Students go through the gears at the iGEM competition for engineering biology

Joshua Lawrence (University of Cambridge, UK)
Siwat Chang (Imperial College London, UK)
Luis Chaves Rodriguez (Imperial College London, UK)
Thomas Ouldridge (Imperial College London, UK)

The annual International Genetically Engineered Machine (iGEM) competition, represents an exciting opportunity for students to experience first-hand the potential of synthetic biology approaches to solve real-world problems. In this article, an iGEM team based at Imperial College London share some of the highlights from their participation in the 2018 iGEM event, including sharing their work at the annual Jamboree in Boston, Massachusetts.

The industrial revolution was driven by engineering. Thanks to innovations in mechanical engineering and, more recently, computing science, we can fly in planes, we can drive cars, and the places we live and work are generally safe and comfortable buildings with hot water, heating and other commodities. Today there is another engineering revolution taking place, one which is ushering in the field of synthetic biology. Development in molecular biology during the 20th century and early parts of this century have allowed us to study how DNA is organized and how it encodes the information needed for the production of the molecular machinery contained within a cell. Parallels can be drawn between DNA and computer programming languages, and between engineering design principles for industrial machinery and the configuration of protein machines within cells.

This fusion of engineering, computer science and biology is leading to the development of novel biological devices with medical, industrial, environmental and computational applications. Synthetic biologists now have a series of tools and parts (biological equivalents of hammers and nails) and engineering principles (e.g. on standardization of components) available to facilitate the realization of these ambitions.

Since 2004, the annual iGEM competition gives students an opportunity to develop novel combinations of genetic components with standardized, interchangeable connections towards a specific goal. These components, known as 'biobricks', are then itemized in an open registry and can be drawn upon by future teams.

In 2018, the PixCell team had the opportunity to represent Imperial College London at the main jamboree, alongside over 340 other teams. This event was a unique opportunity for students from all over the world to meet and share their interest in synthetic biology. Each team will have a unique perspective on an original problem, with the jamboree showcasing the multidisciplinary nature of synthetic biology. The challenge enables students to explore a research project of their own design, providing experience in scientific research, creative design, science communication, teamwork and networking. Here we'd like to highlight some of the work of fellow competitors whose projects we found particularly exciting, as well as explaining a bit more about our own project.

The up-and-comers: mCATNIP, a high school team from Great Bay China

While most teams at the Jamboree were university students, high-school students can also attend and compete in their own category. The winning high-school team, mCATNIP, was made up of students in the Great Bay area of China. They had the aim of biosynthesizing nepetalactone, the active ingredient of catnip (Figure 1). While a precursor to nepelactone, nepetalactol, has therapeutic properties which makes it a valuable target for microbial biomanufacturing, mCATNIP realized that nepetalactone could also be used to attract stray cats that could then be humanely neutered, solving a local problem. To that end, they have even designed a live trap for these cats.

Microbial biosynthesis of nepelactone involves the concerted expression of the many foreign enzymes in

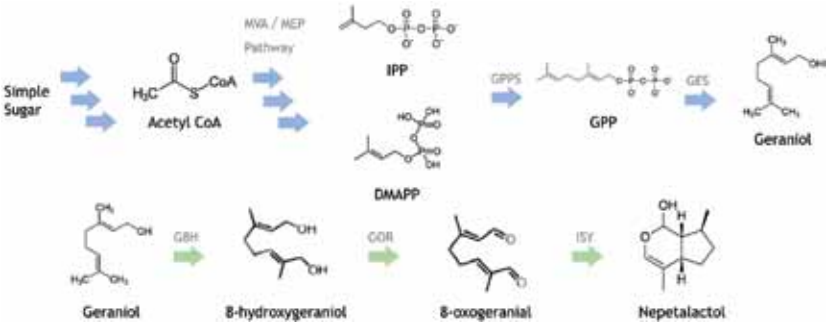


Figure 1 (above). A simplified schematic of the nepetalactol biosynthesis. Originally published on the GreatBay iGEM wiki under a CC BY licence.

