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RESEARCH ARTICLE

Interactive learning and action: realizing the promise of synthetic biology for global health

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Abstract The emerging field of synthetic biology has the potential to improve global health. For example, synthetic biology could contribute to efforts at vaccine development in a context in which vaccines and immunization have been identified by the international community as being crucial to international development efforts and, in particular, the millennium development goals. However, past experience with innovations shows that realizing a technology's potential can be difficult and complex. To achieve better societal embedding of synthetic biology and to make sure it reaches its potential, science and technology development should be made more inclusive and interactive. Responsible research and innovation is based on the premise that a broad range of stakeholders with different views, needs and ideas should have a voice in the technological development and deployment process. The interactive learning and action (ILA) approach has been developed as a methodology to bring societal stakeholders into a science and technology development process. This paper proposes an ILA in five phases for an international effort, with national case studies, to develop socially robust applications of synthetic biology for global health, based on the example of vaccine development. The design is based on results of a recently initiated ILA project on synthetic biology; results from other interactive initiatives described in the literature; and examples of possible applications of synthetic biology for global health that are currently being developed.

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Introduction

Synthetic biology is a relatively new and rapidly developing field of biotechnology that has great potential for improving global health. Synthetic biology can contribute to global health by, for example, the development of novel drugs, vaccines and antibiotics that could contribute to realizing Millennium Development Goal 6—combat HIV/AIDS, malaria and other diseases (e.g. Jain et al. 2012; Blakely this issue). It could also contribute to faster and cheaper production of anti-malarial drugs: development of the precursor molecule of *artemisinin* is likely to make the drug accessible to more people in poorer countries (Keasling 2008). Analysis of the mechanism underlying protein aggregation related disorders, such as Parkinson's disease and Alzheimer's disease, has the potential for earlier diagnosis and treatment of such diseases (Jain et al. 2012). In response to scientific advances and the promise of the field, the World Health Organisation (WHO) has recently published a guidance document that acknowledges the potential application of synthetic biology to health care worldwide (WHO 2010). In 2011, the Bill & Melinda Gates Foundation put out a call for proposals, focusing on synthetic biology applications for global health challenges, to help realize this potential (Rooke this issue).

The potential of synthetic biology for global health is clearly recognized but it is not yet known whether it will reach its potential. History demonstrates that science and technology development is not straightforward and simple but, rather, a meandering and complex process. This complexity is illustrated by mismatches between science and technology and their application or use. In some cases, needs of patients remain unmet. One example of this mismatch can be found in the field of treatment of burns where future research priorities of health professionals and pharmaceutical companies did not fully match the needs of burn survivors. A study was conducted to identify research priorities of burn survivors, health care professionals and researchers. Patients identified new research priorities, such as treatment for itching on scars and donor tissue that were not being addressed by research (Broerse et al. 2010).

Another issue arises when innovations are poorly adopted, as was the case with the introduction of cochlear implants for prelingually deaf children. Manufacturers and health care professionals presented the innovation as a much-needed solution to increase the quality of life of prelingually deaf children. However, some parents and advocacy groups felt that this presentation was degrading to these children and the richness of their culture, causing a less than expected adoption of the new innovation (Van der Wilt and Reuzel 2012).

There are also examples of innovations that turned out to be used in a completely different way than planned or expected, such as the unforeseen use of anti-malaria bed nets for drying fish and fishing in villages along Lake Victoria, Kenya (Minakawa et al. 2008). In addition, innovations can have unexpected negative side effects. The well-known controversy surrounding the use of DDT (dichlorodiphenyltrichloroethane) to combat malaria is an example of the latter. O'Shaughnessy (2008) gives an historical overview of the unintended consequences of the use of DDT, including the bizarre situation in which cats were parachuted into Borneo, Indonesia, to replace domestic cats which had been poisoned by DDT. The death of the cats resulted in an increase in rodents and had negative accompanying effects, such as transmitting diseases and eating crops. This was an unforeseen, unwanted consequence of DDT use (O'Shaughnessy 2008).

Furthermore, the impact of innovations is regularly lower than expected due to constraints encountered during implementation. An example of this is the challenging introduction of vaccines in developing countries. Although there are many successes, such as the eradication of smallpox, there are also examples that show that reaching the potential of vaccines is quite difficult. There are many essential contextual elements that make a vaccine work in the real world, including the effectiveness of the vaccine product itself, the availability of sterile syringes and refrigeration (Cheyne 1989), an effective vaccination programme, an efficient vaccine safety system, and public confidence in the safety and necessity of the vaccine (see e.g. Burgess et al. 2006; Cooper et al. 2008; Hardon and Blume 2005). The difficulty of taking real world conditions into account in a test setting means that reaching the potential of the promises of science and technology developments is a challenging endeavour.

