

Biomanufacturing through iGEM-An International Student Competition

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Abstract

The foundations of synthetic biology are built on molecular biology and genetic engineering. One of the purposes of synthetic biology is to make biology easier to engineer by the creation of standardized biological parts and devices. There are a wide range of potential applications for synthetic biology and a variety of approaches to constructing parts and systems. Undergraduate Science, Technology, Engineering, and Mathematics (STEM) students from around the world apply synthetic biology principles at the annual International Genetically Engineered Machine (iGEM) competition to demonstrate functioning biological systems created from standardized parts. The iGEM competition will continue to add to the growing field of synthetic biology and the global bioeconomy through innovations in projects and training of STEM students.

In this study, a survey was conducted of the iGEM team participants at the 2014 competition, specifically to investigate teams that had biomanufacturing as the foundation for their projects. Teams that participated during the 2014 iGEM competition comprised of STEM undergraduate and graduate students from different geographical regions. The primary source of information for this study was from 2014 iGEM team websites.

The results of this study found that many student-led teams are able to build on the fundamentals of synthetic biology to generate a wide range of useful bioproducts. In doing so, students are training themselves for future careers in STEM and expanding the field of synthetic biology.

Keywords

Synthetic biology, iGEM, Biomanufacturing, STEM

Introduction

Society benefits from synthetic biology through production of new chemicals, aiding in healthcare, and alleviating environmental concerns (Way, Collins, Keasling, & Silver, 2014). The concepts and hierarchical structure of synthetic biology is similar to other more established disciplines such as computer engineering (Andrianantoandro, Basu, Karig, & Weiss, 2006). Synthetic biology has been suggested to be at a comparable stage in its advancement as computer engineering was in the 1960s (Way et al., 2014). As new as the field of synthetic biology is, there are already many practical applications, ranging from biosensors, biofuels, biomaterials, and biologically-derived therapeutics (Khalil & Collins, 2010).

Synthetic biology is a fusion science combining concepts from several different Science, Technology, Engineering, and Mathematics (STEM) disciplines (Linshiz, Goldberg, Konry, & Hillson, 2012). The field of synthetic biology aims to reduce the issues of biological systems complexity by making it easier to engineer through standardization (Endy, 2005). College students with minimal laboratory experience can take advantage of synthetic biology to engineer complex biological systems. The first idea of standardized DNA assembly (BioBrick™ assembly) was published in 2003 and coincided with the start of the international genetically engineered machine (iGEM) competition (Knight, 2003).

A one month class of 16 students at the Massachusetts Institute of Technology first started the iGEM competition in 2003, and has since become the showcase event for synthetic biology (Goodman, 2008). In 2004, five university teams participated (Purnick & Weiss, 2009; Smolke, 2009), 2007 saw 60 teams join (Brown, 2007), and 245 teams competed in 2014. More than 17,000 students have participated in the iGEM competitions from 2004-2014 (<http://igem.org>) with the majority of the students being STEM majors.

Student-led iGEM groups design, build, and test biological circuits and devices in the summer months then compete head-to-head in a World Jamboree at the Massachusetts Institute of Technology in the fall. Teams submit their standardized biological parts used in the competition to the Registry of Standard Biological Parts (<http://parts.igem.org/>), an open source biological parts repository that was started in 2004 and is commonly used by the synthetic biology community (Kahl & Endy, 2013; Purnick & Weiss, 2009). Teams also present their work through the creation of a team website (wiki), and formal conference style podium and poster presentations. Recently, teams have also taken to social media to discuss and promote their projects. A team's project is approved by a safety committee and the iGEM competition encourages safe environments with strict requirements, however it has been suggested that more could be done in this arena (Guan, Schmidt, Pei, Wei, & Ma, 2013; Schmidt, 2008).

The cost of participating in the iGEM competition can be in the tens of thousands of dollars per team due to team and individual registration fees, laboratory materials cost, and travel expenses (Vilanova & Porcar, 2014). Each team is managed differently depending on available funding and team objectives (Materi, 2012). Money spent is not always proportional to success in the competition as there are many factors that are considered when projects are judged and

prizes awarded at the World Jamboree. In many cases teams choose to place emphasis on only a few categories that they feel present the greatest chances for team success.

