size, resolution, defect concentration, and domain size.
5. Designing for “fault-tolerant” and/or “defect-tolerant” application spaces deserves special focus. This emerging vector might imply branches in the SemiSynBio roadmap marking different technology sectors. As the SemiSynBio initiative evolves, it will be useful to develop a matrix that highlights the convergence between specific design and manufacturing-induced defect attributes, for various fabrication modes, e.g., top-down, directed self-assembly, etc. and the set of tolerable defect attributes, e.g., size, shape, location, composition, molecular structure, etc., for the desired application.
6. Developing scalable biosystems 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. For example, biosilica could be used as a natural, renewable source for silicon, and organisms like diatoms could be used for 3D hierarchical inorganic material synthesis and organization.

Acknowledgements

We acknowledge the support of the National Institute of Standards and Technology (NIST) under award 70NANB15H064.

References

- ¹ Gregg Gallatin, "Nanofabrication: A perspective from litho practitioners", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ² Rupp and Selberherr, "The Economic Limit to Moore's Law", Proc. IEEE, 98 (2010) 351
- ³ R. Colin Johnson, "Samsung Breaks Ground on \$14 Billion Fab", EE Times, May 8 2015
http://www.eetimes.com/document.asp?doc_id=1326565
- ⁴ Qinghuang Lin, Keynote: "Nanoelectronic Manufacturing and Opportunities for Bio-nanofabrication and Materials", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁵ D. J. C Herr, "Directed block copolymer self-assembly for nanoelectronics fabrication", J. Mater. Res. 26 (2011) 122-139
- ⁶ Scott Sills, "Integration of bottom-up fabrication techniques & a view on block-copolymers for next generation lithography.", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁷ Robert U. Ayres, Information, Entropy and Progress (1994 AIP Press)
- ⁸ L.D. Landau, E.M. Lifshitz, *Course of Theoretical Physics: Vol. 1. Mechanics.* (3rd ed.). (Butterworth-Heinemann 1976).
- ⁹ Daniel Herr, "Future Nanofabrication Technologies - Targets for Biomimetic Nanomanufacturing", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ¹⁰ E. Gopinath, P.W.K. Rothmund, Optimized Assembly and Covalent Coupling of Single-Molecule DNA Origami Nanoarrays, ACS Nano 8(2014) 12030-12040
- ¹¹ Paul W.K. Rothmund, Keynote: "Bridging the gap between molecular and macroscopic worlds," SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ¹² S. Veneziano, K. M. Ratanalert, F. Zhang, F. Zhang, H. Yan, W. Chiu, M. Bathe, Designer nanoscale DNA assemblies programmed from the top down, Science 352 (2016) DOI: 10.1126/science.aaf4388
- ¹³ E. Benson, A. Mohammed, A. Bosco, A. I. Teixeira, P. Orponen, B. Högberg, Computer-Aided Production of Scaffolded DNA Nanostructures from Flat Sheet Meshes, Angew. Chem. Int. Ed. Engl. 55 (2016) 8869-72. doi: 10.1002/anie.201602446.
- ¹⁴ E. Benson, A. Mohammed, J. Gardell, S. Masich, E. Czeizler, P. Orponen, B. Högberg, DNA rendering of polyhedral meshes at the nanoscale, Nature 523(2015): 441-4. doi: 10.1038/nature14586.
- ¹⁵ L. Chasteen, J. Ayriss, P. Pavlik, A. R. Bradbury, Eliminating helper phage from phage display, Nucleic Acids Res. 34 (2006) e145.
- ¹⁶ F. Praetorius, B. Kick, K. L. Behler, M. N. Honemann, D. Weuster-Botz, H. Dietz, Biotechnological mass production of DNA origami, Nature 552 (2017)
- ¹⁷ Z. B. Peng and H. Liu, Bottom-up nanofabrication using DNA nanostructures, Chemistry of Materials (2016) 28; 4, 1012-1021
- ¹⁸ Haitao Liu, "DNA-Mediated Pattern Transfer", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ¹⁹ Raluca Tiron, "DNA Origami Mask for ultimate Lithography", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ²⁰ C. T. Diagne, C. Brun, D. Gasparutto, X. Baillin, and R. Tiron, "DNA Origami Mask for Sub-Ten-Nanometer Lithography", ACS NANO 10 (2016) 6458-6463
- ²¹ S. Helmi, C. Ziegler, D. J. Kauert, R. Seidel, Shape-Controlled Synthesis of Gold Nanostructures Using DNA Origami Molds, Nano Letters (2014) 14; 11, 6693-6698
- ²² W. Sun, E. Boulais, Y. Hakobyan, W. L. Wang, A. Guan, M. Bathe, P. Yin, Casting inorganic structures with DNA molds. Science (2014) 346, 717
- ²³ Pearson, *et al.*, DNA origami metallized site specifically to form electrically conductive nanowires, The Journal of Physical Chemistry B (2012) 116; 35, 10551-10560
- ²⁴ J-F. Liu, Y-L. Geng, E. Pound, S. Gyawali, J. R. Ashton, J. Hickey, A. T. Woolley, J. N. Harb, Metallization of Branched DNA Origami for Nanoelectronic Circuit Fabrication, ACS Nano 5 (2011) 2240-2247

