The iGEM competition: building with biology

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Abstract: Can simple biological systems be built from standard, interchangeable parts and operated in living cells? Or is biology simply too complicated to be engineered in this way? The international Genetically Engineered Machine Competition (iGEM) is an open design challenge for student teams that addresses this difficult question. Using a library of standardised parts known as BioBricks, groups of undergraduates from around the world spend their summer designing and assembling biological devices, to build genetic machines.

1 Introduction

The engineering of new biological systems is an exciting frontier, with opportunities for collaboration between biologists, programmers and engineers. The iGEM competition throws together students from different disciplines, requires them to initiate a novel scientific programme over the summer, and challenges them to learn and share different skills. The competition has provided a new educational model in an exciting new field. In Cambridge, we are unreservedly positive about the educational aspect of the competition. As well as learning challenging new scientific skills, the competition allows students to experience project brainstorming, management, teamwork, presentation and other organisational skills in a way that is essentially outside the undergraduate curriculum. The competition provides a powerful educational tool, exposing students to engineering challenges and a modern research environment, while in pursuit of their own goals.

The iGEM competition's long-term goals are to enable the systematic engineering of biology, while promoting the open and transparent development of relevant tools. To this end, founders Tom Knight and Randy Rettberg of MIT's Computer Science and Artificial Intelligence Laboratory, and Drew Endy from the Biological Engineering Division of MIT, have pioneered the collection and use of a library of modular biological components. They have established the Registry of Standard Biological Parts (http://parts.mit.edu), which includes several hundred basic parts such as operators, protein coding regions and transcriptional terminators. It also includes many devices such as logic gates and input/output modules built from these basic parts. These parts and devices are known as BioBricks [1].

2 The competition's history

Knight, Endy and Rettberg took their first steps towards realising an international competition in synthetic biology back in 2003 with the help of fellow computer scientist Gerry Sussman. The four established a class, providing a 'hands-on introduction to the design and fabrication of synthetic biological systems' for MIT's IAP (Independent Activities Period), a four week session put aside in MIT's calendar for undergraduates to engage in a wide range of innovative projects that combines learning and fun. A group of 16 students were challenged to improve on Elowitz's Repressilator [2] and construct biological oscillators. The programme proved a success, running again the following year with Pam Silver from Harvard joining the instructors. In IAP 2004, students turned their attention to cellular patterning in bacteria, with final designs ranging from bull's-eyes to polka dots. Both IAP programmes received a substantial DNA synthesis budget and many of the parts are included in the Registry's current distribution.

The IAPs laid the foundations for Rettberg, Knight and Endy to expand the program. The summer of 2004 saw the first US intercollegiate design competition in synthetic biology. Student teams from Boston University, Caltech, MIT, Princeton and UT Austin looked to engineer cellular state machines and counters for SBC (Synthetic Biology Competition) 2004. The competition culminated in the first November Jamboree at MIT, where participants shared their work, experiences and hopes for the future. Campbell's absorbing account of the 2004 Jamboree includes full project descriptions and provides a unique insight into the forerunner of the iGEM competition [3].

The following summer, the competition included international teams for the first time. Student representatives from 13 universities participated in iGEM 2005. North American teams from Berkeley, Caltech, Davidson, Harvard, MIT, Oklahoma, Penn State, Princeton, Toronto, UCSF and UT Austin were joined by European entries from Cambridge and ETH Zurich. Unlike previous competitions, the teams were not given a specific task, but were simply challenged to 'design and test a simple biological system from standard, interchangeable parts and operate it in living cells'. As a result, student projects covered a wide range of subjects. Designs included regulation of chemotaxis, cell–cell communications, biological sketch pads, a digital counter, thermometers, cellular relay races, biological wires and many more. The first weekend of November 2005 saw

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over 150 students and instructors coming together for the Jamboree held at MIT's Stata Center, to share and celebrate their work [4].

3 The ambassador programme

The iGEM competition tripled in size from 13 to 37 teams in 2006, spread throughout North America and Europe, with new entries from South America, India and Japan. With rapid growth came the need for increased team support and programme development. This was addressed through the launch of an ambassador programme. iGEM Director Randy Rettberg approached previous participants of the competition to take lead roles in promoting team–team communication, improving the programme and to ultimately make the teams, projects and competition more successful. Andrew Hessel, Melissa Li and I covered the 22 North American schools. Reshma Shetty looked after the Asian teams while taking a graduate advisory role within the MIT project and Meagan Lizarazo visited the Latin American teams, when not developing the Registry's robotic BioBrick assembly line. Jonas Nart, Tamara Ulrich and Robin Kunzler supported the European teams, based out of ETH Zurich.

