Internship report

LIFE to LEGO

Ethical reflections for participants in the Open Source Synthetic Biology based international Genetically Engineered Machine competition:

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SynthEthics in the TU Delft iGEM project

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Preface

Synthetic biology is a novel approach towards metabolic engineering. It takes recombinant DNA techniques to the extreme; only the sky seems to be the limit. Even students from different disciplines can now participate in modern biotechnology research. Within the MIT's iGEM competition, undergraduate teams compete for producing the best micro-organism based invention. With standardized biological subsystems the students try to build systems within their university labs, while sharing their findings in an open source database.

But is this standardized approach towards biology really a good, beneficial development? The novel character of standardized biology and the used open source approach bring new ethical considerations, and many new questions arise. How synthetic can biology be? Is synthetic biology just another hype? Is the open source approach really a stimulus for scientific progress? What about intellectual property rights? What about naturalness or artificialness?

In this report the ethical issues that arise in synthetic biology are further investigated and then applied to the iGEM competition, to see which issues play a role in this project. Hereafter, a case study is carried out to investigate the project design and actual work of the TU Delft 2008 iGEM team. Interviews with the team members and their supervisors were carried out to investigate the participants' attitudes towards the ethical issues that play a role in the competition.

Executive summary

This report discusses ethical considerations within the iGEM open source synthetic biology student competition. The goal of this study is to investigate the ethical issues that play in this student competition, and to make the participants aware of these issues and investigating their opinions on these issues. A literature survey was carried out to investigate the ethical issues that play in open source synthetic biology. Subsequently a questionnaire was developed by which participants of the TU Delft 2008 iGEM team were inquired, to learn their opinions.

It appears that currently, what is meant by "synthetic biology" is still somewhat unclear: different stakeholders have different definitions. At the least it can be stated that it takes recombinant DNA techniques to the extreme: completely new systems may be built. But currently most research carried out in the area of synthetic biology is not as synthetic as it may be in the future.

The four major ethical issues in open source synthetic biology that are proposed in literature comprise biosafety (for users, producers, the environment, etc.), biosecurity (no intentional or unintentional misuse), naturalness (the artificialness of "life" or living systems), and intellectual property rights (relating to open source knowledge and patents).

Before the opinions of the TU Delft 2008 iGEM team are described, one should first realize which implicit assumptions (on what synthetic biology may mean) are also made in participating in a science project where students from several disciplines are working on. Participants working in areas other than biotechnology are initially unaware of any ethical issues that already play in biotechnology: issues relating to public resistance, trust between stakeholders, naturalness or artificialness, religion and biotechnology, gut-feelings in this area, globalization, etc.

When starting the iGEM project, the students and supervisors brainstormed on possible ideas and project requirements. Meetings with experts from the TU Delft's Biotechnology department were held, to further select topics of interest. In addition, a value sensitive design session was held, in which the values to take into account during the project were assessed. These values were safety, security, usefulness and transparency of data; these values overlap with ethical issues defined in literature to some extent. In the end, the biothermometer project was selected from a number of alternatives.

In the semi structured questionnaire, questions were asked regarding reasons for participation, open source technology, values and value sensitive design, risks and ethical considerations, and regarding naturalness, misuse and responsibility specifically. Differences in opinions on these and more topics were observed: between all participants, between supervisors and students, between those schooled in biotechnology and those not schooled in biotechnology.

It appears that participants have very dissimilar opinions on the way they think open source relates to usefulness and commercialization. Some say it stimulates, some say it inhibits. In literature, experts also warn that probably very few valuable (in terms of money) applications will be developed, and that the relation between patenting and open source is difficult. When asked whether or not the participants would quit the project when an application was developed that could metaphorically turn gold into lead, also very different approaches were observed: some would quit for various reasons, others would continue. It appears that moral values are very dissimilar or even contradictory among the participants, probably much reflecting "public opinion" itself.

Also the participants feel that they have very different responsibilities in safety, security and transparency towards the users of the developed application and towards society in general. Some feel the team should actively try to prevent misuse and guarantee safety (but do not specify how this should be done), others state that this cannot be the team's responsibility.

Relating to both responsibilities and the attitude towards open source, some state that the iGEM competition is currently for the TU Delft team not about developing an application (as assessed in the project requirements initially), but about doing fundamental science. It appears that participants have

different expectations towards the outcome of the project. Yet in the fundamental scientific approach, less moral values seem to play a part: science becomes science "because we can", and does not take into account the moral values that would play if the team would be developing an application for society. Apparently, different stages in development are to be distinguished. Some state it is currently too early to consider usefulness or commercialization or risks in production, because first a working system has to be developed. Others state that in designing a working system, already crucial decisions on end use are made, so in design the relevant values need to be considered. In that sense, the persons with a more fundamental approach generally attribute less value to value sensitive designing than the more application oriented participants. This is also reflected in their attitude towards personal responsibility towards society: "fundamentalists" feel less responsible.

The outcome of the survey may be used to identify some topics on which the iGEM competition may be improved. For example, value sensitive design sessions were appreciated by all team members. Perhaps these value sensitive design sessions are to be obligatory for iGEM participation, and not just as a "gold medal requirement": making students aware of the implications of their research also means that they can understand public concerns, and take these concerns into account when talking about their work, resulting in a more clear description of what they are doing, and moreover, why that is necessary.

Also, regarding the responsibilities of the teams towards safety and security, the responsibilities of the iGEM competition organizers (who send around DNA) remain somewhat unclear. Some state the organizers should be clear on their responsibilities. It can be understandable, nonetheless, that iGEM doesn't want to consider this, since it is a student project and students are not responsible, but their supervisors. Still, it should be clear beforehand where the responsibilities lie.

The same may hold for the position of iGEM on intellectual property rights. Teams can send in any DNA sequence they like, and are expected to check for patent infringement, but at the moment it is unclear who is ultimately responsible for checking any infringement of patents on these sequences: the infringement isn't centrally (re)investigated by iGEM.

As stated above, the goals of this study were to identify ethics in iGEM and to investigate the TU Delft 2008 participants' opinions on the relevant ethical issues and making them more aware of the issues that play. These goals were achieved, but more can be done with the data. As also stated above, some suggestions for the iGEM competition organizers are made. Also, the data may be used as a case study in ethics and technology education, in discussion within biotechnology research groups, etc. Also, it might be used as a study to help improve integration of ethics in science.

In short, it appears that synthetic biology holds many applications with many benefits for society in the future, but we must not forget the ethical considerations regarding the factual risks as can be scientifically assessed and the perceived risk in public concerns. We can be optimistic, but the open source approach also holds some drawbacks and relies on moral values that may not be present in every person's moral palette. This study, "Life to Lego, SynthEthics in the iGEM project" reflects upon the relevant ethical considerations with interesting results.

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1 Introduction

Interdisciplinary sciences have gained momentum over the past years, especially in the field of biotechnology. Synthetic biology is an example of converging technologies. Some would say the goal of synthetic biology is to make biology an engineering science, designing with biology. Other may state that building with biology can be used to further understand life. At the least, one may state that both the bottom-up, constructing part and the top-down, deconstructing aspects of synthetic biology rely on the principle of using more or less "biological" systems in a more or less "natural" way. This novel approach of biology brings about new applications, but also new risks and new ethical considerations. In this report, ethical considerations are investigated in the synthetic biology project called "iGEM". In this international Genetically Engineered Machine competition, undergraduate university students try to build an application with biological components, called "BioBricks". A combination of functional bricks can form a system with a certain application. The TU Delft 2008 team's application is a biothermometer: a temperature sensor that will give, depending on the input, a certain color as output (see *Appendix A* for the project proposal). The goals of the iGEM project for the TU Delft team comprise wet lab activities, modeling activities and ethical considerations. This report reviews the ethical considerations in the iGEM project and contains a survey into what the TU Delft team members, both students and supervisors, think of these ethical issues.

The central question in this study is what these newest ethical considerations as proposed by ethicists in the field of synthetic biology actually mean for the participants in iGEM. On an individual level, which ethical questions play a role for the TU Delft iGEM team? How do the team members work with or around these issues? These are exactly the topics that are investigated in this study: in the past, ethics in science has mainly been discussed by experts in morality, rather than by scientists. It may be interesting to also find out to what extent students and supervisors in iGEM, generally barely experienced in ethics in science, think of certain proposed ethical issues in synthetic biology. Which ethical constraints or motivators do they see? Perhaps there is a difference in approach between supervisors and students, or between the individual students.

These ethical considerations in iGEM are important for different reasons. Here, one approach is given. In the future, the world will run out of fossil fuels. The general idea is that we will go from fossil fuel based economy to a bio-based economy or bio-based society. For many different applications, the planet currently relies on crude oil. The idea is that many biological alternatives are available or will become available in the future, that need to be investigated scientifically. But what should scientists focus on? With limited money available, perhaps only the most useful or profitable products will be further investigated. But who decides what the "needs" are? Politicians? Companies? Other organizations? At least not public scientists by themselves. The money for research indirectly comes from the public at large. Grants are only supplied if the projected (societal) gain is large enough. One can imagine that in all these bureaucratic processes, choices are made, relevant not only to the bureaucratic system, but also to scientists, NGO members, governments, the public, etc. These choices are not purely scientific: many societal issues are addressed, many ethical choices are made. When a new technology (or technological approach, like constructing biology in synthetic biology) is introduced, this brings about new ethical considerations, as stated above. In a changing society, and in our current sociopolitical system, it is probably necessary that scientists themselves also realize what they are doing, what the implications may be, why they are doing what they are doing, etc. That is exactly why ethical considerations are interesting to investigate within the iGEM project group of the TU Delft.

Before these individual team member analyses were carried out, a road-map of the ethical considerations that are associated with synthetic biology was made. For this, a literature survey was carried out, exploring the general, "macro" ethical sides of synthetic biology, with a goal to clarify the ethical considerations that play a role in iGEM. With this road map, a framework for a questionnaire has been developed, by which the ethical considerations on the individual "micro" level will be analysed. The goal of this questionnaire is to create awareness among the participants of the ethical issues that play a role and to learn which issues are important to consider for the iGEM competition.

This report is written at the moment that the BioBricks are developed, but functional analysis of the components is still pending. This means that the eventual results of the project are not known yet: research is in an early, developmental stage, but the project setup has already been designed.

2 Methods

To address the ethics in the synthetic biology field and specifically in iGEM, two approaches are used. In the first approach, the ethical considerations in synthetic biology and iGEM specifically are described on a more general, macro level. In the second approach, ethical considerations within the TU Delft iGEM team on a micro level are investigated.

2.1 Macro and micro ethics

Several articles, readers, reports, fact sheets, websites, etc. were used to create a road map of the ethical considerations in synthetic biology. References are given in the text, where necessary. This road map was subsequently used to develop a survey, by which the ethical questions and ideas the TU Delft team members and their supervisors have, were logged. For the design of the used questionnaire, help was obtained from the Biotechnology & Society working group of the TU Delft Biotechnology department, Ibo van de Poel from the TU Delft Philosophy section of the Technology, Policy and Management department, and from Huib de Vriend of LIS Consult. The used questionnaire can be found in *Appendix B*. In these semi structured questionnaires, questions were not always asked in the same way and in the same order. The outcomes of a typical interview for the micro ethics assessment is given in *Appendix C*. During the design of the TU Delft project, brainstorming sessions were mapped using the program "Compendium", version 1.5.2 (see website[1]).

The qualitative analysis of ethical considerations as perceived by team members and supervisors will not generate statistically reliable numbers on general group opinion. That is not how this survey is to be understood: it is just meant to analyse which issues are recognized by the team members and how these influence their work.

2.2 Introduction of the team

In this project students and supervisors are involved with different scientific backgrounds. The table below indicates the educational background of the participants. Six students form the actual iGEM team. The other four participants are supervisors, working in research positions within the Biotechnology department of the TU Delft Applied Science faculty. The table shows a variety of different backgrounds of the participants. In addition to the students and supervisors, several instructors additionally provided help and assistance where needed. These instructors are TU Delft professors and other researchers, and employees of DSM[2]

Table 2.1: names and backgrounds of participants in the iGEM project.

Name	Position	Background
Bastiaan van de Berg	MSc. Student	Information technology
Oscar Stassen	MSc. Student	Life science & technology
Ruud Jorna	MSc. Student	Life science & technology
Steven Flipse	MSc. Student	Life science & technology
Rad Haghi	MSc. Student	Mechanical engineering
Farzad Ethemam	MSc. Student	Biomedical engineering
Janine Kiers	Supervisor, PhD.	Biotechnology
Domenico Bellomo	Supervisor, PostDoc	Bioinformatics
Emrah Nikerel	Supervisor, PostDoc	Bioinformatics and Biotechnology
Marco de Groot	Supervisor, PostDoc	Bioinformatics and Biotechnology

[1] Compendium information – http://compendium.open.ac.uk/institute/download/download.htm, visited May 2008.
[2] A Dutch company specialized in innovative products and services in life sciences and material sciences - http://www.dsm.com/en_US/html/home/dsm_home.cgi, visited August 2008

2.3 Glossary

Below, some relevant terms in synthetic biology and how they are used in this website, will be described in alphabetical order.

BioBrick
A functional DNA sequence or cluster of sequences, to make a functional biological subsystem that can be used in a biological system, built up according to a standardized method.

Colour pathway output
See *Appendix A* for the project proposal, containing a detailed description of the colour pathway output of the thermometer.

Open source
The term "open source" in scientific research implies that complete transparency of research is guaranteed. The research design is publicized, the findings (both positive and negative) are reported and all conclusions are made available for everyone. The iGEM teams are to publish this data on a publicly accessible website.

PCR[3]
The polymerase chain reaction (PCR) is a technique widely used in molecular biology. It derives its name from one of its key components, a DNA polymerase used to amplify a piece of DNA by in vitro enzymatic replication. As PCR progresses, the DNA thus generated is itself used as a template for replication. This sets in motion a chain reaction in which the DNA template is exponentially amplified. With PCR it is possible to amplify a single or few copies of a piece of DNA across several orders of magnitude, generating millions or more copies of the DNA piece. PCR can be extensively modified to perform a wide array of genetic manipulations.

RNA secondary structure based temperature sensitive sequence
See *Appendix A* for the project proposal, containing a detailed description of the temperature sensitive sequence functionality of the thermometer.

Synthetic biology
The term "synthetic biology" has different meanings for different people, as this report will demonstrate. In this report, synthetic biology means using constructing or deconstructing approaches towards biological systems on different levels of naturalness or artificialness. This somewhat vague description will be clarified in this report.

Transgenics or transgenetics
When genes from a source organism are inserted into the DNA of a host organism, while the two organisms together would not be able to reproduce in nature, we speak of transgenics or transgenetics. This is in contrast with cisgenetics, where genes from an organism are inserted to genes of a related organism, that would be able to mate with the source organism in nature.

[3] PCR on Wikipedia website - http://en.wikipedia.org/wiki/Polymerase_chain_reaction accessed August 2008

3 Ethical issues in synthetic biology on a macro level – discussing synthetic biology

Since the "reintroduction"[4] of the term synthetic biology in 2005, several reports have appeared in which the ethical and social issues related to this field of research are described. Ethical and social reflections in a stage this early in scientific development have not been observed in other novel technologies, like nuclear energy and genetic engineering, some decades ago. Yet with the recent introduction of nanotechnology, experts tend to see the necessity of these considerations. This report will not describe into detail why these social and ethical reflections are said to be necessary; rather, it will describe what has been stated in literature on the ethical and social challenges in modern literature, which questions and values are considered and how this applies to the emerging field of synthetic biology.
To do this, this chapter will start by describing what is meant by "synthetic biology". Thereafter, the risks associated with synthetic biology will be mentioned. Hereafter, the implications and implicit assumptions made in synthetic biology research will be explored. Subsequently the relation between constructive biotechnology in an open source setting and intellectual property rights will be discussed, followed by a brief prospective on synthetic biology.

3.1 A definition of "Synthetic Biology": a discourse in semantics?

Stakeholders in synthetic biology do not use a single definition of synthetic biology. Therefore, the boundaries of the scientific area that can be called "synthetic biology" are also not 100% clear. In this report the moral values related to the technology are described without defining into detail what is meant by "synthetic biology". Further, the used technologies that converge in synthetic biology are also not very clearly defined. E.g., what is meant exactly by industrial biotechnology, nanotechnology, nanobiotechnology, etc., is also not clearly described[5]. To give an impression of what synthetic biology involves, several definitions as defined by different stakeholders are given below[6].

> ***European Union –*** *"Synthetic biology is the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems, rather than on the understanding of natural biology."*
>
> ***Dutch COGEM –*** *"Synthetic biology focuses on the design and synthesis of artificial genes and complete biological systems and on changing existing organisms, aimed at acquiring useful functions."*
>
> ***Jay Keasling –*** *"The development of well characterized biological components that can be easily assembled into larger functioning devices and systems to accomplish many particular goals."*
>
> ***Steven Benner & Michael Sismour***[7] – *"Synthetic biologists come in two broad classes. One uses unnatural molecules to reproduce emergent behaviours from natural biology, with the goal of creating artificial life. The other seeks interchangeable parts from natural biology to assemble into systems that function unnaturally."*
>
> ***Berkeley University*** – *"The design and construction of biological parts, devices and systems and the redesigning of existing natural biological systems for useful purposes."*

Only by looking at these examples, one can observe that what is meant with the term "synthetic biology" involves different things. Therefore, it is probably more appropriate to speak of the "field of synthetic biology" combining different life science related technologies, rather than classify it as a single technology in itself. At least, one can claim that synthetic biology encompasses constructing and deconstructing biological processes of "life", with life in different gradations of naturalness or artificialness. Exactly this suffix, which states that there are several levels of what is considered natural or artificial (synthetic), implies that perception and hence ethical considerations related to the autonomy of life are important topics to consider in the field of synthetic biology. How synthetic can biology actually be? To what extent can biology be engineered? To give at least some answers to these questions in the following paragraphs, one must first analyze which risks are concerned in synthetic biology. These are described in the next paragraph.

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[4] The term was already coined in the 1970s, when people first fantasized about the possibilities of working with DNA.
[5] See e.g. the Industrial Biotechnology definitions by EFB and EPSC: **European Federation of Biotechnology** – "Biotechnology is the integrated use of biochemistry, microbiology, and engineering sciences in order to achieve technological (industrial) application of the capabilities of micro-organisms, cultured tissue cells and parts thereof." and **European Platform on Sustainable Chemistry** – "Industrial Biotechnology is the application of biotechnology for the processing and production of chemicals, materials and fuels. It uses enzymes, micro-organisms and cell lines to make products in sectors such as chemistry, pharma, food and feed, paper and pulp, textiles and energy, materials and polymers."
[6] Adopted from (unless indicated otherwise): Constructing Life – Early social reflections on the emerging field of synthetic biology, Huib de Vriend (for Rathenau Institute), The Hague December 2006, Chapter 2.1
[7] Adopted from: Synthetic biology, SA Benner AM Sismour, Nature reviews genetics, July 2005, V6 p533

3.2 Risks related to synthetic biology: bioerror or bioterror?

As is probably the case with any "new" technology, besides a number of new applications synthetic biology also comes with a number of new risks. In this paragraph, the term "risk" is introduced first. Hereafter, risks associated with new technologies like synthetic biology are mentioned. Finally, risks associated with open source technology[8] are brought up.

3.2.1 Risks and risk perception

When making a decision, like the decision whether or not to use Synthetic Biology in an application, one balances the risks against the benefits. But is actually meant by "risk" isn't always clear. Textbooks state that the Risk is the magnitude of the Hazard when it takes place, multiplied by the Frequency in which these hazards actually occur (R = H * F)[9].

These risks are partially factual risks, which can be scientifically assessed, like assessing the chance that an organism will share DNA with surrounding organisms upon deliberate release into the environment. There are also virtual risks, like exploring the probability of creating a biological weapon with open source BioBricks.

When the future impact of a certain decision, like in the case of using Synthetic Biology in increasing levels of artificialness, risk assessment actually becomes risk perception: the response of the public, NGOs or consumers are unknown, as well as the scientific possibilities and application areas. If the risk is "low enough" (and one has to wonder who decides that), a certain action can be justified. Some would calculate the Justification of a decision as the Impact of something going well, times the Chance of it going well, minus the actual risk (J = I * C – H * F).

The problem with these kinds of analyses is that the (financial) impact or hazard can be calculated, or well estimated, but the occurrence of the events generally cannot. Then, values for impact or hazard are chosen arbitrarily, attributing a certain value to what a stakeholder deems important. Many individual assessments play a role. Experiences of the company or academic institution, experiences of others, experiences of individual employees, public attitudes, litigation, fear of bad media attention, activism by NGOs, etc., all play a role in "calculating" the risk or in justifying the actions of the company as a whole and to make money or generate knowledge within all legal boundaries.

It becomes clear that the risk assessment regarding synthetic biology relies on many uncertainties. Some risks can be scientifically assessed, but many other risk assessments related to this new technology take into account many uncertainties. Ethical considerations can help create some structure on what to focus on in risk assessments. By focusing on synthetic biology and its applications, two main fields of risk perception are distinguished in this report: risks associated with new technology and risks associated with open source technology. These two will be addressed in the next sections.

3.2.2 Synthetic biology as a novel technology

As stated before, probably all new technologies give rise to new risks and risk perceptions[10]. This has been observed for genetic engineering, nuclear energy, cars, etc. Modern research on the newest technology may also come with unforeseen risks or possible mistakes. When these potential errors are noticed, it is too late to prevent them from occurring. BioErrors may occur when e.g. a deliberate release into the environment does not work out the way it was predicted, e.g. new pathogens or toxins are released. In that instance, the problems that NGOs like Greenpeace and Friends of the Earth warn for, will turn out to be real problems. Therefore, caution in using new technology like transgenetics or creating more artificial biological systems is always advised. Regulation on genetic engineering techniques like used in synthetic biology is already in place[11], but BioErrors may not always be foreseen.

Besides unforeseen consequences on a technological level, also new ethical considerations appear in synthetic biology. Creating more artificial systems makes one wonder what "life" actually is and to what extent the autonomy or quintessence of an organism is more important than technological progress. From a biological point, something lives when it has its own energy metabolism and it can reproduce all by itself. From a moral point of view, this may be different, especially with increasing levels of artificialness of "biological" or "natural" systems. That is why in synthetic biology, artificial life is an issue to consider: what is the boundary between "organism" and "machine"[12]?

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[8] See for a definition of Open source: Glossary, *Chapter 2.3*

[9] See e.g. TU Delft "Ethics and Engineering" reader for the courses on ethics and engineering at Delft University of Technology by Zandvoort, van de Poel, Brumsen, Roeser, Dept. of Philosophy, January 2004 edition, Delft.

[10] This may be the case in Europe more so than elsewhere: risk perception may vary per region or culture.

