BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY, PRACTICE, AND SCIENCE
Volume 1, Number 3, 2003


# The Pace and Proliferation of Biological Technologies

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THE ADVENT OF THE home molecular biology laboratory is not far off. While there is no *Star Trek* "Tricorder" in sight, the physical infrastructure of molecular biology is becoming more sophisticated and less expensive every day. Automated commercial instrumentation handles an increasing fraction of laboratory tasks that were once the sole province of doctoral level researchers, reducing labor costs and increasing productivity. This technology is gradually moving into the broader marketplace as laboratories upgrade to new equipment. Older, still very powerful instruments are finding their way into wide distribution, as any cursory tour of eBay will reveal.[1] These factors are contributing to a proliferation that will soon put highly capable tools in the hands of both professionals and amateurs worldwide. There are obvious short term risks from increased access to DNA synthesis and sequencing technologies, and the general improvement of technologies used in measuring and manipulating molecules will soon enable a broad and distributed enhancement in the ability to alter biological systems. The resulting potential for mischief or mistake causes understandable concern—there are already public calls by scientists and politicians alike to restrict access to certain technologies, to regulate the direction of biological research, and to censor publication of some new techniques and data. It is questionable, however, whether such efforts will increase security or benefit the public good. Proscription of information and artifacts generally leads directly to a black market that is difficult to monitor and therefore difficult to police. A superior alternative is the deliberate creation of an open and expansive research community, which may be better able to respond to crises and better able to keep track of research whether in the university or in the garage.

## FACTORS DRIVING THE BIOTECH REVOLUTION

The development of powerful laboratory tools is enabling ever more sophisticated measurement of biology at the molecular level. Beyond its own experimental utility, every new measurement technique creates a new mode of interaction with biological systems. Moreover, new measurement techniques can swiftly become means to manipulate biological systems. Estimating the pace of improvement of representative technologies is one way to illustrate the rate at which our ability to interact with and manipulate biological systems is changing.

For example, chemically synthesized DNA fragments, or oligonucleotides, can be used in DNA computation, in the fabrication of gene expression arrays ("gene chips"), and to make larger constructs for genetic manipulation. Mail-order oligonucleotides were with much fanfare recently used to build a functional poliovirus genome from constituent molecules for the first time.[2] The rate at which DNA synthesis capacity is changing is thus a measure of the improvement in our ability to manipulate biological systems and biological information. Similarly, improvements in DNA sequencing capabilities are a measure of our ability to read biological information; in particular the ability to proofread the results of DNA synthesis. Here I refer to such technology, whether instrument or molecule, as "biological technology."

## THE PACE OF TECHNOLOGICAL CHANGE THROUGH THE PRISM OF MOORE'S LAW

Figure 1 contains estimates of potential daily productivity of DNA synthesis and sequencing based on commercially available instruments, including the time necessary to prepare samples. There have been only a few generations of instruments—there is thus a limited amount of data for examination. These estimates are not intended to absolutely quantify a rate of change, but rather to capture the essence of the trends. Several tech-

[1]See http://listings.ebay.com/pool1/listings/list/all/category11811/index.html.

[2]Cello J, Paul AV, Wimmer E. Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template. Science 2002. 297(5583): p. 1016–1018.

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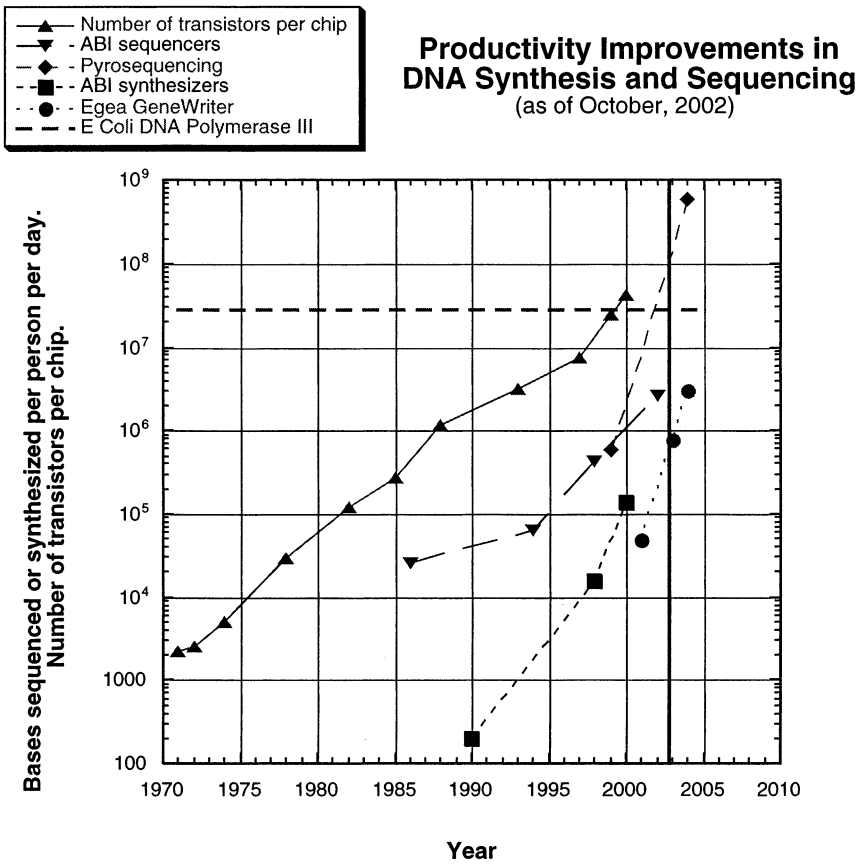


**FIG. 1.** On this semi-log plot, DNA synthesis and sequencing productivity are both increasing at least as fast as Moore?s Law (upwards triangles). Each of the remaining points is the amount of DNA that can be processed by one person running multiple machines for one eight hour day, defined by the time required for pre-processing and sample handling on each instrument. Not included in these estimates is the time required for sequence analysis. For comparison, the approximate rate at which a single molecule of *E. coli* DNA Polymerase III replicates DNA is shown (dashed horizontal line), referenced to an eight-hour day.

