UNIVERSITY OF MINNESOTA

This is to certify that I have examined this copy of a master's thesis by

Todd Masaru Tanji

and have found that it is complete and satisfactory in all respects
and that any and all revisions required by the final
examining committee have been made.

Name of Faculty Advisor

Signature of Faculty Advisor

Date

GRADUATE SCHOOL

OVERSIGHT POLICY IN SYNTHETIC BIOLOGY

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Todd Masaru Tanji

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE IN SCIENCE, TECHNOLOGY,
AND ENVIRONMENTAL POLICY

Dr. Jennifer Kuzma, Advisor

September 2009

Abstract

Researchers in the emerging field of synthetic biology strive to lower the economic barriers-to-entry into genetic engineering by drawing parallels to the historical development of the semiconductor and computer industries. Standardized engineering methodologies are being developed to create "biological circuits" akin to basic electronic computing functions such as Boolean logic gates, switches, time clocks, communication ports, and environmental sensors. Higher level processing is also being developed by employing common biological molecules such as ribosomes, proteins, amino acids, and nucleotides as computing elements akin to data inputs and outputs, software programming, data memory, and data processing. Researchers are developing standardized, open source engineering methodologies to increase the efficiency and efficacy of biological product development in a manner that draws inspiration from open source software development.

With these advancements in synthetic biology come important public policy issues. This paper is designed to uncover a diversity of broad oversight issues by examining case studies from the historical development of the semiconductor industry, information technology, and biotechnology to anticipate future oversight issues with synthetic biology. Similarities and differences between synthetic biology, biotechnology, and semiconductors are examined to determine where it is appropriate to draw oversight comparisons. The issues presented in the cases are framed in the context of four specific biomedical ethical values - autonomy, justice, benevolence, and nonmaleficence. Oversight issues identified in this work include informed consent concerns, biocrimes,

bioterrorism, intellectual property rights, product negligence, technology access, and socioeconomic considerations. The current U.S. regulatory framework is examined in terms of its capability to cope with the anticipated sharp increase in synthetic biology and biotechnological capabilities in the private and public sectors.

This work concludes that oversight policy may anticipate a dramatic rise in the number of practitioners of advanced genetic engineering as well as the number of bioengineered products as a result of synthetic biology. The sophistication of bioengineered products may also increase as genetic engineers adopt efficient development and manufacturing methods inspired from the semiconductor and information technology industries. Also possible to emerge is amateur bioengineering, or so-called "garage biology". In many cases, risks from synthetic biology can exceed risks from semiconductor technology due to the ability of living organisms to reproduce, evolve, and interact with human and natural environments in an unpredictable manner.

Table of Contents

Chapter 1:

Introduction

Synthetic biology is the next generation of genetic engineering that could significantly increase the number of biotechnology products available to the general public, the functional complexity of those products, and the number of biotechnology practitioners - both professional and amateur. One of the ultimate goals of synthetic biology is to shift the field of genetic engineering from the domain of highly educated research scientists and specialized manufacturing into the domain of standardized engineering practices and high-efficiency mass production [Rai 2007, Baker 2006]. In essence, synthetic biology strives to lower the economic barrier to entry into the field of genetic engineering through the development standardized engineering and production methodologies.

Pioneering researchers in synthetic biology envision a future akin to the rise in recent decades of the semiconductor industry, where integration complexities rose and production costs decreased exponentially [Baker 2006]. Indeed, comparisons are being made between Moore's law for semiconductor integration and metrics of DNA sequencing and synthesis capabilities (Figure 1.1.) [Carlson 2003]. The practice of electronics hardware and software development was at one time confined to expensive and elite university, government, and corporate laboratories staffed by relatively small number of researchers with advanced educational degrees. Yet standardized development methods and tools accompanied by decreasing manufacturing costs extended the reach of this practice so that today private citizens in their own residences are capable of

developing highly sophisticated electronic systems at an affordable cost [Baker 2006]. Through similar advances in biotechnology development methods and manufacturing processes, private citizens may one day create highly sophisticated microorganisms that are beyond even the capabilities of advanced researchers today.

Such advances will, quite likely, also extend the capabilities of professionally trained bioengineers in academia and industry. Biotechnology companies will be capable of introducing far greater numbers of highly sophisticated products into consumer markets. Advanced researchers may one day create entire living organisms that are synthesized from raw materials, "boot up" from software-like genetic programming, and perform novel functions that are not currently found in nature [Forster 2006]. Such organisms would defy traditional biological taxonomies. While today, a genetically modified organism (GMO) typically consists of a conventional organism enhanced via the transfer of a single gene from another organism (for example Bt corn that contains a pest resistance gene [Hall 2007]), future bioengineered organisms may contain a large number of gene combinations intended to serve a wide array of functional purposes. The number of genetically engineered traits available will only be limited by the limits of DNA synthesis capability and human imagination.

Figure 1.1. Recent Advances in DNA Synthesis and Sequencing Compared with Transistor Integration [Carlson 2003]

1.1 *Synthetic Biology versus Conventional Genetic Engineering*

It is difficult to precisely define the boundaries that separate the fields of genetic engineering; rather, advancements in biology can be viewed as a continual progression towards greater human design intervention. Indeed, the ETC Group has aptly dubbed synthetic biology "Extreme Genetic Engineering" [ETC 2007a]. Humans have been altering the genetics of living organisms since pre-historic times through selective breeding and the hybridization of animals and plants [APM 2009]. Recombinant DNA technology first provided the means to create synthetic genetic material enabling scientists to transfer specific genetic sequences into a host organism. Synthetic biology represents an increase in the complexity of human genetic design intervention, enabling unlimited combinations of genes from numerous organisms to be combined.

For the purposes of this work, however, it is worthwhile to provide a set of criteria that draw a level of distinction between synthetic biology and conventional genetic engineering. This is necessary to define the scope of this effort and to provide a context and focus for determining relevant policy issues. The five criteria listed are common themes found in synthetic biology literature. A bioengineering activity meeting any one of these criteria is considered to be the realm of synthetic biology for purposes of this effort.

1. *High Engineered Complexity*. Genetic engineering today typically involves the insertion of single genes into host organisms whereas synthetic biology involves higher engineered genetic complexity extending even to the synthesis

of entire genomes. The ultimate aim of synthetic biology is to understand and manipulate the genetic code to program living cells in a manner akin to the way electronics are now programmed via sophisticated software routines [Shapiro 2006].

2. *Engineering and Manufacturing Standardization*. Synthetic biology strives to create a knowledge base of reusable component parts and design methodologies to create engineering economies of scale resulting in enhanced productivity in development and production flows. An example of this is the MIT Registry of Standard Biological Parts [Gibbs 2004].
3. *Novel Life Forms*. Synthetic biology endeavors to create novel microorganisms that do not exist in nature. While most applications will be manipulations of existing life forms for years to come, synthetic biology enables the creation of cells that have fully synthesized genomes and functions. The starting point for this is the self-sustaining minimal cell [Luisi 2002, Nature 2008].
4. *Systems Scope to Engineering*. Through advanced system modeling, synthetic biology enables the development of complex networks of engineered organisms that function and communicate in concert within complex biological environments to solve specific problems [Weiss 2003b].
5. *Increased Scope of Biotechnology*. Through the standardization of design practices synthetic biology can enable a vastly greater numbers of participants, thereby moving genetic engineering from the domain of limited

numbers research scientists to the realm of large scale engineering and amateur practitioners [Baker 2006].

Note that these criteria do not attach synthetic biology to specific biological taxonomical categories. Included are the simplest of living microorganisms, such as viruses (although there is much debate over whether or not viruses can be truly classified as living organisms), as well as more complex microorganisms such as bacteria and systems of microorganisms and plants. Issues regarding genetically engineered animals and even humans, while in a long term outlook will almost certainly be impacted by advancements in synthetic biology, are beyond the scope of this effort.

1.2 *The Benefits and Costs of Synthetic Biology*

Synthetic biology opens an innumerable array of possibilities for products that can benefit humans and the environment. Engineered cells may one day be utilized for the production of therapeutic chemicals to combat a range of diseases including cancers [Gibbs 2004], malaria [Gibbs 2004], HIV [Jarris 2004], and diabetes [Meredith 2003]. They may also aid in the efficient production of carbon neutral biofuels to combat climate change [Stephanopoulos 2007]. Synthetic microorganisms may one day be released into the environment to digest or neutralize hazardous pollutants including toxic chemicals and heavy metals [Lovley 2003]. Artificial cells may one day have the capability to perform simple computations, sensing, and decision making to create more effective drug delivery systems [Tu 2007]. Agriculture could be transformed by the design of crops with even greater yield and resistance to pests than the current generation of GMOs. The

chemical industry could gain the capability to produce novel chemicals and existing with greater efficiency [Rincones 2009].

The next generation of biotechnology is envisioned to draw inspiration from the semiconductor industry. Legions of genetic engineers are targeted to design and simulate artificial biological organisms based on sophisticated computer models [Weiss 2003a]. Once a genetic code is uniquely specified the engineers can then order the customized biological components from large centralized fabrication facilities, or "biofabs" [Baker 2006]. To increase design efficiency, standardization of biological components and methodologies must inevitably occur. This effort has already begun with MIT's Registry of Standard Biological Parts [Gibbs 2004]. As a result, synthetic biologists may one day be as prevalent in industry as software engineers are today.

But the same technology that offers such vast potential for societal benefits is also capable of creating human and environmental hazards. Microorganisms exist in a highly complex environment of chemical signals. Naturally occurring cells derive their genetic functions through the process of evolution honed over millions of years of trial and error. Biologists are now embarking wholeheartedly on a mission to circumvent evolution by introducing human design into that process. But human error is always inevitable, especially when dealing with complex new technologies and, in biology, hazards are heightened by the ability of living organisms to reproduce and proliferate in a manner that is difficult for humans to control.

There is also the potential for intentional harm by malicious individuals who become skilled in this new craft. For example, the sequenced DNA for the polio and smallpox viruses currently exists as computer files in readily accessible online databases [NIH 2009a, Sanger Institute 2009]. As our understanding of genetics increases, so does the knowledge base on how to create lethal pandemics or plagues on humans and the environment. Furthermore, the open publishing academic and educational knowledge in synthetic biology will encourage the creation of large populations of people with the knowledge and expertise to create harmful synthetic microorganisms.

These potential hazards beg familiar oversight questions - How can we maximize the benefits of this technology while minimizing the risks to society? How can we avoid risks while not stifling technology development? Who is responsible for hazardous outcomes and how do we hold them accountable? How do we keep potentially dangerous technology out of the hands of people who wish us harm?

1.3 *Methodology*

Synthetic biology, with its push to extend the field of biotechnology beyond the realm of research scientists into the domain of the broader general public, has potential to make dramatic impacts on society through its beneficial applications as well as its harmful misuses. The scale of this vision behooves us to look "upstream" to anticipate its many possible social impacts. Too often, we are caught off-guard by the effects of technologies on society that are unanticipated. Only in the most speculative science fiction did we foresee the current ubiquity of personal computers, wireless telephones, the Internet,

integrated circuits, recombinant DNA, genome sequencing, and cloning. Synthetic biology now promises to provide us with a means to engineer living organisms, perhaps even allowing us to bypass the process of evolution.

Justifications cited to provide upstream assessments of emerging technologies include the need to boost public confidence thereby encouraging the acceptance of the technology; the need for societal values to be incorporated into technology development process; the need for public engagement and transparency in the oversight development process; and the need to have oversight mechanisms established for products prior to market introduction [Kuzma 2008b]. Furthermore, the current U.S. biotechnology oversight framework, called "The Coordinated Framework for the Regulation of Biotechnology" (CFRB), has been the subject of considerable criticism with regards to its capability to provide adequate oversight due to its patchwork structure of antiquated legislation and governmental agency jurisdiction [PIFB 2004, Rodemeyer 2009]. It could be that synthetic biology is the proverbial straw that breaks the camel's regulatory back. Recent policy efforts in synthetic biology have focused on security in conventional professional settings [Garfinkel 2007, IRGC 2008] but have not stressed or focused on synthetic biology in a broad social context.

But upstream oversight assessment for technologies that are just beginning to emerge presents us with a number of challenges. There is currently little public awareness of synthetic biology. One recent study has found that only 9% of Americans have "heard a lot or some" about the field of synthetic biology while 22% have "heard just a little" and

a whopping 67% have “heard nothing at all” (figure 1.3.1) [Hart 2008]. Furthermore, the number of researchers in the field is limited, confounding the ability to develop consensus opinions. Also lacking is a clear consensus amongst the regulatory community.

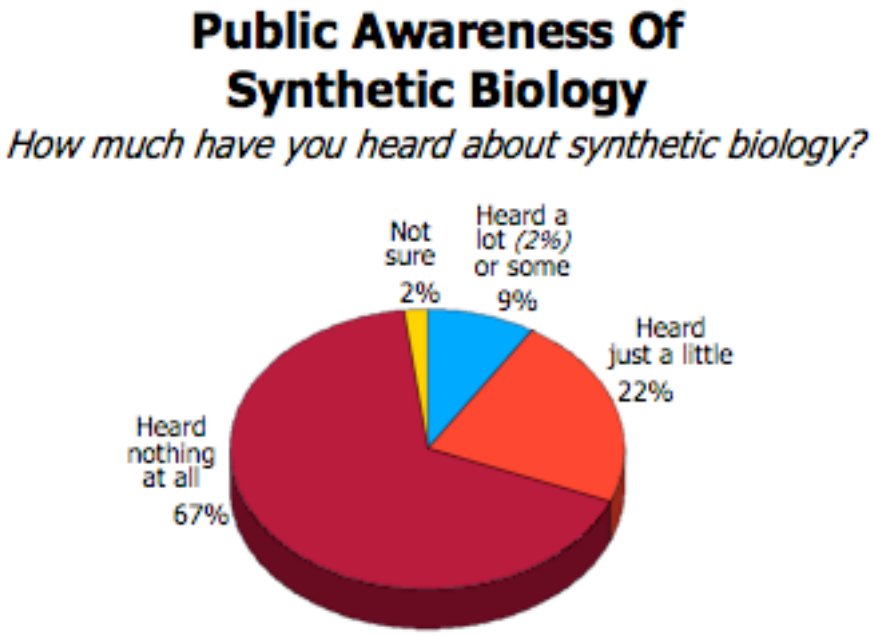


Figure 1.3.1. Public Awareness of Synthetic Biology [Hart 2008]

This work focuses on upstream oversight assessment of synthetic biology by drawing on past experiences with related technologies, namely semiconductor technology and first generation biotechnology. Semiconductor technology was chosen due to its high degree of similarity to synthetic biology. In fact, as earlier stated, semiconductor technology is used as a model for the development of synthetic biology with its successful transfer from heavily funded governmental and industrial laboratories into the realm of the general public. It is the intention of synthetic biology developers to lower the economic barrier to entry into biotechnology in the same manner that occurred in the semiconductor industry by creating standardization in product design and manufacturing methods [Baker 2006]. If successful, this will enable engineering professionals and amateurs alike to develop bioengineered "devices" and systems with the same efficiency that engineers develop semiconductor-based hardware and software today. Both semiconductors and biotechnology utilize very small, molecular-scale components and which can be synthesized using relatively inexpensive raw materials as opposed to, as an example, nuclear technology, which requires the use of expensive, large scale materials processing facilities. Also, semiconductor technology and biotechnology are both based on the processing of encoded information. In semiconductors this is the binary code of "ones" and "zeros" and with biotechnology this is the code of nucleotide base pairs (adenine, thymine, guanine, and cytosine) that make up the DNA molecule [Shapiro 2006]. This enables a virtually unlimited amount of freedom for engineers in both fields to utilize their creativity to develop highly sophisticated and novel inventions.

However, there are important differences to note between semiconductor technology and biotechnology. Biotechnology takes as its starting point the pre-existing complex world of living things, whereas semiconductor-based components did not exist in nature prior to the invention of electronics. Bioengineered organisms have a natural ability to interact and spread into the environment that is difficult to control and predict. Biotechnology deals with living organisms that have the potential to reproduce, evolve, and transfer genetic material to other organisms, including humans. Therefore, there exists an inherently complex safety concern with bioengineered organisms that extends beyond issues dealing with non-living materials such as semiconductors. The result is that, quite often, risks associated with poorly contained bioengineered organisms are highly magnified.

The very broad scope of synthetic biology and its many potential product applications requires an equally broad framework that serves to objectify its societal impacts. Towards this end, this work utilizes an ethics framework consisting of four major ethical principles commonly found in bioethics literature: namely, autonomy, beneficence, nonmaleficence, and justice [Beauchamp 2009]. These principles provide a basis for examining case studies in the semiconductor and biotechnology histories as well as oversight issues and policy options for synthetic biology. This method also provides a basis for extracting relevant case histories from the semiconductor industry, a necessary tool considering the very broad scope of this technology in product areas and social impacts.

A principle-based ethics framework is employed in this work as a tool with which to align technologies of synthetic biology, semiconductors, and first generation biotechnology. This approach is broader than what has been called the "mainstream approach" to technology assessment which focuses on "outcome oriented, data driven, and comparative" evaluations of benefits and risks, with the objective of maximizing overall benefits over costs [Thompson 2007]. The mainstream approach presents barriers to upstream oversight assessment, particularly with just emerging technologies like synthetic biology, due to the lack of available data formed from either group consensus methods or real world outcomes. Furthermore, Kuzma and Besley argue that there is a high degree of interconnectedness between the utilitarian values of benefits and risk and so-called "non-utilitarian values" such as autonomy, nonmaleficence, justice, and integrity [Kuzma 2008a]. In essence, assessments of benefits and risks contain judgments concerning non-utilitarian values. Kuzma and Besley (2008) cite as an example, issues regarding the labeling of food products that contained bioengineered foods. While there is no firm scientific evidence of risk to public health, issues of autonomy and consent regarding the public right to know are implicitly ignored with the utilitarian approach. From example such as this we can conclude that utilizing a non-utilitarian ethics framework can significantly broaden the scope of upstream technology assessment.

Beauchamp's biomedical ethics framework of autonomy, nonmaleficence, beneficence, and justice was chosen due to its strong academic foundation and its ties to biology. This framework has also been utilized outside of the biomedical field in the upstream assessment of nanotechnology [Kuzma 2008a, Burkhardt 2005, Shrader-Frechete 2007].

The flexibility of the ethics framework stems from the fact that the principles employed are in no way specific to biomedical issues. Indeed, ethical principles are notable for their universality and, hence, provide a unique tool for tying science and technology issues directly to human impacts.

Chapter 1 of this work provides a review of the current technological state of synthetic biology. Chapter 2 compares and contrasts synthetic biology with semiconductor and computer technology. Chapter 3 provides case studies from the historical experiences of the semiconductor industry and first generation biotechnology in terms of the four selected ethical principles. Chapter 4 extracts oversight issues and policy options in synthetic biology based on the semiconductor industry cases as well as relevant cases in the first generation of biotechnology. Chapter 5 provides conclusions and summarizes policy options.

This work and method of analysis has a number of limitations. It does not represent a full policy analysis, but rather identifies policy issues that will need to be addressed in future works. It also focuses primarily on U.S. federal policy rather than local and international policy except where these policy perspectives affect or provide insight into U.S. federal policy. This work also is limited to considerations based on four prominent ethical principles (autonomy, beneficence, nonmaleficence, and justice). Not included in this work are religious and philosophical issues such as the moral question of scientists "playing God" by creating artificial life.

The inclusion of additional ethical principles would likely uncover more policy issues and alter the prioritization of policy responses. This work does not claim to have comprehensively extracted all case studies and policy issues, rather, has focused on the most prominent cases that are highly relevant to the selected ethical principles and have been assessed in the literature. This method of upstream oversight assessment can be extended in future works by the inclusion of additional ethical principles and by broadening the scope to include local and international policy issues.

1.4 *Historical Background*

This section provides a brief historical background on the field of genetic engineering, highlighting only major developments to provide a context for synthetic biology. It is readily seen from this perspective that the pace of technological developments is rapidly accelerating.

1.4.1 *Early Genetics*

Although humans have been altering the genetics of living organisms since pre-historic times through selective breeding and the hybridization of animals and plants [APR 2009], classical genetics finds its roots with the Augustinian monk, Gregor Mendel, and his observations on the multi-generational regularity of traits in the pea plants in the mid-19th century [Whipps 2008]. Mendel's comprehensive and groundbreaking work went largely unnoticed in scientific circles until biologists rediscovered it in the early 20th century. It was then that William Bateson first coined the term, genetics, to describe the study of heredity.

1.4.2 *Molecular Genetics*

Although Johann Miescher first discovered the substance now known as the molecule DNA in 1869 [Dahm 2008], the beginning of modern molecular genetics really began with Francis Crick's and James Watson's 1953 co-discovery of the double-helix structure of the DNA molecule (it must be noted that Crick and Watson were greatly aided by Rosalind Franklin's x-ray diffraction photos of DNA molecules [Elkin 2003]). In 1961, Marshall Nirenberg and Heinrich Matthaei from the National Institutes of Health (NIH) determined the genetic coding scheme for constructing sequences of amino acid into proteins, called codons [NIH 2009b]. In 1970, Hamilton Smith, Daniel Nathans, and Werner Arber, co-discovered restriction enzymes, which serve as a means to cut DNA strands upon the detection of specific base pair sequences [Raju 1999]. In 1973, Stanley Cohen and Herbert Boyer employed restriction enzymes in the development of recombinant DNA (rDNA) technology, which enabled the transfer of entire genes between microbes, plants and animals [Golden 2002]. The introduction of rDNA technology led to the 1975 Asilomar conference where leading scientists gathered to develop protocols for the self-regulation of genetic engineering.

1.4.3 *DNA Sequencing*

Walter Fiers performed the first sequencing of an entire genome in 1975 with the decoding of the RNA for the bacteriophage virus, MS2, which consists of 3,569 base pairs [Fiers 1976]. In 1977, Frederick Sanger and his team became the first to sequence an entire DNA genome, the bacteriophage Phi X174, which consists of 11 genes and

5,386 base pairs [Nobel 2005]. In 1983, Kary Mullis developed a revolutionary technique called polymerase chain reaction (PCR), which selectively amplifies sections of DNA base pair sequences [Wade 1998]. Relentless advances in sequencing methods coupled with exponential increases in computing capability culminated in the sequencing of the human DNA genome in 2001 by the private firm, Celera, led by J. Craig Venter, and the multinational publicly funded consortium, the Human Genome Project [Venter 2007]. The human genome consists of 20,000 – 25,000 genes and approximately 3 billion base pairs. Since then the cost of sequencing has dropped 50 fold in the past decade to about 0.3 cents per base pair [NIH 2006]. It is the current goal of the NIH National Human Genome Research Institute to drop the cost of sequencing an entire human genome to a mere $1,000.

