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Synthetic Biology 1.0

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Open development of biological technology is crucial to US domestic security and to the health of our economy.

Misuse of this technology in bioterrorism is a clear threat. Our first response to recent domestic bioterror attacks, and to evidence of bioweapon programs abroad, has been to pursue safety in regulation. However, it is already clear that action to limit domestic access to materials and methods will produce only illusory safety. Reagents required for genetic manipulation are available from manufacturers outside the U.S. Synthetic genes can be ordered with equal ease from fabrication labs in Seattle and Tehran .

Beyond access to the infrastructure of sequencing and synthesis, which enables attempts at state-of-the-art genetic manipulation, the practical knowledge required to assemble objects and processes in cellular and molecular systems is proliferating globally. Moreover, biological technologies are being *developed* globally, and they will be as useful worldwide in developing new crops, drugs, and industrial products as they will be in producing weapons. These factors considerably expand the scope of our security problem.

Ensuring domestic physical security and economic competitiveness requires a long-term plan to integrate public and private sector interests. Serious consideration should be given to the role of government in establishing the design and production infrastructure for biological engineering. In particular, investing in engineering tools as a goal of federal research policy will enable safer and more rapid progress in all areas of biology.

Engineering of biology. Our ability to manipulate biology to produce economically useful products is now on the road traveled by many other technologies in the 20 th Century; biology is becoming engineerable. Plastics, therapeutic drugs, biofuels, and industrial chemicals are all being produced in engineered organisms. This transformation is taking place in a context of global communication and a push by the educated populations of China , India , and other up-and-coming nations to improve their economic lot and influence on the world stage.

Biological engineering, whether home-grown or practiced abroad, will soon be integrated into our society and economy as never before. As with other engineerable technologies, biological design and mass production will be economic cornerstones. But because biological technologies are inherently “dual-use”, we will not be able to pick and choose which research to do, which technologies to develop, and which to avoid. Even with careful preparation, unintended consequences and unexpected applications are inevitable. Managing this technological revolution successfully will thus require a deft touch.

Our greatest challenge is to avoid imposing rigid regulations on biological tools and skills that are intrinsically flexible. Rather than focusing on specific threats, we should instead create a dynamic response capability, based on a broad technological and economic infrastructure that prepares us to deal with novel challenges as they arise.

These challenges will certainly include nefarious applications, but an altogether different source of surprise is that most human-built biological systems do not yet display the same predictability as do cars, airplanes, computers, and bridges. There are, however, efforts afoot to improve the situation. Researchers attempting to build biological systems with quantitatively predictable behaviors have begun gathering in the emerging field of Synthetic Biology. Many of those involved see engineering biology from the ground up as primarily a way to learn about biology, rather than engineering as an end in itself. But a significant fraction of the crowd that embraces the Synthetic Biology label is pursuing applications, some of them quite humanitarian.

Brewing therapeutic drugs. Jay Keasling, a Professor of Chemical Engineering at UC Berkeley and Chair of the new Synthetic Biology Department at Lawrence Berkeley Labs, is modifying bacteria with the aim of producing artemisinin, a powerful antimalarial drug. A single course of artemisinin, naturally found in the Wormwood tree, cures the disease. Keasling’s group has used genes from Wormwood and three other organisms to engineer a

new metabolic pathway in the bacterium *E. coli,* a task significantly more complex than most contemporary genetic modification efforts. Drug production in microbes, as pursued by Keasling, is similar in structure and operation to brewing beer, and can be ramped up very quickly, producing drugs within hours of start-up. Microbial production of therapeutic compounds will dramatically improve access and reduce costs. Keasling expects to reach his goals for producing artemisinin in large quantities at low cost within three years.