Reaching the potential of synthetic biology applications is probably also not straightforward and could suffer from possible mismatches as the ones described above. Moreover, there are several issues, inherent to the development of synthetic biology for global health, that need to be addressed. Several of these issues are elaborated upon in this journal, or have been addressed in a previous special issue of this journal edited by Schmidt et al. (2009). We briefly summarize these issues here.

There are questions around the definition and scope of synthetic biology and the interdisciplinary character of the field (see e.g. Delgado and Porcar 2013). The co-existence of the different, sometimes opposing views of the involved disciplines indicate there are still many possible directions that synthetic biology could take. Delgado and Porcar (2013) argue that it is important to search for the direction in a reflexive and socially robust way.

Other issues that have been identified relate to patenting, intellectual property rights, power relations or differences, equity, symmetry and access (see e.g. van den Belt this issue). These issues also make the development of synthetic biology for global health a complex endeavour. How to account for matters of equity and access? Who is responsible?

There are also ethical, social and legal aspects described in the literature that are important to address in the development of synthetic biology (see e.g. Anderson et al. 2012; Schmidt et al. 2009). If ethical concerns are ignored or the potential negative social impact is underestimated, poor adoption of the innovation or even public opposition can be the consequence as in the case of genetically modified organisms.

In addition, there is also the question of how to deal with uncertainty. As synthetic biology is still in an early phase of development, there are few concrete applications and it is difficult to predict the consequences. It is difficult to realize the potential if neither the potential nor the problems to be addressed are known (see e.g. Zhang et al. 2011).

To bring about robust societal embedding of synthetic biology, the innovation will need to be successful in solving specific problems but, in addition, the right problems need to be addressed. With regard to innovations in health care, Flier (2009) puts it as follows: "without a correct diagnoses there is no cure". The problems in implementation identified above illustrate the need to look at ways to better link science and technology to its application in society.

In this article we will first briefly describe the historical route towards the concept of responsible research and innovation (RRI) as a way to realize robust societal embedding of science and technology. Next, we describe a conceptual framework for RRI as we have developed it in our own research. We illustrate its practical application by presenting some preliminary results of our research on synthetic biology. Furthermore, we hypothesize what an RRI project could look like in the field of synthetic biology and global health.

Opening up science and technology development: towards responsible research and innovation

The examples in the introduction clearly show the potential for synthetic biology to improve global health but, at the same time, there are challenges relating to, for instance, access, power relations, patenting and ethics. This complex relationship between science and technology development and its applications in society has been studied extensively within the field of science and technology studies (STS) since the 1970s (e.g. Fuller 2000; Grin et al. 1997; Nowotny et al. 2001; Rip et al. 1995; Gibbons et al. 1994).

Initially, the innovation process was seen as a chronologically linear process with the following phases: basic research, applied research, product development and use (Sismondo 2011, p. 93; Godin 2006). Reasoning from such a model, better adoption and acceptance of science and technology was achieved by providing more and better information to users so they can appreciate the innovation and know how to use it appropriately. However, several STS scholars have shown that more information does not solve the observed adoption and public acceptance problems (Irwin 1995; Wynne 1995). In the 1990s, a new vision arose in which the innovation process was viewed as a complex social activity in which various actors interact. Innovation comes about through a forked process of variation and selection that is not only technological: social, organisational, political, economic and cultural factors also determine the direction and outcome of innovation development. From this perspective, science and technology are linked to the context of application by the active involvement of the users and other stakeholders in the interactive process of analysis, design and implementation. In other words, in order to address complex societal problems, a broad range of stakeholders with different views, needs and ideas need to have a voice in the innovation process. This idea has been framed in for example transdisciplinary research[1] (Klein et al. 2001), post-normal science (Funtowicz and Ravetz 1993), and mode-2 knowledge production (Nowotny et al. 2001; Gibbons et al. 1994). According to these and other scholars, this requires a multi-stakeholder dialogue (Jasanoff 2003; Nowotny et al. 2001; Rip et al. 1995; Bunders et al. 2010; Feenberg 1999; Hagendijk and Irwin 2006; Mitcham 1999; Weldon 2004; Wynne 2002) .