1.4.4 *DNA Assembly*

Current research focuses on method for efficient assembly of synthetic whole genomes. In 2003, the J. Craig Venter Institute announced the assembly of the entire Phi X174 genome and in 2008 announced the assembly of the *mycoplasma genitalium* bacteria genome, which has 582,970 base pairs [JCVI 2008]. The team plans to use this genome as the basis for the first true synthetic life form, dubbed *mycoplasma laboratorium*.

Chapter 2:

Review of Current Research

This section reviews the major research areas in synthetic biology. The purpose of this section is to provide a general sense of the vast potential of this technology to impact virtually all areas of society.

A broad range of research activity in synthetic biology is currently taking place. Some efforts focus on laying the foundation of synthetic biology through the development of basic engineering methods. Others target general application areas, such as biosensing, while others target specific products, such as biofuels. While advances in synthetic biology will most likely have great impacts on current and near-term biotechnology products, this section focuses on the long-range vision of researchers. Time scales of five to twenty years are often stated as estimates for these research efforts coming to full fruition.

Synthetic biology is still very much in its infancy. There remain a number of obstacles in basic scientific knowledge to overcome before synthetic biology can reach its full fruition and much of this is the focus of current research. Ron Weiss, from the Departments of Electrical Engineering and Molecular Biology at Princeton University has identified four general challenges that must be addressed in order to enable the "programming" of living organisms [Weiss 2008]. The areas are summarized below:

- *The development of libraries of well-characterized biological components.* This will allow genetic circuit designers to re-use components that have been proven effective. As an example, researchers at MIT have created a database called the Registry of Standard Biological Parts to standardize the characterization of biological components across the industry [Gibbs 2004].
- *The development of computer models and simulation tools for predicting the behavior of genetic circuits.* Engineers must be able quantitatively model biological components to a high degree of accuracy to ensure reliable operation once deployed in a real biological environment.
- *The development of genetic circuits that operate robustly in noisy biological environments.* Genetic circuits must perform in environments rich with complex signals and changing ambient conditions such as temperature and nutrient levels. Therefore, engineers must develop circuit configurations that operate in a robust manner in changing environments.
- *Increased efficiency in assembling artificial DNA*. Since this is currently a major bottleneck, DNA assembly must be made faster and less expensive.

Much of the current research in synthetic biology aims, either directly or indirectly, to meet these challenges. The eventual result is hoped to be a standardized "toolbox" of design methods that future bioengineers can employ to create reliable "genetic circuits" that consist of living organisms. This toolbox would consist of databases of component libraries, software-base simulation tools, knowledge bases that will be relatively easy for engineers to access and utilize to create artificial living organisms. Another important

piece of the puzzle is a cellular "platform" that can serve as a generic microorganism into which engineers can program biological features. This platform would be a microorganism that has only the bare essential components to sustain life. Such a platform is called the "minimal cell". Efforts to achieve the minimal cell are described below, but first, a brief history leading up to this work is presented.

2.1 *Historical Background*

This section provides a brief historical background on the field of genetic engineering, highlighting only major developments to provide a context for synthetic biology. It is readily seen from this perspective that the pace of technological developments is rapidly accelerating.

2.1.1 *Early Genetics*

Although humans have been altering the genetics of living organisms since pre-historic times through selective breeding and the hybridization of animals and plants [APR 2009], classical genetics finds its roots with the Augustinian monk, Gregor Mendel, and his observations on the multi-generational regularity of traits in the pea plants in the mid-19th century [Whipps 2008]. Mendel's comprehensive and groundbreaking work went largely unnoticed in scientific circles until biologists rediscovered it in the early 20th century. It was then that William Bateson first coined the term, genetics, to describe the study of heredity.

2.1.2 *Molecular Genetics*

Although Johann Miescher first discovered the substance now known as the molecule DNA in 1869 [Dahm 2008], the beginning of modern molecular genetics really began with Francis Crick's and James Watson's 1953 co-discovery of the double-helix structure of the DNA molecule (it must be noted that Crick and Watson were greatly aided by Rosalind Franklin's x-ray diffraction photos of DNA molecules [Elkin 2003]). In 1961, Marshall Nirenberg and Heinrich Matthaei from the National Institutes of Health (NIH) determined the genetic coding scheme for constructing sequences of amino acid into proteins, called codons [NIH 2009b]. In 1970, Hamilton Smith, Daniel Nathans, and Werner Arber, co-discovered restriction enzymes, which serve as a means to cut DNA strands upon the detection of specific base pair sequences [Raju 1999]. In 1973, Stanley Cohen and Herbert Boyer employed restriction enzymes in the development of recombinant DNA (rDNA) technology, which enabled the transfer of entire genes between microbes, plants and animals [Golden 2002]. The introduction of rDNA technology led to the 1975 Asilomar conference where leading scientists gathered to develop protocols for the self-regulation of genetic engineering.

2.1.3 *DNA Sequencing*

Walter Fiers performed the first sequencing of an entire genome in 1975 with the decoding of the RNA for the bacteriophage virus, MS2, which consists of 3,569 base pairs [Fiers 1976]. In 1977, Frederick Sanger and his team became the first to sequence an entire DNA genome, the bacteriophage Phi X174, which consists of 11 genes and 5,386 base pairs [Nobel 2005]. In 1983, Kary Mullis developed a revolutionary technique called polymerase chain reaction (PCR), which selectively amplifies sections of DNA

base pair sequences [Wade 1998]. Relentless advances in sequencing methods coupled with exponential increases in computing capability culminated in the sequencing of the human DNA genome in 2001 by the private firm, Celera, led by J. Craig Venter, and the multinational publicly funded consortium, the Human Genome Project [Venter 2007]. The human genome consists of 20,000 – 25,000 genes and approximately 3 billion base pairs. Since then the cost of sequencing has dropped 50 fold in the past decade to about 0.3 cents per base pair [NIH 2006]. It is the current goal of the NIH National Human Genome Research Institute to drop the cost of sequencing an entire human genome to a mere $1,000.

2.1.4 *DNA Assembly*

Current research focuses on method for efficient assembly of synthetic whole genomes. In 2003, the J. Craig Venter Institute announced the assembly of the entire Phi X174 genome and in 2008 announced the assembly of the *mycoplasma genitalium* bacteria genome, which has 582,970 base pairs [JCVI 2008]. The team plans to use this genome as the basis for the first true synthetic life form, dubbed *mycoplasma laboratorium*.

2.2 *The Minimal Cell*

The development of the first living minimal cell will almost certainly be hailed as a hallmark in the history of science that was once the sole domain of speculative science fiction. But while scientists rush to claim the first creation of artificial life, there currently is exists no precise, mutually agreed upon definition of life. According to some, artificial life has already been achieved with the construction of synthetic poliovirus in 2002

[Cello 2002]. Constructed by assembling simpler strands of DNA sequences called oligonucleotides, the artificial poliovirus was fully capable of replication and infection when injected into laboratory mice. Not only did the team demonstrate the creation of a simple biological entity, their work also highlighted the potential misuse of synthetic biology by synthesizing a virus that has caused pandemic outbreaks in humans. In 2003, a team at the Institute for Biological Energy Alternatives assembled the genome for the bacteriophage, Phi X174, in only14 days [Smith 2003] thereby demonstrating the swiftness with which technology efficiency can be gained once an initial breakthrough is achieved.

However, while viruses show some characteristics of primitive life, such as the ability to replicate and interact with the surrounding environment, the aims of synthetic biology extend further to cells of higher complexity. Viruses are the simplest of biological entities consisting primarily of genetic material, either DNA or RNA, packaged in a protein coating. Even though viruses are capable of evolution by natural selection, they are incapable of reproducing and performing complex functions such as de novo protein creation without relying on a host cell or greater complexity.

Therefore, one of the current goals of synthetic biology is to synthesize a complete prokaryotic cell, the simplest manifestation of self-sustaining living cells found in nature. A highly simplified conceptual model of a basic prokaryotic cell, dubbed the minimal cell, is shown in Figure 2.2.1. Once achieved, the minimal cell will establish a design platform for future commercial applications.

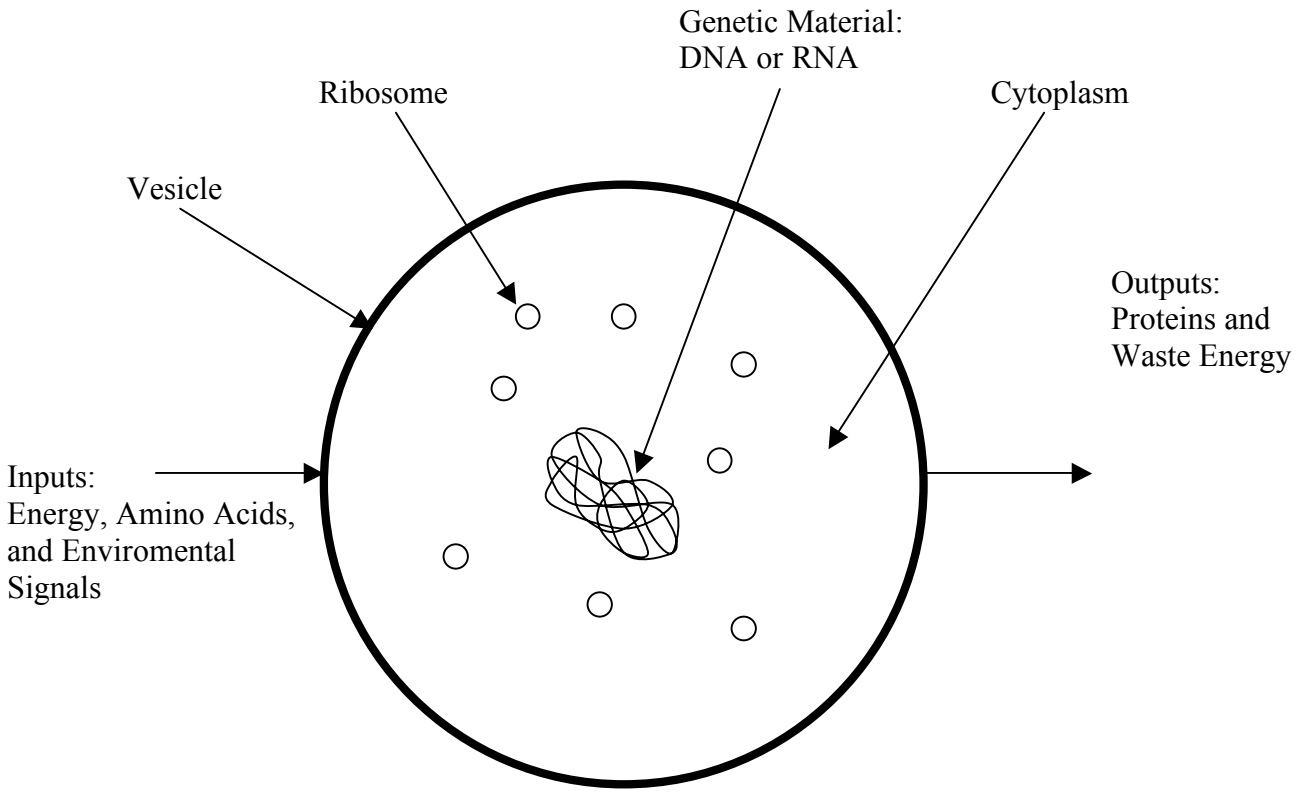


Figure 2.2.1. Conceptual Model of a Minimal Prokaryotic Cell

The minimal cell consists of all the fundamental elements of a prokaryotic cell: a vesicle, genetic material (in the form of DNA or RNA), cytoplasm and ribosomes. The vesicle serves to house the contents of the cell as well as allow energy such as light and heat; biological molecules such as amino acids and proteins; and various environmental signals to pass in and out of the cell. Genetic material provides the functional "programming" of the cell. Cytoplasm is the cell fluid medium that contains proteins and enzymes that catalyze chemical reactions within the cell. Ribosomes serve to manufacture proteins from amino acids via codon "instructions" contained in the genetic material.

The minimal cell functionality is ultimately defined by how it is programmed to accept inputs and generate outputs. For the cell to be life sustaining it is required to input chemical or light energy from its environment. Energy in the form of waste heat must be allowed exit the cell in order to maintain thermal homeostasis. Since one of the primary purposes of the cell is to produce proteins, amino acids must be able to freely to enter the cell. The cell must also be capable of sensing the presence of certain proteins in its surrounding environment.

It must be noted that although this model is highly simplified, a practical living minimal cell is highly complex and contains many "housekeeping" components. Although the complete synthesis of the genetic material for the simplest known bacterial genome, *M. genitalium,* is claimed as an achievement [Nature News 2008], and current knowledge of cell vesicles is considered to be relatively mature [Pohorille 2002], much is yet to be understood about the complex molecular biochemistry within simple cells [Forster 2006].

Figure 2.2.2 shows the epistemological progression leading to the development of the minimal cell. Advances in DNA sequencing has enabled detailed analysis of molecular biology through three parallel approaches: comparative genomics, genetics, and biochemistry. In comparative genomics, scientists search for "homologs", or genes that have common ancestry across multiple organisms throughout evolutionary history. Those genes are subsequently deemed to be essential for cell survivability [Forster 2006]. In genetics, cells are created that have single gene mutations then assessed for survivability. If a cell survives with a mutation the corresponding gene may then be deemed inessential. Biochemistry takes a more reductionism approach by fractionalizing the cell and analyzing the biochemical subsystem kinetics [Forster 2006]. A minimal cell based on *E. coli* and *M. genitalium* bacteria consists on 151 genes that translate into gene products of 38 various RNA molecules and 113 proteins [Forster 2006]. The challenge of current research is to fully understand and model these biochemical mechanisms.

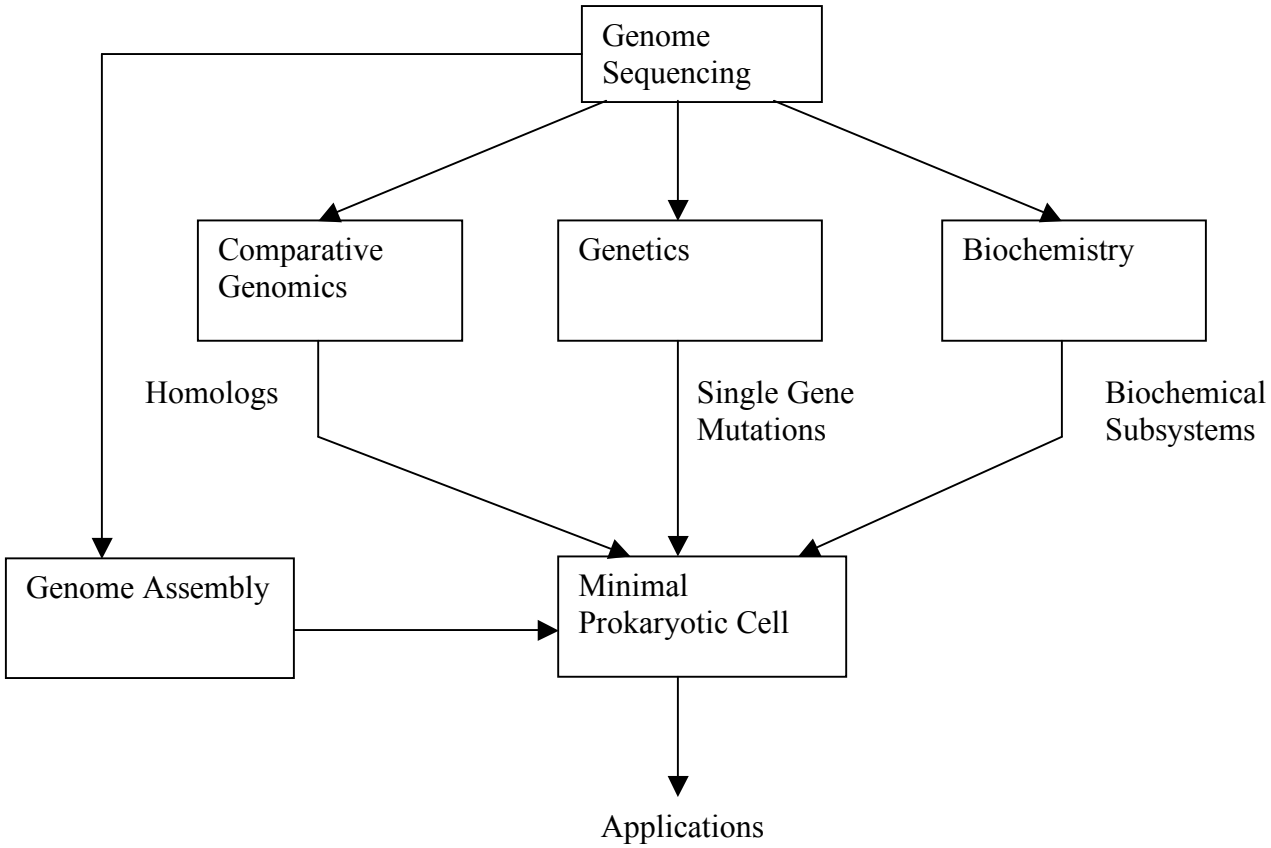


Figure 2.2.2. Epistemological Progression of Synthetic Biology

As is the norm with pioneering science, it is difficult to predict when the gaps in our understanding of cell molecular genetics will be filled in and this critical milestone in synthetic biology will be achieved. It should also be noted that the creation of a minimal cell is not true synthesis of life from the "ground up" achieved by creating complex bio-molecules such as nucleic acids and enzymes from simple more common molecules as occurred naturally over the course of millions of years. Rather, scientists are utilizing existing bio-molecules and assembling them into more complex macromolecules [Luisi 2002]. The approach that scientists are taking is thereby more accurately deemed a "pseudo-synthesis" of a cell since it still employs biological components gathered from nature.

Development of a living minimal cell will be a quantum leap forward for synthetic biology. Not only will it provide a platform for which to program unlimited numbers of product applications but the knowledge gained through the analysis of its inner workings will also be a leap in capability and applicable to future advances.

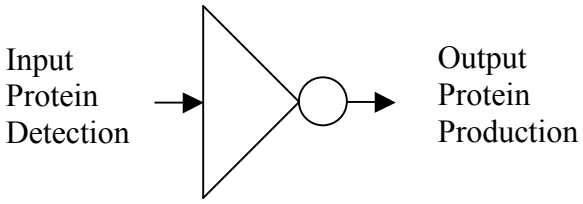
2.3 *Biocomputing*

The term "biocomputing" refers to the use of biological molecules to perform logical operations in a manner akin to electronic computers. While biocomputing does not rival the speed of modern silicon-based computing (equivalent information processing rates in gene translation are a mere hundreds of operations per second [Shapiro 2006] as opposed to electronic processing speeds of billions of operations per second) biological molecules have the potential to perform complex computational algorithms that can be integrated

into living cells. Furthermore, biocomputing has the potential for massively parallel computations that are difficult for electronic computers to perform [Shapiro 2006].

Biological organisms naturally contain molecules that perform computational functions. DNA and RNA consist of sequences of nucleotides that form a coding system that bears similarity to the binary code used modern computing. Enzymes and ribosomes serve the function of data processing by manipulating the DNA and RNA information to create proteins from amino acids. Proteins, the workhorses of living cells, provide inputs and outputs to each cell. The cell itself derives power from its environment and is capable of directed mobility. The result can be viewed as an embedded, programmable biocomputing platform.

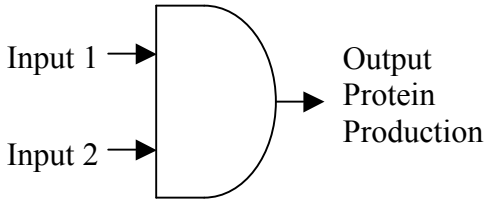
The simplest forms of biocomputing that have been developed are implementations of simple Boolean logical operations using protein in the surrounding environment as inputs and protein production by the cell as outputs [Weiss 2003a]. For example, a simple logical "NOT" gate (Figure 2.3.1) would inhibit production of a protein if a threshold concentration of an input protein is detected in the environment. Conversely, protein production would be enabled with the lack of input proteins. Multiple inputs can be combined to form logical "AND" and "OR" functions (Figures 2.3.1b and 2.3.1c). As was the case in the early era of electronics, implementation of these basic logical operations opened the door to create a seemingly limitless variety of complex functions.



(a) NOT Gate

Boolean "NOT" Truth Table

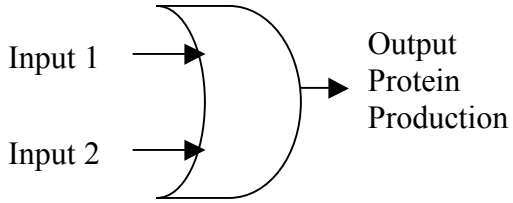
Input	Output
Protein	No Protein
No Protein	Protein Produced



(b) AND Gate

Boolean "AND" Truth Table

Input 1	Input 2	Output
No Protein	No Protein	No Protein
No Protein	Protein	No Protein
Protein	No Protein	No Protein
Protein	Protein	Protein Produced



(c) OR Gate

Boolean "OR Truth Table

Input 1	Input 2	Output
No Protein	No Protein	Protein Produced
No Protein	Protein	Protein Produced
Protein	No Protein	Protein Produced
Protein	Protein	No Protein

Figure 2.3.1. Functional Diagrams for Biological Implementations of Logic Gates

Examples of biocomputing functions, or "genetic circuits", that have been developed are toggle switches, gene expression regulators [Tu 2007], bistables, and oscillators [Weiss 2003a]. Also notable are efforts to create networks for cell-to-cell communication via the use of proteins as the communications medium [Weiss 2003a]. These circuits implement quorum detection by sensing the presence proteins in the environment, then communicating the detection results, via protein production, to other cells. In this manner one can envision networks of cells that can sense and mobilize towards an area of diseased tissue then release biologically manufactured chemicals to destroy the tissue. This is an example of how synthetic biology can create therapeutic tools by embedding a new level of "smarts" into living organisms.

It is clear that the possibilities of this technology are bound only by human imagination and biochemical principles. Researchers are now creating the basic buildings that may one day enable a trajectory for biotechnology where genetic circuitry is gauged in terms of Moore's Law type measurements as occurred in the semiconductor industry. We may one day witness the race in the private sector to become the "Intel" or "Microsoft" of biology by competing to integrate the greatest number of genetic logic gates into a living cell. One can only begin to speculate on all the possibilities for societal benefits and hazards in such a world.