An alternating schedule of team visits and programme development back at MIT's Registry proved a useful, if challenging combination. My visits were stimulating and presented an ideal opportunity to not only inform teams about new features and developments, but to get first-hand feedback from students and faculty on the programme, any problems they were facing and many new ideas. During my visits I witnessed a wide range of projects, approaches and problems. It also presented an opportunity to see first hand some of the best researchers in the field interact with their students. The chance to regularly cross paths with Melissa and Andrew at the Registry during gaps in their schedules provided a sound platform to improve the competition format and structure as well as inform development of the Registry. We later addressed programme publicity, the Jamboree and help lay the foundations for iGEM 2007. The ambassador programme proved a unique, challenging and massively rewarding experience that hopefully aided both rookie and experienced iGEM teams alike.

iGEM 2006 proved a huge success. A wide range of projects were presented at the annual Jamboree, many achieving their initial goals. Significantly more designs were realised than in earlier competitions and several hundred new BioBricks were contributed to the Registry. The teams' work is described in detail in this first issue of IET Synthetic Biology.

4 BioBricks

BioBricks are standard interchangeable parts, developed with a view to building biological systems in living cells. BioBrick parts can be assembled to form useful devices, through a process referred to as 'standard assembly'. This uses normal recombinant DNA manipulation techniques based on restriction enzymes, purification, ligation and transformation. For example, two BioBrick parts, B0034 (blue) and C0010 (green), can be assembled to form a composite B0034–C0010 (blue–green) part via standard assembly, illustrated in Fig. 1. Every BioBrick is flanked by restriction sites, comprising the BioBrick prefix and suffix, including EcoRI and XbaI cut sites on the left (prefix) and SpeI and PstI on the right (suffix).

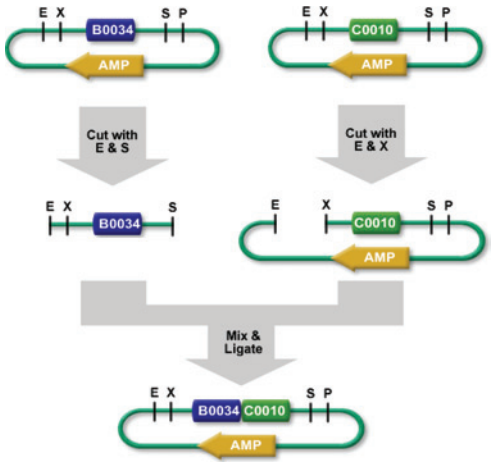

Fig. 1 *Standard assembly example*

Using normal recombinant DNA manipulation techniques based on restriction enzymes, purification, ligation and transformation, two BioBrick parts, B0034 (blue) and C0010 (green), can be assembled to form a composite B0034–C0010 (blue–green) part via standard assembly

For the assembly shown, the part B0034 (blue) is cut out of its plasmid with the enzymes EcoRI and SpeI. The result is called the insert because it will be inserted into the plasmid containing the other part. In a separate reaction, a hole is cut in the plasmid containing the part C0010 (green) using EcoRI and XbaI. Using gel electrophoresis, the insert for B0010 (blue) and the cut plasmid containing C0010 (green) are purified and the unwanted fragments discarded. The purified insert and cut plasmid are mixed under the right conditions to allow ligation of the two EcoRI sticky ends and joining of the compatible SpeI and XbaI sticky ends, which destroys the internal cut sites. The DNA backbone contains a composite B0010–C0010 (blue–green) part and can be transformed into competent *E. coli* cells. These cells may be grown to produce as much of the new BioBrick (B0010–C0010) as desired. An alternative to BioBrick standard assembly is three antibiotic (3A) assembly. A description can be found in the Registry's help section at parts.mit.edu.

Using standardised parts has many advantages. It isolates the construction procedure from the design process, provides a repeatable method allowing BioBricks to be made longer and more complex in function while the construction process remains identical, confers full compatibility to all the BioBricks in the collection, and significantly, means each independent project which uses BioBricks serves to add a larger range of parts and devices to the ever-increasing range of modular components in the Registry of Standard Biological Parts.

5 The Registry of Standard Biological Parts

Information on each BioBrick is stored in the Registry's online library at http://parts.mit.edu. BioBrick parts, devices and systems are arranged in the Registry within an abstraction hierarchy, as proposed in Endy's Foundations for Engineering Biology [5]. Each online record is entirely customisable, allowing the display of relevant information about the part. There are five subsections to each online BioBrick entry (Fig. 2):

