Bridging Gaps in Synthetic Biology Oversight: iGEM as a Testbed for Proactive, Adaptive Risk Management

by

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Submitted to the Engineering Systems Division
in Partial Fulfillment of the Requirements for the Degree of
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Abstract

On the surface, the emerging field of synthetic biology looks highly similar to that of genetic engineering. However, the two fields are based upon divergent underlying logic structures. Whereas genetic engineering affects change through localized modifications of existing organisms, synthetic biology attempts to fuse independent component parts to create wholly novel applications. While legacy regulatory systems were adequate for monitoring biosafety in the early days of the emerging field, as synthetic biology advances, the fundamental differences in its logic structure are creating fissures in the oversight system. A continued reliance on increasingly incompatible mechanisms squanders the limited present opportunity for proactive risk management, and generates increasing potential for significant future risk exposure in the field.

This thesis will describe the current state of domestic and international oversight systems relevant to synthetic biology, and characterize their limits and vulnerabilities. It will argue that the current approach of relying on prescriptive, sequence-based controls creates growing gaps in oversight for a field moving toward amalgam organisms, and that the soft methods intended to bridge these gaps, predominantly in the form of institutional biosafety committees, are instead points of additional significant vulnerability. This thesis will also illustrate the challenges that have arisen because of these gaps, both in theory and in practice, through an examination of the International Genetically Engineered Machine competition (iGEM). iGEM, a university-level synthetic biology contest, first served as a valuable case study for illuminating challenges associated with the current system. Later, the Massachusetts Institute of Technology's Program on Emerging Technologies collaborated with iGEM to establish the competition as a policy testbed for demonstrating innovative approaches to biosafety oversight.

This thesis will conclude by proposing recommendations for improving biosafety oversight based on lessons learned from the iGEM testbed. First, it is not enough for scientists to recognize that risks exist in their field; as the first line of defense in risk management, they must also be able to identify, understand, and engage with the risks inherent in their own work. Second, in light of the limits imposed on policy revisions due to political gridlock, it is necessary to understand what can be realistically accomplished within the existing federal system, and what instead needs to be achieved outside it. Here, a fuller, more invigorated approach to engagement support is coupled with a mix of improved, adaptive interpretations of the existing oversight system.

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PoET has proven to be a welcoming, thought-provoking home for my research efforts over the course of the past two years. The deep knowledge of participants in such a wide array of specialties has greatly broadened my horizons, and has led to a far fuller consideration of science and policy implications than I could have ever managed on my own. For this effort in particular, the insights on iGEM procedures offered by Shlomiya Lightfoot and Kelly Drinkwater have been invaluable, as have been the policy insights provided by Todd Kuiken through our partnership with the Wilson Center. Finally, my many thanks to Kenneth Oye. In his capacity as head of PoET and as my research and thesis advisor, he has provided reliably thoughtful and insightful observations throughout my time at MIT. I am extremely grateful for the many opportunities I was allowed during my two years within the group.

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Chapter 1. Introduction

In May 2014, the Nature publishing group coordinated a feature issue on synthetic biology across its primary journal platforms. The effort marked something of a coronation of the field, welcoming the completion of its evolution from novel offshoot to established -ology. As a result, it also formalized the field in such a way that long-brewing policy issues became unavoidable points of discussion. However, the editors of Nature did not offer suggestions that reflected lessons learned about the need for proactive engagement from failed debates of the past. Instead, they seemed to be advocating a retreat to the corners, emphasizing the need for scientists to quash any potential for public uprisings before they emerged. Wrote the editors, “It is now more vital than ever that synthetic biologists present a united front. …Storm clouds are gathering on the horizon. Not everyone agrees that synthetic biology is a force for good…. It is crucial, says [the co-chairman of IAP], that the balancing voice of science is heard before false assumptions lead to the creation of onerous and unnecessary regulation. Everyone can agree on that” (Nature editors, 2014). Here, the editors suggest that regulations arise because of a misunderstanding of the science; to them, “protective” and “proactive” translates to “onerous” and “unnecessary.” This is a troubling conclusion from the very people who have worked along the front lines of fight after fight endured by emerging fields. Instead of focusing their attention on obfuscating the appearance of fissures in the field, practitioners must take the time to examine these risks in full view, and then initiate appropriate forward action.

By applying engineering principles to living organisms, synthetic biology aims to reinvent life forms and the products they create. In the process, risks are generated. Some are obvious and concerning, like the potential for pathogen optimization, while others are subtler, like unanticipated part interactions. Both require attention. But over the past decade, the field has been dominated by conversations that focus on risks that exist along the extremes. Discussions revolve around the more compelling but less likely risks of bioterrorism and out of control “garage scientists,” as opposed to the less compelling but likelier risks of unexpected component interactions and insufficiently protective work environments. As a result, debates and forward action have been largely limited to focusing on these areas as well. For example, federal regulators have only produced targeted regulations for synthetic biology based on security concerns, while the oversight mechanisms for broader biosafety issues have been left essentially unchanged from those previously developed for genetic engineering. This thesis will make the case that such limited consideration leaves the field highly vulnerable to risk exposure.

Synthetic biology is not unregulated with regard to biosafety, nor would it be correct to label it as over- or under-regulated. Instead, it is simply inappropriately regulated. Fundamental differences exist between the logic structures of genetic engineering and synthetic biology, as the former aims to make changes to existing systems, and thus differences between the old and the new can be compared, while the
latter aims to create wholly novel organisms from an amalgam of parts. Because of these differences, a continued reliance on legacy systems for synthetic biology biosafety oversight threatens to splinter the effectiveness of the approach as synthetic biology moves closer to achieving its long-term goals. The current biosafety oversight approach involves rigid, sequence-based controls on the one hand, and more interpretive institutional biosafety committee (IBC) systems on the other. There comes great comfort from assigning sharp lines in a sea of shades of grey. However, these lines, consisting of sequence-based delineations of organism risk levels, are becoming increasingly arbitrary as synthetic biology progresses in its effort to construct novel organisms without useful baseline comparators. This thesis will explore the potential for reinvigorating and guiding the current system toward a more usable, adaptive, and relevant format appropriate for synthetic biology.

By focusing public debates and private funding decisions on controlling risks along the extremes, we squander the opportunity to engage proactively with the more prevalent source of risk in the field: that which has the potential to emerge from any laboratory, and is a consequence of hubris, not malice. It is not enough for synthetic biologists to recognize that risks exist in the field at large. In order to effectively limit biosafety concerns, they must also be able to recognize the risks inherent in their own work. In reality, as the complexity of projects grows, there comes a point where judgment calls must be made. The IBC system relies on informed groups to weigh-in on the complexity of projects, and assess the risk level of the effort presented based on their best understanding. This flexibility is invaluable for a dynamic field where the rapidity of advances is staggering. However, when these overseeing bodies are insufficiently informed, inadequately empowered, and inconsistently applied, they transform from being strong safety nets interwoven between rigid structures, to gaping holes of weakness and vulnerability. Any solution to fixing the current system must address the insufficiency of the current IBC approach, which in large part begins with the grounding of practitioners in the risk potential of their labors.

**Synthetic biology and the technology frontier**

This thesis will begin by considering the origins of synthetic biology, and establishing the functional novelty of the field’s approach. Chapter 2 will explore the definitional variations in the field, and consider the relative importance of the differences in interpretation and use. It will also consider the primary enabling technologies propelling the field forward, and provide a brief survey of some of the most commonly considered advances thus far, with both near- and long-term commercialization goals.

Synthetic biology would not be where it is today without the decades of work preceding it in genetic engineering and microbiology, but that does not mean that it should only be considered an offshoot of those fields. As an emerging technology shifts from concept to practice, questions inevitably arise about the novelty of its approach and the degree to which existing structures are capable of handling
its new applications. For some fields, the discussion quickly reduces the technology to just another advancement along an existing spectrum; for others, it becomes clear that the approach will result in a paradigm shift. But for a third group, there exists no ready resolution, as the methods may be incremental but the implications revolutionary. This thesis argues that it is here that synthetic biology falls, and as a result, that it is also here where oversight mechanisms fail.

Mechanisms for oversight

In the absence of targeted regulations, synthetic biology has been largely handled by policies previously developed for genetic engineering, which themselves were often re-purposed from non-genetic engineering origins. Because of a mismatch between these existing structures and the growing needs of the field, however, this default approach has resulted in an increasing number of gaps in oversight. This chapter will describe the current state of domestic and international oversight systems relevant to synthetic biology, particularly with an eye toward those relevant to biosafety and biosecurity. It will also characterize the current shortfalls of these mechanisms, and their potential areas of future vulnerability. Much of the confidence placed in the current system is based on two assumptions that synthetic biology’s techniques are rendering increasingly obsolete: 1) that a part from an organism should be regulated at the risk level of its parent organism, and 2) that technical advances will remain largely inaccessible to the general public due to a continued need for deeply specialized knowledge to participate in the field.

The soft methods intended to bridge the gaps resulting from a rigid, sequence-based framework will also be explored. By examining the ways in which these systems have been failing, and are likely to continue failing, this section will also identify that in their current format, these systems are generating additional points of significant vulnerability. This section will also present a series of potential alternative oversight mechanisms for managing biosafety concerns in synthetic biology.

iGEM as a testbed

Chapters 4, 5, and 6 of this thesis center around the university-level synthetic biology contest “iGEM,” or the International Genetically Engineered Machine competition. iGEM presents a valuable opportunity for observing the current failures of the oversight system in real time, as well as a chance to trial and evaluate innovative biosafety policies and procedures through its recently established status as a policy testbed.

Chapter 4 introduces the iGEM organization and its competition structure, and describes the incredible growth that iGEM has experienced in terms of size, geographic scope, and technical capacity over the first ten years of its operation. This section will also present background information on the emerging safety concerns arising within iGEM, and how the organization has struggled to adequately handle them while solely relying on the current oversight system. By 2012, iGEM had experienced
multiple biosafety near-miss events and was put on notice with regard to safety concerns: it could either strengthen its safety program and continue to encourage projects that pushed the technology frontier, or it would have to reduce the allowable risk level assumed by teams in acknowledgment of the observed failures of the system. iGEM ultimately selected the former, and embarked on a collaborative mission with the Massachusetts Institute of Technology’s (MIT) Program on Emerging Technology (PoET) to directly engage with the gaps presented by the current biosafety oversight system.

Chapter 5 will present an analysis of the joint PoET-iGEM effort to establish iGEM as a policy testbed. In disclosure, this thesis is written from the perspective of a research assistant within the PoET group, who worked on the front lines of the iGEM testbed development from its founding through its second iteration, as a safety screener as well as a policy evaluator. Notably, PoET is not the only group to take advantage of iGEM’s status as a microcosm of the broader synthetic biology environment. Other partners include the Federal Bureau of Investigation (FBI) and its attempt at engaging with young scientists; the synthetic biology corporation Synthetic Genomics, Inc. (SGI), and its demonstration of the capabilities of a proprietary sequence screening tool; and Public Health Canada and its efforts to trial and improve informative guidance documents for risk assessments relating to synthetic biology. While these additional partnerships re-emphasize the relevance of the testbed, chapter 5 will largely focus on the attributes of the testbed that make it particularly valuable and relevant to questions of biosafety oversight.

Finally, Chapter 6 will run through findings from the first year of the testbed implementation, 2013, as well as the updates and improvements planned for the 2014 iteration. This section makes clear the motto of “observe, update, iterate” that has permeated the PoET approach to the policy evolution process. The testbed effort has embraced the importance of adaptation in the face of a rapidly evolving field, both in terms of the amount that remains uncertain, as well as the novelty of approaches being introduced each year. This section will further highlight the importance of operating proactively in the face of change.

Policy implications and potential for scale-up

Synthetic biology has been, thus far, a study in failed early warnings. However, it still presents a promising opportunity for employing anticipatory and proactive risk governance methods. This final chapter will evaluate the lessons learned from earlier theoretical analysis, and couple them with the observations made through iGEM as a case study, and then later iGEM as a testbed. As learned in the testbed, it is possible to reinvigorate the existing system in order to turn it into a functioning oversight mechanism. However, this requires the immediate initiation of conversations that depart from the compelling threats of bioterrorism and environmental apocalypse, and instead focus on anchoring practitioners in the knowledge and ability to assess the risks inherent in their own work.
Chapter 2. Synthetic biology as an independent field?

It is not precisely clear when synthetic biology broke away from genetic engineering and became its own distinct field. In many ways, the discipline is a natural follow-on to the recombinant DNA techniques launched in the 1970s. However, the logic structure is independent. Whereas genetic engineering strives to elicit a desired outcome through scattershot experimentation, synthetic biology aims to achieve that same outcome—and more—through adherence to rigorous engineering design principles. Said one synthetic biologist: “To date, genetic engineering can be considered more of an artisan craft than an engineering discipline” (Elfick, 2009). And as another explained: “It is the focus on the development of new engineering principles and formalism for the substrate of biology that sets [synthetic biology] apart from the more mature fields upon which it builds, such as genetic engineering” (Nature Biotech, 2009). This independent logic structure does not by itself define the field, though, as demonstrated by the continued absence of a unified definition.

This chapter will explore how various stakeholders have come to define the field, and how those definitions may affect regulatory alignment. It will trace notable achievements and points of growth thus far, and offer projections for the future ranging from conservative advances to moonshot applications. It will also review the enabling technologies that have allowed synthetic biology to get to where it is today, and consider the leading pair of analytical frameworks through which these advancements have been pursued. Combining the rapidity of advancements, novelty of applications, and diffusion potential of the field, the insights from this chapter establish the motivations behind, and need for, the later-described iGEM interventions. This chapter will also set the stage for subsequent discussions on oversight, which will identify existing oversight mechanisms and their methods for defining and handling the field.

Defining the field

To understand where synthetic biology is going, it is first essential to understand how it is defined. Here, a definition goes far beyond simply explaining the matter of focus; it can shed light on motivating principles, future expectations, scope of work, and potential areas of concern. Disagreements in definition are more illuminating than they are obfuscating, though, as the variety of points of emphasis make clear the immense scopes of interest of practitioners in the field. With biologists, chemists, computer scientists, and engineers all turning to synthetic biology for new insights and processes, each sees the field from a unique perspective that values foundational concepts in vastly different manners. However, most, if not all, would agree on one point: synthetic biology is driven by a desire to shift knowledge acquisition from being based on observation to being based on carefully designed frameworks.
Indeed, the quote by physicist Richard Feynman should be considered a unified rallying cry for the field: “What I cannot create I do not understand.” From there, though, the field splinters.

In 2009, the journal *Nature Biotechnology* surveyed 20 experts in synthetic biology and asked them to define the field in their own words. A selection of responses follows, with points curated to show the broad spectrum of perspectives possible. Interpretations ranged from bright-eyed and empowered by the “newness” to cynical and conservative about any inclination toward “revolutionary” (*Nature Biotech*, 2009):

- “At its heart, all synthetic biology shares a constructivist philosophy of trying to figure out how simpler parts can be combined to build systems with much more sophisticated behaviors, whether the goal is to build something useful or to increase our basic knowledge.” Wendell Lim, Professor, Department of Cellular and Molecular Pharmacology

- “Synthetic biology, by exploring how to remake or assemble the molecules of life, provides a complementary scientific approach for learning how life works.” Drew Endy, Assistant Professor, Department of Bioengineering

- “Synthetic biology comprises the research necessary to develop a living organism that can be described without reference to an existing organism.” E. Richard Gold, Professor, Faculty of Law

- “Synthetic biology aims to make the engineering of new function in biology faster, cost effective, scalable, predictable, transparent and safe.” Adam Arkin, Professor, Department of Bioengineering

- “The term synthetic biology should really be synthetic biotechnology. ... The goal is to leverage exponential information-generation with the precision of biology to create these tools.” David Berry, partner, Flagship Ventures

- “The new name ‘synthetic biology’ reflects an explosion in our ability to genetically engineer increasingly complex systems and the desire of scientists and engineers from fields outside molecular biology and genetics to participate in the fun, contributing to the technology and its applications.” Frances Arnold, Professor, Division of Chemistry and Chemical Engineering

- “Philosophically speaking, the project of synthetic biology crystallizes in one single question: can we or should we, undoubtedly being part of nature, understand ourselves as co-creators of the evolution?” Joachim Boldt, Assistant Professor, and Oliver Müller, Junior Research Group Leader, Department of Medical Ethics and the History of Medicine

- “Multiple streams of scientific inquiry and engineering practice, some decades old, converge under the marketing banner ‘synthetic biology’. The ways we think and feel about biology are evolving along with the technologies used to manipulate it.” Thomas H. Murray, President, The Hastings Center

- “These words [synthetic biology] don’t have much meaning. ... But I’d say synthetic biology’s key utility is to excite engineers, undergraduates and funding agencies. Its key disadvantage is to create hysteria in the defense community.” Andrew Ellington, Professor, Institute for Cellular and Molecular Biology
Scientific progress is incremental, but people holding purse strings, public or private, are most excited by paradigm shifts and the prospect of quick payoffs. Synthetic biology, then, is a useful term to attract funding for the ongoing (~30-year-old) biological revolution, powered by advances in molecular biology techniques coupled with increases in computing power.” Jeremy Minshull, CEO, DNA2.0

Throughout these definitions, there is a consistent trend toward understanding the field as more of a framework for applying techniques than as any single process or technology. How that framework is shaped and understood, though, varies. At the heart of the debate stands the tension between engineering and biological constructs, and what it means to frame the field in light of one or the other. For engineering, work is conducted to meet a purpose, to build something that solves a problem. For biology, on the other hand, there is a need for work to enlighten and for discoveries to increase our comprehension of a system. In practice, this reduces to synthetic biologists either striving to design artificial systems in order to make new discoveries and new theories regarding living organisms (Brenner and Sismour, 2005), or instead for projects to be constructed in such a way that they make the world more manipulable and controllable (Calvert, 2013).

Despite its varied practitioners, many synthetic biology definitions tend toward an engineering perspective owing to the predominantly engineering backgrounds of the field’s early organizers. The National Science Foundation’s (NSF) Synthetic Biology Engineering Research Center (SynBERC) has a tagline of “building the future with biology” (SynBERC, 2014). The central synthetic biology website, www.syntheticbiology.org, is similarly engineering derived, ending each page with the note “making life better, one part at a time” (Synthetic Biology, 2014).

In some pursuits, the dichotomy between engineering and biological perspectives can still result in both parties leaving with increased knowledge despite varying motives for attempting a project. For example, one lasting goal of synthetic biology from an engineering perspective is to “black box” a system, wherein a user of a part does not need to be trained in molecular biology in order to incorporate it into a design. For a biologist, achievement of this goal would result in complete understanding of the system. For an engineer, achievement of the same outcome would result in knowledge of the system so as to be able to control it. Both leave with more knowledge than they came.

At other times, the pursuits of biology-oriented practitioners are distinctly at odds with those coming from an engineering perspective. For example, with regard to project complexity, engineers do everything in their power to remove the hurdles that complexity poses. One dedicated branch of synthetic biology, detailed more fully below, is that of designing a minimal cell wherein only genes deemed essential for organism viability are retained. All non-essential processes are pared from the construct. Explained one computer-scientist-turned-synthetic-biologist: “A biologist is delighted with complexity. The engineer’s response is: ‘How can I get rid of this?’” (Tom Knight in Calvert, 2013). As another put it
more starkly, “You focus on the parts of the science that you do understand and clean out the parts that you don’t understand” (George Church in Breithaupt, 2006). Such an approach, while powerful for the engineer, is antithetical to the biologist. For the biologist, the uncovering of something that is unknown is a puzzle to be solved, not a question mark to be bracketed and set aside.

The first report from the Presidential Commission on Bioethics, “New Directions: The Ethics of Synthetic Biology and Emerging Technologies” (2010), is a comprehensive characterization of the field. However, it, too, was forced to define synthetic biology from each contributing discipline’s perspective. According to the report, for a biologist, “synthetic biology is a window through which to understand how living things operate. ... The ability to model and manipulate living systems using synthetic biology is yielding new knowledge that will better define the functions of genes and physiological systems.” For engineers, on the other hand, the report states: “[synthetic biology] is an opportunity to apply the techniques and tools of engineering to complex living organisms. ... Engineers working in the field of synthetic biology hope to bring a similar level of standardization, predictability, and reproducibility to biology.”

The true import of a unified definition for synthetic biology exists largely in the degree to which it affects the field’s treatment by outsiders, from regulators to citizen groups and all else in-between. Some practitioners, for example, are seeking refuge under the cover of “synthetic biology” to escape current GMO public relation woes; others are fleeing the title, afraid to be associated with a potential future lightning rod for bad press and sensationalized reporting. Otherwise, as multiple practitioners suggested in the definitions above, the ability of “synthetic biology” to mean different things to different people provides great latitude for a wide range of participants to engage in the subset of pursuits that most excite and energize them.