In this study we discuss the iGEM teams that have succeeded in winning various categories from 2007-2014. In addition, we highlight the teams that have biomanufactured or intended to biomanufacture products using synthetic biology during the 2014 competition. We hypothesize that not all biomanufacturing projects were categorized in the biomanufacturing track of the iGEM competition.

Methods

The objective of our research was to uncover the different projects at the iGEM competition that had demonstrated an attempt at biomanufacturing, where we define biomanufacturing as a method/process to produce a product biologically. iGEM Teams are required to select a single team track (or division) in which they will compete. In many cases teams select tracks that best suit their project even though they might meet the requirements for other tracks, thus many biomanufacturing related projects can be in other tracks. To search for teams that demonstrated biomanufacturing principles we used the following questions as a guide when conducting the survey:

Did the team propose a project that demonstrated biomanufacturing?

Did the team design a project taking into account product generation using synthetic biology?

Did the team demonstrated the generation of a product visually, through the use of photographs or analytical methods?

Participants

The participants of this study were 245 teams that competed in the international 2014 iGEM competition. The team compositions were primarily college-aged undergraduates with some of the participants being high school age and also early career graduate students. Teams originated from North and South America, Europe, Africa, Asia, and Australasia. The majority of participants were STEM students. Further information regarding more specific individual team composition can be found on the competition webpage (<http://2014.igem.org>).

Procedure

Literature review

Relevant literature related to iGEM was reviewed and if suitable is discussed in this manuscript. Specifically, literature that focused on students learning experiences at the iGEM competition is discussed. The major findings were compiled from the igem.org website, where past competition results are available. We constructed tables based on the different categories for which teams won awards (Manufacturing, Food and Energy, Health and Medicine, and Environmental tracks). To our knowledge this is the first time that competition results have been categorized in this manner. Furthermore, a survey was carried out of each of the team's website that participated in the competition in 2014

Survey

An exhaustive survey on each team's website for the 2014 iGEM competition was conducted to investigate if a team had a project based on a biomanufacturing context. The iGEM website has a list of teams participating in the biomanufacturing track (n= 14 teams). To find additional teams that demonstrated biomanufacturing (but were not listed as competing in that track), a structured approach was used where each iGEM team's website was studied using Figure 1 as a guide. A total of 231 team's websites that were not classified as manufacturing

were surveyed. In addition to a keyword search, the teams project description, and DNA parts list were examined to determine if there was any evidence for bioproduct production. Once the website survey was complete, data was processed and represented graphically. Through the development of this survey it is hoped that future iGEM competitions could be analyzed using the methods outlined here. This metric could also be used by other iGEM teams when searching for biomanufacturing projects carried out by past teams. Furthermore, the authors also leveraged their own iGEM experience and conclusions were drawn from the information collected.

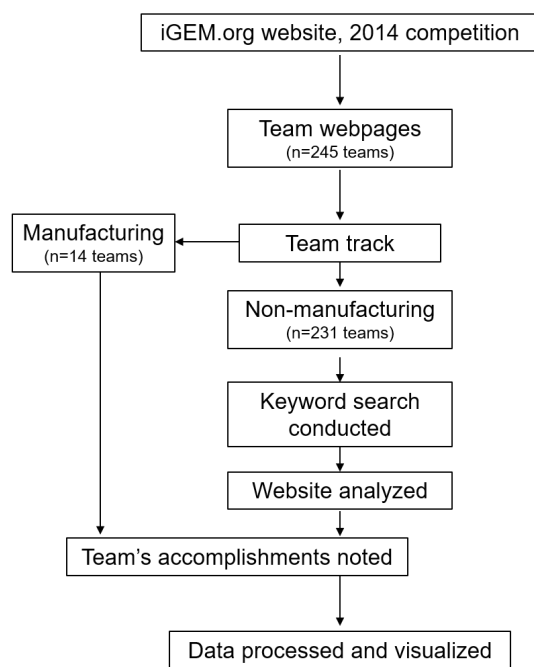


Figure 1. Rationalization for a biomanufacturing survey of iGEM teams during the 2014 competition.