[11] Within the Netherlands by central European legislation

[12] The deeper philosophical question may relate to the image one has of nature: does nature have an intrinsic value of its own or is it an instrument that can be used by mankind?

3.2.3 Synthetic biology and open source databases

Besides issues related to errors in research or application of synthetic biology and issues related to artificial life definitions, ethical considerations on synthetic biology related to the open source character of the technology also need to be examined. The proposed BioBrick approach of the constructing part of synthetic biology gives rise to a number of ethical considerations. One of these is related to the intellectual property issues described in *Chapter 3.8*[13]: the relation between open source technology and commercialization of ideas, patent laws, etc. need to be considered.
But besides these IP related issues, one also must deliberate on the intentional (mis)use of the open source BioBrick database. Some applications or "devices" made out of BioBricks from a publicly available database may have a "dual use" character. This concept can be related to e.g. the sharp edge technology of a knife: a knife-like object can be used to cut a sandwich into pieces or to kill someone. But everyone who has tried to slice bread with a samurai sword knows that's not really the purpose of this particular device. From the BioBrick database also metaphoric samurai swords may be devised. Then it only takes a small step to consider deliberate misuse or Bioterror of the open source technology.
Also, biotechnology research or genetic engineering gets more and more easy to carry out. It is probably possible to conduct research in your own garage, without anyone knowing what you are doing. Moreover, companies that synthesize DNA can create any sequence one likes, currently possibly without any constraints.
These open source, dual use and DNA ordering freedom makes Bioterrrorism an issue to consider in the light of open source biotechnology or particularly, iGEM. That is probably why this issue is addressed in many papers on synthetic biology specifically[14].

3.3 Implications of terminology: a contradiction in terminis?

In synthetic biology many different technologies are converging. Some would say that it is just a modern, advanced version of metabolic engineering. In addition, one may recognize scientific approaches from nanotechnology and biotechnology, but also approaches from information technology are used in synthetic biology. The used laboratory practices rely on recombinant DNA techniques which are already used in genetic engineering. Yet biology has probably always been perceived as a study of nature and natural events. A synthetic prefix results in a contradiction in terminis from a "naturalness" point of view.
But what then, is considered "natural"? What is considered natural[15] is the topic of much discussion, also in the Genetic Modification (GM) field. To elucidate this statement: Arno van 't Hoog, former chief editor of Bionieuws (news paper of the Dutch institute for Biology, NIBI), writes[16]:

> *"Biologists are moralists. That righteous attitude can be found especially in the term naturalness. Think of natural balance, organic food, etc. Naturalness is an odd mix of ethics and science. Namely, naturalness isn't a biological term, in nature you can't see what is natural. You can go and find a certain situation or condition and call it natural.*
> *Naturalness always indicates a favored situation. Or the lack of it, and then we hear defying talk of an unnatural situation. And unnaturalness is about the worst sounding biological accusation one can make.*
> *It is therefore that the terms naturalness and unnaturalness are always heard in discussions on controversial subjects like biotechnology and nature conservancy. Biotechnology with animals, genetic modification of plants and the cloning of humans are, according to critics, unnatural practices. And thus repulsive. End of discussion.*
> *That's how it goes repeatedly. Ecological farmers attempt to use natural cultivation methods. Artificial fertilizer and pesticides are regarded unnatural. There was a time when homosexuality, contraception and IVF were regarded unnatural, but luckily times have changed. With all kinds of unnatural situations it seems like the world is a better place to live.*
> *One who hears the term "naturalness", should ask questions. […] The power of the naturalness argument is seemingly obvious. Naturalness is so good and unnaturalness so bad, that it seems like no further explanation is required. And often, no further explanation is given. It sounds like a scientific observation, referring to a higher, unchangeable order. Such a discussion strategy is called a naturalistic fallacy. One describes a situation as natural, to conclude without further explanation, that that situation is good. A well-known example is the justification of the existence of social inequality because of the natural process of competition between different groups in society.*
> *In short, there is a foul smell around the naturalness argument. In fact, it can only serve as an emotional signal that the people involved think is important. Afterwards, these people really have to explain and give arguments as to why."*

[13] See Chapter 2.3 for the difference between constructing and deconstructing approaches in the synthetic biology definition
[14] See references in this report.
[15] See e.g. GE Moore's Principa Ethica on Naturalness and the naturalistic fallacy
[16] Translated freely from "Natuurlijk", A. v't Hoog, Bioniews 2, 2 February 2008

Van 't Hoog argues that what is "natural" is a matter of perception. The concept can be used in any context, either for the pro and contra parties in the GM debate. Another theory is suggested by ethicist John O'Neill[17], who states that naturalness matters to e.g. environmentalists because of its historical context. It can be compared to an object of art, e.g. a painting of a famous artist. Currently one may be able to make exactly the same painting, with the same kind of paint, colors and autograph, but still it wouldn't be as valuable. That may be exactly why GM can be perceived as "unnatural".
However, in synthetic biology this discussion can become obsolete, as the "naturalness" level of synthetic systems appears to be decreasing. At first, one may think that this is useful for ethicists in a pragmatic point of view, because there is one less thing to consider. But this appears not to be true: the discussion has only shifted to a more sensitive discourse, a discussion on the value, essence or autonomy of life.
Nevertheless, the level of artificialness or naturalness is difficult to define. Currently, synthetic biology has a metabolic engineering character, with a focus on understanding and using nature and natural systems. Making complete artificial systems is still in a distant future. This does not mean that one should not consider moral issues related to artificial life, but one should also realize that the current ethical issues in genetic engineering techniques cannot be omitted just because other issues are arising in synthetic biology. There are some implicit assumptions in synthetic biology that need to be considered.

3.4 Implicit assumptions in synthetic biology: forgetting what's currently important?

Between 2005 and 2008 several papers, fact sheets and reports[18,19,20,21,22] have been published on the ethical and social reflections related to synthetic biology. Within most of these publications the authors elaborate on the following four issues:

- Biosafety: health and environment
- Biosecurity: biological weapons and terrorism
- Intellectual property rights: commercialization and globalization
- Artificial life: ethical considerations

One should notice that the issues raised here relate to synthetic biology applications in higher levels of artificialness than is currently being researched in most instances. Of course one should realize that there is only a vague difference between advanced metabolic engineering and the more artificial levels of synthetic biology, but what is often not considered in modern papers on the ethics of synthetic biology, are issues related to metabolic engineering practices like genetic engineering.
It seems that implicitly stakeholders working in the (self proclaimed?) field of synthetic biology live under the impression that ethical considerations that relate to synthetic biology should be considered in stead of ethical considerations relating to recombinant DNA techniques. Skipping this field, where there is already much debate on what is or should be allowed from a moral point of view, seems to be the easiest thing to do. But in this case we are only omitting some relevant issues that have not really been solved yet. Of course, this also depends on the application area of the application. E.g. in Europe the GM food debate stirs many souls, while GM techniques in medical research are much more appreciated[23]. Discussion topics that seem to be missing in synthetic biology are highly related to ethical issues in nanotechnology and biotechnology. Some relevant issues and examples of related ethical questions are enlisted below:

- **Public knowledge and involvement in scientific development:** should the public be informed about science?
- **Public awareness and appreciation of the technology:** would a highly informed public be more appreciative of scientific developments?
- **Trust of all stakeholders in government, governance and enforcement:** do NGOs, the public, scientists, etc. have faith in regulations?
- **Trust between the stakeholders:** can opposing parties in (ethical) discussions on scientific topics come to terms and on which bases?

[17] Centre for Philosophy, Institute for Environment, Philosophy and Public Policy, Lancaster University,
[18] E.g.: Synthetics: the ethics of Synthetic Biology, IDEA League Summerschool paper, August 2007, The Netherlands
[19] European Commission, NEST Pathfinder Synbiosafe – Safety and ethics of synthetic life, 2007
[20] Synthetic Biology – Social and ethical challenges, A Balmer P Martin, Institute for Science and Society, University of Nottingham, May 2008
[21] Leven maken – Maatschappelijke reflectie op de opkomst van synthetische biologie, H de Vriend R van Est B Walhout, Rathenau Institute, Den Haag, June 2007
[22] Synbiosafe Background Document for the synbiosafe e-conference, 29 April 2008, www.synbiosafe.eu/forum
[23] See e.g. recent Eurobarometer surveys (Europeans and Biotechnology in 2005: Patterns and Trends, 244b)

- **Public or consumer freedom of choice in using this technology and related products:** do consumers wish to buy products made with synthetic biology (genetic engineering)?
- **Naturalness or artificialness issues:** when does a natural system become a mechanical structure?
- **Religion and genetic engineering technology:** what are the religious boundaries for applying genetic engineering techniques?
- **Traditional production methods and related employment:** is technological development also appreciated in artisanal production of e.g. food products?
- **Risk perception and related perceptions on safety:** to what extent are gut-feelings of safety ("is it really, really safe?") scientifically justifiable and allowed to play role in ethical considerations of certain stakeholders?
- **Industrialisation and globalisation and related intellectual property rights:** will scientific development lead to abuse of third world countries by large multinationals?

Digging into these ethical issues a little deeper shows that what people may really be concerned about, is autonomy, security and safety (of self and nature, for now and for the future): these are the underlying considerations of the ethical issues enlisted directly above. These are exactly the four issues raised in synthetic biology, as stated at the beginning of this paragraph, but these four are on a higher level and much more abstract. The moral values, that people may want satisfaction on before these higher issues can be discussed, are the more superficial issues listed directly above.

3.5 The "banner" implications: a pragmatic point of view.

Yet implicitly it seems that in synthetic biology research, these issues are not considered. Scientists probably know about the issues raised in synthetic biology. However, by working in synthetic biology research, it may seem that the scientists[24] do not consider ethical issues related to the public, religion, trust, tradition, globalisation, industrialisation, naturalness, freedom of choice, etc. Does this mean that under the "banner" or flag of synthetic biology, more is or should be allowed than is the case for genetic modification in metabolic engineering? Let's elaborate.

With the term "genetic modification" the focus is on the used technology and hence there is a focus on practicing recombinant DNA techniques. Therefore the focus is on changing DNA and hence the autonomy of an organism is much more prominently present in discussions on ethics of genetic engineering. Discussions about the possibilities (technical and theoretical) and regulations (legal framework and enforcement) of genetic engineering techniques therefore are much more logical to be discussed by the parties that in some way or another are in contact with this technology.

This is in great contrast with synthetic biology. The term "synthetic" probably makes people perceive that the connection with "life" and autonomy of life is, perhaps partially, already lost. With increasing levels of artificialness (irrespective of where the frame of "naturalness" ends) it may therefore seem that more is allowed in terms of use of recombinant DNA techniques, than was the case in metabolic engineering with "genetic modification".

It seems that just this difference in terminology may have important consequences for the public appreciation of the technology, while in fact, synthetic engineering can be considered "worse" from a technical point of view in terms changing DNA and respecting life and living organisms' quintessence; it seems that under the banner of synthetic biology, more may be allowed, while forgetting about the ethical issues raised in the previous paragraph.

But nonetheless, above it was argued that currently, synthetic biology and metabolic engineering are not that different. This should also mean that the ethical issues related to genetic engineering should be considered in synthetic biology and should not omitted or forgotten. Indeed, synthetic biology gives rise to new ethical issues that need to be considered, like the afore mentioned moral issues related to biosafety, biosecurity, intellectual property and artificial life. Papers and reports focussing on the ethics of synthetic biology focus on these new issues, but most of them do not elaborate on ethical issues of genetic engineering in general, like mentioned at the end of the previous paragraph.

[24] A discussion of what scientists think science is or what science should be, perhaps also according to other parties, is also a topic of discussion that I will not go into here.

3.6 The media: a PR stunt or time for a public backlash?

In a different approach, one may also argue that in synthetic biology, the application and related processes within an organism are in the centre of attention, while in metabolic engineering the technology and the organism itself play a more prominent role. This implies that the designer approach of synthetic biology, possibly together with the constructive excitement of this new approach may make synthetic biology appeal more to the public and therefore my be more appreciated by the public.
But this is not how synthetic biology is presented in the media. A quick survey on the news paper websites of the BBC, NY Times, Daily Mail and the Guardian, with search term "synthetic biology", yields a number of articles, which do not put synthetic biology in a particularly good (or bad) perspective:

> ***Synthetic life 'no terror threat'*** *– "Synthetic biology can help in the fight against emerging infections, rather than aid the design of bioweapons, controversial scientist Craig Venter has told reporters." – BBC News*[25]

> ***'Artificial life' comes step closer*** *– "Researchers at Rockefeller University in the US have made the first tentative steps towards creating a form of artificial life." – BBC News*[26]

> ***Venter revives synthetic bug talk*** *– "Craig Venter – one of the scientists behind the sequencing of the human genetic code – aims to construct a living organism from a kit of genes." – BBC News*[27]

> ***Biology's New Forbidden Fruit –*** *"The scientific, commercial and destructive possibilities of this synthetic biology are easily as great as those once offered by the transformation of chemistry. But they will make themselves felt far more quickly, raising ethical and moral questions that many biologists have been poorly trained to handle." – NY Times*[28]

> ***Researchers Take Step Toward Synthetic Life*** *– "Taking a significant step toward the creation of synthetic forms of life, researchers reported Thursday that they had manufactured the entire genome of a bacterium by stitching together its chemical components." – NY Times*[29]

> ***Custom-Made Microbes, at Your Service*** *– "To be sure, scientists have been putting genes into bacteria and other cells for three decades. The term "synthetic biology" seems to include various activities, some of which are not altogether new. "This has a catchy new name, but anybody over 40 will recognize it as good old genetic engineering applied to more complex problems," said Frances H. Arnold, a professor of chemical engineering at Caltech." – NY Times*[30]

> ***One step closer to Frankenstein as scientists create artificial life in the lab*** *– "Researchers in the US managed to swap the entire genome of a bacterial cell with one from a different related bug. Given a completely new set of genes, the bacterium was effectively changed into a new species." – Daily Mail*[31]

> ***Scientists create artificial life in the laboratory – from four bottles of chemicals*** *– "Scientists have made a major step forward in creating life in the laboratory as researchers announce they have rebuilt a living bacterium from four bottles of chemicals. […]The scientists took the natural bacterium and painstakingly replaced its genetic structure, or genome, with DNA stitched together from chemicals. Eventually they had recreated all the genes that had been in the natural bacterium, effectively turning it into an identical but artificial organism." – Daily Mail*[32]

> ***Synthetic biology aims to solve energy conundrum*** *– "Designer enzymes are big business as the need to produce viable biofuels grows – but can they offer a long-term alternative? […]Even with an agricultural system tuned to extract as much biomass as possible, there will not be enough land to supply all fuel. […] Clearly, our need for designer enzymes is growing urgent." – The Guardian*[33]

> ***Biologists join the race to create synthetic life*** *– "The new discipline, established by scientists such as human genome pioneer Craig Venter, involves stripping microbes down to their basic genetic constituents so they can be reassembled and manipulated to create new life forms. These organisms can then be exploited to manufacture drugs and fuels or to act as bio-sensors inside the body.*
> *However, some researchers warn that synthetic biology – which is accelerating at a dramatic pace – also poses dangers. In particular, they fear it may already be possible to create deadly pathogens, such as polio or smallpox viruses, from pieces of synthetic DNA ordered over the internet. In future, completely new – and highly dangerous – microbes could be made this way." – The Observer*[34]

[25] Synthetic life 'no terror threat', Cristina Jimenez, BBC News, 24 October 2007, http://news.bbc.co.uk/2/hi/science/nature/7059490.stm, accessed 25 July 2008
[26] 'Artificial life' comes step closer, Roland Pease, BBC News, 18 December, 2004, http://news.bbc.co.uk/2/hi/science/nature/4104483.stm, accessed 25 July 2008
[27] Venter revives synthetic bug talk, David Whitehouse, BBC News, 4 July, 2005, http://news.bbc.co.uk/2/hi/science/nature/4636121.stm, accessed 25 July 2008
[28] Biology's New Forbidden Fruit, Oliver Morton, NY Times, 11 February 2005, http://query.nytimes.com/gst/fullpage.html?res=9C04E0DA173AF932A25751C0A9639C8B63&scp=2&sq=synthetic%20biology&st=cse, accessed 25 July 2008
[29] Researchers Take Step Toward Synthetic Life, Andrew Pollack, NY Times, 25 January 2008, http://www.nytimes.com/2008/01/25/science/25genome.html?_r=1&scp=3&sq=synthetic%20biology&st=cse&oref=slogin, accessed 25 July 2008
[30] Custom-Made Microbes, at Your Service, Andrew Pollack, NY Times, 17 January 2006, http://www.nytimes.com/2006/01/17/science/17synt.html?pagewanted=1&sq=synthetic%20biology&st=cse&scp=6, accessed 25 July 2008
[31] One step closer to Frankenstein as scientists create artificial life in the lab, Daily Mail UK, 29 June 2007, http://www.dailymail.co.uk/sciencetech/article-465078/One-step-closer-Frankenstein-scientists-create-artificial-life-lab.html, accessed 25 July 2008
[32] Scientists create artificial life in the laboratory - from four bottles of chemicals, Daily Mail UK, 25 January 2008, http://www.dailymail.co.uk/news/article-510276/Scientists-create-artificial-life-laboratory--bottles-chemicals.html, accessed 25 July 2008
[33] Synthetic biology aims to solve energy conundrum, Chris Edwards, The Guardian, 19 June 2008, http://www.guardian.co.uk/science/2008/jun/19/chemistry.agriculture, accessed 25 June 2008
[34] Biologists join the race to create synthetic life, Robin McKie, The Observer, 20 April 2008, http://www.guardian.co.uk/science/2008/apr/20/genetics.controversiesinscience, accessed 25 July 2008

Can we create life? *– "Our knowledge of, and ability to, alter DNA remains rudimentary, in spite of notable scientific advances and the persistent dream of genetic perfection. […] This technique is called synthetic biology and it combines science and engineering to build new biological functions and systems. The US group J Craig Venter Institute hopes eventually to use engineered genomes to make bacteria that can do useful things, such as produce clean fuels or take carbon dioxide out of the atmosphere. But many people are extremely concerned by the possibilities of bio-error (or bio-terror) that artificial life creates. They say artificial microbes could have dangerous consequences if they escape into the environment or if they are used to manufacture bioweapons. At present there are no international laws or oversight mechanisms to assess the safety of synthetic organisms." – The Observer*[35]

From these articles, it seems that people do see the benefits of synthetic biology, but there is also attention for bio-error, bioterrorism, ethical issues, etc. In a way, the benefits are recognized, but the drawbacks also receive attention.

One can debate whether this attention for the potential risks and risk perception is a good development for scientific progress, but at least one can notice that this development is in large contrast with the progress in genetic engineering from the 1970s to 2000: here, much less ethical considerations are generally observed within the scientific community.

Yet still, when we consider scientific evolution of synthetic biology, with a focus on ethical issues such as biosecurity, biosafety, intellectual property and artificial life, one can wonder when the public is going to realize that synthetic biology is not so much different from genetic engineering. Could this lead to a large decrease in public appreciation of synthetic biology or genetic engineering in general? Will the introduction of the term "synthetic biology" in fact cause a public backlash on this technology?

Perhaps different questions should be considered. For example, should we wonder what can be done to prevent this public backlash from occurring? But maybe the questions should be on a different level: is the public interested in this field of science? Should the public know more about the scientific background of this technology? To what extent should the public be involved in scientific development? These ethical/social questions are becoming more relevant when biotechnology (or synthetic biology) applications are going to represent a larger part of our everyday life. Currently, one may argue that in most products we use, in some way or another, biotechnology is already used, people just don't know about it. With the decrease in oil supplies and the introduction of biofuels, bioplastics, agro biotechnology, gene therapy etc., a larger part of the things we take for granted will become biotechnology based: from fossil fuel based economy to biobased economy[36]. It is up for discussion whether this is in all cases a good development.

3.7 From contradiction in terminis to oxymoron: the hype or promise of synthetic biology?

The question that arises from the previous paragraph is whether synthetic biology applications can really live up to their promises in terms of benefits (financial and in application). In other words: the seemingly mistake of the contradiction in terminis of the term "synthetic biology" may really become the deliberate use of the oxymoron "synthetic biology". Is it just another hype (like in the past e.g. Y2H systems, DNA microarrays, systems biology), or can scientists really accomplish something with synthetic biology, and than in particular some applications that everyone is happy with and see the advantages of? To achieve this, there are two kinds of challenges:

- A scientific challenge: can we come up with synthetic "living" systems that do not pose biosecurity and biosafety risks? This may be impossible, but the possibilities and advantages of synthetic biology are numerous.
- A social/ethical challenge: can we make synthetic biology applications appreciated by all direct and indirect stakeholders in the discussion on genetic engineering and related topics? Artificial life and intellectual property issues need to be considered, but also general genetic engineering related ethical issues.

The engineering approach of synthetic biology (biological engineering in stead of only metabolic engineering) may give rise to numerous applications. It comprises a big technological field that will probably involve the whole world. This also means that a thorough discussion on ethical issues, regulation and control is necessary to determine the boundary conditions, in both a social and a legal perspective[37]. Still, whether synthetic biology will prove to be a hype with only loose promises, only the future will tell.

[35] Can we create life?, Vivienne Parry, The Observer, 27 April 2008, http://www.guardian.co.uk/science/2008/apr/27/infectiousdiseases.stemcells, accessed 25 July 2008
[36] See e.g. the EuropaBio website on the future of biotechnology: http://www.europabio.org/biotech_future.htm
[37] As also proposed by Jim Thomas (Research Programme Manager / Writer of the ETC group), in an expert interview at the Synthetic Biology 3.0 Conference in Zurich, June 2007 - http://www.synbiosafe.eu/index.php?page=expert-interviews

3.8 Intellectual property rights: usefulness or commercialization?

Besides the implications of synthetic biology, the terminology and the scientific advantages and disadvantages, another issue needs to be considered in the field of synthetic biology from an engineering point of view. As synthetic biology applications begin to emerge, the applications are also starting to be patented[38]. In our society, scientific research on patented applications is possible without licences, which means in practice that all patented ideas can be researched without financial consequences. Licence fees have to be paid, however, when an investigated application is subsequently commercialized. This has some practical limitations for synthetic biology research: some ideas may already have been patented, without the application being demonstrated to work properly in the lab. This also means that any combination of BioBricks (a "device") can also be patented (of course under the patent requirements that apply), which makes commercialization of certain applications impossible.
One can wonder whether the constructing side of synthetic biology with increasing levels of artificialness is then only meant to be useful and to prove principles in biology, or whether actual applications can also be commercialized without being limited by patent registrations. But besides intellectual property considerations of open source technology, also more specific concerns regarding the iGEM competition can be considered. These will be discussed in the next paragraph.

3.9 iGEM, open source technology and the intellectual property: impossible or naïve?

