

Laying the foundations for a bio-economy

Robert Carlson

Received: 30 November 2007 / Accepted: 6 December 2007
© Springer Science+Business Media B.V. 2008

Abstract Biological technologies are becoming an important part of the economy. Biotechnology already contributes at least 1% of US GDP, with revenues growing as much as 20% annually. The introduction of composable biological parts will enable an engineering discipline similar to the ones that resulted in modern aviation and information technology. As the sophistication of biological engineering increases, it will provide new goods and services at lower costs and higher efficiencies. Broad access to foundational engineering technologies is seen by some as a threat to physical and economic security. However, regulation of access will serve to suppress the innovation required to produce new vaccines and other countermeasures as well as limiting general economic growth.

Keywords Biofuels · Biosecurity · Composable parts · Economic growth · Regulation · Synthetic biology

Welcome to the Paleobiotic Age. Just as today we look back somewhat wistfully on our quaint Paleolithic—literally “old stone”—ancestors, so will our descendants see the present age as that of “old biology”, inhabited by Paleobiotic Man. The technologies we use to manipulate biological systems are experiencing dramatic improvement (Carlson 2003; Newcomb et al. (2007), and as a result are driving change throughout human economies.

In order to understand the impact of our growing economic dependence on biological technologies it is worth taking a moment to consider the meaning of economy.

“Economy” is variously thought of as, “the management of the resources of a country, especially with a view to its productivity” and “the disposition or regulation of the parts or functions of any organic whole; an organized system or method”.¹ Amid a constantly increasing demand for resources, we look to technology to improve the productivity of labor, to improve the efficiency of industrial process and energy production, and to improve the yield of agriculture. Very tritely, we look to technological innovation within our economy to provide more stuff at lower cost. Biological technologies are increasingly playing that role.

What is the bio-economy, and how big is it?

The title of this commentary is, of course, behind the times; we already have a thriving bio-economy. Without high-yield agriculture, human society would be severely limited, and without access to the fossil remains of prior life on Earth, now mined as petroleum, coal, and methane, we would be impoverished further still. Estimates of the total annual contribution of biology to the economy vary; between US\$ 350 billion² and 1 trillion (Pimentel, personal communication) are produced by the U.S. food and agricultural sectors; pharmaceutical sales are approximately US\$ 600 billion worldwide and 250 billion within the US (Herper and Kang 2006). A small, but rapidly growing, fraction of the total constitute products made using biotechnology.

R. Carlson (✉)
Bio Economic Research Associates, Cambridge, USA
e-mail: rcarlson@bio-era.net

¹ <http://dictionary.reference.com/browse/economy>

² The latest data is from 2004, and the US economy has been growing at about 4% per year. See The Statistical Abstract: <http://www.census.gov/compendia/statab/>

The words “biotechnology” and “biotech” are often used by the press and industry observers in limited and inconsistent ways. Those words may be used to describe only pharmaceutical products, or in another context only the industry surrounding genetically modified plants, while in yet another context a combination of biofuels, plastics, chemicals, and plant extracts. The total economic value of biotechnology companies is therefore difficult to assess, and it is challenging to disentangle the component of revenue due each to public and private firms.

Based on surveys from *Nature Biotechnology*, the U.S. Government, various organizations in Europe, and several private consulting firms, what follows is my integrated rough assessment of where the money is for industrial biotech, agbiotech, and biopharmaceuticals (also known as “biologics”). Estimates of total revenues range from US\$ 80 to 150 billion annually, where the specific dollar value depends strongly on which set of products are included. The various surveys that provide this information differ not only in their classification of companies, but also in methodology, which in the case of data summarized by private consulting firms is not generally available for scrutiny. Further complicating the situation is that results from private biotech firms are self-reported and there are no publicly available documents that can be used for independent verification. One estimate, based on data from 2004 (explicitly excluding agricultural, industrial, and environmental biotech firms), suggested approximately 85% of all “biotech” companies are private, accounting for a bit less than 50% of employment in the sector and 27% of revenues (Hodgson 2006).