Sample processing time and cycle time per run for instruments in production are based on the experience of the scientific staff of the Molecular Sciences Institute and on estimates provided by manufacturers. ABI synthesis and sequencing data and Intel transistor data courtesy of those corporations. Pyrosequencing data courtesy of Mostafa Ronaghi at the Stanford Genome Technology Center. GeneWriter data courtesy of Glen Evans, Egea Biosciences. Projections are based on instruments under development.

nologies used in protein structure determination show similar trends (Figure 2), suggesting a general rapid improvement of biological technologies. As a reference, Moore's Law, which describes the doubling time of the number of transistors on microchips, is also shown in Figure 1.

Comparing anything to Moore's Law is already a cliché, but doing so remains a useful device to gauge our expectations of how other technologies will affect socioeconomic change. This comparison starts with the observation that chip doubling times are a consequence of the planning intrinsic to the semiconductor and computer industry.[3] Moore's Law is primarily a function of the capital cost and resource allocation necessary to build chip fabrication plants. In addition, for much of the last thirty years there was feedback between the ability to design new chips and the computational power of the chips used in the design process.

We can now see the beginnings of a similar effect in the development of biological technologies. For example, enzymes optimized for laboratory conditions are used in the preparation of DNA for sequencing, where earlier sequencing technologies were part of characterizing and modifying those enzymes. Recombinant proteins are used every day to elucidate interactions between proteins within organisms, and that information is already being used to design and build new protein networks. Enzymes are directly used in a process known as Pyrose-

[3]Moore, G. Cramming more components onto integrated circuits. *Electronics* 1965. 38(8).

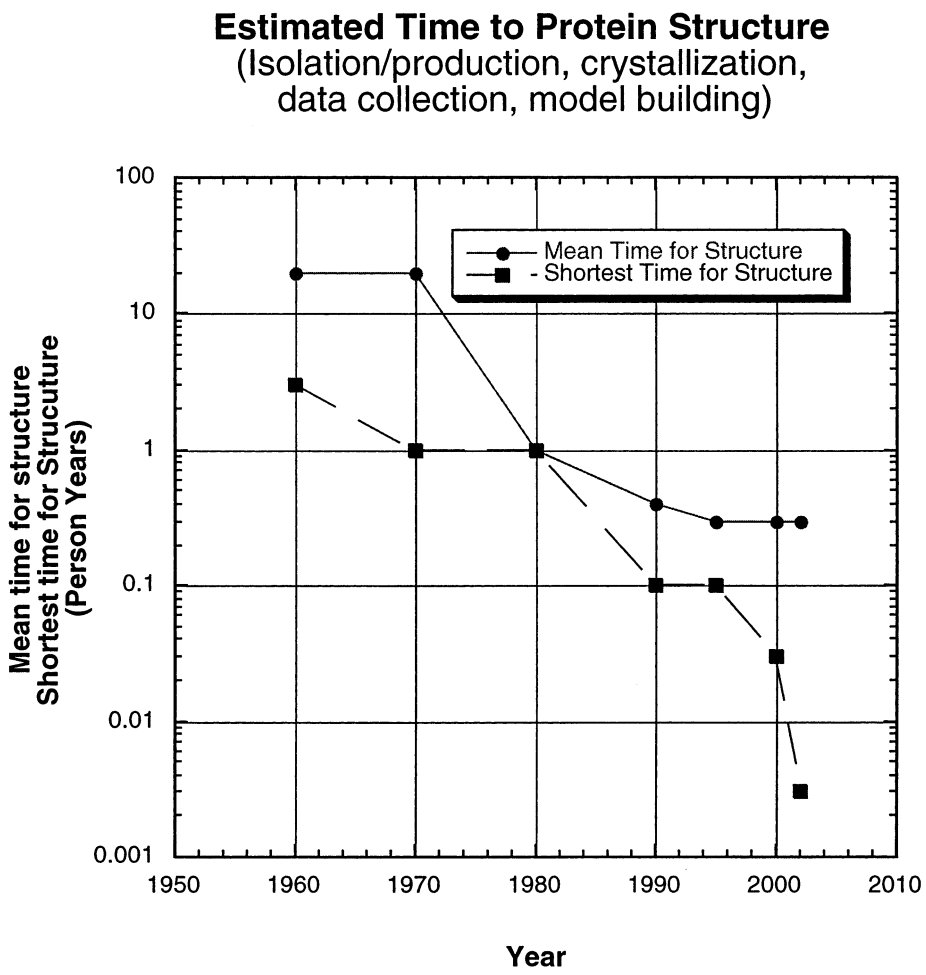


**FIG. 2.** The dramatic improvement in the time required to determine protein structures is evidence of a general trend towards increased productivity in biological technologies. Many of the technologies used in finding protein structures are used widely in biology for other purposes. Raw estimates of time to collect and crystallize recombinant proteins, to take x-ray data, and to build structural models were compiled by Richard Yu (The Molecular Sciences Institute, Berkeley, CA) based on his experience and a survey of five additional crystallographers. From these estimates, the shortest time and mean time to find protein structures were computed. The time required for each step can vary significantly depending upon the protein. For example, successful crystallization may take anywhere between hours and months of effort. The difference between the estimates of the average time to structure and the shortest time to structure illustrates the difficulty in absolutely quantifying productivity.

quencing,[4] and its performance (Figure 1) is an indication of what will happen when we begin to manipulate biology, using biology, on a large scale at many levels of complexity.

Other observers have compared increases in the total number of sequenced genes to Moore's law. But this mixes proverbial apples and oranges because total sequencing productivity is a measure of total industrial capacity (the number of sequencing instruments produced and in operation) whereas the number of transistors is ostensibly a measure of the potential productivity improvements enabled by each individual computer. The total number of sequenced genes is more analogous to the total number of computer chips in existence, or possibly the total number of computational operations enabled by those chips. Comparing Moore's Law to estimates of the daily productivity of one person at a biology laboratory bench is appropriate because that productivity determines how much benefit, or havoc, one person can generate.

