Safety in SynBio

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AND Safety and Security in the iGEM competition

BY

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PREFACE

With the advent of synthetic biology, safety has been a longstanding question in the public minds. The concerns about safety have been even more for the iGEM competition, standing at the juncture of the traditional scientific structure of the field and DIYSynBio. Through this primer, our team tries to allay fears concerning synthetic biology. Synthetic biologists are as much bound by rules as any other group of professionals. We have also collated a list of regulations for genetic engineering in India for the benefit of the readers and to appraise them of the state of biosafety regulations in India. Through these few pages, the authors wish to establish that safety is as much a concern for synthetic biologists as for the general public. Dual use concerns exist not only in SynBio but in every scientific venture, and hence should not be inappropriately cited to curtail the growth of the field of synthetic biology.

Biosafety refers to the prevention of the risks to public health and the environment that could be produced by accidental interactions between dangerous biological agents and other organisms or the environment. In the field of Synthetic Biology, the main concerns relate to research personnel working with synthetic organisms and potential damage to the environment and population surrounding the research area.

Biosafety in synthetic biology – A historical perspective

Some authors believe that differences between Synthetic Biology and traditional genetic engineering are only quantitative, so the biosafety issues raised by Synthetic Biology are not qualitatively different. Others, on the contrary, consider that differences are qualitative, since the construction of new life forms could become considerably easier or could be based on alternative biological systems. This divergence became apparent in SYNBIOSAFE, the first project carried out in Europe to address the ethical and safety concerns raised by Synthetic Biology with the aim of facilitating a socially acceptable development of this discipline. It was also suggested that the risk assessment framework currently in place for GMO may be insufficient to deal with Synthetic Biology from a biosafety standpoint. A second issue regarding the diffusion of knowledge was discussed and, again, opinions were conflicting. Some argued for strict regulation, while others advocated an open source movement. A report signed by three European non-food Scientific Committees (the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)) states that "[n]ew challenges in predicting risks are expected due to emergent properties of SynBio products and extensive genetically engineered systems, including, 1) the integration of protocells into/with living organisms, 2) future developments of autonomous protocells, 3) the use of nonstandard biochemical systems in living cells, 4) the increased speed of modifications by the new technologies for DNA synthesis and genome editing and 5) the rapidly evolving DIYbio citizen science community, which may increase the probability of unintentional harm".

Biosafety measures in SynBio – A Brief Overview

❖ Biocontainment

Biocontainment measures include physical measures (engineering design of equipment, process and production plant) and biological means (among which inducible systems, auxotrophy and cellular circuits are the most established strategies) to prevent accidental escape of genetically engineered (GE) organisms. In inducible systems, the introduced genes are expressed only if a specific inducer is present. The inducer required is not common in the natural environment, so that if the organism escapes the lab, the engineered trait will not be expressed, avoiding any potential advantage given by the genetic construct. Auxotrophy implies that the organism is not able to produce a particular vital compound, which must be provided in its media. Cellular circuits are genetic constructs that can lead to cell death when activated (kill switches) or to the death of the new host in case of horizontal gene transfer (addiction modules). However, these strategies are not effective enough when they are used in isolation, since the evolutionary cost of bypassing or reverting the containment mechanism is very low. Multiple strategies and targets must therefore be combined, in what is called multi-layered containment

❖ Many individuals and organizations are actively **tackling the biosecurity challenge**. There are regulatory bodies like the **CDC and NIH** in the US and the **European Union** which undertake an oversight of the field. There are well-defined statutory regulations in this regard, including multilateral treaties like the **Biological Weapons Convention**. The International Genetically Engineered Machine (**iGEM**) synthetic biology competition, which began in 2004, mandates that organizational leaders and judges conduct rigorous reviews of the materials and planned experiments of each team. Safety and security concerns receive further scrutiny from iGEM's **Safety and Security Committee** (SSC) and are screened for potential hazards by a commercial partner; all of this is part of the competition's guidance for participating students.

Institutional framework for biosafety in India

Biosafety considerations in India are regulated by the Environment (Protection) Act, 1986. With rapid and drastic changes in the rules of synthetic biology research, there has been timely changes incorporate into the rules. Bureaucratic hurdles have been considerably reduced, and the process for obtaining necessary permissions have been simplified.

Under the Rules 1989 of Environment (Protection) Act 1986, laboratory biosafety through appropriate containment has been identified as the fundamental part of any biological research. In this direction, the Dept of Biotechnology had earlier published three guidelines namely "Recombinant DNA safety guidelines, 1990" "Revised Guidelines for Safety in Biotechnology, 1994" and "Revised guidelines for research in transgenic plants, 1998.