As of 2006, biologics accounted for about US\$ 65 billion in sales worldwide, with about 85% of that in the U.S. and a 20% annual growth rate over the last five years (Herper and Kang 2006; Aggarwal (2007). Genetically modified crops accounted for another US\$ 6 billion, with industrial applications (including fuels, chemicals, materials, reagents, and services) contributing another US\$ 50–80 billion, depending on who is counting and how. Annual growth rates over the last decade appear to be 15–20% for medical and industrial applications, and 10% for agricultural applications. After sifting through many different sets of numbers, I estimate that revenues within the U.S. are presently about US\$ 125 billion, or approximately 1% of GDP, and growing at a rate of 15–20% annually. While this torrid pace will ultimately slow, it is clear neither when this will happen nor how large a fraction of U.S. GDP biotech could ultimately provide. The introduction of carbon accounting in regional and national economies could dramatically increase our reliance upon carbon-neutral, renewable resources and manufacturing. The final economic contribution of biotech will depend in large part on the ultimate capabilities of new biological technologies.

Where do we go from here?

We are beginning to use biology in new ways to provide food, energy, materials, and improved health care. Our challenge is to stay on the path of improving both productivity and our general quality of life while simultaneously improving both safety and security. How should we organize ourselves to encourage innovation in biological technologies so as to best manage our resources, improve our security, and benefit the human condition?

We must answer this question in the midst of substantive and dramatic transitions in the way we manipulate organisms. Builders of synthetic biological systems are starting to draw on engineering experience and infrastructure honed in 20th century technological revolutions. An important historical lesson now contributing to our present technological economy is the utility of standardized, composable parts—parts with defined, and therefore predictable, functionalities that enable design and assembly based on specifications alone.

Combining composable parts with modeling and assembly tools enables the existing design-to-build economy for airplanes, cars, and myriad other products, where in silico testing precedes transfer of Computer Aided Design (CAD) files to Computer Aided Manufacturing (CAM) production machinery. These design-to-build processes not only reduce manufacturing costs and increase the productivity of designers but also facilitate rapid physical implementation of new ideas. This methodology defines modern rational engineering. Applied to biology, it provides a distinctly different way of producing a new design than does either tinkering or the combination of processes that defines evolution. While the development of mature biological equivalents of CAD, CAM, and interchangeable, composable parts is still some ways off, this is the clear goal of academic and industrial efforts around the globe (Endy 2005).

The transition from paleo- to neo-biotic is unlikely to be easy, rapid, or obviously discrete. While there is great potential in bringing engineering practices to biology, significant investment in engineering fundamentals is required first (Endy 2005). The DOE-sponsored report, “Genome Synthesis and Design Futures: Implications for the U.S. Economy” (Newcomb et al. 2007), charts analogies between the technological and economic development of biology and eighteenth through twentieth century examples of railroads, electric power grids, aviation, and computers. Before a design-to-build bio-economy arrives, there must be models that accurately and consistently predict the behavior of new systems, test and measurement gear to verify those behaviors, and new industrial-scale assembly and distribution mechanisms.

Even without this infrastructure, biological production is already proving to be less expensive and more efficient

than traditional industrial approaches for fabricating chemicals and materials (for a review, see (Newcomb et al. 2007)). A great deal of investment has recently been made to discover whether the same trend holds true for bio-production of fuels. But before all of this comes to pass, an economy based on the rational engineering of biological systems requires a library of composable parts with defined behaviors.

The history of the last three centuries demonstrates that healthy technological economies are not built on one-off constructions, but rather upon hierarchical systems of parts and methods that when pulled off the shelf and assembled in combination produce many functions:

Each component system or assembly of a technology itself has a purpose, an assignment to carry out. If not, it would not be there. ... And each assembly has its own subassemblies or components. Each of these in turn has an assignment to carry out. Each also is a means—a technology. This pattern, that a technology consists of building blocks that are technologies, that consist of further building blocks that are technologies, repeats down to the fundamental level of individual components. ... Practically speaking it means that a technology is organized in a loose hierarchy of groupings or combinations of parts and subparts that themselves are technologies. This hierarchy can be as many as five or six layers deep (Arthur 2007).

