Building outside of the box: iGEM and the BioBricks Foundation

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Innovative community efforts in academia and non-profits to engage student researchers, encourage open sharing of DNA constructs and new methodology as well as build a Registry of Standardized Biological Parts have been central to the emergence of synthetic biology.

One aspect of synthetic biology is to develop tools that make the engineering of biology easier. Such engineering research can benefit from communities and venues that collectively engage and support work to develop, test and support open technology platforms. Two community-based efforts, the International Genetically Engineered Machines (iGEM) competition and the BioBricks Foundation (BBF), have enabled such communities and venues to form through unconventional approaches. With the field of biological engineering poised to achieve hitherto unprecedented levels of precision, efficiency and scale, I provide here a perspective on the role of these two organizations in shaping the ideology, values and culture of the synthetic biology community.

The genesis of iGEM

Last month marked the completion of the fifth annual iGEM competition. Over 1,100 people from 100 teams participated in the three-day event, the iGEM Jamboree held at the Massachusetts Institute of Technology (MIT; Cambridge, MA, USA), at which students presented their research projects to peers and policy experts and a mixed audience from academia, industry and social sciences.

The iGEM Jamboree is now the largest synthetic biology event in the world and, beyond its intrinsic value for participants, highlights for observers several amazing aspects of the field. First, students at the undergraduate and high school levels are incredibly excited about biotech; by participating in iGEM, teams of students work together with the goal of identifying and prototyping an engineered genetic program that addresses a real-world problem or opportunity. Second, young would-be genetic engineers are capable of getting new ideas to work; just some examples of successful projects include *Escherichia coli* that smell like bananas, that are newly responsive to light, that produce a full rainbow of pigments, that float or sink in response to transcription signals or that detect environmental pollutants. Third, an open technology platform based on standard biological parts—even if the parts collection itself remains incredibly immature—can be a powerful enabling tool. The iGEM students receive a kit of the best available genetic parts at the beginning of each competition, and then contribute their favorite new parts to the collection at the end, so that future students can build upon their work—thousands of parts are now available to iGEM students.

The iGEM competition grew out of month-long courses that were taught at MIT by Drew Endy, Tom Knight, Randy Rettberg, Pamela Silver and Gerry Sussman during MIT's extended January intersessions in 2003 and 2004. The objective of these courses was to learn from students how to become better engineers of biology. On the basis of conversations with Lynn Conway, a pioneer of early VLSI (very large-scale integrated) electronics during her time in the 1970s at the Xerox Palo Alto Research Center in California, the MIT instructors decided to initially focus on the idea of decoupling the design and construction of genetic circuits, and later to explore the use of abstraction as a tool for managing biological complexity.

Because of time and technology limitations, combined with the complexity of the systems designed by the students, the projects designed in these courses were not successfully constructed, much less characterized and debugged. Even so, by working directly with students in these early courses, the instructors learned about and developed solutions to three basic challenges limiting genetic engineering work. First, given a limited budget for *de novo* DNA synthesis, the instructors discovered the utility of having students share and reuse parts; this led directly to the world's first Registry of Standard Biological Parts. Second, given the relative immaturity of the gene synthesis industry at the time, many of the students' desired DNA parts could not be synthesized because of problems in cloning or expression; this led the instructors to help obtain, optimize and freely provide variable copy number vectors with enhanced transcriptional insulation for use in the commercial gene synthesis process. And third, given the complexity of system function desired by the students, too much time was being spent simply trying to understand how each system might work; this led to the formalization of a first functional abstraction hierarchy based on a common transcription signal carrier, now called polymerase per second, or PoPS.

Inspired in part by the success of other student-oriented engineering competitions, such as the FIRST Robotics Competition (an annual competition organized by the For Inspiration and Recognition of Science and Technology, FIRST, organization), the group made a decision to extend their early efforts into a multischool biological design competition with funding from the US National

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The most recent iGEM in October at MIT Killian Court. Teams attended from over 100 universities and from 26 different countries.

Science Foundation. Related decisions were made to extend the event from a one-month design challenge, to a summer-long design, build and test experience.

A competition matures

The first 2004 synthetic biology competition had participation from five invited US universities—Boston University, Caltech, MIT, Princeton and the University of Texas, Austin. The name iGEM was decided upon soon thereafter and the competition has been held each summer since 2005, growing dramatically to its current size of over 100 universities and extending its geographical reach to 26 different countries.

