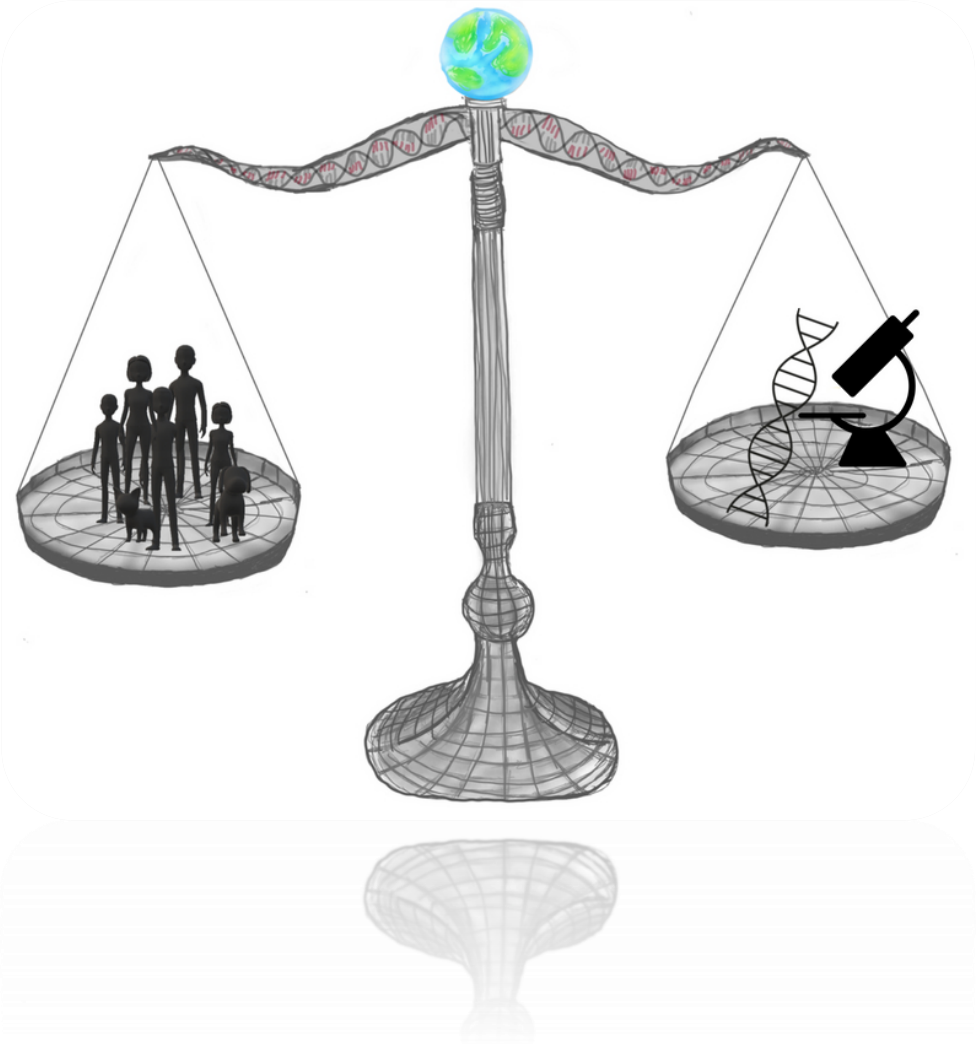
How safe is your project?

iGEM projects from a bioethical aspect



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iGEM Stockholm 2018 Human Practices team

Preface

There is a lot to think of when you start on a project, not only how the project and the research within can be successful and contribute to society, but how it can be used and in what fields they can contribute in. What part of society will the research and product be applied to, and are there any dangers with presenting the project for the world to see? What exactly is an iGEM project, and how is the road from thought to implementation planned out?

In this booklet, the importance of safety in an iGEM project is discussed, and what effects a project could have if not enough attention is paid to the safety aspects. Puck Norell, the writer of the blog of iGEM Stockholm 2018, shares her and her team's reflections and expertise, with the help of a few professionals.

iGEM Stockholm 2018. Photo: *Private collection*

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Walking an idea from thought to product

It is indeed hard to choose a project that will generate important and trustworthy data that could be beneficial to the public. Finding a project means investing countless hours in discussing, and weighing pros and cons for different project ideas. Finding a solution to a real-world problem, as iGEM so beautifully puts it, does not only require insightful argumentation and strategies to find a successful and important project, but also discussion and thought into the implementation of the idea.