An alternative statement of Moore's Law is "Computational resources for a fixed price double every 18 months." Assuming for a moment that the cost of appropriately skilled labor has remained constant, the units of

[4]Ronaghi M. Pyrosequencing Sheds Light on DNA Sequencing. *Genome Research* 2001. 11(1): p. 3–11.

the vertical axis in Figure 1, "bases synthesized and sequenced *per person per day*," match the metric of resource cost, which is explicitly labor in this case. Note that this assumption is too conservative. Labor costs associated with sequencing have actually fallen as bench top laboratory techniques that once required a doctorate's worth of experience have been replaced by automated processes that can be monitored by a technician with only limited training (see below). The capability of individuals has improved dramatically over the last 15 years.

The rapid increase in sequencing productivity is the primary reason that the private effort by Celera was able to sequence the human genome so quickly. Money was always available to buy many slow machines—this was, after all, the original plan for the publicly funded genome project—but coordinating the effort and paying for the labor to run those machines was prohibitively expensive for a private project. The advent of new technology provided an opportunity for a new approach, which Celera seized. Only when sequencing instruments became sufficiently automated that labor was reduced to loading samples, whereupon one person could shepherd several machines and the total task could be completed in an interesting time interval, was a commercial effort possible. This required highly centralized sequence production facilities in order to minimize the number of instruments, given their individual high cost. This infrastructure is similar to that of microchip fabrication plants, otherwise known as "chip fabs."

However, because sequencing instruments are much closer to commodities than are the plasma etchers and vapor deposition systems used in microchip production, it is not at all obvious that the current centralized model will be relevant to the future of biological technology. On the contrary, because there has been to date only limited feedback between biological discovery and the technology it enables, it seems more likely that low cost, highly capable instrumentation will be broadly distributed. Sequencing machines are already widespread in laboratories and there is clear demand for faster, cheaper instruments.

More significantly, the long term distribution and development of biological technology is likely to be largely unconstrained by economic considerations. While Moore's Law is a forecast based on understandable large capital costs and projected improvements in existing technologies, which to a great extent determined its remarkably constant behavior, current progress in biology is exemplified by successive shifts to new technologies. These technologies share the common scientific inheritance of molecular biology, but in general their implementations as tools emerge independently and have independent scientific and economic impacts. For example, the advent of gene expression chips spawned a new industrial segment with significant market value. Recombinant DNA, gel and capillary sequencing, and monoclonal antibodies have produced similar results. And while the cost of chip fabs has reached upwards of one billion dollars per facility and is expected to increase, there is good reason to expect that the cost of biological manufacturing and sequencing will only decrease. Indeed, the continuing costs of sequencing (expendables such as reagents) have fallen exponentially over the time period covered by Figure 1.[5] Lander *et al*., state in *Nature* that by 2000 the total costs of sequencing had fallen by a factor of 100 in ten years, with costs falling by a factor of 2 approximately every eighteen months.[6] With the caveat that there are only limited data to date, it does appear that the total cost of sequencing and synthesis are falling exponentially (Figure 3).

These trends—successive shifts to new technologies and increased capability at decreased cost—are likely to continue. In the fifteen years that commercial sequencers have been available, the technology has progressed, using the simple metric in Figure 1, from labor intensive gel slab based instruments, through highly automated capillary electrophoresis based machines, to the partially enzymatic Pyrosequencing process. These techniques are based on chemical analysis of many copies of a given sequence. New technologies under development are aimed at directly reading one copy at a time by directly measuring physical properties of molecules, with a goal of rapidly reading genomes of individual cells. These include efforts to measure differences in ion currents due to size variations between bases as DNA is electrophoresed through a small pore,[7] and measuring differences in force between complimentary bases as double stranded DNA is unzipped by pulling it apart with an atomic force microscope.[8] While physically-based sequencing techniques have historically faced technical difficulties inherent in working with individual molecules, an expanding variety of measurement techniques applied to biological systems will likely yield methods capable of rapid direct sequencing.

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[5]Editorial. *Genome Technology*, 2001.

[6]Lander ES, et al., Initial sequencing and analysis of the human genome. *Nature* 2001. 409(6822): p. 860–921.

[7]Meller A, et al. Rapid nanopore discrimination between single polynucleotide molecules. *PNAS*, 2000. 97(3): p. 1079–1084.

[8]Bockelmann U, Thomen P, Heslot F. Unzipping DNA with High Sequence Resolution. *European Biophysics Journal* 2000. 29(4–5): p. 249.