2.4 *Biocommunications and Biosensing*

Researchers have also devised a means for engineering cells to communicate with humans. Through the insertion of genes for expressing fluorescent proteins, cells can be

made to emit light of specific colors in response to the presence of certain molecules in the environment [Baker 2006]. Furthermore, the detection circuitry can be programmed to respond to different thresholds representing specified concentrations of input molecules and programmed to emit a different color for each threshold. In this way cells can be programmed to sense and communicate their proximity to the source of a chemical [Weiss 2003a]. These so called "biosensors" have a wide range of applications including glucose monitoring [Pickup 2004], detection of environmental toxins [US EPA 2007], detection of explosive agents [Weiss 2003b], and general molecular assay.

2.5 *Bio-SPICE*

Bio-SPICE is an open source software tool that simulates biological processes [Bio-SPICE 2009]. Its name is derived from the standard software tool used to model integrated circuits in the semiconductor industry (SPICE stands for Simulation Program with Integrated Circuit Emphasis). Originally funded through the U.S. Defense Advanced Research Projects Agency (DARPA) with additional support from some major universities, it is now solely an open source development. The ultimate goal of this effort is to provide an software tool that enables the reliable simulation of living processes with a similar accuracy that semiconductor engineers enjoy today. Systems currently being explored for simulation include bacteriology, virology, eukaryotes, signal transduction, synthetic circuits, and immunology. One of the application examples touts the ability to simulate cell responses to retroviruses used in the combat against HIV infection. A further example is the detailed modeling of bacterial metabolism. It is clear that the aim

of this effort is to provide ready public access to highly sophisticated biological modeling capability that is currently only available to large research institutions.

2.6 *Next Generation Biofuels*

There currently is a growing demand for renewable biofuels to replace the use of fossils fuels for the global transportation sector. This is based on environmental concerns, rising energy prices, increasing global demand, and supply uncertainty. However, the current varieties of grain-based biofuels are not considered to be viable candidates to supplant fossil fuels [Wald 2007]. Therefore, the energy industry is looking towards other sources of biofuels that are more plentiful and less disruptive to the world food supply. One such candidate is cellulosic ethanol, which is derived by a more cheap and abundant part of plant mass that is not consumable as food [Badger 2002]. But cellulosic ethanol currently suffers from high costs due challenges in the production phases of hydrolysis, where biomass is converted to sugars, and fermentation, where sugars are converted to fuel [Stephanopoulos 2007].

To address this challenge, researchers are turning to synthetic biology in an attempt to engineer the genetic pathways of living cells to produce high quantities of enzymes that will reduce to the costs of biofuels production. One way of achieving this is to first find appropriate enzymes that are produced naturally by certain yeasts, albeit, in insufficient quantities for large-scale biofuels production [Stephanopoulos 2007]. Researchers then decode the genetic pathways of the yeast cells then engineer *E. Coli* bacteria that perform

the enzyme production. In this manner researchers allow nature to do the basic research for enzyme development then engineer organisms capable of large-scale production.

This work has already migrated to the private sector. Currently, three private companies are striving to create the next generation of cost effective, environmentally friendly biofuels. Amyris, led by U.C. Berkeley synthetic biology pioneer, Jay Keasling, is looking to adapt a technique developed for microbial production of the anti-malarial drug artemisinin to the production of biofuels [MIT 2007]. LS9 is turning to the production of fatty acids as a precursor to biodiesel [LS9 2009]. And Synthetic Genomics, led by gene sequencing pioneer, J. Craig Venter, has announced its intention to create biofuels by leveraging their extensive capabilities in high-speed genome sequencing, analysis, and assembly [Venter 2007]. Their approach is to collect large amounts of DNA from microorganisms that currently exist in the natural environment (including the oceans), then sequence that DNA in aggregate and analyze it with their proprietary algorithms in the hopes of finding the genes for synthesizing biofuel enzymes.

2.7 *Major Research Groups*

This section reviews the major research groups that are currently advancing the field of synthetic biology.

2.7.1 *SynBERC*

In 2005, the California Institute for Quantitative Biosciences established the Synthetic Biology Engineering Research Center (SynBERC). It is currently funded by grants from the National Science Foundation with matching funds from industry. SynBERC is a joint cooperative involving U.C. Berkeley, MIT, Harvard, U.C. San Francisco, and Prairie View A&M University and boasts a staff comprised of leading figures in synthetic biology such as Jay Keasling, Adam Arkin, Drew Endy, George Church, and Wendell Lim [SynBERC 2008].

SynBERC defines its charter as such [SynBERC 2008]:

> *SynBERC's vision is to develop the foundational understanding and technologies to build biological components and assemble them into integrated systems to accomplish many particular tasks; to train a new cadre of engineers who will specialize in synthetic biology; and to educate the public about the benefits and potential risks of synthetic biology. In essense, we want to make biology easier to engineer.*

SynBERC defines it main research areas (or thrusts) to be the development of biological parts, devices, chassis, and human practices [SynBERC 2008]. Parts are defined to be the molecular building blocks that serve the most basic biological functions, such as genetic RNA translation, protein transcription and gene activation. Since these functions are common elements of synthetic biology it is highly efficient to standardize them in their characterization. Devices are assemblages of parts, put together to serve "human defined" functions, such as gene expression, post-translation, cell signaling, and metabolic and materials processing. Chassis are the cell housings that contain devices, providing both protections from the environment as well as energy for self-sustenance. Human practices consist of issues pertaining to engineering practices as well as policy issues such as technology benefits, risks and cultural considerations.

SynBERC is currently pursuing two research testbeds as a demonstration of this technology [SynBERC 2008]. The first testbed is an engineered cell that will sense the presence of a tumor and launch and attack upon it as in cancer treatment. Using an *E. Coli* cell programmed with engineered genetic material, the cell will sense environmental signals found in the presence of the tumor and propel itself to the tumor via the cell flagellum. While the genes employed will be inspired and obtained from cells found in nature, the genetic material will be engineered, thus demonstrating a overall functionality that is not found in natural living cells.

The goal of the second testbed is to alter the biological pathways of cells to create microbial chemical factories. With this technology it may be possible to manufacture

highly complex novel chemicals or synthetic versions of rare, naturally occurring chemicals that currently are prohibitively expensive to extract in large quantities. SynBERC is also pursuing this testbed in conjunction with the first testbed by pursuing the production of chemicals that will destroy cancerous tumors.

The SynBERC testbeds are notable examples of the type of applications that will initially result from synthetic biology – cells that are similar to those found in nature but are customized in some way to serve specific applications. Future generations will likely feature increasingly sophisticated functionality in ways that are difficult to predict especially given the "new cadre of engineers who will specialize in biology" that is the SynBERC vision.

2.7.2 *iGEM, BioBricks, and the Registry of Standard Biological Parts*

The International Genetically Engineered Machine (iGEM) competition is a summer program intended for university undergraduates to engineer a living biological organism to perform a function of their choosing. Students begin with a "kit" of standard biological components taken from the Registry of Standard Biological Parts. Participation is organized by teams and is rapidly expanding. The inaugural year, 2004, saw 5 participating teams. The 2009 competition anticipates 120 teams with over 1,200 total participants [iGEM 2009].

BioBricks are open source DNA sequences that represent standard biological components. All biological components that are developed as part of the iGEM

competition are contributed to the BioBricks library. This effort is operated by the BioBricks Foundation which is a not-for-profit organization founded by MIT, Harvard and UC San Francisco. Quite literally, any person or organization can "design, improve, and contribute" BioBrick components to the library [BioBricks 2009]. The BioBricks Foundation also operates a technical standards working group to develop standards for defining biological components, as well as a legal working group to address and assist users with intellectual property rights issues. The BioBricks Foundation also organizes an annual international conference, the most recent of which was called "Synthetic Biology 4.0". It was held in October 2008 in Hong Kong and was attended by over 500 participants [Syn Bio 4.0 2009].

The Registry of Standard Biological Parts, created by MIT, is the repository of biological data that defines the BioBricks standard parts. From this online database, iGEM participants download the technical data required to engineer biological organisms. The data is organized into "parts", such as promoters, ribosome binding sites, protein coding sequences, DNA, plasmids, and primers; "devices", such as protein generators, reporters, inverters, receivers, senders, and measurement devices; "functions", such as biosynthesis, cell-cell signaling, quorum sensing, cell death, conjugation, motility, chemotaxis, odor production, odor sensing, and DNA recombination; and "chassis", such as *Escherichia coli*, yeast, Bacteriophage, and *Bacillus subtillis*. The registry is also open source and is readily accessible online by any person or organization [Registry 2009].

2.7.3 *J. Craig Venter Institute*

Founded by the pioneer in genome sequencing, J. Craig Venter, the institute that bears his name is leveraging their prowess in DNA sequencing and synthesis to develop microbes that are engineered to produce enzymes that enable the next generation of biofuels [JCVI 2009]. The institute gained recent notoriety by becoming the first team to chemically synthesize the complete genome of the bacterium, *Mycoplasma genitalium*, which contains 582,970 nucleotide base pairs [JCVI 2008]. The institute is currently pursuing the creation of the world's first synthetic life form, dubbed *Mycoplasma laboratorium*, which will be based on the naturally occurring *M. genitalium* bacterium.

2.7.7 *International Consortium for Polynucleotide Synthesis*

The ICPS consists of private research companies working in the field of synthetic biology. Their primary mission is to develop standards and protocols for safety and security. The are calling for a screening system with respect to DNA synthesis where individuals who place orders would be required to identify themselves and their supporting organization and provide relevant biosafety level information [Bugl 2006]. The participating companies currently include GeneArt, Codon Devices, BlueHeron, Coda Genomics, BaseClear, Bioneer, and IDT [ISPS 2009]. The ICPS also has affiliations with the U.S. Federal Bureau of Investigation, Harvard Medical School, MIT, the National Science Foundation, and the University of Regensburg (Germany).

Chapter 3:

Parallels Between Synthetic Biology and Semiconductor Technology

This chapter examines the parallels between the historical development of semiconductor technology and the envisioned development trajectory of synthetic biology. This examination provides a context for extracting oversight issues from the semiconductor industry that have applicability to synthetic biology. This section also states the contrasts between synthetic biology and semiconductors in order to highlight the limits of drawing parallels between the two technologies and to highlight how some policy issues may have different levels of importance in terms of their impacts on society.

3.1 *Synthetic Biology Inspired by Semiconductor Technology*

It is important to note that the parallels between semiconductors and synthetic biology are far from coincidental; indeed, researchers in synthetic biology draw their inspiration from the semiconductor industry in formulating their approaches to the standardizing of engineering and production methods [Baker 2006]. Their aim is to duplicate the recent explosive growth in the semiconductor industry for the future genetic engineering in the hope that a similar technology revolution will occur, albeit using the molecules of life rather than silicon.

3.2 *Engineering Standardization*

Engineering standardization is necessary to transfer biology from the domain of basic scientific research to the realm of practical engineering. Engineers concern themselves

more with economics and finding near-term problem solutions than scientists, who focus on developing basic knowledge. Jack Kilby, co-inventor of the integrated circuit stated it most aptly when he said, "the essence of engineering … is cost consciousness" [Reid 2001]. Efficiency is a priority for large-scale product engineering where, quite often, reliability and time to market are the most critical considerations.

Towards this end researchers are developing engineering and production methods in synthetic biology that mirror the semiconductor industry. As discussed in Chapter 2, online databases such as the Registry of Standard Biological Parts and BioBricks are being developed to enable bioengineers to share and develop basic technological information in an efficient manner. BioFabs are envisioned to standardize production flows [Baker 2006]. And software tools such as Bio-SPICE are being developed with the goal of enabling detailed and accurate simulation of biological systems. These efforts are inspired directly from the semiconductor industry experience in order to jump start synthetic biology and proliferate the field into the realm of large-scale engineering and production.

3.3 *Comparisons of the Basic Technology*

Both semiconductors and synthetic biology involve small-scale (and often molecular scale) manipulation of raw materials to create their basic functional components. This enables the engineering of highly complex, highly integrated systems utilizing a relatively small quantity of raw materials. This combination of high functional complexity and potential for low economic barriers to entry create an ideal situation for

engineers in both fields. The following two sections describe how researchers are seeking to take advantages of these similarities by categorizing biological components in an analogous manner to the semiconductor field.

3.3.1 *Biological and Semiconductor Components*

Table 3.3.1 shows an example of how synthetic biology and semiconductors can be compared by viewing their "functional hierarchies". Both technologies are based on certain basic molecular materials. For semiconductors these materials primarily consist of crystalline semiconductors and electrically conducting metals; for synthetic biology these materials include molecules such as nucleotides, amino acids, and lipids. Created from these materials are certain basic structures with which systems of higher complexity can be built. In semiconductors those structures are transistors, resistors, capacitors, and inductors, which regulate the flow of electricity in various ways. The analogous structures in synthetic biology are nucleic acids, which contain genetic codes; proteins, which serve as the primary inputs and outputs of cells; ribosomes, which form proteins from amino acids based on genetic code "instructions'; and liposomes, which serve as membrane housings for cells.

Table 3.3.1. – Semiconductor and Synthetic Biology Functional Hierarchies

	Electronics	**Synthetic Biology**
Basic Molecular Materials	Semiconductors, Metals	Nucleotides, Amino Acids, Lipids
Basic Structures	Transistors, Resistors, Capacitors, Inductors	Nucleic Acids (DNA & RNA), Proteins, Ribosomes, Liposomes
Information Encoding	Software based on Boolean 1's and 0's	Genetic code based on nucleotide base pairs
Functional Circuits	Microprocessors, Timing, Sensing, Memories, Communications, Power Supplies	Boolean Processors, Memory, Timing, Sensing, Florescence, Protein Detection, Protein Generation
Autonomous Systems	Computers, Media Players, Communication Devices, Controllers	Engineered Living Cells
Networked Systems	Computer Networks, Phone Systems, Media Broadcast Systems,	Multi-cellular Systems

The next level of complexity consists of "circuits", where the basic structures are combined to perform specific functions. In electronics these functions include data processing, memory, communications, power regulation, timing generation, sensing, as well as a host of other more exotic purposes. Biological circuits can also perform similar operations such as simple logical Boolean processing and data storage as well as timing and sensing [Tu 2007, Weiss 2003a]. Biological circuits have also demonstrated the ability to fluoresce [Baker 2006] as a form of communications as well as detect and generate proteins [Weiss 2003a].

Functional circuits can be combined to form autonomous systems. In microelectronics these consists of any stand-alone electronic systems including computers, media players, controller, and simple communications devices. In synthetic biology, this next step would be engineered living cells of the type envisioned by minimal cell and protocell projects [Luisi 2002]. Beyond this horizon lie networked systems such as computer networks (e.g., the internet), cellular phone systems, and media broadcast systems in the case of electronics. In the long-range future one can envision synthetic biological multi-cellular systems consisting of a multitude functional cells all communicating and operating in concert to perform distributed and highly sophisticated tasks. Such networked systems are already envisioned with the undergoing development of quorum sensing biological circuits [Weiss 2003b].

In the current stage of both technologies the complexity of electronics far exceeds that of engineered biological circuits. While the number of transistors integrated onto a single

silicon chips now exceeds two billion [Intel 2009], synthetic biology is only now constructing the functional equivalent of simple Boolean logic gates. However, the complexity found in naturally occurring biological organisms is also vastly complex. As a point of comparison, the human genome consists of over three billion DNA base pairs with a functional complexity that is beginning to be understood only since its recent sequencing in 2001. This points to a vast potential for synthetic biological circuits of very high complexity.

3.3.2 *Synthetic Biology as Information Technology*

Shapiro et al., have identified the striking resemblance between the operation of ribosomes within a cell, which utilize the genetic code to string together proteins from amino acids, and the Turing machine, which is a theoretical computing device devised in 1936 by mathematician, Alan Turing [Shapiro 2006]. The Turing machine (Figure 3.3.2.1.) consists of a "tape", which is encoded with simple symbols, such as 1's and 0's, and a control unit, which reads the symbols and changes state according to a prescribed set of rules. After the control unit reads a particular symbol and executes the appropriate rule it sequentially moves along the tape to the next symbol. The Turing machine concept provides computer scientists with an abstract mathematic model for analyzing information processing.

Similarly, ribosomes can be viewed as information processors that read an instructional "tape" in the form of nucleotides base pairs within a messenger RNA (mRNA) molecule (Figure 3.3.2.2.). In its most basic mode of operation a ribosome, itself a mass of RNA

and proteins, moves along the “tape”, reading encoded instructions on how to sequence amino acids into proteins. In this process, nucleotide trios on the mRNA, called codons, uniquely encode twenty different amino acids.

It is remarkable that the Turing machine, a theoretical device created by a mathematician for conceptualizing information processing, shows such fundamental similarities to the inner workings of biological cells that are the creation of evolutionary forces. It would appear that, in the drive to create functional complex systems from simple components, humans and nature have arrived at similar solutions. Computer systems have grown immensely in complexity in the past decades since the advent of semiconductors. Biological systems are yet more complex (although they have been spotted a head start of a few billion years). Both types of complex inventions, whether they are the result of human motivations or of natural selection and random variation, contain underlying encoding and processing schemes. Both computers and biological processes are, at their most fundamental level, information processing systems.

Synthetic biology offers a similar opportunity for design sophistication as electronics. Nucleic acids are, in essence, codes of immensely rich digital information. Nature has developed this code to orchestrate biological molecules into life forms with complexity that dwarfs any invention of man. Engineers now have a field beyond electronics to explore with design creativity plus the added bonus of natural biological inventions from which to draw inspiration.

Synthetic biology can be viewed as a means to provide the computing tools that nature evolved to humans. Nature has already demonstrated the limitless creative potential of molecular biology. What remains is for humanity, as a whole, to master that capability in order to apply it to towards societal benefits.

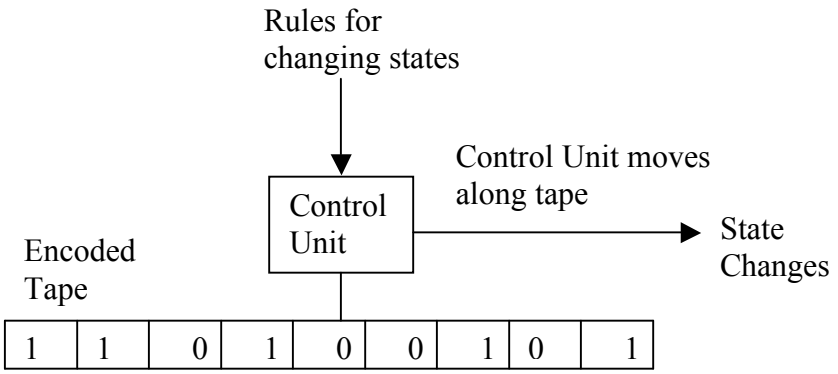


Figure 3.3.2.1. The Turing Machine

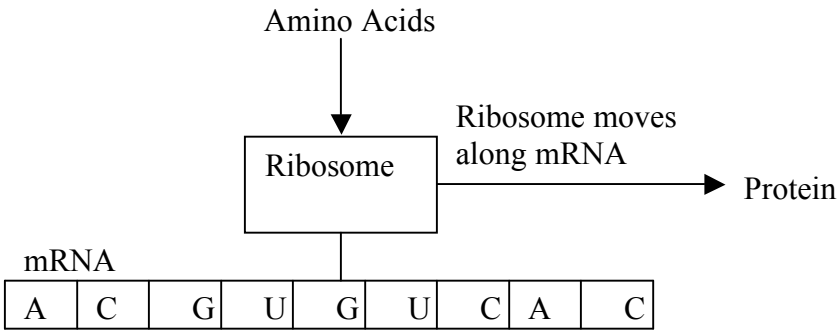


Figure 3.3.2.2. The Ribosome in Protein Construction

3.4 *Contrasts Between Synthetic Biology and Semiconductors*

While parallels between electronics and synthetic biology are notable, there are a number of important differences. The most obvious is that synthetic biology deals with living organisms and their molecular components that are often capable of affecting reproduction, gene transfer, and evolution. Because inspiration for biological inventions comes directly from nature, it can be assumed that they will have many of the same characteristics of naturally occurring organisms, including being less predictable in behavior. One of the inherent characteristics of life is the ability to survive adversity through adaptation. Hence, our ability to make accurate behavioral predictions through mathematical modeling and simulation may have fundamental limitations.

Furthermore, the biological entities exist in less constrained, open environments, whereas electronic systems are often tethered to a power source and lack self-mobility (that may be changing however, with the advent of nanotechnology). Biological microorganisms are capable of drawing energy from a number of different sources in the surrounding environment. Mobility, access to diverse power sources, and the ability to survive in the natural environment will likely result in living microorganisms being less constrainable than electronic systems. As experienced with the first generation of bioengineering, genetic material is notoriously difficult to contain. StarLink corn received approval for animal feed use only yet it was discovered that genes from the engineered corn subsequently spread into the human food supply as a result of human error [Taylor 2003].

For future engineers in synthetic biology there may be slower progress in development as models to perform accurate behavioral predictions will likely be significantly more difficult than for electronics. Much more effort on safety, security, and reliability considerations will have to be made.

Finally, biological systems are capable of interacting with humans in a ways that are not currently exhibited by semiconductor systems. This means that there is an heightened intrinsic risk in organisms developed through synthetic biology. It is one thing to release a malicious computer virus into a data processing system, but releasing an engineered "super-virus" into the environment is likely to carry more potential for dangerous outcomes.

3.5 *Major Milestones in the Semiconductor Industry*

It is worth noting major milestones in the semiconductor industry (Table 3.5.1.) to highlight its rapid growth and pervasiveness in modern society. In the span of sixty years the semiconductor industry progressed from the domain of cutting edge scientific research to becoming one of the world's largest industries. The impact of semiconductors now pervades every aspect of human society. Indeed, it is difficult to name any area of human endeavors that has not been profoundly impacted by semiconductor technology is some way.

The ubiquity of semiconductors is a result of the fact that electronics fundamentally deal with information. Information about a vast array of human endeavors can be converted

into streams of binary encoded data for processing, storage and transmission. Electronics can be inserted into the chain of a wide variety of systems to expand the capabilities of machines and humans.

For purposes of comparison, table 3.5.2 shows major milestones in biotechnology. Notable are the seminal scientific advances that occurred with both technologies in the post-World War II era, the recent rapid advances in technological milestones, and the recent increases in adoption by commercial industries. While future rates of advancements of biotechnology cannot be predicted, recent history has shown that biotechnology can achieve exponential growth in milestone metrics in a similar manner as semiconductor technology. If recent trends are an indicator, biotechnology may be poised on the edge of explosive growth.

Table 3.5.1. Major Milestones in the Semiconductor Industry

1947: Invention of the transistor by John Bardeen, Walter Brattain and William Shockley.
1958: Co-invention of the integrated circuit by Jack Kilby and Robert Noyce [Reid 2001].
1989: Intel 80486 microprocessor contains over one million transistors on a single silicon chip [EE Times 2005].
2005: Intel Itanium-2 microprocessor contains of one billion transistors on a single silicon chip [EE Times 2005].
2007: Global electronics market is $1.169 trillion (includes electronics for home, industrial, information, and communications applications) [Digitivity 2008].
2008: Number of personal computers in use globally tops one billion [Worldometers 2008]. Global Internet usage tops 1.4 billion users [Internet World Stats 2008], Membership in the Institute of Electrical and Electronics Engineers, the world's largest technical professional organization, is 375,000 [IEEE 2008].