Explicitly applying this thinking to the modification of biological systems brings the demonstrated capabilities of rational engineering to a powerful and growing set of composable parts:

By enabling innovation through combination across a wide range of biological components and modules, synthetic biology could radically change the landscape of biotech innovation. The power of innovation through combination of existing components is already demonstrable in technology domains such as combinatorial chemistry, electronics, and software, where decades of innovation have built on previous developments (Newcomb et al. 2007).

The economic impact from these sectors is likely to be recapitulated through building up an infrastructure of composable parts for engineering novel biological systems. The biological world we see out the window works in a similar, though not identical, way.

Terrestrial life reuses a nearly universal set of nucleic acids, amino acids, peptide domains, and general classes of whole proteins and metabolic pathways. It appears that historical examples of natural biological innovation—i.e., evolution—often follow genome replication mistakes that introduce repeated genes, in turn followed by reuse and

remodeling of the newly redundant proteins and circuits to implement new capabilities.

However, the time scales on which biological systems produce and test new combinations—new designs—are quite different than those required of a technology in human hands. Natural biological innovation is constrained on short time scales by growth and replication of individuals and on long time scales by ecological and geological changes that put pressure on populations. Except in very specialized applications, for example, recombination in vertebrate immune systems that results in novel antigen binding domains, paleobiotic mechanisms to produce new combinations of parts through horizontal gene transfer, homologous recombination, or sex, tend to be slow compared to the lifetime of an individual.

In contrast, neobiotic design and construction by human hands must respond to the demands of the human economy, including safety and security concerns, where product development costs are quantified in units of person-days and denominated in the local currency. The product cycle for computing and communications equipment is about eighteen months today and for consumer electronics only about six months; new design and manufacturing cycles are often scheduled to start as soon as an initial product run is loaded into crates for shipping to market, creating an inexorable march of product model numbers. There is ever greater pressure to churn out faster, more capable widgets and gizmos, while margins are constantly being squeezed both by low cost competition and by ever decreasing costs for the basic technology. It remains difficult to apply these notions to biological engineering because many successful projects to date come from academic laboratories, where costs are often externalized as part of existing infrastructure and where labor is artificially cheap. Yet, even as measured in the context of relatively few products with discernable dollar value, there is clearly considerable progress to note.

The new (and old) clothes of synthetic biology

“Synthetic biology” was, until recently, a phrase found in literature at least decades old (Szybalski and Skalka 1978), first appearing nearly a century earlier (Keller 2002), but not used much in the last thirty years. In the year 2000 there was no International Genetically Engineered Machines competition (iGEM), no Biobricks Foundation, no Synthetic Biology N.0 meetings, and no discernable funding structure; there was only a glimmer of a strategy for using composable parts to build biological systems with predictable behaviors.

The scientific landscape has shifted dramatically in the last eight years. While putting the name Synthetic Biology

to a disparate set of efforts did not significantly change the direction of research, it attracted significant numbers of students, focused discussions, and provided a rallying point for a number of people striking out into unknown territory.

Today, academic programs or departments dedicated to synthetic biology are emerging in national laboratories and universities, with quite different intellectual roots and ultimate goals than traditional Bioengineering programs. iGEM has grown from five schools and 30 students in 2005 to almost 60 teams in 2007 comprising more than 500 students from dozens of countries. The National Science Foundation has funded the Synthetic Biology Engineering Research Consortium (SynBERC) to the tune of US \$20 million, and companies that synthesize new genes and engineer synthetic circuits have received tens of millions more in funding.

If this is what is possible in only seven years, with the greatest change coming in the last two or three, then the future is likely to bring tumult as never before. Yet practical applications are by no means left waiting for iGEM and SynBERC to supply new technology and skilled researchers.

In 2006, Amyris Biotechnologies received a US\$ 20 million investment specifically for direct production in microbes of fuels and fuel precursors, and recently received the first tranche of B Series financing to the tune of US\$ 70 million.³ The company is pursuing microbial production of a general aviation fuel comparable to Jet-A, and within three to four years the product could compete with petroleum at prices as low as \$45 a barrel (Singer 2007). Achieving this goal could open up a presently proprietary 3.2 billion gallon per year market—the U.S. Air Force is planning to replace at least half its petroleum-derived JP-8 with synthetic fuels by 2010 (Phillips 2007).