This plea for an interactive multi-stakeholder dialogue has gained much support. It is recognized that more transparency and openness could lead to a more responsive culture for innovation. In many countries, it is no longer the question if stakeholders should be involved but rather how a dialogue between policy makers, scientists, the industry, societal organizations and the public can be successfully set up. In recent years, the umbrella term 'Responsible Research and Innovation' (RRI, see for example the article of Douglas and Stemerding, this issue; Owen et al. 2012) is used to describe these interactive initiatives. Responsible research and innovation means that the innovation process focuses on (1) the realization of societal values in which (2) all societal stakeholders are involved and (3) the social, ethical, legal and environmental aspects, risks and chances are mapped and addressed (anticipated), with (4) openness and transparency as integral components.

Due to asymmetry in knowledge and power, meaningful multi-stakeholder dialogue rarely occurs spontaneously and requires active facilitation and appropriate methods. The number of methods of RRI has increased rapidly over the past decades. Some of these methods are designed to facilitate dialogue between citizens, such as consensus conferences, citizen panels and public advisory boards. Others focus on designing an interaction and dialogue between different stakeholders in the innovation process, such as Constructive Technology Assessment, upstream engagement, public debates such a the Science Café (see Box 1).

However, evaluative studies show a sobering image. Many initiatives do not meet their expectations: the influence on science and technology policies is scarce, the intended support is seldom realized, and the direction of research barely changes (e.g. Hagendijk and Irwin 2006; Irwin 2001; Jasanoff 2003; Weldon 2004). The reasons for this are not always clear because there are not many thorough evaluation studies, although there are some clues. Participatory methods are more informative or consultative and not focused on inclusion in decision making participation. Or involvement of stakeholders occurs too late in the development process to influence decisions. The framing of the topic of deliberation may be too narrow, causing 'real' questions and concerns to stay out of sight. Or policy makers do not take the outcome seriously because it does not match their own ideas and plans. The problems of pseudo-participation are worrying because

[1] Transdisciplinarity is described as'a new form of learning and problem solving involving cooperation among different parts of society and academia in order to meet complex challenges of society' (Klein et al. 2001).

Box 1 Science Café

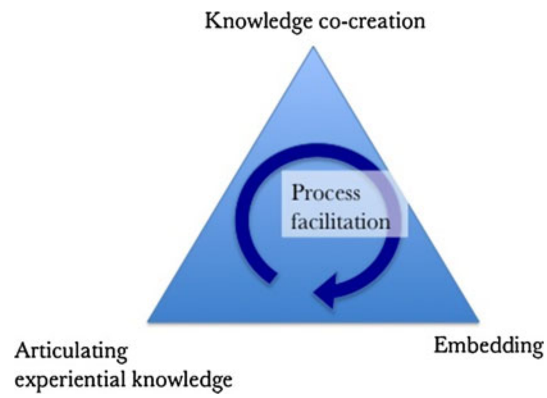
An example of a strategy to facilitate discussion and dialogue between several stakeholders is the Science Café method as described by Navid and Einsiedel (2012). They phrase the goals of a Science Café as: 'to promote public engagement with science and provide a forum for scientific inquiry for the general public' and describe the success of this approach in a sense that 'it brought discussions about an emerging and potentially controversial technology out of the laboratory and into the public realm'

However, they also describe that the scientists in Science Café thought that preparing for and participating was 'troublesome and time-consuming and that they could not perceive any benefit' which shows that there is still some work to do before a meaningful dialogue is realized

they can allow established parties to dismiss inclusion. It is thus essential to gain insights into the factors that facilitate and constrain these kinds of processes.

The question thus is: how to design a successful interactive innovation process? This question was taken up by the Athena Institute, VU University Amsterdam, more than two decades ago. It started with researching 'best practices'. There were already some positive results in the field of agricultural research in developing countries. Since the 1980s, small-scale farmers have been involved in the development of new crops and production techniques through a method called 'participatory technology development' which generally involved joint field experiments, designed and implemented by researchers and farmers (Broerse 1998). By studying these best practices, success factors were identified. We also assessed case studies of successful and failed innovation processes to provide more insights into what works and what does not. This all led to the formulation of the first prototype of our multi-stakeholder dialogue process, the interactive learning and action (ILA) approach. This prototype has been tested, evaluated and adjusted over the years in a large number of projects, including projects in emerging science fields such as genomics and neurosciences and in sectors such as agriculture, environment and health.[2]

All the projects in which ILA was applied have been subjected to a thorough process, outcome and impact evaluation in which the facilitating and impeding factors were explicitly analysed. The large number of projects, combined with findings from the literature on similar initiatives, allows us to make more generic statements about how to design an interactive innovation process (Broerse 1998; Broerse and Bunders 2000; de Cock Buning et al. 2008; Regeer and Bunders 2009). The four key interrelated factors are depicted in the following figure (Broerse 2013) and will be described in more detail.



