Training the Next Generation of Synthetic Biologists – iGEM

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Fig. 1. Giant Jamboree held in Boston in October 2014. Teams attended from 245 universities across 32 countries with more than 2,300 participants. Photo credit: Justin Knight, iGEM Foundation.

The International Genetically Engineered Machine competition (iGEM) is an annual undergraduate competition in synthetic biology. Teams of undergraduate students work on a project over the 'US-summer' vacation, and later present their research at a Giant Jamboree event held in Boston in October, competing for medals and other special awards (**Fig. 1**). Now entering its eleventh year, this global competition in synthetic biology has grown dramatically from a local event run at MIT with five teams to its current size of more than 260 universities competing from over 50 different countries, with some 2,500 participants expected at the Jamboree.

> *"If you want to change the world in some big way that's where you should start – biological molecules"*
> *Bill Gates (1)*

In 2010, a curriculum redesign at Macquarie University, dovetailing with an interest in synthetic biology by some undergraduate students, led us to incorporate the iGEM competition into our undergraduate Biomolecular Science capstone unit. Now entering our sixth team, here we describe the framework of the competition and discuss what we believe are the main challenges when participating in a competition which is mostly geared towards the northern hemisphere summer. We outline the strategies used to ensure competition requirements and deadlines are met, and share our thoughts on what we and our students have gained from our involvement in this unique and often intense experience.

The BioBrick and the Registry of Standard Biological Parts

Synthetic biology has numerous definitions, but in the context of iGEM it relates to the design and use of synthetic DNA to generate interesting and useful biological products or systems. The competition is based around the concept of assembling biological systems from 'standard' biological parts or BioBricks using engineering principles; as well as the open sharing of BioBrick parts. The iGEM Foundation maintains a library of all these BioBrick parts, encoding for biological functions in a Parts Registry (http://parts.igem.org/Main_Page). The Registry is a giant online catalogue that organises and documents all previously constructed BioBrick parts. It is therefore an important central resource for all teams. On registering a team and paying $US4000, iGEM sends out a DNA distribution kit of several 384 well-plates. This selection of about 1000 BioBrick parts includes genetic sequences encoding for promoters, repressors, fluorescent proteins and many other useful biological functions. Receiving this kit always makes the possibilities suddenly appear tangible, especially for a first time team.

Construction of BioBricks and Standard Assembly Methods

To be successful at iGEM, and win medals, teams must design and produce functional and well-characterised new BioBrick parts for inclusion in The Registry. They must also use or improve on existing ones. The standardised flanking of each BioBrick part sequence allows students to use a standard assembly scheme to construct and build larger novel biological 'circuits' (2). Teams must then show that their circuits are functional in a living host, such as *Escherichia coli* or *Bacillus subtilis.*

To fit the Registry's 'Get, Give & Share' philosophy, all submitted parts must be compatible with the RFC 10 BioBrick format (2). Parts are typically submitted on the *E. coli* plasmid pSB1C3, and are flanked by defined prefix and suffix sequences containing four unique restriction enzyme sites so Three Antibiotic (3A) assembly methods can be performed (3) (**Fig. 2**). The assembly process works very efficiently but the DNA parts cannot contain EcoRI, PstI, XbaI or SpeI restriction sites. This is sometimes a problem, however, with the ever decreasing cost and turn-around time for DNA synthesis, the past few years have seen the majority of teams adopt the use of custom synthesised DNA for the generation of their BioBrick parts. This change to genuine 'synthetic' parts, as well as other new assembly strategies such as Gibson and SLIC assembly methods (4,5), has also made the construction and integration of parts more reliable and efficient. Indeed, one of the major sponsors of the 2015 iGEM competition has offered up to 20 kbp of free DNA synthesis per team which will certainly entice most teams to have their DNA synthesised rather than use traditional methods.

Requirements of the iGEM Competition

In addition to submitting at least one BioBrick part to The Registry, the other basic requirements for a minimally successful project involves completing a team wiki, and presenting a poster and talk at the Jamboree. Teams must also complete biosafety forms and demonstrate that they have acted responsibly and followed all national and international biosafety rules; both inside and outside the lab. The team wiki pages act as the laboratory notebook and must be clear, easy to navigate and complete. Wiki pages from past competitions are all open source and showcase an amazing amount of talent and creativity. Higher levels of achievement in the competition require making and characterising an existing or novel working part or system; modelling an aspect of the project; or contributing to the synthetic biology or larger community through a 'Human Practices' based activity.

The inclusion of Human Practice in iGEM is an important element that has provided space for students to interrogate the potential contribution of social science to synthetic biology and to explore the ethical, legal or social implications of their research projects for the broader community. Although high-school visits or displays at University Open Day events are always commended, teams are encouraged to imagine their projects in a social or environmental context and explore issues that might influence the design and use of their technologies. The Human Practice prize winners in recent years often involved social scientists, designers and artists. However, creativity and originality will also score well with the judges. As an example, the 2014 Macquarie University team hosted the first international synthetic biology online reality competition called 'So You Think You Can Synthesize' (6), attracting an audience across some 14 countries with 11,000 views. This platform allowed our students to refine their project based on discussion and enquiry from their interactions with the public.