Results

The iGEM competition first began presenting an award for the Best Manufacturing Project in 2008 (Table 1). The concept was to reward the team that demonstrated production systems in an organism by either programming the organism to produce a novel bioproduct or

optimizing existing production systems. The number of teams selecting manufacturing as their project track ranged from 11-17 each year from 2008-2014. Interestingly the majority of teams that won the manufacturing division from 2008-2014 focused on producing a biomaterial.

Imperial College, the 2008 manufacturing division winner, project titled: ‘Biofabricator Subtilis,’ used the microorganism *Bacillus subtilis* for their chassis to produce self-assembling biomaterials. Cornell University’s division winning ‘BioFactory’ project in 2011 used a cell-free method to produce complex biomaterials from the bacterial strain *Escherichia coli*. Utah State University’s team in 2012, ‘Arachnicoli’, won the biomanufacturing division by demonstrating production of synthetic spider silk in *E. coli* and the Imperial College team ‘Plasticity’ produced the bioplastic polyhydroxybutyrate (PHB) in *E. coli* in 2013. The following year (2014), the Imperial College team expressed cellulose producing genes from *Gluconacetobacter xylinus* in *E. coli*.

While the manufacturing award is presented in a manufacturing context, this is not the only track in the iGEM competition that bioproduct production using synthetic biology is used. For example, teams may select the ‘Environment’ or ‘Health and Medicine’ tracks if their bioproduct has implications in those research areas. Some projects that teams have decided upon also have explicit industrial goals (Balmer & Bulpin, 2013).

Many teams build upon previous team’s work in order to advance their project and this is within the rules of the competition and is encouraged. As an example, the 2008 Utah State team first suggested the production of the bioplastic, PHB in an iGEM context. However, the Utah State team was not able to confirm successful PHB production using BioBricks™ at the time. In 2012, the Tokyo Tech team established a functioning PHB production system from BioBrick™ parts. The following year, the Imperial College team demonstrated an 11x increase in production

of PHB compared to the Tokyo Tech team with the use of a hybrid promoter system and a BioBrick™ based operon. Interestingly, the Imperial College team also collaborated with the Yale 2013 team since the Yale team was trying to produce polylactic acid (another biologically derived plastic) in *E. coli*. The Imperial College and Yale team collaboration is an example of students' ability to not just compete against each other but to also working together, which is how most scientific research is conducted today. Collaborations between teams are typically achieved through the team's wiki that is created and in 2013 the Imperial College and Yale teams cited their collaborative efforts on their respective wikis. In addition, collaborations are mentioned during each team's presentations at the iGEM competition.

Table 1. Best Manufacturing Project prize for iGEM projects 2008-2014 (igem.org).

Year	Team Name	Project name	Bioproduct/process
2014	Imperial College	Aqualose	Bacterial cellulose
2013	Imperial College	Plasticity	Bioplastic
2012	Utah State	Arachnicoli	Spider silk
2011	Cornell	BioFactory	Cell-free bioproduct synthesis
2010	MIT	Living Materials	Self-assembly of biomaterials
2009	Imperial College	The E.ncapsulator	Encapsulation of proteins for therapeutic purposes
2008	Imperial College	Biofabricator Subtilis	Self-assembling biomaterials

Another category that includes groups using BioBricks™ to generate bioproducts is the ‘Food and Energy’ division. This category received a specialized award from 2007-2013 and out of the 8 awarded teams, 5 teams worked towards energy production from BioBricks™ (Table 2). The Harvard University team in 2008 used *Shewanella oneidensis* as a microbial fuel cell and in 2013, the Bielefeld-Germany team used *E. coli* in a similar endeavor. Teams from: Alberta in 2007 (Butanol), UNIPV-Pavia in 2009 (Ethanol), and Washington in 2011 (Biodiesel) all successfully developed drop-in fuel BioBrick™ production systems. Due to increase in the

number of participants, this track was divided into two separate tracks in 2014, ‘Energy’ and ‘Food & Nutrition.’

Table 2. Best Food and Energy Project prize for iGEM projects 2007-2014 (igem.org).