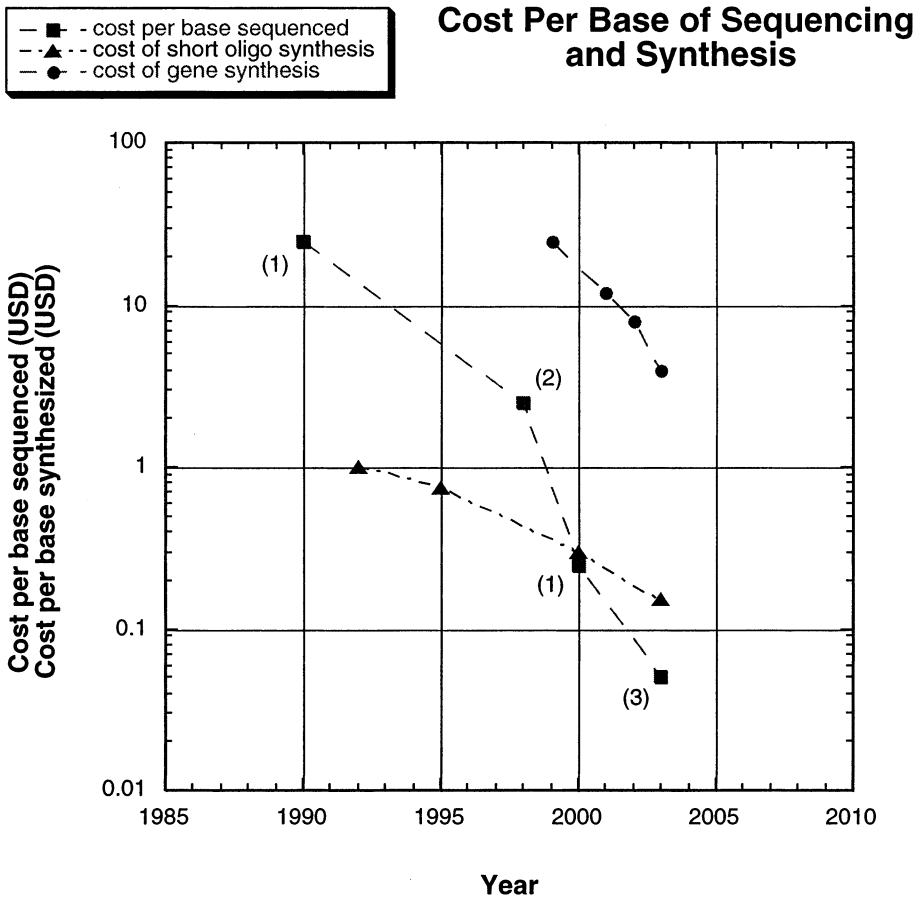


**FIG. 3.** Rough estimates of the cost of synthesis and raw sequencing per base. Only very limited data are available. Estimates of synthesis costs are from John Mulligan, Blue Heron Biotechnology. Historical costs of sequencing are generally not available in the literature, have not been publicized by federally funded Genome Centers, and are, in general, surprisingly hard to come by:[44] (1) from Lander *et al.*;[6] (2) from Dan Rokhsar, UC Berkeley; (3) approximate current commercial rate.

[44]Robert Waterston, Personal Communication.

## ANTICIPATING THE FUTURE OF SYNTHESIS AND SEQUENCING

A rough extrapolation of the curves (as opposed to their tangents) in Figure 1 suggests that by 2010 a single person will be able to sequence or synthesize $\sim 10^{10}$ bases a day. These potential productivity numbers should be compared to the three billion bases ($3 \times 10^9$) in the human genome. Note that while automation may make this productivity level technologically feasible, costs may prohibit reaching it (see Figure 3). Even if actual technological developments do not sustain current trends, the drive towards automation and integration will certainly continue, enhancing distribution. This is the explicit goal of numerous commercial endeavors, particularly those intent on producing the tantalizing "lab on a chip." Tools of this kind will be particularly powerful in the context of the current labor-consuming processes involved in preparing samples for sequence or expression analysis or in purifying them after synthesis. The "microdiagnostics" company Cepheid, for example, will soon begin selling its GeneXpert Platform, which includes technology that spans sample preparation, purification, and detection of pathogen DNA, potentially reducing sample analysis from days to minutes.[9,10] Scientists, clinicians, first responders, epidemiologists, biological weapons inspectors, and biological weapons producers will appreciate these capabilities equally.

[9]Jones M, et al. Rapid and Sensitive Detection of Mycobacterium DNA using Cepheid SmartCycler and Tube Lysis System. *Clinical Chemistry*, 2001. 47(10): p. 1917–1918.

[10]MT Taylor PB, Joshi R, Kintz GA, Northrup MA. Fully Automated Sample Preparation for Pathogen Detection Performed in a Microfluidic Cassette. *Micro Total Analysis Systems* 2001: p. 670–672.

While it is still early in the development of such platforms, they promise to be another important shift in technology, perhaps helping realize the trends in Figure 1. If those trends are born out, within a decade a single person at the lab bench could sequence or synthesize all the DNA describing all the people on the planet many times over in an *eight-hour day*, even given profligate human reproduction. Alternatively, one person could sequence his or her own DNA within seconds.

Despite the fantastic nature of these numbers, there is no physical reason why sequencing an individual human genome should take longer than a few minutes. Sequencing a billion bases in a thousand seconds would require querying each base for only a microsecond, which is well within the measurement capability of many physical systems. Inexpensive disk drives, for example, already read the state of magnetic domains at upwards of a billion times a second. Although storage media is an example of a mature technology, it is also an indication of the sort of interaction that will be possible with biological systems. Indeed, it seems unwise to assume limits on potential applications of our newly developing ability to manipulate and probe matter at the scale of individual molecules. Every week there are exciting new examples of imaging and manipulation of molecules, or small objects such as carbon nanotubes, each pushing back previously imagined limits. Figure 1 illustrates how fast an individual enzyme can copy DNA, and hybrid techniques utilizing physical measurement of the activity of individual enzymes may provide extremely rapid sequencing.[11] Yet at some point, despite ever increasing speed, sequencing capabilities will likely reach an asymptote in utility—how fast is fast enough?

This raises the question of how much longer effort put into developing rapid sequencing technology will be a wise investment. The greater challenge is sensitivity—biology comes in units of single cells, which is the level we must work at to reprogram biological systems and deal with many diseases. Cancer is one such disease. Generally it is not a whole organ or tissue that becomes cancerous, but rather one cell that breaks loose from its developmental pathway—due to chance mutations, changes in the environment, or infection—and runs amok. Similarly, many infections essentially begin with attacks by individual pathogens on individual cells, even if many simultaneous such events are necessary to produce full-blown symptoms. This is of obvious concern for scientists and clinicians interested in novel pathogens, both natural and artificial. Yet no technology currently emerging from the bench can sequence the genome of a single cell without amplification steps that introduce significant errors (though many academic labs and companies promise this ability soon). Most current technology, particularly that applied to determining interactions between proteins, requires a large number of cells and thus produces data that is an average over the states of those cells. Investigating the metabolic or proteomic state of cells (without the use of genetic modification) is similarly often predominantly limited to large samples.