Table 3.5.2. Major Milestones in Biotechnology

1953: Discovery of DNA double helix structure by Francis Crick and James Watson.
1961: Determination of coding scheme (codons) for constructing proteins from amino acids by Marshall Nirenberg and Heinrich Matthaei [NIH 2009b].
1970: Discovery of restriction enzymes for DNA splicing by Hamilton Smith, Daniel Nathans, and Werner Arber [Raju 1999].
1973: Use of restriction enzymes for recombinant DNA by Stanley Cohen and Herbert Boyer [Golden 2002].
1977: First sequencing of an entire genome by Frederick Sanger [Nobel 2005].
1983: Development of polymerase chain reaction by Kary Mullis [Wade 1998].
2001: Sequencing of human genome by the Human Genome Project and Celera [Venter 2007]
2003: Assembly of Phi X174 bacteriophage genome (5,386 bases) by the J. Craig Venter Institute [JCVI 2008].
2008: Assembly of the *mycoplasma genitalium* bacteria genome (582,940 base pairs) by the J. Craig Venter Institute [JCVI 2008].
2009: Majority of all soybean, corn, and cotton crops grown in the U.S. are genetically engineered [USDA 2009].

Chapter 4:

Ethics Case Studies in the Semiconductor Industry and First Generation Biotechnology

This chapter provides four ethics case studies that relate past experiences with the semiconductor industry and first generation biotechnology to possible future scenarios in synthetic biology. The purpose is to draw oversight lessons from past experience in these related technologies by viewing them through the lens of ethical principles. The principles of autonomy, nonmaleficence, beneficence, and justice were chosen from Beauchamp, *Principles of Biomedical Ethics* [Beauchamp 2009]. These principles provide a framework for drawing comparisons between the societal impacts that resulted from semiconductor technology and what might be anticipated in the future with the proliferation of synthetic biology. For each ethical principle, a case studies are presented that raise oversight concerns associated with that principle. Also presented is a technologically plausible (based upon the previously presented review of synthetic biology) scenario where synthetic biology might create a similar oversight concern.

4.1 *Autonomy*

The proliferation of semiconductor technology, and the subsequent advent of the information age have created what may be considered a pandemic of autonomy issues in the form of actions taken without the proper obtaining of informed consent. One visible example of this is the widespread use of spyware by private companies to extract and communicate private information from personal computers. Spyware often accompanies

other software programs that unsuspecting computer users install. Once activated, spyware programs seek out private information such as credit card numbers, social security numbers, marketing information, information on computer usage, and other personal information. Spyware creates a broad spectrum of effects on its victims, ranging from criminals acts such as identify theft, to the dissemination of information on intimate personal relationships [Martens 2005], to the bogging down of computer speed and communications [Fox 2005]. Another salient point that relates spyware to violations of autonomy is the gap in the understanding of the extent of this issue. In a 2004 computer user survey performed jointly by America Online and the National Cyber Security Alliance, 53% of respondents stated that they had spyware or adware on their home computers, yet when tested it turned out that 80% actually did have these types of programs installed [Fox 2005].

While U.S. law bans the most severe and malicious acts involving spyware, such as identity theft and fraud, Federal protection of consumers against many incidences of spyware may be inadequate [Garrie 2006]. The U.S. Constitution generally protects citizens from invasions of privacy perpetrated by the U.S. government but does not explicitly protect them from such invasions perpetrated by private individuals and corporations [Garrie 2006]. There is some limited protection offered by the Stored Communications Act and the Computer Fraud, Abuse Act, and Wiretap Act yet companies that produce spyware have found ways to circumvent that legislation [Garrie 2006]. As a result, computer users rely heavily on anti-spyware programs provided by private companies, such as Symantec and Norton, to safeguard the personal data residing

on their computers. Hence, the battle U.S. citizens' fight against those who wish them harm largely takes place without active governmental oversight.

Such violates of privacy may also take place unwittingly by those who design technologically advanced products. An example of this is Intel's highly publicized decision to include a personal security identifier code into the Pentium III microprocessor for the stated purposes of detecting computer theft. This feature would presumably aid law enforcement in tracing stolen computer equipment. However, when Intel unveiled this feature advocacy groups attacked this design choice as a violation of individual privacy claiming that malevolent parties could use the personal security code to spy on an individual's personal computing behavior. Intel eventually responded by offering a software patch to disable the feature, essentially passing the responsibility off to software and computer manufacturers [Merritt 1999]. The Pentium III example highlights how value decisions enter into the design of basic components of a system and it begs the question: who takes responsibility for the outcome of these actions?

Princeton's Helen Nissenbaum studies how values are embedded in the design of computers and information systems as witnessed by the Pentium privacy case [Nissenbaum 2001]. She argues that component and systems designers often stray beyond scientific based technical specifications to include elements that embody human values such as bias, anonymity, privacy, and security. According to Nissenbaum, professional training can make system designers aware of these hidden value choices and provide a means to make appropriate value choices.

It is interesting to note that such issues of disclosure, public awareness, and informed consent have also been experienced with the first generation of biotechnology. The prevalence of bioengineered foods has grown rapidly in recent years. Figure 4.1.1 show the adoption rates, in terms of percentages, of common U.S. crops such as soybean and corn. In 2006, nearly 40% of corn crops and 90% of soybean crops contained bioengineered elements [USDA 2009]. Given these adoption rates it is likely that the average U.S. consumer regularly consumes food with genetically engineered ingredients. Yet in a 2006 survey just 26% of respondents believed that they had eaten genetically engineered foods and 60% believed they had not [Mellman 2006]. With the lack of informative product labeling, such a gap in public understanding demonstrates a violation of the citizens' abilities to make autonomous, informed decisions regarding their perceived well-being and personal values.

The cases of computer privacy and bioengineered foods are linked in that they are both enabled by the capability for highly sophisticated molecular scale information processing. In the case of computer privacy that capability is the programming of binary electronic information, whereas, for bioengineered foods that capability is the "programming" food crop genomes. Synthetic biology promises to greatly enhance our ability to manipulate crop genomes in ways that have no apparent bounds. For example, one can envision food producers intentionally programming food ingredients to exhibit addictive characteristics to increase product revenues. As new genes become discovered, characterized, and incorporated into standard engineering library (such as the Registry of Standard

Biological Parts), bioengineers will have greater opportunity to incorporate them into food crops in order to enhance their characteristics in countless ways. One can also envision food producers programming characteristics into foods that have unintended negative consequences such as adverse health effects. As a minimum, it is imperative that consumers have a greater knowledge of what technology is used to produce their food than they currently have given the likely increase in the sophistication of bioengineering. It is also imperative that the next generation of food engineers be instilled with awareness that their designs contain embedded value choices.

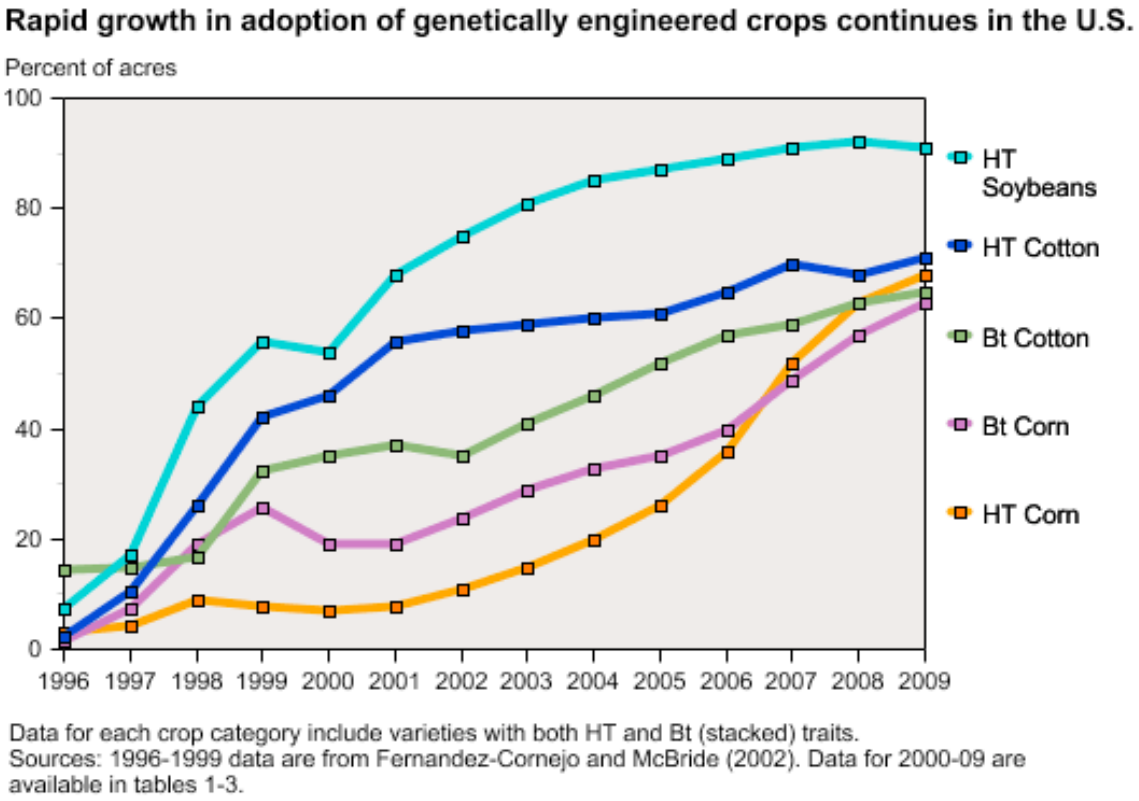


Figure 4.1.1. Recent Adoption of Genetically Engineered Crops in the U.S. [USDA 2009]

4.2 *Nonmaleficence*

In *Principles of Biomedical Ethics*, Beauchamp and Childress define nonmaleficence as "the obligation not to inflict harm intentionally" [Beauchamp 2009]. This section addresses nonmaleficence issues as they occur in the general public and in private industry. Nonmaleficence issues in the general public fall within the domain of criminal and anti-terrorism agencies, such as the FBI, and Homeland Security. In private industry, these issues are the concern of regulatory agencies, such as the FDA, USDA, and EPA. The proliferation of semiconductor and computing technology into the general public has had the effect of enabling ordinary private citizens to gain access to highly sensitive computing facilities and manipulate them towards harmful outcomes. This has given rise to a new class of criminal activity, dubbed "cyber-crimes". In the same manner, open access to synthetic biology could allow individuals to created harmful living organisms. This open access to technology lies at the heart of oversight challenges in synthetic biology.

4.2.1 *Nonmaleficence Issues in the General Public*

In 2007, the FBI reported over 200,000 complaints of cyber crimes resulting in an estimated $239M in damages involving incidents of theft and fraud [O'Connell 2008]. These incidents targeted private citizens as well as private corporations, most notably financial institutions. These reports do not include malicious attempts to disrupt computer operations that are not motivated by monetary gain such as computer viruses, worms, and other malware. According to Consumer Reports, malicious computer attacks now result in over $10 billion in annual costs to consumers [Consumer Reports 2008]. As a

dramatic example of the potential hazard from technology proliferation into the general public, a high school student in Germany managed to disseminate a computer worm that infected millions of computers worldwide, disrupting businesses on at least three continents [BBC 2004]. Except, perhaps, in the most speculative science fiction of the day, this type of scenario was hardly conceivable in the early days of computing when sophisticated programming was the domain of a small number of scientists with advanced degrees. High school students today have access to more computing power than did World War II era code breakers.

As a example of the intended accessibility of synthetic biology to the general pubic, researchers are drawing inspiration from open source code software development. Examples of this are the Registry of Standard Biological Parts [Registry 2008] and the BioBricks Foundation [BioBricks 2008]. The goal is to spur innovation by putting technology into the hands of the general public rather than a small number of scientists or corporate entities. This model stems from successful software development projects for operating systems and communications by large teams of volunteers who openly share computer source code. Somewhat counter intuitively, programs developed in this way have been shown to be as (and in some cases more) reliable and secure than programs developed by teams embedded within private corporations [Hoepman 2007, Boulanger 2005, Witten 2001]. Open source development contains a key step missing from closed source development – a closely coupled relationship with the end user that allows for quick design iterations when fixing operational flaws and holes in security [Boulanger 2005]. In essence, the software developers and software users become intimately

intertwined and, as is often the case, indistinguishable. This method reflects what Eric von Hippel calls the "democratization of innovation" where invention emanates from the needs and creativity efforts of end users themselves rather than the manufacturers [Hippel 2005].

Open source development stands in direct opposition to traditional manufacturer-based development, where private corporations hold intellectual property tightly, often controlling key patents to exclude large numbers of participants. Open source development can increase the pace of innovation by lowering the economic and legal barrier to entry in an emerging field of technology. Much of private industry opposes open source on the grounds that it eliminates one of their key competitive advantages – the ability to hold monopoly power over a technology. There is the key issue of who pays for the development. Open source development often relies on unpaid volunteers to replace professional staff; hence, questions arise on the economic fairness and viability of this approach.

With specific regards to security, open source proponents' claims of equivalent performance comes with a caveat – there is a heightened period of vulnerability immediately following the introduction of a new product preceding the opportunity for software developers to fix software flaws [Witten 2001]. However, proponents claim open source methods serve to resolve vulnerabilities quicker and more effectively due to increased user involvement in the development process.

The lessons learned from open source software methods pertain to synthetic biology at multiple levels. In the development of standardized components and design methods one can envision great power to this method as armies of volunteers offer their skills to identify and correct flaws in openly published databases of knowledge. This has potential to greatly reduce development time as well as enhance the robustness and reliability of the design information such as the Registry of Standard Biological Parts.

Open source development may also serve to uncover and resolve flaws in released products since there would presumably be a much more knowledgeable general public that would have a more in-depth understanding of the underlying technology. This sort of transparency would also have the effect of raising the bar on products, obliging the manufacturers to perform more thorough testing before product release.

However, it is questionable that the same sort of tit-for-tat that takes place in open source software development, where code developers and code fixers iterate back and forth to resolving design flaws, would be acceptable for biological products. Heightened periods of vulnerability immediately following product release may be tolerable for software, but certainly not for biological products that are used for life saving medical purposes or released into the environment where they can exist as self-sustaining, reproducing, and evolving life forms.

There is also the important issue of technology proliferation. Is it wise for such powerful technology to be in the hands of the general public, especially considering the ever-

decreasing economic barriers to entry? Will we one day have high school students empowered with the ability to release real biological viruses into the environment?

4.2.2 *Nonmaleficence Issues in the Private Industry*

The primary aim of synthetic biology is to alter the economics of biotechnology to enable more participants. Most of those participants will likely reside in private industrial sector. Issues of nonmaleficence in private industry arise in two ways: knowingly causing harm in response to profit seeking motives and causing harm due to negligence in the form of low quality product design, testing and manufacturing. As expressed by Bozeman and Sarewitz, it is possible to achieve market success for technologies, in the form of economic efficiency, coincident with public failure [Bozeman 2005]. Synthetic biology has potential to increase harm to the general public by dramatically increasing the economic scale of the biotechnology industry as well as the engineered complexity of biotechnology products.

Biologists are drawing inspiration from the fields of computer science to create highly engineered living organisms, with parallels to both electronic hardware and software. Biologists are researching ways to form Boolean logic gates, which form the basic of digital electronic processing [Weiss 2003a]. Biologists are also researching ways to "compute with DNA" in a way that closely parallels electronic computing [Shapiro 2006]. From this perspective we can consider computer files of genetic sequences to be "biological software" for programming the functionality of living organisms.

But software and complex electronic products are notorious for containing hidden flaws. Indeed, there is an intimate relationship between the complexity of engineered systems, whether electrical, biological, or mechanical, and their reliability [Kuo 2007]. With the capacity for limitless complexity given by modern computing techniques come inherent troubles with adequate testing over all possible inputs, modes and environmental conditions. An enormous field of study in software reliability has arisen in response to this problem that addresses measures of software complexity, failure modes, fault analysis, reliability measurement, testing methods, and design-for-reliability techniques [Lyu 1996].

There is strong reason to believe that these issues will plague future practitioners of synthetic biology. Researchers are currently developing biological analogs of common electronic functions such as switches, logic gates, oscillators, and counters [Weiss 2003a, Tu 2007]. As discussed, the operational of ribosomes reading and processing strips of genetic code bears strong resemblance to the conceptual basis of modern computing: the Turing machine [Shapiro 2006]. Exasperating all of this is the further complexity having to do the inherent nature of living organisms – the potential for reproduction, evolution, and horizontal gene transfer.

Profit seeking and negligence may result in a tendency to release complex engineered biological products with inadequate testing as private companies seek to gain a competitive advantage by early market entry. As in the computing industry, the field of reliability may lag behind the ability to construct new products. Pressure may be applied

to the regulatory oversight system to approve new products for their immediate benefits to society.

Synthetic biology can be advanced by drawing lessons from the computer software experience. Furthermore, a regulatory framework already exists that offers decades of experience in testing complex biological products. In the future, these two areas of experience may need to be coordinated to deal effectively with the scaling up of biotechnology products.

4.3 *Beneficence*

Beneficence, the obligation to direct ones actions towards the benefit of others, should not be viewed as the mirror image of nonmaleficence. To adhere to the value of nonmaleficence one must refrain from harming all persons. In contrast, it is not required, nor is it possible, to provide benefit to all persons with one's actions. Beneficence obliges us to help others only when we have the opportunity to do so presented to us [Beauchamp 2009].

A distinction can also be drawn between economic benefits and beneficence. Bozeman et al., argues that market failure is not correlated with public failure [Bozeman 2005]. Market failure is based solely on considerations of economic efficiency. According to Bozeman, economic considerations are inherently quantitative, dealing solely with the question: "how much?" In contrast, public failure considerations are driven by value-

based questions such as “why?” and “to what end?” To contrast the difference between market failure and public failure, Bozeman cites the example of AIDS drugs availability:

> *To illustrate the disjunction between market efficiency and public value, we need only return to the case of AIDS drugs, an excellent illustration that market failure and public failure are not the end points of a single dimension. AIDS drugs represent a remarkable market success, where initial public investment in research under conditions of market failure led to private-sector development of effective pharmaceutical interventions that also generate considerable profit. However, the vast majority of HIV and AIDS sufferers worldwide do not have access to these expensive drugs.*

This discussion on beneficence focuses on Bozeman’s notion of public failure rather than economic efficiency. This does not imply an assumption that economic inefficiencies cannot occur that require oversight intervention, e.g., undue monopoly power. The emphasis on public failure is based on salience and relevance to this discussion of values.

In examining beneficence issues in the semiconductor and biotech industries, it is illuminating to view similarities and differences in the role that U.S. government funding has played in their inceptions. The semiconductor industry emerged in the 1940’s from collaboration between the U.S. federal government and industry research labs (most notably AT&T Bell Labs) to address the need for more sophisticated weapons and aerospace capability for the military [Borrus 1984]. The need to support the military

stemmed from the national priority at the time: fighting World War II. The federal government, being the primary consumer of semiconductors, funded the research and production infrastructure that eventually enabled commercial applications to emerge. Initially, universities had a backseat role with the industry research center serving as pseudo-government labs. Eventually, the federal government invested in semiconductor technology in academia, bringing them up to speed with industry capabilities. World War II, followed by decades of cold war engagement kept military semiconductors as a top national priority.

Biotechnology, in contrast, emerged from federally funded university research with the NIH being the primary government technology driver. University-developed technology and personnel subsequently fed industry when commercially viable applications emerged. While military applications have been a long-standing, consistent national priority since the infancy of semiconductors, as Borrus states, "the tie between biotechnology and national objectives is less clear [Borrus 1984]." Biotechnology research funding has been held to be in the public's general best interest but no specific policy on product priorities has emerged to ensure the technology bears the most beneficent fruit for society. Once biotechnology products enter the realm of the commercial sector, market forces set the production priorities creating the potential for economic efficiency coinciding with public failure.

The histories of semiconductors and biotechnology involve three distinct sectors - the military, universities and industry. Each sector is accompanied by a distinct set of

objectives. While some, with hindsight, may argue about the ultimate level of beneficence of military objectives, there is no doubt that during the World War II the military was a national priority and was viewed by the general pubic as serving the overall good of the nation. This was also true, but perhaps to a lesser extent, during the cold war, when military objectives continued to drive the pace of semiconductor development. The development of the transistor, integrated circuits, high performance computing and the Internet all originated with federal defense funding mandated by a public perception of beneficence.

University personnel have an interest in advancing the spread of knowledge into the public domain, assuming that this ultimately leads to an overall beneficence to society. However, when academia begins to determine priorities of scientific research, such as whether to pursue cancer research versus biological weapons, for example, the question arises as to the qualifications university scientists have to make these determinations for the public. What processes of accountability are in place to ensure academia responds to the public will? Or as Bozeman states it [Bozeman 2005]:

> *Nobody denies that the scientific community has great skill in assessing technical quality of research, but who has vested it with special training, skill, or legitimacy in assessing the social value of research? Moreover, there is no particular reason to believe that the social priorities of scientists are representative of society. Indeed surveys of scientists' political opinions and values suggest there are often large differences between scientists and the general public …*

For university research to accurately reflect the public's perception of beneficence it cannot determine priorities based on technical considerations alone, nor can researchers be the sole determiners of societal values. A process must be in place to connect scientific research back to priorities. Presumably this is the process of democracy that elects representative officials who in turn determine scientific research priorities. Further questions then arise then as to efficacy and accountability of that process.

The industrial sector determines priorities based on profit maximization and market forces. The particular value of beneficence is one of a multitude of values that play roles in determining market outcomes. Even if market efficiency is achieved (and this is not guaranteed due to failure mechanisms such as excessive monopoly power) public failure, where the aggregated values of a democratic society are not reflected in a market outcome, may occur [Bozeman 2005]. In short, industry requires another "set of eyes" to ensure overall beneficent outcomes.

It is a problem that overall biotechnology is not as clearly focused on national priorities as semiconductor technology was in its infancy. Military objectives provided a lens to ensure at least some degree of beneficent outcomes with semiconductor technology that is not present with biotechnology. The federal government, as the primary fund provider for biotechnology research has the capability to harness the power of synthetic biology for national priorities before efforts become re-prioritized based solely on market forces.