Year	Team Name	Project name	Bioproduct/process
2014*	TU Darmstadt (Energy track)	<i>E. grätzel</i>	Harvesting solar power with anthocyanin
2014*	Wageningen UR (Food & Nutrition track)	Banana Guard	Antifungal for bananas
2013	Bielefeld-Germany	Ecoelectricity	<i>E. coli</i> as a microbial fuel cell
2012	Groningen	Food Warden	Spoiled meat detector
2011	Washington (tie)	Make It or Break It	Diesel production
2011	Yale (tie)	Nature’s Antifreeze	Antifreeze protein production
2010	BCCS-Bristol	agrEcoli	Soil fertility sensor
2009	UNIPV-Pavia	Ethanol? Whey not!	Whey to ethanol
2008	Harvard	Bactricity	Electricity production in <i>Shewanella oneidensis</i>
2007	Alberta	Butanerds	Butanol production

*In 2014 Energy and Food & Nutrition were separate tracks.

The Health and Medicine category has yielded several projects that focused on bioproduct production. The Slovenian team in 2008, a winning team in the Health and Medicine category, focused their efforts first on vaccine production and then in 2012 pursued *in situ* production of various biological drugs (Table 3). The 2012 Slovenian team sought the advice of practicing medical professionals regarding their project, thus interacting with professionals in the field. This interaction with medical professionals was of great benefit to the students as they could see the real world potential of their laboratory work.

Another relevant division to bioproduct production is the Environment track. The 2009 Cambridge team won the Grand Prize at the 2009 iGEM Jamboree by demonstrating the

successful production of a wide variety of pigments called chromoproteins (Table 4). By engineering *E. coli* to produce these pigments, synthetic biologist can visualize bioproduct formation without any special equipment or optical instruments. The NYMU-Taipei team in 2013 developed a project entitled ‘Bee. coli’ that aimed to eliminate colony collapse disorder in bee populations by manipulating *E. coli* so that it produced the bioproduct mannosidase, which inhibits spore formation by the parasitic fungus *Nosema ceranae* that causes the disorder. The NYMU-Taipei team also visited and interviewed professional beekeepers, which added to the development of their project. Interestingly, iGEM team members in recent years have continued to seek advice, and visit local professionals to get input and validation on the team’s project. iGEM team members have also visited their local government officials to discuss safety, public perception, and policy.

Table 3. Best Health and Medicine Project prize for iGEM projects 2008-2014 (igem.org).

Year	Team Name	Project name	Bioproduct/process
2014	Dundee (undergrad)	The Lung Ranger	Biosensor for Cystic Fibrosis
2014	Aberdeen Scotland (overgrad)	An <i>E. coli</i> systems for the diagnosis of human African Trypanosomiasis	<i>E. coli</i> based Trypanosomiasis Diagnostic System
2013	UIUC Illinois (undergrad)	Cardiobiotics	Metabolism of dietary L-carnitine in the digestive system
2013	Paris Bettencourt (overgrad)	Fight Tuberculosis with Modern Weapons	Detect and sabotage antibiotic resistant strains of TB
2012	Slovenia	Switch IT: Inducible Therapeutics	<i>In situ</i> production of biological drugs
2011	MIT	Tissues by Design	Tissue self-assembly via juxtacrine signaling
2010	Freiburg Bioware (tie)	Virus Construction Kit	Virus kit to specifically target and kill tumor cells
2010	University of Washington (tie)	Antibiotics For The 21 st Century	Antibiotic production to fight gram-negative and gram-positive pathogens

2009	Stanford	Immuni-T. coli	Probiotic approach to diagnosing and treating inflammatory bowel disease
2008	Slovenia	Immunobricks	Vaccine production to activate innate and acquired immune response to <i>H. pylori</i>

Table 4. Best Environment Project prize for iGEM projects 2008-2014 (igem.org).