Regardless of the direction of technological development, the synthesis and sequencing capabilities available to an individual in the next decade will be impressive, greatly facilitating the task of manipulating biological systems. The cost of each instrument should generally decrease, following the trend of similar commodities, suggesting that the infrastructure of biological technology will be highly distributed. One indication of this trend is that the parts for a DNA synthesizer—mostly plumbing and off-the-shelf electronics—can now be purchased for approximately $10,000. The assembly effort and monetary sum are similar to that expended by many car and computer hobbyists, and both the parts list and design information sufficient to assemble the synthesizer are available online.[12]

Despite existing infrastructure that provides for downloading sequences directly into a synthesizer, possession of a DNA synthesizer does not a new organism make. Current chemical synthesis produces only short runs of DNA. Although ingenuity and care are required to assemble full-length genes, the techniques are already described in the scientific literature. Moreover, there is significant economic motivation to make such assembly routine, and multiple companies have been founded to sort out the relevant manufacturing details and to take advantage of the growing demand for long synthetic DNA sequences. Many of these companies provide synthetic DNA via mail based on sequences submitted over the Web, and not all such companies screen ordered sequences against sequences of known pathogens and biological toxins.[13] Even if great care is taken to limit the commercial synthesis of DNA from pathogens or toxins, it is unlikely the chemical tricks and instrumentation that companies develop in the course of building their businesses will remain confined within their walls. Eventually, efficient synthesis will be possible using instruments assembled at home. The diffusion of synthesis capability into the garage will no doubt be slowed by the fact that some the reagents used in chemical DNA synthesis are controlled substances. However, history demonstrates that regulating the synthesis of even complex

[11]Braslavsky I, et al. Sequence information can be obtained from single DNA molecules. *Proc Natl Acad Sci U S A* 2003. 100(7): p. 3960–4.

[12]http://innovation.swmed.edu/Instrumentation/mermade_oligonucleotide_synthesi.htm.

[13]John Mulligan, Personal Communication.

compounds does not greatly inhibit illicit production (see below). The requisite techniques are in fact already highly distributed.

## THE PROLIFERATION OF SKILLS AND MATERIALS IS INEVITABLE

Beyond information about writing DNA from scratch, extensive instructions on standard chemistry and molecular biology techniques are available on the Web, notably detailed descriptions of PCR (polymerase chain reaction) and other important DNA manipulation procedures. While some skills are still highly specialized, basic know-how is permeating the educational process.[14] For several years community colleges have offered courses of study aimed at providing the biotech industry with skilled technicians. A case in point: when it was founded in 1990, the sequencing facility at the Whitehead Institute Center for Genome Research employed primarily scientists with doctorates. Over the years these PhD's were gradually replaced by masters degrees, then bachelors and associates degrees. Now many of the staff have completed only a six month qualification course at local community college or are recent Tibetan immigrants who received training in basic skills at the Institute.[15] These technicians are educated in all the steps necessary to shepherd DNA from incoming sample to outgoing sequence information, including generating bacteria containing DNA from other organisms. This point bears repeating: Creating genetically modified organisms is now the province of immigrants with little formal education. More sophisticated practical knowledge is available to many AP Biology students in high school. Pointing the way into the future, several universities now teach a Molecular Biology for Engineers class. Exploring the limits of this trend is a class taught at MIT wherein students ranging from undergraduates to post-docs design and test new genetic circuits.[16] Successful designs will be included in a databook of biological parts.[17]

Where design expertise exceeds practical experience, commercially available kits include recipes that allow moving genes between organisms by following simple recipes. The process might be slightly more complicated than baking cookies, but it is for the most part less complicated than making wine or beer. This broad distribution of biological technology naturally leads to questions of how it will be applied. Our society is just beginning discussions about the role of genetic modifications and the applications of cellular cloning.

More important, perhaps, is the debate over regulation of research and who will be permitted access to which biological technologies. But it is unlikely that regulation of materiel or skills will produce an increase in public safety. The industrial demand alone for skilled biotechnology workers has increased 14–17% per year for the last decade, and many of these workers come from overseas.[18] Not all these workers will remain in this country, and it is safe to say many of those who leave will make use of their skills elsewhere. If we decide to try to limit the practice of certain methods, it will be unrealistic to try to centrally monitor every skilled person in this or any other country. We certainly cannot simply "unteach" the relevant skills to prevent unauthorized use, and any action to limit the proliferation of skills would cripple that portion of the U.S. economy reliant upon biological technologies.

Perhaps more problematic than distributed skills will be ubiquitous materials. The widespread distillation of alcohol during the Prohibition period in the U.S. and the proliferation of modern illegal drug synthesis labs both illustrate the principle that outlawing chemical products merely leads to black markets more difficult to observe and regulate than open markets.

Effective regulation relies on effective enforcement, which in turn requires effective detection. The extent of illegal drug production in the United States and previous failures to detect illicit biological weapons production gives some indication of the relevant challenges of detection and enforcement. Approximately 8,000 clandestine drug laboratories were seized in the U.S. in 2001, with the vast majority of those being "Mom and Pop" operations producing less than five kilograms per day.[19] Yet despite the large number of seizures (which has on average remained constant for the last decade) illegal drug use is apparently still rising.[20] This failure of enforcement, and the detection failure demonstrated when Western intelligence services failed to uncover the existence of extensive bioweapons programs in the former Soviet Union and Iraq,[21] provide explicit challenges to the notion that the risks posed by mistakes or mischief resulting from biological technologies can be mitigated through regulation.

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[14]Carlson R. Open-Source Biology And Its Impact on Industry. *IEEE Spectrum* 2001.

[15]Carrie Sougnez, Personal Communication.

[16]See http://student.mit.edu/searchiap/iap-4968.html and http://web.mit.edu/synbio/www/iap/.

[17]See http://biobricks.ai.mit.edu/.

[18]Sevier ED, Dahms AS. The role of foreign worker scientists in the US biotechnology industry. *Nat Biotechnol* 2002. 20(9): p. 955–6.

[19]http://www.dea.gov/concern/drug_trafficking.html.

[20]http://www.dea.gov/statistics.html.

[21]Pearson GS. How to make microbes safer. *Nature* 1998. 394(6690): p. 217–8.

Given the potential power of biological technologies, it is worth considering whether open markets are more, or less, desirable than the inevitable black markets that would emerge with regulation. Those black markets would be, by definition, beyond regulation. More importantly, in this case, they would be opaque.