-
- ²⁵ J-F. Liu, B. Uprety, S. Gyawali, A. T. Woolley, N. V. Myung, J. N. Harb, Fabrication of DNA-Templated Te and Bi₂Te₃ Nanowires by Galvanic Displacement, *Langmuir* 29 (2013) 3482–3490
- ²⁶ Hareem Maune, “DNA Nanostructures in CNT Nanoelectronics,” SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ²⁷ H. Gradišar, S. Bozic, T. Doles, D. Vengust, I. Hafner-Bratkovic, A. Mertelj, B. Webb, A. Sali, S. Klavzar, R. Jerala, Design of a single-chain polypeptide tetrahedron assembled from coiled-coil segments, *Nature Chemical Biology* 9 (2013) 362-366
- ²⁸ S. Gonen, F. DiMaio, T. Gonen, D. Baker, , Design of ordered two-dimensional arrays mediated by noncovalent protein-protein interfaces, *Science* 348 (2015) 1365-1368
- ²⁹ H. Ohno and T. Inoue, Designed Regular Tetragon-Shaped RNA–Protein Complexes with Ribosomal Protein L1 for Bionanotechnology and Synthetic Biology, *ACS Nano* (2015) 9; 5, 4950-4956
- ³⁰ Hao Yan, Keynote: “DNA Actuated Enzyme Nanoreactors,” SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ³¹ G-L. Ke, M-H. Liu, S-X. Jiang, X-D. Qi, Y. R. Yang, S. Wootten, F. Zhang, Z. Zhu, Y. Liu, C. J. Yang, H. Yan, Directional Regulation of Enzyme Pathways through the Control of Substrate Channeling on a DNA Origami Scaffold, *Angew Chem Int Ed* 55 (2016) 7483–7486
- ³² Zhao, *et al.*, Nano-caged Enzymes with Enhanced Catalytic Activity and Increased Stability against Protease Digestion, *Nature Commun* (2016) 7, 10619
- ³³ J. Zenk, C. Tuntivate, R. Schulman, Kinetics and Thermodynamics of Watson-Crick Base Pairing Driven DNA Origami Dimerization, *J. Amer. Chem. Soc.* 138 (2016) 3346-3354
- ³⁴ G. Tikhomirov, P. Petersen, LL. Qian, Fractal assembly of micrometre-scale DNA origami arrays with arbitrary patterns, *Nature* 552 (2017) 67-71
- ³⁵ A. M. Mohammed, P. Sulc, J. Zenk, R. Schulman, Self-assembling DNA nanotubes to connect molecular landmarks, *Nature Nanotechnology* (2017) 312-316
- ³⁶ F. N. Gür, F. W. Schwarz, J-J Ye, S. Diez, T. L. Schmidt, Toward Self-Assembled Plasmonic Devices: High-Yield Arrangement of Gold Nanoparticles on DNA Origami Templates. *ACS Nano* 10 (2016) 5374-5382
- ³⁷ S. A. Maier, M. L. Brongersma, P. G. Kik, S. Meltzer, A.G. Requicha, H. A. Atwater, “Plasmonics—A Route to Nanoscale Optical Devices”, *Advanced Materials* 13 (2001) 1501-1505
- ³⁸ C. Jeffryes, S. N. Agathos, G. Rorrer, “Biogenic nanomaterials from photosynthetic microorganisms”, *Current Opinion in Biotechnology* 33 (2015) 23-31
- ³⁹ J. Boedicker and K. Nealon, “Microbial Communication via Quorum Sensing”, *IEEE Transactions on Molecular, Biological and Multi-Scale Communications* (2015) 1, 310-320
- ⁴⁰ J. Engebrecht, K. Nealon, and M. Silverman, “Bacterial bioluminescence: Isolation and genetic analysis of functions from *Vibrio fischeri*”, *Cell* 32 (1983) 773–781.
- ⁴¹ T. I. Yusufaly and J. Q. Boedicker “Spatial dispersal of bacterial colonies induces a dynamical transition from local to global quorum sensing”, *Phys. Rev. E* 94, (2016) 062410 <https://doi.org/10.1103/PhysRevE.94.062410>
- ⁴² Operator Sequence Alters Gene Expression Independently of Transcription Factor Occupancy in Bacteria, *Cell Reports* 2 (2012) 150-161 <https://doi.org/10.1016/j.celrep.2012.06.004>
- ⁴³ Sharon Glotzer (U Michigan), Keynote: “Engineering Assembly for Complex 3D Colloidal Architectures”, SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁴⁴ S. C. Glotzer and M. J. Solomon, “Anisotropy of building blocks and their assembly into complex structures”, *NATURE MATERIALS* 6 (2007) 557-562
- ⁴⁵ G. van Anders, D. Klotsa, A. S. Karas, P. M. Dodd, S. C. Glotzer, “Digital Alchemy for Materials Design: Colloids and Beyond”, *ACS NANO* 9 (2015) 9542-9553
- ⁴⁶ J. I. Park, T. D. Nguyen, .G de Queirós Silveira, J.H. Bahng, S. Srivastava, G. Zhao, K. Sun³, P. Zhang, S. C. Glotzer, N.A. Kotov, Terminal Supraparticle Assemblies from Similarly Charged Protein Molecules and Nanoparticles, *Nature Comm.* 5 (2014) 3593
- ⁴⁷ Y. Kim, R. J. Macfarlane, M. R. Jones, C. A. Mirkin, “Transmutable nanoparticles with reconfigurable surface ligands”, *SCIENCE* 351 (2016) 579-582
- ⁴⁸ C. L. Phillips, E. Jankowski, B. J. Krishnatreya, K. V. Edmond, S. Sacanna, D. G. Grier, D. J. Pinei, S. C. Glotzer, “Digital colloids: reconfigurable clusters as high information density elements”, *SOFT MATTER* 10 (2014) 7468-7479
- ⁴⁹ Thom LaBean, “Constructing novel materials with DNA”, SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁵⁰ T. H. LaBean, H. Y. Li, “Constructing novel materials with DNA”, *NANO TODAY* 2 (2007) 26-35