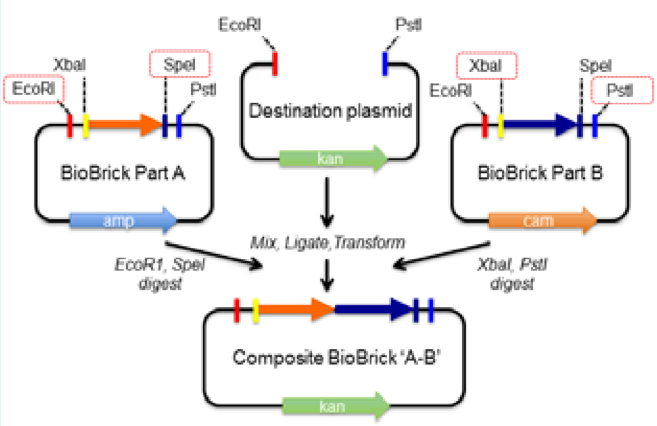

Fig. 2. Three-Antibiotic (3A) assembly method for the joining of two individual BioBricks (Part A and Part B) into a new composite BioBrick (Part A-B). The destination plasmid is cut with EcoRI and PstI. The prefix part A is cut with EcoRI and SpeI. The suffix part is cut with XbaI and PstI. The resulting linearised DNA pieces are then ligated together and transformed before plating on plates with antibiotic corresponding to the destination plasmid.

The iGEM Research Project, Success Stories and Startups

Generating iGEM project ideas is not necessarily all that difficult once some familiarisation with synthetic biology design principles has been achieved. The general idea is to build something useful that fits into a defined theme called a 'track' using parts from The Registry kit, or newly designed and synthesised parts. iGEM tracks include: Energy, Environment, Food and Nutrition, Foundational Advance, Health and Medicine, Information Processing, Manufacturing, and New Applications. New tracks included this year are Art and Design, Community Labs, Hardware, High School, Measurement, Policy and Practices, and Software, with different judging criteria to the traditional tracks.

iGEM team projects are often ambitious as students naturally choose projects that address a familiar real-world problem or opportunity. Complete experimental success after just one competition is rare. At Macquarie, we allow our teams to build on the same project over a 2–3 year period while future projects are 'incubated' in a Synthetic Biology coursework unit offered in our Masters of Research (MRes) program.

Award winning projects often arise from a very simple idea. Many successful iGEM projects have also made important contributions to the field of synthetic biology, with teams publishing in peer-reviewed journals or generating patents. Notable projects include; a living bacterial 'photography' system from a collaborative team at the UCSF and the University of Texas at Austin (7). Other stand-out award winning projects include reengineering *E. coli* to float or sink in response to environmental pollutants (University College London 2012); or to smell like mint during the exponential growth phase and switch to bananas during the stationary phase (Massachusetts Institute of Technology 2006); or a palette of pigmented bacteria in a memorable project titled 'eChromi' (University of Cambridge 2009). In the tracks of Health and Medicine, and Food and Energy, teams have also tackled serious global issues whose goals include new ways to fight cancer or infectious disease, or to generate vaccines. Notable projects in this category include the development of a bacterial arsenic biosensor (Edinburgh 2006), creation of a bacterial red blood cell substitute (Berkeley 2007), and design of bacteria flagellar display of *Helicobacter pylori* epitopes for vaccine development (Slovenia 2008). In the Energy category, projects often seek solutions for producing biofuels, bioplastics or new technologies to remediate biological waste into useable energy. At Macquarie University, our 2013 and 2014 teams worked on a project to introduce the chlorophyll biosynthesis pathway into *E. coli* and were awarded a silver and gold medal, respectively, for their achievements (**Fig. 3**).

iGEM projects can be expanded into projects for graduate students but many teams have also gone on to attract new grant funding or Startup funding as a direct result of their involvement in iGEM. A list of iGEM Startup ventures is kept by iGEM (8) and includes companies such as Ginko Bioworks (from MIT 2014), LabGenius (Imperial College 2011) and bento lab; a 2013 DIY team who developed an all-in-one 'bento box' personal laboratory apparatus. This list of success stories will undoubtedly continue to grow.

Fig. 3. Representatives of the 2014 Gold medal winning Macquarie University 2014 iGEM team presenting their poster, Photophyl – The Green Machine (6), at the Giant Jamboree in Boston. From left: Amit Bhattacharjee, Mitchell Jeitani, William Klare, Leah Simmons, Sunny Wu and Ahmed Elsayed. Photo credit: Edward Moh, Macquarie University.

