

# Synthetic Biology: Navigating the Challenges Ahead

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## ABSTRACT

The emerging field of synthetic biology is broadly defined as the area of intersection of biology and engineering that focuses on the modification or creation of novel biological systems that do not have a counterpart in nature. Potential applications of this technology range from creating systems for environmental cleanup tasks, for medical diagnosis and treatment, to economical generation of hydrogen fuel. This technology is in its nascent state and there are a number of concerns surrounding its potential applications and the nature of research being performed. With the potential to create hitherto unknown "living organisms", it raises a number of challenges along different dimensions. This article reviews the current state of the technology and analyzes synthetic biology using different lenses: patentability, ethics, and regulation. It proposes a classification system for the products of synthetic biology and provides recommendations in each of the above areas (patentability, ethics, and regulation) in the context of this classification system. These recommendations include an improved framework for patentability testing, ethical principles to guide work in this area, a controlled approval process, and reference frameworks for regulation.

## INTRODUCTION

Synthetic biology is broadly defined as the area of intersection of biology and engineering,<sup>1, 2, 3, 4</sup> that is focussed on:

- "The design and fabrication of biological components and systems that do not already exist in the natural world"<sup>1</sup> and
- "The re-design and fabrication of existing biological systems"<sup>1</sup>

This article reviews the current state of the technology and analyzes synthetic biology using different lenses: patentability, ethics, and regulation. It presents a review of the technology behind synthetic biology and outlines the motivation and primary innovations in this area. It proposes a classification system for the products of synthetic biology and provides recommendations in each of the above areas (patentability, ethics, and regulation) in the context of this classification system.

Relevant case law and patent policy is also analyzed in the context of synthetic biology. This work proposes an improved framework for testing the patentability of the products of this technology. It also provides recommendations for patent guidelines in order to stimulate further

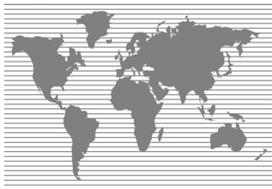
research. Often, new technologies in this area spark an ethical debate in their wake, and ethical frameworks need to be revised to accommodate their impact. In analyzing the ethical issues surrounding synthetic biology, this article outlines the primary ethical concerns, looks at the moral and ethical responsibilities of researchers in this area, and provides a set of principles to address the ethical concerns.

Potential applications of synthetic biology range from creating systems for environmental cleanup tasks, for medical diagnosis and treatment, to economical generation of hydrogen fuel. This technology is in its nascent state and hence there are a number of concerns surrounding its applications and the nature of research being performed. With rapid advances in the field of biotechnology in the recent past, there is also increased concern over the potential risks posed by some aspects of biotechnology. Synthetic biology is no different. This article analyzes the primary risks posed by research and creations in this field and addresses the regulatory needs in this area. It analyzes the role of regulation in this context and provides an appropriate framework to identify regulatory requirements.

Based on an analysis of these areas, some of the recommendations proposed in this article include an improved framework for patentability testing, ethical principles to guide work in this area, a controlled approval process, and reference frameworks for regulation.

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## TECHNOLOGY

This section reviews the technology behind synthetic biology and outlines the primary innovations in this area. It distinguishes synthetic biology from other technologies by identifying the key differentiators. The focus is on addressing the following questions:

- What is synthetic biology and what are its applications?
- How is synthetic biology different from other biotechnology initiatives?
- Can we develop a classification system for the products of synthetic biology?
- What are the major US and EU research initiatives in this area?
- What are the primary innovations that synthetic biology is building upon?

### Definition and Motivation

Synthetic biology is broadly defined as the area of intersection of biology and engineering,<sup>1, 2, 3, 4</sup> that is focussed on using synthetic raw materials to create novel biological systems. The scope of this article is limited to products without an identical pre-existing copy in nature, with the exception of the complete genome of an existing natural organism. The term “living organism” is sometimes used in the context of synthetic biology. Concerns related to the distinction between “engineered machines” and “living organisms” are outlined in the section on ethics.

A frequently cited comparison is that between designing electrical circuits and “designing” biological systems. In designing electrical systems, designers rely on well-characterized components with predictable behavior. Systems can be designed using these components and can be tailored to suit specific applications. Researchers in the area of synthetic biology aim to create such biological “building blocks” of component parts including well-characterized genetic circuits, analogues of input/output devices, sensing elements, and more. Furthermore, by making these genetic circuits (and networks) programmable, researchers can program new cellular and organism level behaviors.

The primary motivation for designing and characterizing these simple building blocks is twofold. On the one hand, they can be used to fabricate new programmable biological systems like novel microorganisms, for specific tasks that are beyond the scope of today’s technology. On the other hand, in the process of designing these elementary building blocks and attempting to synthesize biological systems from them, researchers hope to advance their knowledge of cellular processes and function. This, they hope, will

enhance their ability to control cellular processes.