Year	Team Name	Project name	Bioproduct/process
2014	NCTU Formosa (undergrad)	Operation Debug	Pheromone biosynthesis activating neuropeptide
2014	Minnesota (overgrad)	Mntallica Cleaning up Heavy Metals	Bioremediation of mercury
2013	TU Munich (undergrad)	Physco Filter	Bioremediation of aquatic ecosystems using the moss <i>P. patens</i>
2013	NYMU-Taipei (overgrad)	Bee. coli	Mannosidase production in <i>E. coli</i> to inhibit the parasite <i>N. ceranae</i> , which causes colony collapse disorder in bee populations
2012	Paris Bettencourt	bWARE	Containment module to prevent horizontal gene transfer to out-of-lab microbes
2011	Calgary	<i>Sensomonas</i> <i>NAstytoxins</i>	Electrochemical biosensor for Naphthenic Acids (NAs)
2010	Peking	Heavy Metal Decontamination Kit	Heavy metal biosensor and bioabsorbent
2009	Cambridge	E. Chromi	Pigment production in <i>E. coli</i>
2008	Brown	Toxipop	Conductance measurement of cell lysis as a reporter of toxin presence

Discussion

Over 15% of all participating teams (38 teams total) in the 2014 iGEM competition focused on bioproducts production from BioBricks™. The bioproducts that each group aimed to produce ranged from biomaterials to food additives. Many teams in 2014 used chassis organisms other than *E. coli*, such as *Bacillus* and *Clostridia* for their biological systems, which provides numerous opportunities for future teams. During this year, bioproduct production was seen in several tracks: Manufacturing, Food and Energy, Environment, Health and Medicine,

Community Labs, and Entrepreneurship (Figure 2). Over half of these teams fell into two major categories, Manufacturing track (11 teams) and Health and Medicine track (8 teams).

Interestingly, there were bioproduct production projects in tracks such as Community Labs and Measurement, which demonstrates that while the focus of a team's project might be bioproduction, the team's applications may fit better in a different category.

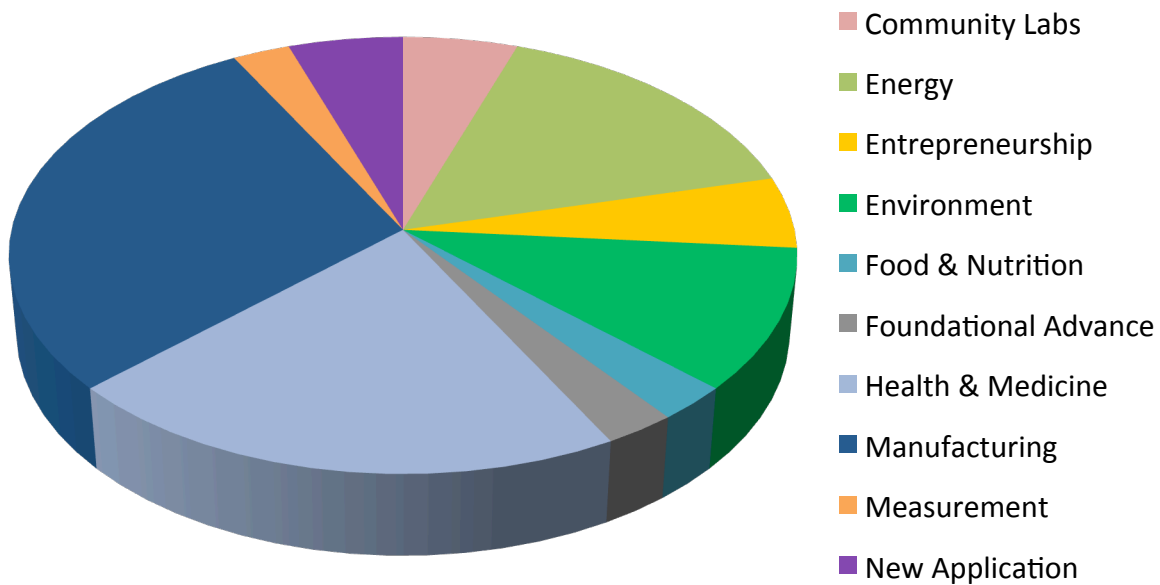


Figure 2. Different tracks of 38 teams that focused on production of bioproducts during the iGEM 2014 competition.