Articulation of experiential knowledge

To develop better innovations, also from the perspective of citizens and users, it is crucial to gain insights into the needs and context of these groups. However, these groups have often scarcely thought about research and have not formed an opinion on the matter, which makes it difficult to understand their visions, ideas and perspectives. Their perspectives are grounded in their personal experiences. Gaining insight into their perspective requires the articulation of their experiential knowledge. Starting from the problems and concerns in their daily lives and via corresponding possible solutions, their ideas on research topics can be elicited.

In our ILA projects, we generally see that citizens and users are perfectly able to deliberate on research and innovation and to set research priorities. The formulated research priorities are generally very diverse, covering all domains in life and concerned with short term, applied research and long-term, basic, research. In almost all projects, groups of stakeholders identify new topics of research. Making experiential knowledge explicit has as an additional benefit in that it supports the self-image of these groups: they feel heard and attach more value to their experiential knowledge. In addition to citizens and end-users, the experiential knowledge of other stakeholders is also articulated. In this respect, diversity is a key factor.

[2] "To indicate the appreciation of programs using the ILA approach in developing countries, at a World Bank conference on Science, Technology and Innovation for Development in February 2007 (attended by ministers from developing countries amongst others) eight showcases were selected as "best practices". Two of the eight cases were in the field of agricultural biotechnology for resource-poor farmers (the Indian and Colombian case) and used the ILA approach." (Bunders et al. 2010, p.133).

Knowledge co-creation

A multi-stakeholder innovation process implies knowledge development between science and society: the more subjective, experiential knowledge of societal stakeholders needs to be integrated with the scientific knowledge of researchers in a process of knowledge co-creation in which the whole is more than the sum of the parts. It takes into account real-life complexity and the wide scale of different views and perspectives that come with this complexity (e.g. de Cock Buning et al. 2008). The innovation process thus takes the shape of transdisciplinary research (see above). A prerequisite of successful co-creation is that the different stakeholders learn from each other. Reflexivity is a key concept here. Based on this, the participants can change their opinions and come up with new ideas. This makes the process interactive: co-creation is established in a meaningful dialogue between scientists and other stakeholders.

Embedding

Research ideas that result from knowledge co-creation subsequently need to be implemented in research projects, leading to innovations that can be successfully applied in practice. However, this is by no means an easy process and it requires a responsive research system that (1) is demand driven, (2) sees societal responsibility as an important value, and (3) considers interaction with societal actors and their experiential knowledge as an enrichment of scientific research. Currently, the standard research system is not very responsive: it is generally driven by scientific curiosity, scientific excellence and peer approval. To counteract this, new ways of thinking about, organizing and doing research are needed. Concretely this means that competences (knowledge, attitudes and skills among societal stakeholders and researchers) and structures (procedures, institutions and incentives) need to be developed that support and *anchor* the multi-stakeholder innovation process. Identifying and implementing 'quick wins', research projects that could yield success on a short term, is in important strategy to experiment with these new competences and structures. These experiments need to be monitored carefully and continuous reflection on the results is needed so that adjustments can be made if necessary. This is a so-called *action-learning spiral*. In this change process, it is essential to have a group of supporters, namely people who are not directly involved in the process but who have key positions in the 'system', for advice and support (Broerse 1998). For example, it is very useful to have close involvement with a designated research funder to achieve the most socio-economic impact. Research funders are in an ideal position to adjust structures.

Process facilitation

The above-mentioned processes do not run automatically, a competent facilitator is necessary. The main goal of the facilitator is to create a qualitatively good process in which the experiential knowledge of different stakeholders becomes explicit, knowledge is co-created, actions are being implemented, and interactions are embedded. An important task of a facilitator is the creation of trust between the stakeholders. At the beginning of the process, the level of trust between different stakeholders is usually low because there are hardly any routines, procedures and protocols to build upon. The facilitator can, as a third party, enhance 'intermediated trust' by giving information concerning the perspective of one group to other groups, so that the participants form a more realistic image of each other and mutual trust develops (Broerse 1998). If this then leads to a shared vision and the first positive results, the willingness to undertake action increases.