To make a business idea of an iGEM project is something that many teams are dreaming of. However, this does not have to be a dream. In fact, there are teams who have realised this, and continued their projects in the form of business ideas. Although they are few in relation to the number of teams that are competing, it shows that it is not impossible.

There are many factors that influence the success of business ideas, and there is a whole field within this area called entrepreneurship. Entrepreneurship will not be the basis of this booklet. What I will focus on instead, is the discussion about what an iGEM project in such an interesting field could enable; the revolutionary use and benefit they can give to society, but also detrimental effects that maybe we do not think of when trying to develop our dream products. I will start off by explaining an approach in synthetic biology, which a project work can be based upon.

Designing a project within synthetic biology

Designing a product and a research project within the field of synthetic biology will always differ depending on what approach you are using, but let's talk about creating a project based on an engineering approach that is used in iGEM; the "parts, devices and systems approach". I will explain the different parts of a project with the help of the book "Synthetic biology – a primer" (Freemont & Kitney, 2012). A schematic figure of the design

of a project (Fig. 1), adapted from the book is included to give a better picture of how the different parts relate to each other.

The "parts, devices and systems" approach utilises parts that are biological, encoding biological functions. These parts are synthetically designed DNA, combined to form a device that encode different functions. Together, they will form systems that perform the tasks they were built to perform. The goal with the project is that the system meets the required specifications. The system designed is constructed with the help of computer modelling in-silico, where the developing system can be simulated in great detail. The system that you have built will then be implemented in a wet-lab research setting, through building the construct made in-silico by combining different DNA parts and inserting them into a chassis. The latter requires testing and validation, to ensure that the product is working according to the simulation made in-silico. The validation and testing process requires iterations, repetitions, repeated until the design is refined enough to work satisfactorily.

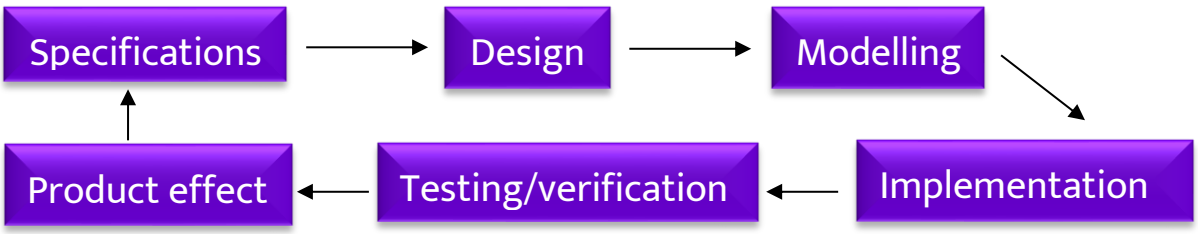

Figure 1. Design cycle of a project within synthetic biology, adapted from "Synthetic biology – a primer" (Freemont & Kitney, 2012).

The beauty with synthetic biology is that it is such an interdisciplinary field, and utilises the qualities of many different professions. In-silico modelling, using computer-based work to predict the outcome of a project before testing it in a wet-lab setting, is important, not only from a toxicological and sustainability aspect, reducing the need for in vivo and in vitro testing, but also when forming interdisciplinary teams with different backgrounds. In-silico testing is an efficient tool that can reduce the amount of wet-lab time significantly. An example comes from the University of Surrey, where they were able

to utilise in-silico modelling for drug discovery for tuberculosis. They were able to reduce the time for growth time simulations from months to minutes, by exchanging in vitro studies for in-silico studies (Science Daily, 2007). This points to the importance and also the benefit for a project, when combining different fields. This is one of the factors that makes synthetic biology such an appealing field of research. One other factor is the usage of already existing parts. The iGEM competition uses the so-called Biobrick system, where Biobricks correspond to DNA sequences with different functions. These sequences can be promoters, terminators, coding sequences or ribosomal binding sites, and are all adapted to a restriction-enzyme standard. New systems can be built with the help of already existing parts, Biobricks, but also with newly designed parts. The work of the iGEM project becomes a circular work, where modelling and wet-lab will work together back and forth to make the system work flawlessly. At least, that's what we're all aiming for as iGEM teams.