A primary objective of this nascent research area is to create a programmable microorganism from scratch, as opposed to modifying components of living cells to achieve desired functionality. This distinguishes it from current genetic techniques that result in genetically modified organisms at the cellular level. Rather than splicing in a gene from one organism to another, or forcing a mutation in a genome for a specific purpose, synthetic biology is concerned with designing and building artificial regulatory elements into genomes or constructing a complete genome from scratch. By its very nature, this is a multidisciplinary field requiring the expertise of biologists, engineers, and systems specialists among others.

### Areas of Application

Potential applications of synthetically engineered biological systems range from simple every day tasks to ones that are well beyond the scope of today’s technology. Some sample applications include<sup>2, 5</sup>:

- *Detection of chemical pollutants and weapons:* Single cellular organisms could be designed to emit a signal (e.g.: fluorescence) in the presence of certain environmental toxins.
- *Environmental cleanup:* Similar to genetically engineered bacteria for degrading oil residues, synthetic organisms and their metabolic pathways could be engineered to breakdown specific environmental pollutants at a much lower cost than we see today.
- *Disease diagnosis and treatment:* Synthetic construction of molecular scale biological systems could respond to the characteristic signatures of disease in infected cells and also aid in their treatment via manipulation of cellular processes through programmed control.
- *Generation of hydrogen:* Generation of hydrogen as a source of fuel, via breakdown of water using sunlight as energy. This would lead to a cheaper source of hydrogen fuel.
- There are a number of potential applications of systems of synthetic cells engineered to implement digital logic.<sup>5</sup> Such cells could function as sensors and actuators and these systems would be useful as “programmable delivery vehicles” for pharmaceuticals or as “chemical factories for the assembly of nanostructures”. Such programmable synthetic networks of cellular computing systems would perform complex tasks at a fraction of the cost of today’s technology.

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### Key Differentiators

How can we compare synthetic biology to other areas of

biotechnology? Transgenic mice, bioengineered plasmids, and other living forms are regularly created in the process of biomedical research. What would be the difference between these modified lifeforms and lifeforms created using a synthetic biology approach? In order to address these questions, the primary differentiators between synthetic biology and other techniques are outlined below. Synthetic biology systems would exhibit one or more of these attributes (first two are mandatory):

- *Raw materials*: Synthetic elements would be constructed from basic elements (synthetic or purified oligonucleotides in the case of synthetic DNA) in the lab (and not as part of a natural cellular process).
- *No natural counterpart*: Synthetic elements or networks would not have an identical copy in natural cells. The caveat would be synthetically created whole genomes of existing organisms – although a minimal genome (critical genes for survival) organism would be more likely.
- *Programmable*: Synthetic regulatory elements and networks engineered in cells would be controllable with external stimulus in a *deterministic fashion*.
- *Synthetic whole genome*: Starting with synthetic oligonucleotides as raw materials, the end product would be an artificially assembled genome or “minimal genome”.

In order to distinguish between synthetic biological creations and other approaches like transgenic organisms, the key difference to be noted is that transgenic organisms are the result of introducing naturally occurring foreign or mutated DNA (genes) into the organism. *Synthetic biology, in contrast, would result in the creation of elements with synthetic raw materials and with no natural counterpart. In order to think of synthetic biology on multiple levels, a classification system is developed and introduced later in this section.*

### Primary US Research Initiatives

Under the auspices of the DARPA/ITO (Information Technology Office) and its Bio-Computation Program, DARPA funds research in “Information Processing using bio-molecular coding and manipulation”. One of the focus areas of this initiative is DNA Computing, which includes research on synthetic biological circuits and systems.

The Massachusetts Institute of Technology has initiated an educational and research effort in Synthetic Biology. Students are taught interdisciplinary aspects of synthetic design through project based classes. The research effort is aimed at creating a library of synthetic biology components (“BioBricks”) tailored along the lines of a databook for digital design. One of the primary goals is to reverse engineer and design a simple artificial bacterium.

The Institute for Biological Energy Alternatives (IBEAA), founded by Craig Venter, is a not-for-profit research organization with the goal of developing cost-effective biological fuels, and biological solutions for the greenhouse effect

using microbes, microbial pathways, and plants. IBEAA was successful in creating the synthetic genome assembly for a simple bacteriophage in the lab,<sup>6</sup> as described elsewhere in this article. The US Department of Energy (DOE) has funded a \$3M effort for such activities at IBEAA.

Research at Lawrence Berkeley National Laboratory (LBNL) is an example of another major government funded push in the area of synthetic biology. LBNL established the world’s first synthetic biology department in June of 2003.<sup>2</sup>

### EU Research Initiatives

The European Commission has made a significant investment in synthetic biology related research areas.<sup>7</sup> As part of the New and Emerging Science and Technology (NEST) program, the EU is providing early stage research funding for synthetic biology as one of three select areas in 2003-04. Focus areas for this funding include the engineering of biological sub-cellular blocks, interfaces, plus control and regulatory systems with an eye towards industrial applications.

