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Synthesizing the Future

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The latter half of the 20th century has seen explosive progress in the fields of microelectronics and biotechnology. The roots of these advances lie in the 19th century, when the doors were opening on the molecular world. James Clerk Maxwell demonstrated once and for all that atoms exist and then wrote down the electromagnetic laws that govern their interactions. He immediately began to wonder about whether he could *control* atoms and speculated where that might lead. Two years earlier, Gregor Mendel, an Austrian monk studying peas in his garden, discerned that inherited traits in his peas were binary. Tall or short. Smooth or wrinkled. Mendel had discovered genes. Moreover, he'd found the patterns by which genes were handed down. By selecting for a desired trait, he could affect the genetic makeup of a population.

These two discoveries, Maxwell's and Mendel's, followed separate developmental paths after their joint birth in the late 1860s. The biggest steps for both happened in the 1950s. With the invention of transistors and integrated circuits, Maxwell's dream of control over the small was finally realized, giving birth to the modern computer industry. It was not atoms that got sorted but electrons, pushed and pulled through the hierarchical semiconductor societies by transistors opening and closing tiny doorways. After decade upon decade of Moore's Law, electronic societies have reached the nanoscale, possessing the complexity of large cities in a space the size of a postage stamp. Furthermore, these cities run on a sped-up clock so fast that they have a lifetime of thoughts every second.

The biotech revolution got underway about the same time, when Watson and Crick unlocked the structure of the double helix of DNA in 1953. The microscopic origins of Mendel's genes were finally resolved, and biology's evolution from a taxonomy-based discipline to an information-based one was fully underway. This genetic revolution has transformed the way we think about ourselves and the way we practice medical science. A few decades later, we have usurped nature's tools, cutting and pasting genes between organisms with ever-increasing skill.

These two paths, Maxwell's and Mendel's, represent two completely separate visions for controlling matter at the nanoscale. They play with different materials and work by different rules, the former corresponding to the rigid control of computer circuits and the latter the flexible variability of biological systems. Now, these two approaches are crashing together. Biologists dream of controlling the machinery of life like engineers control device layouts on a computer chip, and engineers dream of evolving adaptive architectures that can, among other things, build themselves. What will happen as these two worlds collide? What is the future of bio meets nano?

In June 2007, we held a symposium to address this question, sponsored by the

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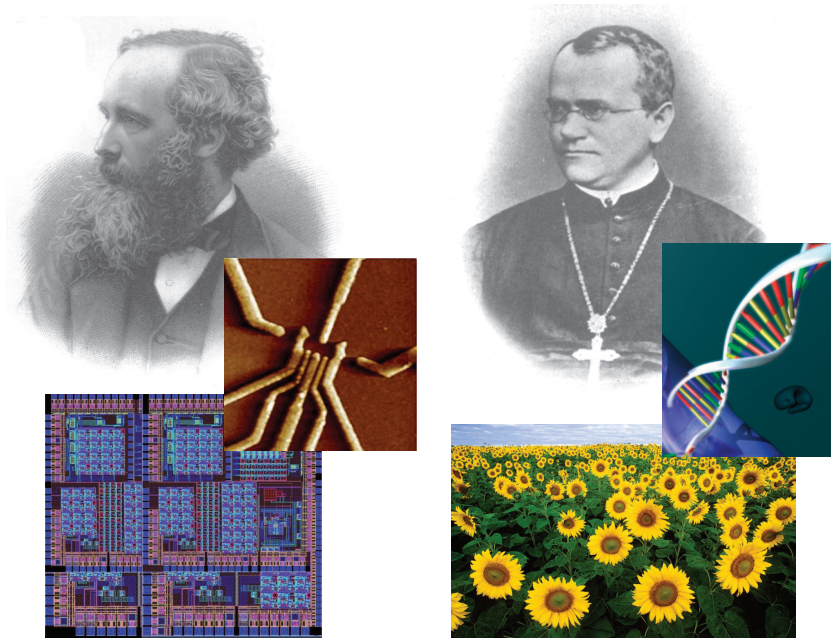

Figure 1. The roots of synthetic biology. Left: James Clerk Maxwell wanted to control the nano world. His dream found reality in the transistor and the information revolution. Photo from *The Life of James Clerk Maxwell* by Lewis Campbell and William Garnett, digitized from an engraving by G. J. Stodart from a photograph by Fergus of Greenock. (http://commons.wikimedia.org/wiki/Image:James_Clerk_Maxwell_big.jpg). Microprocessor manufactured by photographic process. Picture by Angeloleithold 2004, Dec (http://commons.wikimedia.org/wiki/Image:InternalIntegratedCircuit2.JPG) Right: Gregor Mendel discovered the laws of heredity, the random shuffling of genetic traits that underlies the diversity of life. Synthetic biology seeks to marry the two, using both design and evolution to create new forms of life. From *The History of Biology* (Nordenskiöld, E., Ed.) Knopf, New York, 1928. (http://commons.wikimedia.org/wiki/Image:Mendel_Gregor_1822-1884.jpg). Sunflowers in Fargo, North Dakota. Photo by Bruce Fritz, USDA/ARS (http://www.ars.usda.gov/is/graphics/photos/k5751-1.htm).

Kavli Foundation. Seventeen scientists from a broad spectrum of disciplines assembled at an isolated location where the sun never sets (Ilulissat, Greenland) to ponder this future. We held three focused days of discussion on one theme: what is the biggest thing that will happen when bio meets nano? Amazingly enough, we reached a consensus answer.