RCGM, the apex body working under Rules 1989 has the mandate to monitor the safety of on-going research projects or activities involving hazardous microorganisms, GE organisms and cells and products thereof. RCGM therefore, has made an extensive effort to update and bring out a consolidated guideline at par with International best practices to prescribe the containment measures for storage, growth, research, manufacture, exchange, import and export of GE and non-GE organisms (microorganisms, animals, plants, arthropods, aquatic organisms) and products of such organisms.

The latest rules formulated by the RCGM in 2018 are provided below:

1. There is no permanent secretariat to monitor the trials of the GMOs. Instead, the regulations are implemented by various ad hoc committees. The most important committees are
    - the Institutional Biosafety Committees (IBSC), responsible for the local implementation of guidelines
    - the Review Committee on Genetic Manipulations (RCGM) responsible for issuing permits
    - the Genetic Engineering Appraisal Committee (GEAC) responsible for monitoring the largescale and commercial use of transgenic materials.

    These committees have statutory authority.

2. The IBSC committee is constituted by all institutions handling hazardous microorganisms and/or GE organisms. The committee is the nodal point for implementation of the biosafety guidelines and for the interactions within the institution. The composition of the committee has been laid down in
3. Genetic Engineering Appraisal Committee (GEAC) [formerly known as Genetic Engineering Approval Committee (GEAC)] has been constituted under the Ministry of Environment, Forests and Climate Change. The major function of GEAC as

prescribed in the Rules 1989 is to appraise activities involving large scale use of hazardous microorganisms GE organisms or cells in research and industrial production from the environmental angle.

4. The RCGM functions from the Department of Biotechnology to monitor the safety related aspect in respect of on-going research projects or activities involving hazardous microorganisms, GE organisms and cells and products. RCGM is mandated to bring out manuals of guidelines specifying procedure for regulatory process with respect to activities involving GE organisms in research use as well as industrial and environmental applications with a view to ensure human health and environmental safety.
5. The current regulations regarding the import of biological material into India:
    - Import of polynucleotide sequences originating from non-infectious strains or any organism that can be handled at BSL 1 facility can be approved by IBSC upto a quantity of 100 μg. Same applies for non-toxic proteins upto a weight of 20 g. For higher quantities, RCGM approval is needed by applying through the web portal.
    - Import of sequences from infectious strains or organisms that need BSL 2, 3 or 4 facilities for handling or toxic proteins need approval from the RCGM.
6. Guidelines for containment at various biosafety levels is provided here.

Biosafety and iGEM

iGEM has insisted on teams adhering strictly to safety norms since the inception of the competition. The Safety and Security Committee scrutinizes every project actively to understand the risks associated with them and the level of safety training of every member. Teams are required to submit a safety form, and no environmental release of GE organisms is permitted. Teams also are not allowed to work with certain dreaded 'blacklisted' organisms, which are extremely infectious and have potential to cause epidemics and/or pandemics. These regulations are over and above the regulations in the corresponding country.

Presented below is an article authored by P. Millet et al, the Vice-President of the Safety and Security Committee of iGEM:

Maximizing Benefits, Minimizing Risks

BY PIERS MILLETT, PIM KLAASSEN, AND SAM EVANS
ON BEHALF OF THE IGEM SAFETY & SECURITY AND HUMAN PRACTICES COMMITTEES

The iGEM competition should be a challenging, fun, and rewarding experience. But like all science and engineering, every iGEM project has some potential to cause harm. And so iGEM has a number of policies in place, as well as dedicated committees, to help teams do the best science and engineering possible – maximizing benefits for the world while at the same time minimizing any chance of harm.

iGEM Values, Rules, and Resources

It's often said that iGEM isn't easy but it's worth it. In the iGEM competition we expect a high standard of conduct from everyone. We must all live up to our shared values – integrity, good sportsmanship, respect, honesty, celebration, cooperation, effort, excellence – that underpin our collective efforts to build the future in which we all want to live. These values should remain true wherever you are in your career and whatever you're doing with synthetic biology.

All teams must follow the competition's Rules of Conduct. These rules are built upon our community values to support fairness and recognize honesty, integrity, mutual respect, as well as engineering excellence. It's important to honour iGEM's values and follow the rules to reduce the risk of harm and avoid running into problems when working with people, such as carrying out interviews, or conducting surveys, working with animals (including vertebrates and social invertebrates), working with antimicrobial resistance (including the use of selection markers), using human samples or testing your project on people, and keeping your project in the lab.