Within the iGEM competition, the idea is that BioBricks are added to a database in a completely open source setting. Everyone can use these BioBricks to make a certain application. However, in this approach, there are several things that have to be considered:

- **Open source and the role of capitalism in science.** Perhaps ideally, all academic science would be open source; financing for universities comes from a central (national) government, all scientific findings are published and progress is made because everyone has access to the latest scientific developments. Unfortunately, this is currently not the case. Universities have agreements with companies, companies finance research carried out at universities and commercial interests need to be considered. A consequence is that research in an academic environment is not completely open or publicly available anymore. On one hand, it is convenient for universities to have some extra money to spend, but on the other hand it is not an ideal situation for open source research: some research cannot be published or only partially. This means that scientific knowledge lingers in company file cabinets, partly perhaps due to possible commercial losses or gain.
- **Developing real cash cows?** Within this capitalist environment, one can also imagine that developing applications that could really yield a lot of money in the commercial sector, are not made publicly available. It would probably be considered quite obtuse of the inventor of a certain application to not patent it. Of course, the data can still be made publicly available, but one can wonder then what is the point in publishing your secret, with which you could make a lot of money. It may therefore also seem unrealistic for constructive open source synthetic biology (iGEM) to expect really valuable inventions to be deposited in public DNA databanks like the BioBrick database.
- **Academic interests.** Another issue to consider in this respect is the interest of companies that sponsor academic research institutes and the interest of the academic institute itself. Imagine a potentially profitable application being developed by an iGEM team, which deposits its findings in the database. Would the board of the university be happy with this iGEM team or its supervisors or supervising professor? Probably not, since loads of money could have been generated from this certain project, to the benefit of the entire university. Moreover, would it be in the interest of renowned professors to contribute to this particular iGEM project that could have generated a lot of money? Probably not, the professor may even be sacked by the university, for blunt ignorance.
- **Company interests.** Besides the issue described above, also company interests may count here. Supervisors of iGEM student teams are sometimes not allowed to talk about different subjects, because they have agreements with companies that sponsor their research. One agreement may be that the academic institution can do research on a topic as sponsored by this certain company, under the condition that the academics do not contribute or work on other projects related to this sponsored topic. This may not be desirable for the progress of technology or contribution to open

[38] The ethical value of Justice is probably the origin of this ethical consideration on intellectual property rights and patents.

source science, but it is the case in everyday scientific practice. In fact, lots of money (and/or other company interests) may be at stake.

- **Bioterrorism?** The last issue related to open source technology that will be mentioned in this report has to do with bioterrorism. For obvious reasons, open source technology is connected to dual use issues and (deliberate) misuse or bioterrorism.

From the issues described above, one may begin to doubt whether the open source approach of the iGEM competition is actually as useful as is sometimes proposed[39]. It may in fact even be naïve to believe in the success of this approach. Still, from a different point of view, the benefits of the BioBrick database may also be recognized, as presented in the introduction of this report. Having discussed al the above, one topic remains to be described, the risks associated with synthetic biology. This topic will be discussed in the next paragraph.

3.10 Prospective: solutions to ethical problems?

By looking at the future of synthetic biology one can identify all considerations presented in this report to play a part in future research and applications, but also in governance, regulation and enforcement issues, where the issues that were mentioned are to be reflected in. Conventions or international agreements may also be considered. Still, technological advancement and governance are somehow related when speculating about the future of biotechnology. When life science activities are tightly regulated and difficult, this will yield a different future than when synthetic biology turns out to have results easily in an unrestricted research environment. This is further specified by Aldrich *et al*[40]. Here, speculations are made on the likelihood of e.g. deliberate misuse, garage biotechnology and open source approaches towards technology, but no conclusive remarks can currently be made.
Hypothesizing about the future of life science technologies, together with scientific advancement, different stakeholders and many conferences and papers on the ethics of technology may together lead the development of synthetic biology applications into a future with fewer concerns[41] on risks related to synthetic biology.
The discussion on the ethics of synthetic biology classifies as a "wicked problem"[42], as proposed by dr. Jeff Conklin[43], director of the CogNexus Institute. He published on shared understanding of wicked problems[44]: this involves problems with many stakeholders, large technical complexity and where no easy solution or expected outcome is available. If this is the case, fragmentation between stakeholders occurs, resulting in different parties with different opposing opinions, which is not a good development for coming together and deliberating on a certain topic in order to achieve social and technological advancement. Defragmenting activities to prevent this from occurring involve deliberations like conventions and reports on ethical considerations, like currently the SynBioSafe program[45] and Synthetic Biology X.0[46] conferences.

3.11 Summary

Synthetic biology comes with a number of issues in terms of risks and ethics. But first, which research falls under the "synthetic biology banner" remains unclear. In this report it will be used as a term that encompasses constructing and deconstructing biological processes of life, in different gradations of naturalness or artificialness. This extreme form of genetic engineering can also give extreme control over certain (unicellular) organisms. The modern technology used in an open source setting in the iGEM project poses additional questions, e.g.: how synthetic can biology be; which implicit assumptions do we make in participating in iGEM, which ethical considerations play a role; how do iGEM and intellectual property relate; how is synthetic biology presented in the media, is it just another hype? No decisive answers were given in this chapter, just some major considerations. The next chapter investigates the participant's opinions on the issues that were mentioned in this chapter. Also the design process in iGEM is investigated.

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[39] See e.g. the epilogue of this report
[40] Scenarios for the future of synthetic biology, Aldrich Newcomb Carlson, Industrial Biotechnology, Spring 2008, V4 N1 39-49
[41] See also e.g. a bet posed by Martin Rees (author of the book "Our Final Century" about the end of existence of our society) on the Long Bets website (http://www.longbets.org/9), stating that "By 2020, bioterror or bioerror will lead to one million casualties in a single event".
[42] A term first used by Rittel and Webber: "Dilemmas in a General Theory of Planning", Horst Rittel and Melvin Webber, Policy Sciences Vol. 4, Elsevier Scientific Publishing Company Inc., Amsterdam, 1973, p. 155-169
[43] CogNexus Institute offers tools and skills for groups dealing with complex and ill-structured situations. The Institute's mission is creating organizational coherence in the service of world peace and healing. It specializes in teaching the Dialogue Mapping technique, facilitation and consulting using Dialogue Mapping, and research on collaborative technologies for complex problem solving and design situations.
[44] Dialogue mapping: building shared understanding of wicked problems, Jeff Conklin, 2006, Wiley & Sons Ltd., England
[45] See http://www.synbiosafe.eu/ for more information
[46] See for the 3.0 conference in Zurich: http://www.syntheticbiology3.ethz.ch/

4 Ethical considerations in synthetic biology on a micro level – choices in design

In the previous chapter general ethical considerations regarding synthetic biology were described. It was demonstrated that when practicing synthetic biology science, several implicit assumptions are made. Ideas on naturalness or artificialness in relation to appreciating genetic engineering, specifically transgenetics, are easily adopted. Also topics related to intellectual property rights, biosafety and biosecurity were considered.
In this chapter, the ideas of the TU Delft iGEM team members and supervisors are further investigated. Choices that are made in the design of the process are analyzed along with personal ideas of the individual team members. It will be investigated what the opinion of the participants is with respect to implicit ethics-related assumptions that are made in participating in the iGEM project, and what this further implies for the design process of the entire group, both students and instructors. It will further be demonstrated in which design steps, major ethical decisions are made.

4.1 The design process

Two of the four eventual supervisors of the group picked up the idea of participating to iGEM. Six students had applied to iGEM by May 2008, with different backgrounds, as described in the Methods section. During one of the first meetings (see TU Delft iGEM wiki webpage) the requirements for choosing a project were made in a brainstorming session. *Figure 4.1* below depicts a part of this brainstorming session.

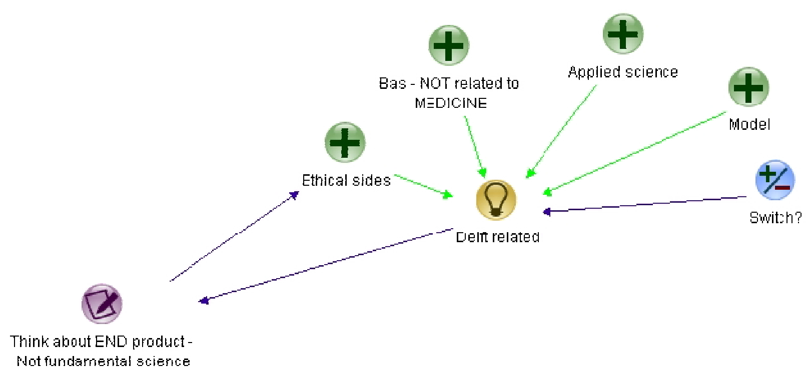

Figure 4.1: Requirements as assessed in the first brainstorming session of the iGEM team. Being from the applied science faculties of the TU Delft, the team members figured that in designing an application, the end product should be kept in mind. Also, ethical issues should be assessed and it should be able to be modeled. Some team members had additional specific wishes, like building a switch-like application or not having to with medical applications.

As can be seen in the figure above, some requirements of the Delft team were made. Being TU Delft related, the application that was to be developed should be an application that can actually be used on its own (a real application) and can be modelled. Also, ethical considerations should play a role in design of the application. Specific team member requirements were also made, e.g. that it should contain a biological switching element and that it should not relate to medical research or applications.
During following brainstorming session, the possibilities were further investigated. In this brainstorming, several applications were mentioned. During this session, also several interested researchers of the Kluyver Laboratory were present.

Figure 4.2: Brainstorming session in which the possible applications are first mentioned. The applications involve several fields of application. Several remarks for additional requirements were also suggested, having to do with general appeal of the application to be chosen.

The figure above shows the outcome of the application brainstorming session. Of these options, six main topics to be investigated further were chosen. These choices were purely on technical feasibility, not on further social/ethical considerations. The list is given below:

- Light emitting lactic acid bacteria for use in dog food to easily detect dog poo
- Magnetic bacteria or moving bacteria based on magnetism
- Sticky bacteria or bacterial glue
- Colorant production
- Temperature sensing
- Flavourings or smelly bacteria

These topics were investigated on technical feasibility by the team members and discussed in a following brainstorming session of the group. It turns out to be technically difficult to make magnetic or sticky bacteria. The light emitting lactic acid bacteria are also hard to produce, but besides, some team members expressed ethical concerns in producing genetically modified dog food afterwards, even though it had already been ruled out as an application, based on technical possibilities.
The colorant production, flavour components and temperature sensing applications were not ruled out on technical feasibility, and soon the collaborative idea originated to combine the input and output in a thermometer with a visible output, being visible colour. This idea was further investigated and resulted, via practical decisions on technical feasibility of the team members with a background in biotechnology. The technical methods and results of the used design strategy can be found on the TU Delft 2008 wiki web page.

4.2 Value sensitive design

After the brainstorming session where the team identifies the topics of interest for the first time, a meeting was organized by Ibo van de Poel of the TU Delft department of Philosophy. The central theme of this meeting was 'value sensitive design'. In this session, the team members came up with moral values which they think are important to consider in a bio based product design. See the table below.

Table 4.1: minimal and additional moral values to play a role in the TU Delft 2008 iGEM project

Minimal moral values	Additional values
Safety (for production, users, environment)	Transparency for users
Security (controllable, intentional harm)	Simplicity
Transparency for designers (process & product)	Contribution to society (short and long term)
Useful (early and later stage distinction)	

The table shows a list of minimal moral values and some additional values that might be taken into account. The minimal values include safety, security, transparency and usefulness. Different things are concerned with safety: safe production and development methods, safe use for end users, but also no negative effects on the environment. Security means that the application can be controlled in technical functionality (perhaps partly overlapping with security for users) and that the possibilities for intentional harm with the application are minimized. Transparency implies that all research data is made public, so designers (but later perhaps also users) are able to learn exactly what the application is, how it is built, what the expectations are, etc. Usefulness of the application can be divided into early and late stages of development. The early stages of development do usually not concern the usefulness of the application, since the functionality first has to be demonstrated properly. After this phase, the usefulness of the eventual application can receive more attention. Additional values include transparency also for users, simplicity in design and in use, and also, if possible, a contribution to society. What this contribution is or may be, is up for deliberation.
But how do these values come back in the eventual product design? In the questionnaire that was carried out, the opinions of the participants on this matter are investigated. The results are given in *Chapter 4.4.5*. One can imagine that at some point, these values may conflict. For example, security as controllability may make design more difficult, so simplicity cannot be guaranteed anymore. In an extreme case, usefulness and safety for the environment may conflict: unforeseen effects on e.g. natural diversity may appear when the application has to be used in an unprotected atmosphere (outside the laboratory, e.g. in nature). The challenge for the designers is to find the right balance of these values, within their responsibility. Where this responsibility lies, is also a subject investigated in the questionnaire, see *Chapter 4.4.9*.

4.3 Ethical decisions in design

From the previous paragraph it can be deduced that for coming to a practical design of a certain application, mainly decisions are made mainly based on technical feasibility. But in the eventual design of the thermometer, also ethical choices are made. Some major choices are indicated below.

The RNA secondary structure based temperature sensitive sequence[47]: the developed sequences are based on known RNA structures from different organisms, some of which pathogenic; others were based on theoretical models without any affinity to sequences that can be found in nature[48]. The group eventually decided that all sequences could be tested, hence all structures were ordered from a DNA sequence manufacturing company. Questions that could be raised here:

- Why not use only known sequences?
- Why not use sequences only from non-pathogenic organisms?
- Why use synthesized DNA rather than natural DNA for the non-pathogenic organisms?
- How 'normal' is it to simply order DNA from a company that manufactures any sequence you like?

The colour pathway output[49]: the developed BioBricks were put together from genes from different micro-organisms and different existing BioBricks. The existing BioBricks also contain genes from different bacterial species, but the pathway is based on colour pathways that can be observed in plants, e.g. in the flowers. All used organisms in this pathway are known to be non-pathogenic. Also, in this case, no DNA was ordered, only genes were taken from the source organisms using PCR techniques[50]. Still some questions could be raised:

- Why use a colour pathway based on plant pathways and not on e.g. bacterial colourants?
- Can or may one so easily construct a pathway using genes from several different organisms?

Some would say it is not the idea of iGEM participation to consider these ethical issues. However, certain ethical decisions are made, explicitly or implicitly, in participating in iGEM. Some of these implicit assumptions were already indicated in the previous chapter. But to what extent do the participants realize this and how are they using their own moral standards within this competition? To answer this question, a questionnaire was held with the participants of the group. To do this, first an ethical framework had to be built, based on the literature survey on ethical issues as shown in the previous chapter. The framework is depicted in *Figure 4.3*.

The framework shows that upon participating in iGEM, several different ethical considerations play a role. The consequences of participation imply using certain technologies. Consequential ethics play a role here and ideas of the participants towards open source technology and novel technology are to be investigated. The ideas on values of life and naturalness play a role more in the background, but are still present, as was illustrated in the previous chapter: implicit assumptions are made in synthetic biology. These values of life are used here as the more deontological ethical side of synthetic biology. The science and values come together in iGEM, a novel, open source approach of synthetic biology.

The questions asked in the survey investigating a team member's opinions can be found in *Appendix B*. The ethical road map as presented in *Figure 4.3* forms the basis of this questionnaire, of which the setup is given in *Figure 4.4*. First, general questions on participating in iGEM are asked to the team members. Secondly, the project goals as determined in the iGEM project proposal (*Appendix A*) are reviewed. The third question should illustrate what the participants think synthetic biology means, after which the science in synthetic biology is further discussed. The fourth question regards open source technology, specifically in the iGEM setting. The fifth item to be discussed is the value sensitive design, as discussed in *Chapter 4.2*. The risks and ethical issues in synthetic biology are further investigated and summarized in the sixth question. The seventh question regards naturalness or artificialness in synthetic biology and to what extent the participants think genetic engineering is allowed within the project. The eighth subject to be investigated is about misuse in synthetic biology, either deliberate or unintentional, and more specifically on misuse of the application developed by this university. The ninth question should illustrate what the participant think his/her responsibilities are towards science and society and which role they can play in science communication. The tenth and last question reviews the survey and further investigates the participant's role in the design process.

[47] See methods section for more information on this topic.
[48] Or at least up to now have not been discovered in any living organism.
[49] See methods section for more information on this topic.
[50] See methods section for more information on this topic.

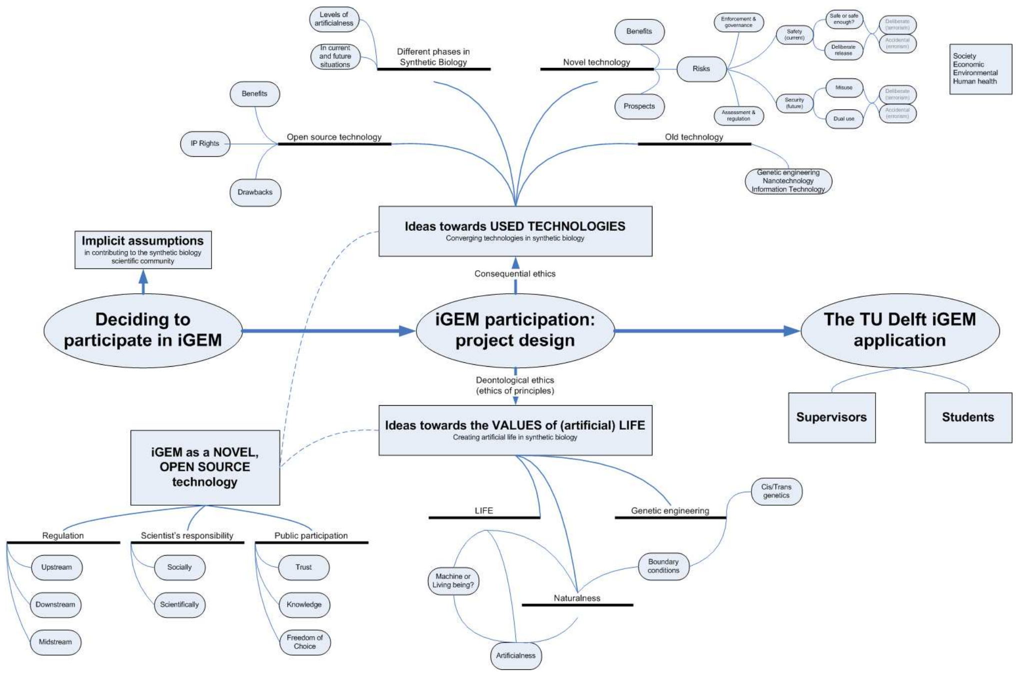

Figure 4.3: this image shows that participating in iGEM has several stages. One has to decide to participate, then the project is designed and an application is developed. In the design process, deontological ethics and consequential ethics play a role, converging in iGEM as a novel, open source technology. In all phases, decisions are made, implicitly and explicitly. Participants have ideas on all these topics, the challenge is to get these out of them, and subsequently finding out how much value they attribute to the different issues.

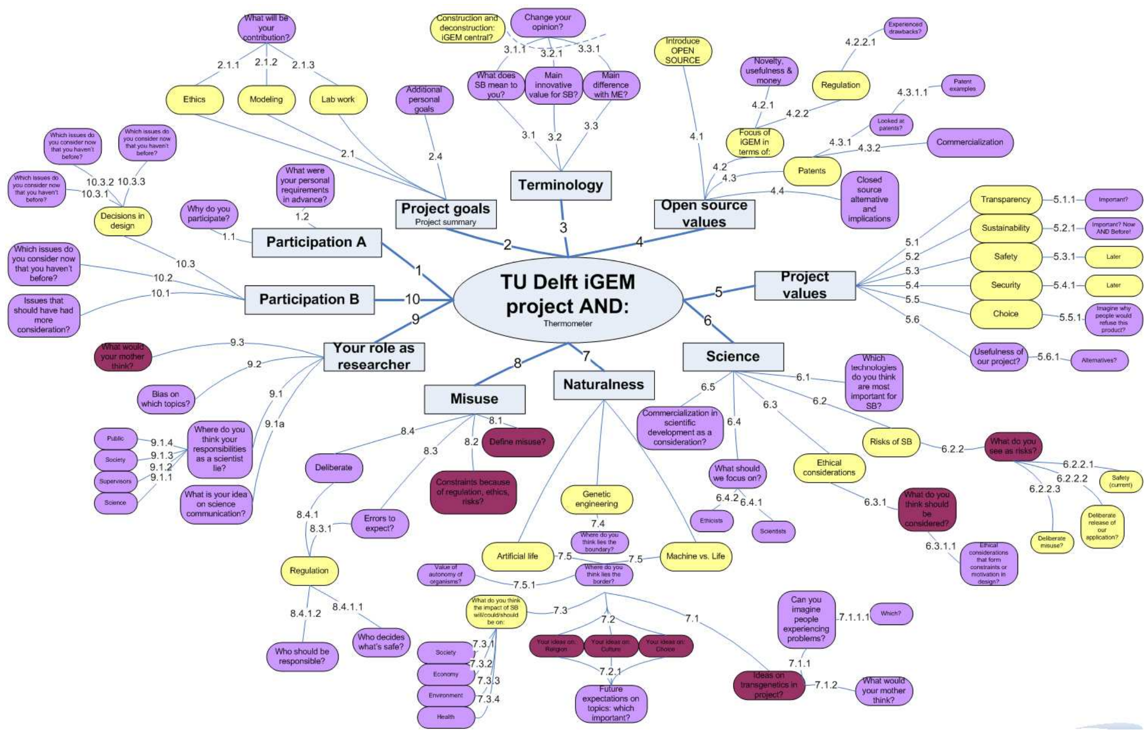

Figure 4.4: the overview shows the questionnaire set-up. 1: general questions about participation are asked. 2: questions related to the project goals as defined in the project proposal (see introduction). 3: questions relating to what synthetic biology means to the participants. 4: investigation of ideas around open source science approaches. 5: the project value sensitive design related issues. 6: risks and ethics in science. 7: issues regarding naturalness of genetic engineering in synthetic biology. 8: questions around misuse of the project. 9: questions about the participant's responsibilities. 10: concluding remarks and the participant's role in design.

4.4 Survey outcome

The results of a typical questionnaire, for which the setup was explained in the previous paragraph, can be found for one person in *Appendix C*. For reasons of anonymity, not all interviews will be included completely in this report. Because the subject group is relatively small (9 persons), no statistical data can be derived from the group. However, interesting topics can be recognized from these interviews. A short review per question will follow in this paragraph. General remarks on the team members' recognized ethical considerations will be illustrated with quotes where suitable.

4.4.1 Question 1 – Participation

The students and supervisors give similar reasons to participate. All team members find synthetic biology an interesting research field with lots of opportunities. Especially the conceptualization and standardization are mentioned as being the most interesting parts in synthetic biology. The participants like the idea of building up biological machinery from scratch. However, the supervisors' reasons for participation are fully interest based (interest in the research itself and in the iGEM approach), while the students give an additional more personal reason for participation: getting credits. This may of course be expected, yet still: it is a different reason than the supervisors give as a decision to participate, and this may have some implications. The obligatory part of participation for students may for example result in less motivation for the project or less optimism or expectations on the result, because one gets credit anyway. On the other hand, for the supervisors there is also nothing at stake.