The real threat from distributed biological technologies lies neither in their development nor use, per se, but rather that biological systems may be the subject of accidental or intentional modification without the knowledge of those who might be harmed. Because this may include significant human, animal, or plant populations, it behooves us to maximize our knowledge about what sort of experimentation is taking place around the world. Unfortunately (though understandably), the first response to incidents such as the anthrax attacks in the fall of 2001 is to attempt to improve public safety through means that paradoxically often limit our capabilities to gather such information.[22]

## THE FALSE PROMISE OF REGULATION

Some view as an immediate threat the proliferation of technologies useful in manipulating biological systems: Passionate arguments are being made that research should be slowed and that some research should be avoided altogether. "Letting the genie out of the bottle" is a ubiquitous concern, one that has been loudly voiced in other fields over the years and is meant to set off alarm bells about biological research.

A favorite rhetorical device in this discussion is the comparison of nuclear technologies with biological technologies. Success in limiting the development and spread of nuclear technologies is taken to mean similar feats are possible with biological technologies. But this sort of argument fails to consider the logistical, let alone ethical, differences between embargoing raw fissionable materials used in nuclear or radiological weapons and embargoing biological technology or even biology itself.

Regulation of the development of nuclear weapons has been successful only because access to raw fissionable materials has, fortunately, been relatively easy to restrict. However, both the knowledge and tools necessary to construct rudimentary weapons have for decades been highly distributed. It is arguable that, with some effort, construction of a rudimentary nuclear device is within the capabilities of most physics and engineering college graduates who have access to a basic machine shop. Building nuclear devices is thus theoretically quite feasible but physically difficult, even for the knowledgeable, because the raw materials are simply not available. Yet the raw stuff of biology has always been readily at hand, and our schools and industries are now equipping students with the skills to manipulate biological systems through powerful and distributed technology. Because skills are already widespread and will only become more so, altering and reverse engineering biological systems will become both easier and more common. Regulation can do little to alter this trend.

If strict regulation held promise of real protection, it would be well worth considering. But regulation is inherently leaky, and it is more often a form of management than blanket prohibition. Certainly no category of crime has ever been eliminated through legal prohibition. In this light, we must ask how many infringements of potential regulation of biological technologies we are willing to risk. Further, will the threat of sanctions such as imprisonment ever be enough to dissuade infringement? Given the potential damage wrought by misuses of the technology, we may never be satisfied that such sanctions would constitute a repayment of debt to society, the fundamental tenet of our criminal justice system. The damages may always exceed any punishment meted out to those deemed criminal. These considerations come down to how we choose to balance the risks and consequences of infringement against whatever safety may be found in regulation and attempts at enforcement. More important than this tenuous safety, however, is the potential danger of enforced ignorance. In the end, we must decide not whether we are willing to risk damages caused by biological technology, but whether limiting the general direction of biological research in the coming years will enable us to deal with the outcome of mischief or mistake. We must decide if we are willing to take the risk of being unprepared.

There are currently calls to limit research in the United States on the basic biology of many pathogens to preempt their use as bioweapons,[22] and the possession and transport of many pathogens was legislated into criminality by the Patriot Act.[23] The main difficulty with this approach is not that it assumes the basic biology of pathogens is static—which because of either natural variation or human intervention it is not—but rather that it assumes we have already catalogued all possible natural pathogens, that we already know how to detect and defeat known and unknown pathogens, and that rogue elements will not be able to learn how to manipulate pathogens and toxins on their own. These assumptions are demonstrably false. Pathogens ranging from HIV to *M. tuberculosis* to *P. falciparum* (which causes malaria) have successfully evolved to escape formerly effective treatments. New human pathogens are constantly emerging, which as in the

[22]Knight J. Biodefence boost leaves experts worried over laboratory safety. *Nature* 2002. 415(6873): p. 719–20.

[23]Check E. Law sends laboratories into pathogen panic. *Nature* 2003. 421(6918): p. 4.

case of SARS might be identified quickly but require much longer to develop treatments against. In the last century governments and independent organizations alike have developed and used biological weapons. Restricting our own research will merely leave us less prepared for the inevitable emergence of new natural and artificial biological threats. Moreover, it is naive to think we can successfully limit access to existing pertinent information within our current economic and political framework.

As is clear from recent efforts to limit peer-to-peer file sharing on the Internet, in today's environment strict prohibition of information flow can only be achieved by quarantine—unplugging wires and blocking wireless transmission. Thwarted by the difficulty of such endeavors, music conglomerates have resorted to flooding file servers with corrupted files (camouflage),[24] and requesting the legal authority to engage in preemptive cracking of file trader's computers (sabotage).[25]

Neither strategy is likely to be a long term solution of controlling information for the music industry, and similar efforts to regulate biological technologies are bound to be more difficult still. Attempting to maintain control of information and instrumentation will be a futile task in light of the increasingly sophisticated biological technologies blossoming around the world.

While the most advanced research and instrumentation developments may occur first in fully industrialized countries such as the US, where export might be controlled, other countries are developing a skill base that will enable broad domestic utilization of biological technologies. China has an aggressive program in plant biotechnology, and as of 2002 plans to increase funding 400% by 2005.[26] This energetic investment also exists in the Chinese private sector, and the national scientific establishment is attempting to lure foreign trained scientists to return with lucrative financial packages.[27] India is in the process of tripling funding to its national biotech center,[28] and is promoting the development and use of genetically modified crops throughout Asia.[29] Singapore has for many years made a practice of recruiting foreign scientists.[30] Taiwan is investing large amounts in biotechnology[31] and is seeking citizens to return home to build up biotechnology in academia and industry.[32] A Brazilian coalition recently demonstrated sophisticated domestic use of biological technologies by successfully sequencing the plant pathogen *X. fastidiosa* in 2000.[33]

Given these developments in the context of the increase in individual capabilities and the independent reduction in cost, it is unrealistic to think biological technologies can be isolated within the borders of officially sanctioned countries. Even if such a regime were implemented, it would merely include those countries that already have a particular technology. We can do little to take technology away from those in whose hands it was developed and resides. The best strategy going forward is in fact to encourage such efforts at all levels in an open environment.