### Technical Progress: Key Initial Developments

There has been some progress in building a few components on the way to realizing the vision of controllable synthetic microorganisms. These efforts represent important recent milestones (1999-2004) that lay the foundation for this effort. A few examples are outlined below:

- Past work<sup>8</sup> includes the successful in-vitro chemical creation of a complete 7000 base pair Polio virus genome starting with purified oligonucleotides and instructions from the polio virus genomic sequence. Furthermore, when this cDNA was transcribed into viral RNA, scientists were able to successfully infect living tissue in the lab with the polio virus. This is a significant step in the artificial synthesis of infectious agents from scratch, using the genomic sequence as a reference.
- A transposon mutagenesis based approach (detecting criticality of genes via insertion of mobile DNA elements in different parts of the genome) to identify a set of “minimal” genes necessary for an organism’s survival has been used in various studies.<sup>9,6,10</sup> Using this information for one of the smallest known genomes (approximately 517 genes in *Mycoplasma genitalium*), scientists were able to map out a set of 265 to 350 protein coding genes as being essential under laboratory growth conditions. Using this approach, the synthetic construction of a 5400 base pair minimal  $\Phi$ X174 bacteriophage (bacterial virus, not human or plant pathogen) genome starting with short pieces of DNA was achieved.<sup>9</sup> This synthetic assembly was significantly faster than the process used in construction of the Polio virus genome.<sup>8</sup> This research effort demonstrates a fast turnover system for artificial genome creation in the laboratory using synthetic raw materials. *In other words, creation of the genome of a living organism from scratch.*

- There have been key advances in synthetic implementation of digital logic and networks in living cells.<sup>11,12</sup> This includes work in creating a genetic circuit in *E. coli* that oscillates with respect to the cell division cycle<sup>11</sup> and a toggle switch that can be switched between two stable states by external signals.<sup>12</sup> Additional work includes an overview of circuit engineering implementation in living cells<sup>13</sup> and a review of these circuits for additional insights on functionality.<sup>14</sup>

### Proposed Classification of Synthetic Products

Products of synthetic biology research will exist at multiple levels of functionality and integration. This report proposes the following classification to grasp the hierarchical complexity of these products and to help analyze legal, ethical and regulatory issues. The proposed levels of classification are: *Synthetic Elements*, *Synthetic Networks*, *Synthetic Organisms*, and *Synthetic Systems*.

#### Synthetic Elements

At the most basic level, synthetic elements are the fundamental building blocks that provide primitive functionality. Analogous to switches, oscillators, flip-flops etc. in the electronics world, these would represent the equivalent of off-the-shelf components. The level of integration would vary somewhat (switch versus flip-flop). However, the basic attribute is a primitive function with a modular implementation. An example of a synthetic element would be the genetic toggle switch or genetic oscillator mentioned earlier in this article. Other entities of this classification system would be composed of such elements at the basic modular level.

At the basic level of the proposed classification hierarchy, synthetic elements should be designed to operate in controlled environments and not function in the wild. This will ensure that natural selection will work against higher levels of integration, satisfying the improved framework for patentability testing.

#### Synthetic Networks

Synthetic networks are composed of interacting components that are individual synthetic elements (described above). The added complexity is achieved via mechanisms to enable communications between these elements. An example of a synthetic network would be a regulatory network of synthetic genes and promoters designed to induce transcription under certain deterministic external stimulus. Preliminary work in this area has produced promising results, as outlined earlier in this article.

#### Synthetic Organisms

Synthetic organisms are the result of synthetic assembly of complete or minimal genomes (set of genes critical for survival) of an organism. These genomes would most likely be substituted in place of an existing genome in a favorable cellular environment. In addition to the artificial genome, the

synthetic organism could contain synthetic networks and synthetic elements. Examples of success in creating synthetic genomes include creation of an artificial genome of the Polio virus (which can infect living tissue) and the artificial minimal genome of a bacteriophage (outlined earlier in this article).

#### Synthetic Systems

The ultimate goal of synthetic biology would be to design synthetic systems composed of multiple synthetic organisms working synchronously to achieve a complex objective. One of the major hurdles to this task would be to design a robust communication system between component organisms. There has been some progress on this front.<sup>4</sup>

### PATENTABILITY ANALYSIS

The case of *Diamond v. Chakrabarty*<sup>15</sup> clearly established the grounds for patentability of genetically altered organisms. The primary criterion for this ruling was that they are not “products of nature”. Creations of synthetic biology take this one step further with the creation of organisms that could be completely synthetic from the ground up,

as opposed to genetically modified versions of naturally existing organisms. They open up the possibility of a custom genome unlike any other found in nature, designed with synthetic components, for a specific purpose. This section presents relevant case law from similar areas of biotechnology, and analyzes the patentability of products of

synthetic biology, highlights some of the main issues involved, and suggests some recommendations for future consideration. Some of the grounds for patentability are discussed below in the context of synthetic biology.

It should be understood that the US Patent and Trademark Office (PTO) is not accountable to the people, and as such, opposing the actions of the PTO is not an effective way to regulate the kind of research conducted in a particular field. As frequently mentioned in the literature, opponents of certain types of research in biotechnology would be better served by lobbying Congress to amend the patent statute or to pass legislation to regulate certain types of scientific research rather than solely focussing on the actions of the PTO. This issue is addressed further in a subsequent section on regulation.