That answer? Synthetic biology. (The complete text of the Ilulissat Statement can be found at www.kavlifoundation.org/uploads/1187777771_ilulissat_statement.pdf.)

Synthetic biology is the code name for engineering using the machinery of the cell, from tinkering with existing organisms all the way to the design of life from scratch. The idea is pretty radical: in the past 50 years we engineered in silicon; now we will engineer in life. The signs that this is happening are already clear. Biotech is on its own Moore's Law that is even steeper than that of semiconductors: DNA sequencing costs halve every year. We can now synthesize strands of DNA the size of small genomes. Soon, we will be able to express these genomes in cells, giving us control over biological development and evolution. Humans will soon fully insert themselves in the reproductive process of simple organisms, taking full control of genome changes between successive generations. Then, we can design by whatever algorithm we choose, Maxwells' hypercontrol or Mendel's shuffle-and-see.

The first steps of the synthbio revolution have already been made. A toolbox of "standardized genetic parts" is being built, as Drew Endy from the Massachusetts Institute of Technology explained at the meeting. These will allow human design of biological networks down to the molecular scale, assembling complex, interactive, and functional systems to meet a particular goal. In other words, to engineer in the domain previously monopolized by life.

Does this mean that bio wins, and nano is unimportant? *Au contraire*: nano makes the revolution possible. It will be the hardware that makes synthetic biology happen, as was emphasized by Freeman Dyson from Princeton. Still, we face enormous hurdles in the creation of the input/output tools to connect up the electronic world to the nano: laboratory-on-a-chip systems to synthesize and sequence DNA and load it into cells, for example. If we could learn to sequence DNA at the clock speed of a cheap computer, we could sequence the human genome in a few seconds. Furthermore, we may be able to expand the palette of life. Imagine cells with artificial organelles for energy generation made from inorganic materials, for example.

There are hurdles beyond the technical ones, however. Synthetic biology faces a conceptual challenge: What is the best way to design life? How do you design to achieve a specific goal but with robustness? Do you painstakingly plan or simply evolve? Can you even tell a designed system from an evolved one? Which is better? Under what circumstances? Here, we are in the dark. Every time we look more deeply at organisms, the more complexity and subtlety we find. The simple dogmas of molecular biology are fading, and we have only glimpses at what lies beyond. What we do see, however, is that the threads connecting the genome to

the ecological environment are many and tangled. The map between the inner and outer worlds is subtle. We are preparing to travel in a landscape whose rules we only dimly understand.

Still, we see the first stumbling strides to explore this. First, one can approach life from bottom up, for example, by contemplating small liposome vesicles as protocells to which one adds protein and nucleic acid components one by one, as discussed by Petra Schwille from Dresden at the meeting. The challenges are huge, and success will probably demand the integration of new cell components, such as an alternative RNA synthesizer that is much simpler than the current, dauntingly complex, ribosome, something dreamed of by Julie Theriot from Stanford. Alternatively, one can come from the top down and strip an existing "simple" parasitic bacteria of all inessential genes to create a *Mycoplasma laboratrium* that may act as a minimal but functional chassis—a goal pursued by John Glass from the J. Craig Venter Institute.

What are the potential risks and benefits? Some benefits are obvious: new medical devices, treatments, and medicine, for example. Jay Keasling from Berkeley discussed his efforts to produce medicine for malaria at a fraction of the current cost by inserting genes of various origins into bacteria and yeast. New ways to generate energy are another big potential benefit, as discussed by Steven Chu from Berkeley. The numbers demonstrate the promise: all of humanity uses 12 TW of power, while the average solar flux is ~174 PW, a factor of 15,000 more. Can we use synthetic biology to consume a larger piece of this solar pie, using bacteria to directly convert sunlight to fuel or creating fast-growing, low-lignin trees that are easily converted to energy? Of course, the most radical changes will be things we can barely imagine now.

Are there risks? Yes, both obvious and subtle. As we use agricultural crops in new ways, manufacturing and energy needs will compete with food; we are already seeing this with the recent spikes in corn prices. Will some people starve so that others can drive Hummers? There is also the possibility of malevolent organisms wreaking havoc, either by accident or by design. This is a major concern, and the true risk is very difficult to accurately assess because we understand so little about the relation between genomics and ecology. Of course, the way the natural world deals with this risk of innovation is to accept the occasional large die-off. This is a method we prefer not to emulate.

So, how do we maximize benefits and mitigate risks? By being proactive. We should make steps to establish best practices, such as "signing" your work with DNA tags. Rules and regulations on this should evolve, first within relevant professional societies, and later in law, as discussed at the meeting following a thoughtful presentation by Endy. Also, we must properly regulate the intellectual property (IP) and innovation environment. The semiconductor and biotech worlds provide interesting contrasts. The semiconductor industry has learned to work together, setting communal goals, cross-licensing widely—practicing what is really a massive collusion to keep to Moore's Law, within which companies compete. The new biotech, on the other hand, tends to view IP as a goal in itself, leading to a mass of legal hurdles to creating complex synthetic biological systems. Many believe this has been an enormous impediment to future developments. Again, decisions now will have enormous impact.

The year 2050 will likely be as different as today is from the 1950: synthetic biological organisms will be as pervasive as electronic computing is now. The shape of that future will be determined by the policy decisions we make in the coming years. The choices are not easy. Do we try to highly regulate synthetic biology, or do we let it evolve however it likes? The answer is surely a little of both. But beyond the means, the key is to concentrate on the ends. We can put our resources into building bugs that eat flesh or bugs that eat trash and make fuel. That is up to us. We must first decide the future we want. Then, we can use synthetic biology help us to synthesize that future.