As previously mentioned, the whole construct, i.e. the system, will require a few or many iteration rounds to ensure proper function. Another important note is that in addition to testing your product, the effects of your product should also be considered. This is important in a Human Practices perspective, since the outcome of your product could show to be harmful. Just to give you an example; If you are trying to develop a method to degrade pesticides from soil, you would not only want to reduce the levels of pesticides in the soil, but also make sure that the by-products that are produced from the inactivation are not toxic to the environment and the wild life. Human practices, the integration of society and professionals, is another vital part in the foundations of an iGEM project. I will not mention Human Practices again, but if you would like to read more about it, I warmly recommend the Human Practices handbook, written by iGEM Stockholm 2017 (iGEM Stockholm, 2017).

Hopefully, after designing and working on your project, the end-product would be a product that is safe to use for end users and stakeholders, and it would not be used in a detrimental way. But what exactly is meant by detrimental way? What difficulties are

researchers faced with when developing new techniques and products to be implemented in our technologically advanced society?

Let me introduce you to the dual-use concept, with the help from my team member Els Alsema who studied the dual use in relation to scientific research in one of her courses.

Dual use – the interplay between risk and benefit

Dual use goods are defined by the European Commission as items that can be used in a civilian as well as military application (European Commission, 2018). Within the field of synthetic biology, a military application could mean harmful use of engineered machines.

An ongoing discussion within the scientific sector is that research should be easily accessible, in order to promote scientific advances within fields such as medicine and technology. However, it could be argued that some research should be censored, especially in cases where the advancements could be misused. But who should enforce these censors, and what kind of research should be the subject of these censors?

Pathogens are a broad variety of different organisms, everything from viruses to fungi. The factor they share is that they are potent in causing disease. Dual use research discussions have partly focused on pathogens and their potential use as biological weapons. Pathogens could be used to target and cause disease in humans and other species, in that way spreading diseases that are difficult to cure. The advantage with using pathogens according to Selgelid is that they are inexpensive to manufacture or produce, but also easily accessible. Another advantage is that most information needed for manufacturing them is already available (Selgelid, 2007). However, a side effect of using pathogens in warfare is that they cannot distinguish people from each other. This poses a

threat to humans and other species, especially today in a globalisation perspective, since pathogens could be transferred between countries. Therefore, targeted weapons using pathogens would be a challenge according to Trevan (Trevan, 2012).

One can therefore see many scenarios where synthetic biology could result in products used for harmful applications, which Els discussed with the help from Lentzos (Lentzos, 2015). One example could be using microorganisms to produce toxins that were made to kill for example algae in water. How do we know and ensure that these microorganisms will not be used in a way that could potentially harm the ecosystem and other species? We are therefore presented with a scenario where we have to weigh our project according to the risk of the project, but also with the benefits.

Another factor that is important to take into consideration, and which Forge brought up in 2010, is that the group's skill set that is required to produce and reproduce the product/project, as well as the materials used for the product/project are just as important as the actual idea. The reason for this is due to the influence of the risk level. If you have a system that is relatively safe, but is then built up again by a person that does not possess the same amount of skills and material to build the product with the same accuracy, the risk can become significantly greater of producing something that could be harmful (Forge, 2010).

There is no real possibility to censor and constrain the publications of methods and materials within iGEM, since the whole point of the competition and the projects is to

show the world what the team has achieved, and how it can be used to provide the environment and species with solutions to already existing problems. So how do we as iGEM team members and competitors come around the issue? The truth is that there is no bullet proof way of predicting the risks and benefits of a project, which you can read about below in the meeting with Per Sandin. What we can do in this case, is to reduce the negative impact that our product could have. The problem with this is that it could require a certain amount of *a priori* knowledge. Take the above example with killing algae with toxins that I brought up. In order to prevent the bacteria that are producing the toxins from being used in a harmful manner, a way to prevent it could be introduced into the system. Many teams introduce kill switches into their constructs, which is an efficient way of shutting down the function of the system, not to cause any harm in an area in which it is not designed for. However, what is used instead of *a priori* knowledge in iGEM, is the open discussion with society about the project. Society can then give you guidance in how the project could be more easily integrated in the community, and what aspects to think of when creating a safe product.

Meet a professional - Per Sandin

Per Sandin. *Photo:* Fredrik Sandberg

Per Sandin is an Associate Professor in Philosophy and a senior lecturer in bioethics and environmental ethics at the Swedish university of Agricultural Sciences, Uppsala. Per has worked for a long time within applied ethics, and carries great knowledge about ethics around catastrophes, risk and environment.

We had the pleasure to talk with him in the beginning of our wet-lab phase, and touched upon many important aspects within safety when working within synthetic research.