Right: Great Bay China team formed by high-school students. Originally published on the GreatBay iGEM wiki under a CC BY licence.

host microbes to create the necessary circuitry. Placing too many enzymes in one host leads to cellular 'burden'. In order to circumvent this problem, the team split the circuitry between two different microbes, bacteria (*E. coli*) and yeast (*S. cerevisiae*). They then had to control the population levels of these two microbes in order to have sustained production of nepelactone. Through careful engineering of cell media, the team came up with a way of creating a microbial consortium, or a co-culture, between the two microbes. This project would be advanced even for a university team, but this high-school team rose to the challenge with smart framing of their solution and being able to deliver on the said solution.

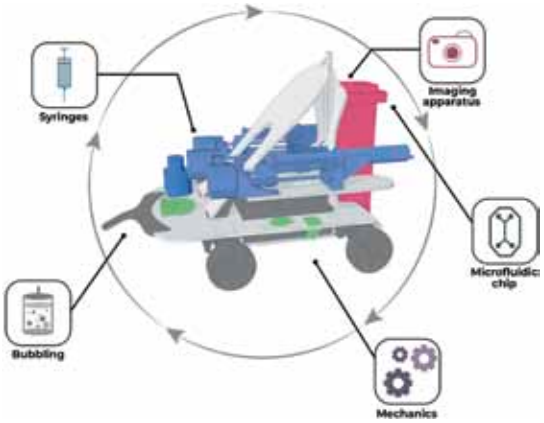
The rise of the machines: AROMA, a hardware-based project from ETH Zurich

iGEM projects often focus on biosensors due to their relatively straightforward applications and ease of design. The team from ETH Zurich, AROMA, pushed this idea to its limit by designing a robot that is capable of detecting the source of a gaseous molecule. To achieve this goal, the team used engineered microbes to work as a 'nose' for a robot (Figure 2).

Microscopes were used to monitor the behaviour of cells that responded to a given molecule. The AROMA team monitored the chemotaxis of the bacteria, which is essentially the mechanism by which microbes move towards a smell they like, or away from a smell they do not.

This project required as much, if not more, hardware engineering as it did conventional synthetic biology.

Figure 2. The design of the AROMA robot and a prototype that could be found running around the exhibition halls at the 2018 Jamboree. Originally published on the ETH Zurich iGEM wiki under a CC BY licence.



The team had to design systems to uptake the gaseous molecules in solution and distribute these solutions to the cells, microscopy systems to detect cellular responses, and algorithms to process image data and define the movement pathway all on top of a moving and working robot. We admired the technical complexity of this project and how well interwoven it was with the synthetic biology of engineering a biosensor.

Fifty Shades of Stress: a project with medical applications from Leiden University

The 2018 Leiden University team focused their iGEM project around the looming antibiotic resistance crisis, which is expected to cause increased mortality rates from infectious diseases in coming years. When searching for antibiotics, researchers have previously focused on molecules produced by organisms in sufficient concentrations to kill bacteria, ignoring dilute antibiotics that stress the cell. Recent advances have made use of co-therapies, where a drug that stresses the bacteria is provided with an antibiotic to increase its effectiveness. For their 50 Shades of Stress project, the Leiden team created eight different genetic circuits that give measurable responses to different types of cellular stress. This suite offers a cheap and effective way of screening for new antibiotic candidates. The team used this system to identify cell stress caused by ascorbic acid, which they further proved improved the antimicrobial activity of certain antibiotics (Figure 3).