**DNA sequencing and synthesis technologies enabling diffusion**

Genetic engineering is based on the concept that the genetic code underlying cellular processes can be modified to meet new endpoints. As seen in the simplified mock-up in Figure 1, deoxyribonucleic acid (DNA) encodes genes, genes encode proteins, and proteins drive cellular processes. In practice, the interactions between each layer can be highly complex and typically involve multiple feedback loops. However, the essence of the structure remains true, and each layer provides an opportunity for modifying the system. By inserting new genes, deleting existing genes, or modifying the systems around genes, genetic engineers are able to confer processes from one organism to another, and to devise systems that are novel in nature. Tools for implementing such changes were first developed in the 1970s with recombinant DNA techniques, but have been greatly improved and expanded since that time.
Figure 1. DNA, genes, and proteins. The genetic code, or DNA, underlies cellular processes. Subsections of DNA encode genes, genes encode proteins, and proteins combine to drive essential cellular process. Image courtesy Presidential Commission on Bioethics (2010).

Recently, significant advances have been made with regard to DNA sequencing and DNA synthesis technologies. Here, sequencing refers to the ability to “read” the genetic code by running DNA through machines that effectively turn base pairs into data points. Synthesis, on the other hand, refers to the ability to “write” genetic code by taking data points on a computer and turning them into base pairs. The speeds at which these processes are performed, and the prices at which such speeds are achieved, have come down substantially over time. Much like the increase in the number of transistors per chip fundamentally drove the progress in computing power, so too has the improvement in sequencing and synthesis abilities for synthetic biology. In fact, synthetic biology has recently found itself with its own version of so-called Moore’s Law, the observation that the number of transistors per chip (and thus, effectively, computing power) increases exponentially over time. While Moore’s Law has recently been explained as a self-fulfilling prophecy, Figure 2 (below) shows that sequencing technologies have recently been moving even faster than the rate observed in Moore’s Law (Carlson, 2014).

Figure 2 compares the “productivity” measure of DNA reading and writing (i.e., sequencing and synthesis) against the standard metric for Moore’s Law of number of transistors per chip. Here, productivity refers to the number of bases sequenced or synthesized per person per day. Sequencing
productivity took a major step forward in 2008 when the field shifted away from the first-generation process of Sanger sequencing to next-generation tools like ion semiconductor and sequencing by synthesis. Importantly, prices have plummeted in response, and thus sequencing is taking place at previously unprecedented rates. This means that a field like systems biology, which seeks to describe natural systems—from organisms to ecosystems—fully and completely, is currently awash in genomic data. Synthetic biology is thus benefitting directly from the sequencing technology gains, as well as indirectly from the ways in which these speed and price shifts have also transformed partner fields.

Synthesis technologies are less advanced than sequencing technologies, yet they, too, have also come a long way over the past two decades. With improvement in synthesis, synthetic biologists have been able to speed up and scale up the design-build-test cycle to an unprecedented rate, such that practitioners are able to test multiple iterations of a design at once, and incorporate feedback from one design into the next over the course of a single week.

**Top-down, bottom-up**

In synthetic biology, there are two primary approaches for engineering systems: top down and bottom up. Xenobiology, or the development of a genetic language orthogonal to our existing system, is also a form of synthetic biology. For the purposes of this effort, however, only the first two approaches will be considered, as xenobiology is currently a niche field requiring governance under a wholly different set of considerations.

The top-down approach to synthetic biology maintains existing genomes as the starting point for system modification, similar to 1970s recombinant DNA work. However, with top-down synthetic biology, there is an increased emphasis on paring down the nonessential components of a genome. The resulting organism is considered a “chassis,” or base organism, into which additional processes can be engineered. The benefits of a biological chassis are immediately evident: engineers would have ready
access to a simple, predictable, and programmable organism into which they could then stack a wide array of targeted processes. And, while a chassis is derived from an existing genome, it can also be modified to include features from other organisms, or simply to be “edited” itself. This means that a chassis could also be engineered in such a way that it simultaneously addresses safety and security concerns like barcoding for monitoring and surveillance purposes, and minimizing the potential for horizontal gene transfer of engineered traits (Esvelt and Wang, 2013).

Development of a minimal chassis presents a non-trivial analytical challenge. It first requires the complete sequencing of a genome, and then requires rigorous analysis of the genes and gene-pairings that are required for cell viability. Some studies have successfully mapped essential knockout and pairwise interactions. As the number of gene combinations increases exponentially, however, what works for examining single or paired interactions quickly becomes intractable at higher numbers. Recently, an international collaboration has begun to develop a designer eukaryotic genome based on the yeast species *Saccharomyces cerevisiae* (Sc2.0, 2014), and has pioneered a novel approach for examining such interactions (Annaluru et al., 2014).

*S. cerevisiae*, or brewer’s yeast, is an organism commonly targeted for engineering. It has a genome consisting of approximately 12 million base pairs (Mb), broken out across 16 chromosomes and approximately 6,000 genes (Goffreau, 1996). In the pursuit of an entire designer eukaryotic genome, researchers took an important first step through the complete re-factoring of chromosome III, dubbed “synIII.” Following stop-codon replacements; deletions of subtelomeric regions, introns, transfer RNAs, transposons, and silent mating loci; and the insertion of sequences to enable genome scrambling, the chromosome was reduced in size from 316,617 base pairs (bp) to 272,871 bp but the organism maintained fitness and chromosome replication timing (Annaluru et al., 2014). This study represents a significant breakthrough on the path to model organism optimization.

In addition to the development of a model chassis, top-down synthetic biology also refers to the process of using properties from one or more living species to create a novel system in a different organism (Gutmann, 2010). For example, a specific bacterium may perform a highly desirable chemical process, but the organism itself is poorly suited for industrial environments. In this case, a scientist would search for a bacterial strain that performed the desired skill, and then once found, shift that trait to an organism better suited for industrial productivity such as *S. cerevisiae*.

The bottom-up synthetic biology approach points toward a similar endpoint as that of top-down methods, in that both approaches seek to create a minimal life form. Whereas the top-down perspective looks to pare that which already exists to its most basic form (i.e., a protocell), however, the bottom-up approach seeks to build such an organism from scratch and thereby transform data and design principles into life forms.
One way to think about bottom-up synthetic biology is to consider the abstraction of the process, as visualized in Figure 3. Here, the genetic code forms the basis of the effort, as it is used to build the “blocks” then stacked for organism construction. A popular metaphor for this approach is to consider parts—which include things like promoters, terminators, and ribosome binding sites—as something akin to Legos®. When these standardized, interchangeable pieces are snapped together, they can then create devices, like a light sensor or a cell-to-cell signaling system. When devices are coupled circuits can be formed, and ultimately those circuits can be built up into full systems. The Legos® metaphor has in fact been cemented into common practice, as the Registry of Standard Biological Parts is home to a catalog of BioBricks, or standardized parts, that can be combined and exchanged in the same manner around the world. The underlying philosophy of the Registry is to provide a resource of available biological parts that have been user tested and characterized, and to “provide these resources for the continued growth of synthetic biology in education, academic research, and new industry” (Registry, 2014). The BioBricks Foundation further emphasizes the importance of open, standardized systems for basic synthetic biology construction, stating: “We envision a world in which scientists and engineers work together using freely available standardized biological parts that are safe, ethical, cost effective and publicly accessible to create solutions to the problems facing humanity” (BioBricks Foundation, 2014).

Standardization is crucial to the bottom-up approach to ensure that parts are usable across organisms and throughout devices. It is rare for a part to be designed entirely from scratch, as most are instead culled from knowledge reported in the scientific literature. An engineer will search for the existence of some desired function, which will ideally have been identified in a previously studied organism. From there, the engineer must make adjustments to the identified part in order to maximize its usefulness for his project as well as for the broader synthetic biology audience. Most importantly, these adjustments must prepare the part for varied use by enabling it to be readily snapped together with any other synthetic biologist’s project. These adaptations of the physical composition of the part include adding defined prefix and suffix sequences containing specific restriction endonuclease sites, and ensuring that those same restriction sites are not found elsewhere within the original part’s sequence. As the field evolves and projects become more complex, it is also becoming increasingly important for
practitioners to coalesce around a standardized “datasheet” for reporting part characterization. (Canton et al., 2008)

The bottom-up approach is driven by a goal of modularity, and strengthened by the prospect of decoupling. Modularity is achieved when a system can be broken out into its component pieces and then fully recombined again. With modularity, a scientist can ideally defer to someone else’s work defining a specific system, seamlessly incorporate it into his own project, and know that it will function as specified. Modularity, in effect, leads to the “black boxing” of biology, which in turn allows for those with no or limited knowledge of biological systems to still be able to build and design given a known input and output (Calvert, 2013). This is directly related to the increasing accessibility of the field, and the ability of Do It Yourself (DIY) synthetic biologists to contribute to system building without first personally attaining deep institutional knowledge. Decoupling, or the separation of design and fabrication processes, further lends to the gap between producers and consumers of organism knowledge, as it allows synthetic biologists to design their sequences and then rely on synthesis technologies to fabricate them (Calvert, 2013; Endy, 2005). This decoupling further expands the distance between that which synthetic biologists can imagine, and that which evolution has previously established as immovable constraints.

Importantly, the concepts of black boxing and decoupling have come under intense criticism by some incumbents in the foundational fields, as well as by advocacy groups and adherents to the precautionary principle. To them, such concepts epitomize the hubris with which they view synthetic biologists as approaching natural life forms and assuming the ability to identify, understand, and overcome all of the nuances of evolution.

Wrote one of the strongest critics of synthetic biology, the advocacy entity the ETC Group (2007): “Synthetic biologists claim that because they are building whole systems rather than simply transferring genes, they can engineer safety into their technology…. That assumes, of course, that the life builders have complete mastery over their art – an impossible standard since synthetic biologists, for all their talk of circuits, software, and engineering, are dealing with the living wetware of evolution and all its unpredictability.” An alternative perspective, as a voice from an adjoining field, shared somewhat similar end points: “An engineer’s approach to looking at a biological systems is refreshing but it doesn’t make it more predictable. The engineers can come and rewire this and that. But biological systems are not simple…. And the engineers will find out that the bacteria are just laughing at them” (Eckard Wimmer in Breithaupt, 2006). From a policy perspective, this sobering view was echoed by Gary Marchant (2011), stating: “The operating assumption at this point – that we both understand these systems, and are capable of managing them so that we achieve desired outcomes without unfortunate unanticipated consequences – is at best whistling in the dark, and more likely an abdication of ethical and rational responsibility.” And in perhaps the most pertinent distillation of the challenges, synthetic biologist James Collins conceded: “If
you have incomplete knowledge then it is highly possible that you are up for a few surprises” (Breithaupt, 2006). Where synthetic biologists see a challenge, critics see a fatal flaw.

**Survey of the field**

Synthetic biology can be defined as much by what it can achieve as by how it can achieve it. The breadth of applications, novelty of products, and speed at which such applications are brought to bear represent a true shift in framing. For this reason, the regulatory system must be considered in terms of its ability to moderate the tools in use as well as its capacity to keep pace with the streaking field. What follows is a brief survey of the field’s accomplishments thus far, and projections for where the field is heading next.

The novel synthetic biology applications beginning to make it to market today were only made possible thanks to a decade of significant investment in foundational advances for the field. And, those advances only got to where they did by standing on the shoulders of the nearly three decades of recombinant DNA research that preceded them. Figure 4, a timeline of early synthetic biology milestones, picks up where the nascent field was just beginning to come into its own with engineered toggle switches and genetic circuits in the early 2000s. In their 2009 review, Purnick and Weiss marked the approach of a turning point for synthetic biology as the field began to make a shift from focusing on modules to using those modules to build systems. While the remainder of this section will on these systems and applications, it is essential to recognize the underlying contributions that led to this point.

Figure 4. Synthetic biology milestones, 2000-2008. Priscilla Purnick and Ron Weiss map the development of major foundational advances in the early years of the field in their paper *The second wave of synthetic biology: from modules to systems* (Purnick and Weiss, 2009).

In terms of reach, synthetic biology has its hands in nearly every field. From food to fuel and drugs to remediation, there is little that synthetic biology has not at least *tried* to address. However, some
of the most notable current areas of emphasis include medical applications, agricultural advancements, fuel development, and chemicals production.

With regard to medical applications, there have been three main branches of development: pharmaceuticals production through metabolic engineering, manipulating organisms to deliver targeted in vivo treatments, and advancements in drug testing environments. One of the earliest synthetic biology success stories was that of the artificial production of artemisinin products by engineered yeast organisms. Artemisinin is an antimalarial medicine, previously only harvested from the wormwood plant. The synthetic pathway production was taken over by the pharmaceutical giant Sanofi, and has now been scaled to meet one-third of total world demand in just two years of production. For drug testing advancements, on the other hand, researchers have been pursuing the development of so-called “programmable organoids.” This involves the development of multicellular systems, and is still in the early stages of research. Conceptually, however, the application would be particularly valuable for conducting drug trials outside of model organisms, and for being able to perform meaningful tests on rare diseases where incidence rates are typically too low for trials to reveal significant insights. (SynBERC, 2014)

On the agricultural front, synthetic biology projects have been tackling crop specialization in ways that simpler recombinant DNA modifications had been unable. One example of this is the on-going work by researchers to confer nitrogen fixation abilities to non-leguminous plants. Despite being one of the leading goals of early genetic engineering, recombinant DNA research was never able to achieve such ends. However, technological advances in synthetic biology have now made it possible to envision this pathway, beginning with the standardization and refactoring of the nif gene cluster from Klebsiella oxytoca to ready the pathway’s transfer to crop plants. At present, such research has not advanced beyond the refactoring and optimization stage; eventually, the cluster will either be moved directly into plant chloroplasts, or into organisms in the soil surrounding plants. (SynBERC, 2014)

Significant amounts of early synthetic biology commercial investments have been allocated to algal biofuels. Here, the goal is to engineer algae species to produce hydrocarbons, which are either then used directly, or further processed to become combustion-ready. Currently, such endeavors have been successful in terms of proof of principle, but have struggled to attain commercial success. As processes become more efficient and the technology advances further, however, it is possible that algal biofuels could become a significant contributing alternative fuel source. Notably, several big-name corporations have signed on to algal biofuel projects in recent years, including Audi, BP, and Chevron.

Perhaps the most immediately accessible commercial application of synthetic biology has been the development of high-value chemical compounds. These have been wide-ranging in their endpoints, from food additives to cosmetics. Further, the applications have provided a relatively easy introduction
for the field, as they largely involve the addition of specific pathways into well-characterized chassis. Several hurdles remain in terms of being able to reliably achieve the same productivity levels at the industrial bioreactor scale as are initially achieved at the laboratory scale.

Synthetic biology is not without its dreamers. Indeed, many of the early pioneers in the field arrived with a vision of eventually being able to engineer living organisms in the same way that they were presently able to engineer the non-living artifacts around them. From designing a tree that builds its own tree house to developing systems capable of propagating throughout an entire population, the goals for synthetic biology applications are only just beginning to be formed.
Chapter 3. Mechanisms for oversight

At present, synthetic biology is notable less for what it has done than for what it promises to do. But as the previous section detailed, delivery on even a small percentage of these goals has the potential to be truly disruptive to society. By challenging the closely held principle that the power of human engineering stops at living organisms, synthetic biology has called into question matters of security, safety, environmental protection, ethics, and equality. It is clear that such advances should not be allowed to proceed unquestioned, evading public discourse through strategic branding and races to the commercialization finish line. However, the democratic, deliberative processes we previously had the privilege of exposing new technological entrants to are becoming increasingly impractical and infeasible given the rapidity of change enabled by synthetic biology technologies. Further, the oversight backstop long provided by the U.S. regulatory system through notice-and-comment rulemaking, legislation, and judicial review is being rendered obsolete, unable to evaluate and manage emerged technologies, let alone emerging ones.

This chapter will survey the existing oversight mechanisms in the United States and elsewhere, and document where and how the current approach is broadening existing schisms in oversight, not bridging them. The chapter will also explore alternative oversight mechanisms that have been proposed to meet the unique challenges presented by synthetic biology. Importantly, the scope of these alternative mechanisms goes beyond that of state, federal, and international agreements. As Gary Marchant explains in his 2011 work “The Pacing Problem” (emphasis added):

The consequence of this growing gap between the pace of technology and law is increasingly outdated and ineffective legal structures, institutions, and processes to regulate emerging technologies. The two basic options for addressing this problem are (i) to slow or stop the pace of scientific progress; or (ii) to improve the capacity of the legal system to adapt to rapidly evolving technologies (even if this means departing from traditional forms of legal regulation into broader forms of governance...).

Believing that synthetic biology can be slowed or stopped is naïve; given what we know of the track records of emerging technologies throughout history, attempts at stopping distribution more often end up quickening the pace of dissemination, not slowing it. Acknowledging synthetic biology’s particular emphasis on modularization and increasing technical accessibility, any hopes of arresting its progress are made all the more impractical. Therefore, the question then becomes how best to implement the second option noted above: improving the capacity of the oversight system.

Federal approach

Current oversight of biotechnology in the United States can best be defined as a patchwork approach. On the surface, this is not a drawback; indeed, by overlapping authorizing bodies, flexibility
and maneuverability can be powerfully incorporated into the system. However, this is dependent upon a strong and clear coordinating framework to serve as the organizing scaffold. For issues of security, this has been largely the case. Elsewhere, though, the gaps in oversight seem to be more a sign of confusion of authority than a conscientious decision to permit a process. The U.S. has not promulgated any new regulations to explicitly target synthetic biology applications. However, multiple existing statutes have been interpreted as applying to the emerging field. In general, federal oversight of synthetic biology hinges on four primary factors:

1. The driver of the work (i.e., research versus production);
2. The funder of the research (i.e., whether or not federal funds are involved);
3. The nature of the application (e.g., medical, agricultural); and
4. The degree to which national security and export controls are involved.

In addition, any given actor may be covered by local, state, or institutional requirements. This section will review how these factors have been interpreted in light of synthetic biology technologies thus far, as well as the degree to which existing frameworks may prove insufficient over time.

The Coordinated Framework

After a decade of exploration in the nascent field of recombinant DNA engineering, what had been a purely research-focused enterprise began to make the transition toward commercialization. As a result, in the 1980s the U.S. government issued a trans-agency guidance document referred to as “The Coordinated Framework,” which stated that agencies should regulate genetically engineered organisms through existing regulatory frameworks, even though such systems had been developed without genetic engineering in mind. The Coordinated Framework remains the primary governing paradigm today, notably made operational by an assessment of applications based on their final characteristics, not the methodologies used to create them.

Broadly speaking, the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) regulate plants, drugs, and food on a case-by-case basis, with the USDA also moderating the interstate passage of plant pests, pathogens, and infectious agents; the Environmental Protection Agency (EPA) regulates the entrance of new chemicals to market that are not otherwise captured by alternative agencies; the Occupational Safety and Health Administration (OSHA) regulates the safety of workers interacting with such materials; the Department of Transportation (DOT) and Department of Commerce (DOC) regulate the import, export, and migration of materials, with a particular emphasis on those posing potential safety or security risks; and the National Institutes of Health (NIH) and the Centers for Disease Control (CDC) regulate laboratory practices through the promulgation of risk assessment and containment guidelines. Security risks are predominantly covered by the joint
administration of the Federal Select Agent Program (FSAP) by the CDC, the Animal and Plant Health Inspection Service (APHIS) of the USDA, the Federal Bureau of Investigation (FBI), and the Department of Health and Human Services (HHS). (Gutmann, 2010)

Although the existence of the Coordinated Framework may seem to suggest some lasting infrastructure through which various U.S. agencies can coordinate on questions of biotechnology, that is largely not the case. The following sections on specific regulatory mechanisms will pay particular attention to those aspects regulating biosafety and biosecurity concerns given their greatest relevance to iGEM’s potential testbed points of intervention.

Biosecurity

Biosecurity, or the prevention measures used to minimize accidental or intentional harmful outcomes caused by biological agents, has been the most active of all regulatory areas relating to synthetic biology. This has been motivated in large part by biotechnology’s perceived threat as dual use research of concern (DURC). According to the NIH, DURC is defined as “life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security” (NIH, 2013). DURC oversight aims to enable the pursuit of beneficial research by mitigating the chance of such findings being harmfully applied. In addition to DURC concerns, biosecurity measures have received renewed attention following a 2008 conclusion from the congressionally mandated Commission on the Prevention of Weapons of Mass Destruction (WMD) Proliferation and Terrorism, which stated that a bioterrorist attack was “more likely than not” within the next five years (Commission on the Prevention of WMD Proliferation and Terrorism, 2008). Synthetic biology is but a subset of biosecurity concerns; however, in recent decades, even minimal association with the U.S. security machine has demanded a course of ongoing and escalating engagement.

Biosecurity is unique from other forms of scientific oversight in that for it to be most effective, it must intervene during the research process as opposed to only when an application is being considered for commercialization. An early security measure affecting synthetic biology research was that of the FSAP. Congress passed Section 511 of the Antiterrorism and Effective Death Penalty Act of 1996, which directed HHS to establish a list of select agents and toxins and create procedures for overseeing their use. Following the September 2001 terrorist attacks, access to select agents was restricted under the USA PATRIOT Act. Rules were further tightened as a result of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, and made to include animal and plant agents as determined by the USDA under the Agricultural Bioterrorism Protection Act of 2002. Both agencies published their final
rules in the Federal Register in October 2012, with additional updates included in 2013. (Select Agents, 2014)

At the center of the FSAP is a list of biological agents and toxins that have been deemed elements of concern due to their potential to “pose a severe threat to public, animal, or plant health or to animal or plant products” (CDC, 2013). Projects incorporating the use of a select agent in their design trigger the following oversight activities:

- Inspection of facilities that possess, use, or transfer select agents;
- Security risk assessment by the FBI of all individuals who work with any such select agents; and
- Investigation of incidents in which non-compliance may have occurred.