Another important task of the facilitator is to avoid exclusion. Hierarchical differences are highly ingrained and processes of exclusion can be very subtle. Researchers often have a rather narrow definition of knowledge and research; they have the tendency to label experiential knowledge as subjective and to sideline topics that concern policy and implementation research, thereby reducing the input of citizens and users (Elberse et al. 2011). To fulfil his or her tasks, it is important that the facilitator is competent in executing transdisciplinary research, knows which methods and techniques to use for which goals, and adheres to the criteria of scientific research: 'transparency' and 'validity'. The quality of the process of data collection and analysis influences the legitimacy of the outcomes. This is a particularly important argument for researchers and professionals. In larger projects, the role of facilitator will not be performed by one person but by a team. A team has the ability to do justice to the complex and interdisciplinary character of complex problems.

Designing an ILA process

To operationalize the concepts and success factors mentioned above, the ILA approach comprises several design guidelines. In the ILA methodology, five phases are distinguished, each with their own objective.

Exploratory phase: In this phase, a research team is established. Through literature research and exploratory interviews, a preliminary overview is obtained of the developments in the scientific field, the relevant stakeholders and their perspectives, as well as the problem context.

In-depth phase: The aim of this phase is to identify and analyse the problem perceptions, opinions and ideas of the different stakeholders, including researchers. Given asymmetry in power and knowledge, as well as the different framing of the topic by the various stakeholders, organizing a dialogue early in the process is less effective. In particular, those who have not had the chance to familiarize themselves with the matter will not yet have formed an opinion. An early dialogue is then likely to lead to dominance by experts. For this reason, the stakeholders are first consulted separately.

Integration phase: The perspectives of the different stakeholders are compared and, as much as possible, integrated by means of multi-stakeholder dialogue.

Prioritization and action planning phase: Mutual visions are formulated and quick wins are identified. In addition, responsibilities are determined and follow up meetings are planned.

Implementation phase: The plans are put into practice in multi-stakeholder learning-action spirals.

We have recently initiated an ILA project on synthetic biology. This project is non-sector specific and thus does not specifically aim at possible synthetic biology applications for global health, but it does address (global) health-related opportunities, besides covering applications for energy and agriculture. In this project, we have first identified various relevant stakeholders, explored the topic through desk study and exploratory interviews, and we are currently in the second, in-depth phase in which we are consulting various stakeholders and researchers in the field of synthetic biology. To illustrate the type of information yielded by the ILA approach, some initial results of the project are presented in Box 2.

From these preliminary results, it is clear that there are differences between the manner in which citizens and researchers articulate their ideas and opinions. Both groups recognize opportunities but differ greatly in the extent to which the future is viewed positively. This needs to be addressed in a multi-stakeholder dialogue. What are their expectations and desires? And where do these expectations meet each other? And how can the concerns be taken into account adequately?

Researchers often mentioned that it would be very useful to have some concrete ‘good examples’ of synthetic biology to minimize public distrust while, at the same time, being realistic and not exaggerating possible positive applications to avoid disappointment and lack of confidence in the field. As described in Box 1, participants often linked the future of synthetic biology to stories from the news. Since these stories are mostly negative, it is important to address these issues and discuss them freely. However, highlighting good examples and the positive potential of certain applications might not prevent public distrust. And even if the need for positive stories is acknowledged, it remains unknown what the public considers to be desirable. From the focus groups, it seems that medical applications are considered more desirable than those in the field of agriculture and energy. Ethical concerns are raised in all fields of application but seem to be more easily overcome if related to health than in the field of agriculture and energy. It also seems to matter whether the synthetic biology part was applied during the process of making a new product or if the end product was something that was synthetically manufactured; the latter being considered less desirable. It is very likely that a dialogue in which this is taken seriously will contribute to enhancing the embedding of synthetic biology.

Applying the interactive learning and action approach on synthetic biology in the context of global health

In this section, we use the experiences with interactive processes, insights described in the literature and the recent experiences with an ILA project on synthetic biology (see Box 2) to propose how a multi-stakeholder interactive process could be deployed for the field of synthetic biology in the context of global health. To make this more tangible, we will focus on one example, namely the role of synthetic biology in vaccine development.