As iGEM has grown, it has expanded its goals, refined its approach, and responded to the needs of a young and rapidly growing community. Early on the leadership within iGEM made a decision to focus the experience on standardized parts and open sharing, where teams were tasked with examining whether integrated biological systems could be efficiently built from standard biological parts. The Registry of Standard Biological Parts, envisioned as an online catalog that would organize and document parts encoding biological functions, thereby became a central resource for making available samples of DNA encoding parts to all participants.

The requirements associated with defining a 'standard' biological part were related to the first technical standard introduced by Tom Knight for a physical parts assembly method[1]. This technical standard specified an idempotent assembly method (assembly reactions that leave the key elements unchanged) for physically linking parts together and associated sequence requirements. These ideas were disruptive to prevailing practice in molecular biology at the time, and as a result met with significant resistance from many in the basic and applied biological research communities. As resources and broader support for such work were not available at the time within the biotech community—whether from federal agencies, foundations or industry—to help develop a registry at a professional scale, the leadership of iGEM asked the teams to build the registry over time through their accrued contributions.

This participant-based 'get' and 'give' approach to developing a collection of standard biological parts led to the first set of challenges faced by iGEM. First, getting people to adopt standards in a field that has been operating without them is difficult. Many laboratories build up their own assembly methods and constructs and will have a laboratory-specific catalog of parts that are incompatible with any proposed standard, such that transferring over those parts and knowledge base to a new standard will require a significant amount of effort, time and resources. Although the purpose of standardization is to streamline a process and ultimately make the integration of parts more reliable and efficient, any such payoff would be on a longer time scale. Therefore, younger laboratories with less of a historical backlog would find it easier to adopt any proposed standards. Second, the first proposed standard was not broadly accepted. As researchers worked with the initial physical assembly standard, they found that it was problematic for coupling certain types of parts together. This led to a feeling from some participants that standards were being imposed that were not applicable for many of the systems they would like to build. And third, the quality of the parts in the registry was not generally good, which presented a huge challenge to the major goal of the registry—the reuse of parts to support efficiency in design and construction. A glance through the registry will show that many parts have not been confirmed as working and do not have any, much less thorough, associated characterization data. Complaints and frustrations grew as teams attempted to use parts from previous years' projects and found that they did not work as designed or in some cases were not even the correct sequence. Although iGEM headquarters (currently at MIT) has more recently implemented a quality control check at the level of sequencing, the sheer number of parts received makes it impractical for iGEM staff to have a direct role in parts characterization and functional validation.

In response, the leadership began putting in place a value system within iGEM that would enable the community to address these challenges over time. In particular, mechanisms were put in place that rewarded team participation in the areas of contributing and documenting biological parts that were compatible with approved standards, contributing characterization data for these parts, and even for developing and documenting new and improved technical standards (see the BBF request for comment process below). Although prizes recognize specific achievements of a select number of teams (best in class), medals are also awarded to those who meet specified requirements; any iGEM team can earn a gold medal. In addition, the teams are provided with the medal requirements up-front, so that they know what the judging will be based on, and are asked to evaluate their own projects in terms of meeting these requirements. In addition to addressing the issues outlined above, the medal system rewards teams for helping another iGEM team, characterizing or improving existing registry parts, and developing advances in human practice issues as they relate to synthetic biology. This reward structure has worked extremely well in building the value system within the community. The iGEM competition has also used the rewards structure to explicitly celebrate

foundational and applied advances by setting up tracks (food/energy, environment, health/medicine, manufacturing, new application, foundational, information processing and software), where the best project in each track is awarded a prize. In addition, special prizes are awarded for specific contributions such as best part, standard, human practice advance, wiki and experimental measurement. The most valued prize for the teams is the Grand Prize, for which the team is awarded the BioBrick Trophy (a gigantic Lego-like machined aluminum brick with the names of winning teams etched on it, similar to trophies used in professional sports) that the winning team holds for a year and then passes off to the Grand Prize Winner at the following year's competition.

Community building

By engaging student researchers directly, an interesting thing has happened over time. The iGEM participants are forming a community and are invested in building out the necessary technologies supporting the engineering of biology. They are actively engaged in tackling the challenges and proposing solutions, as opposed to just complaining about the problems. Through the iGEM experience, they learn the importance of having high-quality, well-characterized parts and standards that support the sharing of these parts. And you can see it working in the community; the parts that work, the parts that are easy for others to take and build into their systems—these get picked up by other teams and used in new projects and new applications (in technology-driven work, this represents success). When teams waste precious time trying to work with poor-quality parts, they can share and document their experiences through iGEM, thus giving back important information to the community. This type of reuse, validation and feedback is often not available through traditional scientific reporting mechanisms, which generally celebrate novelty versus distilling processes to practice. When teams identify problems with existing standards, they can go through the process of identifying new standards that might address existing issues and then put them out to the community for use and comment. These collective experiences have over time helped build a sense of responsibility in many of the teams and have led to improvements in the quality and documentation of parts in the registry.