4.4 *Justice*

The principle of justice includes concern with the overall distribution of the benefits and risks of technology to society. There are greatly differing moral philosophies on what are considered fair and just distributions of goods, including utilitarian, libertarian, communitarian, egalitarian, and Rawlsian [Beauchamp 2009] considerations. This work assesses justice utilizing Rawlsian principles as a basis, where the goods of a society should be distributed to benefit of the least well-advantaged.. Furthermore, this work adheres to the argument put forth by Bozeman, that market success/failure is not necessarily correlated with public success/failure [Bozeman 2005]. This does not imply a statement for the superiority of those philosophies. Utilitarian, libertarian, communitarian, and egalitarian conceptions of justice could be employed as well with this ethics case study approach, albeit one would likely obtain different results.

Semiconductor advances in computing and communication has given rise to a social justice concern dubbed the "digital divide". This is a division in the availability of computers and Internet access between wealth strata, gender, race, age groups, and geographical locations (e.g. urban versus rural areas). This is of particular concern due to the strong role of efficient information access in educational success, economic development, and general societal welfare. Such a situation currently exists with the access to high-speed broadband Internet home access. According to a 2008 Pew Research poll, 55 percent of all U.S. households now have broadband access while that rate for low-income Americans (with income of $20,000 or less) is only 25 percent [Horrigan 2008]. Furthermore, only 43 percent of African Americans have broadband access at

home. Growth rates for low-income and African American groups are flat while the growth rate for the general population is currently increasing.

However, there are contrary arguments on the severity and nature of the digital divide. Compaine argues that technology divides are overstated and transitory in nature and that decreasing costs eventually minimize the gap [Compaine 2001]. He further argues an advantage of allowing market forces to guide early distribution of technology development:

> *New and expensive technologies have to start somewhere and almost variable that means with two groups: those who find it undeniably useful - often commercial entities - and those who can simply afford it. Similarly, where infrastructure must be built, the provider will start their build outs aimed at audiences who are most likely to understand the value and be amenable to their service. Again, that means a focus on commercial ventures and wealthier residential areas. The economic advantage of this market-driven self interest is that it creates an invisible cross subsidy for those who follow. The early adopters pay higher per unit costs that reflect lower production volumes of manufactured products - such as PCs - or start-up costs of services, such as Internet access via cable systems.*

From these two perspectives (Pew and Compaine) we can surmise what is likely to occur with an emerging technology such like synthetic biology. There will inevitably be an

initial period of unequal distribution of technology benefits when costs are high and only those who have either the greatest desire or the greatest wealth have access. Also, decreasing costs benefit all people and market forces may be the best way to achieve that most efficiently. However, there is also likely to be some residual imbalance in distribution even after market maturity.

However, synthetic biology is likely to yield products that are immediately life critical, such as treatments to previously incurable diseases. For many, there will not be ample time to wait for market forces to settle. There is an inherent moral difference between wealth disparity in access to high-speed information and access to life saving treatments, that difference being the boundary between life and death. As in the case of the AIDS drug access given by Bozeman, the potential for public failure is quite real [Bozeman 2005]. It is therefore likely that public policy will be required to counter market forces that give early access only to groups that are unduly favored at the technology onset.

The distribution of technology benefits is also impacted by policy on intellectual property rights. In the U.S., patent holders are granted a twenty-year period of monopoly power over their inventions, offering the potential for excluding competition and controlling market pricing. However, patent policy has not been static throughout history and the U.S. court system has experienced varying periods of favorability towards patent holders. Most notably, the year 1982 marks a boundary for patent holders between an earlier unfavorable legal environment and a more generous later era. This occurred with the creation of the Court of Appeals for the Federal Circuit (CAFC) [Ziedonis 2002, Hall

2002, Henry 2005]. The creation of the CAFC centralized court jurisdiction over patent appeals and shifted the tables towards advantage for patent holders in terms of exclusionary rights, evidentiary standards for invalidation, criteria for infringement, violation damage awards and litigation success rates [Ziedonis 2002]. The result was a stark increase in patenting activity beginning in the mid-1980s where, prior to then, patents were viewed more negatively as a barrier to competition and technological progress.

The era of basic inventions and infrastructure development in the semiconductor industry took place prior to the 1980s. By that time the intellectual base had "diffused widely across the industry" and major developers of basic inventions, such as AT&T and IBM, did not find it economically or legally viable to exercise tight control over the technology [Ziedonis 2002]. Fundamental semiconductor technology developed at AT&T (notably developed with a considerable amount of public funding) was licensed broadly across the industry early on thereby fueling rapid industry growth. Given this early culture of even play across the industry it is not surprising that semiconductor firms now consider "patents are among the least effective mechanisms for appropriating returns to R&D investments" and that they "rely more heavily on lead-time, secrecy, and manufacturing or design capabilities than patents" [Ziedonis 2002] for gaining competitive advantage.

In contrast biotechnology (and particularly synthetic biology) is coming of age in the current patent-holder-friendly era. Today, the most basic inventions in synthetic biology are still underway. For example, a patent issued in 2004, entitled "Molecular Computing

Elements, Gates and Flip-Flops", covers the most basic elements of computing Boolean logic and can, according to patent claims, be expanded in scope to much greater complexity. Regarding the broad claims of this patent, Rai etal., raises a warning flag:

> *As the patent documentation notes, the invention could be used not only for computation but also for complex ("digital") control of gene expression. The broadest claim does not limit itself to any particular set of nuclei-acid binding proteins or nucleic acids. Moreover, the claim uses language that would cover not only the "parts" that performed the Boolean algebra but also any device and system that contained these parts. Such a patent would seem effectively to patent the basic functions of computing when implemented by one likely genetic means. Would such a foundational patent hold up in court?*

That such far-reaching claims appear in patents and are even issued is not uncommon or surprising. The key test is whether such claims hold in the CAFC when challenged. If such claims were upheld in courts during the infancy of the semiconductor era it is likely that things would have turned out quite differently with patent grantees controlling much more tightly key inventions such as computers, calculators, cell phones, networking equipment and many more common place items, the availability of which we now take for granted. Given this important difference in the way patent litigation is now decided, synthetic biology is likely to take a different course than semiconductor technology in terms of the distribution of benefits to society.

The open source approach to technology development offers a means to avert some of these issues by providing a model that creates intellectual property that is freely and openly accessible to all users. Some researchers envision this approach as the preferred path for synthetic biology, examples being the Registry of Standard Biological Parts, the BioBricks Foundation and the International Genetically Engineered Machine competition, all of which encourage the use and development of openly accessible engineering databases [Registry 2009, Biobricks 2009, iGEM 2009]. Furthermore, comprehensive genome sequence databases for many microorganisms are openly available online via the NIH and the Sanger Institute websites [NIH 2009a, Sanger 2009]. Therefore, it is worth examining the open source model in more detail and comparing it with other, more conventional approaches to technology development.

One conventional approach is called the "private investment" model. In the private investment model, firms are provided the incentive to invest in research and development via the promise of private returns in the form of future profits. The private returns for firms are secured by the issuance of monopoly power enabled by the issuance of patents and copyrights as well as the maintaining of trade secrets. This means that society experiences a net loss in the form of inflated prices and restricted usage of these protected technologies [von Hippel 2008].

This stands in stark contrast to another conventional development approach, called the "collective action" model. The collective action model features outputs that are considered to be non-excludable and non-rivaled public goods in the sense that there is

free and open access to the outputs and their usage by an individual does not prohibit the usage by another individual. Science itself is an example of the collective action model. The results of science are accessible to all and the use of scientific knowledge by an individual does not reduce the pool of knowledge available to anyone else. Contributors to the collective action model do not extract private returns from the results of their work in the form of direct profits. Other means of rewards need to be created, for example, one's social status and reputation may be enhanced, or perhaps one's employment within a research institution may be secured [von Hippel 2008]. Another characteristic of the collective action model is the free rider problem where users of a freely accessible technology may simply extract benefits without contributing any level of effort or investment.

The open source model of software development has been characterized by von Hippel as a hybrid of these two approaches, dubbed the "private-collective" model of innovation [von Hippel 2008]. In the private-collective model the results of contributors' labors are openly accessible as in the collective action model, yet contributors are able to extract private benefits as in the private investment model. These benefits sometimes come in the form of profits. An example of this is the development of software that has commercial applications, for example, GNU/Linux operating systems. Sometimes, however, the benefits are less tangible and include what Spaeth et al. calls "communal resources", that include an individuals personal reputation, control over technology, and learning opportunities for the contributors [Spaeth 2008]. The importance of these benefits is that they provide incentive for a technology developer to become a contributor rather than a

free-riding user. Furthermore, there is evidence that as one's more contributions increase, private benefits also increase in turn.

Therefore, the private-collective model provides a potential means to avert the loss to society experienced by firm monopoly power derived from patents, copyrights, and trade secrets. However, it must be noted that the private-collective model is a relatively new phenomenon that has just emerged in recent times with the advent of open source software development. Social scientists are now just beginning to study this approach and models are, as yet, new and untested. We do not have experience with the private-collective model as the dominant approach to development of a technology. It is by no means certain that this model could provide the same level of incentives that the private investment has been proven to provide to technology developers. There exists a real, yet unquantifiable risk, that the private-collective model might slow the pace of development in synthetic biology by not providing sufficient tangible private returns.

Regarding the just distribution of risk, issues have recently arisen regarding the disposal of electronic waste created by the rapid increase in consumption of semiconductor based products including computers, computing peripherals, cellular phones, and other consumer products. These products frequently contain toxic materials such as lead, mercury, and cadmium [EPA 2009]. Furthermore, the amount of electronic waste (currently almost two percent of the total waste stream) is steadily increasing [EPA 2009]. Electronic waste creates a justice-risk issue due to the tendency for the disposal of hazardous waste to pose inequitably risks to certain segments of society, such as the poor

and racial minorities [Brown 1995]. These risks result in direct threats to health, such as cancer, respiratory disease, reproductive disorders, birth defects, skin conditions, and psychological impacts, as well as socioeconomic costs, such as decreased social mobility, intergenerational inequity, poor education, and decreased property valuations [Brown 1995].

Synthetic biology has the potential to exacerbate these so-called "environmental justice" issues by adding to the stream of hazardous waste through the increased production of toxic chemicals as well as the release of highly engineered microorganisms and genetic material into the environment. These new flows of "bio-waste" may become concentrated in industrial regions, waste disposal sites, and water resources that tend to be geographically distributed near the poor and minorities. Furthermore, synthetic biology may pose risks beyond the relatively simple toxic materials contained in consumer electronics. Complex biological materials and organisms such as viruses and bacteria often have the capability to interact with humans in ways that are difficult to trace and assess. The release of such organisms created with synthetic biology could one day result an entire new category of hazardous waste.

Chapter 5:

Oversight Policy Assessment

This chapter provides a discussion of oversight issues emerging from comparisons of synthetic biology with lessons learned from the semiconductor industry and the first generation of biotechnology. Further experience is drawn from the first generation of biotechnology. It is, once again, organized under the themes of the biomedical ethics principles of autonomy, nonmaleficence, beneficence, and justice. The section on nonmaleficence contains discussions of issues pertaining to, both, the general public and private sector.

5.1 *Autonomy*

Central to the notion of autonomy is the free flow of information to product users regarding important aspects of a product's ingredients, characteristics, and long-term effects that enable the user to have an adequate "informed consent" on their consumption. One contentious issue that has arisen with the first generation of biotechnology is the labeling of foods that contain so called "genetically modified" (GM) ingredients. This section reviews the GM foods labeling debate and decisions, then assesses the need for policy changes with the onset of synthetic biology with emphasis placed on the ethical principle of autonomy.

The FDA, which oversees the use of biotechnology in food additives, maintains a voluntary food labeling policy with regards to GM ingredients [FDA 2001], meaning that

it is left to the discretion of food producers and retailers whether or not to label a food as containing GM ingredients (it should be noted that FDA prefers the term "bioengineering" over the label "GM" since consumer focus group studies indicate that most people do not understand the acronym). Since food that is labeled as containing GM ingredients looses its appeal to consumers when presented side-by-side with non-labeled food, this policy, in effect, results in only "non-GM" foods being labeled. Food producers have no economic incentive to voluntarily add GM food labeling since it would inevitably decrease product sales. The FDA justifies this policy by pointing to the lack of evidence that GM foods have either substantially different characteristics or any safety concerns beyond their traditional counterparts. Furthermore, the FDA follows a "product, not process" method of oversight and maintains the position that GM foods as chemically equivalent to conventionally produced foods [FDA 2001].

Critics of voluntary labeling argue issues of consumer transparency; environmental biodiversity; ethical, religious, and cultural concerns; health; and economic justice [Greenpeace 2009, Friends of the Earth 2009]. They claim that the lack of labeling denies the public of their basic right to know what they are consuming. They point to known difficulties in containment of foods and the resulting inevitability of genetically engineered material escaping into the environment. GM foods may also violate religious dietary codes such as kosher and vegan traditions. Health concerns include allergic reactions to transferred genes. Furthermore, critics note that food producers have reaped most of the economic benefits of the first generation of GM foods and enabled unfair competition by establishing an intellectual property rights barrier. Public surveys

consistently show that consumers want GM food labeling (yet it is unclear how much in practice they are willing to pay for it) [Smyth 2003].

Huffman [2001] has argued that the FDA is justifiable from an economic welfare perspective since voluntary labeling results in labeling costs only being incurred by producers of non-GM foods. Furthermore, the Huffman study claims that carefully designed experiments demonstrate that the purchasing decisions by consumers in the cases of voluntary and mandatory labeling are equivalent, therefore equivalent informational signals on GM foods must reach consumers in both labeling approaches. Presumably the public receives the information via knowledge of the existence of non-GM foods and that fact eliminates the necessity for GM foods labels. Also noted are the heavy costs that would be incurred by producers and the public to maintain strict separation between GM and non-GM foods (costs that small producers would bear proportionally more than large producers), and the governmental costs of programs to monitor and verify the separation of GM and non-GM foods.

An important lesson to learn from the GM foods experience is that oversight needs to a find a way to get information to consumers that is accurate and economically efficient. With the added complexity of the next generation of biotechnology products resulting from synthetic biology, that challenge will likely increase. Just as the complexity of semiconductor products increased, from simple transistor radios to modern day networked computers, the next generation of bioengineered products could contain a level of sophistication far beyond the GM products of today.

The potential for synthetic biology to result in high degrees of sophistication in bioengineered products elevates the need to adequately inform consumers about product characteristics and ingredients. In the future, simple labels such as "made using bioengineering" may not capture the dramatic increase in product sophistication. Since labeling products with notices of genetic engineering could decrease consumers' willingness to buy them, food producers will likely be reluctant to voluntarily provide this information. Therefore, there is an important role to play for regulatory agencies in providing comprehensive guidelines for producers of food and other consumer products to inform the public.

Due to spatial constraints, product labeling may not be capable of conveying adequate information on the essential characteristics of sophisticated bioengineered products. Fortunately, the near ubiquity of the Internet provides a possible alternative. Regulatory agencies could require producers to maintain an Internet web page to provide information about important characteristics of a bioengineered product. The label appearing on the product itself need only be a web address that points the consumer to the website. Consumers could then download the information from the Internet in real time (for example, with a handheld, mobile web browser) or at a later time of their choosing.

There is some precedence for regulatory agencies requiring web information from producers. The FDA currently requires producers of bioengineered foods to provide a "scientific description" of any bioengineered product 120 days prior to market release

that is posted on the Internet during this period [Rousu 2001]. This program could be expanded to have food producers permanently maintain descriptive information with detailed guidelines on what information needs to be displayed; the accessibility and accuracy of the information; and the understandability of the information to the non-scientific general public. The posted product descriptions should focus on product characteristics rather than process. This is important to balance the public's need for essential information with private companies' need to maintain trade secrets.

This type of oversight can be employed beyond food additives, as synthetic biology has the potential to enable a host of advanced bioengineered products for commercial and medical applications. One can envision products for industrial and residential applications to be used as cleaners, water purifiers, fertilizers, pesticides, herbicides, cosmetics, medical devices, and pharmaceuticals. These products may contain bio-computing functions, similar in sophistication to modern electronic products. These functions include the ability for micro-organisms to collect, process, store, and communicate data from the surrounding environment and take specific actions such as creating and releasing proteins or other biological chemicals.

This type of bioengineered product "intelligence" also leads to questions of autonomy. Consumers may be unaware that advanced bioengineered products are making sophisticated decisions and taking specific actions based on those decisions in ways that could affect humans and the environment. And regardless of the scientific evidence of safety, many people would prefer to opt out of any interaction with products of this

nature, as was the case with people's objection to GM foods. The principle of autonomy demands that people be fully informed in order to make decisions in accordance with their personal values, regardless of scientific knowledge. Such is not the case if products are making decisions and taking actions without the general public's full knowledge.

It is worth noting that complete, accurate, and easily accessible product information could have the benefit of boosting consumer confidence in the overall deployment of synthetic biology by ensuring adequate transparency to the general public, concerned NGOs, and the scientific community. In this way, the disclosure of complete product information could have the effect of furthering the benefits created by synthetic biology.

5.2 *Nonmaleficence*

Since current U.S. regulation in biotechnology primarily focuses on the deterrence of nonmaleficence issues, a brief review of this regulatory system is provided below in Section 5.2.1. Nonmaleficence issues pertaining to both the general public and private industry are subsequently discussed in sections 5.2.2 and 5.2.3.

5.2.1: *Review of Current U.S. Biotechnology Regulation*

This section provides a brief review of current U.S. oversight policy in biotechnology to provide a context for assessments of synthetic biology oversight issues presented subsequent chapters. The primary U.S. biotechnology vehicles are contained in the Coordinated Framework for Regulation of Biotechnology (CFRB) and the Bioterrorism Act of 2002. The CFRB has been evaluated for its adequacy to cover synthetic biology

[Rodemeyer 2009] and is the most likely route of oversight for synthetic biology. Also included is a summary of common critiques of the CFRB.

Much of U.S. laboratory experiment policy is rooted in the early recombinant DNA research controversy that inspired the Asilomar Conference on Recombinant DNA Research in February of 1975. While the Asilomar conference is claimed to have "given way to dangerous overreaction and exploitation", it is also regarded as a positive example of a precautionary approach to new technologies, and set precedence for self-regulation in the academic research as well as public transparency and engagement [Frederickson 2001].

The Asilomar conference directly led to temporary moratoria on certain high risk classes of research experiments and the formation of the highly influential NIH Recombinant DNA Advisory Committee (RAC), which oversees all federally funded recombinant DNA research safety issues. The NIH published the *NIH Guidelines for Research Involving Recombinant DNA Molecules* in 1986 to provide containment of genetic material. The NIH also jointly published *Biosafety in Microbiological and Biomedical Laboratories* with the CDC to provide guidelines for safe handling of infectious materials. Research conducted by the USDA, EPA and NSF commonly defer to NIH guidelines. Central to NIH guidelines were the requirements for institutions that perform federally funded research in recombinant DNA to form Institutional Biosafety Committees that report to the RAC and to appoint Biosafety Officers for research that requires high degrees of containment.

Current NIH recombinant DNA policy provides the foundation for regulating research safety in synthetic biology. Federally funded research efforts in synthetic biology will likely be required to maintain Institutional Biosafety Committees and Institutional Review Boards that report to the NIH via the Recombinant DNA Advisory Committee. But concerns may arise that pertain to the reach of NIH policy outside of the realm of federally funded research. These concerns pertain to private biotechnology companies as well as private individuals performing so-called "garage biology" who are not bound by NIH guidelines and have no clear incentive to follow them voluntarily. And with an open access approach to engineering information in synthetic biology; encouraged by such things as open NIH genome databases and the Registry of Standard Biological Parts; private companies and individuals may be enabled to perform advanced bioengineering research without requiring federal research dollars. This raises a policy challenge to determine ways to extend NIH research safety guideline beyond their current reach.

5.2.1.1 *Coordinated Framework for Regulation of Biotechnology*

In 1986, the White House Office of Science and Technology Policy (OSTP) released the Coordinated Framework for Regulation of Biotechnology. The intent was to take the patchwork of U.S. government legislation and agencies and sew them together to form a more effective policy blanket. Some overarching assumptions guiding this policy are that regulation should be performed on a "product" basis, not on the "process" through which they were developed; and that the risks of biotechnology are the "same in kind" as the

risks associated with conventionally developed equivalents, i.e., the risks associated with biotechnology are not new or unique.

In developing the CFRB, the OSTP solicited inputs from the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the National Science Foundation (NSF) and the Occupational Safety and Health Administration (OSHA) to aid in determining each agency's role in biotechnology oversight and to establish how historical legislation should be interpreted and applied in the regulation of products resulting from biotechnology. The following summarizes each federal agency's oversight role.

The FDA regulates human and animal drugs, food additives and cosmetics in accordance with the Federal Food, Drug and Cosmetics Act of 1938, with amendments to include medical devices in 1976. Biological products, including vaccines, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins, are regulated under the authority of the Public Health Service Act of 1944 by the FDA's Center for Biologics Evaluation and Research [FDA 2009]. In clarifying their policy position for the development of the CFRB, the FDA proposed "no new procedures or requirements for regulated industry" in biotechnology and stated that each product would be reviewed on a "case-by-case basis" [OSTP 1986].

With regards to the regulation of bioengineered food additives, the FDA has adopted a voluntary product labeling policy [FDA 2001]. The reasoning for this decision is contained in the 1992 "Statement of Policy: Foods Derived from New Plant Varieties" which states that "the FDA has no basis for concluding that bioengineered foods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding." Exceptions occur if a bioengineered food differs significantly from its traditional counterpart, if an issue exists with how the food is used, if the food contains different nutritional properties, or of the food contains an unexpected allergen. For all bioengineered food, the FDA requires notification 120 days prior to the market introduction with a "scientific description" of the food to be posted on the Internet during that time.

The EPA regulates hazards to the environment under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947 and the Toxic Substances Control Act (TSCA) of 1976. The EPA clarified its position on the reporting of biotechnology products with the 1997 issuance of the Microbial Products of Biotechnology: Final Rule. The EPA position specifically requires review of all microorganisms formed by "inter-generic combinations" before any environmental release including small scale testing and research and development. Microorganisms that contain "pathogens" are subject to similar restrictions [OSTP 1986].

The USDA regulates animal biologics under the Virus-Serum-Toxin Act (VSTA) of 1913, the Food Security Act (FSA) of 1985, the Federal Plant Pest Act (FPPA) of 1957 and the Plant Quarantine Act of 1912. The USDA's policy position is that "products developed by biotechnology will not differ fundamentally from conventional products and that the existing regulatory framework is adequate to regulate biotechnology." In the area of plant pests there is regulatory overlap with the EPA. As a result, microorganisms that contain inter-generic material must be reported to both agencies [OSTP 1986].