-
- ⁵¹ S. K. Bose, C. P. Lawrence, Z. Liu, K. S. Makarenko, R. M. J. van Damme, H. J. Broersma, W. G. van der Wiel, "Evolution of a designless nanoparticle network into reconfigurable Boolean logic", *NATURE NANOTECHNOLOGY* 10 (2015) 1048
- ⁵² Derek Lovley (U Mass), "Bacterial electronic materials", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁵³ Y. Tan, R. Y. Adhikari, N. S. Malvankar, S. Pi, J. E. Ward, T. L. Woodard, K. P. Nevin, Q. F. Xia, M. T. Tuominen, D. R. Lovley, "Synthetic Biological Protein Nanowires with High Conductivity", *SMALL* 12 (2016) 4481-4485
- ⁵⁴ N. S. Malvankar, M. Vargas, K. P. Nevin, A. E. Franks, C. Leang, B. C. Kim, K. Inoue, T. Mester, S. F. Covalla, J. P. Johnson, V. M. Rotello, M. T. Tuominen, D. R. Lovley, "Tunable metallic-like conductivity in microbial nanowire networks", *NATURE NANOTECHNOLOGY* 6 (2011) 573-579
- ⁵⁵ Marco Rolandi, "Bioprotonic devices", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁵⁶ Why IBM Made a Liquid Transistor, *MIT Technology Review*, <http://www.technologyreview.com/news/512721/why-ibm-made-a-liquid-transistor/>
- ⁵⁷ I.B.M. Research Points to Circuits That Mimic the Brain's Design, *NY Times*: <http://bits.blogs.nytimes.com/2013/03/21/i-b-m-research-points-to-circuits-that-mimic-the-brains-design/>
- ⁵⁸ E. E. Josberger, Y. X. Deng, W. Sun, R. Kautz, M. Rolandi, "Two-Terminal Protonic Devices with Synaptic-Like Short-Term Depression and Device Memory", *Advanced Materials* 26 (2014) 4986-4990
- ⁵⁹ Z. Hemmatian, S. Keene, E. Josberger, T. Miyake, C. Arboleda, J. Soto-Rodriguez, F. Baneyx, M. Rolandi, Electronic control of H⁺ current in a bioprotonic device with Gramicidin A and Alamethicin, *Nature Commun.* 7 (2016) 12981
- ⁶⁰ Fiorenzo Omenetto, "Silk protein materials", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁶¹ D-H. Kim, J. Viventi, J. J. Amsden, J. Xiao, L. Vigeland, Y-S. Kim, J. A. Blanco, B. Panilaitis, E. S. Frechette, D. Contreras, D. L. Kaplan, F. G. Omenetto, Y. Huang, K-C. Hwang, M. R. Zakin, B. Litt, J. A. Rogers, "Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronic", *NATURE MATERIALS* 9 (2010) 511-517
- ⁶² P. Tseng, G. Perotto, B. Napier, P. Riahi, W. Y. Li, E. Shirman, D. L. Kaplan, I. V. Zenyuk, F. G. Omenetto, "Silk Fibroin-Carbon Nanotube Composite Electrodes for Flexible Biocatalytic Fuel Cells", *ADVANCED ELECTRONIC MATERIALS* 2 (2016) 1600190