Amyris is by no means alone in this effort. LS9 has received significant investment for the microbial production of “Renewable Petroleum” and of hydrocarbon fuels, and SunEthanol is focused on improving the yield from the “Q Microbe”, *Clostridium phytofermentans* (Warnick et al. 2002), an anaerobic microbe that converts cellulose to ethanol with a surprisingly high efficiency.

Assuming these companies are successful, it is worth considering the resulting impact on the liquid fuels market, and more generally the effects on structure of the economy as a whole.

The economic considerations of scaling up direct microbial production of biofuels are fundamentally and radically different than those of traditional petroleum production and refining. The costs associated with finding a new oil field and bringing it into full production are considerable, but are so variable, depending on location, quality, and local government stability, that they are a poor

metric of the average required investment. A very straightforward measure of the cost of increasing supplies of gasoline and diesel is the fractional cost of adding refining capacity, presently somewhere between US\$ 1 and 10 billion for a new petro-cracking plant, plus the five or so years it takes for construction and tuning the facility for maximum throughput. Even increasing the capacity of working facility is expensive. Shell recently announced a US\$ 7 billion investment to roughly double the capacity of a single, existing refinery (Seba 2007).

In contrast, the incremental cost of doubling direct microbial production of a biofuel is more akin to that incurred in setting up a brewery, or at worst case a pharmaceutical grade cell culture facility. This puts the cost between US\$ 10,000 and 100,000,000, depending on size and ultimate complexity. Facilities designed to produce ethanol by traditional fermentation and distillation can cost as much as US\$ 400 million.⁴ Pinning down the exact future cost of a microbial biofuel production facility is presently an exercise in educated speculation. But, for both physical and economic reasons, costs are more likely to be on the low end of the range suggested above.

This is particularly true for a fuel like butanol. While distilling or filtering alcohol from the fermented mix would reduce the palatability of beer, it is absolutely required to produce fuel grade ethanol. However, unlike ethanol, butanol has only a limited miscibility in water and therefore does not require as much energy to separate. If an organism can be built to withstand the ~8% concentration at which butanol begins to phase-separate, the fuel could simply be pumped or skimmed off the top of the tank in a continuous process. Costs will fall even further as production eventually moves from alcohols to hydrocarbon biofuels that are completely immiscible in water. Moreover, beer brewing presently occurs at scales from garages bottling of a few liters at a time to commercial operations running fermenters processing thousands to many millions of liters per year. Thus, once in possession of the relevant strain of microbe, increasing production of a biofuel may well be feasible at many scales, thereby potentially matched closely to changes in demand. Because of this flexibility, there is no obvious lower bound on the scale at which bio-production is economically and technically viable.

Towards distributed biological production

The scalability of microbial production of biofuels depends in part on which materials are used as feedstocks, where

³ See http://www.amyrisbiotech.com/news_091907.html

⁴ See “BP, ABF and DuPont Unveil \$400 Million Investment in UK Biofuels”: <http://www.bp.com/genericarticle.do?categoryId=2012968&contentId=7034350>

those materials come from, and how they are delivered to the site of production. Petroleum products are a primary feedstock of today's economy, both as a raw material for fabrication and for the energy they contain. Bio-production could provide fuel and materials from a very broad range of feedstocks. There is no obvious fundamental barrier to connecting the metabolic pathways that Amyris and other companies have built to produce fuels to the metabolic pathways constructed to digest cellulose for ethanol production, or to the pathways from organisms that digest sewage. Eventually, these biological components will inevitably be enhanced by the addition of photosynthetic pathways. Conversion of municipal waste to liquid biofuels would provide a valuable and important commodity in areas of dense human population, exactly where it is needed most. Thus microbial production of biofuels could very well be the first recognizable implementation of distributed biological manufacturing (Carlson 2001).