1. The 'Main Page' gives an overview of the part and can provide links to appropriate data or specific subpages.

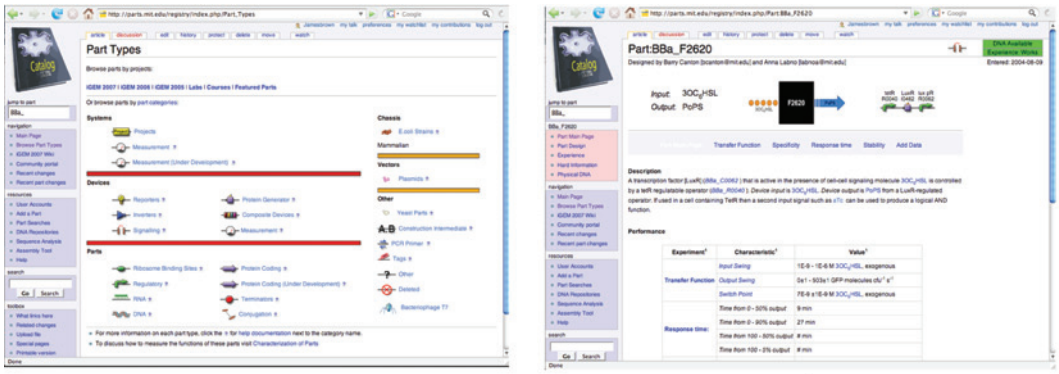

Fig. 2 *Screenshots from MIT's Registry of Standard Biological Parts at http://parts.mit.edu*

a The 'Part Types' page from showing BioBricks within an abstraction hierarchy
b A good example of a well-characterised part (BBa_F2620 by Barry Canton and Anna Labno)

2. The 'Part Design' section details design considerations, where the part was sourced and any relevant references.
3. The 'Experience' section allows other users to rate and leave comments on the BioBrick, indicating a reliable working part or highlighting any issues, much like an online book or DVD review.
4. The 'Hard Information' page simply contains the data that allow the Registry to run efficiently as a searchable database.
5. The 'Physical DNA' section includes an exhaustive list of all versions of that BioBrick, which plasmid it resides in and from which well an iGEM participant can obtain the DNA, from the current distribution of four 384 well source plates.

The Registry provides several tools that aid the design and understanding of BioBrick systems and devices. Users can easily 'Add a Part' to the Registry with a few simple clicks, pasting in sequence information and annotation. The 'Part Searches' tool allows users to quickly and easily scour the Registry for information, trace the origin of more complex parts and list associated sub-assemblies, and see which higher systems have been constructed with any part of choice. The 'Sequence Analysis' tool is used to organise and analyse a set of DNA sequencing runs by comparing DNA sequences against parts in the Registry. The 'BioBrick Repository' maintains information on the DNA of the BioBrick parts in plasmids and cells. The same functional part such as a particular Quad Part Inverter may be available in different cell strains or plasmids and may have been built with different assembly techniques resulting in different scars between its components. All of this information is stored in the repository database. Finally, the 'Users & Groups' tool allows users to manage their user information, see their groups, join new groups, and find names to use for new parts here.

6 What lies ahead?

The iGEM competition has proved a valuable educational tool, inspiring many young minds from a multitude of disciplines to pursue further study in synthetic biology. It is uniquely positioned to place students at the cutting edge of an exciting young research field that holds huge potential. As the competition has grown rapidly over the previous years, correspondingly so has the collection and complexity of available BioBricks. This growth looks set to continue, both in terms of iGEM teams, geographical spread and available BioBricks. Significantly, established laboratories, many of them advocates of iGEM, have started to contribute to the BioBrick collection through their day-to-day research and in doing so look set to provide a range of better characterised parts and devices.

The Registry's biggest shortcoming at this early stage in its development is the varying quality of its BioBricks. The iGEM competition's short ten-week summer period means a large proportion of the parts are not well documented and contain inaccurate information. There are currently very few well-characterised, accurate parts available. The Registry's founders are very much aware of this issue and are actively taking steps to address it. A system is being put in place that would see official BioBrick status given to parts that meet established quality criteria and pass peer review. Tom Knight is to chair the review committee and he is looking for members who will first decide how the process should work and then organise the reviews. If you are interested, please state your interest online on the Registry's website.

The future promises many exciting developments. The introduction of new software and standards to aid the design and modelling of increasingly complex engineered biological systems. The falling cost of DNA synthesis looks set to eliminate the laborious, difficult, time-consuming process of construction, replacing standard assembly with an online order form for designed BioBrick systems. Free from the constraints of traditional DNA manipulation techniques and equipped with these new software tools, this new era of biotechnology promises more complex and effective biological devices, aiding research and providing end applications alike. There is no doubt in my mind of the growing importance of synthetic biology and its potential to address prominent global issues relating to energy, the environment and healthcare. Synthetic biology looks set to fuel a new generation of biology-based industries and certainly has a very bright future. So too does the iGEM competition, which has contributed so much to the growth and prosperity of synthetic biology over the last four years. We can expect many past and future iGEM participants to find themselves working for or even running this new generation of bio-based industries.

iGEM 2007 is underway with almost 60 teams participating from Asia, North America, Central and South America, Australia, the UK and Europe. Ahead of all of them lies an exciting summer of hard work mixed with enjoyment, as they strive to design and build novel biological systems. We can all look forward to an exciting Jamboree in

November and another vintage of inspired synthetic biologists.

7 Acknowledgments

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8 References

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