The FSAP is also responsible for developing guidance documents to assist entities in achieving compliance with the regulations, and to maintain an updated and evolving list of select agents and toxins. (CDC, 2013)

The FSAP aims to balance limiting the potential for harmful outcomes against unduly burdening beneficial research projects. This is a difficult line to walk, and it is not uncommon for researchers and security experts to leave the table dissatisfied. The FSAP is no exception, and has come under fire on both fronts. On the one hand, the effectiveness of the program has been called into question due to its organism- and toxin-based rigidity and its lack of clarity regarding the operational definition of how modified agents or subcomponents of such agents may be regulated. With regard to synthetic biology work, this is of primary importance given the near guarantee that an organism will not remain in its original form over time. Guidance does exist regarding rule applicability given genetic modification of agents and toxins and the covered functional forms of the agents; however, in practice there still remains significant uncertainty. On the other side of the issue, research has shown that there is a significant and lasting increase in operating costs associated with select agent work due to increased technical and administrative requirements. For example, the Regulatory Impact Analysis for the select agent regulations cited an annualized cost per facility of $15,300-$170,000, while commenters stated annual operations and maintenance costs ranging from $100,000-$700,000, with start-up costs even higher (HHS, 2005). Costs include installing electronic card access, alarm systems, security cameras, and additional recordkeeping and personnel requirements. Further, time costs can be significant, both in terms of ensuring compliance, and in terms of seeing researchers through complete FBI background checks. (NRC, 2009)

In addition to research within the laboratory, scientists must also be cognizant of select agent rules that involve the export, import, and transfer of regulated materials. Under the Export Administration Regulations, the DOC is responsible for regulating the export of select agents and toxins, relevant biological materials, and the technology associated with the pathogens and toxins (HHS Public Health Emergency, 2014). Applicability of shipping regulations is determined based on the material in question,
as well as the person (or entity) to whom the material is being sent. With regard to materials, items are subject to licensing based on the Commerce Control List, of which Category I ("special materials and related equipment, chemicals, “microorganisms,” and “toxins”) is relevant for synthetic biology. Following a category listing, items are further classified based on their reasons for control: anti-terrorism, chemical and biological weapons, crime control, Chemical Weapons Convention, encryption items, Firearms Convention, missile technology, national security, nuclear nonproliferation, regional stability, short supply, United Nations embargo, significant items, or surreptitious listening (DOC BIS, 2014). The ensuing classification comes with highly specific licensing requirements and policies for screening potential recipients. The end user must then be screened against a series of lists of known individuals and organizations, including the Entity List, the Denied Persons List, the Unverified List, the Specifically Designated Nationals List, the Debarred List, and Nonproliferation Sanctions (Gutmann, 2010). Given that the sharing of engineered resources is common throughout laboratories around the world, these controls have the potential to create significant additional burdens for researchers.

Scientists transporting materials within the confines of the US may also be regulated under DOT rules, which permit the safe and secure transportation of hazardous materials. If classified as a hazardous material, a range of oversight measures are triggered, including labeling and packaging requirements through the Pipeline and Hazardous Materials Safety Administration (PHMSA), which applies to hazardous waste being moved by air, rail, highway, or water (Gutmann, 2010). States, municipalities, and home institutions may also add their own layer of requirements regarding the use, transfer, and disposal of synthetic biology materials specific to their local jurisdictions.

Finally, in late 2010, HHS issued guidance to gene synthesis companies for screening orders of synthetic double-stranded DNA. As will be considered in the subsequent “Alternative Oversight Mechanisms” section, one year earlier, the International Gene Synthesis Consortium (IGSC)—at the time representing approximately 80 percent of all commercial gene synthesis business—had launched its own screening protocol, to which the HHS model is highly similar (IGSC, 2009). Stated HHS, “The Guidance was developed, in light of providers’ existing protocols, to be implemented without unnecessary cost and to be globally extensible, both for U.S.-based providers operating abroad and for international providers” (HHS, 2010). The Guidance is centered on a two-pronged framework, wherein providers of synthetic double-stranded DNA:

1. Should know to whom they are distributing a product; and
2. Should know if the product they are synthesizing and distributing contains, in part or in whole, a “sequence of concern” (HHS, 2010).

If either a potential customer or a potential sequence raises any flags, then the provider should perform a follow-up screen to verify that the customer is equipped to handle the risk level of the organism, and that
the organism is not above the appropriate risk level specific to the customer. Recipients of concern can be checked against existing lists such as those used in the Export Administration Regulations, while sequences of concern can be checked against those from the FSAP.

A major vulnerability of the screening type of framework is that rigidity in sequence screening has the potential to miss functional analogues of regulated organisms or toxins, despite differences in sequence coding, and that the screening framework is only as strong as the list cultivated to screen against. To the first point, HHS makes an important recommendation to mitigate that risk by suggesting a “best match” strategy wherein sequences are screened against known registries (e.g., NIH’s GenBank) and the resulting “hit” is the sequence closest to that which was screened, even if it was not a direct match. Further, HHS recommends that all screening verify the sequence against its six-frame translation, and that it actively work to bracket subsets of sequences that are highly conserved across organisms as primary “housekeeping” genes. To the second point, even HHS noted its limitations, stating that although it recognized its list was limited—and that the industry consortium were more proactive in the area—due to “the complexity of determining pathogenicity and because research in this area is ongoing and many such agents are not currently encompassed by regulations in the U.S., generating a comprehensive list of such agents to screen against is not currently feasible….” (HHS, 2010)

As highlighted by the HHS voluntary Guidance document, a critical weakness of the current federal biosecurity infrastructure is the emphasis on a known set of pathogens and toxins. This is an outdated approach that fails to acknowledge the increasingly divergent world synthetic biology is enabling, wherein “sequences of concern” may share no known comparator to past or existing organisms of concern. Further, synthetic biology undermines the idea that parts from all “safe” organisms can only be combined in safe ways, as it is possible that when brought together in novel combinations, safe components may combine to become a dangerous whole.

**Biosafety**

Biosafety refers to the practices, procedures, and equipment necessary to ensure safe conditions in facilities working with potentially hazardous biological organisms. Laboratory biosafety specifically refers to actions taken in the laboratory to mitigate biohazards, driven primarily by the principles of hazard recognition, risk assessment, and hazard mitigation. A system of biosafety level (BSL) designations has been developed to reflect escalating laboratory protections in the face of increasing perceived risk levels of projects. Typically, a review board will assess the hazard potential of a proposed project, and subsequently assign the work to be done in a laboratory meeting a specific BSL threshold. In the US, levels run from 1 (least protective) to 4 (most protective). Some countries share similar BSL systems as that of the US, while others have modified versions, or none at all.
At the federal level, biosafety oversight in the US is achieved through a mix of regulatory and guidance mechanisms. State, municipal, and institutional entities also often overlay some form of requirements. The broadest level of oversight comes from OSHA's General Duty Clause (29 U.S.C. § 654), which states, in part, that: "Each employer shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees." The General Duty Clause is typically cited when an inspection reveals a hazard to employees that is not directly addressed by another section of the OSH Act. Other potentially relevant OSHA standards include the Bloodborne Pathogens Standard and the Personal Protective Equipment Standards. Other overarching regulations include the HHS and USDA Select Agent Regulations, which include the oversight of select agent and toxin use (in addition to access), and the HHS/CDC Foreign Quarantine Regulations, which require a permit for the import of known or suspected agents causing disease in humans (PHE, 2014). Further, for workers exposed to new intergeneric microorganisms, EPA may require personal protective equipment and engineering control restrictions based on assessed risk levels through the Toxic Substances Control Act (TSCA) (40 CFR § Part 721).

Outside of the above regulations, the bulk of federal oversight comes in the form of a pair of guidelines relating to laboratory biosafety and biocontainment: the “Biosafety in Microbiological and Biomedical Laboratories” (BMBL) manual by the NIH and CDC, and the “NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules” (“NIH Guidelines”). The NIH Guidelines was drafted in 1976, and has been updated frequently since then to reflect new knowledge and changes in technologies over time. The BMBL followed about a decade later, and is now in its fifth edition. The BMBL and NIH Guidelines are closely related and are important complements to one another. In general, the BMBL has broader coverage than the NIH Guidelines’ recombinant DNA focus, and goes into greater depth regarding biocontainment and risk assessment. Both rely on institutional biosafety committees (IBCs) as cornerstones of their approaches.

The NIH Guidelines was first issued in 1976, a year after the 1975 Asilomar Conference on Recombinant DNA. At the conference, scientists from industry, government, and academia convened to discuss safety measures for addressing potential hazards arising from the emerging field of genetic engineering. In 1974, the NIH formed the Recombinant DNA Advisory Committee (RAC) to advise the Director of NIH on the subject. The RAC published the NIH Guidelines following the Asilomar effort by documenting specific practices for using and handling recombinant DNA molecules (Pew, 2001). The NIH Guidelines are not federal regulations; however, any researcher receiving NIH funds for recombinant DNA research, or any researcher working at a public or private entity that receives any NIH funds for recombinant DNA research, must be in compliance. Additionally, several government agencies require that any recombinant DNA research conducted or funded by them must also meet the standards, like the
USDA, the Department of Energy, and the Department of Veterans Affairs (Fauci, 2010). In September 2012 (effective March 2013), the NIH Guidelines were updated to include oversight of synthetic nucleic acids (NIH, 2013). This addition was the result of a growing recognition that biosafety considerations are relevant regardless of the technology used to generate an agent, and because of a recommendation by the National Science Advisory Board for Biosecurity (NSABB) that the government should work more closely with the scientific community to ensure that existing biosafety guidelines are clearly explained with regard to their applicability to synthetic nucleic acids (NIH FAQs, 2013).

The NIH Guidelines structures biosafety considerations as a two-stage evaluation process, wherein a risk assessment is first performed for the proposed project, and then a biocontainment strategy is matched to the perceived project risk level. Importantly, the NIH Guidelines is not prescriptive; the document actively acknowledges that risk assessments are an inherently subjective process. While the NIH Guidelines does provide a basic framework for this process, it places significant responsibility on the local IBC to make the final judgment. The starting point for the risk assessment is based upon the “Risk Group” (RG) of the parent organism, which can fall into one of four categories:

1. RG1: Agents are not associated with disease in healthy adult humans;
2. RG2: Agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available;
3. RG3: Agents are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available; or
4. RG4: Agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available. (NIH, 2013)

RGs are based off potential effects on a healthy human adult; NIH provides a list of biological agents and RGs in Appendix B of the Guidelines, “Classification of Human Etiologic Agents on the Basis of Hazard.”

After establishing the parent organism RG level, the assessor must then make changes to the overall project risk level based on a series of factors regarding how the agent will be modified during the process. For example, making changes that could affect agent virulence, pathogenicity, infectious dose, environmental stability, and quantity, as well as gene products effects such as toxicity, physiological activity, and allergenicity (NIH, 2013). A modified strain could have a higher or lower RG assignment than the original wild-type strain.

The process of comparing a modified strain to its parent organism becomes increasingly challenging as synthetic biology travels further along the bottom-up approach spectrum. The NIH Guidelines notes this issue, but is unable to move beyond providing general guidance for the risk assessor. For example, the Guidelines uses language like “it may be prudent to first consider...” (NIH,
2013). It does more helpfully provide a potential structure for addressing these scenarios, though, through the suggestion of a two-level analysis that first considers the RGs of the various sequence-providing organisms, and then an assessment of the specific functions of the sequences included. One can imagine that using a housekeeping gene from a high RG organism would not present the same risks as using the same organism’s primary virulence factor. The recommendation still does not provide a straightforward implementation process, however, as there currently exists limited function-specific data per organism, and an understanding of how these functions may change based on biological context requires continued knowledge attainment along the synthetic biology frontier. For many IBCs, this presents a tall order, and often requires an over reliance on information or opinions provided by the Principal Investigator (PI) for the project.

Once the RG of a project has been established, a final assessment must be performed to match the experiment’s risk level to an appropriate containment strategy. For recombinant and synthetic nucleic acid research, containment is typically achieved through a combination of three approaches. First, a system of standard laboratory practices has been developed and honed over time to minimize the chances of, and outcomes from, incidents and accidents. Second, a variety of physical containment strategies have been developed over time as a way of using equipment and laboratory installations to introduce physical barriers to reduce biological spread. Finally, a more recent development has been in the area of biological containment. This refers to highly specific biological barriers that can either limit the infectivity of an agent, or reduce its ability to disseminate and survive in the environment. Biological containment is a promising development, but it still requires significant improvements until it can be relied upon more heavily as a containment strategy.

Like the risk assessment process, the containment designation process is also somewhat subjective and highly project specific. Acknowledging the subjectivity of both of these areas, it is essential to consider who is making the classification decisions, and when. The NIH Guidelines presents a detailed account of experiments covered by the Guidelines, as well as the roles and responsibilities of various parties throughout the process. Depending on the risks presented by an experiment, it may trigger oversight and review by a variety of groups. The six designated experimental levels are listed here in descending order of coverage: 1) those that require IBC approval, RAC review, and NIH Director approval before initiation; 2) those that require NIH/Office of Biotechnology Activities (OBA) and IBC approval before initiation; 3) those that require IBC and Institutional Review Board (IRB) approvals and RAC review before research participant enrollment; 4) those that require IBC approval before initiation; 5) those that require IBC notification simultaneous with initiation; and 6) those that are exempt from the NIH Guidelines (NIH, 2013). The first level is also referred to as a “major action,” and refers to projects like those that deliberately transfer a drug resistance trait to microorganisms, subsequently compromising
the ability to control the disease agent. If a major action has already been approved, then any subsequent submission will be reviewed at the second level, as are projects that deliberately include genes for the biosynthesis of toxin molecules lethal to vertebrates at an LD<sub>50</sub> of less than 100 nanograms per kilogram of body weight. The third level of review involves projects deliberately transferring modified DNA or RNA into human research participants, hence the inclusion of IRB approval in addition to IBC approval.

The fourth level of review, where a project only requires IBC approval prior to initiation, is more common. In this instance, the PI must submit information to the IBC documenting data points relevant to the risk assessment process, like the sources of DNA, the nature of the inserted sequences, the hosts and vectors used, and the containment conditions to be implemented. The IBC then reviews the submitted information, and projects can only begin after IBC approval. Experiments triggering such review include those using RG2, RG3, or RG4 agents as the host-vector systems, and those moving DNA from RG2, RG3, and RG4 agents into nonpathogenic prokaryotic or lower eukaryotic host-vector systems (excluding those already covered at a higher experiment review level). Other projects covered at this level include experiments using infectious DNA or RNA viruses (or defective DNA or RNA viruses in the presence of a helper virus) in tissue culture systems; experiments involving whole animals; experiments involving whole plants; experiments involving more than 10 liters of culture; and experiments involving influenza viruses.

Projects requiring IBC notification simultaneous with experiment initiation, or the fifth level of review above, largely involve low RG organisms undergoing minimal revision. For example, such projects include those involving the formation of recombinant (or synthetic) nucleic acid molecules containing less than two-thirds of the genome of a eukaryotic virus, and experiments involving transgenic rodents that only require BSL<sub>1</sub> containment. Exempt experiments, or the sixth level of “review,” include those that deal only with synthetic nucleic acids that cannot replicate or generate nucleic acids that can replicate in a living cell, or those that involve the use of nucleic acids from a host when only propagated in that same host (or a closely related strain of the same species). A variety of experiments are exempt from review, and the NIH periodically updates such lists through the determinations of the NIH Director, as well as from advice of the RAC.

Ultimately, the responsibility for ensuring that research is conducted in compliance with the NIH Guidelines falls to the institution where the work is being conducted. To accomplish this, each institution must create and sustain an IBC, and appoint additional safety officers depending on the highest RG level of research at the entity, the volume of work conducted, and the nature of the work conducted (e.g., plants, animals, or human research specialists may be required). The IBC must be comprised of at least five members, including at least two members who are not affiliated with the institution and are capable of speaking to the health and environmental interests of the local community. The institution must submit
an annual report to NIH/OBA that lists all IBC members, including the chair and topic-specific point people, as applicable. (NIH, 2013)

At major research institutes or enterprises, it is possible to imagine a sufficient array of practitioners in the field who would be capable of serving on the IBC. At smaller universities, however, it is much easier to envision the challenges that can arise from attempting to gather a sufficiently knowledgeable group of individuals. In particular, for experiments involving synthetic biology techniques that increasingly reduce the availability of a baseline comparator, such a group of individuals must be able to fully consider the risks that could arise from synergistic interactions or context specific changes in trait behavior unlike anything previously observed. This shift away from being able to heavily rely on the parent organism’s RG level places more and more responsibility on the interpretations of the IBC.

Similar to the NIH Guidelines, the BMBL (Wilson and Chosewood, 2009) outlines principles and practices for biosafety and risk assessment. The BMBL is far broader in scope, though, and provides more detailed technical content regarding agent information and best practices for the development and implementation of biosafety and biosecurity programs. It also states: “The NIH Guidelines are the key reference in assessing risk and establishing an appropriate biosafety level for work involving recombinant DNA molecules” (HHS, 2009). The BMBL does include a special note on the unique hazards posed by genetically modified agents, warning risk assessors that multiple investigators have observed unanticipated enhanced virulence post-agent modification, and thus that it is essential to remain alert to the possibility that modification of virulence genes could lead to increased risk (Wilson and Chosewood, 2009).

**Regulatory oversight beyond biosecurity and biosafety**

In addition to the research interventions posed by the biosecurity and biosafety oversight mechanisms discussed above, multiple federal agencies retain direct authority over specific applications, sometimes independently and sometimes with overlap. This section will overview the most frequently invoked of these regulations by synthetic biology applications. Importantly, no immediate, significant changes are expected to be made to the ways in which these regulations have been previously applied to recombinant DNA applications.

TSCA, administered by EPA’s Office of Pollution Prevention and Toxics (OPPT), regulates new chemicals and microorganisms. The 1997 TSCA Biotech Rule (40 CFR 725) retained the interpretation of new “intergeneric” microorganisms as published in the Coordinated Framework Policy Statement more than a decade prior (OSTP, 1986). Here, “new” microorganisms refers to those formed by the deliberate combination of genetic material from organisms in different genera; those constructed with synthetic genes that are not identical to DNA that could be derived from the same genus of the recipient cell; those
not listed on the TSCA Inventory; and those used in TSCA applications. Exemptions are made for naturally occurring microorganisms, non-intergeneric genetically engineered microorganisms, and intergeneric additions sourced solely from the addition of well-characterized non-coding regulatory regions. TSCA reporting includes the following mechanisms:

- Microbial Commercial Activity Notice (MCAN): Any manufacturer, importer, or processor must file a MCAN 90 days prior to initiating manufacture/import (unless exempted).
- TSCA Experimental Release Application (TERA): Persons who wish to introduce a new microorganism into the environment for commercial research and development purposes must submit a TERA 60 days prior to initiation of the field test.
- Tier I/II Exemptions: Exemptions from MCAN filing available for closed system commercial activities using approved recipient organisms, meeting certain criteria for the introduced genetic material, and using specific containment or control technologies.

For TSCA Section 5 (the Biotech Rule), whether or not an effort is being undertaken for commercial purposes is crucial for determining coverage. If research and development is being conducted with the purpose of obtaining an immediate or eventual commercial advantage for the researcher, then it is covered. Therefore, if academic work is seeking a patent, then it, too, is covered. Research is exempted if it meets the following three conditions: the microorganism is manufactured, imported, or processed solely for research and development activities; there is no intentional testing of a microorganism outside of a structure; and the research is funded by another agency, contingent on compliance with the NIH Guidelines. Importantly, a research exemption is also provided for activities conducted inside a structure (here, a “structure” refers to a building or vessel which effectively surrounds and encloses the microorganism and includes features designed to restrict the microorganism from leaving).

Following submission of an MCAN, EPA can rule that sufficient information has been submitted to determine “no unreasonable risk” for any potential use (which will then land it on the TSCA Inventory), to determine “no unreasonable risk” in the intended situation but not all potential uses (which results in a Significant New Use Rule), to determine “unreasonable risk”, or to determine that insufficient information exists to determine effects, but that the possibility exists for unreasonable risk and/or significant/substantial exposure. TSCA is a risk-benefit statute, and in making these decisions, EPA performs risk assessments to balance a mix of data points and information areas. (EPA, 1997; Segal, 2013)

TSCA’s ability to effectively oversee synthetic biology applications down the road has the potential to be hindered in two important ways. First, TSCA is limited to commercially related research and development activities, which may leave uncovered multiple other activities of concern. Second, for those that it does cover, EPA has limited reach in terms of the amount of information available to it prior
to performing a risk assessment. It is possible for a submitter to suspend the notification review period if EPA determines that insufficient information is available, thereby allowing the entity time to generate additional data. EPA can also limit approval to a specific use, and require new applications for use in novel circumstances. As applications become increasingly complex, though, risk assessments do, too, and are often left to make assumptions about organism behaviors that cannot be substantiated with any existing data. It will be hard for EPA to put the brakes on projects it deems likely safe but incompletely understood. Companies are, however, required to immediately report any subsequent findings that may suggest that the application is harmful.