Running a Successful iGEM Team in an Australian Context

There are quite a few challenges to success for an iGEM team in an Australian context. To begin with, the closure of the regular iGEM registration in March typically corresponds with the start of the Australian teaching semester. This timing can make it difficult to identify students who genuinely have the time needed to commit to the sizeable challenge that is iGEM. Further, and depending on the size of the team, it may be difficult to find a lab space with the guaranteed access needed to do the experimental work. Incorporation of iGEM into our undergraduate science teaching unit allowed us to work around some of these issues. Linking in with a unit provides us with a ready-made team with suitable background knowledge, an allocated wet and dry-lab space, as well as some resourcing (consumables, equipment and technical support staff).

However, even in the planning stage, considerable effort is needed to design a project and ensure that it fits into one of the iGEM tracks. Aligning a project with current research within the department helps with expertise and resourcing. We also start the wet-lab component in early January with a few summer scholarship students designing and working on the project. From February to April, we begin fundraising and continue planning with interested students. In May, the parts kit arrives and we encourage as many students as we can to continue with the lab work before semester starts at the end of July. However, despite planning ahead, we still find that most of our lab work is done within a very short six to eight week teaching block from August to mid-September. This intense but highly productive period is driven by the enthusiasm of the students and the mentors; pushed along by the looming 'wiki-freeze' deadline whose eventual arrival is an event to experience in itself!

The non-selective make-up of our team from our undergraduate unit contrasts with how most iGEM teams are formed. Ideally teams need molecular biologists, microbiologists, biochemists, web designers, math modellers, fundraisers, communicators and even t-shirt designers so as to satisfy the various components of the competition. Several of the 'power-house' teams decide on their team composition via a competitive application process. In our experience, we find that by not actively recruiting for each skill requirement at the start of the competition year, we have provided a unique learning space and freedom to our students to each develop these other 'non-scientific' roles. We find that our students often exceed both our and their own expectations when given the opportunity to practice other professional skills. It is also fascinating to observe the process where, several weeks into the project, the students will migrate into three distinct working groups: (i) project design and dry lab work including wiki editing; (ii) wet lab work; and (iii) public outreach and fundraising. However, the assessment requirement for our teaching unit encourages all our students to do some work across these different areas, especially the wet lab work and project documentation components.

The cost of iGEM is undoubtedly another important consideration (**Table 1**). While the cost of chemically synthesising and assembling the BioBrick parts used by an iGEM team is now relatively affordable and the equipment required to do this is standard in most teaching laboratories (thermocycler, gel equipment, incubator, etc.), there may be a requirement for other expensive materials and technologies to perform the ambitious functional characterisation of the products the students produce during their wet lab experiments. The more challenging cost to meet is to find research funds to support student travel costs. In our case, fundraising has allowed us to send only a third to half the number from our team to the final Jamboree event. Even though all team members receive any prizes awarded, individual disappointment with not seeing a project through to completion at a Jamboree is unfortunately unavoidable.

Table 1. Costs of running iGEM and attending the Jamboree.

Component	Cost
iGEM team registration (and DNA distribution kit)	$4,000 USD
Lab reagent costs	$500–$5,000 depending on project
Travel and accommodation at Jamboree in Boston	~$3000 per attendee
Jamboree registration	$695 USD per attendee
Total costs for six attendees at Jamboree	~$25,000–$32,000
Total per team member	$1000–2000 (team size ~15– 25)

So external funding and sponsorship has been an essential component of iGEM and again is best driven by the students. Our team has received support from a variety of sources including university support, individual student travel grants, industry sponsorship and NSW State Government sponsorship. For the first time in 2015, the NSW State Government, through the NSW Office of Science and Research, is opening a competitive funding grant program for 'Science and Engineering Student Competition Sponsorship' (9). We hope other Australian government bodies and scientific agencies will follow the example set by the NSW government for supporting undergraduate research.

iGEM - A case of Education Driving Research

It is important to stress that iGEM is an educational program in synthetic biology with hopes that students might contribute to transformational advances at some time in the future. The six- to nine-month time frame of the competition is sufficient that students with only basic training in biology can participate, provided technical and theoretical support is given by mentors. Our students are motivated by a genuine problem to solve and feel the overwhelming satisfaction of presenting hard work and seeing a project from start to finish, often for the first time. They not only have a rich learning experience at the bench mastering skills in biochemical, molecular biology, bioinformatics and modelling techniques but they also have the opportunity to participate in other elements of research training not possible in a typical recipe-based teaching unit. The iGEM journey has provided our students with opportunities that have often taken them beyond the confines of their parent discipline. Opportunities to exhibit and develop entrepreneurial skills, to engage in a multicultural and interdisciplinary exchange of knowledge with an international community, as well as to engage with the public.

Get Involved

In conclusion, the best way to learn about iGEM is to participate. The next best way is to review previous competitions by viewing presentations, posters and wikis which are all available online through the most recent igem.org website, e.g. 2014.igem.org. Award winning projects tend to be imitated. Contact teams that have participated before and organise a visit. Familiarise yourself with the online judging rubric. Recruit advisors, of which you will need several, that have the requisite experience with the iGEM protocols, as well as the iGEM ethos; and with any luck, guide the team to success. Be prepared to be impressed by the next generation of synthetic biologists!

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