4.4.2 Question 2 – Project goals contribution

The supervisors and students have several different backgrounds. The project goals, as defined in the introduction of this report, concern laboratory achievements, modelling achievements and ethical considerations. The participants with a background in biotechnology expect to contribute mainly in the lab, the people with a different background expect to contribute mainly to the modelling part. All participants did not see at first what their contribution to the ethics part in iGEM could be, besides participating in the questionnaire. The goal of the questionnaire was to make the participants aware of the ethical issues that play in synthetic biology and to investigate their opinion. After the questionnaire, all team members indicated to have heard at least some issues they hadn't considered or even heard of before. In that sense, the goals of the questionnaire related to creating awareness are achieved.

The biotechnologists did not mention any other, more personal things they wanted to achieve, while the participants with a different background hoped to learn about the biological backgrounds in synthetic biology. One might expect that the biotechnologists would want to learn more about the modelling, like the modelling members would like to learn about biotechnology, but this was not mentioned as an achievement that the biotechnologists wish for.

4.4.3 Question 3 – Synthetic biology terminology

The third question of the questionnaire focuses on the terminology of the synthetic biology concept. When asked what synthetic biology, purely in a scientific way, means to the participants, they all answer that it relates to building with biology, synthetic biology in a constructing sense. In a sense, that is what is to be expected, since they are all participating in the iGEM competition, which is about building cells with BioBricks. All participants seem to have far less attention for the deconstructing part of synthetic biology, relating to building e.g. minimal cells or understanding cellular fundamental processes. Some participants brought up the idea that the deconstructing part automatically follows the constructing part, in a sense that when building, one also learns about the biological systems that are involved.

4.4.4 Question 4 – Open source in iGEM

With the goals and terminology in synthetic biology made clear in the previous question, the fourth question of the survey asks the participants their opinion on the use of an open source setting in synthetic biology. The following relations were brought up:

- Open source and technological novelty
- Open source and usefulness of developed applications
- Open source and commercialization
- Open source and patents in iGEM
- Turning lead into gold and participating in iGEM

The first thing to notice after the questionnaires is that the participant's opinions really differ on these topics. When asked what the relation is between the open source approach of biology in iGEM and the technological novelty, or innovation, of the discoveries that are made in research, the participants all agree that open source stimulates innovation. When sharing information, people all around the world can look at your data and look at it from a different perspective and come up with something additional or new.
Yet when asked what the relation then is between open source and the usefulness of the newly developed applications, the opinions start to differ. Some state that in the open source setting, the different perspectives of the people that look at a certain BioBrick can result in a large number of creative applications, and in that sense technological novelty in open source stimulates usefulness and development of new applications. However, other participants do not agree and state that when something really useful is developed, the inventors will not publish their data in an open source database and will patent their application. Hence, no really innovative or useful applications will result from iGEM.
Again some others think that innovation and usefulness in an open source environment will not stand in each other's way. Inventions can be patented and the biological background can be published in an open source database. This way, the knowledge is available, while the application is protected.
The answer the participants give on the question relating to usefulness of inventions greatly influences their opinion on the relation between open source and commercialization. The team members stating that no useful applications will follow from iGEM generally think that open source and commercialization of products are hard to combine, because of e.g. patent regulations and protection of property. The participants stating that usefulness is increased by open source generally state that commercialization is possible and perhaps even stimulated in an open source setting.
The relation between patents and open source within the iGEM competition is also a topic on which the team members have very different opinions. A device made with different BioBricks can be patented (from a legal point of view), with the data on the biological background also being published in the open source database. As an example, there are patents in the area of application the TU Delft team is working on[51]. See *Table 4.2* below for an example of different answers of participants.

Table 4.2: answers of two different participants to the question whether patents should be considered in the iGEM project. Participant A had never even considered patents, Participant B would look for a compromise between open source and patents, Participant C has given it some thought, but feels it's not the team's responsibility.

Participant A	Participant B	Participant C
A. What do you mean? **Q.** Do they relate to our project? **A.** Yes. **Q.** Then should consider them? **A.** What do you mean? **Q.** Do they give any restrictions on the work we are doing, these patents? **A.** I'm not sure, but I think maybe they do. **Q.** And how, then? **A.** Do we use something that is previously mentioned? I don't know…	**A.** Difficult… I think looking at iGEM, letting BioBricks be completely free, but applications patentable, would be a perfect compromise. A certain degree of open source, but still be able to file a patent.	**A.** On one hand, maybe we should, but well… I don't think iGEM encourages you to look at patents. By the way, that is no excuse to not look at it yourself, but anyway: there is no encouragement. If this application turns out to be patented already, maybe it is wrong to publish it open source. On the other hand: this should be checked by the iGEM competition organizers, or it should be mentioned what their position is on this matter. But that, I don't know.

Table 4.2 shows the different approaches the different participants of the TU Delft team have. Some think that in an open source setting, no patents can be granted. Others don't think patents are related to open source, because no really useful or commercializable products are developed anyway. Others state that "in the spirit of iGEM", patents are not to be considered, because the goal of iGEM is to participate in a

[51] For the TU Delft 2008 iGEM team application related patents, see e.g. patent publication numbers CA2550133 (16 August 2007), US2008171378 (17 July 2007).

scientific project, not in a project resulting in something that is to be commercialized. Others had not considered patents at all or do not know what they really mean. The question then is, whether patents and, highly related, the commercialization of products are to be considered within the project. Some state that patents are important to consider in research, others state it is too early to start thinking about patents. Some state that commercialization in an early phase of development is to be considered in design; others state it is too early for that. Within the iGEM project, taking into account commercialization and patents is not a prerequisite.

Still, when thinking about commercialization and patents, it may be interesting to see what the relation between open source and the (practical) usefulness of the developed applications is. The opinions of the TU Delft team members can be very different, as is indicated in *Table 4.3* below.

Table 4.3: Answers of two different participants to the question whether open source synthetic biology would result in more useful applications or more fundamental scientific knowledge. Two different approaches yield two different outcomes: participant A thinks more fundamental knowledge will be generated, participant B thinks more useful products will be developed.

Participant A

A. Usefulness, translated to industrial product that are really used… I think that the industry has a sort of steering factor in that, doing research into what they think is really interesting, and financing that research. That can steer research in a certain direction, so you expect that that delivers more useful results. In an open source environment there is less pressure into that direction, so less pressure for applications.

Participant B

A. I think that open source would generate more useful products.

Q. Why?

A. Well, difficult… Fundamental knowledge is a little more difficult… In open source, people can look at discoveries from many different perspectives. Different people can have different ideas. I think that can be very inspiring, and if people share their new findings, that can generate many useful products.

The table above shows that participants have very different opinions. Two general lines of thought are observed. The first (as indicated by Participant A) gives research pressure a central role, stating less pressure in open source generates less pressure for useful applications. The second gives the transparency of research in open source the central role, stating that one person is never as smart as all the rest, and that different viewpoints can result in many useful applications.

But what if the developed application could be so successful (from a commercial point of view), that enormous amount of money could be made. *Chapter 3.9* also reviewed the role of real "cash cows" in open source science. On this topic, the participants also have very different opinions. Would the team still be able to participate in iGEM? See *Table 4.4* below.

Table 4.4: Answer of three different participants to the question whether or not the TU Delft team should still participate if an application was discovered that could metaphorically turn lead into gold. Participant A states that the science is most important not making money, participant B isn't sure, participant C thinks that the team should not submit it to iGEM and go for personal gain.

Participant A

A. If this does not give you neither better or fundamental understanding of biology, neither does it give any useful application, I don't really think it is a useful application that you mention. Besides being able to make money out of it.

Q. Enormous amounts of money…

A. One of the things of iGEM is this idea of progressing of science, of international effort. If you just submit your BioBrick it would be ok to participate.

Q. Do you think the TU Delft board would be happy with us participating in iGEM, with an application that could generate enormous amounts of money for the TU?

A. I don't think they would be very happy, I expect. Now I understand what you mean. You have a nice application and in a way you have the choice to submit it to iGEM and let it free or you can patent it and get money out of it…

Q. So where would the border be for you then?

A. In my case, I would just go for the open source. With these things it would just be something that would be patented; I think I would lose my main drive and just drop it.

Q. So the fundamental science and the usefulness are really a drive for you?

A. In our application, it is not a problem that we are doing only fundamental science, but the whole idea is doing it in a transparent way, in an open source framework. You saw in the beginning, when brainstorming, […] said that if the application relates to biofuels, he could not help, the same said […]. They have that constraint, I would not like to have it for myself.

Participant B

A. The point with this example is that it has great influence on the world. I don't think… Eh, within iGEM, you successively develop something. At first, it is quite idealistic, and at a certain moment you find out that perhaps you can do something with it. What you would do with it then, submit it or keep it for yourself, I can't really say at the moment.

Participant C

A. To be honest, I would tend to *not* submit it to iGEM. That wouldn't be very smart. I think I would be crazy to submit a great finding that I did, as open source in iGEM.

The table shows that participants have different opinions on participating if a product is developed that could generate large amounts of money, with different moral approaches. One team member thinks the science is most important, and would still participate. Another states that the team should not participate anymore and go for personal gain. The third participant isn't sure.

4.4.5 Question 5 – Value sensitive design

In the fifth question of the questionnaire, the value sensitive design session (see *Chapter 4.2*) played a central role. In this session, the values of transparency, usefulness, security and safety came forward was minimal moral values to consider in design. But to what extent do these values really come back in the project? Which values do the team members think are important? Regarding transparency, all participants think this is important to consider. Of course, participating in iGEM implies that the teams are 100% transparent on what they do, by publications on a website. But regarding the other values that were considered important, different participants have different opinions. For example, relating to usefulness of the application: see *Table 4.5*.

Table 4.5: Answer to the question how important the participants think the value "usefulness" really is. Participant A feels generating knowledge is more important than making a useful application. Participants B and C think that more focus on usefulness should have played a more important role.

Participant A

A. Do you mean of the final product or of the knowledge we gain?
Q. The end product.
A. The usefulness of the product, I don't think that is very important.
Q. Should it have been more important?
A. No, we are currently in too early a stage, we are learning rather than producing.
Q. So that means generating knowledge?
A. Yes, we do this purely to gain knowledge, that's my opinion

Participant B

A. Right now, because little work has been done, usefulness has been down rated. Usefulness should have more importance in design. Try to figure out in which areas the temperature sensor on nano scale can be useful.

Participant C

A. I think we should think about this more. For example, which applications can be thought of? It's nice to make a thermometer, but what can we really do with it? Which realistic things can be achieved? Currently, it's not very clear what we can do with it. That is important for the iGEM contest. But…
Q. At this moment there is too little a focus on the applications?
A. Yes, I think that we don't think about that enough.

The table above shows that some participants think it is important to consider the application and the usefulness on the application, even in early stages of design. Others think that the group should focus on the knowledge (science) related to the application, and consider usefulness of the application later. Yet still, applications are not something that is considered into much detail or with very much attention in early stages of design, i.e. before testing functionality of the application.

Table 4.6: Questions and answers related to sustainability and safety. Both values are expected to play a more important role, while this is currently not the case.

Participant A – Sustainability

Q. You say sustainability is very important, but how does it come back in the application?
A. In our case? I find it difficult to relate it to sustainability. When I gave the score, it was in general, not specifically about our application. In our case, well, I would have a hard time to think about sustainability. Of course you don't want something that is harmful for the environment, but we don't have a very large scale application in mind. We want to measure temperature, but yes, we don't have a specific application in mind. That would allow thinking about sustainability.
Q. You think it should, in our case, become a more important subject to consider?
A. I think it would become an issue once you start thinking about not just specific applications or design, but what application field you are considering. So you want to use it for water treatment or for energy production whatever, than it becomes a question about sustainability.
Q. And at this time?
A. I don't think at this time we could include sustainability in design.

Participant B – Safety

You said safety is important to consider, but to what extent does it come back in design?
A. If we comply with the current legislation, we have no problem or threats that are not already addressed. We have to strictly comply with the regulation, but I don't think we need any additional concerns. What we are going to realize is a temperature sensitive, we are not building anthrax or HIV virus…
Q. What about deliberate release into the environment, if the application needs that?
A. It depends where the application ends up. If it has to spread on the ground, or long term goal, insert into people, these applications need thinking about safety release.
Q. Is safety taken into account enough?
A. I don't think that at the moment this has been done. Safety in terms of thinking of where this sensor will end up.
Q. So that should be done?
A. Yep

Than the value of sustainability: almost instantly the participants state that they think sustainability is a very important value to consider. However, when asked what exactly is sustainable about the developed application, the participants have to conclude that sustainability is not very relevant. The biothermometer is not considered to be a highly sustainable development, while sustainability was a key value to consider in design. Also see *Table 4.6* (participant A) for a reason why sustainability should not be included in the project at this moment. Still, none of the participants commented that the application may contribute to sustainable applications in the future. In that sense, the innovative value of the biothermometer is a sustainable component.
Safety and security were also components to consider in design. These values come back in Question 6 (next section) on the scientific risks and further ethical considerations within iGEM. Most participants feel that safety and security are important to consider, but how this is currently happening, the participants also don't know, like was the case for sustainability. When asked how the application could be made safer for the environment or more secure in use or for misuse, the participants don't really have an answer ready. They do think it is something to consider in e.g. a dedicated meeting. The participants also feel that it may be too early to consider these issues now, because no functional apparatus has been developed yet. Also see *Table 4.6* (participant B) for a line of thought that indicates the importance of taking these values into account, but that this should be done in a later stage.

Summarizing: the value sensitive design session did not really result in a value sensitive design in the sense that the indicated values come back in the eventual application. The participants do think these values are important to consider, but not in this early a stage in development. When applications can become more realistic to achieve, it is the right moment to consider the values of sustainability, safety and security. Apparently there is a difference between the phase of conceptual design and the implementation phase. The team members recognize that the values are placed in the back in this project. It seems very easy to just forget about them and start doing more fundamental science. Also, in developing the application, perhaps new values to consider may arise. This is an issue that has not been considered in this questionnaire.

4.4.6 Question 6 – Ethical risk evaluation

In a way, ethical concerns can be considered as risks, and taking risks into account can be an ethical consideration. In the sixth question of the survey it was investigated where the participants see risks or have (ethical) concerns in synthetic biology in general or in participating in the iGEM project specifically. Ethical considerations in synthetic biology were given in *Chapter 3.4*. They relate to biosafety and biosecurity, naturalness and artificial life, and intellectual property issues. So which thoughts do participants of the TU Delft iGEM team have in terms of risks and in terms of ethical considerations? In *Table 4.7* some the thoughts on risks are indicated.

Table 4.7: Answers to the question which scientific risks the participants see in the iGEM project. Particpant A, who doesn't have a background in biotechnology, looks at risks in the scientific outcome of the project. Participant B, who does have a background in biotechnology, also involves societal effects and recognizes the danger in genetic engineering in general.

Participant A	Participant B
A. A risk may for example be that our predictions on how the final product will work or evolve are not accurate enough. **Q.** What may then be the consequences? **A.** If it is used, for example, by people, it could have bad effects or unwanted effects. **Q.** Which effects? Could be anything… **A.** I don't think of anything special…	**A.** I think the biosecurity issue plays a role: others may use it later. Or perhaps a certain combination of genes doesn't work the way you expected. It only has to happen once, and that's the dangerous side… On one hand you might say: the odds are not so big, but on the other hand, if something happens…

The table above indicates the difference in approach of synthetic biology that biotechnologists and non-biotechnologists have. The team members without a background in biotechnology relate the risks purely to scientific outcome of the project: that the product doesn't behave in the way it was predicted to do. Participants schooled in biotechnology perceive risks related to societal issues: biosafety and biosecurity are indicated as major risks. One may wonder whether the same may be observed for ethical considerations in iGEM. *Table 4.8* indicates the approaches of different participants.

Table 4.8: Answers to the question which ethical considerations play a prominent role in synthetic biology. Participant A, who doesn't have a background in biotechnology, seems to be unsure of what the ethical considerations are, but does seem to recognize some problems. Participants B, C and D do have a background in biotechnology, but see different ethical considerations that need consideration. Participant B wonders whether genetic engineering should be the solution to every problem. Participant C feels public opinion is important to consider. Participant D doesn't have any particular concerns.

Participant A	Participant B	Participant C	Participant D
A. I think one of the things is that we always ware inventing things. Sometimes maybe we should ask whether we are allowed to change anything we want or not. **Q.** What do you mean by "everything"? **A.** We have something, you're going to engineer that, and then we have another thing. **Q.** What do you mean by "thing"? **A.** Like there's a part of a biological system that we are changing: the structure of a gene to get another one, in such a way that it is useful for us. Maybe we should consider whether we are allowed to do these changes, because it is against the will of other groups, other humans…	**A.** One of the things is naturalness: what is still natural and where does it end? But also the question "what" we are really talking about: for which applications can you use certain genetic modifications or certain genes in other bugs or whatever. For an everyday application like a thermometer, is it really necessary? When people need medication, a lot more seems to be possible…	**A.** Well, perhaps public opinion will turn against you. Perhaps it is not really necessary to change so much in an organism, but well…	**A.** In that respect, I have no particular concerns. I don't find it odd, that you build synthetic DNA and use artificial genes in existing living organisms. I don't see a particular concern in that.

The table above shows that different participants have different opinions. As was the case for risk perception, the participants not schooled in biotechnology approach the question in a more shallow way, and more questions are needed to learn the participant's opinion. Still, without knowing the details, the issue of naturalness is recognized. The participants with a background in biotechnology answer the question more directly, but have different ideas on what the most important in synthetic biology. Some seem to have no concerns whatsoever (other than technological risks, as indicated in *Table 4.7*), others have concerns relating to naturalness or intellectual property rights, sometimes also taking into account also public attitude towards genetic engineering.
The question now is how ethical considerations should play a role in design. Question 5 (*Chapter 4.4.5*) already indicated the importance of some ethical considerations and how these play their part in the project. But what about the role of ethicists in science? *Table 4.9* shows the answer to the question how the participants see ethicists play a role in biological product design.

Table 4.9: Answers to the question on how the participants see ethicists and scientists come together. Participant A feels that scientists have to think about ethical issues by themselves, while Participant B feels they should be stimulated to do so.

Participant A	Participant B
A. A group of scientists work, and from time to time ethicists come knocking on the door, I don't think that's going to work. I would rather see scientists that have been trained themselves to take ethics into account.	**A.** I think scientists should do science and that occasionally, from time to time, you should stimulate them to think about issues and let them draw their own conclusions.

The participants all conclude that ethicists and scientists should work together in some way. Yet the table above shows two opposite opinions two participants seem to have. One states that scientists should be stimulated to take ethics into account by direct stimulus of ethicists. The other states that this "knocking on the door" of ethicists is not the right approach, but feels that scientists should take ethical considerations into account all by themselves. This particular participant did nonetheless recognize that it is hard for scientists to let ethical considerations form direct constraints on their research setup or product design.
One may argue that taking into account ethical considerations or risk assessment in product design, also makes sure that when a real product is developed, it can be commercialized safely. The question that arises then, is whether commercialization should be a goal in itself, or that taking into account these ethical issues or risks is a goal in product design, without it being related to commercialization. The question whether or not commercialization should have a focus in design, was already asked in Question 4 (*Chapter 4.4.4*) in a different context, but is asked again in Question 6. The answers are indicated in *Table 4.10*.

Table 4.10: Answers to the question whether commercialization should be taken into account in design in iGEM. Participant A states that commercialization should be considered in design, but also states that within the iGEM project, commercializing an end product is not a goal. Participant B states that commercialization doesn't always have to be considered, but issues of safety and security should. Participant C states that commercialization should be considered, but also indicates that he/she isn't interested in this goal and also thinks there is a difference between developing an application and commercializing it.

Participant A

A. I think so.
Q. Why?
A. In early phases of design, you already make decisions about e.g. deliberate release into the environment.
Q. Did we focus enough on commercializing our end product?
A. I think so, because this is not really a focus related to iGEM participation. I don't think it is really necessary. The scientific principle is still not proven. For me, it is more a fundamental science project than an applied science project.

Participant B

A. Well, good one… I think it often has a focus in design, especially when designing within a company. Whether or not commercialization should always have a focus: not necessarily I think. It would be good however, to think about other issues like biosafety and biosecurity.

Participant C

A. It should have a focus, yes, but in that sense I am more the kind of scientist that wants to investigate interesting things. But if you have a certain commercial goal in mind, you should think about commercialization. But within iGEM, do we have a commercial goal? We said that we wanted to come op with a certain application, but that was mainly because we are in an applied science university. So we want to produce or measure. We have an application as a goal, not a commercial goal.

The table above indicates different approaches towards commercialization. The answers indicate that the participants are somewhat unsure about whether or not commercialization should be a goal in itself. Implicitly they recognize the difference between general synthetic biology product design and participation in the iGEM project. Within the project, commercialization is not an obligatory goal, and hence it should not have a great focus in design. Still, participants have different approaches. One thinks that in early phases of design you already decide whether or not your product is going to be deliberately released into the environment, and hence when you commercialize this product, this release is to be taken into account. Another participant states that commercialization should perhaps have a focus, but this is not his/her particular interest: the science is. Also it is indicated that making an application is different from commercializing. "Usefulness" and "application" are highly entwined, while "usefulness" and "commercialization" or "application" and "commercialization" are not necessarily related. Another participant indicated that commercialization is not always a goal, but this is no excuse to think about other values like safety and security. Hence: application by value sensitive design and commercialization are not necessarily related.

4.4.7 Question 7 – Naturalness and genetic engineering

The seventh question of the interviews relates to what the participants think is to be allowed or not allowed in genetic engineering. Where do they draw the line? *Table 4.11* shows the different approaches the participants have towards host and source organisms in genetic engineering. Within the project, the host organism is a bacterium. The restrictions the participants feel on the organism that the genes come from, are indicated in the left column, the restrictions the team members have for the host organism (where the genes can go into) are indicated on the right.

Table 4.11: impression of what is allowed or not allowed according to various participants, distilled from interviews. Differentiated between originally biotechnology schooled vs. not originally biotechnology schooled.

	Source organism: which gene into bacteria?	**Host organism: any source genes into which host?**
Participant A	As long as there are no harmful effects.	As long as there are no harmful effects.
Participant B	No constraints.	No useless cruelty.
Participant C	No constraints.	Keep it in the lab. Plants is OK, but not for food.
Participant D	Would not be happy with human genes in bacteria.	Preferably no animals, preferably not even if it can save lives. But if we really have to…
Participant E	No constraints, but no pathogens.	Evaluate case by case.
Participant F	No constraints.	Human cells preferably not.
Participant G	No constraints.	Stick to the law.
Participant H	No constraints.	Somewhere in the animal kingdom, when you can have a bond with an animal.
Participant I	No constraints.	Preferably no animals, but if used for medication, perhaps, as long as it is in a controlled environment.