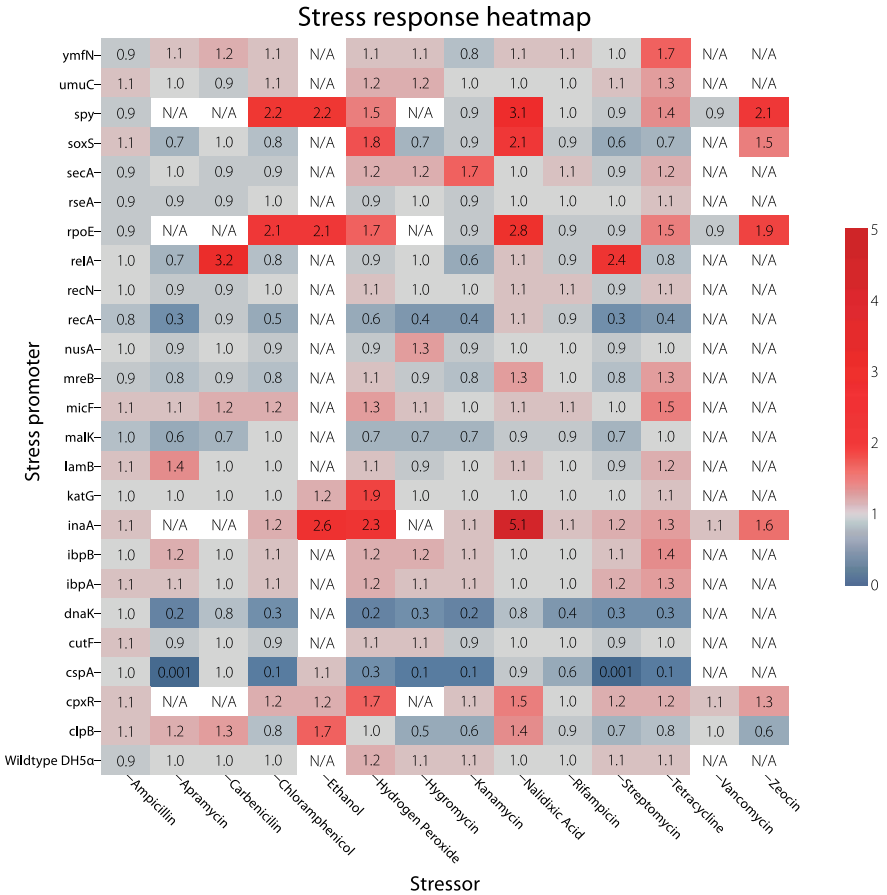


Figure 3. Heatmap showing how different stress promoters respond to different substances that could cause bacterial stress. Originally published on the Leiden iGEM wiki under a CC BY licence.

Decoder: a computational project from William & Mary, Virginia

Computational modelling is a key part of the framework that allows precision electrical and electronic engineering. It is, therefore, a key part of synthetic biology, which seeks to replicate that success with genetic circuits. Numerous iGEM teams have created minimal biological models to provide important predictions of the behaviour of biological systems, and the majority use modelling to test their gene circuit in silico, before even setting foot in the lab. This process allows synthetic biologists to improve the design of their circuits to be more robust and effective. Experimental results can then be used to improve the model in turn, which can then be used again to provide further improvements to the experimental design. This workflow is the design-test-build-improve cycle that serves as the core mantra of synthetic biology.

Some iGEM teams focus on and excel in the modelling side of iGEM, with many of these teams winning top prizes in previous iterations of the competition. The 2018 William & Mary team (Decoder) demonstrated what is known as an abstract model. Instead of modelling the behaviour of a specific genetic circuit, they modelled the behaviour of a blueprint (known in the field as a topology) that can be applied to many different genetic circuits. They focused on a circuit blueprint known as an IFFL (incoherent feed-forward loop), which has been observed in many natural systems. The team showed how this blueprint can be used as a decoder of information in a time-varying signal, providing a simple framework to construct information-processing genetic circuits for a range of applications. For example, cancer can be detected by how regularly certain proteins are produced, or water quality can be assessed over time with bacterial biosensors to improve public health. The William & Mary team used impressive mathematical modelling approaches to show how this system could be tuned to detect inputs that changed differently over time, backing up some of their results with experimental verification.

PixCell: Electronic control of genetic circuits by Imperial College London

A key motivation of synthetic biology is to emulate the success of electrical and electronic engineering in cellular contexts. Our team, PixCell, sought to integrate electronic and biological circuits directly. In the language of iGEM, achieving this goal would be a "foundational advance": rather than engineering a device with direct medical, agricultural, industrial or environmental applications, we instead focused on advancing the core technology of synthetic biology itself. We designed an improved method of electronic control of gene expression, essentially an electrical switch for turning biological systems on and off (Figure 4). This provides an alternative to chemical and optical approaches, which have a number of weaknesses.