The FDA regulates new drugs and devices prior to their introduction to the U.S. market. It has included biotechnology products in its permitted applications for several decades, beginning with its 1982 approval of recombinant DNA insulin (Junod, 2007). The FDA’s animal drug provisions cover genetically engineered animals—regardless of whether they are being used for pharmaceutical production or as food for human or animal consumption—because the added genetic elements meet FDA’s definition of a drug (“an article (other than food) intended to affect the structure or any function of the body of man or other animals”) (FDA, 2010; Gutmann, 2010). This regulatory authority was recently witnessed in the case of genetically engineered salmon; however, FDA also has the ability to exercise “enforcement discretion” and decline to require pre-market approval for low-risk animals. Here, “low-risk” refers to genetically engineered animals that are not intended to be consumed as food, and where the modifications are shown to present low animal health and environmental risks. FDA exercised this discretion, for example, when it did not require approval of aquarium fish that had been modified to glow in the dark (FDA, 2010).

The FDA cannot require pre-market clearance for plant- or animal-derived foods, though it can demand evidence that food additives are safe at the intended level of use prior to their addition. If a product on the market is deemed a risk to public health, however, FDA may remove it from circulation. Further, FDA has interpreted its ability to regulate food additives as also applying to genetically engineered organisms, wherein it studies the implications of the added elements. (FDA, 2010)

As mentioned in the biosecurity discussion above, USDA’s APHIS is responsible for regulating genetically engineered organisms that are known to, or have the potential to, pose a plant pest risk. Here, a plant pest is that which may cause damage to a plant, either directly or indirectly, including via engineered organisms. Additionally, if a plant was engineered to include plant pest genes using vector agents, then it, too, will be covered. APHIS permit and notification decisions are based on whether the regulated article is likely to introduce or disseminate a plant pest in the environment. Characterizations of organism fitness, genetic stability, and potential for horizontal gene transfer are all important for such
decisions. APHIS also tightly controls the import, export, and interstate movements of genetically engineered products through permitting, licensing, and inventory requirements. (APHIS, 2007)

Finally, the National Environmental Policy Act (NEPA) requires all federal agencies undertaking major actions significantly affecting the quality of the human environment to assess the impact the project may have on the environment. Many states also have such mandates. An important component of NEPA is the requirement that an impact statement include a consideration of reasonable alternatives; although actors are not required to use the option posing the least environmental harm, it does force the actor—and the public—to be more conscientious of the chosen actions and considerations. NEPA’s applicability to biotechnology applications was fiercely debated following a rider attached to a March 2013 continuing resolution. In the relevant Section 735, it was made explicit that when a biotech crop has been approved for use but is subsequently challenged by a lawsuit, USDA shall grant temporary permits to farmers allowing them to continue planting the crop (H.R. 933, P.L. 113-6, 2013).

Hurdles from the current regulatory structure

As outlined in the preceding sections, the federal government presents a largely patchwork approach to the oversight of synthetic biology research and applications. An optimistic interpretation of the Coordinated Framework is one that sees an intentionally overlapping system left loosely interpreted to allow for growth and adaptation; a more cynical perspective identifies an ill-equipped, feeble mechanism that does the best it can to extend existing bodies’ oversight to new applications as they emerge over time. Of course, all regulations are some approximation of a patchwork approach. The degree to which they can twist and stretch to meet expanding and contracting concerns, however, is the true marker of their effectiveness. For synthetic biology, this “flexibility” has been repeatedly proven brittle and unyielding.

Regardless of motivating forces, it is obvious that the current structure is straining under the pressure exerted by the quickening pace of technological change, and that the gaps in oversight are only growing larger. The system retains multiple vulnerabilities in the face of synthetic biology scale-up, and is already pocked by scars from early run-ins with the nascent technology. For example, confidence in the self-reporting relied upon by the NIH Guidelines and the FSAP was severely undermined following the recent exposure of a series of violations at universities and other research facilities across the country. The most significant of these violations came from Texas A&M University, an important player in the national biodefense research program. But while A&M made some egregious errors—including multiple missing vials of Brucella bacteria; unauthorized employees working with select agents; a faculty member performing a recombinant DNA experiment without CDC approval; inappropriate disposal of animals used in select agent experiments; and three unreported cases of individuals exposed to Coxiella burnetii, (which causes Q fever)—the findings reflected about as poorly on CDC (Couzin, 2007). In the Fall 2007
incident report, CDC noted that it had only uncovered minor problems in a February 2007 inspection, and did not have any sense for the severe violations it later reported until it was prompted to return by an independent whistleblower in July (Couzin, 2007). Following the findings, CDC immediately suspended A&M’s program, which only reopened nearly a year later after implementing a series of changes and settling for a $1,000,000 fine. A&M was not an isolated case, though. A review of enforcement actions by the HHS Office of the Inspector General relating to select agent and toxins violations shows entities both large and small in trouble for a variety of missteps (OIG, 2014). Further, all of these violations were uncovered several years after the watershed report blasting the performance of IBCs in the US oversight system. Titled “Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research,” the October 2004 report was an aggregation of results from the Sunshine Project’s survey of IBCs around the US (Sunshine Project, 2004). Most notably, the effort documented trends of significant underreporting across institutions, the failure to maintain systems as required under the NIH Guidelines, and a general disregard for the operation of the system at large. The findings were highly damning of IBC performance, and the subsequent conclusions were extremely critical of the viability of the oversight system to be sufficiently protective in the face of increasingly complex work.

In addition to flaws in the self-reporting and self-regulating aspects of the biosafety and biosecurity programs, there is also the issue of coverage. The NIH Guidelines, for example, only applies to a subset of laboratories working on recombinant and synthetic nucleic acids work. Further, those that are covered are arguably those least likely to be of concern, as at least they are qualified enough to be awarded an NIH research grant. DIY researchers, on the other hand, are unlikely to be covered, and more likely to be operating without regard for protective laboratory practices. EPA and USDA are also both limited in the scope of entities covered. Further, as all of the oversight mechanisms rely on some form of risk assessment, they are also all vulnerable to the dearth of pertinent material available for informing such endeavors. As synthetic biology applications move increasingly away from having baseline comparators of relevance, risk assessments must be able to grow and adapt to make insights more readily available regarding scenarios in which parental information was previously heavily relied upon.

Finally, the most intractable of these issues is the mismatch in operating speeds between technological development and evolution of federal oversight. Marchant (2011) refers to it as a “pacing problem,” and Steven Popper (2003), a senior economist at RAND Corporation, writes: “We see a growing divergence between time cycles of government and those of technology development. Quite simply, this presents government operations with a Hobson’s choice: Either live within a shorter response time and run the concomitant risk of ill-considered actions (or inactions) or see government input become less relevant and assume reduced stature.” The federal system is situated so as to be vulnerable to delays from the legislative, regulatory, and judicial sides when emerging technologies are involved. While the
judicial case-law system was intentionally designed to provide a conservative check on emerging systems, the other two were not. On the legislative side, even attempts at incorporating opportunities for adaptation into legislation have proven unsuccessful, as political gridlock settles in to cement the old version into outdated place (Campbell, 2008). On the regulatory side, the burden on agencies for developing rule support is growing rapidly, while at the same time the pace of technology moving from laboratory to market quickens.

While the federal system need not remain in lockstep with the technology frontier, Lyria Bennett Moses (2007) neatly identifies four scenarios that can arise from a general pacing problem:

1. The failure to impose appropriate legal restrictions and precautions to control the risks of new technologies;
2. Uncertainties in the application of existing legal frameworks to new technologies;
3. The potential for existing rules to either under- or over-regulate new technologies; and
4. The potential for technology to make existing rules obsolete.

Without enough information to unravel the uncertainty surrounding these emerging technologies and insufficient political action to be able to expect adaptive change at the legislative or regulatory levels, it becomes necessary to take action to supplement the federal system with alternative oversight mechanisms in order to avoid the consequences described by Moses above.

**International collaborations**

In addition to federal oversight, several existing international agreements are also applicable to synthetic biology practices in the US, either explicitly or through interpretations of their written scope. Of these, the Australia Group, the Convention on Biological Diversity (and its associated Cartagena Protocol on Biosafety), and the United Nations Biological Weapons Convention figure most prominently. However, as detailed below, two of the three of these agreements are not legally binding, and all are hamstrung in their ability to sufficiently protect international safety, security, or environmental concerns. Further, because of the nation-specific interpretations of several of these agreements, confusion and non-compliance is ultimately increasing, not decreasing, as a result.

**The Convention on Biological Diversity and the Cartagena Protocol**

The Convention on Biological Diversity (CBD), entered into force in 1993, is an international treaty designed to achieve three primary goals: conserve biological diversity, support the sustainable use of biological resources and diversity, and enable the fair and equitable sharing of the benefits arising from genetic resources. Article 8, section g, mandates that each Party, "as far as possible and appropriate," establish or maintain the means to manage risks associated with the "use and release" of living modified organisms likely to have adverse environmental impacts (including affecting the conservation of
biological diversity, and posing risks to human health) (CBD, 1992). Importantly, the CBD does not establish specific actions that Parties must take to regulate, manage, or control these risks (as required in the text). However, the Cartagena Protocol, adopted in 2000, significantly expands on such biosafety provisions. The Cartagena Protocol is trade focused, in so far as it applies to the transboundary development, handling, transport, use, transfer, and release of living modified organisms (Cartagena Protocol, 2000). The agreement requires Parties to undertake risk assessments and implement risk management measures to manage and control the risks associated with “use, handling, and transboundary movement of living modified organisms” (Wilson, 2013; Cartagena Protocol, 2000).

The CBD and the Cartagena Protocol are limited in the strength of their implementation. The CBD does not include specific requirements for implementation, nor does it include an enforcement mechanism. The Cartagena Protocol, on the other hand, is undermined by the nation-specific interpretations of risk level. Risk assessments are subjective, with each Party making a decision of acceptable risk level based on its own domestic protection goals. This results in the inconsistent application and implementation of risk management policies across Parties. Additionally, although the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety was recently developed to address the lack of recourse under the Cartagena Protocol (and still has not entered into force due to a lack of acceding Parties), it is only a reactionary measure—Parties may receive redress for actions against them, but there is no mechanism for proactive protective measures (Wilson, 2013). Further, the US is not a party to either the CBD or the Cartagena Protocol, which severely limits the reach of the instruments given the nation’s status as a significant actor in the genetically engineered organism space.

The Australia Group

The Australia Group first convened in 1985 as a response to the use of chemical weapons by Iraq in the Iran-Iraq war, which Iraq had developed from tools and compounds legally purchased from Western nations (Bar-Yam, 2012). The Australia Group, which has grown from an original 15 countries to now include 42, convened to harmonize national export controls to help prevent the transfer of tools, knowledge, and materials likely to contribute to the development of chemical or biological weapons (Australia Group, 2014). Seven years after its founding, the Australia Group added biological agents and dual use biological technology to its guidelines. The Group maintains a control list of organisms and toxins that is regularly updated. The guidelines regulate genetic elements containing nucleic acid sequences associated with the pathogenicity of any of the microorganisms on the control list or coding for any of the toxins on the list (or their sub-units), as well as genetically modified organisms that contain nucleic acid sequences associated with the pathogenic parts of any of the organisms, or coding for the
toxins (or their sub-units) on the control list (Australia Group, 2014). This flexibility is important for ensuring adequate coverage of elements of concern; however, it has posed operational challenges given the lag in knowledge of delineating pathogenic parts from non-pathogenic parts of an organism, as well as modifications in sequences that still result in the same final end product.

Importantly, while the Australia Group provides a set of guidelines, it has no enforcement mechanism, the agreement is non-binding, and all actions are implemented at the national level. However, all parties are also members of the Biological Weapons Convention, discussed below.

**The Biological Weapons Convention**

The Biological Weapons Convention (BWC), formally known as the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological and Toxin Weapons and on their Destruction, entered into force in 1975. The BWC currently has 170 States Parties and 10 Signatory States (UN BWC, 2014). The aim of the BWC is to prohibit the pursuit for, and stockpiling of, biological (or toxin) weapons. Existing biological weapons should be destroyed or diverted to peaceful purposes, and no efforts may be made to transfer, assist, encourage, or induce other nations to acquire or retain biological weapons. There is flexibility in implementing the BWC, however; Article IV of the BWC notes that State Parties can take any national measures necessary to implement the provisions of the BWC domestically.

Because of its focus on biological agents and toxins that have no “prophylactic, protective or other peaceful purpose,” the BWC is severely limited in its scope of coverage (UN BWC, 2014). Even research that poses significant risks can typically be justified for peaceful purposes, and thus the BWC is limited in its ability to apply to any DURC endeavors (Wilson, 2013). Additionally, the BWC does not retain a formal compliance monitoring body or a verification mechanism to ensure enforcement. And, even if it did, the BWC still only covers a subset of nations, and thus harmful work could take place outside of its reach (Wilson, 2013). Therefore, although the BWC presents a useful framework for nations to discuss biological and toxin security and safety concerns, it is insufficiently empowered to be able to effectively manage risks.

**Alternative oversight mechanisms**

Where synthetic biology has been regulated, it has been almost universally folded into existing oversight mechanisms developed to govern recombinant DNA practices. This process has been largely adequate for handling the field’s advances thus far; however, such frameworks were constructed based on an old view of biology, and their rigidity of focus on parent organisms and sequence specificity poses increasing risks as the field pushes forward. Further, such mechanisms rely on the understanding that biological engineering of significance requires access to advanced laboratories, significant training and
institutional know-how, and a large amount of money. However, with every advance in the field these foundational assumptions become increasingly eroded, such that we are looking toward a not too distant future when the motivating assumptions will require a paradigm shift. This section discusses some of the leading alternative oversight mechanisms that have been proposed for synthetic biology thus far, as well as several more that have been proposed for emerging technologies more broadly. Particular attention will be paid to issues of safety and security.

Oversight mechanisms fall into one of two groups: those that are administered by the government, and those that are not. To consider the extent of possible government oversight, it is first necessary to establish the bounds of government control. Here, the legitimate purview of the government is assumed to be limited to ensuring the viability of national political and economic institutions (Popper, 2003). And, there are some things that governments are inherently better at enforcing than private entities. However, the rapidity of advances and sheer novelty of applications introduced by recent emerging technologies, coupled with the paralysis by which government faces them, have forced the recognition that the contemporary legislative, regulatory, and judicial systems in the US are thoroughly outmatched in their ability to keep apace. The following are a series of possible workarounds to increase the adaptability and flexibility of the oversight system, and subsequently decrease the lag time between technological advancements and meaningful oversight. Note that several of these approaches were addressed directly in Marchant’s “The Pacing Problem” (2011).

Enabling proactive and adaptive governmental risk management

One method for reducing lag time is to target options for expediting the rulemaking process head on. For example, one effort has involved an agency directly publishing a final rule, without allowance for the traditional notice-and-comment period. If enough public comments are received in opposition to the final rule, however, then the agency will enter into a full deliberative process. This allows agencies the opportunity to bypass significant lag periods inherent to the rulemaking process while still providing the public recourse should a rule be significantly objected to.

An important consequence of lag time in the rulemaking process is that it challenges the opportunity for adaptability in the final product, given that the length of the original effort alone often leaves the final product outdated from the outset. Some alternative oversight mechanisms have worked to directly target that weakness by incorporating opportunities for revisiting the rule. For example, a sunset clause can make legislators return to a rule by forcing automatic expiration after a given time period. Alternatively, a rule could incorporate periodic reviews, such that programmatic adjustments may be made as necessary. This has, however, at times been seen to introduce instability into the system such that the regulated are afraid to commit to a project without knowing whether the requirements will again
change five years down the line. Further, some mandatory calls for periodic review have been outright ignored. For example, as recently as 2011, every single environmental statute was past its reauthorization date, and in some cases well, well beyond (Marchant, 2011; Campbell, 2008). Here, sunset clauses demand that legislators revisit a topic, whereas reauthorizations are more likely to be undermined by political gridlock.

Cooperative regulation has been trialed by several agencies in recent years. Such a practice involves industry effectively designing its own oversight protocols, but under the watch of the relevant supervisory agency. This has the advantage of involving the most relevant, knowledgeable stakeholders from the outset. Further, it is faster and more adaptable than a formal rule given that it is able to bypass the notice-and-comment rulemaking process. However, some have expressed concerns regarding the availability of public participation outlets in such regulatory decisions, as well as the overall lack of accountability that arises when the regulated entity directs the regulatory process (Caldart and Ashford, 1999).

An alternative to cooperative regulation is that of assigning an independent institution to the policy making process for a specific topic. This would theoretically free the process from the politics surrounding an issue, and allow for adjustments to be made as the entity deems necessary. Successfully identifying a neutral, knowledgeable, and credible organization is a nontrivial task, however, and can itself be subject to political wrangling.

Finally, “principles based regulation” was recently proposed as a mechanism for incorporating the opportunity for flexibility and adaptation without locking in prescriptive rules that have the potential to become outdated. The general concept is not new—OSHA’s General Duty Clause has long been used

<table>
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<tr>
<th>Table 1. Twelve late lessons. Based on the case studies of Volume 1 of Late lessons from early warnings (Harremoefs, 2002), twelve key lessons for better decision-making were drawn.</th>
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<tr>
<td>1. Acknowledge and respond to ignorance, as well as uncertainty and risk, in technology appraisal and public policymaking</td>
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<tr>
<td>2. Provide adequate long-term environmental and health monitoring and research into early warnings</td>
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<td>3. Identify and work to reduce ‘blind spots’ and gaps in scientific knowledge</td>
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<td>4. Identify and reduce interdisciplinary obstacles to learning</td>
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<td>5. Ensure that real world conditions are adequately accounted for in regulatory appraisal</td>
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<td>6. Systematically scrutinise the claimed justifications and benefits alongside the potential risks</td>
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<tr>
<td>7. Evaluate a range of alternative options for meeting needs alongside the option under appraisal, and promote more robust, diverse and adaptable technologies so as to minimise the costs of surprises and maximise the benefits of innovation</td>
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<td>8. Ensure use of ‘lay’ and local knowledge, as well as relevant specialist expertise in the appraisal</td>
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<td>9. Take full account of the assumptions and values of different social groups</td>
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<td>10. Maintain the regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering</td>
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<td>11. Identify and reduce institutional obstacles to learning and action</td>
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<td>12. Avoid ‘paralysis by analysis’ by acting to reduce potential harm when there are reasonable grounds for concern</td>
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as a broad mechanism for citing hazards as they come to be known over time—but an explicit turn toward its incorporation is. One could imagine a scenario where synthetic biology biosafety concerns broadly require safe practices meeting some risk threshold, but without specifically delineating the processes per technology or advancement.

In addition to mechanisms that account for adaptability and flexibility, proponents of an updated system have also called for the explicit incorporation of anticipatory governance measures. The consequences of failing to act on early warnings have been well documented, from asbestos to DDT. In 2001, the European Environment Agency published a study titled “Late lessons from early warnings,” detailing a series of episodes where, in spite of documented early warnings to suspected risks and hazards, decision makers failed to act (Harremoës, 2002). Table 1 outlines 12 key lessons from the report, ranging from “identify and work to reduce ‘blind spots’ and gaps in scientific knowledge,” to “avoid ‘paralysis by analysis’ by acting to reduce potential harm when there are reasonable grounds for concern.” As David Rejeski, director of the Science, Technology, and Innovation Policy program at the Wilson Center, succinctly stated: “Without early warning, early action is difficult and a reactive response is almost preordained” (Marchant, 2011). In addition to the lessons pulled from the EEA report, Rejeski proposes embedding an “Early Warning Officer” within agencies to focus on threats as well as to leverage emerging technologies to help achieve agency missions (Marchant, 2011). More important than the development of such a position, though, is the acknowledgement by agencies that they are operating in an ever-evolving world, wherein static perceptions of risks and controls will prove insufficient over time. Therefore, a conscientious effort to stay on top of emerging technologies—and their potential implications—is critical. In 2007, a Wired Magazine reporter contacted the press offices of the EPA, the FDA, and the US Patent Office to inquire about how their agencies are thinking about synthetic biology; all had to ask what “synthetic biology” was (Keim, 2007). Since that time all of the contacted groups have had to work with the field head on, but in a world of anticipatory governance, the goal is to be moving toward action before the field has arrived.

**Alternative federal oversight tools**

Many outside stakeholders have called for more government intervention, but they differ significantly in how they would like to see that increased presence play out. The slightly more advanced emerging technology of nanotechnology, for example, was able to agitate enough concern as to result in the development of the 2003 Nanotechnology Research and Development Act, which has subsequently led to a series of new issue-specific regulations. One of these requirements is the explicit mandate that the National Nanotechnology Infrastructure include room for the consideration of “ethical, legal, environmental, and other appropriate societal concerns” during the development of the field (Marchant,
This action was achieved in spite of the political gridlock deemed paralyzing to new initiatives, and some stakeholders believe that synthetic biology could, and should, be able to overcome this impasse as well.