## WHAT SHOULD (AND SHOULD NOT) BE DONE

If regulation is not merely an ineffective option but will actually be an impediment to security, how can we attempt to mitigate coming risks? The goal is clearly to counter both mistakes in the laboratory and weapons created from biological components and, ideally, to make such threats irrelevant before they become a problem.

It may be many decades before our understanding of biology provides for the requisite rapid detection, analysis, and response. Fortunately, it is also probably true that we have some time to prepare before both technology and skills become truly pervasive. In the meantime, we can lay the groundwork for an increase in security with dramatically improved communication and focused technology development.

We should focus on three challenges:

1) We should resist the impulse to restrict research and the flow of information. Ignorance will help no one in the event of an emergent threat and, given the pace and proliferation of biological technologies, the likelihood of threats will increase in coming years. Among the greatest threats we face is that potentially detrimental work will proceed while we sit on our hands. If we are not ourselves pushing the boundaries of what is known about

[24]Chmielewski DC. Music industry swamps swap networks with phony files, in *Mercury News* 2002: San Jose.

[25]Bridis T. Senator favors really punishing music thieves, in *Tribune* 2003: Chicago.

[26]Huang J, et al. Plant Biotechnology in China. *Science*, 2002. 295: p. 674–678.

[27]Breithaupt H. *China's leap forward in* biotechnology. *EMBO Rep*, 2003. 4(2): p. 111–3.

[28]Taylhardat AR, Falaschi A. Funding assured for India's international biotechnology centre. *Nature* 2001. 409(6818): p. 281.

[29]Jayaraman KS. India promotes GMOs in Asia. *Nat Biotechnol* 2002. 20(7): p. 641–2.

[30]Singapore attracts foreign talent. *Nature* 1998. 394: p. 604.

[31]Swinbanks D, Cyranoski D. Taiwan backs experience in quest for biotech success. *Nature*, 2000. 407(6802): p. 417–26.

[32]Cyranoski D. Taiwan: Biotech vision. *Nature* 2003. 421: p. 672–673.

[33]Simpson AJ, et al. The genome sequence of the plant pathogen Xylella fastidiosa. The Xylella fastidiosa Consortium of the Organization for Nucleotide Sequencing and Analysis. *Nature* 2000. 406(6792): p. 151–7.

how pathogens work or ways to manipulate them, we are by definition at a disadvantage. Put simply, it will be much easier to keep track of what is in the wind if we don't have our heads in the sand.

2) The best way to keep apprised of the activities of both amateurs and professionals is to establish open networks of researchers, perhaps modeled on the Open Source Software (OSS) movement, and potentially sponsored by the government during their embryonic phases. The Open Source development community thrives on constant communication and plentiful free advice. This behavior is common practice for professional biology hackers, and it is already evident on the Web amongst amateur biology hackers.[14] This represents an opportunity to keep apprised of current research in a distributed fashion. Anyone trying something new will require advice from peers and may advertise at least some portion of the results of their work. As is evident from the ready criticism leveled at miscreants in online forums frequented by software developers (Slashdot, Kuro5hin, etc.), people are not afraid to speak out when they feel the work of a particular person or group is substandard or threatens the public good. Thus our best potential defense against biological threats is to create and maintain open networks of researchers at every level, thereby magnifying the number of eyes and ears keeping track of what is going on in the world.

3) Because human intelligence gathering is, alas, demonstrably inadequate for the task at hand, we should develop technology that enables pervasive environmental monitoring. The best way to detect biological threats is using biology itself, in the form of genetically modified organisms. Unlike the production and deployment of chemical weapons or fissile materials, which can often be monitored with remote sensing technologies such as aerial and satellite reconnaissance, the initial indication of biological threats may be only a few cells or molecules. This small quantity may already be a lethal dose and can be very hard to detect using physical means. Alternatively, "surveillance bugs" distributed in the environment could transduce small amounts of cells or molecules into signals measurable by remote sensing. The organisms might be modified to reproduce in the presence of certain signals, to change their schooling or flocking behavior, or to alter their physical appearance. Candidate "detector platforms" span the range of bacteria, insects, plants, and animals. Transgenic zebrafish[34] and nematodes[35] have already been produced for this purpose, and there is some progress in producing a generalized system for detecting arbitrary molecules using signal transduction pathways in bacteria.[36]

None of these recommended goals will be trivial to accomplish. Considerable sums have already been spent over the last five decades to understand biological systems at the molecular level, much of this in the name of defeating infectious disease. While this effort has produced considerable advances in diagnosing and treating disease, we should now redouble our efforts. We have entered an era when the ability to modify biological systems is becoming widespread in the absence of an attendant ability to remediate potential mistakes or mischief. Maintaining safety and security in this context will require concerted effort, and an immediate, focused governmental R&D investment would be a good start. Although "bug to drug in twenty four hours" sounds much flashier than "bug to drug in six to eight weeks," the latter is the more realistic timeline to shoot for—even if it is a decade or more away—and this goal may serve as an organizational focus for an endeavor organized and sponsored by the government.

Previous governmental efforts to rapidly develop technology, such as the Manhattan and Apollo Projects, were predominantly closed, arguably with good reason at the time. But we live in a different era and should consider an open effort that takes advantage of preexisting research and development networks. This strategy may result in more robust, sustainable, distributed security and economic benefits.[14,37] Note also that though both were closed and centrally coordinated, the Manhattan and Apollo Projects were very different in structure. The Apollo Project took place in the public eye, with failures plainly writ in smoke and debris in the sky. The Manhattan Project, on the other hand, took place behind barbed wire and was so secret that very few people within the US government and military knew of its existence. This is not the ideal model for research that is explicitly aimed at understanding how to modify biological systems. Above all else, let us insist that this work happens in the light, subject to the scrutiny of all who choose to examine it.

The only way we will be able to keep track of the fruits of biological technologies, regardless of merit, is a combination of ubiquitous measurement and networks of people. For several decades, the Soviet Union employed tens of thousands of people in research, testing, and pro-

[34]Amanuma K, et al. Transgenic zebrafish for detecting mutations caused by compounds in aquatic environments. *Nat Biotechnol* 2000. 18(1): p. 62–5.