While many teams have lofty goals when first initiating a team project, most teams are not able to fully accomplish their objectives due to a variety of reasons such as: complexity of the project, lack of experience, short time frame, or insufficient funding. From the bioplastic example mentioned previously, the first team that came up with the idea did not necessarily

achieve all their project objectives, but rather provided a foundation for other groups to build upon. Building upon previous scientific knowledge is the key to any successfully project. The purpose of iGEM is not solely to make a tangible bioproduct from BioBricks™ because regardless of the final product that is created, the students will have gained valuable teamwork and laboratory experience. Furthermore, student members of the iGEM competition are from various geographic regions around the world, with the majority of participants from North America, Europe, Asia, and South America (Cruz & Van Sluys, 2015). The diversity of participants contributes to the exchange of information between different cultures and countries. As the competition continues to expand, the geographic diversity of iGEM attendees should also see an increase. This increased diversity will benefit students since learning to work within the international community will enhance the next stages in their careers.

A recent survey found that approximately 30-40% of the student participants were having their first laboratory research experience through iGEM and that the iGEM experience increased student interest in laboratory based research. This survey also found that approximately 80% of respondents (n = 177) were more interested in the field of biological engineering after being involved in the iGEM competition (Mitchell, Dori, & Kuldell, 2011). It has been previously mentioned that undergraduate research opportunities increase a student's interest in STEM careers by as much as 68% (Russell, Hancock, & McCullough, 2007). Another study found that approximately 42% of students who participated in undergraduate research would pursue a PhD in the future (Lopatto, 2007). Undergraduate research experiences help students with professional identity growth and competency (Nadelson, Warner, & Brown, 2015). If iGEM is providing a platform for students to gain research experience then it suggests that it is also directly encouraging students to pursue full-fledged STEM careers.

The quality of iGEM projects can also be demonstrated through the publication of peer reviewed manuscripts. The University of Washington team in 2011 that won the Best Food and Energy prize for production of biodiesel published their findings in the ACS Synthetic Biology journal (Harger et al., 2013). The 2012 University of Texas team also published their findings for the development of a caffeine biosensor (Quandt et al., 2013). In 2014 there was a special issue in ACS Synthetic Biology for iGEM teams and the Public Library of Science (PLOS) published an iGEM collection in 2016. Recently, the first large-scale interlaboratory study in synthetic biology was conducted as part of the 2014 and 2015 iGEM competitions. Eighty-eight iGEM teams participated in the study and participants were listed as co-authors on the resulting manuscript (Beal et al., 2016). The publication of peer reviewed manuscripts based on projects from the iGEM competition demonstrates the quality of research conducted by students. Furthermore, peer reviewed publications by undergraduate students could potentially encourage students to enter graduate level STEM research.

In addition to iGEM promoting STEM centric career development by providing research skills, it can also benefit students through developing valuable skills in communication and project management (Kelwick, Bowater, Yeoman, & Bowater, 2015). Alumni of the iGEM competition have become entrepreneurs, with approximately 17 synthetic biology start-ups founded by former iGEM participants as of 2015 (igem.org). This is an encouraging sign for iGEM as it is not just helping train the next generation of synthetic biologist, but is also helping create a platform for future commercial ventures and a bioeconomy.

While this study focused on iGEM and biomanufacturing, it is not exhaustive. Some future work could include conducting a more in-depth survey of the teams that participated in the competition and their reasons for choosing to carry out a biomanufacturing based project. In

addition, as the iGEM competition is over a decade years old, a survey could also be conducted to investigate what former iGEM participants are currently doing and if the iGEM experience helped shape their careers.

Conclusions

One of the purposes of synthetic biology is to make biology easier to engineer and this idea is seen most prominently in the iGEM competition. iGEM will have a greater role in the global Bioeconomy and continue to add to the growing field of Synthetic biology through innovations in projects and training of STEM students. With the sustained expansion of the Registry of Standard Biological Parts (<http://parts.igem.org/>) and the iGEM competition, there will be a continued development of synthetic biology-based bioproducts. From this study we hope that future groups could use a similar approach when analyzing other categories at the iGEM competition. Future teams could also use the findings of this study to help them decide on future iGEM projects.

Acknowledgements

The authors would like to acknowledge Utah Science Technology and Research (USTAR), Synthetic Bioproducts Center (SBC), and the Sustainable Waste-to-Bioproducts Engineering Center (SWBEC), at Utah State University for their support. Special thanks to past Utah State University iGEM team's for motivating the writing of this manuscript.

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