Members of the RCC at the 2019 Giant Jamboree

The Responsible Conduct Committee (RCC) was established to deal with behaviour and practices that are inconsistent with iGEM's values and rules of conduct. They are the point of contact for anyone who has concerns about any an iGEM participant, whether that be a member of a team, an entire team, a judge, an advisor, or a member of iGEM HQ. The RCC helps ensure the Giant Jamboree, the culminating event for the competition, is an exciting celebration of the commitment and accomplishment of all iGEMers.

We understand there are differences of opinion as to what is desirable and what is not desirable. We know that thinking about things like risk and benefit is inherently human and

that makes it complicated. To help teams think through these and other issues, iGEM also has a dedicated Human Practices Committee, Safety & Security Committee, and Diversity & Inclusivity Committee who have created numerous resources that are available on the iGEM 2020 competition website.

Human Practices

Since very early days, human practices has been integrated into the iGEM competition to help teams think about how their work affects the world and how the world affects their work. Indeed, human practices is a requirement for silver and gold medals and there are special awards to recognize excellence in human practices. Human practices helps teams

integrate all the various values that are pertinent to their project and to become aware of the risks the project might carry and the potential for harm.

To succeed in human practices, teams must carefully consider a number of rather big questions throughout their project. It helps to figure out what values are at the heart of your work – what motivates you to work in synthetic biology in the first place? Once you've figured that out, you can think about what good your project will bring to the world – how might your project contribute to human well-being or environmental sustainability? And also think about what unwanted impact your project might have – how could your project further inequalities or vulnerabilities?

Not only must teams thoughtfully engage with these issues, but they must also report their work in human practices by demonstrating the "Three Rs" of Reflection, Responsibility and Responsiveness:

Reflection: Reflect on your goals and the values central to your project, throughout your project. This means that time and again you ask yourself if indeed your work contributes to the values that are central to your project.

- What personal knowledge, ideals, or motives are the driving force behind your project?
- What positive change do you seek to make in the world?
- In what ways might your project benefit society?
- How did you decide that synthetic biology is an appropriate means to reach your project's goals?

Group of volunteers the at the 2019 Giant Jamboree

Responsibility: Align your process and products with iGEM's values and display your awareness your powers and the limits to your powers. This means that you do what is within your powers to maximize benefits and to minimize harms.

- How might your team's solution to one problem lead to other problems (e.g. social/political/ecological)? Which communities may be left out or negatively impacted if your project succeeds? Could your project be misused?
- How can your team minimize the impact of these concerns?
- What gaps in the knowledge or skills of your team require attention?
- What's your plan to inform relevant authorities or stakeholders on potential risks related to your project, and to work with them?
- How might current policies and regulations apply to your project? Are they sufficient, and if not, how might they be changed?

Responsiveness – Display a sensitivity to (novel) contextual knowledge and adjust your course in response to others' needs or values. This means showing how the values, needs, perspectives, and knowledge of others, which you have actively sought out, has indeed impacted the course of your project.

- What work, both outside and inside of iGEM, inspired your project?

- Which communities may be most interested in or affected by your project? How can you responsibly engage them in your project?
- How might you get feedback on the viability and desirability of your approach? How will you adapt your project based on this feedback?
- How might your approach compare to alternative solutions to the same or similar problems (including approaches outside of biotechnology)?

In essence, human practices is about finding ways to incorporate knowledge, values, interests and needs that you won't necessarily find in the lab. This year the COVID-19 pandemic has posed some challenges to iGEM teams with regard to active engagement with others. You'll find some helpful guidance on approaches to consider during the pandemic, as well as tips and techniques for conducting Human Practices work in the sessions from iGEM's 2020 Opening Weekend Festival, including Doing Human Practices During A Global Pandemic (YouTube)(Bilibili), How to Find Insights from Social Science Research (YouTube)(Bilibili), Designing Scientifically Valid Surveys (YouTube)(Bilibili), iGEM Insights: Understanding iGEM Through Data (YouTube)(Bilibili), and iGEM and the Sustainable Development Goals (YouTube)(Bilibili).

You can learn even more by visiting the Human Practices Hub, where you'll find an introductory video, some answers to frequently asked questions, links to exemplary projects from previous years, additional resources that can help guide your thinking, as well as the history of Human Practices in iGEM. And if you have any questions or thoughts on human practice, please get in touch with the Human Practices Committee at humanpractices@igem.org.

Members of the 2019 Lambert team at the Giant Jamboree

Safety & Security

iGEM's Safety and Security program helps you to identify and manage risks from your projects. In many labs this is often done for you; there's a biosafety officer that thinks about this. But iGEM believes that a good synthetic biologist is also a safe and secure scientist or engineer. Our program is built around safe and secure project design, safe and secure lab work, safe and secure delivery, both in terms of physically moving things around and also in terms of sharing information.

iGEM believes that safety and security is everybody's responsibility. We expect both students and instructors to work on safety and security issues. Together you ensure that teams meet international, regional, national, and institutional rules and regulations. Teams are expected to provide safety and security information on their projects at different points in the competition lifecycle.