The table above indicates that for the source organism, the participants do not really have any constraints. Some indicated specifically that they do not want to use genes that have known harmful effects, like would be the case for e.g. pathogenic gene combinations. Only one participant indicated that he/she has a problem with using human genes in research.

The restrictions the team members have for the host organism are actually quite various. No obvious differences in opinion could be observed between people with or without a background in biotechnology or between supervisors and students. Apparently the restrictions are very personal within the group. The participants without a background in biotechnology do, however, needed slightly more time to come up with an answer and sounded a little uncertain, while the participants with a background in biotechnology had their answers ready and were quite certain.
Also, the team members recognize that members of the general public may have constraints on what they think is technologically possible. Religion or environmental concerns are given as reasons for people to reject genetic engineering. On the other hand, all participants indicate that the people in their direct environment (family and friends) do not have particular concerns about genetic modification after the participants inform them of the possibilities and benefits.

4.4.8 Question 8 – Misuse in iGEM

The eighth question of the survey focused on misuse of the developed application. A distinction is made between unintentional misuse (error) and intentional misuse (terror) and the responsibility of the researchers in safety and security issues. The participants were asked where they see chances for errors or terrors in use and development. See *Table 4.12*.

Table 4.12: Answers of participants to questions relating to safety and security. Participants A and B were asked which errors may be expected, and answer in relation to different topics. Participant A (biotechnology schooled) relates errors to the open source character of iGEM, participant B (not schooled in biotechnology) is very application focussed. Participants C and D were asked what can be done to prevent misuse. Participant C thinks the team can actively try to prevent misuse, while participant C feels that this is not the case.

	Participant A	**Participant B**	**Participant C**	**Participant D**
Q.	Where can we expect errors in the project?	Which errors may we expect from the application?	In which way could we prevent misuse?	In terms of security, what should we consider then?
A.	I already see it in the registry. The iGEM website states that for some of the BioBricks we were sent, the documentation says that it may even be a totally different brick, and that this should be checked before use. Because of all the bricks of Lego, it's easy to make errors by working inaccurately.	That it doesn't sense the temperature properly. People may rely on specific results, which could have unforeseen effects for the users.	Well, maybe by looking at the ways in which misuse is possible, and then try to eliminate these possibilities. You will never get it totally safe, but you can make it difficult to misuse.	One thing to consider is whether what we are doing could be used in wrong ways, or have some harmful effect. If you consider them or mention them, you make sure people know about them. […] the most we can do is give information.
Q.				So there's nothing we can design into the part that makes it harmless?
A.				In the project we are doing, I don't think that's the case.

The table above shows that participants have very different attitudes towards safety and security within the project. Typically, non-biotechnology schooled participants relate their answers to the question on where errors and terrors may be encountered, directly to the science of the application, e.g. that the application doesn't work properly. The participants schooled in biotechnology relate their answers not directly to the application: they see errors in the open source setup, mistakes in the work by using e.g. unknown pathogenic combinations of genes.
When asked which terrorist actions could be done with the application the team develops, the terrorist application the participants think of, rely on the temperature sensitive switching ability of the used RNA structure. A temperature sensitive switch could be used to activate any kind of application, all sorts of applications could be imagined by the participants[52]. The colour output is not expected to have any potentially harmless effects. But do the participants think these (un)intentional misuses can be prevented? The table above also shows two opposing answers. Some participants state that the team could actively try to prevent misuse (it is not further specified how this would be possible), other participants state that this is not possible. But is the team also responsible for the safety and security of the application? This question was also asked in the survey, see *Table 4.13*.

[52] Also see question 6 (Chapter 4.4.6) on risks

Table 4.13: Answer of participants to the question who should be responsible for the safety/security of the potential application the team is going to develop. Participant A thinks that the team is. Participant B states that the developers should limit misuse possibilities. Participant C said that besides the team, the biological safety officer of the involved laboratory is. Participant D feels that responsibility ends when someone else starts to use the application.

Participant A	Participant B	Participant C	Participant D
A. We should be. **Q.** No one else? **A.** We are producing it, so we are responsible	**A.** Yes, that's always difficult. It depends on the setting it is used in… You are always responsible yourself for the goals you have in mind, and only partially for what other people are doing with it, in terms of misuse. You should always try to limit the possibility of misuse, of course. But sometimes you just can't help it, it may be used for all kinds of things.	**A.** The team of scientists, and the lab's biological safety officer [BSO, SF]. **Q.** And not an independent governmental organization? **A.** That's intrinsically represented by the BSO. **Q.** Does he/she look at the bug to check it's safe? **A.** He/she's responsible in the role as safety officer.	**A.** In the first place, we are, but afterwards the persons using it.

The table above shows that participants have different opinions on who is to be responsible for the safety of the developed application. Some participants state that the team is always responsible, some say that it is the team's responsibility to develop a safe application in a safe way, but that the user of the developed application is afterwards. Others state that the responsibility lies with the involved laboratory's biological safety officer, and also another stated that the organizers of iGEM should be. But the question of who is responsible for safety of the application is somewhat different than the question who should decide if the developed application is safe. Responsibility for this decision lies with different people, according to the participants. See *Table 4.14*.

Table 4.14: Answer of participants to the question who should decide whether or not the application is safe. Participant A states the team is responsible, participant B states the iGEM organizers are, participant C states the user is responsible.

Participant A	Participant B	Participant C
A. We should. **Q.** So no external organization? **A.** Maybe there's some kind of protocol or standard. We are working with it, so we know whether it's safe or not. It should be safe for ourselves, so it should be safe for everybody.	**A.** I think in this case, the iGEM organizers are responsible. We can't have that responsibility, judging your own application isn't really representative. Because you develop under the iGEM umbrella, they should check whether or not it's safe.	**A.** The one who does something with the application should decide if it's safe. Regarding our own responsibility… We are not graduated yet. A driving instructor is also responsible for his teacher… I don't know to what extent we are to be responsible for safety anyway.

The table shows that participants have different opinions on who should decide the application is safe. Some say that the team itself should be, but others recognize that one would be biased to judge one's own application on safety. Others state that the iGEM organization should be responsible, others don't know. Apparently this is a topic the participants did not really consider before asking the question, since all participants did need some time to think about their answers and seemed somewhat unsure in their response.

4.4.9 Question 9 – The scientist's responsibilities

The ninth question of the questionnaire focuses on the scientist's responsibility as a researcher. The participants were asked what they think their responsibilities are towards science and the scientific community, their supervisors, society and the general public specifically. All participants answer differently to the questions. Very different approaches are observed, but generally, when asked what their ideas are on science communication and their responsibilities in this communication, they answer that for them, science communication is towards the public. This quite open question can be interpreted in multiple ways, to it is interesting to see that the participants all focus on the public specifically. See *Table 4.15* below for different ideas on what these responsibilities may be.

Table 4.15: Answer to the question what the participant's ideas are on science communication and where they have responsibilities in that. Participants below both focus on their responsibility towards the public. Participant A focuses on why you are doing the research, explaining your long term goals. Participant B focuses on gaining trust by explaining what your are doing and making sure that what you do would not harm the public.

Participant A	Participant B
A. You have responsibilities in being sure and clear on the reasons *why* you are doing the research, which long term goals you have. On the other hand, in contributing to the depository of BioBricks, you have to make sure to the public that you are not playing in a competition in a Frankenstein way.	**A.** We have the responsibility to gain the public's trust. That they know *what* we are doing and that they trust that we don't do anything that would damage them. If you have that trust, communication isn't necessary further. You need science communication to gain trust. Of course, you will not win everyone's trust, but still…

Table 4.15 shows that two different participants have a different idea on science communication towards the public. One would say that explaining your goals is most important, while the other states that explaining exactly what you are doing will earn most trust. Implicitly also the first participant recognizes that science communication towards the public is a trust issue. Of course, one may question whether communication to the public is even a responsibility for scientists, so debate on how to communicate may even be redundant. It may even be debated whether or not communication towards the public is purely a scientific responsibility: see *Table 4.16* below.

Table 4.16: Answer to the question what the participant's ideas are on their responsibilities towards the public. Participant A states that communication towards the public should focus on safety. Participant B indicates that responsibility towards the public is not purely a scientist's responsibility, but a responsibility you have as a human being.

	Participant A		Participant B
A.	My responsibility is to predict whether what you do is safe or not. Explaining what you are doing, and make sure it's safe, to the public.	**A.**	It [science communication, SF] comes back in your responsibility as a human being, not specifically as a responsibility that only scientists have.

Table 4.16 shows two different approaches in responsibility towards the public. Most participants answer that their responsibility as a scientist towards the public relates to explaining what they are doing and why they are doing that, and to make sure that what they do is safe. One participant answered that this is not purely a scientist's responsibility, but that everyone has a certain responsibility towards the public. It is always your responsibility to validate what you are doing, in whatever profession you are active.

4.4.10 Question 10 – Evaluation

The tenth question reviews the questionnaire. It appears that all participants could think of at least one issue they had not considered in this questionnaire. This indicates that one of the goals of the questionnaire, to make people aware of the ethical issues in synthetic biology, was achieved. Especially issues relating to intellectual property and commercialization in an open source environment were things to reflect upon that were new for the participants.

Also, most participants indicated that there was at least one issue mentioned in the questionnaire of which they think it should have had more attention in project design. Especially the usefulness and application were things that need more consideration. Still, participants realize that at the moment that this report is written, the group is still in the early phases of design. According to most participants, focus should be on developing a working application. Afterwards, other issues relating to intellectual property, safety, security and perhaps commercialization should be considered.

Another question in this evaluation regarded the participant's preference for either the thermometer's input or output system: the input system that is used relies on RNA structures, of which the functionality is unknown, also in literature. The output system relies on well documented research, with known functionality. The question was asked which of the two had the participant's preference. All but one participant indicated that the more fundamental research on the RNA structure input had their preference.

4.4.11 Survey summary

It appears that all participants have different reasons for participating, but the most heard argument was to participate in a "fun" project. The participants without a background in biotechnology had the additional goal to learn about biological principles. Biotechnology schooled participants did not state they wanted to learn about other related fields of research, like computer modelling of biological systems.

Participants have different ideas towards the relation between open source in iGEM and concepts of usefulness and commercialization. Some feel that open source enhances usefulness of the things that are published in the open source database, other feel that usefulness is not enhanced in open source. Some feel that more commercializable products are developed, others think less. Different opinions are observed to base their opinions on.

Participants have different opinions on whether or not commercialization related issues (economic issues, issues related to market introduction, relating to safety and security, etc.) are to be considered in this project. Some state that it is always necessary to think about commercialization of the product, others feel that it is not a goal in the project. However, these issues are not necessarily concerning commerciali-zation, but other values can be considered, like usefulness, safety, security, transparency.

These values were also mentioned in the value sensitive design session that was held in the very early stages of design. They were considered important to take into account, but in general conclusion, most participants feel that it is currently too early in design to consider issues like safety, security, sustainability and commercializability. First the focus should be on making a functional application. Later, other values can be considered.

The participants recognize different risks and ethical considerations in synthetic biology. Biosafety and biosecurity were mentioned as prominent risks. Ethical considerations were more various, but generally related to naturalness and in which instances genetic engineering should be applied. All participants indicate that a certain cooperation between ethicists and scientists is needed to incorporate value sensitive design or ethical decision making in scientific projects.

The idea on what is or is not allowed in scientific processes in terms of genetic engineering is a subject on which all participants have different opinions. As long as the team is working safely and responsibly, with bacterial cells, generally no moral restrictions are mentioned. All participants do realize that there are groups of people in the general public that may oppose the use of genetic engineering, based on various reasons like religious reasons or environmental concerns.

In terms of misuse, a differentiation can be made between errors and terrors. The team members realize that there is a certain chance of error, but the risk can be minimized by working by the rules of the laboratory. Regarding erroneous applications, the participants feel that it is only to a certain extent the team's own responsibility to make a safe application in an open source environment. The eventual user of the produced BioBricks is responsible for proper use, as long as a safe product is delivered by the team. What this implies in technological terms is somewhat unsure: to what extent bioterror can be prevented in a BioBrick is probably unknown.

The participants all feel responsible in some way in science communication. Most participants relate science communication to interaction with the public. Demonstrating to the public what they are doing and why they are doing it is mentioned as being important.

Also, in the survey, all participants mentioned that there was at least one issue they had not considered before. In that sense, the interview has stimulated them to think about the ethical issues in synthetic biology, which was a goal of the survey as mentioned in the introduction of this report.

4.5 Summary

In this chapter the ethical considerations in the iGEM project were investigated and the opinions of the team members regarding the involved ethical issues were captured. Furthermore, the design process was monitored.

For developing the project's design, the participants had several brainstorming sessions. First the project requirements were mentioned, of which the key one was that it was Delft University of Technology related, meaning an applied scientific application. Hereafter, a session on value sensitive design was held, which resulted in the idea that the project should take into account safety (for production, users and the environment), security (controllable applications and no intentional harm), transparency (for designers and of the project) and usefulness (of the application). Additional values included scientific simplicity, contributions to the good of society and transparency for end users.

In the following brainstorming sessions, wild ideas were generated, out of which a selection of potentially scientifically interesting and viable ideas were distilled. Further scientific probability assessment and ethical decision making, resulted in elimination of other projects, resulting in one project to be continued: the biothermometer.

The attitudes of the participants towards ethical issues and decisions within the project, and the attitudes towards the values that were previously adopted as important to consider, were further investigated with a questionnaire. The road map of *Figure 4.3* was used to develop the questionnaire, which was conducted in a semi-structured way: the general line of the conversation is the same, but small deviations in question methods and order of questions are possible. In the survey, the focus was first on science to get the participants familiar with the used technologies and terminologies. Later the focus was on the ethics in synthetic biology, specifically in iGEM.

It appears that on most topics, no general group opinion is observed: individual participants give different reasons for participating, have different approaches towards risks and ethics in science, think differently about their responsibilities, etc. In the next chapter, the different attitudes the participants have are related to general ethics in synthetic biology as presented in *Chapter 3*.

5 Discussion

The study described in this report reviews ethical considerations in the open source synthetic biology student science competition called "iGEM". As a case study, the opinions of the participants of the TU Delft 2008 team on moral issues that play a role in this project were monitored. The goals were twofold: firstly to investigate which ethical considerations play a role in the iGEM project; secondly to create awareness among the participants on these ethical issues. The results of the study can lead to some discussions, some of which are brought up in this chapter.

5.1 The general ethical issues in iGEM

From a literature review it appears that four main ethical issues constantly return in synthetic biology. Two relate to the novel character of the scientific backgrounds used in synthetic biology, being biosafety and ethical considerations around artificial life. The other two relate to the open source approach that is proposed (and partially implemented already) in synthetic biology, being biosecurity and intellectual property.

The issue of biosafety involves a guarantee for safety in development, in production of the application, upon use of the application and for the environment it is developed, produced or used in. The question here is to what extent absolute safety can be guaranteed. Currently, much research and development of application probably revolves around risk analysis, rather than the possibilities in terms of projected benefits (in terms of money, general good for society, safety, etc.). It cannot be stated that this is a bad or good development, but at least it can be observed that this is reflected in society (or the other way around), which is probably one of the main reasons why biosafety currently is an ethical issue in synthetic biology and, more specifically, in the iGEM project.

The issue of artificial life relates to the level of naturalness in synthetic biology research. More and more "unnatural" components can be added to "natural" cellular systems. The level of artificialness generally increases in synthetic biology application, more so than was the case in the more classical "metabolic engineering". Currently, components that can not be found in nature can be incorporated into biological systems. Biological subsystems can be integrated into other biological systems, creating new, complex and more or less "natural" (or artificial) systems. The question is how "synthetic" biology (the study of life) can actually be. Should recombinant DNA techniques be the solution to all the world's problems? This makes artificialness or naturalness an issue to discuss within the iGEM project.

The issue of biosecurity revolves around the open source character of the iGEM project. Participating teams are expected to be fully open and honest about their research setup and their results. This open source approach, together with standardized biological parts and recombinant DNA techniques becoming cheaper and more easy, has some consequences in terms of biosecurity: applications can be developed that may cause intentional harm to the environment, human life, etc. Currently, any DNA sequence can be ordered from synthetic DNA manufacturing companies all around the world. Pathogenic systems may therefore easily be developed. The question is how much attention a team participating in iGEM can give this issue and to what extent the teams are responsible for what other people do with developed applications.

The issue of intellectual property rights also involves the open source character of the iGEM project. To some, it is somewhat unclear what may be patented and what may not. But one may also question whether the open source (in comparison with closed source) is a good development from a scientific point of view. Will fundamental or applied science really benefit from complete openness? These questions are also to be considered within the iGEM project.

5.2 Recombinant DNA techniques: going too fast?

But one may question whether it is good to consider these issues in synthetic biology, while many ethical concerns in the predecessors of this novel technological approach with recombinant DNA techniques, are still not addressed. Is society ready for this new, extreme form of genetic engineering[53]? It sometimes seems as if under the "banner" of synthetic biology, all the science is morally justified. But don't issues relating to public opinion, like religion, trust in science, naturalness concepts, globalization, need to be resolved first? Then the question lies deeper, e.g. whether science should always depend on public involvement. But still, science has advanced, so probably the thing to do now is take these new ethical considerations into account, in addition to the previous ethical considerations. But this also means that we cannot forget about the previous issues. In that sense, synthetic biology can be a PR stunt to get the science appreciated by the public, but when presented incorrectly, it may result in public backlash, because the public is perhaps not ready yet for the next step in "biology".

5.3 Designing with biology: the points of ethical decision making

Ethical decisions are made throughout the entire project. The project has different stages. In the initial stage, the project has to be defined. In this stage, different ethical issues play a role than in the next stage, when a project is slowly starting to lead to an application. That is exactly the stage the project is in during the time this report is written. Hereafter, product development and potentially commercialization will play a role, which also involves different ethical decisions. But even before the iGEM project has started, participants have to be found that are willing to participate. Deciding to participate of not can be an ethical decision: the team will be working with recombinant DNA techniques, play with nature or natural biological systems, etc. Even though this probably doesn't play a role for students who just need the credits for participating in a scientific project, the choice to become involved can still be a moral one (see *Chapter 3.4*).
Before the project was defined, already some minimal moral values to take into account were defined by the team. These values helped to bring more guidance in the brainstorming sessions and also helped defining the project after brainstorming (see *Chapter 4.2*). But also in design of the project, ethical decisions are made.
Also in designing the bricks themselves ethical decisions are made. One can question why certain sequences from certain source organisms are used, or whether or not DNA should be ordered from a company (*Chapter 4.3*). Also, during the project, interviews were held with the participants to investigate their opinions on ethical issues that play in synthetic biology and simultaneously making them more aware of these ethical issues. In these interviews the participants also learn about their ethical decisions.
Whilst the project is slowly evolving, the team is starting to think about realistic applications. In thinking about these applications, some people are slowly thinking towards market introduction and related issues of biosafety and security, public opinions, etc. These are also ethical decisions, but in different future stages of design.

5.4 Conceptualization in design: standardized BioBricks or standardized science?

Synthetic biology is currently largely about making standard biological parts that can be used to make any sort of application. The iGEM organizers cry for large scale standardization in an open source setting with a publicly accessible database. But some criticists have stated that biology cannot be standardized, for different reasons: biological processes may be too complex, behave unpredictably, etc. But one can wonder to what extent biotechnology research has already been standardized or conceptualized. In the weekly meetings with the TU Delft team, typically once or twice remarks like "and than we can easily check that with an assay" or "but there are methods for that" are heard, without further defining what actually has to be done. This conceptualization also means that the biological side of research is suggested to be easier than it may actually be, since these vague conceptualized statements need to be interpreted, investigated, incorporated into the project. All these steps take additional time and may give participants unschooled in biotechnology the wrongful idea that the biological science is predictable.

[53] One may also wonder whether science has advanced that much already. Currently, some research that according to the researchers falls in the synthetic biology category, doesn't really use many "artificial" components or not very extensive genetic modifications. In that sense, synthetic biology is currently probably not very "synthetic". Getting the completely "synthetic components" to work in applications will probably take some time.

5.5 Ethics in the 2008 TU Delft iGEM team

The outcome of the survey was already described in *Chapter 4.4*. Some issues about which there can be much discussion are further analyzed in this paragraph. The feasibility of the iGEM project is discussed first. Hereafter, the relation between fundamental science and applied science will be further examined. Then, how ethical considerations come back in the project is described into more detail. Next, the role of value sensitive design in the project is discussed. Subsequently the team's responsibility in safety and security is further discussed. The last topic of this paragraph regards the difference in opinions that scientists have on the values that play a role in the project.

5.5.1 A little too ambitious?

In the introduction of this report it was stated that synthetic biology generally has two approaches: the constructing approach and the deconstructing approach. In the first, biological subsystems are used to build a certain application. In the latter, an organism is used to analyse these subsystems and to learn about living systems. The participants in iGEM mainly use the constructing part, while in fact the team is also learning about the biological subsystem that is used. In trying to make an application, actually fundamental science is involved. This can be observed in many iGEM teams. On their WIKI websites, the teams start off with the wildest biological ideas, with most promising applications. But when time goes by and projects evolve, the teams are conducting more and more fundamental science to prove basic biological principles. In fact, many proposed applications are not actually made by the end of the project, because the fundamental biological principles are not fully understood and still under investigation. It is questionable whether the façade of iGEM as being an applied science project (implicitly represented in the "building with biology" slogan) can be justified from this point of view.

5.5.2 A fundamental conflict

Continuing on the ambitious usefulness on the project, this gives some difficulties within the TU Delft team. When asked whether the participants preferred the fundamental scientific approach of developing an RNA structure dependent switch or the more applied color output research, all but one participant stated that the fundamental science was more interesting for them (*Chapter 4.4.10*). To some extent is in contrast with the requirements and the value sensitive design as assessed before the project was defined. These requirements stated that a useful, Delft related application was to be investigated, and usefulness was a minimal moral value. Now that the project has been defined and research is being carried out, the participants generally think the fundamental science is more interesting.

Of course, fundamental knowledge is needed to develop an application. But even making an application doesn't seem to be a goal anymore for some team members (*Chapter 4.4.5*): commercialization and the application are not stated as an iGEM goal, so the team doesn't have to think about them anymore, according to some. Others still think the application needs to be considered, along with ethical issues like biosafety, biosecurity, public opinion, intellectual property and commercialization. Others think that thinking about an application has nothing to do with commercialization and money. But the relation between open source and usefulness and the relation between open source and commercialization are largely unclear for the participants, and all have a different opinion on these relations (*Chapter 4.4.4*).