For those highly concerned with the security risks introduced by synthetic biology, proposed government intervention measures have been much more involved. For example, in a widely read 2013 *Foreign Affairs* piece, Laurie Garrett argued that the outsized risks posed by synthetic biology demand immediate and substantial intervention (Garrett, 2013). One example of involvement that she cited included that seen in Denmark, where the government required licensing of all public and private laboratories, and experiment approval was required before laboratory activities could begin. However, given the small size of the country and its similarly small synthetic biology community, the Dutch government was only responsible for monitoring approximately 100 licenses. In the US, a similar system would require investment in a much greater infrastructure. Notably, while Garrett supported the licensing oversight step, she would not commit to whether it should be conducted by the government or private actors.

Other stakeholders have latched on to the licensing idea, but with the intent of overseeing other parties. For example, in the 2007 report “Synthetic Genomics: Options for Governance,” a group of leaders in the field proposed a variety of oversight options (Garfinkel, 2007). The proposals came without recommendations, but did serve to help identify some of the option boundaries. One primary point of intervention considered was that of DNA synthesizers and the reagents used in DNA synthesis. As opposed to considering synthesizer self-regulation, the authors proposed that all owners of DNA synthesizers must register their machines, owners of the DNA synthesizers must be licensed, and a license must be required to both own DNA synthesizers and to buy reagents and services (Garfinkel, 2007). Such licensing oversight would be best administered at the government level, although as costs of synthesizers decrease, their proliferation could grow to unmanageable numbers.

Finally, those stakeholders most concerned about the immediacy and severity of risks from synthetic biology have called for even more drastic government interventions. These proposals have ranged from demanding strict adherence to the precautionary principle, to calling for an immediate moratorium on all field releases of synthetic biology applications until the public has been sufficiently involved in the debate (ETC Group, 2007). Importantly, even actions as drastic as instituting a moratorium can be readily undermined if it is limited to national discussions, given that future applications are unlikely to respect nation-state borders.
Non-governmental oversight schemes

Non-governmental oversight is commonly manifested as a form of self-regulation. Some mechanisms are widely supported and encouraged by those inside the field and out, like increasing the engagement of all technical practitioners with the potential safety, security, and ethical implications of their work. Other mechanisms, however, can be more contentious. For example, while scientists may have confidence in their ability to comprehensively consider the risks posed by their projects and proceed accordingly, outside stakeholders more often view such efforts with cynicism, seeing the practitioners as working to avoid more stringent government regulations instead of truly believing in the need for more controls on experiments.

Facilitating practitioner engagement with the risks and uncertainties posed by their projects is a critical component to fostering the conscientious development of the field. By imbuing scientists with a framework for considering the broader implications of their “purely” technical problems, it is more likely that subsequent projects will begin from a point of fuller consideration. In “Synthetic Genomics: Options for Governance,” a set of policy options was dedicated to educating practitioners, like “incorporate education about risks and best practices as part of university curricula” (Garfinkel, 2007). iGEM and the BioBricks Foundation have been leaders in this area.

Self-regulation, or oversight of the field by the field, has been far more contentious. Stephen Maurer and Laurie Zoloth, for example, stated that “protecting the public from the risks of synthetic biology depends on the scientific community’s will, capacity, and commitment to regulate itself” (Maurer and Zoloth, 2007). Notably, neither Maurer nor Zoloth are technical practitioners—one teaches public policy, and the other heads a center for bioethics, science, and society. On the other hand, the ETC Group preceded the “Recommendations” section of its seminal 2007 report with the following Plato quote: “‘The discoverer of an art is not the best judge of the good or harm which will accrue to those who practice it’” (ETC Group, 2007). The latter sentiment—that it is not for scientists to control public discourse or determine regulatory frameworks—won out in the first confrontation between the technical practitioners and civil society back in 2006. Although synthetic biologists had intended to discuss and adopt a formal self-governance proposal at SB2.0, the failure to include civil society representatives at the conference ignited a firestorm so great that the entire action was tabled. As Sue Mayer, director of GeneWatch, wrote at the time, “Scientists creating new life-forms cannot be allowed to act as judge and jury....Public debate and policing is needed” (ETC Group, 2007). Co-signers included representatives from social justice advocacy groups, environmental groups, and bioweapons watchdogs.

Self-regulation is not always undertaken to pre-empt government regulations, however. For example, leading practitioners in the gene synthesis industry self-organized to develop a set of screening protocols for gene synthesizers in response to an identified need. After being the subject of sensational
press coverage about security vulnerabilities in the gene synthesis field, commercial leaders saw an imperative to act given the potential for more bad press to bring the entire field to its knees. Because government was not acting with sufficient speed or knowledge to develop protocols and best practices, the companies moved forward themselves (IGSC, 2009). Notably, following the debut of their screening consortium protocols, representatives from two of the leading commercial firms stated the following: “Although we stand behind our self-imposed regulation, there is no doubt that the government could act to improve its efficacy. ... We have done our best to craft a screening list, but we believe that our governments should be able to provide the most up-to-date and accurate list of restricted sequences” (Minshull and Wagner, 2009). The transnational voluntary action demonstrated by the formation of the gene synthesis consortiums actively displays the multi-dimensional motivations behind various non-governmental oversight mechanisms.
Chapter 4. iGEM: 2003-2012

iGEM, or the International Genetically Engineered Machine competition, is a university-level synthetic biology contest that challenges students to create novel systems using standardized biological parts. The competition began as a month-long interterm course at the Massachusetts Institute of Technology (MIT) in January 2003. It grew into a summer-based project in 2004 involving five universities, and has been an institutionalized event ever since. The competition has exploded in size and geographic scope over time, most recently documented in the 2013 enrollment of more than 200 teams from over 30 countries. This growth in size, coupled with concomitant growth in technical capacity, has established iGEM as an invaluable microcosm through which to study the broader emerging field of synthetic biology. iGEM was born from the exuberance of practitioners in the early days of the field, and is still best defined by its participants’ infectious enthusiasm for the thrill of creating new things and contributing to a community-based resource. However, it has also faced challenges as the realities of defining a field and functioning in an unproven space are brought to light.

This chapter will detail the iGEM competition, from its underlying foundations and philosophies to its methods of practice and scale of operations. It will also map the evolution of projects over time, and the rewards system established by the organization that encouraged, and at times discouraged, such trends. The chapter will characterize the competition’s investment in safety and education over time, including methods of engagement, evolving safety assessment procedures, and degree of observed participant buy-in. Finally, it will present a gap analysis of the troubles laid bare by the early safety assessment process, thereby setting up the following chapters examining iGEM as a testbed for safety and security policy experimentation.

Engineering origins

With regard to discussions of dueling synthetic biology design philosophies, iGEM is very much rooted in the engineering-based, bottom-up approach. The organization’s background information explains the role of a synthetic biologist as someone who “looks to co-opt and improve upon the genetic blueprints of existing organisms, to design and create novel biological devices and systems” (iGEM, 2014). Further, iGEM precipitated the birth of, and later served as the proving ground for, the Registry of Standard Biological Parts (“the Registry”). Adherence to standards and parts was the primary driver of iGEM in the early years; later, it continued to maintain this philosophy, but diversified its aims to also include considerations of impactful community building, incorporation of safety and ethics into design principles, and public outreach through student ambassadors.
iGEM was founded through a collaboration of five engineering-trained individuals: Drew Endy (biological engineering), Tom Knight (electrical engineering, computer science), Randy Rettberg (physics, computer science), Pamela Silver (biological chemistry), and Gerry Sussman (electrical engineering, computer science) (Smolke, 2009; iGEM, 2014). In addition, Knight developed the first technical standard for assembling physical parts, which iGEM then incorporated into the Registry; Endy co-founded, and remains the Board President of, the BioBricks Foundation; and Rettberg eventually assumed the role of iGEM President (Smolke, 2009; BioBricks Foundation, 2014; iGEM, 2014). The engineering spirit is also reinforced in program materials. For example, the organization’s logo is a gear overlaid by a cartoonized cell, which itself is powered by interlocking gears. And, the annual award for the competition’s grand prize recipient is an oversized, machined Legos®-like “biobrick.”

Beneath the organization’s drive toward engineering new biological processes, though, stands a strong foundation of considered project development. Much like the more mature engineering disciplines from which it grew, the founders rooted the competition in an environment of conscientious project development. Further, the Registry is built on a collaborative, open-access paradigm; iGEM teams are rewarded for considering the ethical, environmental, and societal implications of their projects; and adherence to rigorous safety protocols is now a requirement for participation.

**Competition how-to**

The January 2003 and 2004 MIT intersession courses proved so successful and enlightening as to be deemed worthy of scale up to a summer-long, multi-university competition, supported in part by a grant from the NSF. In the transition from January to summer, the structure underwent a major shift from a month-long design project to a full-scale, design-build-test competition. Since that time, iGEM has continued to evolve to reflect the significant technical evolution of the field over the same period. This section will summarize the early evolution of the competition, and then more fully characterize the requirements of recent years.

iGEM leadership decided early that the competition would be centered around the use of standardized parts to create novel biological systems, strongly supported through teams’ adherence to principles of open sharing and collaboration. At the outset, this was not an established path in the field. However, the organization’s leadership envisioned a future for the field supported by an infrastructure essentially non-existent at the time, and through sheer dedication to its vision, willed that version of the future into existence. This early decision has proven to be a lasting compass bearing for iGEM, as it continues to orient the group’s strategic choices even as the field has twisted and turned down its own path over time.
In the early years of iGEM, an “adherence to standardized parts” meant that teams were tasked with designing, building, and testing parts to contribute to the Registry more than they were able to take existing parts and apply them to their own endeavors. In light of the Registry’s philosophy of “Get, Give, and Share,” this meant that these early teams were charged with giving more than getting. Importantly, the efforts made by such teams directly enabled the tremendous leaps and bounds achieved by later participants.

To build up the Registry, a technical standard for part composition was required such that submitted parts were truly standardized. Knight’s assembly method, the first technical standard designed for the field, established an idempotent system wherein parts could be linked together by known “end pieces” without affecting the underlying composition of the part (Smolke, 2009; Knight, 2007). The transition from a freewheeling field with laboratory-specific methods for linking parts to an environment demanding the universal use of a highly specialized process was not an easy one. Indeed, it was akin to going from laboratories each using their own version of Legos®—some with four interlocking nodes, some with three; some with interlocking squares, some with circles—to only allowing participation by those who transitioned to a fixed-width, interlocking-circle system. Standardization was an essential transition for the field to undergo in order for it to eventually pursue higher-order engineering goals, but the implementation required many laboratories to take several steps back before they could receive any significant pay-off.

As Smolke describes in her 2009 review of the competition’s founding years, iGEM’s early adherence to a single technical standard was not roundly supported, but was necessary for establishing the Registry as a truly functional and useful catalog. She noted three particular objections that grew out of iGEM putting the Registry, and its associated protocols, at the center of the event: 1) it would take significant time, resources, and effort for existing laboratories to transition their own catalogs of parts and knowledge bases to a new standard, so newer laboratories would have an easier time adopting the standard than older laboratories; 2) certain types of parts were found to interact poorly with the initial standard, so some practitioners believed that a system was being forced on them that would not support their particular interests; and 3) the quality of the existing Registry was poor at best as many parts lacked characterization and verification, so the goal of easy re-use was in fact a frustrating experiment in sequence errors, design errors, and output errors in the early days (Smolke, 2009).

Early objections to iGEM’s decisions and processes should not be viewed as exclusively negative, however. Indeed, the fact that practitioners even bothered to object signaled the relevance of the competition and its objectives to the construction and evolution of the field. Further, the initial struggles illuminated challenges associated with the design of the process, and prompted iGEM leadership to review and revise its own efforts. The iterative review process enabled by hosting an annual competition...
was ultimately hugely valuable to the orientation and re-orientation of the mission, as it allowed for
decision-makers to reflect on what worked, what did not, and to what goal they should next point. In the
case of objections to the Registry’s early design and composition, iGEM incorporated the feedback by
revising its reward structure such that quality contributions to the Registry were emphasized. Further,
every team could receive some level of award if they submitted parts meeting the standard and provided
part characterization and documentation, or if they improved or re-characterized an existing part. The
competition was also redesigned to include awards for applied and foundational advances in specific
tracks.

iGEM faced significant challenges in its early years, and for a time it was unclear whether the
program would persist. Indeed, it was wholly possible that iGEM would be subsumed by a dueling set of
standards and visions. However, by coupling its strength of vision with flexibility in the face of
immediate hurdles, iGEM emerged from its early years stronger than ever. More importantly, it
successfully forged a community of collaborators dedicated to supporting and growing the Registry, as
opposed to activating a movement to work around it. With this history in mind, competition requirements
for the most recently completed edition are detailed below.

In 2013, iGEM participation began with registration in late spring at a cost of US$2,750 per team
(US$3,250 if paid after April 15). This fee included rights to the annual parts distribution kit, but did not
include the additional costs involved with running experiments and using a laboratory. The registration
fee also did not cover the cost of jamboree attendance, which was US$375 per individual attending the
Regional Jamboree (“jamboree” is iGEM’s term for competition), and US$425 per individual attending
the World Championship Jamboree. Further, attendance fees did not cover airfare or lodging. To
subsidize these substantial costs, many teams recruit industry and community sponsors. Further, some
organizations have begun offering financial and in-kind resources to competing teams. For example, in
2013, all European iGEM teams that advanced from the Regional Jamboree to the World Championship
Jamboree received financial support by the European synthetic biology organizer ERASynBio (iGEM,
2013). In-kind support also came from organizations like Mathematica, who offered complementary
downloads of its popular modeling and analysis programs such as MATLAB and SimBiology, and IDT,
who offered reduced pricing on synthesis fees (iGEM, 2013).

Following registration, each team is sent that year’s version of the iGEM parts distribution kit.
The 2013 DNA Distribution was mailed in late May, and included more than 1,000 part samples stored as
dried DNA. Over time, iGEM has worked to improve the quality of its distribution. In 2013, parts were
only shipped after being sequence confirmed or ends confirmed (the latter used when parts were longer
than 1,600 bp), and having passed the additional verification steps of sequencing, restriction digests and
gels, and antibiotic testing (Registry of Biological Parts, 2013).
While many teams dedicate time over the spring term preceding the competition to consider possible project themes, most begin working in earnest over the summer months. In 2013, project descriptions were due August 9; Regional Jamboree attendance fees were due August 23; and track selection, safety forms, project titles and abstracts, and team rosters were due August 30. The final month leading up to regionals is a frantic one, with teams often only then being able to pull together their results, and at the same time being required to submit the last of their project documentation to iGEM Headquarters. Dates differed slightly by region, but for most teams, DNA for newly submitted BioBrick parts was due at iGEM by September 18, and judging forms and project and part documentation (including documentation for all medal criteria) were due September 27. Additionally, team wikis—the teams’ online portals for project documentation—were frozen on September 27 in advance of the Regional Jamborees the following week. The freeze is used to allow competition judges time to review project pages ahead of the competition, ensuring that what they view the preceding week remains consistent to what teams present the following weekend.

In 2013, teams were divided into four regions: Asia, Latin America, North America, and Europe. Of the more than 200 teams competing in the Regional Jamborees, 73 went on to compete at the World Championship Jamboree one month later at MIT. Those teams had until October 25 to submit their World Championship attendance fees, as well as a chance to submit any additional BioBrick parts to the Registry. The 2013 World Championships took place November 1 through 4.

There are three layers to the iGEM competition process. First, any team is eligible to receive a bronze, silver, or gold medal by meeting a series of requirements, such as by submitting a new BioBrick to the Registry (alongside complete part documentation), improving the function of an existing BioBrick part or device, and considering novel methods for assessing societal implications of a project. Over time, modifying medal criteria has proven to be a useful leverage point for emphasizing, or de-emphasizing, various aspects of the competition. Additionally, all teams select one track within which to focus their project. In 2013, tracks were as follows: new application, food/energy, foundational advance, health/medicine, environment, manufacturing, information processing, and software tools. In 2014, “food/energy” will be separated into “energy” and “food and nutrition,” and six new tracks have been added: art and design, community labs, entrepreneurship, measurement, microfluidics, and policy and practices. Awards are then given in each of the tracks to the top contributor, as determined by a panel of judges. Finally, teams nominated to advance from the Regional Jamboree to the World Championship Jamboree are eligible for the spots of Grand Prize (holder of the aluminum BioBrick trophy for the following year), First Runner-up, and Second Runner-up. While much of the iGEM experience is centered on team building, science exploration, and community collaborations, the top teams still place significant weight on receiving an award.
Growth in size and geographic scope

iGEM began as an intersession course at MIT, but after the January 2004 iteration, the course organizers elected to scale the operation. Subsequently, invitations were also extended to Boston University, the California Institute of Technology, Princeton University, and the University of Texas at Austin. In 2005, the competition went international with 3 of the 13 participants hailing from other nations. From there, iGEM never looked back: to date, more than 1,000 teams from over 40 countries have participated in the intercollegiate competition. The growth of the organization was marked in a different sense when iGEM was officially spun out from MIT in 2012 to become an independent 501(c)3.

As seen in Figure 5, the representation of non-US teams in the iGEM competition eclipsed that of US-based teams in 2007, and has remained the larger share ever since. Figure 6 sheds light on the regional representation of these teams. In the early years, North American and European teams led the charge, with Latin American and Asian teams lagging behind. Over time, however, growth in participation by Asian teams has exploded, and the Asian region is now the single most represented in the competition.

Notably, the trends seen in these figures reflect the broader trends witnessed in the field at large over the same period. Many of the founders of synthetic biology grew up out of American laboratories, supported by important collaborations with counterparts in the European Union and Canada. Over time, however, the field has become increasingly adopted around the world, with particularly strong growth seen throughout Asia. For example, in 2010, 14 Chinese teams and 40 US teams participated; in 2013, 42 Chinese teams and 59 US teams took part. Given the tremendous government support currently lent to synthetic biology endeavors in China (e.g., Specter, 2014), it unlikely that this growth trend will be slowing anytime soon.
iGEM’s expansion over time has not been without its challenges. With regard to size, there is a tremendous difference between 5 and 13 teams (2004 and 2005 enrollment totals) and more than 200 teams. Quality control becomes limited, one-on-one advising is difficult, and diversity in abilities is significant. These hurdles made the dedication to a collaborative environment all the more important, with the forming of community connections between teams, as opposed to just between teams and the organization, essential. The establishment of this community has been, by all measures, an incredible success. No doubt aided by a concomitant growth in social media, the iGEM community is now defined by inter-team collaborations, outreach events, and regional meet-ups. More established teams have repeatedly been seen to be “tutoring” newer entrants, sharing parts and knowledge with them directly. As will be discussed in greater detail in the testbed chapter, this collaborative spirit has been a formative outgrowth of the competition.

iGEM’s expansion in geographic scope (Figure 7, below) has presented a set of challenges unique from those due to its increase in size. In terms of communication, all instructions, forms, Registry submissions, and competition presentations are conducted in English. iGEM Headquarters has also established international points of contact to assist when communication challenges arise, which has been particularly useful for questions of translation relating to safety requirements and documentation.

To account for physical dispersion and enrollment size, in 2011 iGEM established a set of regional jamborees in advance of the final jamboree. The implementation of the regional system met with mixed review, with the regionals allowing all teams to receive more individualized attention, but prohibiting the chance for teams to see all other projects. In 2014, iGEM will be reverting to a single championship event, dubbed the “Giant Jamboree,” to be held at the Hynes Convention Center in Boston, MA, over the course of five days. With this setup, all participating teams will again be able to see each other present.
Geographic differences have been most significant, however, in terms of their implications on regulatory coverage. This has presented ongoing challenges for the organization, and has not yet been satisfactorily resolved. When participation was limited to American, Canadian, and European teams, there was a general assurance of involved oversight, with universities mandating protective laboratory environments. As the competition has expanded, however, this *pro forma* assurance dissolved.

Institutional oversight from entities like institutional biosafety committees is not universal, adherence to global security agreements like the Australia Group differs among nations, and shipping restrictions can vary. iGEM has engaged with this challenge most directly on the safety front given its own liability exposures, but has also recently faced issues relating to shipping restrictions.

**Figure 7. International participation in iGEM.** The map at left plots a point for all registered iGEM teams from 2004-2013. Orange dots represent a one-time involvement; red dots represent multi-year participation. For regions with widespread participation, a “glow” surrounds the dots. *Image courtesy SynBio Consulting (2014).*

**Project evolution**

The quality of parts and devices emerging from iGEM projects has evolved significantly over time. At the outset, iGEM participants strove to make a cell “blink”; in 2013, the Grand Prize Winner developed a mechanism for creating novel non-ribosomal peptide synthetases, supported by the concurrent development of a software tool for predicting the optimal modular composition of the device per desired output (University of Heidelberg, 2013). Much of this growth is a reflection of the maturation of the field over the past decade. Whereas the modularization and characterization of basic parts was a foundational advance in the early 2000s, now top teams must look further afield to make a mark. This section will review a selection of notable projects from the past few competitions as a summary of where the competition now stands and as a means of documenting from where it has come.

Prior to the summary of outstanding projects, however, it is important to recognize that while much of the attention iGEM receives centers on the annual awardees, many participating teams fail to achieve such significant gains. The strength of the iGEM format lies in the competition’s ability to enable all such teams to participate, and further, to facilitate more advanced teams sharing their accrued knowledge with newcomers to the field. Full and open documentation on archived team wiki sites records
processes used by past winners, and the open-access format of the Registry means that new entrants have full access to past winning parts. Additionally, because teams can still receive medals even if they are not awarded a track-leading prize, all contributions are deemed important and valued. The strong support provided by the organization regardless of project achievement level also helps to reduce tensions surrounding significant differences in teams’ access to capital.