The international community recognises that vaccine development can make a key contribution to global health. According to the GAVI Alliance, vaccines development and immunisation programmes can make an important contribution to seven of the eight MDGs,[3] international goals for development during 2000–2015 agreed at the UN Millennium Summit in 2000. The GAVI Alliance also calculates that “vaccines have helped reduce child deaths by 30 % since 1990, that they prevent over 2.5 million child deaths each year, that 79 % of children in developing countries are now being reached by national immunisation programmes compared with 66 % in 2000. In recognition of the importance accorded to vaccine development by the international community, the GAVI alliance, the World Bank, the Bill & Melinda Gates Foundation and the WHO are working together to increase access to immunization and improve the health system. In addition, vaccine development covers about half of the Grand Challenges in Global Health, an initiative launched by the Bill & Melinda Gates Foundation in 2008.

By contributing to vaccine development, the field of synthetic biology might have much to offer when it comes to realizing the MDGs. For example, vaccines could be developed to combat pneumonia and diarrhoea, two major causes of infant and child mortality, and would make an important contribution to MDG 4 on ‘reducing child

[3] See http://www.gavialliance.org/about/ghd/mdg/.

Box 2 Articulation of experiential knowledge of citizens and perspectives of researchers

A. Public perceptions of synthetic biology in the Netherlands

To identify citizens' perceptions of synthetic biology and to look for opportunities of early stage public engagement, we conducted eight structured focus groups with Dutch citizens (n = 46). The focus groups followed the same structure, the main part being three discussion rounds in which vignettes, short and nuanced examples of synthetic biology applications, were used to get the discussion going. The vignettes were divided in three applications, each with a different underlying discussion: (1) health: ethical aspects, (2) food and agriculture: social aspects and environmental aspects, and (3) energy: legal aspects. We outline some of the preliminary results here, with a focus on what these results could mean for a future dialogue

Despite the fact that the majority of the participants had never heard of synthetic biology and that there are not many concrete examples of applications in their life worlds, discussions were rich and lively. Opportunities are clearly mentioned, ranging from opportunities for the public good, the environment and the world as a whole to opportunities within their own life world. Participants found it easy to come up with possible interesting applications that were not mentioned in the vignettes. However, we observed that the discussions often had a negative pattern. Participants tended to link the cases to stories from the news media that were often negative. Associated topics included genetically modified organisms, stem cell research, embryo selection, cloning, nuclear disasters, famine, the oil crisis, and climate change. There was a certain level of distrust in almost all groups, especially about spending money on research and about whether the issues, mentioned in the vignettes or by fellow participants, were related to 'real' problems or reflected only self-interest. For example, to what extent is the climate crisis really taking place or is it a fabrication of politicians; are fossil fuels running out or is this a fabrication by large oil companies that only want to make money; and do we really have food shortage in the world or is it just a matter of unequal division of food. Differences between the three fields of application became apparent. The case of synthetically manufactured food products triggered questions on necessity and responsibility, whereas the health case, a vignette about synthetic organs, triggered more fundamental ethical questions about the limits of life and the 'artificial creation' of life. The case about bio-fuels raised questions about potential environmental damage, responsibility and money issues

A possible explanation for the negative pattern of the discussions may be that participants link this new technology to earlier technological developments with negative side effects. However, the explanation could have a more psychological nature, namely that people experience a lack of control in their own life and feel that the technology is forced upon them. The underlying reasons for this negative pattern should be investigated in further research and need to be taken into account in the development of communication tools and the design of dialogue

B Future visions of synthetic biology: researchers and partners from industry

To explore ideas and future visions of synthetic biology, and perceptions on interaction with societal stakeholders, we have conducted ten interviews with researchers and research partners within a large international research consortium: the bio-based ecologically balanced sustainable industrial chemistry (BE-Basic) consortium. BE-Basic is based in the Netherlands and aims to develop bio-based solutions for a sustainable society. The synthetic biology flagship initiative is part of the BE-Basic consortium. Fields of application include health, soil and ground water ecology, and energy

Researchers and research partners describe the field of synthetic biology as broad in which small pieces of large puzzles are being researched; it concerns mechanisms that play a role in many biological processes. Concrete examples of applications that will change the world, except for the examples from literature such as the development of synthetic pathways in the production of anti-malarial drugs and vaccines, were not given. Most synthetic biology research was said to be in an early phase, possibly contributing parts to a larger successful application in the future. Trying to understand these small pieces and parts is a major motivation of the researchers but they all acknowledge also being interested in the direction their research might take in the future and the problems it might solve. Researchers were of the opinion that it is important to consider possible applications in the early phases of research because this will benefit the eventual translation from knowledge into products, as long as it does not hamper basic research, freedom and creativity. Sustainability was a key word in talking about the future of synthetic biology and possible applications: more sustainable use of resources, more sustainable production processes from an energy perspective, and more environmentally friendly end products