iGEM's initial goal of inventing and improving the underlying technologies of synthetic biology has expanded and evolved to become much more about education of students and teachers, community building and growing a standard biological parts collection. Many schools have developed courses in synthetic biology based on their experiences with iGEM and some have started or are starting entire research centers focused on the topic. Even the number of successful projects is increasing over time. Although several projects have resulted in peer-reviewed publications with significant follow-up work from the researchers after iGEM[2–5], many more are succeeding in pushing the limits of biological systems that can be engineered under time, financial and expertise constraints.

And this gets to the real test of iGEM: can the process of engineering biological systems be made so efficient and reliable that a team of undergraduates (or high school students) with little experience can successfully build an interesting and exciting system in several months? And, will these systems ever approach the complexity and scale of projects conducted through traditional genetic engineering tools that currently take on the order of 150 skilled researcher years to complete[6]?

Ongoing challenges

By most measures iGEM is a fantastic success; however, it is facing new challenges as a result of this success. iGEM headquarters and individual teams face challenges in continued financial support. Teams are responsible for their own fundraising, which includes fees associated with participating in iGEM and running the team and its research project. The international nature of iGEM, and the differences in fundraising models between countries make this particularly challenging. Funds supporting research through traditional federal agencies or foundations in many countries are scarce, and many of the more successful teams have significant buy-in from their universities or are turning to industrial sponsorship when they can. This is highlighted in the cramming of sponsor names and logos onto the backs of team T-shirts, giving iGEM a feel of NASCAR or professional sports. The differences in funding levels between teams and the intense competitive spirit associated with iGEM bring up questions as to whether something should be done to level the resource playing field (e.g., setting upper limits to budgets), such that huge disparities in resources do not lead many teams to feeling like hopeless participants in the competition. iGEM as an organization has run on lean resources, and at the organizational level additional resources could make a significant difference in the ability to improve the student experience through improvements to the registry, parts collection and educational materials.

There is also an ongoing question about the competition aspect of iGEM. Specifically, many of the students take the competition very seriously. Although this results in high-quality and impressive research projects—and has importantly not hindered the open and supportive culture—it also may have undesired personal consequences. Many students are so disappointed when their team does not make it to the list of finalists that they can be seen crying after the finalist announcements. There are also stories that the amount of time some teams dedicate to their projects is so intense it can be detrimental to other parts of their lives, often leading to the break up of personal relationships. Is this something that iGEM can or should try to change? Or, is this part of the human experience around competitions, especially of this scale? Without the competition part of iGEM, would the community invest as heavily? Finally, there are questions around the post-iGEM experience. After the students finish iGEM and return to their schools and plan for their future career goals, what community do the students find, if any, supporting synthetic biology beyond iGEM?

The BioBricks Foundation

The BBF is a not-for-profit organization that was started in 2004 by many of the people involved in iGEM to represent the public interest in the foundational technologies that help define the field of synthetic biology. The original goal of the BBF was to invent and bring to life a legal framework that accelerates and enables the accrual of an open collection of functional genetic elements encoding standard biological parts. However, as highlighted through experiences with iGEM, the successful development of an open technology platform requires several components to be in place, the first being, in particular, a community of people that supports the platform's development and benefits from its existence. In addition, an open technology platform based on standard biological parts requires that the technical standards that define the parts exist and are open. Therefore, the BBF has also directed its efforts to standards development for the field (legal and technical) and community engagement and development. The subsequent text explores each of these activities in more detail.

To encourage the development and use of technical standards in synthetic biology, the BBF has run several workshops on the topic. These workshops were organized to discuss the importance of technical standards in bio-

tech and prioritize areas most critically in need of standards. From these discussions, the BBF developed and launched a process by which people can define and propose technical standards for biotech through the BBF request for comment (RFC) process, which was inspired by the Internet Engineering Task Force (Fremont, CA, USA) RFC process. An RFC can propose a standard, describe best practices/protocols, provide information, or comment, extend, or replace an earlier RFC. The RFC document is made available online through the BBF website (http://biobricks.org/) and feedback and comments are collected for each RFC.