Table 2 displays the winning iGEM teams, and brief project descriptions, from 2004 through 2013. The technical complexity displayed by projects in recent years is impressive, and the diversity of areas of interest is rapidly expanding. For example, the 2013 First Runner-up, TU Munich, was also the winner of the Best Environment Project award. Their project, called “PhyscoFilter – Clean different,” focused on the challenge of cleaning up polluted waterways. They proposed engineering the organism Physcomitrella patens to degrade or bind (depending on the substance) pollutants, and to release the system in the form of floating mats atop chosen waterways. Further, the team demonstrated that they had considered potential environmental consequences of organism field release by designing the system to be viable only within a certain filtered light spectrum.

<table>
<thead>
<tr>
<th>Year</th>
<th>Team</th>
<th>Project description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2005</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2006</td>
<td>University of Ljubljana</td>
<td>Engineered feedback loop in mammalian cells to represent artificial immunotolerance (motivated by threat of sepsis)</td>
</tr>
<tr>
<td></td>
<td>(Slovenia)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Peking University</td>
<td>Developed two forms of cellular differentiation systems, including hop counting through conjugation and on/off switches through UV sensing</td>
</tr>
<tr>
<td>2008</td>
<td>University of Ljubljana</td>
<td>Assembled two types of designer vaccines to improve innate and acquired immune response to H. pylori via modified flagellin and Toll-like receptors</td>
</tr>
<tr>
<td></td>
<td>(Slovenia)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>University of Cambridge</td>
<td>Engineered E. coli to produce different pigments in response to different concentrations of an inducer</td>
</tr>
<tr>
<td>2010</td>
<td>University of Ljubljana</td>
<td>Employed DNA sequence as a scaffold for optimizing location and order of enzymes in biosynthetic pathway</td>
</tr>
<tr>
<td></td>
<td>(Slovenia)</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>University of Washington</td>
<td>Targeted diesel production through engineered E. coli for alkane production, and gluten destruction through increase of targeted protease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>University of Groningen</td>
<td>Engineered B. subtilis to up-regulate expression of a pigment reporter promoter in response to the detection of spoiled meat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>University of Heidelberg</td>
<td>Developed the basis for novel and customizable synthesis of non-ribosomal peptides via non-ribosomal peptide synthetases</td>
</tr>
</tbody>
</table>

The 2013 Second Runner-up, Imperial College, also won the Best Manufacturing Project award for their project “Plasticity: Engineering microbes to make environmentally friendly plastics from non-recyclable waste.” The team observed the challenges and harms associated with landfilled plastics degrading into toxic byproducts, and thus developed a mechanism for up-cycling that waste. The team engineered E. coli to process mixed waste into the bioplastic poly-3-hydroxybutyrate (P3HB), intended to be performed in a sealed bioreactor as a closed loop recycling system.
Over time, there has also been an increasing trend toward the internationalization of projects, wherein teams tackle problems of greatest significance to their homelands. For example, the 2012 iGEM team Calgary focused on problems relevant to their area with the project “Detect and Destroy: Engineering FRED and OSCAR.” In light of the environmental threats posed by tailings ponds from area oil and mining extraction, the team developed a detection system for identifying threats, and a bioremediation system for removing impurities from the remaining material.

Safety and engagement

iGEM was developed with a pursuit of the technology frontier in mind. However, the organization has simultaneously maintained a strong commitment to educating its participants on issues affecting synthetic biology beyond the laboratory walls. In the early days of iGEM, these considerations primarily focused on matters relating to open access biology and developing a strengthened community through a commitment to the Registry. Over time, however, this has expanded to include concepts of biological risks and potential impacts of projects on society and the environment. Further, as projects move out along the technology frontier, the level of assumed risk by teams frequently increases, too. Such advancements in project complexity, coupled with a series of near-miss events, led to the eventual acknowledgement by iGEM of a growing need for more deliberate safety assessments for the competition. This section will present an overview of how the overall engagement effort, and more specifically the safety assessment process, has evolved for iGEM since its inception.

From the outset, iGEM has directly engaged with participants on questions of open access, technology collaboration, and community building. To build support for, and later develop champions of, the Registry, such an emphasis on engagement was essential. This emphasis has persisted over time, but the area of focus has been expanded to include broader discussion points like what it means to practice synthetic biology, both as a researcher and as a member of society at large. For the former, this relates directly to issues of biosafety and biosecurity, while for the latter, this includes assessing projects in terms of their potential impacts on humans and the environment.

In 2005, materials prepared by co-founder Drew Endy were made available to participating iGEM teams as a means of considering risks in synthetic biology. The opening paragraph of the piece concludes with the following statement: “Any responsible efforts that seek to enable the systematic engineering of biology must take place in the context of current and perceived future biological risks” (Endy, 2003). And indeed, iGEM has done a remarkable job of balancing the excitement and enthusiasm of its participants for pursuing the unknown with the need to ground them enough such that they are capable of assessing their projects in the broader context that Endy mentions. The Presidential Commission on Bioethics (2010) memorialized this sentiment with its recognition of the organization in its report, concluding with

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the following: “Beyond building biological systems, the broader goals of iGEM include growing and supporting a community of science guided by social norms.” iGEM encouraged such team discussions by providing reading materials and talks on the subjects, as well as by—potentially more consequentially—incorporating their components into scoring rubrics. For example, certain medal eligibility criteria included making contributions to “human practices” (renamed “policy and practices” in 2014). Additionally, a special prize was developed specifically for awarding notable team achievements in the area. Overall, the iGEM approach to such engagement can best be summarized as preparing participants to be considerate, thoughtful ambassadors of synthetic biology as they mature into leaders in the field.

On the safety front, engagement and education has followed a somewhat less intentional route within iGEM. In January 2003 and 2004, iGEM was an interterm course being led by a team of field pioneers at one of the top research institutes in the world. Even if the projects being attempted at the time had been more advanced, it is still unlikely that safety would have been a leading concern for the practitioners. After all, few in the world knew how to operate in this field as well as they did, and thus students were trained under the tutelage of highly informed practitioners. When the project scaled to include other universities in the summer of 2004, the additional four teams had been directly invited to participate by the competition founders, and all similarly hailed from top schools around the country. In 2005, the pool of participants from top institutes grew larger, and for the first time the competition included schools from outside the United States. Again, however, these newcomers included elite schools from the United Kingdom, Switzerland, and Canada. Quite clearly, in the early years there was a strong confidence in the establishment of safe, responsible practices from within each laboratory, and thus safety education, assessment, and requirements were not something that needed to be layered on by iGEM Headquarters. By contrast, the early questions of standardization, community contributions to a single Registry, and open access to other teams’ methodologies were something that very much had to be implemented at the organization level.

2008 marked the first year that iGEM awarded a special prize in human practices, as well as the first year that the competition required teams to answer questions about the safety of their projects on their wiki sites. In the listing of questions, iGEM Headquarters noted that judges would be asked to evaluate projects in part on the basis of how—and if—questions of biological safety were considered and addressed. As tallied in an early assessment of safety within iGEM, only 12 of 77 teams (16 percent) included a safety section on their wiki sites in 2008; this figure grew to 74 percent in 2009, 82 percent in 2010, and 100 percent in 2011 (Guan et al., 2013).

The early evolution of safety questions in iGEM can be seen in Table 3, where questions asked in the first two years (2008-2009) are slightly revised and mapped to new areas in the following two years (2010-2011). Some of these changes are in recognition of the shifting composition of participants,
moving away from a US-centric assumption of IBCs at universities. Other changes are more reflective of the increasing complexity of projects undertaken, such as the addition of “devices” as opposed to just “parts” in questions of BioBrick safety.

### Table 3. Safety questions addressed in the iGEM competition, 2008-2011.

This table documents the evolution of safety questions asked by iGEM Headquarters to participating teams. Table adapted from Guan et al., 2013.

<table>
<thead>
<tr>
<th>Thematic area</th>
<th>Main questions</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raised issues</strong></td>
<td>Would any of your project ideas raise safety issues in terms of researcher safety?</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Would any of your project ideas raise safety issues in terms of public safety?</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Would any of your project ideas raise safety issues in terms of environmental safety?</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Logical biosafety regulation</strong></td>
<td>Is there a local biosafety group, committee, or review board at your institution?</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>If yes, what does your local biosafety group think about your project?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>If no, which specific biosafety rules or guidelines do you have to consider in your country?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>What does your local biosafety group think about your project?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>BioBricks parts</strong></td>
<td>Do any of the new BioBrick parts that you made this year raise any safety issues?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>If yes, did you document these issues in the Registry?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Do any of the new BioBrick parts (or devices) that you made this year raise any safety issues?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>If yes, did you document these issues in the Registry?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>If yes, how did you manage to handle the safety issue?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>If yes, how could other teams learn from your experience?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Suggestions</strong></td>
<td>Do you have any other ideas how to deal with safety issues that could be useful for future iGEM competitions? How could parts, devices and systems be made even safer through biosafety engineering?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: In 2011, some teams were sent a different, unofficial questionnaire. Those questions are not reflected here.

Initially, the safety questions iGEM asked could be classified as a type of pro forma consent. As much as synthetic biology, and especially iGEM founders, envisioned the BioBrick concept as means for increasing accessibility to the field, there was still a tremendous amount of know-how required in the early years. Therefore, there was some measure of trust in team advisors by virtue of their being willing and able to take on overseeing a team. Over time, however, the projects became more complex, the technologies became more accessible, and the spread of teams made it so that a number of schools and advisors were wholly unknown to the founding group.

Notably, although iGEM collected answers to safety questions starting in 2008, the organization did not implement a review process for those questions until days before the 2010 Jamboree. At that time, iGEM President Randy Rettberg and Board Member Drew Endy reached out to Kenneth Oye, associate professor of political science and engineering systems at MIT, and requested that he gather a team to
perform a “quick review” of the safety and security aspects of the projects submitted for the 2010 Jamboree. Oye, alongside Piers Millett (United Nations Biological Weapons Implementation Support Unit) and Todd Kuiken (Woodrow Wilson Center), performed a cursory review of the more than 100 team projects. While those efforts revealed no actionable concerns, the group still felt rushed and unable to fully consider the projects before them given the time allowed. Therefore, the newly formed Safety Committee committed to developing and implementing an improved review process for the following year.

As a primary process improvement measure, the Safety Committee began the 2011 screening process much earlier than they had in 2010. Beginning in August 2011, the Committee reviewed the approximately 150 projects submitted for that year’s October competition. The reviewers paid particular attention to teams working with pathogens, and made sure to verify that completed safety forms matched each team’s project description. In iGEM, all project information is housed on teams’ openly accessible project wiki pages, so information was readily available to project reviewers.

In 2011, the Safety Committee found that most teams were working with BSL1 organisms, the lowest risk categorization. Further, almost all teams met adequate safety provisions and were appropriately operating under institutional review. However, two teams raised flags in the review process, as both appeared to be working with pathogens but offered weak safety declarations. Upon follow-up, one American team was quickly approved given that additional information revealed it to be working under effective institutional biosafety review in an appropriate BSL2 laboratory. The other team, however, could not be so readily resolved, and ultimately triggered a frenzied safety assurance process.

For the second team, despite a safety page stating no use of parts from pathogenic organisms, the project description included mention of using parts from a pathogen included on the Australia Group list. The team also stated that its home nation’s laws did not require institutional review, nor that there existed an IBC at its institution. Upon review, the Safety Committee found that in fact both the nation and the university required such review given the project’s stated description. The Safety Committee worked with the iGEM Asia Regional Coordinator to contact the team’s faculty advisor for additional information, such as the origin of the pathogen-derived part, reasons for use of the part, safety measures employed in the laboratory, and reasons for why no institutional review had been implemented. In parallel, the Safety Committee reached out to several biosecurity experts to gain additional perspective on the project as stated. All agreed that while the project was likely safe, no guarantee could be made given: 1) the lack of documentation on project scope, and 2) the apparent lack of safety competency given the inaccuracies on the safety form. With that, the Safety Committee disqualified the team from laboratory work, recruited the head of the Asia Pacific Biosafety Association to educate the team on matters of appropriate biosafety.
protocols, and eventually allowed the team to re-enter the competition as a software-only participant. (Oye, 2012)

Despite reaching a workable solution for the 2011 team, the screening findings prompted the Safety Committee to take a closer look at the team’s previous activities. This uncovered a pathogen-derived part submitted to the Registry for the prior year’s competition. iGEM Headquarters immediately froze distribution of the part, and verified that no teams had received shipment of the item in question over the past year. However, the Safety Committee was unable to determine whether the Australia Group guidelines had been violated in the shipping and receiving of the part the year prior. Conversations with US authorities did not lend clarity to the operational definition of “associated with pathogenicity.” Ultimately, in order to determine the function of the part, the Safety Committee turned to synthetic biologist George Church to personally examine the part in his laboratory. While it was eventually deemed safe, the path followed for resolving the matter was neither scalable nor reassuring. (Oye, 2012)

In 2012, the Safety Committee undertook its review process with an even keener eye for projects raising flags in light of the 2011 experience. Overall, while several projects required follow-up with teams to gain more information about project details and safety practices employed, no true project scares were uncovered during the screening process. However, between the Regional Jamboree and the World Championship Jamboree a month later, a team incorporated work dealing with a pathogenic organism into its project. The team did not report use of the organism on its safety page, and the information was only learned during the team’s final presentation. Upon interviewing the group, it was learned that the team had received the DNA from a U.S. academic laboratory, after having first tried to use a part shipped to them from the Registry. After reviewing the sequence, it was determined that the part in question was only 14 bp long, which is too short to be of pathogenic consequence to an organism. However, the incident highlighted the continued holes and vulnerabilities that existed in the safety review process.

**Gap identification**

As iGEM has expanded in size, geographic scope, and technical capacity, it has been forced to reckon with evolving operational challenges. Many of these shifts occurred naturally, reflecting the needs of the group as they changed over time. Others, however, have required more intentional efforts, most notably being that of safety engagement and assessment. In 2008, iGEM began to incorporate questions of project safety into team requirements. In 2010, it initiated a comprehensive review process for these submissions, which was further formalized in 2011 and 2012. However, even at quick glance, the efficacy of these processes could be rightfully challenged. This section compiles the gaps revealed by the early safety assessment process, and then sets the stage for the decision to develop iGEM as a testbed for innovative safety oversight policies and procedures.
In advance of the 2010 Jamboree, iGEM Headquarters realized that there was no systematic review of safety information in place, and thus the organization scrambled to initiate such a process. With only a few days notice, it is unsurprising that the 2010 process was rushed. However, that first review marked an important step in the program’s evolution, as it demonstrated for the first time identification by the leadership of a need to actively engage on the safety front. The 2011 and 2012 safety reviews were more systematically implemented, and were executed in similar manners. The 2012 review built off lessons learned in 2011, but despite the closer consideration paid to potential safety flags, vulnerabilities were again exposed given the near miss event reported above. Additionally, the 2010, 2011, and 2012 reviews revealed a serious lack of safety comprehension by many teams. Although the quality of reporting improved year-on-year, by 2012 there was still a large amount of follow-up required between safety reviewers and teams to determine the adequacy of their implemented safety precautions. It was evident that teams were often confused by safety designations, appropriately determining the risk level of their projects, and delineating the applicability of various regulations.

The 2011 and 2012 reviews highlighted the need for an improved biosafety education program and a tightened safety assessment process. Moreover, the near miss identified in 2012 marked a turning point for iGEM Headquarters on the safety engagement front. After spending a brief window of time unsure of whether it had violated U.S. regulations on biosecurity measures, iGEM was ultimately cleared of any wrongdoing. The organization’s potential for exposure was laid bare, though, and the risks associated with operating at arm’s length from safety concerns became too great to ignore. Therefore, in the absence of a coherent international framework for evaluating these risks more closely, iGEM engaged with the MIT Program on Emerging Technologies (PoET) to develop a progressive approach for handling questions of project safety and security.
Chapter 5. iGEM as a testbed

The 2011 and 2012 competitions revealed that safety threats persisted within iGEM despite the organization’s increase in screening efforts over the same period. As a result, iGEM was faced with a choice heading into the 2013 season: improve the quality of its safety program, or reduce the allowable risk level assumed by teams. iGEM has encouraged projects that push the technology frontier since its inception, and thus was loathe to introduce significant operating limits to the freedom it allowed teams. Because the field’s technologies have been outpacing associated regulatory developments, however, the increasing assumption of risk in projects has not been matched by similarly evolving oversight mechanisms. And indeed, the 2011 and 2012 competitions revealed that iGEM’s reliance on existing systems was insufficient for assuring participant safety. Therefore, in order to continue to encourage the pursuit of project goals along the technology frontier, iGEM was forced to initiate the complete overhaul of its safety system. To do so, the organization recruited PoET to help.

PoET is run by Kenneth Oye out of MIT’s Center for International Studies, and has evolved in recent years to focus primarily on policy development and regulatory analysis for synthetic biology. By engaging with PoET, iGEM Headquarters signaled that it was ready to formally explore questions of safety and oversight in ways that it had previously not been willing. For PoET, the project offered an opportunity to apply the group’s accruing observations of the problems, and potential solutions, associated with regulating synthetic biology safety and security concerns. Further, iGEM presented the chance to perform such trials in a controlled but malleable testbed environment, thereby increasing the value of the resulting observations due to the relevance of their insights on potential future policy scale-ups.

The preceding three chapters characterized the origins and goals for synthetic biology as a field, examined the strengths and weaknesses of the oversight mechanisms currently in place, and explored the growth and challenges faced by iGEM over the past decade. Those sections in turn laid the groundwork for this chapter, which builds from the earlier points to validate iGEM as a testbed for broader synthetic biology research, and to justify the need for developing improved oversight mechanisms. The subsequent chapter will characterize the actual testbed development process, including the design, implementation, re-design, and re-implementation of novel safety and security oversight mechanisms.

Components of a good testbed

Here, the term “testbed” refers to a platform for experimentation that permits the rigorous and replicable testing of technologies or theories. Testbeds are useful in that they enable the evaluation of innovative products or processes in a controllable yet realistic environment. In technical fields, testbeds
are often used to trial a product in isolation of the outside environment, though with a skeleton frame of the existing system constructed around the testing environment to simulate outside interactions. For policymaking, testbeds are often used to perform a controlled rollout of a policy that can subsequently be changed or retracted without issue. Importantly, the more relevant a testbed is to the true operating environment, the more external validity it has and thus the better it can inform observers as to its expected performance in the broader environment. Further, testbeds must be controllable, flexible, iterative, relevant, and reproducible to generate the most cogent findings. This section will consider the key characteristics of iGEM that make it such a valuable and unique testbed for considering issues of safety and security confronting synthetic biology today.

Controllable

As a private organization, iGEM has complete authority over the rules and regulations that it promulgates. Importantly, these rules must be in compliance with U.S. regulations, and all competing participants must meet their home nations’ and institutions’ respective requirements, too. In the case of biosafety and biosecurity oversight, however, the fact that this presents such a low threshold for the organization to meet is exactly the reason that iGEM is interested in modifying policies to make them more conservative than those required by law. On the other end of the spectrum, the organization is bounded by the risk of making its policies so restrictive that they trigger the outgrowth of a new, less regulated competition in which teams are more willing to participate.

Since its inception, iGEM has been able to update its policies—from operating requirements, to participation fees, to medal eligibility criteria—and still maintain its supremacy in the synthetic biology competition environment. It is benefitted in this regard by two key aspects: 1) iGEM is still strongly supported by some of the most prominent leaders in the field, and these practitioners can lend voices of support to new iGEM campaigns; and 2) the leading teams are often at universities along the cutting edge of technical and policy considerations, so less mature teams are presented with strong role models.

Flexible and iterative

iGEM has proven over time to be a reflective organization. It has repeatedly implemented revisions to policies when they have not performed as expected, and supplemented existing procedures with additional requirements where gaps have been identified. Such flexibility is essential when working with an emerging technology, as projected trajectories of a nascent field are often later off the mark. That iGEM has a recognized history of identifying areas requiring change, and then implementing new policies or procedures to amend those problems, strengthens its ability to again make changes down the road.

For iGEM to work well as a policy testbed, it is essential that new policies can be rolled out smoothly and efficiently. Given that participation is contingent upon meeting all iGEM requirements,
uptake is assured. Further, past participants are likely to be receptive to policy changes, given the organization's history of modifications over time. It is also important for testbeds to be iterative, whereby policies can be revised and re-implemented in following cycles. This allows for multiple versions of a policy to be tested, and thus for feedback from earlier versions to be incorporated into later versions. With iGEM operating on an annual cycle, there exists a built-in opportunity to revisit policies and procedures each year. Additionally, unlike in other circumstances where constant policy evolution could introduce paralyzing uncertainty into the system, for iGEM, teams optimize per year, so changes made prior to a new competition will not significantly affect the next round of entrants.