While transportation fuels are an obvious early target for commercialization of synthetic biology and metabolic engineering, it will eventually be possible to treat biomass or waste material as feedstocks for microbes producing more than just fuels. Dupont and Genencor have constructed an organism that turns starch into propanediol, which is then polymerized into a fiber called Sorona now successfully competing in the market against petroleum products. Sorona's competitive advantage comes from building biology into the production process, resulting in an integrated system that is approximately a factor of two more efficient than the industrial process it replaces, while consuming considerably less energy and resulting in lower greenhouse gas emissions.⁵ The production pathway starts in microbes, and requires a more traditional facility to polymerize the propanediol. As a result, Sorona is now competing in a multibillion dollar market at a substantial operating advantage, with only US\$ 110 million invested in the finishing facility and of order US\$ 10 million (my estimate) in developing the microbe.

But this is just the first step in implementing biological manufacturing, and it is important to highlight the contrast with technologies to come. More and more of the total production of economically important compounds will soon be "miniaturized" within biological systems, internalized within single-celled (and eventually, multi-celled) organisms. There is substantial funding behind these efforts.

To much fanfare, BP recently invested US\$ 500 million in the Energy Biosciences Institute (EBI), a ten-year

project to develop new biofuel technologies at UC Berkeley, University of Illinois at Urbana-Champaign, and Lawrence Berkeley Labs. A significant fraction of the funds pledged to the EBI are reportedly to be used for building new fuel production and processing pathways in modified organisms.

Closer to commercialization, Amyris Biotechnologies and Allylix are both working on the generalized implementation of microbial synthesis of terpenoids, a broad class of compounds with myriad industrial and healthcare uses. As a measure of the complexity of what is now possible, Amyris' production pathway for artemisinic acid was assembled in yeast using ten genes from four organisms. As of spring 2007, the company had demonstrated a billion-fold improvement in yield in about six years; it would be difficult to find a comparable example of yield improvement in human industrial processes during the last two hundred years. This is just a hint of the potential for biological production as more parts are included in synthetic systems.

Every month, and every iGEM, brings news of synthetic systems of surprising complexity—systems that function more or less as intended. But the difference between "more" and "less" is the crux of many concerns about the future. The behavior of many synthetic biological systems is still difficult to predict, a state of affairs likely to persist for some time. Whether synthetic vaccines, genetically modified crops, or simple summer projects, systems composed of many poorly defined components, and their poorly defined interactions, are bound to display unexpected behaviors.

The importance of recognizing biology as a human technology

Crucial to the future development of technologies used to manipulate biology is the explicit acknowledgement by practitioners, policy makers, and consumers that biology is itself a technology. As such, biological technology requires a decision-making process, based on the best available data, to evaluate the wisdom of particular implementations. No bridge, dam, airplane, car, or computer is today built in developed economies without an evaluation of failure modes and consequent impacts. There are, of course, exceptions to this way of doing business. Risk factors and impacts may be ignored or overlooked, resulting in buildings or bridges that collapse, cars that tend to roll over or explode in collisions, genetically-modified cotton plants whose bolls fall to the ground for mysterious reasons, and gene therapies that, rather than cure, cause disease or kill.

Design and construction standards for large and visible infrastructure are easy to police because it is hard to

⁵ "Corn used as raw material for plastic bottle and fabric," EngineerLive.com, October 1, 2006; <http://www.engineerlive.com/european-chemical-engineer/safety-in-the-plant/13234/corn-used-as-raw-material-for-plastic-bottles-and-fabrics.shtml>

practice anything resembling civil engineering while incognito. Similarly, when cars or airplanes cost lives, or when medical personnel cause injury, these red flags are relatively easy to spot and those responsible tend to be held accountable according to the precepts of local legal systems.

In evaluating such consequences of bad decision-making, and in drafting regulations or legislation to improve safety, we must distinguish between technological stumbles and negligence. There is a great difference between a plane crash resulting from failure of the air traffic control system, or mechanical failure of a faulty or poorly maintained part, and a crash resulting from phenomena that were not previously understood as important in the engineering process, such as metal fatigue or wind shear. Lives may be lost in all cases, but differentiating individual negligence from collective ignorance is a key role of existing criminal and civil justice systems, legislation and administrative rules. It is by no means clear that *extra* regulation is needed in the case of biological technologies.