In its first year, 51 RFCs have already been published. Many of these have been submitted by iGEM teams, as one of the optional tasks for teams to earn a gold medal is to develop and define a new technical standard through the RFC process. Glancing through the list of RFCs, they cover concepts as broad as standard definitions, assembly strategies, part characterization and reporting methods, visual description languages, modeling languages and design tools. Over time, as more knowledge is gained regarding best technical standards, the BBF will likely need to play a role in filtering through the RFCs and determining the smaller set of standards to be used by the field.

A legal framework

The BBF and a team comprising Lee Crews and Mark Fischer of the law firm Fish & Richardson (Boston), Drew Endy of Stanford University (Stanford, CA, USA), David Grewal of Harvard University (Cambridge, MA, USA) and Jennifer Lynch and Jason Schultz of the University of California, Berkeley (Berkeley, CA, USA) have also been developing a legal framework that supports an open collection of biological parts. The final draft of this framework—the BioBricks Public Agreement (BPA)—is now available online through the BBF website for comments (http://hdl.handle.net/1721.1/49434). The BBF felt that an ownership, sharing and innovation framework based on patents (the property rights mechanisms most commonly used in biotech) had substantial limitations in the context of an engineering process based on the reuse of thousands of different components across many different systems. Specifically, the cost and time to define and obtain patent-based protection is too great to support the engineering of many-component, integrated, genetic operating systems. In addition, the costs associated with freedom-to-operate searches become prohibitive for systems comprising dozens of genetic components, never mind anticipated genome-scale engineering projects. Although the BBF has advocated for the need to consider new property rights law in support of the future of biotech, they developed the BPA to support the immediate maturation of an open technology platform supporting genetic engineering.

Mark Fischer was involved in helping to draft the legal frameworks for free software in the 1980s. However, the differences in property rights between biotech (patents) and software (copyright) presented several challenges to a direct translation of the licenses used to support open and free software. As a result, the BPA represents a bilateral agreement (or contract) between the contributor and user. The language within the BPA allows the contributor to acknowledge invention over the uses of a part, disclose information on whether there is a patent on it or not, and promise not to assert any property rights against others under certain conditions of use, so that the part can be freely used. The BPA also allows the user to state acceptance of use of the part and promise to use it according to the conditions put in place by the agreement. However, the agreement does not put any encumbrance on downstream uses, such as a give-back or share-alike clause. In doing so, the BBF hopes that the BPA will support the development of a shared open platform that both academics and industry can use, while still allowing proprietary systems to be built upon this open platform. The aim of the BPA is to reduce the legal ambiguity around the use and reuse of standard biological parts, and the BBF hopes that the BPA will encourage both industry and academia to support and play a role in the development of a next-generation open technology platform in biotech.

Community engagement

The BBF has also worked to support the broader synthetic biology community. In particular, the BBF has recently taken on the role of lead organizer of the synthetic biology conference series (most recently SB4.0 in Hong Kong; http://sb4.biobricks.org/). BBF's leadership of this conference series has allowed many diverse communities to learn about and engage with issues of safety, security, equity and ethics relating to the field of synthetic biology. In addition, the activities of the BBF in iGEM, technical standards and technical standards workshops play an important role in building and engaging the community. The BBF also directs efforts to developing educational materials regarding policy issues related to synthetic biology, in particular ownership, sharing and innovation frameworks underlying biotech.

Because of the diversity of backgrounds represented in the synthetic biology community, the BBF plays a key role in providing leadership and a focal point for this growing field. The BBF has focused its early efforts on addressing very challenging concepts in the field. Property rights law in biotech through patents is well established and entrenched, such that work to change this system to one that might be more appropriate for a future biotech meets significant resistance. The BPA is a step toward building a community that supports an open technology platform in biotech. However, for this vision to truly succeed, high-quality open parts are needed. In addition, most people (including foundations and companies) look to biotech as a set of applications. The BBF is working below the level of applications. Although their work in community building and legal and technical standards supports all biotechnological applications, raising funds for such foundational work is typically much more challenging.

Conclusions

The systematic application of engineered biological systems to the problems posed by hunger, disease, environmental quality and finite resources remains both extremely compelling, yet challenging, given the current state of tools supporting biotech. Both iGEM and the BBF are leading different, but synergistic, efforts focused on developing community, sharing and open technology platforms supporting biotech. Importantly, although advanced technologies can be used for good or harmful purposes, the activities of iGEM and the BBF, including education, outreach and community building, are directed toward biasing systems heavily in favor of constructive outcomes. The ideology, values, tools and culture realized by iGEM and the BBF seem likely to continue to make important contributions to the foundations of synthetic biology going forward.

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