**Relevant**

Despite the importance of the above constraints, construct validity is a necessary but insufficient measure of testbed utility. For a testbed to be of true value from a research perspective, it must also be relevant to the broader questions being asked. iGEM is uniquely qualified in this regard, particularly with an eye toward the broad geographic scope of participants, the range of technical complexity of projects being conducted, and the immediate availability of findings from trialed interventions. The following section will more closely consider what iGEM can teach us, but here let it be enough to state that iGEM presents a platform for testing ideas of biosafety oversight at nearly the exact level and scope of their intended intervention.

Importantly, iGEM's relevance as a testbed is not limited to the scope of PoET's questions of biosafety oversight. In fact, the competition has been used for testing and demonstration by multiple other agencies and organizations. For example, the FBI has maintained a strong relationship with iGEM, and regularly trials outreach efforts with the contest's young scientists. Public Health Canada, too, has been a major partner in recent years. Before moving forward with finalizing a synthetic biology guidance document, the group experimented with the usefulness and alignment of the document alongside iGEM's evolving safety policies. Finally, Synthetic Genomics, Inc. (SGI), has taken advantage of the vast troves of sequence data in the Registry to test its proprietary screening tool, and examine its findings against those of the pre-existing Safety Committee. This effort focuses on the PoET experience, but the overlapping efforts help to support and validate the resultant findings.

**Reproducible**

In addition to the need for testbed relevance, it is also essential for a testing environment to generate reproducible results. If a testbed is constructed around a scenario that is too contrived, moving the trialed policies to the real world is likely to produce results unlike those initially observed. In such a situation, the value of the testbed is significantly diminished given that its predictive power is reduced.
Therefore, when approaching testbed construction, it is vital to maintain perspective on the realistic limits of what can be achieved in a testbed versus what can be achieved in the outside world.

In the case of iGEM, it was important to be able to distinguish between policies and procedures that were specifically being planned for iGEM's sake, and those that were being implemented with an eye toward potential future scale-up opportunities. Indeed, iGEM was not constructed to serve as a testbed, nor did its mission ever shift to position itself as a testbed first and competition second. This meant that there were some limits to what policy changes could be imposed, as iGEM Headquarters drew a line at that which threatened the founding principles of the competition. In particular, although iGEM had evolved to recognize the increasing importance of its safety program—both from an outreach and from a liability point of view—it did not believe that safety engagement came first, second, or even third in terms of prioritization. Therefore, the PoET group had to work within the constraints of proposing policy revisions that were suitably progressive as to test novel ideas, without imposing too great a burden on participants outside the competition's primary point of interest (namely, getting team projects to work).

What can iGEM teach us?

Before considering the extent to which iGEM can shed light on broader questions of synthetic biology, it is first appropriate to identify exactly what questions we want answered. In large part, this requires mapping the gaps identified in the section on existing oversight mechanisms to those later identified specific to iGEM. This section will reconcile the two charges.

The 2011 season highlighted, and the 2012 season underlined, the gaps in oversight that could occur when safety reviews were performed solely based on existing, external oversight mechanisms. Coming into the 2013 season, then, there was the immediate question of how the safety program should be revised in order to flag and remediate all projects posing potential hazards. There was also the question, though, of what could be done to target the origins of the safety problem. Many teams appeared to have little regard for questions of safety and security, and some appeared to have no understanding of the concepts whatsoever. Indeed, it was apparent that many teams were operating safely by chance. Were they to increase the risk level of projects undertaken in subsequent years, it was more likely than not that their safety precautions would be insufficient. Therefore, a two-pronged intervention scheme arose:

1) Develop oversight mechanisms to ensure participant safety, and
2) Increase participant awareness of, and engagement with, concepts of biosafety.

For iGEM, the identified interventions were the primary points of focus when considering revisions to the safety program. For PoET, however, there was additional interest in framing these interventions from a testbed perspective. This meant that PoET studied possible interventions from an iGEM-centric perspective as well as from a broader public entity perspective. It also meant that further
down the road, PoET would evaluate successes and failures not only in terms of how they served the iGEM population, but also in terms of how they could potentially be scaled up to serve needs identified outside the confines of the immediate organization.

For both parties, updates to the safety program would be deemed unsuccessful if participant safety was not achieved. This was a non-negotiable endpoint. On the other hand, while an increase in participant engagement with biosafety issues was thought to contribute to participant safety by encouraging conscientious and informed actions, students could still be protected from harm even if they remained relatively disengaged from the topic of biosafety. Indeed, this latter intervention aimed for the longer term and more nebulous goal of attempting to influence a new generation of scientists. By iGEM and PoET logic, were this intervention to succeed, then even if the young scientists were to continue to work in areas with limited official oversight, they would still continue to act thoughtfully and safely due to the norms they grew accustomed to when they were introduced to the field.

The priority goals identified for the safety program overhaul are directly related to many of the concerns raised in the earlier chapter on safety and security oversight mechanisms. In answering the question of “what can iGEM teach us,” then, there is strong reason to believe that the answer is, in short, “a lot.” The following issues, as raised in the earlier chapter, look to be of particular relevance to that being directly tackled by iGEM. First is the issue of the patchwork state of regulatory and non-regulatory oversight systems. For iGEM, this challenge is exacerbated by the international scope of participants. Not all entities in the US fall under the oversight of the NIH Guidelines, let alone those in other countries. Many European counterparts have similar IBC-like systems, but the case is not so for many Asian competitors. Additionally, the struggle by experts to interpret the operational definitions of regulations, such as those that become active when dealing with a sequence “associated with pathogenicity,” is even greater for those brand new to the field. In terms of assigning risk level designations when projects combine multiple “safe” parts that result in a risker whole, teams are also faced with challenges. For all of these issues, iGEM was looking to add clarity without sacrificing safety or increasing bureaucratic burdens. As the next chapter will outline, while these interventions have been a work in progress, they undoubtedly contribute significant insights from a testbed angle into what could work in terms of broader policy solutions.
Chapter 6. 2013 and 2014 iGEM safety interventions

The near misses exposed during the 2011 and 2012 seasons prompted iGEM Headquarters to approach the 2013 season with an increased emphasis on safety policies and procedures. However, as this section will detail, the 2013 competition proved to uncover more challenges with implementing a thorough and effective safety screening process than it resolved. Additionally, the collaboration between iGEM and PoET took some time to become productive, and the priorities of the two groups were at times misaligned. Thanks to the iterative assessment enabled by the annual competition, though, the issues encountered in 2013 were ultimately used to inform and improve the 2014 implementation plan.

This chapter will describe the motivations and philosophies underlying the 2013 update, the review findings and the procedural challenges encountered, and finally the planned implementation strategy for the revised 2014 program.

2013 safety program interventions

Since the implementation of a comprehensive review process in 2010, the foremost goal of the iGEM safety program has been to ensure participant safety. Despite revisions to the process each year, however, the assurance of participant safety has remained an elusive endpoint. This has become additionally challenging due to the escalating average risk level of projects over time. In the early years of the safety program, increased safety was thought achievable through a strengthened, more diligent review process. However, as 2011 and 2012 illuminated, regardless of how well the review process was executed, it would not catch unreported or misreported projects of concern. Further, the timing of the review process forced all actions to be reactive, not proactive, as teams were beginning work with organisms and parts prior to the Safety Committee being made aware of their plans (Figure 8). Therefore, the central revision proposed for the 2013 process was to require the pre-screening of any projects planning to use organisms, or parts from organisms, designated risk group level two or higher. A second

![Figure 8. Advancing the point of intervention. In 2011 and 2012, the safety process was limited to screening after projects had been completed (right); in 2013, the screening shifted closer to intervening during the design-build-test cycle (middle).]
The proposed revision was that the application forms require the provision of names and contact information for both a corresponding advisor and a corresponding team member. This was intended to facilitate communications between the Safety Committee and individual teams, which had previously presented a challenge during time-sensitive hunts for additional information on identified projects of concern.

In the final rollout of the 2013 safety program, both of the primary revisions were reduced to moderated versions of the original plan. Due to a series of miscommunications and delayed conversations between iGEM and PoET, a lack of changes to the system persisted late enough into the summer such that it eventually became impractical to implement the application-based procedure. Therefore, PoET and Health Canada (a supporter of iGEM biosafety efforts) worked with iGEM to quickly draw up a modified plan that incorporated process revisions wherever remained possible. The final product of this effort was the published iteration of the 2013 safety screening process, as well as a selection of guidance materials added to the iGEM website on understanding risk groups, laboratory biosafety levels, and additional biosafety concerns. Teams were notified of a modification to the process via email, as well as through an explanation on the website’s 2013 “Safety” page. Any general questions about the safety process were directed to the email listserv for iGEM’s Safety Committee. (PoET, 2013)

All teams were required to submit a completed version of the basic safety form to their region’s safety listserv by August 30, 2013. The form included questions on the following information:

- Chassis: organism, risk group level (and link to source of information if available);
- Parts: part number, risk group level of parent organism, source of physical DNA, and description of part function;
- Safety precautions undertaken;
- Potential safety concerns presented by project;
- Laboratory biosafety level;
- Institutional biosafety committee response to project;
- Explanation of applicable national biosafety standards (and link if available); and
- Advisor signature.

Any team using a chassis with a risk group above level one, a part from an organism with a risk group above level one, or a mammalian part, was also required to submit a secondary safety form for each qualifying entity. The secondary form required the provision of a more in-depth consideration of the organism or part in question. Teams working with well-characterized, low-risk organisms and parts were therefore able to circumvent additional paperwork. The follow-up form included reports on the following information:

- An explanation of the function of the part;
- A justification for using the specified part as opposed to a lower-risk alternative;
- A more detailed description of the safety procedures in place to protect against the risks posed by the element; and
- Advisor signature.
Following form submission, the safety screening process commenced. Forms were first assessed for completeness; any document that contained unanswered questions or lacked an advisor’s signature was immediately returned to the team with a request for completion. Once a form was deemed administratively complete, a screen was conducted to assess safety considerations. If information was unclear, incomplete, or incorrect, the team was contacted to request clarification by way of a resubmitted form. Further, if the primary form indicated use of a chassis or part that was mammalian or above risk group level one, the screener verified that an accompanying secondary form had also been submitted. Otherwise, any concern raised during the screening process that could not be resolved by the region’s safety screening pair was forwarded to the broader Safety Committee for consideration. These included issues of team safety, laboratory oversight, and policy implications.

Following a completed safety screen, each team was alerted via form letter that it had passed the safety screening process, and was instructed to post a dated statement on its wiki verifying project approval. Any team that did not submit a safety form by the August 30th deadline was informed that form completion was a requirement of the iGEM competition, and that they were at risk of disqualification unless and until they submitted the necessary documents. In a continuation of recent trends, the 2013 competition saw an expansion in the level of complexity and assumption of risk taken on by competing teams.

The 2013 safety screening process involved the consideration of 184 wet lab teams by six individuals. The review took place between September 1, 2013, and October 4, 2013—the date of the first regional jamborees. Limited follow-up was required between the first round of jamborees and the world championships taking place November 2-4, 2013. The screening process involved six research assistants—two assigned to each region, with the European and Latin American teams combined—as well as the entirety of the Safety Committee. On average, multiple email communications were required per team (Table 4).

Table 4. 2013 iGEM safety process findings. The safety screening process involved email communications between teams and safety screeners, and review of primary and secondary forms.

<table>
<thead>
<tr>
<th>Region</th>
<th>Email communications</th>
<th>Forms filed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary</td>
</tr>
<tr>
<td>North America</td>
<td>220</td>
<td>54</td>
</tr>
<tr>
<td>Europe</td>
<td>209</td>
<td>59</td>
</tr>
<tr>
<td>Asia</td>
<td>288</td>
<td>62</td>
</tr>
<tr>
<td>Latin America</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>751</td>
<td>186</td>
</tr>
</tbody>
</table>

Approximate count of the number of individual email messages sent. It is estimated that the true number may be as much as 20 percent higher, because many responses were sent to individual screeners and not copied to the appropriate listserv.

Teams were requested to provide information on the highest risk group chassis used in their projects. The vast majority of iGEM teams used chassis from the lowest risk group level (Table 5); across
all competitors, 90 percent employed no higher than a risk group level one chassis. An additional 10 percent of teams used risk group level two chassis. No teams reported using risk group level three chassis.

Three teams (one each from North America, Europe, and Asia) were classified as “other”: one as “2+,” one as “0” (no chassis employed), and one as an unresolved 1/2 classification.

Table 5. Highest chassis risk group level per team. Values are presented as numbers and percentages, as well as by region and in sum.

<table>
<thead>
<tr>
<th>Risk Group Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>48</td>
<td>92%</td>
<td>3</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Europe</td>
<td>51</td>
<td>86%</td>
<td>7</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td>Asia</td>
<td>56</td>
<td>90%</td>
<td>5</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Latin America</td>
<td>10</td>
<td>91%</td>
<td>1</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>165</td>
<td>90%</td>
<td>16</td>
<td>9%</td>
<td>0</td>
</tr>
</tbody>
</table>

The safety screen also required information on any new or modified coding regions that teams were using in their projects, with the exception of materials disseminated through the iGEM Distribution Kit, which were exempted from review. Importantly, SGI, a synthetic biology corporation, used its proprietary screening tool Archetype to screen all parts in the Registry, including those in the Distribution Kit. The screen returned no concerns beyond those previously identified by the Safety Committee.

Additionally, a secondary safety form was required for any part sourced from a mammalian organism or a risk group two or higher organism. Overall, 55 percent of iGEM teams reported use of no parts outside the 2013 Distribution Kit that were sourced from higher than a risk group level one organism (Table 6). A further 31 percent reported use of parts from risk group level two organisms; this ranged from 27 percent of European and Latin American teams, to 31 percent of Asian teams and 37 percent of North American teams. No North American or Latin American teams reported use of parts from risk group level three organisms, but one from Europe and two from Asia did. Importantly, an additional 22 teams were categorized as “other,” for reasons ranging from unknown risk group level (common), to uncertainty over which classification level was appropriate. This figure highlights the challenges that come with mapping organism-level risk groups to individual parts, and from working with parts from organisms that have not been assigned risk group levels at all.

Table 6. Highest part risk group level per team. Values are presented as numbers and percentages, as well as by region and in sum.

<table>
<thead>
<tr>
<th>Risk Group Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>29</td>
<td>56%</td>
<td>19</td>
<td>37%</td>
<td>0</td>
</tr>
<tr>
<td>Europe</td>
<td>35</td>
<td>59%</td>
<td>16</td>
<td>27%</td>
<td>1</td>
</tr>
<tr>
<td>Asia</td>
<td>32</td>
<td>52%</td>
<td>19</td>
<td>31%</td>
<td>2</td>
</tr>
<tr>
<td>Latin America</td>
<td>6</td>
<td>55%</td>
<td>3</td>
<td>27%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>55%</td>
<td>57</td>
<td>31%</td>
<td>3</td>
</tr>
</tbody>
</table>
To ensure that teams were operating under sufficient safety precautions, the basic safety form required information about the biosafety level (BSL) of the laboratory (or laboratories) in which their iGEM work was performed. If the BSL did not meet the highest risk group of the parts or organisms used by the team, additional analysis was conducted to verify conditions were sufficiently protective. Many teams were working in laboratories more protective than required by their projects. Uncertainty often centered on understanding the exact level of classification covered by a laboratory, particularly for Asian teams. Overall, 63 percent of teams worked in BSL1 laboratories, 29 percent in BSL2, 2 percent in BSL3, and a final 5 percent of teams were between classifications (Table 7).

Table 7. Laboratory biosafety level per team. Values are presented as numbers and percentages, as well as by region and in sum.

<table>
<thead>
<tr>
<th>Biosafety Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>35</td>
<td>67%</td>
<td>16</td>
<td>31%</td>
<td>1</td>
</tr>
<tr>
<td>Europe</td>
<td>35</td>
<td>59%</td>
<td>20</td>
<td>34%</td>
<td>2</td>
</tr>
<tr>
<td>Asia</td>
<td>37</td>
<td>60%</td>
<td>16</td>
<td>26%</td>
<td>1</td>
</tr>
<tr>
<td>Latin America</td>
<td>9</td>
<td>82%</td>
<td>2</td>
<td>18%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>63%</td>
<td>54</td>
<td>29%</td>
<td>4</td>
</tr>
</tbody>
</table>

Even with the revised safety process, near misses were not eliminated in 2013. However, they also did not increase in number despite the escalating average degree of project complexity. Further, the detailed information in the basic and secondary forms allowed for intervention on all projects of serious concern prior to the jamborees. And, although not every safety concern was wholly resolved, there were no last-minute surprises. On the other hand, teams completed safety forms to varying degrees of quality. Some teams provided exemplary answers demonstrating deep consideration of the relevant issues, while other teams were either cursory in their efforts, or uninformed about the biosafety regulations of their home universities and countries. In light of the heavy reliance of current oversight mechanisms on institutional overview of experiments, the most troubling mistake repeatedly observed was that of teams asserting that their universities had no IBC or equivalent group, when in fact such a group did exist.

The 2013 safety updates marked an important step in the evolution of safety priorities for iGEM. For the first time, the organization engaged in an intentional consideration of its safety policies, and took action to directly confront areas of concern. However, the update was only partially implemented, and multiple issues were observed with that which had been implemented. Policy updates are an iterative process, so lessons learned from 2013 will necessarily inform changes to the 2014 effort. Procedurally, delayed updates significantly inhibited the opportunity to implement major changes to the program. It was thus immediately obvious that proactive engagement with process and policy conversations had to both begin and be resolved earlier in the timeline. Such a proactive approach would allow sufficient time to ensure that all proposed actions have been closely considered prior to implementation.
With regard to modified policy content, the 2013 review valuably allowed for real-time evaluation of the implemented changes. Some alterations were successful, but others presented challenges when they transitioned from the theoretical to reality. In particular, it was quickly apparent that while the policies forced teams to consider risk group levels of organisms and parts, the teams were not always sure what they were looking for or how they should operationally interpret the information outside of base case examples. Therefore, teams need additional reference materials beyond those that already exist, as the vast majority of guidance is unsuitable for the increased complexity found in most synthetic biology projects today. The onus was on iGEM, then, to create and provide such materials if the organization decided to continue to require teams to understand the concepts underlying the new safety policies. Increasing the emphasis placed on advisor involvement could also assist in improving participant engagement and comprehension of the more nuanced aspects of safety considerations specific to synthetic biology work.

Finally, despite all of the other updates made to the safety program in 2013, there remained a clear need for pre-screening of projects exceeding certain risk thresholds. The system remained dangerously reactive as it stood: even when projects of concern were identified prior to the jamborees and thus shipping violations were avoided, there was no ability to protect participants from work they had already done. Looking ahead, the organization will need to develop a policy that increases participant safety without limiting project flexibility.

2014 theory of change

Updates to the 2014 safety program began before the 2013 season had concluded. Instead of being cause for concern, negative outcomes and unexpected behaviors observed over the course of the safety rollout were viewed as valuable data points, shedding light on where to focus attention the following year. Indeed, there was a deep sense of observe-update-iterate, and thus close attention was paid to potential system weaknesses from the outset. Further, given the opportunity to consider potential innovations throughout the 2013 season, the PoET team was ready with recommendations for how to best tackle the above-discussed challenges shortly after the conclusion of the 2013 World Championship Jamboree. In particular, in light of the procedural hurdles encountered the year prior, PoET identified several policy-based decisions that would require iGEM and Safety Committee input prior to being able to make certain update decisions. These conversations included determining the accepted degree of reliance on IBCs by iGEM, the level of team advisor involvement demanded, the organization’s comfort level with various risk groups used by projects, and maintaining organizational concurrence with institutional, national, and international policies and procedures.
In making these decisions, PoET deferred to iGEM’s organizational priority scheme: namely, that while ensuring near-term participant safety was of foremost importance, unduly burdening participants to achieve such ends through novel means was not. Therefore, the policy updates continued to strive for identifying the minimum size and scope of requirements that were able to attain sufficiently protective gains. The resulting theory of change, including the expected inputs and activities used to meet short-term, and later long-term, outcomes, can be seen mapped out in Table 8. The underlying assumptions supporting the causal links are also included at the bottom of the table. The short-term outcomes are largely expected to be attained through improved safety guidance, review, and documentation requirements. The longer-term outcomes, on the other hand, are expected to be the result of increased participant engagement with biosafety issues over time.

Table 8. Log frame for iGEM safety screening program. A log frame is used here to map the resources and activities required by the 2014 safety program updates, and the expected short- and long-term outcomes over time.

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Activities</th>
<th>Short-term Outcomes</th>
<th>Long-term Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>iGEM HQ staff</td>
<td>Develop revised policies</td>
<td>Reduce late-game surprises</td>
<td>Develop generation of scientists trained in safety and security</td>
</tr>
<tr>
<td>MIT PoET staff</td>
<td>Develop updated screening forms and safety documentation</td>
<td>Decrease instances of hazardous activities</td>
<td>Facilitate environment for cooperative threat prevention, not</td>
</tr>
<tr>
<td>Safety screening</td>
<td>Develop updated guidance materials</td>
<td>Prevent liability issues for iGEM</td>
<td>reduction</td>
</tr>
<tr>
<td>volunteers</td>
<td>Employ new methods during safety screen</td>
<td>Increase participant engagement and understanding</td>
<td>Hone innovative policies for scale-up at national and</td>
</tr>
<tr>
<td>Team advisors</td>
<td>Answer questions regarding changes</td>
<td>Assess need for iterative policy evolution</td>
<td>international level</td>
</tr>
</tbody>
</table>

Assumptions: This model is based on the belief that iGEM will remain a relevant entity in the synthetic biology space over the coming decade. It assumes no progress in outside regulatory oversight, which—if incorrect—would influence the policies forced on iGEM. Finally, this structure relies on the continued support of iGEM HQ to the policy development cause; should this support erode, the opportunity for innovative procedures could be lost.