Synthetic biology may present a particular problem to the U.S. regulatory system with its emphasis on product-by-product approval of market products. Due to the patchwork nature of current U.S. biotechnology regulation, it is not clear how oversight will perform in terms of combating aggregate effects. It is one thing to assess the risk of one bioengineered product entering the market, but it is an entirely different challenge to assess the effects of large quantities of engineered genetic material accumulating in the environment resulting from a sharp increase in the number of bioengineering firms. Issues of containment become far more critical when synthetic biology is viewed as a whole with an ever-expanding proliferation.

No single regulatory agency currently has the charter to assess the aggregate effects of synthetic biology on the environment and it is not clear how resulting policy recommendations would be implemented when the agencies responsible for approval of market products, such as the FDA and the USDA, act on a product-by-product basis. Protection of biodiversity, for example, may require an overarching degree of

coordination of regulatory agencies that is not currently present. This in itself will likely present a unique challenge. How does one, given a set of negative aggregate effects, construct a policy for averting those effects when the market approval process operates on a product-by-product basis? Simple quotas may alleviate aggregate effects but could create logjams in the product approval process that prevent the approval of products with societal benefits.

The first large-scale test of the U.S. biotechnology regulatory system involved the introduction of genetically engineered (GE) plants and animals into the food supply. This experience resulted in assessments of the CRFB ranging from general support for the system, to calls for fundamental change to U.S. biotechnology policy. The Pew Initiative on Food and Biotechnology (PIFB) has published a comprehensive summary of the leading arguments both for and against change to the regulatory system [PIFB 2004]. According to the 2004 Pew Report, arguments against change are based on the lack of scientific evidence of harm to human and environmental health from the first generation of GE foods. Also cited is the presence of sufficient flexibility in the system in adapting to the introduction of novel products, high levels of public confidence in biotechnology to provide societal benefits, and the high potential costs of changing regulatory policy. Arguments for change note the high degree of acceleration in technological development and question whether the current patchwork of antiquated laws can keep pace. Most laws that form the basis of the regulatory system were enacted long before the advent of biotechnology and are being stretched in their legal interpretations in the attempt to cover GE products. And while the current generation of GE products have close similarities to

conventionally bred plants and animals, future generations may increasingly diverge. As a result, risk assessments based on prior records of safe deployment may not be applicable.

5.2.1.2 *Bioterrorism Legislation*

The Bioterrorism Act (BTA) of 2002 is the primary U.S. legislation that addresses the threat of attack from biological agents. The Bioterrorism Act was direct result of the terrorist attacks of September 11th, 2001, and was mandated by the USA Patriot Act of 2001. The BTA addresses four main areas of concern: national preparedness, controls on biological agents, food and drug supply protection, and drinking water protection [FDA 2009]. It also calls for the creation and maintenance of a list of select agents and toxins "that have the potential to pose a severe threat to public health and safety" [NSAR 2009]. The Center for Disease Control (CDC) and the USDA Animal and Plant Health Inspection Service (APHIS) manage this list and coordinate the overlap between human and animal/plant safety according to the Agricultural Bioterrorism Protection Act of 2002.

The select agents and toxins list currently contains 39 human agents, 24 animal toxins, 8 plant toxins, and 10 "overlap" toxins. Some notable examples are botulinum neurotoxins, Ebola virus, herpes B virus, ricin, swine fever, and foot-and-mouth disease virus. The list is updated every two years. The CDC and APHIS maintain separate sets of regulations for possession, transport and use of selected agents. The regulations are applied to all entities, not just those that accept federal funding. Entities that wish to possess, transport

or use selected agents must register with either the CDC or APHIS to aid in traceability for potential FBI Criminal Justice Information Services (CJIS) investigations.

The BTA also has mandates for coordinating bioterrorism prevention and responses with state and local governments. This is particularly necessary for the protection of the U.S. food and water supplies.

Synthetic biology has the potential to heighten the risk of bioterrorism by increasing the number of practitioners of advanced bioengineering and by providing them with readily accessible information and laboratory equipment. In the future, it may no longer be the case that only accredited scientists with cutting edge facilities can create biological toxins and pathogenic organisms such as synthetic viruses and bacteria. “Recipes” for creating harmful biological materials may one day be readily downloadable from the Internet. Amateur practitioners of synthetic biology may develop new hazards, beyond the select agents and toxins list, that are unknown to law enforcement and undetectable by currently available methods and equipment. It may be the case that those who would use biotechnology for intentional harm will be given a boost in their efforts. It is policy challenge to ensure that synthetic biology does not tip the scales in favor of the bioterrorist.

5.2.2 *Nonmaleficence Oversight Issues in the General Public*

In the case of individuals or small groups of persons who strive to inflict harm intentionally to people with biological pathogens, it is likely that they will draw

inspiration from organisms already found in nature. Notable examples of naturally occurring pathogenic bacteria are *Bacillus anthracis* (anthrax), *Mycobacterium tuberculosis* (tuberculosis), *Rickettsia prowazekii* (typhus) *Vibrio Cholerae* (cholera), *Escherichia coli O157:H7* (toxic strain of E. coli), Yersinia pestis (plague), and salmonella. All of these organisms are capable of causing widespread illness and fatalities [WHO 2007]. Furthermore, all of the genomes for these organisms have been sequenced and the data is readily available to the general public online via the NIH [NIH 2009a] or the Sanger Institute [Sanger 2009]. With reports now emerging on the advent of amateur genetic engineering [Johnson 2008], this raises important questions regarding the open publishing of potentially dangerous scientific information.

The most commonly cited reason for openly publishing the genome sequences of pathogens is to enable scientists to develop a deep understanding of these organisms that aids in the creation of effective vaccines. A notable example is the recent response to global outbreaks of severe acute respiratory syndrome (SARS) and meningococcus B [NRC 2004a, Portillo 2007]. It is also important that genome sequences be openly available to the world's vast scientific community to allow the participating scientific community to correct errors in these databases in a manner similar to that of open source software development. Furthermore, the National Research Council (NRC), based on an interdisciplinary expert committee, concluded that "effective restriction of genome data is not practical" and that "pathogen genome sequences are not uniquely dangerous". The NRC panel points to the ease with which files of digital data are stored and transported and the international scope that would require absolute control over the information.

They also conclude that registration requirements for data access would not effectively deter a "determined malefactor" and would raise "troubling questions" regarding who would and would not be allowed access to genomic sequences.

Further confounding the issue is difficulty in classifying sequences according to risk. Pathogens often have closely related organisms that are not dangerous yet can be used to characterize the related pathogen. An example of this is the close relationship of Bacillus anthracis (anthrax) and Bacillus cereus, which is commonly found in soil (NRC 2004a). Knowledge to understand the workings of pathogen is not so closely coupled to genome sequences. One must understand the operation of biological processes including gene expression, protein creation, and interactions with the host environment. Indeed, knowledge of the human genome can potentially be used to enhance the effectiveness of an engineered pathogen. For these reasons, there is expert consensus for open access to genomic databases.

But open access of information for scientists also opens the door to the general population including those who would strive to do harm. As economic barriers to entry continue to decrease, future biocriminals will gain access to pathogenic genomes and supporting knowledge on gene expression and experiment with ways to develop new strains of pathogen that are immune to modern vaccines. To achieve this, future biocriminals will need to finds ways to synthesize genomes that are undetectable by suppliers of DNA. However, this may not present much of a challenge. The recent development of synthesis via construction of whole genomes uses overlapping

"cassettes", or smaller molecules of DNA (a few thousand base pairs each) that are subsequently connected to form a larger complete chain. The first synthetic whole genome was constructed using this technique [Ball 2008]. This means that a DNA supplier would not necessarily have knowledge of the intended use of the sequence, especially if biocriminals use multiple suppliers. In this way, biocriminals can fly under the radar of conventional oversight methods when synthesizing DNA.

Restricting access to information genomes is problematic in the United States. Genome sequences exist as raw information in the form of a DNA code. Such information is not likely to be restricted due to precedents in interpretations of the First Amendment of the Constitution. The mere possession and dissemination of information without malicious intent is not a criminal act. Rather, it is the actions undertaken using the information that is considered punishable crimes [Montana 2000]. An example of this is how the law deals with computer viruses. It is not a crime merely to possess or even distribute computer viruses. Under the Computer Fraud and Abuse Act (CFAA) of 1986, for one to be prosecuted of a computer crime one must either use the virus to create damage or exhibit the intent to create damage to persons or institutions [Montana 2000, Skibell 2003]. Furthermore, it is highly questionable in this age of the Internet and instant communications that controlling information on genetic information could be achieved even if it were deemed illegal. Given the ease of transferring computer files in the modern world the genie may be forever released from the bottle.

Nevertheless, it is worth examining how a more restricted approach to information access in genomic sequences might work. The primary objective of would be to allow database access to the scientific community yet restrict access to the general public. Ideally, the databases would be easily accessible to enable the scientific community to quickly respond to infectious outbreaks and to update the databases with new advancements. This could be achieved with a secure online approach where only a limited number of approved scientific personnel are given database access. The first challenge of such a system is determining the approval process for access. Such a process could be modeled after the Department of Defense security classification system where background checks are performed on individuals who have a justifiable need for access to secure information. The Federal security classification system has the appropriate scope as, according to a recent General Accountability Office report, 2.4 million Americans currently have security clearances to handle classified information [US GAO 2009]. This system also allows for the clearance of both Federal government employees and private contractors to the Federal government. This would include many scientific personnel who would be called upon to combat infectious disease outbreaks but may also exclude many scientists in private industry who are not Federal contractors.

Another challenge is the real effectiveness of such a system. Internet databases are prone to hacking via direct access or via tapping into communications. Certainly, advances in information security will aid in preventing intrusions but such systems can never be fully secure when large numbers of people have access. There is little doubt, however, that

restricted access would be more secure than the current system of open access with respect to keeping information out of the hands of nefarious individuals.

Yet another important consideration is the fairness of the classification system. Due to the dual-use nature of synthetic biology, where the same technical information that can be used to create weapons of mass destruction can also be used to create beneficial commercial products [Tucker 2007], private entities that have access to secure databases will also be given a competitive edge in bringing new products to the market.

It is conceivable that synthetic biology could tip the scales in favor of restricted information access due to the increasing ease of creating pathogenic organisms from raw databases of pathogenic genomes. As DNA assembly technology advances and allows increasing members of the general public to practice advanced genetic engineering, the risk that certain individuals and organizations will acquire the technological prowess to create and release pathogenic organisms will grow. This risk must inevitably counterbalance the benefits of an open scientific. While such a restricted access system can never be perfectly constructed either in fairness or effectiveness, it may become necessary in order to avoid future catastrophic occurrences put into effect by nefarious individuals or organizations.

But if we assume a continuation of the current open access policy on pathogenic genome information combined with the decreasing economic barriers to entry into the field of

synthetic biology, what policies can be implemented to minimize incidences of biocrimes?

It is important to point out that the proliferation of synthetic biology will result in many benefits to society. Legions of amateur biologists will be free to participate in finding biological solutions to many of society's problems much in the same manner as open source software development does today. Effective policy would encourage this powerful capability to the degree possible without enabling nefarious usages of the technology. This is undoubtedly a difficult task, however, since it is difficult to systematically separate those who would do good from those who would do harm.

Drawing from the experience in computer crime, it is important to understand the nature of the criminals likely to be seen as an aid to developing effective and just policy [Skibell 2003, Calkins 2000]. Skibell categorizes computer network hackers using the "underground lexicon" of "script-kiddies", "hackers", and "crackers". Script-kiddies are the least skilled amateurs that download software tools to penetrate obvious security weaknesses, causing relatively minor damage. Hackers, on the other hand are more skilled and experienced yet they penetrate the security of computer networks for the personal satisfaction, or thrill, of beating the system. Crackers are similar to hackers in skill level but are motivated by outright maliciousness, seeking personal gain or political power. Crackers are potentially the most dangerous cybercriminals because of their motivations, not simply because of their level of expertise.

Currently, U.S. policy in computer crimes centers on the CFAA. Critics of the CFAA claim that the legislation is both ineffective and unjust [Montana 2000, Skibell 2003]. Montana states:

> *few virus perpetrators are found and prosecuted. In the average month, as many as 500 new viruses may be created and set loose on the Internet (Vibert 1998). Only occasionally is the author successfully located and prosecuted. In 1998, the FBI and all other federal investigative agencies sent 419 computer crime cases to federal prosecutors, of which only a handful involved viruses. in only 83 cases were charges actually filed. Of cases completed the same year, there were only 21 convictions for computer crimes of all types.*

Furthermore, Skibell claims that, due to increases in penalties in CFAA amendments as a result of the USA Patriot Act enactment, coupled with the lack of distinguishing between types of computer crime motivations (as stated above), the current policy results in overly severe punishment for minor crimes.

Application of this model to the future world of biocrimes results in three distinct groups of "biohackers". Group 1 could consist of low-skilled amateurs who employ techniques developed by more highly skilled professionals to recreate already existing results. Group 1 could cause damage more as a result of accidental outcomes or from reckless negligent practices. Group 1 practitioners would not be expect to develop advanced technologies,

such as highly anti-biotic resistant pathogens, that would circumvent known mitigation technologies.

Group 2 could consist of advanced practitioners who try to push the boundaries of current technology to develop novel organisms with sophisticated functionality. They do not have outright malicious intent but also have potential for reckless negligence in their practice that could lead to highly damaging outcomes.

Group 3 is potentially the most dangerous. These practitioners are highly skilled and are motivated by nefarious intent, seeking to advance themselves in some way, such as monetarily, politically, or psychologically.

It must be pointed out that there is a strong case for the criminalization of the creation and dispersion of biological pathogens, rather than relying solely on civil tort law. This is an activity that should be banned outright due to the high potential for direct damage to human health. Criminal law carries more moral weight as a deterrent than civil regulation [Calkins 2000]. Furthermore, individual perpetrators do not necessarily have the "deep pockets" to pay sufficient compensatory damages to their victims [Calkins 2000]. This is not to say that there should not be civil laws acting in parallel with criminal laws for cases where total costs – both direct and social – can be assessed and the offender is a corporation or institution with substantial financial means.

It is important, however, to invoke laws that do not over-criminalize offenses. Encouraging the growth of the numbers of practitioners of synthetic biology will lead to more swift progress in using the technology to solve world problems, as well as provide economic benefit through entrepreneurship. We do not want a situation where individuals are steered away from synthetic biology for fear of dire punishment upon the slightest infraction. This could lead to the injustice of having the technology only being accessible to corporations and institutions with access to highly advanced legal power. On the other hand, we do not want to encourage reckless behavior amongst less skilled amateurs. All practitioners must been compelled to have a minimum standard of safety and quality.

If experience in computer crimes is to be our guide, Groups 1, 2, and 3 should not be lumped together in assessing punitive measures. Considerations of the intent of the offender, as well as the severity of the outcome, are important. To achieve this, a tiered system, where minor recklessness results in fines and mandatory safety courses and chronic maliciousness for personal or political gain result in extended prison sentences, could be employed.

Coordination of Groups 1 and 2 through local and national organizations may also help to set minimum professional standards for practitioners as well as aid in the fight against intentional malicious acts. As in the case for open source software development, Groups 1 and 2 could be used, through a coordinated reporting system, to identify emerging pathogens and combat them through vaccines. Professional associations in biotechnology

should be extended to include amateurs so safety and quality standards as well as codes on conduct can be disseminated.

Policy experience can be drawn from the realm of professional research. The National Research Council has identified seven experiments of concern to be used as criteria for raising a red flag on biotechnology research projects, the results of which could enable terrorist attacks [NRC 2004]. These experiments:

1. would demonstrate how to render a vaccine ineffective.
2. would confer resistance to therapeutically useful antibiotics or antiviral agents.
3. would enhance the virulence of a pathogen or render a nonpathogen virulent.
4. would increase transmissibility of a pathogen.
5. would alter the host range of a pathogen.
6. would enable the evasion of diagnostic/detection modalities.
7. would enable the weaponization of a biological agent or toxin.

These guidelines are as applicable to amateur research as they are to professional research and should be communicated to the general public with the aid of national, international, and local biotechnology associations. This would create an overall awareness of the inherent dangers of biotechnology research and encourage the reporting of projects being carried out beneath the radar of governmental authorities.

The NIH is currently responsible for maintaining standards for laboratory safety funded biotechnology research. The primary document for guiding researchers is the "NIH Guidelines for Research Involving Recombinant DNA Molecules" [NIH 2002]. The NIH jurisdiction and reach of enforcement extends only to entities performing biotechnology research that accept Federal government funding mechanisms. In the age of synthetic biology it can no longer be assumed that widespread biotechnology research will be traceable to Federal funds, therefore, the Federal government will lose this method of enforcement. Furthermore, some requirements that the NIH holds in place for laboratory safety may not exist in private endeavors such as Institutional Biosafety Committees, Biosafety Officers, or even formal Principle Investigators.

Nevertheless, the NIH guidelines contain much that is directly applicable for the development of "privatized" standards that could be adopted by professional organizations and amateur cooperatives. The NIH guidelines define four categories of risk groups (RG1 through RG4) of increasing hazard levels listing specific bacterial, fungal, parasitic, and viral agents. Although the list will certainly require regular updates as new agents are discovered and invented, the list provides a solid starting point and framework for private research. The NIH guidelines also define applicable containment requirements for four biosafety levels (BL1 through BL4) including large scale uses and cloning of genes that code for toxins.

Professional and private associations may be appropriate vehicles for transferring the standards and experience of biotechnology research from the public to the

private/amateur sector. This might be achieved through a certification process that provides local safety training. Federal law could require that all laboratories, whether public or private, small or large, be registered into a national database. This database could be used as an aid in increasing the transparency of amateur laboratories. Registration and certification fees can be used to pay for the maintenance of safety standards and procedures.

In accordance with the Bioterrorism Act of 2002 (BTA), the CDC and APHIS maintain a select agents and toxins list that currently contains 82 human, animal, plant, and "overlap" (human, plant, and animal) pathogenic organisms. This list could be viewed only as a starting point since synthetic biology will likely result in the engineering of more toxins with increased levels of sophistication. This may necessitate the adoption of new, more complex taxonomies as practitioners invent novel ways of engineering pathogenic organisms. Many of these might be offshoots of naturally occurring organisms, but many may become novel human inventions. It is possible for this list to be maintained in the open access realm. The advantage of this would be the elimination of the bottleneck of government control over the list. By enlisting amateur volunteers, the list could be seen by a far greater number of eyes, thereby enhancing the efficiency and robustness of the list in the same manner as is currently achieved by open access software development.

It is possible to impose restrictions to entry into synthetic biology by adopting a licensure policy. Licensure expressly prohibits engaging in a profession unless granted permission

by an overseeing organization, which is often a state level governmental office. Licensure contrasts with certification in that certification is typically voluntary, and hence, it does not prohibit the practice of a profession. With certification, consumers are given the choice to purchase certified or non-certified services. Furthermore, certification is often administered by private organizations such as professional associations and corporations. As a result, standards are not tied to state level offices and can be national or international thereby allowing a greater degree of mobility for practitioners.

Licensure, while enabling a more strict control on professional practitioners, comes with a number of drawbacks. Licensure is markedly more costly than certification to both consumers and practitioners [Cox 1990]. The act of restricting access to an occupation inherently decreases the supply of the resulting services thereby creating a tendency towards price increases. Furthermore, empirical studies have not shown an increase in the quality of licensed professional services and it is sometimes the case that quality actually decreases with licensure [Cox 1990]. Costs to practitioners include training costs and lost opportunity for those who are excluded from participation.

Licensure should be employed when the necessity for restricted practice outweighs the costs to consumers and practitioners of controlled supply of services. Such may be the case for synthetic biology where safety and security concerns are markedly high. Licensure would not only control the number of practitioners, it would also enable a mechanism for tracking them. This traceability could aid in the communication of important technical and safety information regarding synthetic biology as well as aid law

enforcement in detecting the source of safety issues after they occur. Such a licensure system would require the adoption of national, or even international, standards to ensure uniformity of standards as well as the occupational mobility of practitioners [Parker 2002].

The primary challenge of implementing an effective licensure system in synthetic biology would be to restrict practitioners in a manner that does not stifle important innovations that would provide societal benefits. That is a difficult task since it is not the case that innovations come only from accredited individuals and not from the general public at-large. A licensure system can never be perfectly designed to only exclude those who would cause harm. Furthermore, licensure does not guarantee higher quality of service amongst practitioners so the potential for accidental safety concerns is still very present. Further work is needed in this area in order to examine in greater detail the true costs and benefits of implementing such a system.

It is important to acknowledge that whenever a powerful new technology is dispersed into the general public there is a risk of wrongdoing and this risk may never be completely eliminated. Minimizing that risk may require more resources than state and federal governmental agencies have available to them. The general public could itself be employed in the battle against biocrimes. It is conceivable that the private sector could become involved in the fight against the misuse of biotechnology. We may one day have companies dedicated to combating synthetics pathogens using essentially the same business model as companies that currently fight computer viruses (such as Norton and

Symantec). But to enable this, technical information on synthetic biology would need to be free and open. That same openness that would result in the proliferation of this technology may be harnessed to protect the general public from its misuse.

5.2.3 *Nonmaleficence Oversight Issues in the Private Industry*

Challenges that synthetic biology will likely present to the U.S. product regulatory system can be viewed through two stress factors: increased industrial scale and increased product complexity. As synthetic biology transfers biotechnology from the realm of a relatively small number of scientists to vast legions of engineers, we can expect the number of new product introductions to increase dramatically. Regulatory agencies will be required to scale up appropriately to avoid either the approval of unsafe products for market introduction or the creation of a bottleneck that prohibits beneficial products from entering the marketplace. This represents added economic costs to society in the form of tax payments or lost opportunity from products unnecessarily trapped in the product approval process.

This is a particular concern given lessons learned on the difficulty of containment of bioengineered products from the StarLink corn case. StarLink corn received approval for animal feed only yet the corn readily spread into the human food supply [Taylor 2003]. Another example is the recent case of so-called “PharmaWater”, where “a vast array of pharmaceuticals including antibiotics, anti-convulsants, mood stabilizers and sex hormones have been found in the drinking water supplies of at least 41 million Americans” [Donn 2009]. These cases demonstrate that technological advancements are

often accompanied by unforeseen costs that are borne by all of society and nature. This problem is exacerbated by the fact that products resulting from synthetic biology will be amongst the most complex and cutting edge products to face the regulatory system. We simply cannot foresee and test experimentally, all the long-term effects that will result from the release of such novel organisms into the environment. Therefore, regulators should plan on scaling-up efforts to monitor and enforce standards on the containment of bioengineered organisms.

