Policy Initiatives for Safe Realization of Synthetic Biology's Power

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Executive Summary
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Synthetic biology promises to be one of the major innovating fields of this century and is poised to make impacts in some of the most significant problem areas. It has the potential to solve some of the world's most important problems, ranging from decreasing the cost of expensive therapeutics to weaning our dependence on foreign sources of energy. However with its great potential for positive societal impacts, also comes a great potential for misuse; of greatest concern is the potential for bio-terrorism. Additionally, the long-term sustainability of synthetic biology will depend upon correct structuring of intellectual property policy in the field.

To address the growing concern over the potential for bio-terrorism by small groups of individuals we propose a number of policy recommendations:

Create a centralized organization responsible for screening DNA synthesis orders.
Individuals intending to produce synthetically engineered pathogens will need to have the DNA for the organism synthesized by a gene synthesis company. Current DNA screening practices occur inside synthesis companies and are ineffective at identifying pathogenic orders. We propose the establishment of a centralized clearinghouse to screen orders. This clearinghouse will also be able to more effectively maintain a watch-list of pathogenic genes, proteins, people, and organizations. Finally a central organization will be able to more rapidly implement higher standards of screening as they become available.

Restrict access to the public databases of gene and protein sequences.
Currently the public can freely access *all* known DNA and protein sequences through online databases. Some of these sequences are pathogenic and could be used for bio-terrorism. We propose to restrict access to sequences deemed to have the potential for misuse.

Link the Recombinant DNA Advisory Committee (RAC) to the synthetic biology community for advice and safety.
The RAC was established in the 1970s during the advent of genetic engineering in order to provide safety standards and advice to the scientists. The organization therefore should be easily accessible to the synthetic biology community.

To address the concern that intellectual property laws will inhibit synthetic biology's potential power and innovation we propose the following:

Structure intellectual property to promote innovation with alternative licensing strategies.
Currently, intellectual property laws governing synthetic biology are largely an extension of those applied in traditional genetic engineering. It has been recognized, however, that synthetic biology needs to be evaluated independently. There is concern that current IP structuring may squelch the potential innovation within synthetic biology due to a rapidly accumulating number of patents. Synthetic biology relies upon the integration of many different parts and if all the parts are traditionally patented, the high royalty cost may offset the benefit to society in addition to dissuading innovation. Therefore, alternative licensing strategies should be implemented. These alternative strategies may include non-assertion, copyleft, or non-exclusive terms.

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I. The Industrialization of Biology

Synthetic biology is the field of science whose goal is the industrialization of biology. The industrialization of biology holds the promise of increased open innovation and the development of solutions to problems previously believed to be unsolvable by modern day biotechnologists. The purpose of this discourse is to both highlight the areas in which policy action should be taken to prevent or mitigate potentially negative implications of this science, while promoting and ensuring its potential for innovation. One way to depict synthetic biology's potential for innovation may be viewed in relation to the historical developments that occurred during the Industrial Revolution, which greatly impacted manufacturing processes.

Up until the late 19th century every single rifle produced would have been hand crafted; every single component would have been tailor made for use in that specific rifle, and would likely not function in any other rifle. While such tailor made goods may hold nostalgic value in consumers today, the process was needlessly expensive and time consuming to say the least. Things would rapidly change, however, when Eli Whitney proposed a remarkably simple, but revolutionizing, way to think about manufacturing: the use of interchangeable parts. Whitney developed manufacturing processes to make all the components of a musket by machine; thus, every part met a certain standard, possessed known characteristics, and most importantly, could be produced by an unskilled operator with little prior knowledge of the underlying processes.

While the U.S. Industrial Revolution is often overshadowed by the monolithic images of individuals such as Ford, Rockefeller, and Carnegie, the very heart of the industrial revolution was a small set of simple ideas. Concepts such as the assembly line, interchangeable parts, standards, and economies of scale were the true catalysts. These concepts all embodied the idea of ease of use: the movement from the tailor made to the mass produced, and with that the belief that society as a whole would benefit from a set of standards that promoted advances in new frontiers. We predict that synthetic biology will have a similar impact on society by providing a powerful technology that has immense potential for innovation. Following, we define the field, discuss its importance and finally elucidate areas where policy should be considered.