The impact of success in producing an inexpensive antimalarial should not be underestimated. In addition to the staggering human cost, the World Health Organization estimates that the disease reduces GDP growth in affected countries by about 1.5 percent. These countries contain about forty percent of the world's population, and over the past thirty years that growth penalty has created a difference in GDP that exceeds the many billions in yearly foreign aid they receive. The fruits of Synthetic Biology, in this context, will be significant foreign policy tools. Biological technologies have the potential to significantly improve our long-term security by reducing poverty and, in Colin Powell's words, "alleviat[ing] the hopelessness that feeds terror".

Extending the influence of biological technologies into the realms of economic and foreign policy makes perfect sense. In light of the human and economic costs of malaria, the recent $40 million grant from the Gates Foundation to Keasling and his collaborators may rank among the most significant foreign policy investments ever made. Moreover, investment here in the United States to develop tools for biological engineering will provide for more rapid understanding and a more rapid response to both natural and artificial emerging pathogens. This strategy will enhance domestic expertise and will position the U.S. to provide knowledge and technology to a growing world market, whether for bioindustrial production or preventing and treating infectious disease.

Dealing with potential harm. The potential of biological engineering to improve the human condition is often lost amid concerns over modifications of humans and the crops upon which we rely. As the technology and expertise that enable genetic manipulation spread, fears are becoming more common that modified organisms will result – intentionally or otherwise – in harm.

The attendees of Synthetic Biology 1.0, the First International Meeting on Synthetic Biology, held at MIT in June 2004, were well aware of this threat, and of the potential public backlash it may incite. As a result, the community is attempting to be proactive about precautionary measures. Unfortunately, not all recommendations were of equal utility. Not for the first time in this circle did I hear suggestions of licensing for scientists and of strict controls on the distribution of technology and reagents. But such measures are not likely to be effective. Worse, they will instill a false sense of security. During discussion of the safe and secure use of reagents, I was surprised to hear the suggestion that it is possible to track down the source of a GM organism through forensic analysis of altered DNA, thereby identifying the maker. But techniques to assemble DNA free from synthesis artifacts – to erase the artist's signature – were demonstrated as long ago as 2000, an eternity in a field that is only thirty years old.

Beyond the technological limitations to effective regulation, there are general structural problems with the approach. Regulation reduces access to information about activities that might otherwise be easier to monitor. Just as regulation of the drug trade has reduced our knowledge of illicit drug production and trafficking through the creation of opaque black markets, so too will regulation of biological research limit our knowledge of what research is being done and of how powerful biological technologies work. Although there has not been a strong economic incentive to participate in a biological black market, things are changing. A number of proteins and other biologically derived compounds have been developed as drugs, and those drugs are being used to illicitly enhance athletic performance. Doping with Erythropoeitin (a.k.a. EPO or Epogen) is an excellent example of emerging "under the counter" applications of biological technologies. And it is worth considering what sorts of markets and incentives might emerge if a global avian flu pandemic creates severe shortages of vaccines and antiviral drugs, particularly if both production and distribution of those countermeasures are highly localized.

Regulation of work in the lab will be just as problematic as regulation of compounds. Legislation intended to address the threat of bioterrorism has in fact reduced the number of researchers in this country working on pathogens. In a recent interview in the *New York Times*, Nobel Laureate Robert Richardson lamented the effect of post 9/11 legislation on pathogen research at his home institution, Cornell University , which has lost 36 of 38 talented researchers working on pathogens on the select agents list. It is hard to see how this improves our chances of dealing with emerging or intentionally released pathogens. In fact, the anecdote suggests increased regulation will further impair our security.

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Regulation and small business growth. Regulation is also likely to limit the industrial growth, and thus the economic benefit, of biological technologies. Industrial biotech already accounts for upwards of one percent of GDP, and is growing at about twenty percent per year. In terms of employment and R&D productivity, this economic ferment is likely to follow the path of other technological revolutions. The many small Computing and Communications (C&C) technology businesses have consistently spent about as much collectively on R&D as the few large ones. In other words, a significant fraction of the economic and technical benefits of the C&C revolution have been driven by small business.