Other topics raised concerned the broad multidisciplinary character of the field. Interviewees often talked about 'working together' and collaboration as a key feature of the field. This was frequently expressed as looking for synergy, being close to market opportunities, and the need for new modes of governance

Results also show that there is a general consensus that societal dialogue is very important. However, opinions differed on the way in which such a dialogue should take place and how active the researcher should be. They all agreed that engaging the public could be helpful for the image of synthetic biology but none of them considered pro-actively searching for inputs from outside the scientific community. An open approach towards the public at large was thought to be important. Some interviewees considered that openness to the public had already improved much in recent years, shifting from providing information about synthetic biology to engaging in a dialogue. They referred to their own activities and to the specific flagship initiative within BE-Basic that focuses on engagement and education. Some interviewees said that they felt that the public was interested in developments in the field of synthetic biology. On the other hand, interviewees felt it is important to avoid creating a hype that could lead to disappointment. Being realistic and communicating 'good examples' to the public is key. In addition, the majority of the interviewees also expressed their concerns with regard to public engagement because the level of technical knowledge, such as 'basic words like atoms, chromosomes and molecules', was thought to be quite poor. Talking about difficult technical matters would therefore be complex and could even lead to adverse responses

mortality'. The GAVI Alliance, the WHO, the World Bank and the Bill & Melinda Gates Foundation are all investigating the potential contribution of synthetic biology to the development of vaccines (Rooke, this issue). However, as we mentioned in the introduction, the working of vaccines is context dependent and complex, and calls for a process of interactive vaccine development in which the ILA can be deployed.

In the *first 'initiation and preparation' phase,* an interdisciplinary research team needs to be established to gather preliminary and contextual information to define the objectives and roles of stakeholders. This phase includes the identification of the scientific state-of-the-art through literature study, (explorative) interviews with involved researchers and attendance of conferences, as well as ELSA (or ELSI) research into the ethical, legal, and societal aspects. The scene is set in this phase: who are the (international) stakeholders active in the field? A stakeholder analysis, with a specific focus on diversity, will be conducted. In the case of vaccine development, this would include the GAVI Alliance, the World Bank, the Bill & Melinda Gates Foundation, the WHO, the UN Children's Fund (UNICEF), international non-governmental organisations (NGOs), international patient organizations, researchers, policy makers, and the vaccine development industry. For robust financing mechanisms and good quality of the process, influential stakeholders in the field of policy making and research funding need to be involved from the beginning, and throughout the whole process, to ensure that plans will be implemented. Questions that need to be answered in this phase thus include: which stakeholders are important, how do they work together, what are their interests and points of view? What are the overall expectations of the developments at this moment? Which concerns are at stake? Which initiatives are important? When the stakeholder analysis is conducted, it is important to map the different stakeholders that should be consulted in the next, in-depth, phase.

Global health is a global issue but, at the same time, needs to be linked to the local level. For this reason, a few countries per continent should be selected as case studies with ILA being undertaken at a national level. This procedure was also followed in a previous ILA project on biotechnology and developing countries of the Dutch Directorate General for International Cooperation (Broerse 1998). In such case studies, the specific context can be explored to facilitate making the link from a global to a local level.

In the *second phase,* needs, visions and interests of relevant stakeholders are identified using a variety of data collection methods, such as interviews and focus groups. This phase aims to reduce asymmetry of knowledge between researchers and societal stakeholders to some extent. Information that comes out of this phase will be used as input for the dialogue organized in the next phase. In our proposed ILA, the societal stakeholders are facilitated to become acquainted with, and form an opinion on, vaccine development, the opportunities and concerns in this development, as well as on the field of synthetic biology and the role the field can play in vaccine development. The societal stakeholders then reflect on this from their own practice, before entering a dialogue. These reflections provide the researchers with insights into practices with which they are normally largely unfamiliar. This phase also aims at increasing commitment for the process among the stakeholders involved, which is crucial for the success of the next phase.