II. Synthetic Biology

While the term synthetic biology may appear to have only recently entered the lexicon of popular culture, its foundation has been in the works for the past quarter century. The term is often cited as first being coined in an editorial comment by Waclaw Szybalski in the journal *Gene* in response to the 1978 Nobel Prize being awarded for the discovery of restriction endonucleases:

> "The work on restriction endonucleases not only permits us easily to construct recombinant DNA molecules and to analyze individual genes but also has led us into the new era of synthetic biology where not only existing genes are described and analyzed but also new gene arrangements can be constructed and evaluated."[1]

It was not until the turn of the current century, however, that synthetic biology would come into vogue as a term describing the development of a new engineering discipline. In brief, synthetic biology is the design and construction of new biological parts, devices, in a standardized form that can be combined in a system for a specific application or purpose[2]. DNA, which composes the genetic sequences that encode all the functions of life, is at the root of synthetic biology. Synthetic biologists manipulate pieces of DNA, and insert these pieces into new contexts, producing novel characteristics and outputs. In this manner, entire pathways, circuits, and all the logic necessary to

regulate the connections between the various components can be dictated by the synthetic biologist at the DNA level. A parallel is often drawn to the logic systems developed by early electrical engineers during the development of computer and semiconductor industries, substituting binary code with genetic code. Bioinformatics and associated software is another central part of synthetic biology and are used to manipulate DNA sequence and protein structure.

One of the central goals in synthetic biology is the attempt to bring engineering principles into the realm of biology. This takes many forms, with clear parallels to the industrialization of manufacturing indicated above. As Drew Endy outlines in a 2005 article in the journal *Nature*, there are several key concepts espoused by synthetic biology[3]:

1. Standardization: by applying a standardized, easily interpretable system of metrics the costs of constructing biological systems are decreased and the field is open to non-specialists.
2. Decoupling: "It is useful to separate a complicated problem into many simpler problems that can be worked on independently..."
3. Abstraction: By hiding information and complexity the user approaches a problem without needing to know the background information about how a part was produced or how the part fits into the grand scheme of an organism.

In brief, biology is being industrialized to a level never imagined. This has been achieved by breaking the complexities of intracellular reactions and mechanisms into their basic DNA components. Once characterized, these components achieved a level of standardization, and the synthetic biologist gained a degree of intuition into how this part would function in a new context and in conjunction with other parts. As will be addressed below, this simple approach has generated a great number of success stories in just the past half decade.

A. Growth Trends in Synthetic Biology

If one were to examine the field of synthetic biology in the year 2000 there would have been no major successes to its name. The first papers published demonstrated proof of principle in scientist's ability to produce simple genetic circuits[4], and possessed little real world relevance or application. Fast forward to the year 2007 and the scene has changed dramatically. Research articles in synthetic biology frequently appear in some of the most prestigious journals, conferences devoted to topics in synthetic biology have developed[5], an International Genetically Engineered Machine Competition (iGEM) was established[6], and a registry for standard genetic parts was built[7]. While much of the above developments are at the research laboratory level, synthetic biology has begun to exit the research lab and start to produce real world results. Most notably, synthetic biology has been credited with enabling the production of precursors to the anti-malarial drug artemisinin at levels that reduce the final drug cost to levels affordable by developing nations[8].

The potential for synthetic biology to produce tremendous results has grabbed the attention of scientists, government funding agencies, as well as the venture capital community. The National Science Foundation provided funding for the Synthetic Biology Engineering Research Center[9] (SynBERC), a research institute solely devoted for the development of the field. British Petroleum recognized the potential in synthetic biologists to invigorate the biofuels industry in their decision to provide $500 million in funding to a consortium of researchers this year[10]. Current funding trends for synthetic biology research show no signs of abating, increasing the need for active discourse on potential problem areas in the field.