This section addresses the following questions and concludes with some recommendations for patentability of synthetic biology inventions:

- What is the case law and patent policy for patents on living organisms?

- Is there an improved framework to test the patentability of biological innovations like those in the area of synthetic biology beyond the arbitrary process currently used by the Patent and Trademark office (PTO)?
- What hurdles do inventions in the field of synthetic biology face with respect to traditional patent requirements?

### Relevant PTO Actions And Case Law

The following is a brief history of case law with respect to patents on living organisms:<sup>16,17</sup>

- The US Patent and Trademark Office (PTO) issued the first patent for a living organism in 1873 to Louis Pasteur for a purified form of yeast. Subsequent to this, however, the PTO rejected patent applications for living organisms (especially in the 1970s) on the basis that they were products of nature, and hence not patentable subject matter.
- Prior to *Diamond v. Chakrabarty*,<sup>15</sup> Congress had authorized limited protection for cultivated plant varieties.<sup>18</sup> However, animal related inventions based on biotechnology were denied patents based on moral and ethical grounds. This category included living organisms ranging from single cell micro-organisms to multi-cellular lifeforms.
- In *Diamond v. Chakrabarty*,<sup>15</sup> the court ruled that: “The patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature’s handiwork, but his own: accordingly it is patentable subject matter under 101.” Further, the Supreme Court held that patents may be granted for “anything under the sun that is made by man”. This established the precedent for patentability of living micro-organisms modified through human intervention. However, the court did not define any boundaries for this new area of patentable material. As a result, thousands of patent applications regarding animal related patents were not acted upon by the PTO.
- Then in 1998 the US PTO granted the first patent for a multi-cellular living organism: the Harvard Oncomouse,<sup>19</sup> described as a “non-naturally occurring non-human multicellular living organism”. It was a mouse engineered to develop cancer at a high rate. This prompted a number of lawsuits from groups opposing animal patents.
- In 1991 the U.S. Court of Appeals for the Federal Circuit consolidated the legal challenges and disposed of them, dismissing the claims for lack of standing.<sup>16, 20</sup> However, the court did not provide any clarifications on the guidelines for patentable living organisms. It establishes a case-by-case review process for the PTO to use their discretion for granting animal related patents. This arbitrary process is still in use with respect to patenting of living organisms.
- The lack of standards used by the PTO was further exposed by the processing of a 1997 patent application

by Professor Stuart Newman and Jeremy Rifkin for a part animal part human chimera, which was denied. It highlighted the fact that the PTO does not have a well-defined framework to grant or deny patent applications for living organisms.

### Patentability Analysis Of Synthetic Biology

Given the arbitrary framework used by the PTO for granting patents to living organisms, it is instructive to analyze the patentability of synthetic biology innovations along two fronts. First, let us borrow a framework proposed earlier<sup>16</sup> as an improvement to the patent analysis process of living organism-related patents. We will analyze synthetic biology in this context. Second, let us look at the traditional patentability criteria used by the PTO and ensure that synthetic biology innovations meet those criteria. Finally, we can look at licensing in the context of synthetic biology and its relation to stimulation of further research.

#### Improved Framework for Patentability Testing

We can adapt frameworks proposed in the context of plant and animal patents to the needs of synthetic biology. A test based on evolutionary biology as a remedy to the arbitrary process used by the patent office today for plant and animal based biotechnology patents, has been proposed before.<sup>16</sup> This test is designed to clearly show human innovation in applications that should be patentable. The test has two parts:

- *Part 1*: “Applicants must show that the organism under review would have little chance of developing naturally”.<sup>16</sup>
- *Part 2*: “Applicants must also provide evidence that natural selection would actually work against the organism but for the intervention of human interest and technology”.<sup>16</sup>

This proposal addresses some of the ambiguity in granting live organism patents — only patent applications related to living organisms that satisfy both parts of the test would be patentable material. *In the context of innovations related to synthetic biology, application of the two parts of the test lead to the following observations:*

- *Part 1 (natural evolution test) in the context of synthetic biology*: Given the scientific approach of creating organisms from scratch using artificial raw materials or creating minimal genomes using synthetic materials, one can infer that it would be relatively easy for synthetically generated organisms to pass this test. Unless the goal is to mimic an existing organism in every detail, which is not in the current scope of synthetic biology research, this test can be passed. Any attempts to mimic an existing genome in its entirety using synthetic components, and to engineer an organism would fail this test from a genomic standpoint. *If, at the lowest level of hierarchy, synthetic elements are creations*

*that implement logic functions without natural counterparts, higher orders of synthetic systems can meet the requirements of this test.*

- *Part 2 (natural selection test) in the context of synthetic biology:* In considering natural selection, this part of the test effectively denies patents to any human generated organism that can survive in the wild with greater probability than it would in a laboratory under controlled conditions. In order to pass this test, synthetic organisms should be engineered to survive under specific conditions that are not found in the “wild type” environment. For synthetic microbes that need to survive in the wild to perform specific functions (cleanup etc.) there should be a mechanism whereby the organism should cease to function permanently after a given timeframe or after the given task has been completed (e.g.: toxin does not exist anymore). *At the basic level of the proposed classification hierarchy, synthetic elements should be designed to operate in controlled environments and not function in the wild. This will ensure that higher levels of integration of synthetic networks and organisms will meet this test.*

These restrictions for patentability would offer scientific basis for evaluation of patent applications. Also, they would enable the mapping of the patent granting process to environmental, moral, and ethical considerations with clear reasoning regarding the acceptance or denial of a patent application.