"Then it is just like having a preacher telling you what to think"

Per sees bioethics and biosafety as ethical questions within science and medicine, within both the research and application parts of a project. However, everyone has their own definition of what is ethical and what is not. As individuals, we are very affected by our own morals and our life experiences. This is something that we got to understand when

we met Per, on a sunny day in Stockholm. He himself does not believe in having just one or a few people deciding on what is ethical, since it would be just like a preacher telling you what to think. He however thinks it is wise to gather as much knowledge within the field as possible, to be able to contribute to ongoing discussions.

Morals

Per thinks that it is important to distinguish between ethics and morality. Our morality is the values and behaviour that we are more or less taking for granted. Morality will differ a bit depending on your background, but mostly our morality overlaps. Something interesting with morality is that it can change with time, depending on people we meet, cultures we experience and life events. Ethics is connected to morality, since it is the critical thinking about morality – *why is this morally wrong?* This in turn is connected to laws and justice, since some moral rules are enforced in laws.
When it comes to biotechnology, there will always be someone who thinks that a project within the field is morally wrong. However, people working within the field, both as academics or within industry should not be scared of these opinions, since they do not have to be well-founded views. Nonetheless, risks within the field do always have to be considered.

There are different kinds of problems within the field, being both research ethical problems, and downstream problems when implementing a product. Some problems are juridical, requiring lawyers to help defining the needs and impact of the product and the research ethical questions needs attendance from supervisors and other senior staff. The connections between ethics and justice, law and morality are something that are interesting, yet very complicated. Especially, the legal landscape within bioethics and biosafety are complicated due to the fact that the regulations are global in many cases. Since research is very international as well, it can be hard to adapt it on a national level. Therefore, one problem we are faced with is our national politics not being able to regulate it on a national level, if the population would wish to do so.

Dual use

Again, going into the subject of dual use, Per explains that most things could be used as dual use objects. An example could be a truck, which could be used to drive school children or food, but also bombs or weapons to a warzone. In the case of a truck, a way of reducing the impact of transporting bombs and other warfare objects could be to reinforce more protection at different borders, and regulate the number of weapons that can be taken into a country for example. The same kind of thinking has to be applied to genetically engineered machines. The research ethical side is therefore how you make a legal project, but also a safe a reasonable project.

It takes a long time before a product can be implemented. Take drugs for example, going through risk assessments and evaluations, in vivo animal assessments and then through clinical trials. This work flow takes years to complete, and the future and possible applications have to be weighed into the flow. The problems that we might be faced with in the future are important for the implementation of the product, but can be hard to establish.

Risk and uncertainty

Possible risks and uncertainties are first and last priority in a project and its implementation. But what is risk, and uncertainty?

Risk is often understood as the combination of what could happen, and the likelihood of it actually happening. Within toxicology, risk is always dependent on the exposure to a hazardous chemical. There is no risk if no one is ever exposed to the compound that will cause a hazardous effect.

Uncertainty, on the other hand, is knowing that something could go wrong, without knowing the likelihood that it will.
Taking everything together, there are some things that can be anticipated, but some things are impossible to calculate in advance. The uncertainties within biotechnology are of

concern to people, Per mentions, and this is one of the struggles that we are faced with today.

Concluding remarks

Like my colleague Els Alsema so nicely put it, the ongoing discussion about dual use has mostly evolved around weighing the risks for society versus the benefits for public health. It is however extremely important for iGEM teams to start thinking about how the project could be misused, and also what could happen if other people tried to replicate the results but/and not having the same skillset as the members of the team. When planning and executing the project after these matters, the product and constructs could be designed according to safer methods, disabling the misuse of the setup.

Since iGEM teams are supposed to be transparent and focus on integrating society into the final product and the research, it is important to understand that it is hard to censor the research. Instead, focus should be put on limitations, where the potency of the product to be used for detrimental effects should be limited (such as the kill-switch). Ultimately, iGEM teams need to understand what the general public could think of the work. The Human Practices part of the circular work is vital, to get to the bottom of different individuals' feelings towards synthetic biology and the project in general. Talking to professionals within the field gives a strong foundation on which the project can be built upon. However, it is the community that will come with the verdict and help shaping the product the most, making it ready for the world. Talking about bioethics, it is however also important to find out if the world is ready for the product.

Acknowledgements

On behalf of the Human Practices team and the iGEM Stockholm 2018 team, I would like to thank Per Sandin for meeting us to talk about challenges that researchers meet within

environmental and biological ethics. I would also like to thank Els Alsema for sharing her essay and knowledge about dual use and how it could be limited.

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