The trend possessing perhaps the most far reaching implications is the predicted movement of synthetic biology research out of the academic research lab and into the backyard garage of a "biohacker," which should not be read with a negative connotation. This trend is akin to the

development of the modern day software industry out of the garages of young inventors in silicon valley during the mid to late 20th century, where standardization of computers and their language (in binary code) allowed for "hackers" or software junkies to custom build programs with specific, desired functionality *in their homes*. In the case of synthetic biology, movement away from the academic lab, in which there is an established regulatory framework already in place, will serve to both promote innovation, but will also exacerbate the potential for misuse of the technology.

There exist three primary drivers in the development of the biohacker mentality and industry. First, there needs to be a means for biohackers to obtain customized sequences of *DNA at low cost*. This need is provided for by gene synthesis companies. In the past seven years, the cost per base pair of synthesized DNA has dropped by an order of magnitude, and some scientists believe that costs will drop by an additional order of magnitude within the next few years[11]. A typical part, having 1000 base pairs (the unit for measure DNA length), costs around $1000 and takes two weeks time to produce today; however, within a few years time the same sequence will cost around $100 and take a few days to produce. Second, the establishment and increase in size in the Registry of Standardized Biological Parts at MIT creates a nexus of *easy to use information* that aid in construction of biological devices. This repository is fast becoming the Home Depot of the synthetic biology community: a single location that possesses both the tools and parts for do-it-yourself projects. In addition to the tools and parts the MIT registry provides, there is access to the experts in the field who designed, tested, and use the parts in their research. Finally, the predicted rise in the biohacker community will likely be spurred by access to online information on how to construct some of the various pieces of equipment needed for routine genetic manipulation. For example, the chemical biology wiki through the American Chemical Society provides the necessary information to produce many standard pieces of equipment used in today's biological laboratories[12].

III. Policy Discussion

It should be stressed that much of the policy solutions that address synthetic biology have to an extent been formulated from best practices that were naturally adopted by synthetic biologists and have been birthed from practices in genetic engineering. To date, there exists little regulatory or policy framework specifically guiding synthetic biology. There exist a number problems that are highly specific to the technologies advanced by synthetic biology and are not covered in the existing policy framework. Here we identify two issues that have the most profound implications: bio-terrorism and intellectual property.

Current Synthetic Biology Policy: Bio-terrorism

While the rise of the biohacker community has not been realized to date, there is still significant impetus for discussion today on the implications of synthetic biology. In the past five years the DNA encoding two lethal virus was synthesized (poliovirus in 2002 and 1918 influenza in 2005)[13,14]. While some synthetic biologist would claim that this research was not synthetic biology at all – and just customized DNA synthesis – these events have been inextricably linked to the field. But what should be recognized is that both events were scientific projects in established research institutions; the real potential for harm exists from outside the Ivory Tower. In 2006, a correspondent from *The Guardian*, who was not affiliated with any research institution, ordered DNA from a standard gene synthesis company encoding part of the smallpox virus[15]. Although the biohacker community could provide an enormous positive, intellectual effort in synthetic biology and is often regarded as providing the impetus for significant open innovation, it also presents the greatest possibility for ill-deeds. One focus of our discussion will be how potentially malevolent synthetic biologists could be thwarted by improvements in and amendments to existing policy.

Current Synthetic Biology Policy: Self-Governance Model

Current best practices in the field with regard to bioterrorism largely sprang from community-based solutions proposed by Maurer, et al., prior to the convergence of synthetic biologists at the Synthetic Biology 2.0 conference[16]. We will refer to Maurer's recommendations as "self-governance model," as they are mainly organized at the level of the synthetic biology community. While a complete critique of the self-governance model is beyond the scope of this discussion, we will indicate key shortcomings in the model with regard to bio-terrorism and provide an alternative set of policy initiatives.

In order to address the rise in potentially hazardous experiments conducted by backyard biologists it has been noted that limited access to key pieces of technology may prove to be effective first steps. The self-governance model recognizes DNA synthesis as a primary avenue in which regulation and policy can intervene to mitigate the potential for hazardous situations; the policy guidelines include:

- Insist that all commercial gene synthesis companies adopt current best practice screening procedures.
- Create and endorse new watch-lists to improve industry screening programs.
- Endorse surveillance across multiple orders.