Synthetic elements should be engineered and targeted for well-defined functions in order to meet the utility requirement. Although not frequently invoked in the US, the moral utility doctrine is still part of patent law and is relevant in the area of synthetic biology as higher levels of integration are achieved.

### Meeting Traditional Patent Requirements

Given that traditional patent requirements such as novelty, non-obviousness, and enablement would be satisfied by most patentable innovations in this field, we can examine other relevant criteria such as utility, moral utility doctrine, and licensing (to enable further research in the context of synthetic biology innovations) as illustrated below.

- *Utility:* In response to criticism that the PTO issues patents to biotechnological innovations on a broad utility scale,<sup>21</sup> the PTO issued revised interim utility guidelines in 1999,<sup>22</sup> in 2000,<sup>23</sup> and final utility guidelines in 2001.<sup>24</sup> The 2001 Utility Guidelines “require that a claimed invention either have a well-established utility or assert a specific, substantial, and credible utility”.<sup>21,24</sup> The utility requirement would be satisfied if a claim in the patent application has a “well-established utility”.<sup>21</sup> The PTO would need to provide evidence of lack of utility and allow the filer to contest this, in case of patent rejection. In addition to this, the PTO also published training material for patent

examiners in 1999-2000<sup>25</sup> which defines “credible utility as one that an ordinary person with skill in the art would believe”.<sup>21</sup> Overall, it is evident from PTO guidelines and case law that a patent application should assert a specific and substantial utility to meet the utility requirement. *In the context of synthetic biology inventions, synthetic elements (the lowest level of classification) should be engineered and targeted for well-defined functions.* For example, a switch to enable or shut-down regulation. Given that these basic elements are engineered for specific utility, higher levels of integration can be conceived to serve some aggregate complex function (e.g.: Environmental cleanup of specific pollutant). Utility can then be clearly articulated at higher levels of the hierarchy.

- *Moral utility doctrine:* The Moral Utility doctrine<sup>17</sup> is a rarely invoked aspect of patent law. Whether or not the patent granting process should consider the morality of an invention is in itself a controversial issue. However, in the case of synthetic biology innovations, researchers should be aware of the possibility of failing this test. Essentially, the moral utility test would prohibit patenting

of life-forms considered to be immoral. In *Lowell v Lewis*,<sup>26</sup> Justice Joseph Story ruled that “all that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society. The word ‘useful’, therefore, is incorporated into the act in contradistinction to mischievous or immoral”.<sup>17</sup> The

PTO can apply this doctrine to the patent applications regarding inventions “historically frowned upon by society”.<sup>17</sup> Over the years this doctrine has been relaxed such that an invention has to have at least one beneficial purpose to meet the moral utility requirement. Some court decisions<sup>27</sup> would suggest that the federal courts have ceased to use the moral utility doctrine.<sup>17, 28</sup> In contrast, the PTO indicated in April 1998, through an advisory, that it continued to rely on the moral utility doctrine. This followed the PTO’s rejection of Dr. Newman and Jeremy Rifkin’s human-chimera patent application on the basis that it “embraced” a human being and was thus not patentable.<sup>28</sup> *Although the moral utility doctrine is not an actively invoked feature of US patent law, synthetic biology innovations need to demonstrate at least one beneficial application to society in order to pass this test.* For example, a possible synthetic minimal genome organisms could demonstrate that it can perform a beneficial task similar to the full genome natural counterpart (probably with lesser energy requirements). Or a custom synthetic organism could perform a chemical conversion leading

to production of a desired chemical for industrial consumption (e.g.: production of hydrogen). Thus, the moral utility test barrier can focus research efforts on beneficial applications of synthetic biology. It should be noted, however, that patent policy is not a barrier to research efforts that could be harmful to human health or the environment. This issue is addressed in a subsequent section on regulation of synthetic biology research.

- *European moral utility doctrine*: The EU's Biotech Directive<sup>29</sup> and the European Patent Convention's (EPC) morality provisions clearly enforce a moral utility doctrine in the patent granting process. Article 53(a) of the EPC notes that: "The EPO will not grant patents against ordre public or morality". In contrast to the US patent system, creations of synthetic biology will face tougher scrutiny in Europe from a patentability perspective. However, in the context of single-cell synthetic microorganisms with a beneficial purpose, and demonstrated to have no adverse effects on mankind or the environment, the moral doctrine should not be a barrier.