Building a safe and strong bio-economy I: the applicability of current laws

In general, there are two types of restrictions on actions in our society. The first type, coming into play before any action is taken, consists of limits on practicing certain skills, in the form either of legislation by the state or of professional certification. The second type comes in the form of remediation once action results in physical, economic, or social harm. But it is a very different style of regulation to restrict access to, or outlaw use of, biological technologies than to penalize harm to property or person resulting from negligent or premeditated use of those technologies. And it is by no means clear who should be subject to regulation or certification.

A case can be made that engineers or artisans designing synthetic biological systems for healthcare, or vaccines, or even houses, should perhaps be required “sign their drawings” as professionals. But this begs the question of what to do about hobbyists and do-it-yourselfers. While even those who remodel their own houses are subject to building codes, there are always places where codes do not exist, are not enforced, or are not enforceable. The lesson is that where access to tools and skills is ubiquitous, those who choose to do things their own way can always find a place, or a set of conditions, that allow them to express themselves or to experiment. The level of intrusive surveillance required to monitor everyone who wants to build glow-in-the-dark bacteria would in all likelihood be exceptionally expensive, and probably infeasible even within the U.S. (Carlson 2003) As more parts become

available in the Biobrick registry, and as more people have general access to a combination of sequence specifications and synthesis, the task of enforcement resulting from restricted access or practice will become increasingly untenable.

The DNA synthesis industry is attempting to bring discussion of risks and benefits of different governance strategies into the public spotlight:

A governance framework that stymies the open commercial development of synthesis technology will retard research and make the challenge of responsibly developing the technology more difficult. Likewise, a regulatory framework that hampers a single country’s or group of countries’ commercial market without international consensus will drive consumers to the most facile and cheapest available source, and have a limited impact on enhancing global security (Bugl et al. 2007).

These recommendations are informed by the desire for safety and security, the rapid pace of technological innovation, and the wide global distribution of oligonucleotide synthesis technologies and gene assembly methods. In such a context, implementing regulation of technologies that are already broadly distributed inevitably drives innovation by users of those technologies. As I first noted in 2003, attempts to control production of illicit drugs continue to provide an excellent example of the effects of regulation on proliferation (Carlson 2003).

Building a safe and strong bio-economy II: the unintended negative consequences of restricting access to distributed technologies

Despite a recent significant increase in domestic arrests and prosecutions, U.S. consumption of methamphetamine continues to increase.⁶ The total number of methamphetamine-associated “clandestine laboratory incidents” actually declined sharply in 2006,⁷ but the consequent reduction in supply by “mom and pop” producers has been more than offset by a combination of increased centralized domestic production and imports, both of which appear to be in the control of large criminal organizations.⁸ Centralized production and the greater flow of drugs across U.S. borders is consistent with the argument that policing

⁶ See the Drug Enforcement Agency’s Statistics Page at: <http://www.dea.gov/statistics.html>

⁷ DEA statistics. See http://www.dea.gov/concern/map_lab_seizures.html

⁸ National Drug Threat Assessment 2007: <http://www.usdoj.gov/dea/concern/18862/index.htm>

internal to the U.S. encourages the creation of elaborate, and evidently very effective, black-market drug manufacturing and distribution networks. Thus increased enforcement efforts are paradoxically producing an infrastructure that is, according to the U.S. Drug Enforcement Agency, “[M]ore difficult for local law enforcement agencies to identify, investigate, and dismantle because [it is] typically much more organized and experienced than local independent producers and distributors.”⁹

The relevance of this observation to building a secure and robust bio-economy is twofold. First, methamphetamine is a manufactured product, and attempts to constrain manufacturing have resulted in both greater production capacity and greater market opacity. As has always been the case in policing and intelligence work, information is the key to successful enforcement or defense, respectively. Therefore, looking forward to the bio-economy, maximizing the free flow of information to authorities is crucial for security, perhaps even at the cost of allowing access to technology and skills by individuals who are the subject of concern by those same authorities.

Second, focusing regulation on the supplier, rather than the buyer, does nothing to alter demand but rather displaces production elsewhere and enhances substitution. Moreover, attempts to constrict supply, and the consequent proliferation of alternatives, can arise from not just from regulation but also from economic conditions. From the perspective of security, this problem is simply exacerbated when the subject of the transaction has value beyond the buyer, as is the case in the marketplace for synthetic genes. There is a clear and growing demand for synthetic genes not for their own sake, but for their value in producing materials and fuels that have even greater economic value. Thus any bottleneck, whether economic, technical, or regulatory, in turning electronic sequence specification into physical DNA will simply encourage alternate supply in an already international market. This dynamic is developing in the gene synthesis market sooner than I expected (Newcomb et al. 2007).