However, a decentralized, community-based method of regulation has inherent drawbacks that will lead to the failure of these recommendations and include: 1. lack of economic incentive and therefore participation, 2. lack of a governing organization to identify a watch-list, and 3. inherent flaws and evasion methods with screening.

1.Lack of Economic Incentive to Screen. There is a concern that sequencing facilities can be contracted by bio-terrorists to produce entire pathogenic organisms or provide the genes that encode for the production of hazardous small molecules. One proposed solution is to persuade gene synthesis companies to adopt screening protocols for all orders. Although some companies currently screen orders, or at least claim to,[17] others do not. This lack of screening identifies a flaw: there is no economic or policy incentive to conduct screening. All things equal, in a perfectly competitive market the non-screening company will gain an economic advantage by foregoing any screening process. Thus, one area for policy recommendation lies herein.

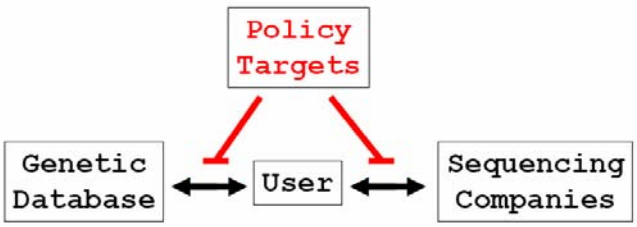
2. Lack of a Governing Organization to identify a watch-list.

A set watch-list for screening of sequences does not currently exist, and there is no consensus as to what should be included; the watch-list may only contain sequences, but it could also be formatted to contain persons and institutions. Today, the identification of harmful and non-harmful sequences is currently left to the gene synthesis houses. Inevitably this leads to differences in watch-lists between synthesis companies and discrepancies in how screening is undertaken. The implications are twofold; first, there will likely be sequences that will pass through one synthesis company's filter and not another's, and second, there is an economic incentive to create filters that are less effective and reduce the number of false positives that will need to be examined by hand. Even if a standard watch-list and computer program was created that all gene synthesis companies had access to, there may still remain significant discrepancies between screening procedures dependent upon the skill of the bioinformaticist running the program.

3. Inherent Flaws and Screening Evasion. Further, individualized screening by gene synthesis companies does not adequately address the issue of a single individual dividing an order between multiple companies. As a rule, the smaller the length of DNA sequence being ordered the more difficult it will be for a screening program to identify it as potentially harmful. Thus, a single individual can divide a gene that has a length of 1000 base pairs into 20 orders of 50 base pairs between multiple companies and it would likely go undetected as a potentially harmful sequence.

Alternative Policy Recommendations

A key component of our policy recommendations here is an understanding of how information flows between the synthetic biologist and third parties. As discussed in detail below, the two key points through which policy can intervene are in the flow of information between databases and users and then between users and DNA synthesis houses as illustrated.



Flow of information and the potential areas where policy can regulate the flow at two points: 1. restricting database access and 2. restricting sequencing

1. Creation of a Centralized DNA Clearinghouse

A solution that addresses the shortcomings in the self-governance proposal is the establishment of a central clearinghouse that serves as an intermediary in the flow of information between the user and the gene synthesis house. This solution addresses both the need for improved biosecurity in addition to recognizing limitations of screening performed by the gene synthesis companies. All orders would be processed through this agency prior to being sent to the synthetic biologist's synthesis house of choice, in essence giving the sequence a stamp of approval that it is believed to be safe. A central clearinghouse addresses the major issues with DNA sequence screening, by:

- Developing a standardized screening procedure, removing any discrepancies between those used by synthesis houses
- Removing the burden placed on synthesis companies that have no vested interest in developing and implementing improved screening efforts
- Addressing the need to screen across sequences that have been split into multiple orders
- Serving as a nexus for the development of more complete and effective watch-lists. These watch-lists should include both organism DNA and protein sequences that have been identified as pathogenic. Additionally, watch-lists of people or organizations may also be beneficial in reducing the number of screens that are necessary. For example, universities or large companies may be exempt from screening.
- Shortening the time between development and adoption of improved screening technologies and watch-lists.