Regulators and accompanying resources will not only have to scale in number, they will also be required to advance in scientific knowledge. Future biotechnology products could include highly sophisticated algorithmic operations similar to electronic products that contain software. That increase in functional complexity could dramatically alter the behavioral response of an engineered organism to variations in sensory inputs, environmental conditions, or communications inputs. Current taxonomies of organisms may no longer be applicable in assessing safety based on "substantial equivalence" to previously approved products. Private entities seeking product approval must be urged to fully disclose internal algorithms and demonstrate adequate testing over all the possible conditions a product could encounter in usage. Testing is further complicated by considerations unique to biological organisms such as reproduction, evolution, and horizontal gene transfer.

Increases in complexity may invalidate one of the assumptions upon which the current U.S. regulatory system is based – that risks of biotechnology are the "same in kind" as

risks associated with conventional organisms. The ability to program functionality into an organism in a manner similar to computer software could open nearly limitless possibilities for human engineering. We may no longer be secure that past experience with living things provides adequate guidelines for assessing risk. Future regulators may not be able to justify safety based on "substantially equivalence" to previous biotechnology products. "Process", rather than "product" may need to be taken into consideration by specifically reviewing the methods used to develop and test algorithms embedded into living organisms.

5.3 *Beneficence*

There is great potential for synthetic biology to deliver benefits to society. Although specific outcomes may be impossible to predict, advances are anticipated in improved medicine, chemical manufacturing, food production, environmental remediation, and energy production. Synthetic biology also has the potential to spur economic growth by scaling up the biotechnology sector in a manner similar to the dramatic rise of the semiconductor industry. Competitive market forces can create powerful industries that harness basic scientific knowledge to deliver affordable products in mass production. Does public policy have a role to play in determining what products should be targeted by industry and in enabling the early adoption of those products?

To examine this question, this section focuses on the use of synthetic biology in developing cost-effective and environmentally friendly biofuels. As stated previously in Chapter 2, challenges remain in developing biofuels that are both ecologically benign

[Wald 2007] and cost effective [Stephanopoulos 2007]. Climate change due to the accumulation of atmospheric greenhouse gases resulting from the burning of fossil fuels is prompting calls for "Apollo program" scale efforts to overhaul U.S. and global energy policies [Sokol 2007]. Economic development now comes with the qualifier of multigenerational environmental sustainability [Kate 2005]. Further justification for biofuels come from calls for U.S. energy independence from regions of political instability and global price shocks [Yergin 2007].

One policy intervention to spur the development of beneficial products from industry is the use of subsidies. Heavy government subsidization of basic commodities has many critics. Economists state that subsidies can distort markets and create dead weight losses in consumer and producer surpluses [von Massow 1989]. Corn-based ethanol subsidies in particular have been the target of recent criticism for raising overall food prices [Sauser 2007] although this comes with the benefit of increased farm income [USDA 2007]. International development economists contend that subsidies hurt poor countries by creating an unfair advantage for richer countries in trade relations [Cassel 2002]. Based on these claims one might argue for prohibiting subsidies for new biofuels and let market forces only be the sole determinants of product outcomes.

However, existing subsidies are currently established for the product with which the next generation of biofuels will compete: conventional fossils fuels. These subsidies, both direct and indirect, include reduced corporate tax rates, lowered gasoline sales taxes, public funding of infrastructure, and externality costs of environmental degradation (e.g.

pollution and greenhouse gas emissions) [UCS 1995]. Some also argue that a sizeable portion of military defense spending should be considered an oil industry subsidy because it is used to provide security in regions, such as the Middle East, that are of primary U.S. interest due to demand for oil [Delucchi 2007]. Based on these arguments the next generation of biofuels will enter a market where the entrenched incumbent, oil producers, are heavily guarded by existing public subsidies. The essential question then changes from "should biofuels be subsidized?" to "how do we level the playing field to enable biofuels to compete with fossil fuels?"

It is worth repeating that considerable challenges remain in creating the microorganism that enables the mass deployment of environmentally benign biofuels that can compete in the market with conventional gasoline. It cannot be predicted when, or by whom, the discoveries will take places. It is therefore unwise to pick specific players as likely winners but rather to ensure a large playing field to increase the likelihood of success. That playing field contains elements such as basic technology, equipment, financing, and research labor. Open access to information regarding all aspects of synthetic biology can serve to quicken the pace of breakthrough advancements. Research grants in synthetic biology can enable the training of future scientific and engineering labor forces as well as encourage the development of specialized research and manufacturing equipment. An open commitment to synthetic biology may also encourage private sector financing of small businesses pursuing the development of biofuels.

When the next generation of biofuels become available it is critical that markets are leveled between conventional oil and the biofuel substitutes. Biofuel should be subsidized enough to counter existing oil subsidies, both direct and indirect. Public policy has a strong role to determine the complete costs of markets externalities related to fossil fuels, including environmental and other social costs such as the U.S. military. A cap and trade system for pollution and greenhouse gases may help determine externality costs by providing a market mechanism to determine the price of carbon emissions. And given the recent experience with corn-based ethanol in the U.S. where unanticipated environmental degradation, such as excessive water usage, occurred [Chiu 2009]; environmental and associated with new biofuels must be taken into account in assessments of total societal beneficence.

5.4 *Justice*

The primary policy issue in synthetic biology with regards to justice is the appropriate distribution of the benefits and risks of the technology to the general public. Distribution of benefits comes in two forms: access to products resulting from synthetic biology as well as access to its socioeconomic benefits.

An important aspect of just distribution of products is affordability. If synthetic biology follows a "Moore's law" trajectory, where product prices decrease at an exponential rate, a broad swath of the general public could reap huge benefits from competitive market forces. On the other hand, monopolistic behavior by private corporations could confound affordable product pricing through the control of key intellectual property or excessively

aggressive business practices. High market prices can also result from supply shortages in the form of raw materials, labor, technology, and physical capital.

Of particular concern is the delivery of life-saving drugs and therapies to those who are most in need, especially during the initial onset of synthetic biology before market forces have to had ample time to drive down prices. Those who are most in need of a treatment cannot be assumed to coincide with those most capable of paying it. There may be a strong role for public policy to help identify poverty-stricken individuals who can benefit from advanced biotechnology products as well as subsidize their treatments to mitigate a public failure.

A central issue with regards to justice is patent policy. Intellectual property rights are set forth in the U.S. Constitution, which directs Congress "To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries" [US Constitution 1787]. This statement makes clear that the purpose of securing intellectual property rights are to serve the public by providing an incentive to practitioners of "Science and the useful Arts" to make "Discoveries" that benefit society and that those benefits will best serve the public if that "exclusive right" is given for "limited Times" only. That is, the public is best served when the results of creative invention in the long term become readily accessible to everyone in the general public at affordable prices.

The case of pharmaceutical drug pricing provides a real world example for assessing the justice level of patented technology. Resnik [2004] argues that the current patent system is just from a Rawlsian perspective because it respects the property rights of inventors and benefits the least-advantaged members of society in the long run by spurring the development of new technologies. In the absence of a system for protecting intellectual property rights, an inventor has no economic incentive for developing medical solutions that improve the health and well being of the general public. Resnik acknowledges, however, that during the initial period of exclusivity guaranteed by U.S. patent law (20 years) that prices, and therefore, accessibility by all members of the public to technology benefits may be limited.

Some practical considers can work to confound this issue. As stated in Chapter 4, the age of invention in biotechnology has occurred after the creation of the Court of Appeals for the Federal Circuit, which tilted the playing field in favor of patent holders rather than patent challengers. Furthermore, there is no absolute basis for deeming the patent exclusivity period at 20 years (although Resnik points out that the average time to develop and obtain market approval for a new drug is 10 years so there is a justifiable downside to having a patent duration that is too low [Resnik 2004]). Realities of market conditions also are a strong determination of drug pricing. When patents expire, in theory, generic equivalents enter the market and drive prices downwards. There is evidence, however, that often generics prices can become tied to prices of branded originators due to such factors as brand loyalty, ineffective insurance policies, and product differentiation [Kanavos 2008].

The case of emerging generic biologics is particular relevant to the future of synthetic biology. Biologics are biological products that are derived from living organisms and, like the products of synthetic biology, will be more complex, more difficult to manufacturer, and more difficult to accurately classify than conventional pharmaceuticals that are based on more chemical synthesis. Grabowski et al. [2007], has performed projections for the future prices of generic biologics that have had recent patent expirations and has concluded that biologics prices will likely be tied significantly closer to their branded originators than conventional pharmaceuticals (see Figure 5.4.1).

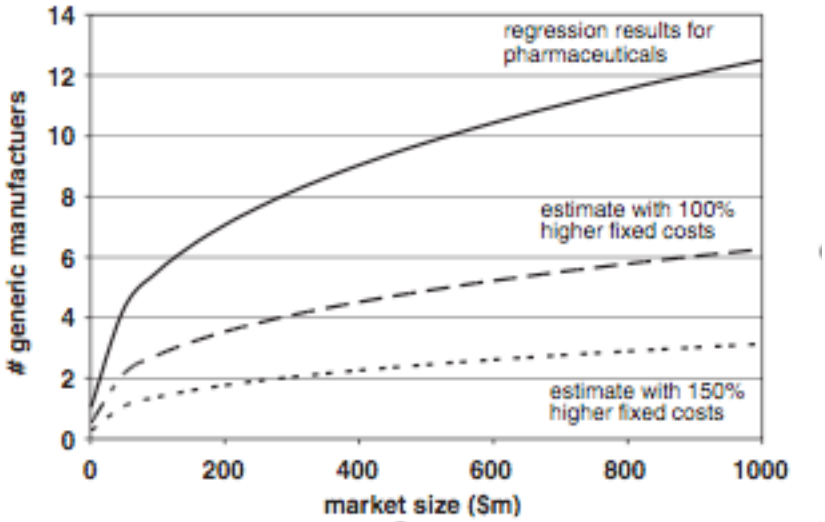


Figure 5.4.1. The Ratio of Generic Price to Branded Price as a Function of Market Size [Grabowski 2007]

This assessment points to a number of policy issues of concern. While the patent system can be considered in principle, to be just in the long term, there is potential for economic realities to create injustice, especially in the short term. Policy should consider means to enhance the accessibility of life-saving medicines resulting from synthetic biology to those most at risk and without adequate financial means. This may emerge as subsidies or perhaps even temporary suspensions of patent exclusivity in the case of large-scale emergency outbreaks. For example, such an emergency provision is provided for internationally by the Trade Related Aspects of Intellectual Property agreement, which is administered by the World Health Organization [Resnik 2004]. Of particular concern are specific segments of society where poverty is prevalent, such as dense urban areas and sparsely populated rural areas.

Another policy issue is enabling competitive market forces to drive down the prices of products resulting from synthetic biology once patents expire. To achieve this, regulators

must precisely define what constitutes “substantial equivalence” so that potential suppliers of generics can navigate the product approval process efficiently. This promises to be a difficult challenge given the cutting edge complexity the next generation of biological products and may require the development of new means of classification. There may also be a policy role to ensure that health insurance providers encourage the use of low-priced generics to ensure that brand loyalty and slight product differentiation do not result in “price stickiness” to originators.

With regards to public access to the technology of synthetic biology itself, policy should consider open access to information and its impacts on security concerns. Ideally, future practitioners should have ready access to the tools of synthetic biology to enable them to invent solutions to societal problems and patents on overly broad claims and basic technical knowledge should not be allowed. These are critical issues for the U.S. Patent and Trademark Office as well the overall U.S. court system, especially the Court of Appeals for the Federal Circuit. Along this line there may be policy roles in preventing shortages of inputs beyond technological knowledge such as the availability of raw materials, trained professional labor, and manufacturing capital equipment. Policy can potentially alter the costs of raw materials through trade agreements, provide a force of skilled labor through educational programs, and encourage the building of manufacturing capabilities through tax incentives.

Chapter 6:

Conclusions

Emerging technologies such as synthetic biology present a challenge to policy makers. On the one hand, these technologies have yet to demonstrate their effects on society. On the other hand, they present potential for creating both benefits and harm to humans and the environment. Since direct experience with products utilizing these technologies lies in future, we must rely on experience gained from other related technologies in order to anticipate societal impacts and not be caught off guard by the swiftness with which technology can often proliferate.

This work identifies policy issues through a principle-based ethics framework. Semiconductor technology and first generation biotechnology are identified in Chapter 2 as closely related technologies that offer past experience with policy issues. Contrasting semiconductor technology with biotechnology presents the limits of this type of examination and points out differences in the severity of policy issues associated with each technology. The review of early research efforts presented in Chapter 1 helps determine overall technology capabilities, which in the case of synthetic biology are the dramatic increase in both the scope and sophistication of biotechnology products. The use of ethics principles in Chapters 4 and 5 enables the examination of societal issues associated with synthetic biology.

Based on this analysis, this chapter discusses both general conclusions regarding the potential impacts of synthetic biology as well as specific policy issues.

6.1 *General Conclusions*

It is clear from the review of research in synthetic biology in Chapter 1 that researchers are attempting to place genetic engineering on the same exponential development trajectory that semiconductor and information technology have experienced through the standardization of engineering and manufacturing methods as well as the adoption of an open access approach to technology development. Thus, one of the basic goals of synthetic biology is to lower the economic barriers to entry into genetic engineering for the scientific and engineering community.

It is not surprising that researchers in synthetic biology are drawing inspiration from the semiconductor industry. Chapter 2 showed how synthetic biology and semiconductor technology share commonalities in basic molecular scale component integration as well as in information processing. These commonalities are being exploited to justify a similar approach towards engineering standardization between semiconductors and synthetic biology. If this is successfully achieved, synthetic biology has the potential to dramatically scale both the quantity and complexity of genetically engineered products.

Future practitioners of genetically engineering may include amateurs in the general public due to the open nature of engineering information and the lowering of economic barriers to entry. The future may see the rise of “garage biology” where amateur

practitioners create living organisms using computers and inexpensive laboratory equipment thereby paving the way for a new generation of “biohackers”.

Chapter 2 identified key contrasts between synthetic biology and semiconductor technology. Risks associated with synthetic biology may far exceed risks associated with semiconductor technology due to the inherent unpredictability and mobility of living organisms and their inherent capability to reproduce, evolve, transfer genetic material, and interact with the environment. Heightened risks also may exist due to the ability of living organisms to interact directly with humans.

If researchers are successful, synthetic biology has the potential to impact nearly every aspect of human society. Potential applications are broad ranging, including advances in medicine, food production, fuel production, environmental remediation, and chemical production. As with semiconductors, many applications could emerge that cannot currently be foreseen by examining today’s research efforts.

6.2 Discussion of *Policy Issues and Options*

The following is a summary of policy issues identified in the analyses presented in Chapters 4 and 5, once again organized by the ethical principles of autonomy, nonmaleficence, beneficence, and justice.

6.2.1 *Autonomy Issues*

The principle of autonomy requires that the general public be fully informed on the usage of synthetic biology technology to the greatest extent possible to enable them to make autonomous choices. Much experience has been gained with the first generation of bioengineered foods where adequate product labeling and containment presented much controversy. In accordance with this principle oversight policy could require producers of foods and other products to utilize modern information technology, such as Internet websites, to provide accurate and detailed information on the use of genetically engineered ingredients. The information should be adequate for consumers to make informed autonomous decisions regarding health and ethical values. The information would also need to be presented in a standardized format and be comprehensible by the general public.

Synthetic biology will offer future bioengineers with a vast tools set to create exotic biological products. That sophistication presents untold opportunities for innovation that could be used with nefarious to entice consumers to buy products. As one example of how regulatory agencies might specifically protect consumers from violations of autonomy, oversight policy could invoke a ban on the use of genetic engineering to create food ingredients that can be considered addictive or in some way manipulates consumers to form dependencies on genetically engineered ingredients.

Currently there exists little awareness of synthetic biology in the general public. To the extent possible oversight policy should, through modern information technology, engage the public in discussions regarding the rapidly increasing usage and powerful capabilities

of synthetic biology. This could be achieved through the use of mass media such as television, radio, and (perhaps most forward looking) the Internet.

6.2.2 *Nonmaleficence Issues*

The principle of nonmaleficence requires that practitioners of synthetic biology refrain from causing intentional harm to persons and the environment. Public policy needs to consider nonmaleficence issues as they pertain to both the general public and with private industry.

A singular focus on maleficence may lead one to conclude that technical information regarding synthetic biology should be highly restricted in order to avoid harmful misuses of the technology. However, in light of the vast potential for beneficial uses of synthetic biology, restricting information could be viewed as causing harm by withholding lifesaving products from benefiting society. Therefore, one option is for oversight policy to maintain an open access policy towards databases of genomic sequences, yet form a "tiered" criminal policy towards misuses, such as biocrimes committed by the general public. The tiered policy would distinguish casual "biohackers" from more malicious criminals that seek either direct harm to persons and the environment or personal gain through motivations such as finance or political ideology.

Technical information that could result in harmful uses of synthetic biology may inevitably enter the realm beyond federally funded research. The NIH has formulated

research safety and security guidelines. A policy that might be effective is to encourage professional research associations to disseminate these guidelines as a form of self-regulation. Federal agencies could maintain databases of pathogens developed by synthetic biology with the current CDC/APHIS select agents and toxins list serving as a starting point. A further extension of current policy into the general scientific and engineering communities could include the promoting of cautionary procedures regarding the National Research Council's "seven experiments of concern" with research involving pathogens [NRC 2004]. The goal would be to extend NIH policy further beyond the reach of Federally funded research. Also applicable in this regard would be the formation of Institutional Biosafety Committees within any private entity that is engaged in research or production involving synthetic biology. Furthermore, NIH standards defining microorganism risk groups (RG1 through RG4), as well as biosafety levels (BL1 through BL4) for determining containment requirements, could be extended into privately funded research and production.

With regards to private industry, the capabilities of Federal regulatory agencies may need to be adequately scaled to deal with a rapid increase in both the number of products and the complexity of products that utilize genetic engineering. To aid in the risk assessment of bioengineered products, Federal agencies may need to develop more advanced "process oriented" means to perform risk assessments of genetically engineered products as they pertain to human and environmental health. This may be necessary to combat the aggregate environmental effects of a sudden increase in bioengineering activities brought on by synthetic biology. As highly engineered microorganisms and genetic material

accumulate in the environment, adverse effects could occur that may not have been foreseeable by risk assessment performed on a product-by-product basis by multiple regulatory agencies. Regulatory oversight may be required to adopt a more holistic approach to bioengineering that views risks to humans and the environment from a broader lens than is currently present with the patchwork structure of current policy. One possible approach is to charter, one agency, such as the EPA, with this holistic perspective and endow them with overarching authority to regulate the whole of bioengineering. However, this may prove to be difficult in practice since a more hierarchical approach to oversight could lead to regulatory logjams or high cost to developers.

It might also be highly advantageous for regulatory agencies to develop more advanced taxonomies of genetically engineered organisms to aid in a more accurate and efficient means of determining "substantial equivalence" to previously approved products in order to keep unsafe products from entering consumer markets as well as quickly give market approval to important new products. It may also be of great benefit to develop detailed standards for the monitoring and containment of genetically engineered organisms.

6.2.3 *Beneficence Issues*

The principle of beneficence requires practitioners of synthetic biology to seek outcomes that provide benefits for society. Federal policy can help achieve this by determining a set

of national priorities for synthetic biology technology that provide the greatest public beneficence.

The onset of the semiconductor industry serviced the national priorities of its day through heavy Federal spending on research and infrastructure in national defense. One example of a national priority of today is dealing with climate change from the use of fossil fuels. Much of current research in synthetic biology focuses on the use of engineered biological organisms to lower the cost of biofuel production. Federal investment could enable the development of the next generation of biofuels as well as train professional labor forces and build critical capital infrastructures in synthetic biology

With regards to markets, while artificially creating low prices for products is not economically viable practice, it may be justifiable to subsidize efforts that address the national priorities to the level that offsets subsidies and externality costs for competing products, such as fossil fuels. To ensure that benefits are achieved, it could be of great usefulness to determine accurate models for determining the true externality costs for national priorities.

6.2.4 *Justice Issues*

The principle of justice requires that the benefits of synthetic biology be appropriately distributed to all sectors of society. Open access policy towards databases of genomic sequences and information regarding synthetic biology technology could enable

accessibility to all persons and organizations. In contrast, restrictions of technical information could likely serve to exclude large segments of the population from the economic fruits of synthetic biology. However, it must be noted that security issues stand in stark contrast. Open information access, in a sense, places considerations of justice against considerations of nonmaleficence. The resolution of this conflict may pose the greatest challenge of all for policy makers if both ethical principles are to be respected.

Another important aspect of just technology access is intellectual property protection. The approval of overly broad patent claims on basic technology in synthetic biology could restrict future innovations. This is especially important when one considers that synthetic biology will come of age in the more "patent holder friendly" era subsequent to the 1982 formation of the Court of Appeals for the Federal Circuit.

Product pricing is an important justice concern as, generally speaking, affordability determines the breadth of access to products. Public policy could, where possible, encourage competitive market forces to minimize prices for products resulting from synthetic biology. Where beneficial products are not accessible it may be necessary to subsidize new, medical treatments for life threatening illnesses that, for some, are prohibitively expensive. This would enable product access to those who are most in need. Of specific concern are products that are heavily protected through patents and are priced highly through monopoly power. On occasion it may be necessary to allow for the temporary suspension of patent rights in cases where emergency treatments are required. And finally, regulatory agencies may consider policies that encourage the market entry of

generic products after the expiration of key patents in order to allow competitive market forces to decrease product pricing.

6.3 *Summary*

Synthetic biology promises to be a transformative technology that benefits humans and the environment in far-reaching ways, many of which may be difficult to foresee at this time. If the rapid rise of semiconductor technology is to be used as an example, we can expect those impacts to occur swiftly. However, synthetic biology promises to carry with it certain unique risks stemming from the ability of biological components to proliferate into and interact with the natural world. Minimizing risks and encouraging societal benefits requires us to adopt a broad perspective to view synthetic biology in its entirety. A broad ethical framework offers one means of achieving this. And given the swift pace at which technology can advance, we may now have the only opportunity to steer the course of synthetic biology in alignment with human values.

