The Imperative of Synthetic Biology: A Proposed National Research Initiative

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The oxygen in the air we breathe, the plants or animals we eat, the environments we cherish and struggle to protect, the fuels that keep us warm and power our industries and vehicles, our medicines and clothes, ourselves and future generations as yet unborn – we are of biology and dependant upon her. In turn, our ability to develop and deploy biology as a technology – for sustainable energy production, green manufacturing, agile crop development, affordable healthcare and medicines – depends on the tools we have for engineering life itself.

35 years ago researchers learned to directly manipulate DNA using crude molecular tools to construct relatively simple genetic programs. These first tools gave birth to the biotechnology industry, resulting in new drugs and therapies (e.g., from recombinant insulin for treating diabetes to cheap artemisinin for fighting malaria), concerns (e.g., biological security), controversies (e.g., genetically engineered foods), and unmet promises (e.g., nitrogen fixing crops). Today, more powerful tools are being developed to help make biology easier to engineer via an emerging field of research known as "synthetic biology." Using early versions of these new tools, researchers have begun constructing genomes – the entire DNA program encoding an organism – from scratch[2]. Catalogs containing thousands of standardized DNA parts are being produced and freely distributed[3]. Undergraduates and high school students are developing genetic programs of their own designs such as bacteria that take living photographs, smell as bananas, detect and warn of arsenic contaminated well water, or provide probiotic supplements[4].

As biology becomes easier to engineer, many more individuals and groups, not just researchers, will have the opportunity to use biotechnology to solve (or cause) problems, just as many people now program computers or websites. Given that our ongoing existence and future happiness, including our economy and security, directly depend on biology, we believe that the United States should invest in, guide, and lead the emerging field of synthetic biology, so that the development of tools that make biology easy to engineer remains overwhelmingly constructive, and their application is clearly focused on our most pressing needs including energy, healthcare, food, and sustainable manufacturing.

Tools of Mass Construction

When somebody buys a Blackberry or iPhone they typically do not consider the advances in information theory, signal processing, device design, computer languages, standardization and abstraction, silicon wafer fabrication, computer-aided design, electronic design automation, and control and dynamical systems made over the last 70 years. Yet it was our investment, development, and leadership in these foundational engineering tools that powered the computing

[1] For the most current version of this essay, as well as related essays, visit http://www.cra.org/ccc/initiatives
[2] Gibson et al., *Science* **319**:1215-20, February 2008
[3] The Registry of Standard Biological Parts, http://partsregistry.org/
[4] iGEM, the International Genetically Engineered Machines Competition, http://igem.org/

revolution we inherit, taking us from von Neumann's team in the basement of the Institute for Advanced Study to today's cloud computing environments. As with computing and other technology revolutions, there is now a similar, singular opportunity for the United States to make a deeply strategic investment in the coordinated invention and improvement of tools that support the engineering of biology, and to further coordinate such an investment with ongoing concerns and opportunities in areas including education, commerce, law, security, and international relations. Practically, no one federal agency or department can tackle these opportunities and challenges alone; strategic executive leadership is needed. The 21st century has long been predicted as the time when engineering and biology will finally realize their true, partnered potential. By working together, we can imagine and build a biological future in which our needed fuels and chemicals, crops, and therapeutics can be quickly and reliably produced in a sustainable and responsible fashion. We can also foresee a much richer future, in which the full diversity of biotechnology becomes practical. Our initial and ongoing successes will ensure the United States' leadership in biological technologies, and help secure our environmental and economic security.

Technology Investments

Focused studies conducted over the past 5 years have identified new categories of tools for engineering biology[5,6,7]. Each tools category draws inspiration from past engineering lessons, from the standardization of screw threads for nuts and bolts, to the development of virtual-machine approaches to computer programming. None of the so-identified categories currently receive any meaningful or well-organized public investments supporting their development.

<u>*DNA Construction:*</u> The United States should initiate a focused program to enable the rapid, accurate, and fully automated construction of any arbitrary nucleic acid sequence, including genes, plasmids, and genomes. Effective DNA construction and editing technologies will enable the decoupling of biological system design from biological system manufacture, allowing for further advances in each area. DNA construction and editing investments should be informed by past and ongoing efforts to improve silicon wafer manufacturing. Public-private partnerships and open technology roadmaps will likely be essential. Strong coordination of programs across all federal agencies, including NSF, NIH, DOD, DOE, NIST, and NASA, should be required.

<u>*Standard Biological Parts:*</u> The United States should launch a focused program supporting the design, manufacture, characterization, and distribution of standardized biological parts that can be readily reused. An initial set of publicly available parts should be developed that would support all biotechnology applications, by focusing on the core biochemical functions comprising molecular biology's "central dogma." Additional parts collections should be developed in response to national strategic needs (e.g., renewable energy, rapid response vaccination, and therapies for both natural or engineered agents). Public-private partnerships and open technology roadmaps will again be essential, as will cross agency and department coordination. A parts production program should be informed by the Human Genome Project's experiences in developing professionally staffed high-throughput DNA sequencing facilities.

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5 DARPA ISAT Synthetic Biology Study, http://dspace.mit.edu/handle/1721.1/38455
6 "Foundations for Engineering Biology," *Nature*, **438**:449-53, 24 November 2005
7 "Engineering Life: Building a Fab for Biology," *Scientific American*, **294**:44-51, June 2006

<u>*Tools for Managing Biological Complexity:*</u> The United States should invest in a diverse portfolio of foundational research focusing on the development of tools for managing complexity in engineered biological systems. Just as sequencing the human genome did not instantly result in cures to all human diseases, an improved ability to construct DNA and collections of standard biological parts will not by themselves be sufficient to fully enable the engineering of biology. Investments in engineered biological simplicity should be informed by past successes across all of engineering, with particular attention to electrical engineering and computer science.

Human & Social Investments

For some, biology is a technology, now poised to combine the excitement and power of the recombinant DNA and personal computer revolutions from a generation ago. For others, biology is sacred, a worst-case security threat, or incomprehensible. As we develop technologies that make biology easy to engineer, we must renew and expand our investments in developing and educating communities – local, national, and world-wide – that can engage in constructive and persistent dialog and take actions regarding the consequences of our success. Retrospective or decoupled efforts, akin to the Human Genome Project ELSI programs, will likely be insufficient in developing the resources and capabilities needed to recognize and address many foreseeable issues, including biological ethics, safety, security, and ownership, sharing, and innovation frameworks.

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