[35]David HE, et al. Construction and evaluation of a transgenic hsp16-GFP-lacZ Caenorhabditis elegans strain for environmental monitoring. *Environ Toxicol Chem* 2003. 22(1): p. 111–8.

[36]Looger LL, et al. Computational design of receptor and sensor proteins with novel functions. *Nature* 2003. 423(6936): p. 185–90.

[37]R. Carlson and R. Brent, Letter to DARPA on Open Source Biology, October 2000, http://www.molsci.org/~rcarlson/DARPA_OSB_Letter.html.

duction of biological weapons.[38] During that time, the USSR was the primary focus of intelligence agencies in the West, and, despite the size of the Soviet bioweapons project, none of those agencies was able to provide conclusive evidence of the project's existence. The extent of biological weapons development and deployment in Iraq during the early 1990's was also an unpleasant surprise.[39] A more integrated worldwide community of professionals and amateurs might provide earlier and more accurate warning of such developments.

Beyond their innate intelligence gathering capability, open and distributed networks of researchers would provide a flexible and robust workforce for developing technology. This resource could be employed in rapid reaction to emerging threats and in the development of a response that might include assembling novel compounds or organisms. The rudiments of such a system were demonstrated during the recent SARS outbreak, but much more is required.[40] One lesson from the OSS community is that even distributed technology development that starts at the grass roots level eventually requires some centralized leadership and coordination.[41] This is often provided by a strong-willed individual, though increasingly independent foundations are formed to coordinate work, gather and distribute funds, and disseminate results.[42]

Some may consider several decades of experience with open source software insufficient as an organizational model to serve as a basis for a response to biological threats. The best model may in fact be found in the history of biology itself. In order to bring the focus of an Apollo Project to the task at hand, the traditions of open discourse amongst academics and the sharing of reagents and biological stocks might be strengthened and adapted. Hoarding of results or materials should be strongly discouraged, and in fact sharing information and stocks should be required. It may be prudent to write down these guidelines in documents with legal standing, if only to give added weight to peer pressure. To be sure, this might be viewed as a form of self-regulation, but it would be in the context of open markets rather than black markets emerging under regulation from above. These agreements might be structured so that voluntary participation would provide ready access to information or reagents otherwise difficult to procure, thereby encouraging participation but not outlawing the activities of those who choose to remain independent. New or existing foundations might take these agreements in hand to provide coordination analogous to that cropping up in the OSS community. There is already some structure of this sort extant in the biological community, with organizations such as the American Cancer Society, the Wellcome Trust, the Bill and Melinda Gates Foundation, amongst many others, providing funding for meetings, journals, physical infrastructure, and particular directions of research.

Finally, the best argument for encouraging the adoption of Open Source organizational principles in amateur, academic, and industrial contexts is that the resulting technology may be considerably more robust and bug free.[43] This goal is nowhere more important than in the burgeoning enterprise of manipulating life at the genetic level. Creating international networks that coordinate an Open Source Biology may be the most important step we can take to improve our security in the coming decades.

## CONCLUSION

Our ability to manipulate biological systems is rapidly improving and this naturally raises concerns both about how relevant technology will be applied and about potential consequent dangers. The straightforward answer is that those dangers are real and considerable. We may view this as a threat or an opportunity. The common response to a perceived threat is to reduce the likelihood of it coming to fruition, an effort that often takes the form of regulation. However, the argument for strict regulation of biological technologies is misleading and therefore dangerous. Fear of potential hazards should be met with increased research and education rather than closing the door on the profound positive impacts of biological technology.

We could err disastrously in the short term by restricting the development of science and technology, thereby stunting our ability to respond to natural or artificial threats. Restriction of research could leave us woefully unprepared to deal with mistakes or mischief. I am not suggesting that all regulation is without merit, but rather that rules and restrictions will not eliminate problems; they never have. Given the power of biological technologies, the only way to ensure safety in the long run is to push research and development as fast as possible.

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[38]Alibek K, Handelman S. *Biohazard: the chilling true story of the largest covert biological weapons program in the world, told from the inside by the man who ran it*. 1st ed. 1999, New York: Random House. xi, 319 p., [8] p. of plates.

[39]Seelos C. Lessons from Iraq on bioweapons. *Nature* 1999. 398(6724): p. 187–8.

[40]Pearson H, et al. SARS: What have we learned? *Nature* 2003. 424(6945): p. 121–126.

[41]For a very readable introduction to the structure of the Open Source community see http://www.theinquirer.net/?article=10114 and http://www.theinquirer.net/?article=10222.

[42]For example, http://www.mozillafoundation.org/.

[43]Ball P. Openness makes software better sooner. *Nature Science Update* June 25, 2003, http://www.nature.com/nsu/030623/030623-6.html.

We should maintain an open environment as possible and make sure that we move rapidly beyond the point where we can alter systems without the ability to understand them or learn to fix them. Improving such capabilities will also aid in diagnosing and treating rapidly emerging natural pathogens. The existing technology lag between our ability to manipulate and our ability to detect, understand, and remediate must be eliminated with all haste. Regulation or proscription of either science or technology is unlikely to ease the way forward. In the dark we cannot see the road ahead, navigate, or avoid collisions with either natural or artificial hazards.

Regardless of the outcome of the debate explored above, the stage is set for remarkable change. We have clearly entered a period in which our understanding of biological systems is itself producing new biologically based technologies. These in turn lead to new insight and new technologies, further enhancing our ability to understand and manipulate biological systems. The demand for more capable technology is both broad and deep suggesting that, as the trend to increasingly sophisticated yet less expensive instrumentation continues, biological technology will become ever more commoditized. The resulting wide distribution will further accelerate discovery and invention.

## ACKNOWLEDGMENTS

The author wishes to thank Drew Endy, Roger Brent, Stewart Brand, Freeman Dyson, Sydney Brenner, Rik Wehbring, Brad Smith, and Sarah Keller for thoughtful conversations, and Richard Yu, Robert Waterston, Dan Rokhsar, Mostafa Ronaghi, Glen Evans, and John Mulligan for estimates of cost and/or productivity.

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Published online: August 20, 2003