We can expect the same to be true of biological technologies. In fact, biology is so cheap when compared to C&C that biological innovation may well be dominated by smaller, widely distributed organizations, whether at home or abroad. Thus to realize the economic and technological benefits of Synthetic Biology we must ensure that small innovators have the same opportunity to contribute as large ones, and that access to education and materials is not constrained. Moreover, our political course should be to facilitate research and development at the small scale by increasing access to federal contracts and support.

Because these matters are clearly in the realm of national politics, our political leaders need to take care that decisions are not based on what appears to have worked in the past, but on a sober evaluation of technologies with potential unlike anything that has come before.

In the end, however, it may be the insurance industry, rather than government, that has the largest impact on the pace of progress. The reinsurance giant Swiss Re recently released a report suggesting that because so many unknowns exist in nanotechnology, insurance firms should carefully consider how much coverage to offer on nanotechnology products. In today's litigious environment, it is clear that reduced indemnity is likely to slow the introduction of such products.

How long will it be until this same scrutiny is applied to the products of Synthetic Biology? The answer is short; who should I find sitting beside me at "Biology and Borders", organized by Bio Economic Research Associates (www.bio-era.net), but a representative from Swiss Re. It is a matter of public policy as to whether we should let fear of litigation, through the proxy of the insurance industry, determine the course of research.

Open biology. I have argued elsewhere that our greatest resource to combat emerging natural and artificial biological threats is an open and broadly distributed technological capability[1]. Regulation that is demonstrably ineffective in improving security could easily end up stifling the technological innovation required to improve security. And make no mistake; we desperately require new technologies to provide for an adequate biodefense capability.

Creating policy to address our technological deficit is complicated by current confusion about the meaning of the term "biodefense". At the moment, "biodefense" is clearly construed in the press and public mind to mean a strategy of stockpiling vaccines against specific threats. This strategy is undermined by our present technical inability to produce a vaccine using the highly virulent H5N1 strain of Avian Flu. Our only recourse currently is to make a vaccine based on a virus that is modified to be less deadly, introducing significant uncertainty about its utility in preventing disease. Thus while we may be able to identify and sequence a pathogen rapidly, as in the case of the SARS virus, the development of a treatment or vaccine fit for human use requires considerably longer.

Our response is slowed primarily because we do not have an adequate technology base from which we can rapidly intervene when pathogens threaten human systems. We need better tools, and we need them in a hurry. A historical comparison of the current state of biological technology to mature fields in mature markets, such as computer engineering and aviation, reveals the sort of tools we need. We need the equivalent of oscilloscopes, stress gauges, voltmeters, and wind tunnels to provide quantitative information about how biological parts function. These tools will help us understand existing biological systems, as well as help in building new ones, such as new vaccine and treatment systems. Thus some tools will be physical objects used to manipulate molecules, familiar to most people who have worked in or visited labs, while other tools will themselves be cells or molecules.

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We also need to identify a set of biological parts that can be assembled into systems with predictable behaviors. And we need to build and maintain an adequate manufacturing capacity for those cells, molecules and other biological parts. Again, history provides insight into how technologies proceed from R&D to manufacturing. Through large-scale procurement, the U.S. Government has played a significant role in establishing and maintaining production infrastructures for automobiles, aviation, and integrated circuits, thereby guaranteeing private investment and providing an extraordinary economic leg up to American industry. Similarly, the best way to develop the diversity of biological tools we absolutely require to improve our safety and security is to encourage a distributed economic capability to generate those tools. Which brings us back to small business and its traditional crucial role in our economy.

With appropriate investment, and involvement of businesses at all scales, we have the opportunity to create a distributed manufacturing infrastructure that will provide for a stronger, more secure country and an economy based on biological technologies.

Synthetic Biology 2.0 is scheduled for June of 2006. We have an enormous amount of work to do before then.

Notes

1. "The Pace and Proliferation of Biological Technologies", Robert Carlson, *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, **1**(3), Sept. 2003, Pages 203-214, (doi:10.1089/153871303769201851).

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