#### Synthetic Biology Patents and Stimulation of Further Research

The current narrow interpretation of the "experimental use exception" doctrine has been analyzed in other work<sup>30</sup> and changes have been proposed to this doctrine based on different types of inventions, with the goal of a better approach to promote use of these inventions for further research. The experimental use doctrine refers to the use of inventions in academic research settings without the problems of infringement liability. The problem being addressed is that research may be hindered due to inventors not licensing their inventions on acceptable terms to other researchers for experimental purposes. Furthermore, the degradation of the experimental-use exemption by recent court rulings has been analyzed before.<sup>30</sup> In a recent Federal Circuit case, *Madey v. Duke University*,<sup>30,31</sup> the court found university research ineligible for the experimental use exemption based on the fact that it "unmistakably furthers the institution's legitimate business objectives, including educating and enlightening students and faculty participating in these projects".<sup>31</sup> This decision extends the definition of "commercial use" of inventions, hence degrading the usefulness of the experimental use exemption. *In the context of synthetic biology, the impact is similar to other areas of cutting edge biomedical research.* The basic innovations leading to the creation of building blocks need to be accessible to the larger research community to build upon and promote innovation in this area. A practical experimental exemption policy would be invaluable. A two-tiered system has been suggested<sup>30</sup> with a period of complete exclusivity followed by a period of compulsory licensing, which would alleviate some of the issues discussed above. *At a bare minimum, these requirements should be applicable to the lowest level of hierarchy in the synthetic biology product classification system introduced earlier. Synthetic elements should be freely avail-*

*able (or compulsory licensing should apply) to the research community in order to promote further research that builds upon existing components.*

#### Recommendations for Patentability

Based on the discussion above, here are a few key recommendations for synthetic biology inventions from an intellectual property and patentability perspective:

- Synthetic elements (the lowest level of classification) should be engineered and targeted for well-defined functions in order to meet the utility requirement at the most basic level and at higher levels of integration.
- Although not frequently invoked in the US, the moral utility requirement is still part of patent law and is relevant in the area of synthetic biology as higher levels of integration are achieved. Clear articulation of at least one beneficial purpose, *ideally at the level of synthetic elements*, is extremely important.
- At a minimum, synthetic elements (lowest level in the synthetic biology product classification) should be freely available to the research community (or compulsory licensing should apply). This is imperative to stimulate rapid scientific advances in this area.

There is a need for additional regulation of intellectual property related to products of synthetic biology to address some of the moral issues discussed in the context of meeting the moral utility requirement. The overall public good needs to be considered.<sup>32</sup> However, Congress would be the right body to address these issues through legal pre-emption rather than relying on the PTO to make moral judgements. This is discussed further in the section on regulation.

#### ETHICAL ANALYSIS

Scientific advances in biotechnology are taking place at a rapid pace. Often, new technologies spark an ethical debate in their wake, as ethical frameworks need to be revised to accommodate their impact. The advances and consequences of synthetic biology will no doubt have a similar impact. A number of ethical issues will arise, some common to other areas of biotechnology, and others specific to this area. Some of these issues and the questions they raise are addressed in this section with a focus on new aspects due to synthetic biology. Recommendations to address these ethical concerns are also outlined. In particular, this section seeks to address the following questions:

- What are the primary ethical concerns with respect to synthetic biology research? What are the moral and ethical responsibilities of researchers in this area?
- Can we develop an appropriate framework or a set of ethical principles to guide work in this area?

## Ethical Concerns

- One of the main ethical concerns is drawing a distinction between an engineered machine and a living organism. Building a synthetic biological system from scratch or a constructing a minimal genome raises the question of the difference between life and nonlife. A report from the Ethics of Genomics Group<sup>32</sup> outlines the contemporary view in the scientific world about “life” being related to possessing metabolic properties, being responsive to the environment, and having the ability to replicate. The goals of current synthetic biology initiatives lie within this definition of “life”. However, what is the “value” assigned to such creations of synthetic biology? A distinction between *instrumental* and *intrinsic* value assignments has been made in the literature.<sup>33</sup> Instrumental value is assigned solely based on an entity’s usefulness to mankind. In contrast, intrinsic value is based on an entity being valuable “in and of itself”, whether it is useful to mankind or not is immaterial. *Given that creations of synthetic biology can qualify as living organisms designed to be useful, can they be regarded solely as having instrumental value and being devoid of any intrinsic value?* How does this change if the principles of synthetic biology are applied to develop higher lifeforms in the future? Does this suggest an ethical limitation on the kind of work that should be pursued in this area?
- Furthermore, there is a school of thought based on a reductionist approach that subscribes to the concept that genes are the essence of living organisms.<sup>34, 32</sup> Accordingly, construction of a synthetic lifeform with a set of genes can be considered a living organism. There is the expected opposition to this view based on the fact that reducing the definition of life to a set of genes ignores the non-physical aspects of life held dear by many religions.<sup>32</sup> This is particularly relevant in the case of higher organisms. Ethical issues are most visible when biotechnical research affects mammalian or higher organisms.<sup>35</sup> The public at large can relate to the impact of such research and concerns can be widespread. With future advances in synthetic biology, one can envision synthetic or minimal genomes for mammalian species like mice. Is it ethical for scientists to experiment at this level? Would such research have any benefits to society? A major area of concern arises when this definition is extended to humans. For example, with rapid advances in synthetic biology in the future, would human embryos based on synthetically

Most creations of synthetic biology will have instrumental value to mankind. However, as we move up the classification hierarchy to higher levels of integration, researchers and ethicists should give thought to any intrinsic value that these products might have.

generated germ cells with a reduced set of “essential” genes, be possible? Would this be considered human? Should such research be conducted?