Regardless of whether iGEM Headquarters values safety as a key tenet of the overall synthetic biology program, the organization has been ultimately forced to embrace the debate if it wants to continue to operate along the technology frontier in the absence of applicable regulatory oversight. With PoET at its side to guide in the policy discussions, it is also possible for iGEM to continue its long and storied history as a norms-setter in the field, this time while attempting to answer open questions of safety and security. The proposed 2014 updates reflect this growing commitment to the cause.
2014 implementation

The 2014 iteration of the safety program is a reflection of the lessons learned over the past four years of safety screening implementation, as well as the procedural lessons gained after activating the testbed in 2013. For the first time, the safety program has been intentionally designed to target two explicit branches of intervention: safety screening and documentation, and participant engagement and awareness. With an increasing understanding that both areas are necessary for improved safety—especially in light of the patchwork state of existing external oversight mechanisms—the safety program has worked to target both for improvement. These changes are detailed below.

Arguably the most significant change implemented to the safety program was the addition of a pre-screen requirement. Dubbed the “check-in” form, the pre-screen is intended to alert safety officials of potentially hazardous projects before they begin, and thus allow the opportunity to confirm that the team is employing sufficiently protective measures before proceeding with its work. Importantly, the pre-screen does not apply to all, or even most, work conducted for iGEM projects. Only projects employing elements above a certain risk threshold will trigger such oversight.

Drawing the line to distinguish between “white list” and non-white list items posed a significant challenge, and brought iGEM into unprecedented safety policy space. Whereas nearly all applicable organisms have been designated a risk group level, the parts from such organisms have decidedly not been outside of certain broad strokes. For whole organisms, all RG1 are on the white list, while all RG2 and above will require review. Certain well-characterized mammalian cell lines (e.g., CHO) are exempt, as well as the multicellular organisms Caenorhabditis elegans, Physcomitrella patens, and Drosophila spp. For parts from organisms, the grey areas become far greater. For the pre-screen program’s inaugural implementation, the list errs on the conservative end of the spectrum. All parts from RG1 organisms go on the white list, while parts from all RG3 and above organisms will require a pre-screen application. Parts from RG2 organisms pose the greatest classification challenge. Here, an attempt is made to separate risks out by part function. It is expected that the list will evolve significantly over time. See Figure 9 for a schematic of the preliminary white list designations, and Table 9 for the written classifications.

<table>
<thead>
<tr>
<th>RG 1</th>
<th>RG 2</th>
<th>RG 3</th>
<th>RG 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proceed</td>
<td>Check-in first</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 9. Schematic for pre-screen criteria. In general, parts from risk groups fall into neat bins. Parts from risk group (RG) 2 organisms, however, fall on both sides of the line. Figure courtesy iGEM.
The pre-screen application is meant to flag the projects of greatest concern, but it is not intended to replace the safety program’s traditional safety documentation and review process. That process has remained largely the same, with one major exception: the timeline has been updated to initiate the documentation and review process earlier in the project cycle. This will be implemented through the required submission of a preliminary form in June prior to the submission of a finalized form at the end of August. Concurrently, iGEM’s newly hired biosafety point-person will engage in early, “casual” conversations with teams to field any biosafety content or procedural questions they may have. Importantly, the biosafety program is viewed within iGEM as protective and informative, not punitive. The idea is to inform teams where to make improvements, not where they are acting incorrectly.

Table 9. Preliminary pre-screen requirement criteria. This table presents an example list, separated by whole organism and part, of elements requiring a pre-screen application and those that do not. Table courtesy iGEM.

<table>
<thead>
<tr>
<th>Whole Organisms</th>
<th>Exempt / White-List</th>
<th>Application Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Group 1 (bacteria, fungi, viruses)</td>
<td>Risk Group 2, 3, 4</td>
<td></td>
</tr>
<tr>
<td>Well characterized mammalian cell lines</td>
<td>Other animal cells, including primary isolates</td>
<td></td>
</tr>
<tr>
<td><em>C. elegans, Physcomitrella patens, Drosophila spp.</em></td>
<td>Other multicellular organisms</td>
<td></td>
</tr>
<tr>
<td>Anything from a Risk Group 1 organism, regardless of function</td>
<td>...and anything not explicitly listed</td>
<td></td>
</tr>
<tr>
<td>All Registry parts, except those previously flagged by Archetype or Safety Committee</td>
<td>Anything from Risk Group 3 and above, regardless of function</td>
<td></td>
</tr>
<tr>
<td>Promoters, RBSes, terminators, binding sites for transcriptional regulators</td>
<td>Registry parts flagged by Archetype or Safety Committee</td>
<td></td>
</tr>
<tr>
<td>Protein-coding genes from RG2 organisms, animals, or plants that are in any of the following functional categories:</td>
<td>Other non-protein-coding parts</td>
<td></td>
</tr>
<tr>
<td>• Structural/cytoskeletal elements</td>
<td>• Other protein-coding genes from RG2 organisms, animals, or plants</td>
<td></td>
</tr>
<tr>
<td>• Transcription factors</td>
<td>• ...and anything not explicitly listed</td>
<td></td>
</tr>
<tr>
<td>• Kinases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Most catalytic enzymes (except those producing known toxins)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The casual engagement with teams on questions of biosafety also aligns with the increased emphasis being placed on participant awareness and engagement. The aim of the safety program goes beyond simply ensuring near-term participant safety. As described above, there is a growing push toward increasing the awareness of all participants, thereby increasing safe and conscientious future actions as well as present choices. This mission is being fulfilled through a revised “Safety Hub” off the iGEM main
page, which works to guide students through the general questions and considerations that should arise during project planning regarding biosafety. Additionally, several active faculty members have contributed guidance materials for iGEM to share with students, including a biosafety quiz by Terry Johnson from the University of California-Berkeley. Finally, iGEM has continued to push questions of policy and practices to the center of its project encouragements, including through the addition of a new track for the 2014 competition specific to questions relating to policy and practices.

Although iGEM significantly updated its safety policies and procedures for 2014, one change it conspicuously did not make was to offer any assurance of safety to teams that met its requirements. iGEM continues to rely on institutions and home nations to assume liability, as it has no ability to verify self-reported answers or monitor laboratory work. What iGEM can do, and now will do, is provide a guide that prompts questions and documentation that are intended to steer participants toward safe and protective actions. The 2014 program marks an important step in that direction.
Chapter 7. Policy implications and potential for scale-up

There has been no shortage of hyperbole in synthetic biology reporting. From warnings of “imminent” bioterrorist attacks to cries of field releases triggering permanent environmental disasters, the headlines generated by the nascent field are bold and eye-catching. The enduring question, however, is to what degree is this level of concern merited? Here, iGEM has proven to be a valuable divining rod. While the organization’s attention was initially drawn to questions of safety and security because of a series of high-risk incidents, its continued involvement in the area has been the direct result of everyday challenges arising from oversight gaps and failures. It is not hyperbole to state that the current oversight system is failing, in theory and in practice. Early testbed findings confirm that the broader oversight mechanisms are insufficient for ensuring safety, and moreover, that because of their structure, they are widening the gaps—not bridging them. Importantly, the testbed has also illuminated an apparent path forward for the field through a two-pronged proactive and adaptive risk management approach, involving refined risk assessment procedures on the one hand, and increased biosafety engagement and awareness on the other.

This section will map preliminary findings from the revised iGEM safety program to the broader synthetic biology environment, and distill a series of recommendations from the testbed’s results for potentially scaling the interventions’ implementation. While the government has failed to take a proactive stance on synthetic biology thus far, the window of opportunity for getting ahead of the field has not yet closed. However, regardless of whether legislators can be spurred into action, biosafety oversight can still be improved. Recent experiences with the iGEM testbed show that significant and meaningful action can be taken without directly altering the federal oversight system. The proactive and adaptive approach put together here faces the biosafety challenges presented by synthetic biology head on, and attempts to demonstrate a viable path forward in the face of technical uncertainty and regulatory inaction. Importantly, this approach does not address the matters of ethics, equity, or social justice that synthetic biology applications are bound to evoke. Instead, its aim is to ensure that when the time for these conversations arises, the relevant applications are assessed based on the merits of their contributions, and not the safety risks that they provoke.

Risks exist. Acknowledge them.

This thesis builds from the proposal that the current mechanisms responsible for synthetic biology biosafety oversight are insufficiently protective. However, inherent in such a statement is the assumption that synthetic biology is risky, and therefore that it requires controls. Without this finding, the entire premise for having, let alone improving, oversight mechanisms is undermined. Concerned citizen groups fall neatly in line behind the “risks exist” end of the spectrum. Practitioners, on the other hand, have been less uniform in their identification. Most, if not all, acknowledge that somewhere within the field, risk-
generating work is taking place, and that oversight of those areas is appropriate. However, few have been able or willing to recognize the risks inherent in their own work. While this has been evolving in recent years, it poses one of the most significant hurdles to biosafety work: if practitioners cannot identify that risks exist, they will not look for means to control them. Therefore, any efforts to improve oversight must first be tied to grounding practitioners in the risks involved with their projects. iGEM presents a useful case study here.

Despite its current status as a biosafety innovator, iGEM did not always embrace questions of safety and security relating to its practices. It took four years for safety questions to make it into project reporting, another two years for those questions to be systematically reviewed, and a further two years of multiple near misses before iGEM agreed to fully engage with the matter. Ultimately, until it was confronted with the threat of needing to significantly limit the scope of allowable projects, the organization was unwilling to acknowledge that consequential risks were getting past the domestic and international biosafety oversight systems it had been deferring to. Eventually iGEM was motivated to act, in large part as a result of needing to protect its own self-interest with regard to maintaining a cutting-edge endeavor while minimizing its liability in the face of uncontrolled risks. However, if the FBI had not been in the room the day the organization was found to be in potential violation of the UN Biological Weapons Convention, it is not clear whether all of the progressive work that has taken place since that time would have occurred. Therefore, when thinking of ways to strengthen biosafety programs, beginning with increasing the engagement and awareness of the very practitioners being overseen is a vital first step.

Following the increase in engagement with safety issues at the Headquarters level, there subsequently arose an increase in such engagement at the team level, too. One important endorsement for this improvement has come by way of the State Department. In acknowledgement of iGEM’s long reach and diffusion potential, as well as its recent successes with increasing young scientist engagement on questions of safety and security, the State Department has issued a preliminary grant to iGEM and PoET for scaling iGEM practices in the Middle East and North Africa. A key region of concern from the biosecurity angle, the State Department sees cooperative threat reduction potential in iGEM’s approach for awakening a new generation of scientists to the risks inherent in their work, and instilling in them the importance of conscientiously controlling such risks from the outset.

Risks exist. Control them.

Once risk is acknowledged as being present within a field, it follows that if practices are left unabated, the potential exists for hazardous scenarios to be generated. As a result, controls are implemented in order to limit exposure to those risks. A successful oversight system, then, is one that monitors and limits practices with high hazard potentials. Admittedly, scientific exploration chafes at
limits and controls, and pioneers in emerging fields often fear that overblown concerns will stifle their efforts before they can even get them off the ground. However, controls need not result in a reduced scope of allowable projects; indeed, it is more common for such systems to expand the universe of allowable projects, as they ensure that potentially hazardous work is conducted under sufficiently protective conditions. Further, having functioning controls in place serves to strengthen the scientist’s hand in two important ways. First, the field can point to the oversight system as an assurance of safe and responsible work when questioned by concerned citizens, regulators, and institutions. Second, controls are intended to protect against the occurrence of serious incidents and accidents, which in turn helps to prevent the nascent field from being splashed across the headlines and thrust under the glare of the public eye for all the wrong reasons.

Importantly, the benefits generated by a strongly functioning oversight system quickly unravel when the system fails to operate as intended. There are multiple possible points where such systems can breakdown, and the biosafety oversight of synthetic biology seems to hit nearly all of them. Described more fully in earlier sections of the document, some of the key failings of the current system are summarized here:

- **Scope of entities covered.** Oversight systems must cover all applicable practitioners, not just a subset of them. If they do not, then the chance of high-risk project flight from regulated to unregulated entities is introduced into the system. Synthetic biology oversight does not come remotely close to covering all relevant practicing entities. On the regulatory front, many agency rules are limited to commercial efforts. With IBCs, there is coverage failure on two fronts. First, IBCs are only required at institutions and entities receiving relevant NIH grants, as well as a select number of agency laboratories. This leaves many synthetic biology practices uncovered. Second, IBCs have been repeatedly found to have lapsed, or be altogether absent, at a wide range of purportedly covered entities. Such extensive holes in coverage serve to strongly undermine confidence in the reach of the oversight systems.

- **Scope of projects covered.** At present, biosafety oversight does not apply to all project types. As previously documented, regulatory coverage is only triggered by a subset of efforts, most commonly those posing obvious security threats. When uncertainty is introduced into the system in terms of whether or not something should be regulated, it often leads to a default position by practitioners that surely such stringent regulations could not apply to their work. This is directly related to increasing awareness of practitioners to the risks inherent in their projects.

- **Feasibility of operational implementation.** There have been multiple documented instances, and many more anecdotal reports, of complete breakdown within the system as projects move from looking like genetic engineering efforts toward encompassing full-on, multi-attribute
synthetic biology applications. As the bottom-up engineering approach takes hold, parts-based organisms will not readily, nor potentially even possibly, map to existing risk assessment frameworks. For regulatory oversight, such questions can be bumped to a single decision maker; for IBC oversight, though, such questions will need to be determined at the entity level, and commonly by insufficiently informed practitioners.

These issues with the oversight system can lead to splintered confidence in the level of protection provided. In such a situation, advocacy groups default to calling for more regulations (or more severely, a complete moratorium), while scientists are left protecting the viability of their field on the one hand, and scrambling to reduce the risks presented on the other. Given the current faults in the oversight system, and the many observations of high-risk projects making it unimpeded to iGEM’s last line of defense, the mechanisms currently in place must be ruled insufficiently protective.

**Maintaining the status quo will worsen problems moving forward, not solve them.**

Synthetic biology is a dynamic, flexible, and forward reaching field, but the oversight mechanisms governing it are static, rigid, and backward looking. In fact, many of the genetic engineering oversight mechanisms now used to oversee synthetic biology were themselves re-purposed from initially non-genetic engineering aims. In their current state, these mechanisms miss the big picture; were they to be re-purposed with synthetic biology in mind, they would still be likely to miss the nuances woven throughout the field. Therefore, this reliance on increasingly incompatible mechanisms squanders the limited present opportunity for proactive risk management, and generates increasing potential for significant future risk exposure.

One of the greatest challenges facing synthetic biology oversight is the field’s departure from meaningful baseline comparators. For example, as opposed to being able to assess changes to a known organism based on a single added gene, synthetic biology projects weave together parts from a multitude of organisms, casting doubt on known or expected part behaviors, and increasing the potential for unexpected interactions. Therefore, sequence-based, organism-level risk group assignments entirely miss the point. Such regulations do provide a sense of security, as their definitive high-risk/low-risk cut-offs signal confidence in the system, and an ability to draw hard lines in an environment full of shades of grey. And at this point in synthetic biology’s progress, they are not too far off the mark. However, by continuing down a path that suggests there remains the possibility to use lists to acknowledge safe and unsafe efforts, we support a false sense of security in an increasingly failing mechanism. As Marchant (2011) wrote: “The operating assumption at this point – that we both understand these systems, and are capable of managing them so that we achieve desired outcomes without unfortunate unanticipated consequences – is at best whistling in the dark, and more likely an abdication of ethical and rational
responsibility.” Therefore, instead of blindly pressing on into an increasingly unprepared tomorrow, this period should be treated as a window of opportunity for acknowledging that significant gaps in understanding exist, and thus devoting research time and funding toward closing them.

Importantly, this position relies on the assumption that synthetic biology will continue to push toward increasingly novel organisms. It is, of course, possible that this will not occur, either due to regulations yanking the reins before the field gets there, or a recognition by scientists that simpler designs raise fewer concerns and manage to function nearly as well. Given the current trajectory of the field and the investment dollars lining up behind cutting edge projects, this seems unlikely. However, it is valuable to keep such a possibility in mind when considering future iterations of the oversight system.

A dynamic field requires a dynamic approach.

When considering possible alternatives to the current oversight system, it is first prudent to acknowledge the limits imposed on policy revisions due to political gridlock. Noting these potential limits, one can then understand what can be realistically accomplished within the existing federal system, and what instead needs to be achieved outside it. For example, while a complete overhaul of existing regulations could present the strongest path forward, it is unlikely to occur, and thus unproductive to place expectations on such a drastic change. Therefore, the following recommendations are intended to be applied in concert with the existing system.

While much of this thesis makes the claim that the current oversight system is a patchwork approach and that gaps in oversight are arising as a result, it is important to note that in actuality, all regulations follow some approximation of a patchwork methodology. Thus, the question becomes: can the patchwork be improved? Can the current system be expanded to cover more, or should new approaches by interwoven with that which already exists? The current system theoretically invokes both soft and hard methods. It pairs a rigid, inflexible, sequence-based approach with a malleable, interpretive IBC system that can be stretched and pulled to cover the gaps that the former creates. Both are necessary, with the rigid screening providing a guiding framework from which IBCs can build, and IBCs bridging the gaps where the list-based system cannot be meaningfully expanded. However, both are also failing in their current state, and thus opening up significant fissures in oversight coverage. These recommendations aim to address those failings, and in turn, reduce such gaps.

As a case study, iGEM presented an invaluable opportunity for getting an inside look at the operational capacity of the current oversight system. Setting aside those teams operating in countries without oversight systems in place, during the systematic screening reviews of 2010, 2011, and 2012, safety screeners repeatedly encountered teams with no knowledge of the risks posed by their projects, the regulations that might apply to them, or even the existence of IBCs within their home institutions. Despite
having questions about risk laid out in front of them, teams frequently reverted to “not applicable” in reference to their own projects. Safety screeners engaged in significant follow-up with teams to get complete answers to questions deemed absolutely necessary for ensuring safety; however, it was not within iGEM’s purview to assume responsibility for the thoroughness and correct functioning of each and every university’s IBC. With iGEM teams typically representing universities at the cutting edge of synthetic biology work, such persistent lack of awareness is striking, and supports earlier findings from the Sunshine Project report of major failures within the IBC system.

That being said, as a testbed, iGEM also allowed policy researchers the opportunity to examine whether, and how, the existing system could be modified to strengthen biosafety oversight. For example, 2013 marked a major turning point for safety review findings. While many problems existed within the overall 2013 program iteration, there was a notable improvement in form completion. Although no causal relationships can be determined, it is likely that at least in part, reformulating the safety forms away from open-ended questions assisted teams in thinking about the crucial aspects of their projects that could generate risks. Many teams continued to require follow-up to attain fully completed forms, but compared to previous years, many fewer ignored the risk potential of their projects altogether.

In large part, the iGEM testbed was used to develop policies that forced teams to think like an IBC. The system asked questions that an IBC would need to know, and safety reviewers used that information to determine whether or not teams were working in sufficiently protective environments. The 2013 iteration showed the promise of such an approach, and the 2014 version has expanded upon it to experiment in methods for better informing the overall risk assessment process. Importantly, this effort has shown that IBCs, or IBC-like systems, can work. However, most institutions have insufficient awareness and understanding to be able to effectively implement a useful version of the approach. By increasing the outreach and awareness training component of its biosafety program, iGEM was able to strengthen the reporting quality by teams. This suggests that if sufficient guidance is provided in terms of the project elements that should be considered and how to best evaluate them, the IBC system can be returned to a highly useful mechanism that is valuably adaptive in the face of a quickly evolving field.

Further, iGEM has shown that this can be achieved without modifying the overall structure of the operating regimes, provided sufficient encouragement and information is made readily available.

In the face of change, embrace a proactive and adaptive approach.

Synthetic biology’s story is still being written. The field is not, or at least not yet, a new case study for the late lessons from early warnings project. At the same, it is also not an example of proactive risk governance. The field is rapidly approaching a tipping point, however, where such a determination can no longer be avoided. Without significant action in improving biosafety oversight in the coming
years, synthetic biology is poised to generate uncontrolled risks that threaten environmental and public health. Importantly, these risks are not the ones arising from rogue actors; instead, these are the ones arising from events occurring on a daily basis, thanks to repeatedly observed lapses in the baseline oversight system currently employed. Amending these failures will take dedicated research and funding, but it can be done. As the iGEM testbed has shown, biosafety engagement can be trained, and risk assessment can be strengthened, even in the face of uncertainty.

Synthetic biology is a dynamic field, defined by the novelty of its outputs and the rapidity at which it can leap from today to a previously unimagined tomorrow. It cannot be monitored by a static system. Instead, synthetic biology demands that researchers, regulators, and observers constantly evolve their approaches, and proactively stride forward to greet new findings in the field as opposed to being greeted by them. The policies must evolve alongside the technology, and to achieve that, a constant emphasis on learning and adaptation must light the way.
Bibliography


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