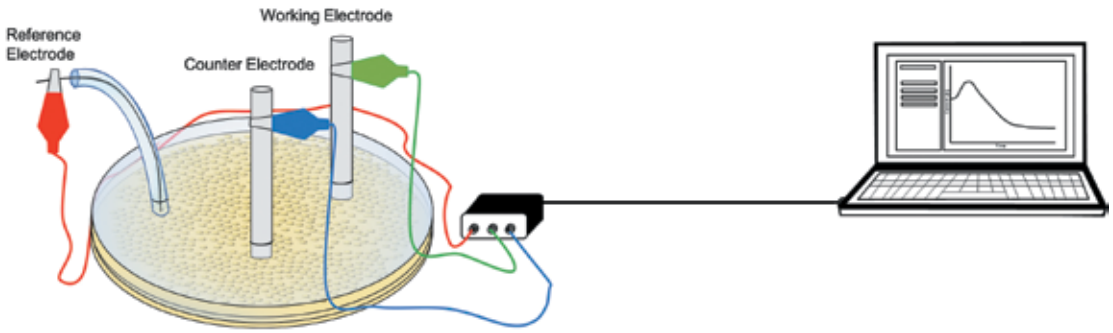


Figure 4. A schematic of our electrode set-up that was used to electro-genetically control cells. Originally published on the Imperial College iGEM wiki under a CC BY licence.

Building this system involved the integration of synthetic biology with another field of research, that of electrochemistry. We engineered our cells to produce a protein in response to the oxidized form of a specific chemical messenger. To activate production, we inserted an electrode into the medium and applied a positive voltage to it generated the required oxidized messengers. Since the messengers only escape from the vicinity of the electrode slowly, the pattern of the electrodes can be translated into a spatiotemporal pattern of protein production.

Conclusion

Hopefully these snapshots demonstrate the amazing potential and diversity of student-led research and innovation that can happen through competitions such as iGEM, in a growing field like Synthetic Biology. Synthetic Biology not only connects multiple scientific disciplines, but also people from across the globe who are working on positive solutions to local and global problems. Synthetic Biology is still an emerging field with plenty of discoveries to uncover, many of which we cannot even imagine yet but that will certainly shape the future. If any students reading this are considering taking part in future years we would strongly encourage them to do so. If your university does not already run an iGEM programme we recommend that you identify someone within the institution who will be willing to put this right! ■

Joshua Lawrence is a student at the University of Cambridge. He took part in iGEM because he loves feeling like a genius and an idiot on alternating days. Email: jml203@cam.ac.uk

Siwat Chang is a student undertaking a summer internship at Imperial College London. Email: siwat.chang16@imperial.ac.uk

Luis Chaves Rodriguez is a student at Imperial College London. He found iGEM to be an amazing opportunity to learn about synbio but also about so many other things in life, including working as a team, organization and creativity. In addition, he enjoyed getting to share the experience with thousands of other students from around the world in Boston. Email: luis.chaves15@imperial.ac.uk

Dr Thomas Ouldridge is a Royal Society University Research Fellow in the Bioengineering Department at Imperial College London, where he leads the Principles of Biomolecular Systems group. Email: t.ouldridge@imperial.ac.uk

About iGEM

- The International Genetically Engineered Machine (iGEM) Foundation is an independent, non-profit organization dedicated to education and competition, the advancement of synthetic biology, and the development of an open community and collaboration.
- iGEM began in January 2003 as an independent study course at the Massachusetts Institute of Technology (MIT) where students developed biological devices to make cells blink. This course became a summer competition with 5 teams in 2004 and continued to grow to 13 teams in 2005; it expanded to 340 teams in 2018, reaching 42 countries and over 5,000 participants.
- iGEM runs three main programmes: the iGEM Competition—an international competition for students interested in the field of synthetic biology; the Labs Program—a program for academic labs to use the same resources as the competition teams; and the Registry of Standard Biological Parts—a growing collection of genetic parts use for building biological devices and systems.

Find out more: https://2019.igem.org