- What are the moral and ethical responsibilities of a researcher in this area? Should a researcher have the moral responsibility to restrict work on organisms that would not affect public safety adversely? Can this be done in a new field with many unknowns? How should a researcher control information related to findings that could potentially be used by someone to generate synthetic organisms harmful to humankind or the environment? These questions pose an ethical minefield for individual researchers and research efforts. A set of ethical guidelines is necessary for synthetic biology researchers to abide by.

## Recommendations for Synthetic Biology “Ethical Principles”

In the context of developing a framework for ethical conduct by synthetic biology researchers, ethicists have called for a summit meeting with biologists modeled on the 1975 Asilomar Conference.<sup>2</sup> The 1975 conference resulted in safeguards for the containment of microbes used in genetics research. A similar effort is now needed to address the moral and ethical responsibilities of researchers in the field of synthetic biology, in order to implement appropriate safeguards against misuse and abuse of this technology.

To develop ethical guidelines for synthetic biology research, we can look to other areas of biomedical research that have developed ethical principles. In the area of animal experimentation in biomedical research, three guiding principles<sup>36</sup> are key to an ethical framework. These principles of *refinement*, *reduction* and *replacement* aim to reduce animal suffering to a minimum, minimize the number of animals used, and to replace animal testing with non-animal testing when possible.<sup>35</sup> We can envision a set of ethical principles for synthetic biology research. The following principles are being proposed as a step in this direction:

- Clearly articulate Instrumental and Intrinsic Value:** Most creations of synthetic biology will have instrumental value to mankind. However, as we move up the classification to higher levels of integration (e.g. synthetic elements → networks → organisms → systems), researchers and ethicists should give thought to any intrinsic value that their products might have.
- Expand the universe one step at a time:** As part of this nascent technology, we need to be mindful of the fact that at higher levels of integration, there are additional unknowns. Researchers should be careful in proceeding

to the next level of classification (i.e. synthetic elements → networks → organisms → systems) until the component parts at each level of classification are well characterized and their impact is known.

## REGULATORY ANALYSIS

With rapid advances in the field of biotechnology in the recent past, there is increased concern over the potential risks posed by some aspects of this technology. Examples such as the failure of some high profile gene therapy trials serve to illustrate some of the pitfalls. In addition to technological risks, there is also the issue of researcher conduct and adherence to prescribed guidelines and the law.

As with any new technology in this area, synthetic biology poses similar risks given the potential of this technology to engineer new organisms in the future. There needs to exist some proactive framework to regulate the kind of research performed in such areas along with safeguards to ensure researcher conduct adheres to established guidelines. This section identifies some of the potential risks posed by research in synthetic biology, identifies an appropriate framework to analyze the need for regulating research in this area, and proposes some recommendations. In particular, this section addresses the following questions:

- What are the potential risks posed by synthetic biology?
- What is an appropriate framework to analyze regulatory requirements for synthetic biology?
- What should regulatory agencies focus on in this area?

### Primary Risks Posed By Synthetic Biology

Some of the risks posed by products of synthetic biology are outlined below. As we move up the classification hierarchy of synthetic biology products, and thus on to higher levels of integration, the risks increase.

- *Risk of negative environmental impact:* This includes scenarios in which a synthetically created micro-organism designed for a particular task (e.g.: Environmental cleanup) could have a side effect of interacting with another environmental substance and impact the overall environment negatively.
- *Risk of natural genome pool contamination:* Any genetic exchange between a synthetic biological entity and a naturally occurring biological entity would result in natural genome contamination. This is similar to the problem of “gene-flow” in the context of transgenic plants.
- *Run-off risk (“Grey-goo” problem):* This is similar to the problem often discussed in the context of nanotechnology. Synthetic biology products released into the environment to accomplish a specific task should have a controlled lifespan outside the lab. If this is not the case, one can envision unintended consequences of a system run amuck.
- *Risk of creation of deadly pathogens for the purposes of bio-terrorism:* The creation of the complete genome of

Polio virus in the lab shows the potential of synthetic biology to engineer harmful pathogens. This technology, in rogue hands, could be used to engineer the genomes of deadly pathogens. The fact that the synthetic Polio virus was proven to be infectious shows the deadly potential of this technology.