The market is defining a niche for rapid and confidential DNA synthesis

The cost advantage held by a small number of synthesis companies funnels many orders to their foundries, but the extant structure of proprietary gene synthesis is already causing some dissatisfaction among customers. First, parties interested in building synthetic genetic circuits or organisms are uncomfortable with exposing proprietary

designs to scrutiny by any potential competitor, or any third party with a potential conflict of interest. This would include all gene synthesis companies that aim as part of their strategy to build design services atop their synthesis business. Second, while multi-gene length sequences are now usually delivered within two or three weeks, this delay has already become the rate-limiting step for design cycles in synthetic biology companies. That is, the quest to field a marketable product is slowed by delivery times for outsourced DNA fabrication, which simultaneously requires exposure of proprietary design work and strategy to outside observers.

This effect is at least an implicit goal of those who consider centralized gene synthesis to be a security advantage. Low-cost, high-volume, centralized foundries are said to allow for more effective screening of orders for sequences of concern. But the combination of intellectual property (IP) issues and inefficiencies caused by lengthy delivery times will undoubtedly create a market for alternative synthesis technologies. As a result, I suspect there will soon exist, if it doesn't already, a market for desktop gene synthesis instruments even at a premium price point.¹⁰ These instruments would eliminate IP concerns and could provide significant cost savings (primarily in labor) as genes are produced in house in days rather than weeks.

The role of government funding and regulation

An ability to rapidly innovate within commercial contexts is just one component of the bio-economy. Regulatory and funding environments are crucial components of the system, with government setting priorities by its preferences. But the massive funding supplied by governments should be put in perspective. While significant government support was crucial to the eventual success of aviation and of desktop computers, in both cases commercialization was driven in large part by innovators operating literally in garages.

In early years of aviation, many critical components—primarily control systems, power plant design, and construction techniques—were demonstrated before government funding for the industry materialized in the U.S. Financial support from the government was, in any event, originally available in the form of procurement contracts for functioning aircraft rather than as support for research. The development of the technology underlying personal computers received enormous government

⁹ See “Methamphetamine Strategic Findings”: [#Strategic](http://www.usdoj.gov/dea/concern/18862/meth.htm)

¹⁰ Note that the probable emergence of a market for such an instrument constitutes a hypothesis, and time will provide the experimental test.

support for software development, integrated circuit manufacturing and design, and display technology, but it took innovation by individuals in start-up companies to successfully design, assemble, and demonstrate a market for the precursors to today's powerful machines. The notion that innovation in synthetic biology could be maintained in spite of limited access to tools and skills is based on a misunderstanding of the history of innovation in the 20th Century.

Driving innovation in biological technologies

Whether at the hands of Michael Dell, Steve Jobs and Steve Wozniak, the Wright Brothers, Otto Lilienthal, William Boeing, or the yet-to-be-named transformative individuals working in biology, successful innovation requires wide access to both technology and a multitude of parts. Innovation requires, in effect, a healthy ecosystem consisting of people, ideas, and a great many more pieces than those provided by individual innovators. In other words, innovation requires an existing set of ideas or things that provide the context for the last piece to fall into; that final piece is just one of many. Moreover, as Scott Berkun makes clear in the recently published *The Myths of Innovation*, for any given invention or particular scientific advance to have an impact it has to get it into the marketplace and into the hands of people who will use it; "While there is a lot to be said for raising bars and pushing envelopes, breakthroughs happen for societies when innovations diffuse" (Berkun 2007). Diffusion of an innovation through a society relies on a complex set of interactions that play out at the intersection of the actual technical advance and factors much larger than any individual or group providing that innovation:

Systems that foster prolific innovation through combination are not just technical; other preconditions include economic, social, and regulatory frameworks that determine the appropriability of value by innovators and intellectual property systems that can support the creative accumulation of innovations over time (Newcomb et al. 2007).