References

- Ajo-Franklin C., Drubin D., Eskin J., Rational Design of Memory in Eukaryotic Cells, Genes & Development, 21:2271-2276, July 22, 2007
- Aleksic J., Bizzari F. Cai Y., Davidson B., de Mora K., Ivakhno S., Seshasayee S., Nicholson J., Wilson J., Elfick A., French C., Kozma-Bognar L., Ma H., Millar A., Development of a Novel Biosensor for the Detection of Arsenic in Drinking Water, IET Synthetic Biology, Vol. 1, No. 1-2, 2007
- American Public Media, "History of Genetic Engineering", http://americanradioworks.publicradio.org/features/gmos_india/history.html, accessed June 3, 2009
- Anderson J., Elizabeth J., Arkin A., Voigt C., Environmentally Controlled Invasion of Cancer Cells by Engineered Bacteria, Journal of Molecular Biology, 355, 619-627, November 14, 2005
- Badger P., Ethanol From Cellulose: A General Review, Trends in New Crops and New Uses, ASHA Press, 2002
- Ball P., Genome Stitched Together by Hand, BioEd online, January 24, 2008, http://www.bioedonline.org/news/news-print.cfm?art=3753, accessed January 6, 2009
- Baker D., Church G., Collins J., Endy D., Jacobson J., Keasling J., Modrich P., Smolke C., Weiss R., Engineering Life: Building a Fab for Biology, Scientific American, June 2006

- Beauchamp T., Childress J., Principles of Biomedical Ethics, Sixth Edition, Oxford University Press, 2009
- BioBricks Foundation website, http://openwetware.org/wiki/The_BioBricks_Foundation, accessed June 18, 2009
- Bio-SPICE website, http://biospice.sourceforge.net/, accessed June 19, 2009
- Borrus M., Millstein J., A comparison of the U.S. semiconductor industry and biotechnology, Appendix C, pp. 531-541, Office of Technology Assessment 1984 Commercial Biotechnology: An International Analysis. Washington DC: U.S. Congress, 1984
- Boulanger A., IBM Systems Journal, Vol. 44, No. 2, 2005
- Boyle A., Decoding the DNA Decoder, MSNBC online, December 19, 2007, http://cosmiclog.msnbc.msn.com/archive/2007/12/19/525944.aspx, accessed June 6, 2009
- Bozeman B., Sarewitz D., Public Values and Public Failure in U.S. Science Policy, Science and Public Policy, Vol. 3, No. 2, pp. 119-136, April 2005
- British Broadcasting Company, Sasser Net Worm Affects Millions, http://news.bbc.co.uk/2/hi/technology/3682537.stm, accessed November 11, 2008
- Brown P., Race, Class, and Environmental Health: A Review and Systemization of the Literature, Environmental Research, Vol. 69, pp. 15-30, 1995
- Bugl H., Danner J., Molinari R., Mulligan J., Roth D., Wagner R., Budowle B., Scripp R., Smith J., Steele S., Church G., Endy D., A Practical Perspective on DNA Synthesis and Biological Security, December 4, 2006, http://pgen.us/PPDSS.htm, accessed September 15, 2009

- Burkhardt J., Agricultural Biotech Ethics at 25: Lessons Learned (and not learned), Presented at The First International Institute for Food and Agricultural Conference on Nanotechnology, October 26-27, 2005, https://www.msu.edu/~ifas/presentations/Jeffrey_Burkhardt.pdf, accessed September 26, 2009
- Calkins M., They Shoot Trojan Horses, Don't They? An Economic Analysis of Anti-Hacking Regulatory Models, The Georgetown Law Journal, Vol. 89:171, November 2000
- Carlson R., The Pace and Proliferation of Biological Technologies, Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science; Vol. 1, No. 3, August 2003
- Cassel A., Why U.S. Farm Subsidies are Bad for the World, Philadelphia Inquirer, May 6, 2002
- Cello J., Paul A., Wimmer E., Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template, Science, Vol. 297, August 9, 2002
- Chiu Y., Walseth B., Suh S., Water Embodies in Bioethanol in the United States, Environmental Science & Technology, 2009, vol. 43, no. 8, pp. 2688-2692
- Compaine B., Re-Examining the Digital Divide, The Digital Divide: Facing a Crisis or Creating a Myth?, July 2001
- Consumer Reports, State of the Net 2008, http://www.consumerreports.org/cro/electronics-computers/computers-

internet/internet-and-other-services/protect-yourself-online/state-of-the-net-2008/protect-yourself-online-state-of-the-net.htm, accessed November 11, 2008

- Cox C., Foster S., The Costs and Benefits of Occupational Regulation, Bureau of Economics, Federal Trade Commission, October 1990
- Dahm R., "The First Discovery of DNA", American Scientist, July-August 2008, Vol. 96, No. 4, pg. 320
- Delucchi M., The Cost of Protecting Oil in the Persian Gulf, Weekly Policy Commentary, November 5, 2007
- Digitivity, Electrical and Electronic Industry Overview, http://www.digitivity.com/industry-overview.html, accessed October 7, 2008
- Donn J., Mendoza M., Pritchard J., An AP Investigation: Pharmaceuticals Found in Drinking Water, Associated Press, http://hosted.ap.org/specials/interactives/pharmawater_site/day1_01.html, accessed May 18, 2009
- Eaton D., van Tongeren F., Louwaars N., Visser B., van der Meer I., Economic and policy aspects of 'terminator' technology, Biotechnology and Development Monitor, No. 49, p. 19-22, 2002
- The Economist, Ethanol, Schmethanol, September 27, 2007
- EE Times, October 10, 2005, Intel Enters Billion-Transistor Processor Era, http://www.eetimes.com/news/latest/showArticle.jhtml%3bjsessionid=1DC2O3C1H4F2OQSNDBESKHA?articleID=172301051, accessed October 7, 2008
- Elkin L., Rosalind Franklin and the Double Helix, Physics Today, pg. 42, March 2003

- ETC Group, Extreme Genetic Engineering: an Introduction to Synthetic Biology, January 2007
- ETC Group communiqué, Terminator: the Sequel, Issue #95, May/June 2007
- Federal Bureau of Investigation Internet Crime Complaint Center, 2007 Internet Crime Report, 2007
- Fiers W., Contreras R., Duerinck F., Haegeman G., Iserentant D., Merregaert J., Min Jou W., Molemans F., Raeymaekers A., Van den Berche A., Volckaert G., Ysebaert M., Complete Nucleotide Sequence of Bacteriophage MS2 RNA: Primary and Secondary Structure of the Replicase Gene, Nature, 260(5551):500-7 April 8, 1976
- Food and Drug Administration Center for Food Safety and Applied Nutrition, Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering, January 2001
- Food and Drug Administration, The Bioterrorism Act to 2002, http://www.fda.gov/oc/bioterrorism/bioact.html, accessed February 27, 2009
- Food and Drug Administration, Center for Biologics Evaluation and Research, Frequently Asked Questions, http://www.fda.gov/cber/faq.htm, accessed March 16, 2009
- Food and Drug Administration, Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering, January 2001 http://vm.cfsan.fda.gov/~dms/biolabgu.html, accessed May 1, 2009

- Forster A., Church G., Towards Synthesis of a Minimal Cell, Molecular Systems Biology, 2006
- Fox S., Spyware: The Threat of Unwanted Software Programs is Changing the Way People Use the Internet, Pew Internet & American Life Project, July 6, 2005
- Frederickson D., The Recombinant DNA Controversy - A Memoir: Science, Politics, and the Public Interest 1974-1981, ASM Press, 2001
- Friends of the Earth, The Need for Labeling, http://action.foe.org/dia/organizationsORG/foe/content.jsp?content_KEY=3008&t=2007_Genetically-Engineered-Food.dwt, accessed May 12, 2009
- Fung E., Wong W., Suen J., Bulter T., Lee S., Liao J., A Synthetic Gene-Metabolic Oscillator, Nature, Vol. 435, 5 May 2005
- Garfinkel M., Endy D., Epstein G., Friedman r., Synthetic Genomics: Options for Governance; J. Craig Venter Institute, October 2007
- Gibbs W., Synthetic Life, Scientific American, May 2004
- Golden F., The Pioneers of Molecular Biology: Herb Boyer, Time Magazine online, http://www.time.com/time/covers/1101030217/scdprofile2.html, February 9, 2002, accessed June 9, 2009
- Greenpeace International, Say No to Genetic Engineering, http://www.greenpeace.org/international/campaigns/genetic-engineering, accessed May 12, 2009
- Hall B., Ziedonis R., The Patent Paradox Revisited: an Empirical Study of Patenting in the U.S. Semiconductor Industry 1979-1995, RAND Journal of Economics, Vol. 32, No. 1, Spring 2001

- Hall H., BT Corn: Is It Worth the Risk?, The Science Creative Quarterly, http://www.scq.ubc.ca/bt-corn-is-it-worth-the-risk/, September 07 – April 08, Issue 3, accessed June 3, 2009
- Hamilton S., Hutchison C., Pfannkoch C., Venter J., Generating a Synthetic Genome by Whole Genome Assembly: ϕX174 Bacteriophage from Synthetic Oligonucleotides, Proceedings of the National Academy of Sciences, Vol. 100, No. 26, December 23, 2003
- Peter D. Hart Associates Inc., Awareness Of And Attitudes Toward Nanotechnology and Synthetic Biology, Project On Emerging Technologies, Woodrow Wilson International Center for Scholars, September 16, 2008
- Henry, The Court of Appeals for the Federal Circuit's Impact on Patent Litigation, June 2005
- von Hippel E., Democratizing Innovation, The MIT Press, 2005
- von Hippel, E., von Krogh, G. (2003). Open source software and the 'private-collective' innovation model. *Organization Science*, vol. 14, no. 2, pp. 209-223.
- Hoepman J., Jacobs B., Increased Security Through Open Source, Communications of the ACM, Vol. 50, No. 1, January 2007
- Horrigan J., Home Broadband Adoption 2008, Pew Internet & American Life Project, July 2008
- Huffman W., Rousu M., Shogren J., Tegene A., Should the United States Regulate Mandatory Labeling for Genetically Modified Foods?, Iowa State University, Department of Economics, Working Paper #02013, October 2002
- IEEE, IEEE Quick Facts, http://ieee.org/web/aboutus/home/index.html, accessed October 7, 2008

- iGEM website, About, http://2009.igem.org/About, accessed June 18, 2009
- Intel website, World's First 2 Billion Transistor Microprocessor, http://www.intel.com/technology/architecture-silicon/2billion.htm, accessed June 23, 2009
- International Consortium for Polynucleotide Synthesis website, http://pgen.us/ICPS.htm, accessed June 19, 2009
- International Risk Governance Council, Concept Note, Synthetic Biology: Risks and Opportunities of an Emerging Field, 2008
- Internet World Stats, World Internet Users and Population Stats, http://www.internetworldstats.com/stats.htm, accessed October 7, 2008
- J. Craig Venter Institute, J. Craig Venter Institute Researchers Publish Significant Advance in Genome Assembly Technology, December 4, 2008, http://www.jcvi.org/cms/press/press-releases/full-text/article/j-craig-venter-institute-researchers-publish-significant-advance-in-genome-assembly-technology/?tx_ttnews[backPid]=4&cHash=5d160ab67f, accessed June 9, 2009
- J. Craig Venter Institute website, Synthetic Biology & Bioenergy, http://www.jcvi.org/cms/research/groups/synthetic-biology-bioenergy/, accessed June 18, 2009
- Johnson C., Hackers Aim to Make Biology Household Practice, Boston Globe online, http://www.boston.com/news/science/articles/2008/09/15/accessible_science/, September 15, 2008, accessed January 16, 2009

- Kanavos P., Costa-Font J., Seeley E., Competition in Off-Patent Drug Markets: Issues, Regulation and Evidence, Economic Policy, July 2008
- Kates R., Parris T., Leiserowitz A., What is Sustainable Development?: Goals, Indicators, Values, and Practice, Environment: Science and Policy for Sustainable Development, Vol. 47, No. 3, 2005
- Kuo W., Compatibility and Simplicity: the Fundamentals of Reliability, IEEE Transactions on Reliability, Vol. 56, No. 4, December 2007
- Kuzma J., Besley J.; Ethics of Risk Analysis and Regulatory Review: From Bio- to Nanotechnology, NanoEthics, Vol. 2, No. 2. Pp. 149-162, 2008
- Kuzma J., Romanchek J., Kokotovich A. Upstream Oversight Assessment for Agrifood Nanotechnology: A Case Studies Approach Risk Analysis, Vol.28, No. 4, 2008
- Lambrianou A., Demin S., Hall E., Protein Engineering and Electrochemical Biosensors, Advanced Biochemical Engineering Biotechnology, Vol. 109, pp. 65-96, October 25, 2007
- Lovley D., Cleaning Up With Genomics: Applying Molecular Biology to Bioremediation, Nature, Vol. 1, October 2003
- LS9, Renewable Petroleum Technology, http://www.ls9.com/technology/, accessed June 16, 2009
- Luisi P., Toward the Engineering of Minimal Living Cell, The Anatomical Record, Vol. 268, pp. 208-214, 2002
- Lyu M., Handbook of Software Reliability Engineering, McGraw Hill, 1996

- Martens C., ‘Loverspy' program creator indicted, on the run, ComputerWorld, August 30, 2005, http://www.computerworld.com.au/article/138588/loverspy_program_creator_indicted_run?fp=16&fpid=0, accessed July 1, 2009
- von Massow V., Dairy Imports into Sub-Saharan Africa: Problems, Policies, and Prospects, May 1989, FAO Corporate Document Repository, http://www.fao.org/wairdocs/ILRI/x5459E/x5459e00.HTM, accessed April 28, 2009
- Mellman Group, Review of Public Opinion Research, Pew Initiative on Food and Biotechnology, November 16, 2006
- Meredith D., “Engineered Proteins Will Lead to ‘Synthetic Life’”, dukemed news, May 7, 2003
- Merritt R., Privacy Groups Boycott Intel Over Pentium III, EE Times, January 25, 1999
- MIT Technology Review, A Better Biofuel, April 3, 2007, http://www.technologyreview.com/Biotech/18476/, accessed June 16, 2009
- Montana J., Viruses and the Law: Why the Law is Ineffective, The Information Management Journal, October 2000
- National Institutes of Health, NHGRI Aims to Make DNA Sequencing Faster, More Cost Effective, http://www.genome.gov/19518500, October 2006, accessed March 25, 2008
- National Institutes of Health, NIH Guidelines for Research Involving Recombinant DNA Molecules,

http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm, accessed February 4, 2009, revised April 2002

- National Institutes of Health, Entrez Genome, http://www.ncbi.nlm.nih.gov/sites/entrez?db=genome, accessed June 6, 2009 (a)
- National Institutes of Health, Profiles in Science: The Marshall W. Nirenberg Papers, http://profiles.nlm.nih.gov/JJ/Views/Exhibit/narrative/biographical.html, accessed June 9, 2009 (b)
- National Research Council 2004, Seeking Security: Pathogens, Open Access, and Genome Databases, National Academies Press, 2004a
- National Research Council 2004, Biotechnology Research in an Age of Terrorism, National Academies Press 2004b
- National Select Agent Registry, Select Agent/Toxin List, http://www.selectagents.gov/agentToxinList.htm, accessed February 27, 2009
- Nature News, Genome Stitched Together by Hand, January 24, 2008, http://www.nature.com/news/2008/080124/full/news.2008.522.html, accessed April 23, 2008
- Nissenbaum H., How Computer Systems Embody Values, Computer, March 2001
- Nobel Prize, Frederick Sanger: Biography, Addendum May 2005, http://nobelprize.org/nobel_prizes/chemistry/laureates/1958/sanger-bio.html, accessed June 9, 2009
- O'Connell K., INTERNET LAW - FBI: In 2007 Internet Crime Netted $240 Million, Internet Business Law Services,

http://www.ibls.com/internet_law_news_portal_view.aspx?s=latestnews&id=2033, accessed July 2, 2009

- Office of Science and Technology Policy, Coordinated Framework for Regulation of Biotechnology, June 26, 1986
- Parker W., Bower W., Weissman J., Costs and Benefits of Practitioner Certification or Licensure for the Solar Industry, Presented at the IEEE PV Specialist Conference, May 2002, http://www.irecusa.org/fileadmin/user_upload/WorkforceDevelopmentDocs/CertificationorLicensure.pdf, accessed September 10, 2009
- Pew Initiative on Food and Biotechnology, Issues in the Regulation of Genetically Engineered Plants and Animals, April 2004
- Pickup J., Hussain F., Evans N., Rolinski O., Birch D., Fluorescence-based Glucose Sensors, Biosensors and Bioelectronics, pp. 2555-2565, November 21, 2004
- Pohorille A., Deamer D., Artificial Cells: Prospects for Biotechnology, TRENDS in Biotechnology, Vol. 20, No. 3,March 2002
- Portillo P., Reyes A., Salazar L., Menendez M., Garcia M., Tuberculosis 2007: From Basic Science to Patient Care, Chapter 4: Genomics and Proteomics, www.tuberculosistextbook.com, 2007
- Rai A, Boyle J, Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons. PLoS Biol, Vol. 5, No. 3), 2007
- Raju T., The Nobel Chronicles, The Lancet, Volume 354, Issue 9189, Page 1567, 30 October 1999

- Registry of Biological Parts website, http://partsregistry.org/Main_Page, accessed June 18, 2009
- Reid T., The Chip, Random House, 2001 edition, pp. 66-7
- Reza F., Chandran K., Feltz M., Heinz A., Josephs E., O'Brien P., Van Dyke B., Chung H., Indurkhya S., Lakhani N., Lee J., Lin S., Tang N., LaBean T., You L, Yuan F., Tian J., Engineering Novel Synthetic Biological Systems, IET Synthetic Biology, Vol. 1, No. 1-2, 2007
- Resnik D., Fair Drug Prices and the Patent System, Health Care Analysis, Vol. 12, No. 2, June 2004
- Rincones J., Zeidler A., Grassi M., Carazzolle M., Pereira G., The Golden Bridge for Nature: The New Biology Applied to Bioplastics, Polymer Reviews, Volume 49, Issue 2, April 2009
- Rizvi H., BIODIVERSITY: Don't Sell "Suicide Seeds", Activists Warn, IPS News, http://ipsnews.net/news.asp?idnews=32582, 2006, accessed August 26, 2009
- Rodemeyer M., New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology, Woodrow Wilson International Center for Scholars, Synthetic Biology Project, March 2009
- Rousu M., Huffman W., GM Food Labeling Policies of the U.S. and Its Trading Partners, Staff Paper no. 344, Iowa State University, September 30, 2001
- Sanger Institute, Pathogen Genomics, http://www.sanger.ac.uk/Projects/Pathogens/, accessed June 6, 2009

- Sauser B., Ethanol Demand Threatens Food Prices, MIT Technology Review, February 13, 2007
- Shapiro E., Benenson Y., Bringing DNA Computers to Life, Scientific American, May 2006
- Shrader-Frechete K., Nanotoxicology and Ethical Considerations for Informed Consent, Nanoethics Vol. 1, pp. 47-56, 2007
- Smyth S., Phillips P., Labeling to Manage Marketing of GM Foods, TRENDS in Biotechnology, Vol. 21, No. 9, September 2003
- Sokol D., An Apollo Program for Climate Change, Washington Post, June 22, 2007
- Spaeth, S., Haefliger, S., von Krogh, G., Renzl, B., Communal resources in open source software development, Information Research, Vol. 13, No. 1, paper 332, 2008
- Stephanopoulos G., Challenges in Engineering Microbes for Biofuels Production, Science, Vol. 317, February 9, 2007
- SynBERC 2008, http://www.synberc.org, accessed April, 28, 2008
- Synthetic Biology 4.0 website, http://sb4.biobricks.org/, accessed June 19, 2009
- Taylor M., Tick J., Post Market Oversight of Biotech Foods: Is the System Prepared?, Pew Initiative on Food and Biotechnology, April 2003
- Thompson P., Food Biotechnology in Ethical Perspective, 2nd Edition, Springer, 2007
- Transcontainer Project Website, http://www.transcontainer.org/UK/, accessed August 29, 2009

- Tu D., Lee J., Ozdere T., Lee T. You L., Engineering Gene Circuits: Foundations and Applications, Nanotechnology in Biology and Medicine, pp. 20-363:72, 2007
- Tucker J., Dual Use Dangers: Biotechnology and Global Security are Intertwined, Science Progress online, http://www.scienceprogress.org/2007/10/dual-use-dangers/, October 16th 2007, access August 31, 2009
- Union of Concerned Scientists, Subsidizing Big Oil (1995), http://www.ucsusa.org/clean_vehicles/vehicle_impacts/cars_pickups_and_suvs/subsidizing-big-oil.html, accessed April 24, 2009
- United States Constitution, Copyright Clause, Article 1, Section 8, Clause 8, 1787
- United States Department of Agriculture, Farm Income and Costs: 2007 Farm Sector Income Estimates, Net Farm Income, Up Over 50 Percent in 2007, Sets New Record, http://www.ers.usda.gov/Briefing/FarmIncome/2007incomeaccounts.htm, accessed April 28, 2009
- United States Department of Agriculture, Adoption of Genetically Engineered Crops in the U.S., Economic Research Service, http://www.ers.usda.gov/Data/BiotechCrops/, accessed July 1, 2009
- United States Environmental Protection Agency, Biosensors for Environmental Monitoring, http://www.epa.gov/heasd/edrb/biochem/env-monit.htm, accessed April 30, 2008
- United States Environmental Protection Agency, eCycling Frequent Questions, http://www.epa.gov/epawaste/conserve/materials/ecycling/faq.htm#howmuch, accessed September 25, 2009

- United States General Accountability Office, Personnel Security Clearances: An Outcome-Focused Strategy Is Needed to Guide Implementation of the Reformed Clearance Process, May 2009
- Venter J., A Life Decoded, My Genome: My Life, Penguin Group, 2007
- Vidal J., World Braced for Terminator 2, The Guardian, 1999, http://www.guardian.co.uk/science/1999/oct/06/gm.food2, accessed August 26, 2009
- Wade N., Scientist at Work/Kary Mullis; After the 'Eureka,' a Nobelist Drops Out, New York Times online, http://www.nytimes.com/1998/09/15/science/scientist-at-work-kary-mullis-after-the-eureka-a-nobelist-drops-out.html, accessed June 9, 2009
- Wald M, Is Ethanol for the Long Haul?, Scientific American, January 2007
- Weiss R., Challenges and Opportunities in Programming Living Cells, The Bridge, Winter 2003 (a)
- Weiss R., Basu S., Hooshangi S., Kalmbach A., Karig D., Mehreja R., Netravali I., Genetic Circuit Building Blocks for Cellular Computation, Communications, and Signal Processing, Natural Computing, 2003 (b)
- Whipps H., How a Monk and His Peas Changed the World, Live Science web site, http://www.livescience.com/history/080728-hs-mendel.html, July 28, 2008, accessed June 9, 2009
- Witten B., Landwehr C., Caloyannides M., Does Open Source Improve Security?, IEEE Software, September/October 2001

- World Health Organization, World Health Report 2007: A Safer Future, Global Public Health Security in the 21st Century, 2007
- Worldometers: World Statistics Updated in Real Time, http://www.worldometers.info/computers/, accessed October 7, 2008
- Yarris L., A Model Virus Could Mute the Effects of HIV, Berkeley Lab Science Beat, July 14, 2004
- Yergin D., Energy Independence, Wall Street Journal, January 23, 2007
- Ziedonis R., The Enforcement of Patent Rights in the United States: Insights from Cases Involving US Semiconductor Firms, Conference on New Research on the Operation of the Patent System, April 2002