The self-governance model suggests that a mere boycott of the non-screening synthesis companies will suffice in forcing their participation. However, we pose that this is not as effective without government intervention. While in the ideal world one would have a single clearinghouse with worldwide reach this remains difficult to perceive. A much more readily implemented strategy is the development of a U.S. based clearinghouse with the intent to expand internationally over time,

potentially to the UN. Further, if the clearinghouse is run by a government agency, there would be greater capacity to work with organizations such as the CIA and FBI.

2. Limited Database Access

A second chokepoint that may prove both more easily regulated and more effective than gene synthesis is the flow of information between the current, central DNA databases and the individual users. This strategy is grounded on the fact that any bio-terrorist who wanted to create a pathogen or harmful compound from scratch needs to start at the DNA sequence level. These sequences are all currently stored in central databases that are open to the public. The problem lies in that DNA sequences encoding functions innocuous in nature are side by side those that could be used for nefarious purposes. Currently, any individual can access the repository of all DNA sequences online, for example, the National Center for Biotechnology Information (NCBI[18]) serves as a popular gateway through which to obtain sequence information. Any individual can type "HIV-1" into the search engine and within seconds obtain the complete DNA sequence HIV. The same process is applicable for smallpox, ebola, and any other previously sequenced organism.

Our policy suggestion is to restrict access to the genetic information on organisms and proteins identified as potentially hazardous by the centralized watch-list. Access to the DNA sequences that are deemed innocuous should remain wholly open to the public. Access to the restricted sequences should only be open to individuals and institutions conducting active research on the organism/protein. Further, appropriate steps should be taken to restrict further dissemination of this genetic information outside of the direct research context.

This policy suggestion would likely raise the ire of many individuals concerned with restrictions on information and knowledge. However, it should be recognized that in the synthetic biology paradigm of engineering, abstraction enables all the information above the sequence level to flow without restriction. For example, the only people who need to know the exact sequence of DNA or amino acid bases in the smallpox sequence are the individuals who are constructing or studying the organism at this level; this represents a small minority of researchers and should include no lay persons. All other individuals are free to understand how the organism works, what its parts are, and other questions that will never necessitate having access to the genetic sequence. Thus, in practice there is little loss of knowledge by hiding the genetic information from view, only the ability to reconstruct the organism from scratch.

3.Hotline for Biosafety & Biosecurity – Extension of Recombinant DNA Advisory Committee

It is beneficial to have an organization dedicated to safety assessment as new technologies develop or new organisms are created or identified. The self-governance model proposes that a hotline be created for such issues. However, instead of reinventing or over-inventing tools for safety and security, it is important to take advantage of the existing infrastructure and policy that has arisen from genetic engineering. The Recombinant DNA Advisory Committee or RAC was developed in 1974 at the NIH for the purpose of evaluating technologies and providing safety assessments[19]. Synthetic biology is an extension of genetic engineering and relies upon many of genetic engineering's principles. Therefore, RAC is an obvious establishment for maintaining safety[2]. Although, reaching broader, global synthetic biology communities is important; therefore, it may be beneficial to extend RAC's reach into the level of the UN.

Much of the focus of synthetic biology policy has been toward what can be done to avoid terrorists from using the technology for harm. This outlook fails to address what harm can be done solely from good-intentioned workers or how the community will react to certain applications of synthetic biology. RAC is currently serving these purposes for genetic engineering and thus should be linked to the synthetic biology community.

Current Synthetic Biology Policy: Intellectual Property (IP)

In addition to the potential for bio-terrorism, there is an equally important discussion on intellectual property in the field. Since the rise of genetic engineering there has been extensive patenting of everything from genes, to the enzymes that are responsible for the replication of those genes, and any slight modification therein that could provide marginal improvements. The same patent frenzy has continued in synthetic biology, while more laboratories and industries are realizing the power of the field, they seek to snatch up all intellectual property. The buildup of patents is going to severely limit innovation, a negative side-effect that will be addressed and may be alleviated by policy or alternative licensing strategies.