To make this difference more general: there seems to be a clash between those who think in consequences (consequential ethics, e.g. if the team does "this", we should take into account "that") and those who think in principles (deontological ethics, e.g. "we should always take "that" into account).

This fundamental science vs. application oriented science conflict seems to be something that also needs to be considered by the iGEM competition organizers. It is currently largely unclear for the participants to what extent they have to investigate patents and commercialization. One may not expect this science project to also involve making business plans for starting companies with the developed application. In fact, it was also stated that it is questionable whether iGEM will really generate useful applications (*Chapter 3.9*) and the team members also don't agree on this matter (*Chapter 4.4.4*).

5.5.3 Why does a dog lick itself? Because it can…

Whether anything useful will come from the TU Delft project or not, still some ethical issues need to be considered. Here the focus is on science for the sake of science. It seems that the iGEM competition has a very strong focus on modern biotechnology, in all its facets. But participants need not be biology or biotechnology students. The TU Delft team also consists of an informatician, a mechanical engineer and a biomedical engineer. But can people from different disciplines really participate in this project? One striking finding was that one of the participants, not schooled in biotechnology, was not happy with the idea that human genes (without questioning what makes a human gene a human component, scientifically speaking) could theoretically be used in this project, because of personal moral beliefs. What if the TU Delft team had decided to use a gene responsible for human eye colour for the output of the thermometer? The question then is whether these matters of personal beliefs should be investigated before participating in the project. Should iGEM be responsible for letting the participating teams decide on participation because of moral restrictions? Perhaps this should be investigated.

But besides these personal beliefs conflicts, it can also be questioned whether or not it is a good development that people without a background in biotechnology start working in synthetic biology research. From the interviews it can be concluded that the participants schooled in biotechnology have less difficulty in formulating their opinions on ethical issues than the participants without a biotechnological background, indicating a very limited overview of the ethical concerns in biotechnology research. Together with the large scale conceptualization of biological principles and biotechnology research becoming more and more standard and more and more easy, one may wonder whether this is a good development for the future. Is scientific research becoming science for the sake of science, or can ethical considerations play a role in modern biological research?

A different issue regarding ethics in science regards the biological design of the project. In the project proposal the goals of the project are clearly described. The benefits for society are mentioned, but the methods in how to achieve the goals are still somewhat vague. The group has to come from any starting point to a certain end point (metaphorically, from A to D). The ethical conditions under which this is possible have been assessed and the ethical considerations are defined in value sensitive design. But still, the steps to go from A to D, being B and C, have to be defined. In this intermediate research stage, also new or other ethical principles are appearing, some maybe conflicting with the initially defined ethical conditions. For example[54]:

> *In value sensitive design it was assessed that the design should be simple: an RNA structure in front of a gene should regulate gene expression and hence functionality of the biological part. But how does one check this principle? The output system, the color pathway, is also still under development, so "easy" testing methods should be found. Let's say the team comes up with a testing method where a human gene is used that is easily incorporated in the part to be tested, but requires a little more effort to analyse. A balance has to be found between checking the functionality in a good, quantitative way, and the ease of checking this functionality. Here, in deciding on how to get from A to D, ethical considerations seem to play a minor role, in comparison to technological possibility. In other words, in the intermediary steps, science is becoming science for the sake of science in stead of science for the sake of society, as it was previously defined in the project proposal.*

5.5.4 Value insensitive design?

But does the above mean that the value sensitive design concept has failed completely for this project? All participants stated that it was necessary to consider ethical issues during the project, so in that sense probably it is useful to consider ethics. Also the value sensitive design session was appreciated by all team members who were present. Also the participants did not mind talking about ethical issues during the project. But taking into account the values from the value sensitive design setting is a different matter. Apparently it's not that the team doesn't want to consider it, it may be just (too) hard to implement during the project, or at least during the initial phase of the project. Some participants stated that currently the focus of the project should be on making functional subsystems and thinking about applications. Others stated that the values from value sensitive design should be taken into account after applications were developed. All in all, this seems to indicate that the team members recognize different stages in design. Before the project has been described, values can be mentioned that are important to incorporate into the project, but perhaps during the project these values become irrelevant, because of the nature of the proposed applications. Also, new ethical issues may arise during development of the project.

[54] Hypothetical example by the author.

The values as assessed in the value sensitive design session currently do not come back in the current stage of the project. While the functional units are being developed, the team starts to think about applications, and when these applications have been found, the general expectation is that the values are going to play a more prominent role. It can be expected that the value sensitive design will play a more prominent role in future stages in design. Also, all iGEM teams may benefit from experiencing value sensitive design sessions. In that sense, it may be useful for the iGEM organizers to incorporate values in the project participation requirements.

5.5.5 The misuse dilemma

Two of the values that were considered important to consider beforehand, are also proposed major ethical considerations in synthetic biology in general, being safety and security (also described above in *Chapter 5.1*). But one has to question to what extent biosafety or security can be guaranteed, from a scientific point of view: it depends on many different aspects, like the proposed application. It may seem easy to assess whether or not an application can have harmful effects or may be used in terrorist activities, but how is this to be assessed? E.g., evaluation of "likeliness to be misused" in terms of errors or terrors is quite an arbitrary, intuitive assessment. But also one should question what can be done to prevent misuse to prevent safety or security issues. What can be designed into the developed application to actively prevent misuse? Participants proposed being clear in documentation and giving detailed manuals on how to use the application is all you can do. Others state that maybe failsafe systems need to be developed, but that first a functional unit needs to be developed before this can be considered.
Probably, scientifically, not much is possible to prevent misuse. It seems that currently we have to rely on people's morality and sense of responsibility. The team members did feel responsible for the safety of the application that is being developed, but opinions on where this responsibility officially lies are somewhat diverse. Some even state that the iGEM organizers could be held responsible for misuse, because the organization sends the DNA around. Others state the laboratory in which the research is conducted is responsible. Nevertheless, a little clarity on liability from the iGEM organizers would be very much appreciated.

5.5.6 Scientific homogeneity

The most obvious general conclusion of the conducted interviews is that the "scientists" (students and supervisors) in the iGEM project have dissimilar opinions on various ethical issues. Apparently, like "the public", "the scientific community" doesn't ventilate a single, homogenous opinion. One may question what can be done with this information, since relating this finding to ethics in technology goes much further than just the ethics in synthetic biology. One may for example wonder whether it would be wise to let the public know, explicitly, that scientist also do not always agree on the way science is conducted. But at the least this finding indicates that it is very useful to think about ethics in a project like iGEM, or perhaps even in general in working with innovation. Thinking about ethics can change the course of research in such a way that values are taken into account, that the good for society is always considered, and that not always the scientific principle of efficienty ruled the course of science conduct.
The 2008 TU Delft iGEM team members indicate that ethicists and scientists probably need to work together in the future to make sure that ethics are taken into account in natural science (*Chapter 4.4.6*), and that is exactly the area where currently much research by science and technology studies (STS) researchers is done. It is probably a good development that the iGEM organization values taking human values into account, since it is a "gold medal requirement". But perhaps it should be obligatory to think about ethics for all participating teams.

6 Conclusions

In this chapter the results of the study will be summarized, conclusions will be drawn from the findings and the goals of the project will be further discussed. In addition, future research and the value of the information of this report to the iGEM organizers will be suggested.

6.1 Research summary

Since the reintroduction of the term "synthetic biology" a simultaneous effort has been made by social scientists and natural scientists to make synthetic biology a success. This is a new kind of science, which needs lots of deliberation. There is still a long road ahead, but at the least, the ethical issues that play a role in synthetic biology research and product development have been recognized and are currently being thought over. The key ethical issues in synthetic biology regard biosafety, biosecurity, naturalness concepts and intellectual property rights.

Over the past decades, biology has started to become an engineering study and with the introduction of synthetic biology in 2005, this process accelerated. Students from different disciplines can currently contribute to scientific research in an open source setting, in the synthetic biology student competition called "iGEM". In this report, the ethical considerations that play a role in this project were investigated and the ideas the students and supervisors of the 2008 TU Delft team on the related ethical concepts have been investigated. For this investigation, a semi structured questionnaire was developed by which the participants were inquired.

It appears that ethical considerations play a role at different levels in this project. It starts with implicit assumptions on what is possible with the technology from a moral point of view, even before the project has started: first, the participants have to decide to participate. At the start of the project, a value sensitive design session was held in collaboration with the TU Delft's Philosophy department. Values that appeared to be found important (biosecurity, transparency, safety, usefulness) show similarities with what is found important in synthetic biology ethics literature. This indicates that the team is already quite aware of the issues that may play in biotechnology research.

During the project[55], several ethical considerations the participants have came forward. Decisions on the biological parts used, designed and tested; ideas on the application areas, the use of recombinant DNA techniques, all are related to ethical points of view of the participants. But still, not a single general opinion could be distilled from the participants. There are clashes in scientific approach, being either fundamental or more applied. The values that were to play a role are judged on importance differently by all participants. Team members have different ideas on responsibilities towards the public, the scientific community, etc. in terms of safety, security and transparency.

It also appears that during the project, it turns out to be difficult to take all the values or ethical considerations into account. It appears that the participants feel that different issues play a role in different stages of design. Once an application is produced, the issues as proposed for synthetic biology can play a role, according to most participants, but also in design phases, thinking about applications is already necessary. A related risk/benefit analysis is currently perceived as necessary, but still lacking.

The standardization concept through the BioBrick idea in synthetic biology also experiences some resistance. Some say that biology is to complex to be standardized. Other state that the open source BioBrick approach will never generate successful products, because in the capitalist system we live in, personal gain will always be involved and hence the good products will not be added to the registry of standard biological parts.

It was also argued that currently science is already highly conceptualized: in design, concepts for proving principles are stated, which are said to be very easy. But as it appears later, testing methods have to be customized to the application that is being developed, which also means that the concepts are not as easy as is sometimes perceived. Also, in development, scientists must be aware that during the research project, practical or efficiency based decisions will not overrule ethical principles as previously assessed in value sensitive design.

[55] At the moment this report is finished, the team is beginning to test functionality of the biological parts.

6.2 Project goals

The goals of this study were twofold. The first was to investigate the ethical issues in the iGEM project, and the second to investigate the TU Delft participants' opinions on these ethical issues and to increase awareness about these issues. This report summarized the ethical considerations in participating in iGEM and discusses several issues relating to open source novel biotechnology research. The participant's opinions were monitored by means of a questionnaire. All participants answered that issues had been brought up that they had not considered earlier. In that sense increasing awareness on the relevant ethical issues has also succeeded.

6.3 Further research

The research for this report was finished by September 2008. However, the iGEM project still continues until November 2008. During the final months, topics relating to some ethical principle in the project will be discussed in weekly meetings, to continuously keep the participants thinking about the relevant societal implications of the work that is being done. These group reflections can contribute to generating further awareness of the societal issues that play, of the role of ethics in science in different phases of development, and also to the way the scientists can "sell" their research. Especially this last contribution of thinking about ethics is sometimes forgotten: by thinking about the issues in relation to the public, it becomes easier for the scientists to talk about the science of their research, to articulate their motives and to describe what their research means to society.
But there are also other things that can be done with the data in this report. It can be the basis of a modern case study in ethics education in the field of biotechnology: the moral dilemmas the participants experience, relate to real life, modern biotechnology research, something perhaps currently missing in science education.
The synthetic biology case may also be discussed in other research groups, or perhaps in a "science café" setting, to make researchers aware of the ethical issues that play in modern biotechnology research, with "biology" becoming more and more "synthetic". This case can be interesting and challenging for researchers, with the different opinions of scientists so clearly stated.
In addition, this report can be used for improving the relation between considering ethics and considering science in the iGEM project. See the next paragraph for a summary on the possibilities for the iGEM competition organizers.

6.4 Suggestions for the iGEM organizers

This final paragraph of the report suggests how the information of this report might contribute to the iGEM competition. These suggestions relate to value sensitive design incorporation, competition goals, liability cases, etc. See the list below for a number of suggestions:

- Generally scientists start to realize that ethics should be a part of science research. When the research can have great impact on society or poses several moral challenges, as is the case in synthetic biology research, especially in an open source setting, this should be the case. Perhaps these ethical considerations should not be a gold medal requirement, but a minimal requirement, as is the case for modern research. This report could perhaps be a basis for an ethical checklist, before the project has started, once the project is starting, during the project and afterwards.
- Value sensitive design sessions were appreciated by all team members. These sessions ensure (when someone in the team makes sure of it) that these values are considered during the project. This report can be the basis of a value sensitive design brainstorming session or checklist for future iGEM teams. Perhaps value sensitive design sessions should even be a medal requirement.
- Also, all iGEM teams may benefit from experiencing value sensitive design sessions and thinking about moral issues. Thinking about ethics in the project ensures thinking about the potential impact on society, helps scientists articulate their motives and generally helps scientists understand ethical concerns, which contributes to more fruitful public engagement strategies, also on small scale (i.e. family and friends).

- Within the project, it is currently unclear whether the focus should be on application or on fundamental science. It is understandable that the iGEM organization doesn't want to focus on either of these (to let teams decide by themselves), but one has to consider how "real" science (and not an undergraduate student project) is conducted and how grants are obtained. Being clear about your goals, and explaining the contribution the research has to society (or company interest) is becoming more and more important. The focus of iGEM is for a large part on experiencing the real scientific culture: teams have to arrange their own labs, get their own permits, etc. But from the iGEM competition organizers, a little more steering could be given in terms of clearly setting goals. There are "best area" prizes for the best application in a certain research area, but this is not the same as setting clear goals in a project summary. Perhaps protocols can be developed with the help of this report to let teams think about their goals and make sure that all noses within the team are in the same direction. For example, that certain team members perceive the project as fundamental, while other see it as applied, as was the case in the TU Delft team.
- This also means that the way in which iGEM is currently perceived ("building with biology" in a student competition) may be unjustifiable from a moral point of view: it is not fully an "applied science" project, but in many instances a fundamental science project. Teams start off with ambitious ideas, but along the way most of them realise that fundamental knowledge is needed.
- Moreover, the iGEM website main page should perhaps indicate what iGEM is, and which goals there are for the competition. Currently, the iGEM goals are only defined on the iGEM wikipedia site[56]. The goals are to find out whether biological systems can be standardized, to enable systematic engineering of biology, to promote open source engineering of biology and to help construct a society that can productively apply biological technology. But especially for this last goal it is unclear as to how the organization tries to achieve this. In fact, no active effort can probably be demonstrated. But still, if this is a goal of the iGEM competition, thinking about societal issues should be a requirement for all teams.
- Some participants of the TU Delft team state that the iGEM organizers are (at least partially) responsible for misuse and safety. Yet the organizers of iGEM send DNA around, and some people feel that the senders are responsible for the safety and security of parts. Others again state that the laboratory where the research is conducted should be held responsible, others state the team itself is responsible. Nevertheless, clarity on liability issues (relating to safety and intellectual property, see below) from the iGEM organization, e.g. on the iGEM website, would be appreciated.
- Uncertainties are also observed in intellectual property issues. Currently, the only link to e.g. intellectual property rights on DNA can be found on the Help:Standardization website[57], stating that "We recommend getting your gene synthesized, but be forewarned, this can be a costly process with issues about intellectual property (more on this later...)". One might think that the iGEM organization deliberately doesn't mention its opinions (or the rules) on intellectual property rights. Nonetheless, apparently it is working out for the organization, since no legal cases regarding iGEM have been observed.

[56] iGEM on wikipedia: http://en.wikipedia.org/wiki/IGEM , accessed August 2008
[57] Link to intellectual property on iGEM website: http://partsregistry.org/Help:Standardization , accessed August 2008

Epilogue

Joachim Henkel (Technical University of München) and Stephen Maurer (University of California at Berkeley) write the following[58] in an article in Nature's Molecular Systems Biology journal in June 2007:

> *"Synthetic biology contains almost all of the same ingredients that make embedded Linux successful. First, synthetic biology's parts approach emphasizes strong modularity. This allows the work of creating a parts library to be spread over many companies. It also makes it possible for companies to earn profits by patenting some parts while making others openly available. Second, we expect companies to have fairly idiosyncratic parts needs. This means that they cannot simply 'free ride' by waiting for others to make what they need. It also suggests that companies can often share parts without losing their technological 'edge' to competitors. Third, different companies will have different expertise. This suggests that community-based libraries will often outperform company ones. Finally, the synthetic biology market will probably include large numbers of small, idiosyncratic customers. This makes patent licensing less lucrative and, by comparison, openness more attractive."*

But should we really be this optimistic? Can we expect protesting men in white suits attending the Jamboree in the near future? The interesting novel field research that synthetic biology may encompass comes with a number of new ethical considerations. Generally, the researchers (both social science researchers and natural science researchers) do not have a "general opinion" towards these issues: they have in fact very different individual opinions on the subjects, not all of them very positive towards the implications of the novel open source approach as it is used in iGEM. The main concerns are reviewed in this report. The open source approach contains many benefits, but one should also recognize the potential benefits. The technology itself gives rise to numerous creative applications, but also brings new risks. Life to Lego? This is perhaps not currently the case, but only the future will tell…

[58] The economics of Synthetic Biology, J Henkel & S Mauer, 5 June 2007, Nature Molecular Systems Biology 3, Article nr. 117 – http://www.nature.com/msb/journal/v3/n1/pdf/msb4100161.pdf

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Appendix A – Project proposal

Participants: B.A. van den Berg, F. Ehtemam, S.M. Flipse, R. Haghi, O.M.J.A. Stassen, R.J.J. Jorna
Instructors: E. Nikerel, M.J.L. de Groot, D. Bellomo, J. Kiers

Background

The international Genetically Engineered Machines or iGEM competition is an initiative of the Massachusetts Institute for Technology (MIT). From 2005 on this competition in synthetic biology has been organized and grown from five participants in 2005 to 80 participants this year. Basically the iGEM competition likes to address the following question: "Can simple biological systems be built from standard, interchangeable parts and operated in living cells? Or is biology just too complicated to be engineered in this way?" The three main reasons to begin organizing iGEM were:

1. To enable the systematic engineering of biology
2. To promote the open and transparent development of tools for engineering biology
3. To help construct a society that can productively apply biological technology

In practice, the first two reasons comprise constructing an open source library of standardized biological parts. These parts of standardized stretches of DNA are called BioBricks. These BioBricks can be used to make sensory systems, oscillators, or other applications that can be performed by bacteria. The standardization of the parts is achieved by placing a known standard sequence before and after each part (pre- and suffix) that is made. The prefix and suffix consist of three known restriction enzyme sites, this means every part can be cut and pasted if the right combination of restriction enzymes is used. Of course this requires the restriction sites to be absent in any of the stretches of DNA between pre- and suffix. At present, there are thousands of these BioBricks. These make up promoters, terminators, regulatory elements and protein coding sequences of different sorts are some examples of what the BioBricks are. Within this setting student teams from all over the world are challenged to build an applicable system and add parts to the BioBrick library. Participants are encouraged to pursue ambitious projects, although there are no real requirements other than that it has fit into the iGEM setting.

Our aim is to make *Eschirichia Coli* act as a thermometer, showing different colors when incubated at different temperatures. A micro sized thermometer can serve a number of purposes, e.g. creating surface temperature profiles in electronic and biological devices[1]. Also these thermometers can play a analytical role in industrial fermentation. It can be hard to control the temperature within a big-sized fermenter. If the temperature should never be above (or below) some control temperature within the fermenter at any time, one could add the thermometer bacteria to the fermentation. With these bacteria added, one could take samples and look whether the bacteria have changed color. This would indicate that the temperature in the fermenter somewhere is too high (or low).

Goals

Our project comprises several research goals. The first goal is to construct a RNA thermometer[2] *in vivo*. Because it is probably not feasible to construct the whole system in the time available we will focus on several subgoals that would help create the RNA thermometer in future. These subgoals are: providing a sound theoretical basis for the functioning of an *in vivo* RNA thermometer, designing and testing temperature sensitive stretches of RNA and cloning protein coding sequences of enzymes involved in the color pathway. We will focus on standardizing all parts made during the project according to iGEM regulations. The second goal is to predict behavior of this system using computer models. The third goal of this project is to focus on ethical considerations of synthetic biology in general (on a macro scale) and the implications of using synthetic biology within the open source technology setting of iGEM (on a micro level).

For sensing temperature (input) we are focusing on RNA thermometer. From literature, we will take 5' UTR RNA sequences from organisms that have temperature sensitive induced protein expression or synthetic RNA sequences that have been shown to be able to induce temperature sensitive translation. The sources of these 5' UTR sequences are heat shock proteins from e.g. *Bradirhizobium japonicum*[3], transcription factors from pathogenic bacteria[4,5] and designed temperature sensitive sequences[6]. We will screen different varieties on the designed RNA thermometer sequences. Furthermore, we want to make an inducible system, so all influences except temperature can be kept constant. How a RNA thermometer works *in vivo* is depicted in figure 1.

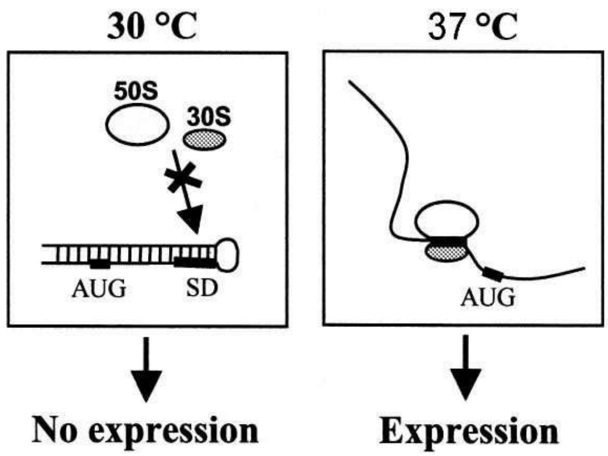

Figure 1. Schematic model for temperature sensitive gene expression. The Shine Dalgarno sequence and the AUG start codon are indicated in the schematic hairpin structure at the 3′-end of the element. Grey ovals represent large (50S) and small (30S) ribosomal subunits. Adapted from Nocker et al[7].

For the output on the system we want to obtain visibly colored *E. coli* colonies. To achieve this, we will introduce enzymes that originate from *Saccharomyces cerevisiae* and overexpress other *E. coli* enzymes in *E. coli.* These enzymes have been shown to be able to produce Farnesyl Pyrophosphate (FPP) in *E. coli*[6]. FPP is a precursor for pathways that lead to color production. When production of FPP in *E. coli* is achieved, the production of color will be the next goal. To obtain colored cells we could use the standardized pathway that is already made available by another iGEM-team (Edinburgh 2007).

Labwork

During this project we will work with *E. coli* K12 derived strains. For both the thermometer and the FPP pathway, *E. coli* cells will be transformed. In order to do this, vectors containing the relevant (c)DNA of the genes or temperature sensitive RNAs will be cloned into vectors provided by iGEM. Protocols available on the OpenWetWare (OWW) website will be followed in the laboratory. If no protocols are available on the OWW website, supplier's protocol will be followed or we will make our own protocols.