Even when all the requisite preconditions are met, technologies can take many decades to penetrate an economy, particularly in the context of pre-existing investment in alternatives or cultural resistance. Biological technologies will be no different, even in circumstances where a biological process is dramatically more efficient or less expensive. Yet when synthetic biology enables successful rational genetic modification of plants, animals, and then humans—that is, modification based on predictive models—there will be an enormous uproar. Today's

scuffles over stem cells and gene therapy will pale in comparison.

However, when it truly becomes possible to build microbes that programmably kill tumors, when it becomes possible to control the growth of new tissues and organs from donor-specific stem cells, when human health and longevity are positively impacted by synthetic biology, there will be a rush to implementation that will overwhelm cultural resistance and, because of the distributed nature of both technology and skills, may very well undermine existing regulatory structures.

The benefits of exploring this frontier are both exceptionally promising and, even after three decades of developing recombinant DNA technologies, largely and frustratingly elusive. But the work will continue because the possibility of improved crop yields, increased meat production, plentiful biofuels, and improved human health through new vaccines and replacement tissues are too scientifically, politically, and economically enticing for humans to resist. And as in any other field, the implications of a mature biological technology will take decades to play out and to appreciate.

Conclusion

In this, the Paleobiotic Age, our society is only just beginning to struggle with all the social and technical questions that arise from a fundamental transformation of the economy. History holds many lessons for those of us involved in creating new tools and new organisms and in trying to safely integrate these new technologies into an already complex socio-economic system. Alas, history also fails to provide examples of any technological system as powerful as rational engineering of biology. We have precious little guidance concerning how our socio-economic system might be changed in the Neobiotic Age to come. We can only attempt to minimize our mistakes and rapidly correct those we and others do make.

The coming bio-economy will be based on fundamentally less expensive and more distributed technologies than those that shaped the course of the 20th Century. Our choices about how to structure the system around biological technologies will determine the pace and effectiveness of innovation. As with the rest of the natural and human built world, the development of this system is decidedly in human hands. To paraphrase Stewart Brand (1968): We are as engineers, and we'd better get good at it in a hurry.

Acknowledgements I would like to thank W. Brian Arthur, Stewart Brand, Pawan Dhar, Eric Carlson, and my colleagues at Bio-era, Jim Newcomb and Steve Alrich, for many helpful comments and discussions.

References

- Aggarwal S (2007) What's fueling the biotech engine? *Nat Biotechnol* 25(10):1097
- Arthur WB (2007) The structure of invention. *Res Policy* 36(2):274
- Berkun S (2007) *The Myths of Innovation*. O'Reilly
- Brand S (1968) *Whole Earth Catalog*. Point Foundation
- Bugl H et al (2007) DNA synthesis and biological security. *Nat Biotechnol* 25(6):627
- Carlson R (2003) The pace and proliferation of biological technologies. *Biosecur Bioterror* 1(3):203–214
- Carlson R (2001) Open-source biology and its impact on industry. *IEEE Spectrum*
- Endy D (2005) Foundations for engineering biology. *Nature* 438(7067):449
- Herper M, Kang P (2006) The World's ten best-selling drugs, in *Forbes*
- Hodgson J (2006) Private biotech 2004—the numbers. *Nat Biotech* 24(6):635
- Keller EF (2002) *Making sense of life: explaining biological development with models, metaphors, and machines*. Harvard University Press. xii, Cambridge, Mass, p 388
- Newcomb J, Carlson R, Aldrich S (2007) *Genome synthesis and design futures: implications for the U.S. economy*. Bio economic research associates
- Phillips D (2007) Air force hopes to cut oil's role in fuel, in *The New York Times*. New York, NY
- Seba E (2007) Shell, Saudi commit to massive U.S. refinery project, in *Reuters*
- Singer E (2007) Greener jet fuel, in *Technology Review*
- Szybalski W, Skalka A (1978) Nobel prizes and restriction enzymes. *Gene* 4(3):181–182
- Warnick TA, Methe BA, Leschine SB (2002) *Clostridium phytofermentans* sp. nov., a cellulolytic mesophile from forest soil. *Int J Syst Evol Microbiol* 52(4):1155–1160