As in any normal year, we ask you to tell us about possible hazards from your project and how you're going to manage them – before you start working the lab – roughly when you've finished the planning stages and you're moving into the implementation. Then we ask you to outline what you're planning to do and what the safety and security procedures and practices are in place to make it okay. Then we ask you to tell us again similar sorts of information when you're moving from the experimental phase to beginning to write it up and communicate your findings. We also want you to tell us and give us more information

whenever you use a part, an organism, or an activity that isn't on the competition's White List, which specifies parts, organisms, and activities generally considered safe for work in a standard lab.

We have a variety of safety forms that you will become familiar with throughout the year:

- ALL teams need to use the main Safety Form to tell us about their plans, including what you'll use and what you'll do with it, any risks you've identified, and the measures that you've put in place to manage those risks.
- Any team wanting to carry out a project that's more risky than a standard laboratory project (in other words use a part, organism, or activity NOT on the White List) must also use the Check-in Form to get permission in advance. Examples of projects requiring a Check-in Form are those that use a pathogen or any part from a pathogen, any project involving gene drives, and most work with insects, animals, or plants.
- Finally, any team that wants to work with animals must get permission in advance by justifying their need to use animals in the Animal Use Form. In this form you'll need to consider how you might replace, reduce, and refine the use of animals in your project.

Some things are not allowed in iGEM at all. Teams are not allowed to work with any risk group 3 or risk group 4 pathogens. This year we're asking teams not to work with the live SARS-CoV-2 virus that is responsible for causing the COVID-19 pandemic. It is possible to work with parts or fragments from that virus, but you will need to submit a Check-in Form in advance. You can learn more by checking out the session on COVID-19 projects in iGEM from the IGEM Opening Weekend Festival (YouTube)(Bilibili).

iGEM also gives a special prize for excellence in safety and security. In recent years, a team from the Netherlands (2017 Wageningen UR) won the prize for integrating safety into all stages of their project. The year prior, a team from the US (2016 Arizona State) won the prize for producing a white paper that discussed context-specific risk, specifically how what they did in their project changed the risk for other people carrying out other research inside their institution. In 2014, a team in Germany (2014 Aachen) won for conducting lab tests to determine whether the equipment they were building would actually work in practice and how they might improve safety features of their technology. In 2012, a team from Paris (2012 Paris Bettencourt) won for developing a three-level genetic containment mechanism. In 2011, a team from India (2011 IIT Madras) won for developing alternative selection markers, thereby reducing the need to use antibiotics. And in 2010, the very first special prize for excellence in safety and security was given to a team from Denmark (2010 SDU Denmark) who did a really good job of integrating safety into their project. In fact, they

integrated it so well they abandoned their first project because they were worried about the risks and they changed their entire work structure around safety concerns.

If you have any questions or thoughts about safety and security, we do want to hear from you. You can learn more by checking out the Safety & Security Hub. We also have a dedicated Safety & Security Committee who are here to support your efforts, and we encourage you to get in touch with us at safety@igem.org.

Members of the 2019 StonyBrook team at the Giant Jamboree

Diversity & Inclusivity

Historically, participating in research has been an exclusive privilege. Many people around the world have not been allowed to have a voice in science because of their gender, ethnicity, socioeconomic status, or other personal identities. Over time this exclusion led to a critical lack of diversity and representation. Not only does being exclusive limit our current knowledge and capabilities, but it also defines our path moving forwards.

There are a number of ways you can help strengthen the diversity and inclusivity of your project, including

- thinking about diversity and inclusivity when you decide what topic to work on and how you're going to interpret your work,
- including diversity and inclusivity as part of project design by asking questions, such as Who is included in this project design? Who benefits from the research? Who can access the project's technology?
- considering diversity and inclusivity in your human practices work, for example when thinking about survey design, or how you're going to carry out interviews, and
- prompting an inclusive team culture, for example ensuring there's an equitable distribution of workload and skill development, accessibility for all members in terms of flexible working hours or physical disabilities, etc.

You can learn more by checking out the Diversity & Inclusivity Hub. If you have any questions or thoughts about diversity and inclusivity, we want to hear from you. We also have a Diversity & Inclusivity Committee dedicated to this issue and they are here to help us achieve a balanced representation in iGEM. We want to set an inspiring example for others on what a truly diverse and welcoming scientific community looks like.

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