## Recommendations and Reference Frameworks for Regulation

Three legal frameworks the law uses to regulate genetic technology have been described in the literature:<sup>37</sup> Individual Rights and Duties, Scientific Regulation by Administrative agencies, and Legislative Pre-emption. Each framework involves different decision-makers and is designed to oversee a different aspect of genetic technology. We can use this framework to analyze the regulatory needs of synthetic biology. The three regulatory frameworks are described below and an analysis of the needs of synthetic biology is presented with each definition.

### Individual Rights and Duties

“Actions to enforce Individual Rights and Duties are initiated by individuals. This framework involves the lowest level of government oversight over genetic technology. The core of this approach is to establish legal rights for individual citizens under the traditional sources of law: the common law, specific remedial statutes and the Constitution. Under this framework people are free to act unless and until they harm others. The law makes no attempt to prevent harm other than to deter it by acknowledging the right of an affected person to sue for damages.”<sup>37</sup>

Synthetic biology is no different than other biotechnology research areas in this area. Researchers have to be aware of the possible impact of their research methods and products. The ethical principles outlined in an earlier section provide some guidelines to minimize risk scenarios in this area. Individuals impacted by one of the synthetic biology risk scenarios outlined earlier have the right to sue for damages.

### Scientific Regulation by Administrative Agencies

“Scientific Regulation is conducted by administrative agencies and results in a higher level of scrutiny over genetic technology. This is currently the most common form of regulating the biotechnology industry in the United States. Nevertheless, our national experience has not resulted in a very strict level of administrative oversight. Administrative regulations take years to develop because each agency bears the burden of justifying the regulations in court, and agency policy is subject to revision by each new presidential administration. Adding to the difficulty is the fact that administrative agencies in the United States have had to act under existing laws that have not been amended to deal with the novel challenges of genetic technology.”<sup>37</sup>

With respect to the classification of synthetic biology products, most of the regulatory needs would come in at the level of synthetic networks and above. Synthetic elements by themselves are independent building blocks

that provide basic levels of functionality. In the context of synthetic biology, regulatory agencies need to address the following issues:

- Generating a set of criteria for approval of synthetic organisms to be released into the environment for a given task. The following criteria are proposed for this purpose:
  - *All products at any level of the synthetic biology product classification scheme should have a well-defined lifespan outside the controlled environment of a laboratory.* This should be well characterized through controlled testing. At the very least, there should be a well characterized “disable signal” that can be applied externally to terminate the useful life of an entity. This discussion assumes that we are dealing with simple unicellular organisms.
  - *Synthetic organisms should not have the potential for genetic exchange with naturally occurring life forms.* Replication should be permitted only under specially controlled laboratory conditions.
  - *Targets that synthetic organisms work on, must be well characterized through an extensive test protocol.*
- *Outline a controlled approval process for “application specific” versus “general purpose” synthetic organisms.* This is a form of risk mitigation where only synthetic organisms designed or programmed for a single purpose (application specific) would be released into the environment as required to perform a given task. By doing so, the risk of side effects is reduced. An example is the design of a synthetic organism to clean-up a particular pollutant as opposed to one that would clean up a collection of unrelated pollutants.
- *Classification of synthetic biology research based on the system of classification of biological laboratories based on the pathogens handled in the lab.* Current synthetic biology research is focussed on Biosafety Level 1 in approved research facilities. However, any work with respect to synthetic genomes of dangerous pathogens should be permitted under tightly controlled conditions at appropriate Biosafety Level classification, similar to the controlled environment for “select agents” today.
- Work funded by government agencies should ensure that synthetic elements created as part of the work are

freely available to the research community (or compulsory licensing) in order to promote further research in this area.

### Legislative Pre-emption

“The highest level of oversight, Legislative Preemption, is essentially hostile to genetic technology and would severely restrict the application of this new science. The fundamental precept of this framework is “safety first” — the precautionary principle. Under this regulatory framework the government — usually the legislative branch — forbids or severely limits the development and application of new technology until it is proven safe. But because we do not yet know all of the consequences of genetic technology — since it cannot be proven safe in advance — this type of precautionary legislation operates as a virtual ban.”<sup>37</sup>

Legislative pre-emption is most visible in the case of human cloning. Numerous countries have used this approach to ban human cloning.

In the context of synthetic biology, at this point the science is in its infancy and there isn’t an immediate need for legislative pre-emption on any issue. However, synthetic biology does have the potential to engineer higher level complex life-forms in the future, as technology allows progression upstream in the classification hierarchy (at higher levels of integration). At that point in time, one would expect the “engineered machine/artifact” versus “life” debate to intensify. At some point in time one can envision some level of legislative pre-emption as synthetic biology develops the capability to handle complex genomes (e.g.: mammals) to regulate such research on ethical and moral grounds.

### CONCLUSION

Synthetic biology holds immense promise as a beneficial technology. As with any other area of biotechnology, there are associated areas of concern and risk. This article has provided an outline of the technology and proposed a classification system for dealing with multiple levels of its products. We have analyzed this technology from a patentability, ethical, and regulatory standpoint with appropriate guidelines and recommendations at each stage. The technology itself is in a nascent stage and some of these issues will no doubt evolve as the technology progresses. 

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