- ⁶³ H. Tao, B. Marelli, M. Yang, B. An, M. S. Onses, J. A. Rogers, D. L. Kaplan, F. G. Omenetto "Inkjet Printing of Regenerated Silk Fibroin: From Printable Forms to Printable Functions", *ADVANCED MATERIALS* 27 (2015) 4273-4279
- ⁶⁴ Christopher Bettinger, "Edible Electronics: Bioinspired Materials and Structures for Next-Generation Ingestible Devices", SRC/IBM/ONR Workshop on Bio-nanofabrication and Materials, IBM Almaden, Nov. 16-17, 2016
- ⁶⁵ Y. J. Kim, W. Wu, S. E. Chun, J. W. Whitacre, C. J. Bettinger, "Biologically derived melanin electrodes in aqueous sodium-ion energy storage devices", *PNAS* 110 (2013) 20912-20917
- ⁶⁶ C. J. Bettinger, "Materials Advances for Next-Generation Ingestible Electronic Medical Devices", *TRENDS IN BIOTECHNOLOGY* 33 (2015) 575-585.
- ⁶⁷ D. R. Lovley, "e-Biologics: Fabrication of sustainable electronics with "green" biological material", *mBio* 8 (2017) e00695-17
- ⁶⁸ K. H. Nealson and A. R. Rowe, "Electromicrobiology: realities, grand challenges, goals and predictions", *Microbial Biotechnology* 9 (2016) 595-600
- ⁶⁹ N. F. Polizzi, S. S. Skourtis, D. N. Beratan, "Physical constraints on charge transport through bacterial nanowires", *Faraday Discuss* 155 (2012) 43-62
- ⁷⁰ L. Zanetti-Polzi and S. Corni, "A dynamical approach to non-adiabatic electron transfers at the bio-inorganic interface", *Phys. Chem. Chem Phys.* 18 (2016) 10538-10549
- ⁷¹ C. M. Ajo-Franklin and A. Noy, "Crossing over: nanostructures that move electrons and ions across cellular membranes", *Adv. Mat.* 27 (2015) 5797-5804
- ⁷² E Kalyoncu, R.E. Ahan, T.T. Olmez, U.O.S. Seker, "Genetically encoded conductive protein nanofibers secreted by engineered cells", *RSC Advances* 7 (2017) 32543-32551
- ⁷³ U.O.S. Seker, A.Y. Chen, R.J. Citorik, T.K. Lu, "Synthetic biogenesis of bacterial amyloid nanomaterials with tunable inorganic-organic interfaces and electrical conductivity", *ACS Synth. Biol.* 6 (2016) 266-275
- ⁷⁴ K. K. Sakimoto, N. Kornienko, S. Cestellos-Blanco, J. Lim, C. Liu, P. Yang, "Physical Biology of the Materials-Microorganism Interface", *J. Am. Chem. Soc* 140 (2018) 1978-1985

⁷⁵ C. D. Bostick, S. Mukhopadhyay, I. Pecht, M. Sheves, D. Cahen, D. Lederman, “Protein bioelectronics: a review of what we do and do not know”, Rep. Prog. Phys. 81 (2018) 026601