An inducible system will be made in order to keep environmental conditions as equal as possible in all tests. All cells will be grown at 37^{o}C, induced, and placed at different temperatures to investigate the temperature sensitive RNA structures. The *lac* operon will be in place before the RNA structures and after that the luciferase protein.

The *lac* operon can be induced by the presence of Isopropyl β-D-1-thiogalactopyranoside (IPTG), a molecular mimic of allolactose, which is a metabolite of lactose. By spraying IPTG on dishes, a concentration between 100 μM and 1.5 mM of IPTG should be reached in order to induce the system effectively.

The inducible temperature sensitive RNA structures will be tested by luciferase assays. Luciferase will be expressed under control of a standard promoter and temperature sensitive RNA. Luciferase is a 62 kDa protein obtained from the firefly. Luciferase catalyzes (in the presence of Mg^{2+}) the bioluminescent reaction (1):

$$\text{luceferin} + \text{ATP} + O_2 \longrightarrow \text{oxyluceferin} + \text{AMP} + PP_i + CO_2 + \text{light} \quad (1)$$

The amount of light produced by this reaction can be measured and gives as a clue about the relative amount of luciferase present. The amount of luciferase present correlates with promoter strength and the effect of the temperature sensitive RNA present. As long as cells from the same bacterial colony (i.e. cells with the same amount of plasmids present and the same RNA temperature sensitive part and promoter) are handled, relative expression of luciferase induced at different temperatures can be compared. For creating variations in the riboswitch structures, we intend to introduce small (One or two mutations in the sequence) alterations in the DNA. We can achieve this, for example, by performing error-prone Polymerase Chain Reaction (PCR). Screening of the resulting RNA sequence library could again be performed by LacZ screening at different induction temperatures. This way, we might be able to create RNA thermometers sensitive to different temperatures.

As has been stated before, FPP overproduction is needed to produce colored *E.coli* cells. In *E. coli* there is endogenous expression of FPP, it is produced by the DXP pathway. Simply overexpressing this pathway has led to only small increases in FPP production, as there are enzymes involved with very limited capacity. This is why we seek to overproduce FPP in another way. The color pathway we want to introduce consists of endogenous *E. coli* enzymes combined with enzymes 'borrowed' from the yeast *S. cerevisiae*, some of the mevalonate pathway. It has been shown that this combination of enzymes is a more potent producer of FPP than the endogenous DXP pathway[6]. An overview of the compounds involved in the color pathway with names of the enzymes can be found in figure 1. To investigate the presence of the enzymes of the FPP pathway in transformed *E. coli*, we will screen for the products of the pathway in the transformed cells and compare them to wild type *E. coli*. This screening will be performed using gas chromatography or mass spectrometry analysis. Overexpressing FPP in *E. coli* bears a potential risk to the cells while FPP is toxic to *E. coli* if present in high concentration[7]. One way to prevent a concentration buildup of FPP within the cell is by draining the FPP pool by expressing a colorant, as we plan to do. However, it will be important to tune FPP production: there should be enough to produce a visible color, but not more than the enzymes that produce the color can handle.

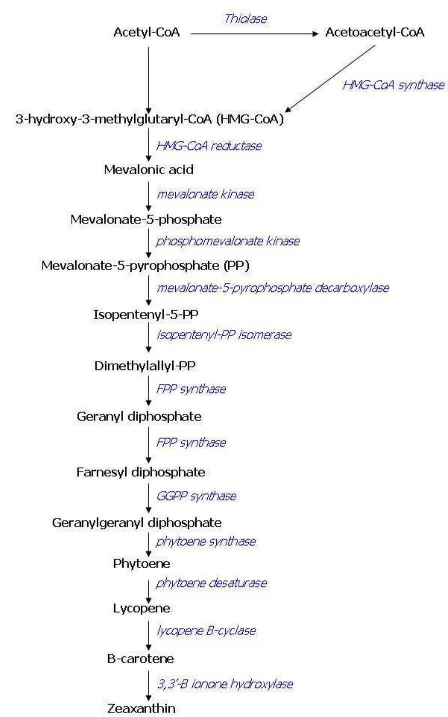

Figure 1. Overview of the pathway we want to introduce into E. coli for color production. Lycopene is a red colorant, β-carotene an orange one and zeaxanthin is a yellow-colored compound.

Modeling

Part of the project will be focused on building models to predict the dynamic behavior of mRNA and proteins in the cell taking into account the effects of temperature on translation. The software used to model the metabolic activities in the cell is CellDesigner™ and/or MATLAB. The goal of setting up a mathematical model of the biological processes is to avoid pitfalls that can be predicted beforehand.

Furthermore, the modeling of the system is in itself a goal: results from the laboratory can be used to test the model. Using the results, the model could be changed or optimized by fitting the parameters using experimental data. We aim to be able to predict at what temperature these RNA thermometers will allow translation using mathematical models.

Besides these models we will investigate in silico how to alter the temperature sensitivity of the 5' UTR by mutating the RNA sequence. Alteration of this sequence will change the stability of the RNA secondary structure occluding the ribosome binding site (RBS). More stable structures will denaturate at higher temperatures while less stable structures will denaturate at lower temperatures. This way we aim to design temperature sensitive sequences that act at different temperatures. We will use mfold[8] and the Vienna RNA fold suit[9] to predict the secondary structures and their stability.

Ethical considerations on macro and micro level

Synthetic biology can generally comprise several goals. Some would say the goal is to make biology an engineering science, designing with biology. Others may state that building with biology can be used to further understand life. At the least, one may state that both the bottom-up, constructing part and the top-down, deconstructing aspects of synthetic biology rely on the principle of using more or less biological systems in a more or less natural way. This new approach of biology brings about new applications, but also new risks and new ethical considerations. The question is to what extent the participants in the iGEM competition realize this.

We are interested in what these new ethical considerations as proposed by ethicists in the field of synthetic biology actually mean for the participants in iGEM. On an individual level, which ethical questions play a role for the TU Delft iGEM team? How do the team members work with or around these issues? These are the topics that are investigated in this study.

Before these individual team member analyses can be carried out, a road-map of the ethical considerations that are associated with synthetic biology need to be investigated. Therefore, a literature survey is carried out, exploring the general, "macro" ethical sides of synthetic biology. With this road map, a framework for a questionnaire has been developed, by which the ethical considerations on the individual "micro" level will be analyzed.

Predicted results from practical work

When input and output come together, a bio- thermometer could be created that changes color (or smells differently) at defined temperatures. A possible application of this project (temperature induced color production) can be to produce heat maps of surfaces on a microbial scale. A different application for the temperature sensitivity is to use this system for triggering bi-stable genetic switches or detection of temperature variations in cultivations. Furthermore, we hope the lab results will yield results to confirm or improve mathematical models based on the structure variations introduced in the temperature switch parts.

The modeling part itself could result in a predictive temperature sensitivity algorithm of RNA. Also, it could give insight in the enzymatic reactions that happen in the color pathway.

Finally, the ethics will provide us with a better insight of what iGEM participants know and think of developments in synthetic biology.

Contact:

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Appendix B – Interview questionnaire

In this appendix the setup for the questionnaires is given. The setup is based on the roadmap of ethical issues as given in *Chapter 4.3*.

Participant: ______________________________ **Date:** ____________________

Question 1 – Participation A

Goal: investigate personal reasons for participating

1.1 Why do you participate in iGEM?
1.2 What are the personal requirements for participating in advance?

Question 2 – Project goals

Goal: create awareness of project goals and investigating competencies

2.1 Introduce the goals: wet lab, modelling, ethics
2.1.1 What will probably be your major contribution to the laboratory activities, as proposed in the project summary?
2.1.2 What will be your major contribution/competency in Modelling in the goals, as proposed in the project summary?
2.1.3 What will be your major contribution/competency in Ethics in the goals, as proposed in the project summary?
2.4 What do you personally wish to achieve, additionally?

Question 3 – Terminology

Goal: investigate SB implications as realized by participants

3.1What does SB mean to you, scientifically?
3.2What do you think the main difference between SB en ME?
3.3What do you think the main additional innovative value of SB is?

Constructing and deconstructing topics in synthetic biology, artificialness. What about iGEM?
3.1.1Does this correlate with your view of SB?
3.2.1Does this change your opinion on the difference between SB and ME? --> if so: how?
3.3.1What do you think the main additional innovative value of SB is after this definition?

Question 4 – Open source values

Goal: investigate participant's ideas on open source and patenting/commercialization

4.1 Open source technology setting in iGEM
4.2.1 What do you think open source science implicates for technological novelty, usefulness of eventual products and commercialization of products?
4.2.2.1 Have you experienced (any kind of) drawbacks due to regulation or legislation in this project at any point?
4.3.1 Have you looked at patents in the area of application you are thinking of?
4.3.1.1 if YES: Which patents have you found? If NO: look at these patents. Anywah: do you think we should consider this further?
4.3.2 Should we keep commercialization of our application in mind already? Why Yes/No?
4.4 E.g. commercial research (DSM, Organon): contribution to technology?

Question 5 – Project values

Goal: re-evaluation of project goals as assessed beforehand in value sensitive design

5.1 Introduce value transparency
5.1.1 How important do you judge transparency
5.2 Introduce value sustainability
5.2.1 How important do you judge sustainability?
5.3 Introduce value safety
5.3.1 Value: later rest
5.4 Introduce value security
5.4.1 Value: later rest
5.5 Introduce value choice and what it would mean
5.5.1 How important do you judge freedom of choice? Can you imagine people refusing this project? Based on what?
5.6 How useful do you judge the application?
5.6.1 Do you see good or better alternatives to the application?

Question 6 – Science

Goal: Implications of technology for society

6.1 Which technologies (scientifically speaking) do you think are most important for SB?
6.2 Introduce risks in synthetic biology, without mentioning them
6.2.2 What do you see as "risks", generally in synthetic biology, NOT specifically in our application!
6.3 Information on ethical considerations
6.3.1 Which ethical issues do you think should be considered?
6.2.2.1 Safety (currently): what is your opinion on this?
6.2.2.2 Deliberate release: what is your opinion on this?
6.2.2.3 Deliberate misuse: what is your opinion on this?
6.3.1.1 Are there ethical considerations that may form motivations or constraints in your point of view?
6.4.1 Which risks should scientists focus on?
6.4.2 Which risks should ethicists focus on?
6.5 Should commercialization have a focus in design? Why, Y/N?

Question 7 – Naturalness

Goal: investigate participant's opinion on naturalness and boundary conditions

7.1 What are your ideas on transgenics in this project? Possible, constraints?
7.1.1 Can you imagine people experiencing problems with transgenetics?
7.1.1.1 Which problems and why?
7.1.2 What would your mother think of the topic?
7.2 How does transgenetics relate to your idea of: Religion, Culture, Choice?
7.2.1 Which of these topics do you think will become important in the future?
7.3 Information on impact of SB, future of fossil fuels, biobased economy
7.3.1 Which influences, both *positive* and *negative*, do you foresee on society in the future?
7.3.2 Which influences, both *positive* and *negative*, do you foresee on ecnomy in the future?
7.3.3 Which influences, both *positive* and *negative*, do you foresee on environment in the future?
7.3.4 Which influences, both *positive* and *negative*, do you foresee on human health in the future?
7.4 Where do you think the boundaries of GE should be?
7.5 Where do you think the boundary is between a machine and a living organism?
7.5.1 How important is the autonomy/essence of different organisms to you?

Question 8 – Misuse

Goal: participant's ideas on misuse in project

8.1 What do you think misuse in synthetic biology actually means?
8.2 Have you experienced constraints in design or work because of (regulation) (ethics) risks?
8.3 Which errors with severe effects may/can be expected in synthetic biology, specifically in our application?
8.4 Consider our application: which deliberate misuses can you imagine?
8.4.1/8.3.1Introduce regulative framework, engineering
8.4.1.1 Who should be responsible for the safety of the application we've developed?
8.4.1.2 Who should decide if it's safe?

Question 9 – Your role as researcher

Goal: investigate participant's idea on science communication and social responsibility

9.1a What is your idea on science communication? Where do you have responsibilities?
9.1.1 What do you think your responsibilities are towards science & scientific community?
9.1.2 What do you think your responsibilities are towards your direct supervisors?
9.1.3 What do you think your responsibilities are towards society?
9.1.4 What do you think your responsibilities are towards the public?
9.2 What would your mother say/expect on these responsibilities?
9.3 On which topics do you think your answers may be biased because of your academic background?

Question 10 – Participation B

Goal: review session & investigate group process

10.1 Are there issues that have been brought up in this session that should perhaps have received more consideration in the project design?
10.2 Have issues been brought up that you had not considered earlier?
10.3.1 Would you consider to work on easier topics sooner than on uncertain, perhaps more innovative or potentially innovative applications?
10.3.2 Were decisions made in design (after brainstorming), that you do not agree with or are not happy with afterwards?
10.3.3 How do you feel your input is respected by the group?

Appendix C – Typical Questionnaire outcome

In this appendix, a typical questionnaire outcome is presented. Please not that the interviews were conducted semi-structured, so certain questions main be asked in a different way, depending on the interview progress. Hence, the setup is slightly different from the questionnaire setup as presented in *Appendix B*.

Participant: Bas vd Berg **Date:** Tuesday 12 August 2008

Question 1 – Participation A

Goal: investigate personal reasons for participating

1.3 Why do you participate in iGEM?

Waarom doe je eigenlijk mee aan iGEM?
Omdat ik het heel interessant vindt, omdat het iets nieuws is, waar ik veel toekomst in zie. Vooral het nieuwe, iets ontdekken, nieuws creëren, dat is mijn belangrijkste motivator.
Gezien je afkomst, informatie, naar biologie, puur interesse?
Heeft ook te maken met gericht op software in informatica, minder maatschappelijke vooruitgang. Nu biologie, maatschappelijke invloed groter: energieprobleem, problemen oplossen. Met alleen informatica is dat minder.

1.4 What are the personal requirements for participating in advance?

Wat zijn verder je persoonlijke voorwaarden om mee te doen? Wat is hetgeen geweest waarvan je zei van: ik doe mee?
Voor meedoen, wist ik niets van synthetische biologie. Voornamelijk interesse naar het nieuwe, wat nieuws ontdekken.
Niet andere persoonlijke doelen, zoals punten halen?
Ja, onderzoeksproject, deze in de plaats.
Waar ligt dan de nadruk?
Op het nieuwe.

Question 2 – Project goals

Goal: create awareness of project goals and investigating competencies

2.2 Introduce the goals: wet lab, modelling, ethics

2.2.1 What will probably be your major contribution to the laboratory activities, as proposed in the project summary?

Dan nu het tweede puntje, over projectdoelen. In projectvoorstellen hebben we drie doelen… Wat is je grootste waarde voor het labwerk?
Labwerk… Ik zou het eigenlijk niet weten. Ik kan weinig bijdragen.

2.1.2 What will be your major contribution/competency in Modelling in the goals, as proposed in the project summary?

En als we het hebben over modelleren?
Nu toch het meest over het RNA. Hoe je een RNA thermometer kan ontwerpen. Ook wel het modelleren wat Rad en Farzad doen, daar heb ik ook bij geholpen.
Als we dat even terugbrengen naar het lab: de sequenties die we hebben gevonden, die dragen toch ook bij aan het labwerk?
Ja, je draagt toch bij aan iets dat in het lab gebruikt of getest gaat worden. Maar dat is niet echt in het lab…?

2.2.2 What will be your major contribution/competency in Ethics in the goals, as proposed in the project summary?

Als we het hebben over ethiek? Hoe zie je jezelf een rol hebben in de ethiek in het project?
Ja, lastig. Als er iets is waar ik het niet mee eens ben, dan zou ik daar wel mn mening over geven?
En daar blijft het bij?
Nee, als er iets gebeurt waar ik het niet mee eens ben, dan zou ik niet meer meedoen misschien. Maar bij dit project bevindt alles zich in zo'n vroeg stadium, dat we dit nog niet echt zijn tegengekomen. Ik denk ook niet dat we iets gevaarlijks zullen gaan ontwikkelen.
En hoe weet je dat zeker?
Nou dat weet ik niet zeker, dat is ook een beetje lastig voor mij, ik heb misschien ook een gebrek aan kennis. Het gevaarlijke zit m volgens mij in het biologische toepassen. Men zegt altijd van "virussen zijn gevaarlijk" enzo, maar hoe dan en hoe dat gevaarlijk is dat weet ik niet zo.
Ok, hier kunnen we later nog even op terugkomen.

2.4 What do you personally wish to achieve, additionally?

Dan verder nog over de projectdoelen, heb je nog persoonlijke doelen? Iets dat je wilt bereiken?
Binnen het project?
Ja, of binnen meedoen aan het project?
Ik vind het belangrijk dat we alles goed documenteren. Of het project een succes wordt vind ik niet zo belangrijk, maar het is belangrijk dat we straks een website hebben waar op staat wat we gedaan hebben, wat goed gegaan is, voor de volgende generatie iGEM'ers.
Denk je dat de volgende generatie van de TU wil doorwerken aan dit project? Of zelf verzinnen?
Aan het begin zullen ze wat zelf willen verzinnen, dat is toch wel leuk. Zelf vond ik dat ook een leuk onderdeel. Maar misschien gaan ze ermee verder, en ander wellicht een ander team, want als je goed documenteert dan is het een interessant project voor een ander team om mee verder te gaan.

Ok ja, daar ben ik het ook wel mee eens. Misschien wordt je als groep wel hechter als je het project samen doet.

Question 3 – Terminology

Goal: investigate SB implications as realized by participants

3.1 What does SB mean to you, scientifically?

Gaan we door met de derde vraag over synthetische biologie in het algemeen. Wat betekent voor jou, wetenschappelijk gezien, synthetische biologie?
Voor mij is het standaardiseren van biologische systemen om zelf nieuwe biologische systemen te kunnen bouwen, kunstmatig.
Dus de nadruk ligt op het opbouwen om iets te maken?
Ja.

3.2 What do you think the main difference between SB en ME?

Als we kijken naar de achterliggende biologie, wat denk je dan dat het belangrijkste verschil is tussen synthetische biologie en genetische modificatie in metabolic engineering?
Ehm,Van dat laatste weet ik niet heel veel af, maar je hebt iets bestaands en je wilt het optimaliseren, of ja, optimaliseren of beter maken. Synthetische biologie is er toch op gericht om wezenlijk nieuwe dingen te maken.

3.3 What do you think the main additional innovative value of SB is?

Wat denk je dat de belangrijkste innovatieve waarde is, die synthetische biologie met zich meebrengt?
Ja, echt nieuwe dingen maken, maar dan, ehm, ja, het innovatieve is dat je echt toegespitst op een ding, ja toch een levend machientje kan maken.

Constructing and deconstructing topics in synthetic biology, artificialness. What about iGEM?

Experts zeggen over synthetische biologie: 2 kanten, opbouwend en deconstructing: in elkaar zetten en uit elkaar halen om systeem te leren kennen, begrijpen.

3.1.1 Does this correlate with your view of SB?

Komt het beeld dat de experts hebben met jouw beeld van synthetische biologie overeen?
Ja, op zich wel, allleen een deel van wat jij noemt, afbreken, dat heb ik pas eigenlijk sinds kort ervaren, ingezien, want het is inderdaad een manier om heel veel te leren, want je sluit heel veel factoren uit, je kijkt naar een heel klein systeem, en daar leer je meer van als je naar het geheel kijkt. Maar ik ben het wel met de experts eens.

3.2.1 Does this change your opinion on the difference between SB and ME? --> if so: how?

Deze introductie, verandert die het beeld dat je hebt van het verschil tussen SB en ME?
Dat afbraakgedeelte, waarbij je iets probeert te leren, lijkt ook op onderzoek in de biologie, nog steeds niet echt metabolic engineering.

3.3.1 What do you think the main additional innovative value of SB is after this definition, in the future?

Na deze introductie, wat denk je dan dat in de toekomst het belangrijkste innovatieve deel is van SB?
Toch wel het bouwen. Daarmee kun je innovatieve dingen bereiken, met het afbreken kun je zien hoe het werkt. Dat draagt bij aan de innovatie, denk ik.

Question 4 – Open source values

Goal: investigate participant's ideas on open source and patenting/commercialization

4.1 Open source technology setting in iGEM

Hebben we het even over synthetische biologie in het algemeen gehad, een ding dat heel erg komt kijken bij SB en specifiek in iGEM, is het open source systeem. Je weet wat open source is?
Ja
Kun je een korte uitleg geven?
Open source is eigenlijk alles wat je doet (ja ik ken het eigenlijk voornamelijk van de software, het houdt daar in dat je je code openbaar houdt, zodat iedereen ook achter de schermen kan zien hoe het is opgebouwd, en het ook mag gebruiken. Alles wat je maakt mag door iedereen gebruikt worden.

4.2.1 What do you think open source science implicates for technological novelty, usefulness of eventual products and commercialization of products?

Wat denk je dat open source in de biologie, synthetische biologie, betekent voor de technologische vernieuwing in de biologie? Open source science en wetenschappelijke vooruitgang, hoe hangen die samen?
Ik zie open source als katalysator van de wetenschap. Ik heb het idee dat door alles open source te doen, help je elkaar, je voorkomt dat je op veel plekken hetzelfde onderzoek doet.
Jep, voor een deel ben ik het met je eens, maar denk je niet dat dit een beetje teveel een ideaal beeld is?
Eh, nee dat denk ik eigenlijk niet. Het is natuurlijk wel een ideaal beeld, maar ik denk wel dat het die kant steeds meer op gaat.
Je bedoelt SB in het bijzonder of wetenschap in het algemeen?
SB in het bijzonder, maar uiteindelijk denk ik dat het op veel vakgebieden zo zal zijn.

Wat denk je dat open source betekent voor het nut van het uiteindelijke product?
Het nut van het uiteindelijke product? Ik denk op zich, ik denk dat je je beter kunt richten op echt nuttige dingen.

Denk je dat open source technologie meer nuttige of meer fundamenteel wetenschappelijke uitkomsten zal bieden of ideeën zal genereren, of kennis?
Meer nuttige producten.
Waarom?
Omdat eh, ja het is een lastige. Fundamentele kennis zal toch wat meer eh, ja dat is allemaal wat lastiger. Het open source, als allerlei mensen dat bekijken, krijgen verschillende mensen meer ideeën. Dat werkt volgens mij heel inspirerend, en dan , als mensen dat ook weer delen, levert dat heel veel nuttige producten op.