Although the field of synthetic biology has the potential to show extreme innovation in the coming years and to aid in solving many societal problems, this innovation and power may be stifled if developments in the field are viewed in the normal domain of IP. Prohibitive royalties or exclusivity from licensing may squelch widespread use of the technology. Synthetic biology is essentially the confluence between bioinformatics or computation and DNA synthesis. Rei, et al, provide the first analysis of specific IP issues in synthetic biology in an article to appear in PLoS Biology[20]. The two different domains, when brought together in the form of synthetic biology Rei argues, are predicted to clash and create a "perfect storm" due to their different IP laws. Their analysis of synthetic biology identified the following key problem areas:

Patenting Non-obviousness in Biotechnology / Synthetic Biology. The model for patenting in biotechnology or gene synthesis has allowed for patents on gene products that may be obvious to a biologist, but not to the population at large. Therefore, a plethora of patents have been obtained and upheld in the courts. Thus, the "non-obviousness" clause has been stretched and relaxed.

Patenting Broadly in Biotechnology / Synthetic Biology. Many patents that have been issued for synthetic biology are broad and over-reaching. For example entire classes of molecules have been patented, like the zinc-finger DNA-binding proteins. Not only have they been patented for binding DNA, but also for performing Boolean computations with the protein's corresponding DNA.

IP & Software: Copyright or Patent? There has been a difficult history in interpreting the IP law surrounding software and whether it fits into copyright or patent law. Copyright law is for novel works of expression that cannot have functionality, while patent law is for inventions that have utility, but has excluded formulas and algorithms. Furthermore, people believe neither patent nor copyright law should be applied to software because it eliminates network effects and thwarts innovation that has been noted in open source programming.

To reiterate, the fear is that if synthetic biology is allowed to follow either the software model or the biotechnology model for IP, it will not benefit from its appealing characteristics that lend the field to open innovation and network effects, where each new invention or discovery can build and bolster the previous ones.

Alternative Policy Recommendations / Solutions for IP & Synthetic Biology

1. Open Parts Registry: Since the courts have held up patents in biotechnology that may seem obvious amongst the members of the field *and* broad, over-arching patents have been extended it seems the flaws may be used for a benefit. Specifically, if the right people patent broadly early, as seen with the MIT parts registry, and establish non-exclusive licensing that binds future users or contributors to give back to the registry and maintain non-exclusivity, then open-innovation and

continued progress may follow. Since synthetic biology relies upon the use of many different parts in conjunction to build a complex systems with specified functions it is imperative that the field maintains and complies with an open registry.

2. Non-exclusive, Non-assertion, Copyleft or Open Source Licensing: Copyleft licenses have been historically used by software programmers and have two innovation leveraging mechanisms. First, they make the software source code freely available and second, they require any improvements be distributed and licensed in the same way. Copyleft licenses essentially perpetuate the open-innovation software. The same principle could be applied to synthetic biology in order to dissuade the accumulation of highly restrictive patents.

Non-assertion clauses can be amended to obtained patents to stimulate innovation. The clauses can be crafted so that the patent holder will "not assert" the patent rights against anyone working toward innovation and development. In this way, even if patents are obtained, there terms can be manipulated in a way to promote innovation. An example of this would be the MIT parts registry that may persuade parts posters to abide by non-assertion.

Other variations of these solutions to maintain the value of intellectual property *and* to promote innovation in synthetic biology include non-exclusive licensing with low cost or open-source licensing.

IV. The Future of Synthetic Biology: Policy to Prepare for the Impact

Synthetic biology is a powerful, emerging field and holds the capacity to significantly impact society by providing solutions to some of the world's previously unsolvable problems. As the field continues to evolve, the fundamental tools of synthetic biology become less expensive and easier to use, requiring less knowledge from the user. Although this is excellent for promoting innovation and clever thinking from an ever expanding network of users, it also provides a greater potential for misuse of the technology.

Two key issues stand at the forefront of the debate on how synthetic biology will progress in the future. First, there are areas for policy improvement related to bio-terror that target the flow of information between user–database and user–sequencing facility. Second, we discussed how intellectual property should be implemented in a way that does not thwart innovation by using alternative licensing strategies. Throughout the discourse on how policy should play a role in synthetic biology it is imperative that policy is structured in order to protect the legitimate research being conduced by research institutions, promote the capacity for increased innovation by individuals, and all while concomitantly decreasing the potential for malevolent use.

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