Als we het hebben over nuttige, hebben we het uiteindelijk over commercialisatie.
Eh ja.
Hoe hangen open source en commercialisatie dan samen?
Nou ja, als je. Je kan producten verkopen, ook al is het open source?
Dan zit je toch met rechten?
Nee, als je wat verkoopt, moet je wel laten zien wat je verkoopt. Je kunt er prima geld voor vragen, zolang de mensen het product ook maar onder de motorkap kunnen zien. Je mag niet de broncode van het product als het ware afschermen.
Zolang mensen ervoor willen betalen…?
Ja, zolang je een goed product levert, als je kijkt bijvoorbeeld naar Linux. Je mag het verkopen, als je de broncode maar niet verborgen houdt. De technieken die je gebruikt om het te maken moeten voor iedereen beschikbaar zijn. Maar dan kun je nog prima een product maken waar mensen voor willen betalen.

4.3.1 Have you looked at patents in the area of application you are thinking of?

En hoe zit het dan met patenten?
In principe bij open source, heb je geen patenten toch?
Nou, iedereen kan een patent ergens op aanvragen.
Ja, maar als je ergens een open source licentie aanhangt, dan zeg je eigenlijk dat je het wel mag gebruiken, maar als je het gebruikt, dan moet je het open source houden, dus mag je er geen patent meer op aanvragen. Nou, nu haal ik dingen door de war denk ik.

4.3.1.1 if YES: Which patents have you found? If NO: look at these patents. Anywah: do you think we should consider this further?

Ok, we halen er wat voorbeelden bij. Een belangrijke speler op het SB gebied is Jay Keasling, van de mevalonate pathway opheldering etc. Voor de kleurpathway heeft hij een patent aangevraagd, GM host cells for producing isoprenoid compounds. Blabla. Daar staan een aantal eiwitten in die wij ook willen gebruiken. Betekent dit dat je zomaar kunt commercialiseren?
Hoe bedoel je dat, dat je zomaar kunt commercialiseren?
Stel je voor dat wij dalijk een thermometer hebben gemaakt, op basis van iets wat hij heeft uitgevonden…
Ja dan zullen we hem ook moeten betalen waarschijnlijk, toch, als hij er patenten op heeft?
Dat ligt er een beetje aan…
Ja in principe zijn dat de regels, toch? Ik ben het er niet mee eens, ik heb een hekel aan zulk soort patenten een beetje, het houdt een beetje de ontwikkeling tegen?
Heb je uberhaubt wel naar patenten gekeken voor onze applicatie?
Nee, helemaal niet.
Want ook op het gebied van RNA thermometers zijn er een aantal patenten uitgegeven. Specifieke sequenties, etc. blabla. Denk je dat dit invloed heeft op ons project?
Nee, want wij doen niets commercieels.
Maar uiteindelijk, als je er een applicatie uithaalt?
Dan zou het wel van invloed zijn. Ja.

4.3.2 Should we keep commercialization of our application in mind already? Why Yes/No?

Gaan we even terug naar een van de eerste vragen in deze vraag. Hoe denk je dat open source en commercialisatie samen gaan?
Ik denk dat dat goed samen gaat. Het voordeel is, je hebt niet het gezeur met patenten. Zodra je patenten hebt heb je vertraging in je ontwikkelingsproces, dat kost heel veel tijd en moeite, terwijl je in de open source, heb je daar helemaal geen omkijken naar. Dat is wat dat betreft een voordeel omdat je daar geen tijd aan hoeft te besteden.
Je moet misschien verschil maken tussen kennis en producten. Als je een goed product levert, kun je dat verkopen.
Moeten wij in dit project dan commercialisatie ook een rol laten spelen, nu al of later?
Later wel, nu nog niet.
Op welk moment is dat dan?
Als je iets ontwikkelt met als doel winst te maken. Als je een bedrijf begint met de applicatie dan is dat van belang. In ons onderzoek zijn we niet op winst uit, maar op kennis.
Stel je nu voor dat we iets vinden wat echt goed werkt, perfecte input/output, waar we heel veel geld mee kunnen verdienen, persoonlijk of als TU. Zou de TU dan blij zijn met ons?
Je bedoelt omdat ze dan veel mislopen, omdat het open source is? Misschien niet blij. Maar ik denk dat je dat ook op andere manieren kunt uitbuiten. Als jij de eerste bent met die techniek heb je al een voorsprong en moet je er gelijk iets mee doen.
Kun je een concreet voorbeeld geven, hypothetisch?
Als we als eerste die techniek ontwikkeld hebben en die blijkt te werken, dan zit de kennis bij ons. Als een bedrijf daar iets mee wil, hebben ze toch kennis nodig, die ze kunnen kopen.
Maar als de kennis open source is, kan elk bedrijf daar zijn voordeel mee doen.
Ja, iedereen kan ermee aan de slag.
Dus je zou dan zeggen als inspiratie of katalysator, is het een altruïstisch gebeuren, idealistisch zou OS dus goed zijn voor alles en iedereen, maar…
Ik weet niet hoe het echt is… Ik denk dat het meer die kant op zou moeten gaan dat bedrijven ergens iets in zien…
Geld?
Ja, en dan, zoals bijvoorbeeld bij Linux, die wordt heel veel gesponsord. Misschien is sponsoring nodig om de ontwikkeling voort te zetten.

4.4 E.g. commercial research (DSM, Organon): contribution to technology?

Vergelijk dit eens met gesloten source, zoals bijvoorbeeld bij bedrijven. Leveren zij dan geen technologische vooruitgang?
Jawel, maar ik denk minder.

Minder of minder snel?
Minder snel ook. Je ontwikkelingsproces wordt onwijs vertraagd ook. Patenten aanvragen, etc.
Maar dat is toch een beetje hoe het werkt in een kapitalistisch systeem.
Ja, maar als je het niet zo zou doen, zou het een stuk sneller gaan.
Is dat heel realistisch?
Dat is moeilijk in te schatten, omdat we nog niet zo ver zijn. Het zou die kant op kunnen gaan.
Heeft het iets te maken met jou persoonlijke ideeen?
Ja ik persoonlijk, voor mij is dat open source gebeuren wel een ideaalbeeld, maar ik ben wel zo realistisch dat het niet gaat gebeuren zolang ik leef. Het zal wel die kant op gaan, maar het bedrijfsleven zal wel altijd zo commercieel ingesteld zijn als nu.

Question 5 – Project values

Goal: re-evaluation of project goals as assessed beforehand in value sensitive design

Kun je nog uit je hoofd zeggen welke waarden het waren toentertijd, die we besproken hebben?
Nee, ik zou het… Eh, veiligheid,
Op welk gebied?
Eindgebruiker. Duurzaamheid. Je had ook versch soorten waarden.
Ik zal ze even opnoemen. We hebben het gehad over transparantie, ect…

5.1.1 How important do you judge transparency

Hoe belangrijk vind je die, als je moet schalen van 1 tot 10?
8
Waarom?
Ik denk dat het belangrijk is, vooral als je in een gebied zit waar ethiek van groot belang is, dat je transparant bent. Het is tweezijdig. Je wilt dat iedereen ziet wat je doet, aan de andere kant heeft het als nadeel dat slechteriken ook kunnen oppikken wat je doet, dat is weer een nadeel.

5.2.1 How important do you judge sustainability?

Gaan we door naar sustainability, hoe belangrijk vind je die?
Wel een belangrijke, een 9.
En wat is er duurzaam aan onze applicatie?
Hmm, nou ja, het is niet zo dat we een grote impact op de natuur of samenleving hebben. Ja, het speelt nog niet erg zolang je niet gaat produceren. Zodra het zo ver is, dan is het van belang dat je applicatie een niet te grote impact heeft op het ecosysteem.
Is dat dan sustainability of safety voor environment?
Ja, ook.
Wat is voor jou sustainability?
Dat is voor mij toch dat je zo min mogelijk de omgeving/ecosysteem/hele leven beinvloedt, dat je het evenwicht behoudt, niet te veel omver gooit.

In hoeverre heeft ons project wellicht later invloed op de omgeving?
Ik denk helemaal niets, of weinig.
Vergelijk eens met alternatieven, zoals de laserthermometer, of kwikthermometer?
Die hebben ook geen grote invloed.
Is sustainability dan een grote waarde in ons project?
Nee, in ons project eigenlijk niet. In ons project is het eigenlijk een 5 denk ik. De 9 is dan voor SB in het algemeen.

Als persoon vindt je sustainability dus wel belangrijk, maar in het project niet?
Nou, als je iets gaat doen dat een onwijze impact heeft op de samenleving, dan wordt het belangrijk.
Wat is dan de toegevoegde waarde van ons project, als sustainability dat niet is?
We maken een thermometer, die heeft niet zo veel impact op de rest van de wereld. Misschien een nuttige functie met slechte implicaties, dan moet je over duurzaamheid nadenken.

5.3 Introduce value safety

Later terug
Wil ik toch even scoren van 1 tot 10.
Eigenlijk niet van toepassing, 3

5.4 Introduce value security

Security komt straks nog even terug, maar als je nu zou moeten scoren van 1 tot 10, specifiek voor ons project?
Als je nu naar ons project kijkt, vind ik security niet echt aan de orde.
We komen er later nog even op terug.
Wil ik toch even scoren van 1 tot 10.
Eigenlijk hetzelfde

5.6 How useful do you judge the application?

Hoe belangrijk vind je usefulness?
Je bedoelt van het eindproduct of van de kennis die je verwerft?
Eindproduct.
De usefulness van ons eindproduct vind ik maar een 6, niet heel erg…
Had dit belangirjker moeten zijn?
Nee, daarvoor zitten we nu in een te vroeg stadium, we zijn nu meer aan het leren dan aan het produceren.
Dus leren betekent kennis?
Ja, we doen het toch puur om kennis op te doen, dat is mijn mening.

Question 6 – Science

Goal: Implications of technology for society

Gaan we nu even focussen op de wetenschap. Puur wetenschappelijk… blabla

6.2.2 What do you see as "risks", generally in synthetic biology, NOT specifically in our application!

Technologie, of nieuwe technologie eigenlijk, neemt normaal gesproken ook wat risico's met zich mee. Tenminste, dat idee leeft. Kun je een aantal risico's noemen in SB? Wat zie jij als risico's?
Het ontwerpen of maken van een gevaarlijk virus ofzo, wat bedreigend is voor de mens.
Nog iets misschien? Risico's van SB, nieuwe technologie?
Duurzaamheid misschien, aantasting van het ecosysteem, gaan er geen wezens worden uitgeroeid, of monsters ontstaan. Zelf zie ik dat eigenlijk niet als risico. Ik denk, misschien op een ander niveau, een beetje onrust veroorzaken. Als het te hard gaat, dan gaan de mensen heel veel tegenstand bieden, denk ik.

6.3.1 Which ethical issues do you think should be considered?

Ok misschien, kunnen we even doorbouwen. Behalve risico's zijn er ook ethische bezwaren, dus niet zozeer wetenschappelijk. Welke ethische bezwaren kun je zien, behalve onrust veroorzaken?
Tja, de belangrijkste is denk ik nieuw leven creeren, voor god spelen zoals mensen dat zeggen.
En denk je dat op dit moment die veiligheid van SB een issue is?
Ja, ik denk het wel.
En hoe dan?
Nou ja, je kunt dus al zelf dingen klussen, dus ik neem aan datje ook gevaarlijke dingen kunt maken?
Op dit momeent al?
Eh, ja zulke dingen kun je nooit uitsluiten.
Als je het hebt over vrijwillig of opzettelijk loslaten in het milieu, zoals de thermometer, kan dat zomaar?
Nee niet zomaar, dan moet je goed voorzorgsmaatregelen nemen, goed onderzoek doen, i kdenk voornamelijk, het belangrijkste nog, goed communiceren naar de onwetende mensen.
Communiceren komt later terug. Misbruik, je zegt net dat we het niet kunnen uitsluiten?
Nee, niet uitsluiten, maar aan de andere kant, misbruik kan met alles. Dus hier is het niet veel anders dan met andere technieken. Eigenlijk is dat met alles zo.

6.3.1.1 Are there ethical considerations that may form motivations or constraints in your point of view?

Welke vormen een motivator? Laten we het eerst hebben over wat je motiveert, welke ethische principes moeten een motivator zijn om onderzoek te doen naar…
Een bezwaar dat als motivator werkt?
Niet zozeer een bezwaar, meer een principe dat als motivator werkt.
Is open source dan ook ethisch?
Dat kan.
Dat is voor mij een motivator in ieder geval. Om daarmee te werken, of het werkt.
En op technologisch vlak, moeten we dan actief moeite doen om misuse te voorkomen?
Dat je dat als motivatie ziet?
Ja.
Nee, het moet wel gebeuren, maar niet een motivator op dit moment, in de latere applicatie.
Op welke manier zou dat dan kunnen?
Nou, misschien door te kijken op welke manieren misbruik mogelijk is. En dat dan zoveel mogelijk proberen uit te sluiten. **Je krijgt het niet waterdicht, maar je kunt het wel moeilijk maken.**

We hebben het gehad over motivators, maar welke dingen kunnen het ontwikkelingsproces tegenwerken?
Wat ik denk dat een tegenstand zou kunnen zijn, is tegenstand vanuit de samenleving.
Is die er op dit moment?
Nee, maar ik denk dat is omdat mensen het niet weten.
Moeten mensen dan meer weten?
Ja, dat vind ik wel, ik denk dat we daar snel mee moeten beginnen.

6.4.1 Which risks should scientists focus on? / Which risks should ethicists focus on?

Welke ethische risico's zouden wetenschappers op moeten focussen, en op welke ethici?
Wetenschappers zullen zich toch voornamelijk richten op het voorkomen van misbruik. Duurzaamheid, aantasting van ecosysteem. Ethici zouden zich bezighouden met de samenleving en de acceptatie van het geheel.

6.6 Should commercialization have a focus in design? Why, Y/N?

Zou commercialisatie, of het in de samenleving brengen, ook een focus moeten hebben in het ontwerp?
Ja.
Is dat bij ons gebeurd?
Nee, voglens mij helemaal niet, maar daarvoor zitten we ook in een te vroeg stadium heb ik het idee.
Waarom?
Nou, hoewel, vroeg stadium, het is ook niet ons doel. We zijn bezig om kennis op te doen, niet om producten te maken, dan moet je daar beter naar kijken.

Question 7 – Naturalness

Goal: investigate participant's opinion on naturalness and boundary conditions

Gaan we het nu hebben over een ander ethisch principe, …

7.1 What are your ideas on transgenics in this project? Possible, constraints?

Wat is jouw idee over transgenics, dus genen van het ene beestje in een ander zetten? In hoeverre moet dat mogelijk zijn en waar moet de grens liggen?
Op dit moment zijn er voor mij niet echt grenzen.
Ook niet wat betreft beestje, stel dat we een aap zouden nemen?
Daar ben ik wel tegen, ik denk wel dat je bacteriën enzo, muizen, wat nu ook proefdieren zijn, dat vind ik kunnen. Maar een aap, tja, dat is lastig, dieren… Het moet natuurlijk wel nuttig zijn. Voor ons onderzoek ligt de grens bij bacteriën.
En planten dan?
Planten kan ook, als het maar… eh… Ja, dat moet ook kunnen vind ik, zolang je maar… eh
En mais, die je op gaat eten?
Nee, dat zou ik nu nog niet doen…

Even zo terugdenkend, waar ligt de grens?
Ligt eraan waar je in de tijd zit. Op dit moment eencelligen, planten, maar niet om te eten.
En testvelden voor die planten dan?
Eigenlijk weet ik het niet zo goed, ik heb te weinig kennis om hierover te oordelen.
Het is ook een gevoelskwestie.
Tja, ik weet er het fijne niet van. Eigenlijk kan ik dan moeilijk een grens trekken.

7.1.1 Can you imagine people experiencing problems with transgenetics?

Waarom dan en op welke manier? Waar gaat het nou echt over?
Het gaat over leven, spelen met het leven. Mensen zijn volgens mij bang voor onwetendheid.

7.4 Where do you think the boundaries of GE should be?

Kort samenvattend, waar denk je dat de grenzen van GE moeten liggen?
Nu op dit moment?
Ja, nu op dit moment.
Ik vind op dit moment, moet je het zoveel mogelijk in het lab houden. Voornamelijk met eencelligen, simpele organismen werken. Als het om nuttig of potentieel goed product gaat werken, moet je kijken naar hogere organismen.

7.5 Where do you think the boundary is between a machine and a living organism?

Waar ligt voor jou de grens tussen een machine en een levend wezen?
Zodra het DNA heeft, leeft het. Dat is eigenlijk een soort machientje, leven is een soort van machine.
Dat is puur op celniveau, hoe het in elkaar zit. Ik bedoel meer een industrieel toegepaste machine.
Dan eh, tja, wat wij nu maken nomen we ook machienes, terwijl het levende beestjes zijn. Bacterien moet je wel als machine kunnen zien.
Dus bacteriën zijn de grens?
Eigenlijk wel ja.
Of eencellingen?
Ja eencelligen dan.

7.5.1 How important is the autonomy/essence of different organisms to you?

Hoe belangirjk is dan het innerlijke, de essentie van een organisme?
Dat is wel van belang, als een beestje een bewustzijn heeft, dan…
Wat is dan bewustzijn? Emotie? Bijvoorbeeld plantjes die genetisch gemodificeerd zijn, gaat het dan over het plantje dat gemodificeerd is of dat je het zelf niet wilt eten?
Dat plantje mag dan best GM zijn, als ik het maar niet hoef te eten.
Ook als het bewezen is dat het veilig is?
Als bewezen is dat het veilig is, dan kun je het ook best eten.

Question 8 – Misuse

Goal: participant's ideas on misuse in project

8.1 What do you think misuse in synthetic biology actually means?

Wat denk je dat misuse in synthetische biologie eigenlijk betekent?
Eh, gebruiken om, eh, met als doel mens of dier in gevaar brengen.
Mens of dier?
Ja, de samenleving. Ingevaar brengen of schade toebrengen.
Hebben we het niet over de natuur?
Ja, maar dat valt onder de samenleving…

8.3 Which errors with severe effects may/can be expected in synthetic biology, specifically in our application?

Wat zou er fout kunnen gaan dat een effect kan hebben?
Ik denk dat we nu nog weinig fout zouden kunnen doen.
Dus je hebt wel vertrouwen?
Tja, alles wat we maken is in het lab, en anders gaat het dood.
Hoe weet je dat?
Ik ken de details niet, maar wat wij produceren is toch sowieso zwakker dan wat er in de natuur is? Selectie zal ervoor zorgen.
Dus je hebt er wel vertrouwen in, ook al heb je het niet zelf onderzocht?
Dat heb ik me laten vertellen.

8.4 Consider our application: which deliberate misuses can you imagine?
Gaan we het hebben over deliberate misuse, als je kijkt naar de biothermometer, welke misuses kun je dan voor je halen?
Ja, input, temperatuurinput een soort van switch die iets kan activeren. Dat kan alles zijn, dusse…
Voorbeeld?
Bijvoorbeeld een switch die je eh, koel ergens heen transporteert en die vervolgens door warmte wordt geactiveerd. Beetje een Science fiction, maar toch. Gewoon een input syteem. Dat kun je ook misbruiken.

8.4.1.1 Who should be responsible for the safety of the application we've developed?
Wie is er denk je verantwoordelijk voor de veiligheid van de applicatie die wij ontwerpen?
Dat ligt voornamelijk bij de overheid.
En hoe zit het dan met open source, die autonoom is, en geen regulering kent?
Die kan toch ook gereguleerd worden door de overheid? De kennis mag er wel zijn, maar als je gevaarlijk stukje DNA bestelt, zou de overheid moeten reguleren dat dat niet kan.
… DNA synthese

8.4.1.2 Who should decide if it's safe?
Wie moet er dan beslissen uiteindelijk of iets veilig is of niet?
Ook de overheid, die de regels moet opstellen.
Waar ligt onze eigen verantwoordelijkheid dan?
Ja, die heb je natuurlijk ook wel, maar ik kijk dan meer naar of je een dodelijk gen maakt. Daar moet je dan regels voor hebben. Eigen verantwoordelijkheid heb je altijd wel, in de cultuur ofzo.

Question 9 – Your role as researcher

Goal: investigate participant's idea on science communication and social responsibility

9.1a What is your idea on science communication? Where do you have responsibilities?
Hebben we het even over jouw rol als wetenschapper. Blabla… Wat is jouw verantwoordelijkheid in wetenschapscommunicatie?
Mensen bewust maken van wat er op dit moment allemaal wordt gedaan. Wat de laatste ontwikkelingen zijn en hoe gevaarlijk of niet gevaarlijk dat is.
In hoeverre heb je daar zelf verantwoordelijkheden in?
Ik denk dat de verantwoordlijkheid hiervoor ook bij de wetenschappers zelf ligt.
En hoe komt dat dan naar voren?
In je naaste omgeving, bekende wetenschappers op tv of in de krant.
Naar jouw persoonlijk, waar denk je dat jouw verantwoordelijkheden liggen?
Qua communicatie?
Ja.
Alleen m'n naaste omgeving. Familie, vrienden, informeren.

9.1.1 What do you think your responsibilities are towards science & scientific community?
Kennisoverdracht

9.1.2 What do you think your responsibilities are towards your direct supervisors?
Kennis, potentiele gevaren

9.1.3 What do you think your responsibilities are towards society?
Onderzoek doen, nut op de samenleving. Dat is een verantwoordelijkheid. En communiceren, WAT je aan het doen bent.
Is WAT genoeg?
Ook hoe de toekomst eruit gaat zien, wat je ermee gaat doen.

9.1.4 What do you think your responsibilities are towards the public?
Communicatie.

9.4 On which topics do you think your answers may be biased because of your academic background?
Zolang het maar goed is voor de mensheid, geen schade aanrichten. Communicatie komt te weinig voor in het algemeen. Eigen wereldje, bezig met dingen die je zelf leuk vindt.

VERGELIJK EENS MET ANDER BEROEP: doen wat je leuk vindt, weinig verantwoordelijkheid, etc.

Question 10 – Participation B

Goal: review session & investigate group process

10.1 Are there issues that have been brought up in this session that should perhaps have received more consideration in the project design?
Nee. We zitten nu nog in een fase waar ethiek wel belangrijk is, maar waar je niet op hoeft te focussen.
Waarom is ethiek dan wel belangrijk?
Het is toch iets dat speelt.
Dus het is meer de bewustwording?
Ja, je maakt nog niet echt een product, je hebt nog niet echt een invloed, maar je moet wel bewust zijn van wat er is.

10.2 Have issues been brought up that you had not considered earlier?
Ja, die waren er wel. Even graven… Verantwoordelijkheid, heb ik sowieso nog niet zoveel over nagedacht. Dus…

10.3.1 Would you consider to work on easier topics sooner than on uncertain, perhaps more innovative or potentially innovative applications? – blabla
Fundamenteel onderzoek, het moet wel nieuw zijn. Toegepast is wel belangrijk, maar niet zozeer mijn interesse.

10.3.2 Were decisions made in design (after brainstorming), that you do not agree with or are not happy with afterwards?
Jammer: misschien is in en output toch iets te veel voor een team. Parts maken kost meer tijd dan verwacht.

Notes