Given that synthetic biology is in an early stage of development, it would be appropriate to start this phase with the consultation of a wide variety of scientists to obtain their perspective and ideas on future applications of synthetic biology in the field of vaccine development. To this end we would propose the use of the method of 'vision assessment' (Grin and Grunwald 2000). Visions can be described as 'mental images of attainable futures that are considered desirable and shared by a collection of actors' (Roelofsen et al. 2008). These visions of the future can be useful to stimulate learning about possible impacts, orient future actions, guide activities and bridge the gaps between different social levels and dimensions (Borup et al. 2006; Robinson et al. 2007; Grin and Grunwald 2000; Roelofsen et al. 2008, 2010). However, scientists in an emerging scientific field find it difficult to think about future applications with a 30–50 years time frame and do not want to exaggerate the potential, preferring to restrict themselves to short-term knowledge questions and the obvious applications that are already being researched (Kloet 2011; Roelofsen 2011). An expert meeting with scientists can complement the data obtained through interviews by focusing specifically on developing desirable (not necessarily feasible or probable) futures (Roelofsen 2011).

As mentioned above at the case country level, different stakeholders such as citizens, patients and their organisations, health care professionals, policy makers and representatives of local NGOs are consulted separately to obtain their views on vaccines and synthetic biology. In addition to interviews, group-based methods, such as focus group discussions, citizen panels, citizen juries, expert and community meetings and consensus conferences, are appropriate to articulate the experiential knowledge and develop opinions of the different stakeholders. In a group meeting, we would propose starting with the daily life experiences of the practice of immunization and focus on diseases that may be addressed by immunization through synthetic biology (e.g. malaria and diarrhoea). This would be followed by a discussion on participants' ideas on how these problems could be solved. Next, the participants would be asked to relate their problem definition and solutions to the opportunities provided by synthetic biology using, amongst other inputs, the identified future visions of scientists. Possible concerns relating to the suggested applications of synthetic biology would also be discussed. As a last step, participants could be asked to prioritize possible applications of synthetic biology.

From the consultation of the researchers and stakeholders it will become apparent that they frame problems, solutions and relevance of synthetic biology differently. This might hamper constructive and meaningful dialogue (Schon and Rein 1994). Therefore, the different 'frames of reference'[4] are studied and made explicit before heterogeneous dialogues are organized. It is important to analyse to what extent differences are more semantic or whether they are of more a fundamental nature. At the same time it is crucial to look at overlaps. It is the overlaps from which people derive their motivation to go into a dialogue.

The *third phase* concerns the 'integration' of these differing perspectives and needs of the stakeholders in heterogeneous dialogue meetings. The result of this third phase should be a thorough understanding of the problem and solutions from the perspectives of the stakeholders: where do views overlap and what are fundamental differences. During this phase, connections between research and practice are actively explored, resulting in the identification of desirable directions for research and the identification of new research opportunities. It develops common agreement on future directions for synthetic biology can contribute to vaccine development. In this case, such mixed dialogues could first take place at the national level in the case study countries, involving researchers and the various stakeholders in dialogue meetings (approximately 30 participants).

An important next step would then be to take the results of these meetings up at the international levels, where representatives of large international stakeholders, already identified during the first phase are invited to participate in an international dialogue meeting.

In the *fourth 'priority setting and planning' phase,* the stakeholders review and reflect upon preliminary results from the previous phases to identify priorities and establish a plan of action in which specific programmes or projects are formulated and implemented (Bunders et al. 2010; Broerse and Bunders 2000). Apart from identifying more general joint visions on vaccine development and the role of synthetic biology, it will be important to identify quick wins, so that the momentum is not lost and new collaborations are strengthened and experimented with.

More concrete example of possible outcomes in this phase are that stakeholder groups could together come up with a joint action list that acknowledges both the introduction of new vaccines as well as the other important aspects of combating these diseases. This joint action list could also tackle the issue of patenting, for example, and make a joint policy agenda to realize shared future visions. If this is a joint venture, and everyone is aware of his or her responsibilities, the process is more likely to end with policy change, and also that the new policies are more widely accepted.

During the *fifth* phase, the plans that were made in the previous phase will be implemented. What this phase will look like depends on the outcomes of phase four but it is of utmost importance to continue to involve the different stakeholders in this phase so that they do not go back to their 'business-as-usual' mode and only focus on answering their specific research questions. Thus, depending on the topic and involved stakeholder groups, concrete agreements will be made for follow up. It is also important to keep an eye on, for example, matters of funding and aspects that came up in previous phases.

In this section, we have outlined what an ILA project focusing on synthetic biology for vaccine development could look like. The scope of an ILA approach could be narrower or broader than this outline. For example, it would also be possible to conduct an ILA to set a common agenda for synthetic biology research for global health or an ILA that more specifically focuses on a certain application of a new vaccine, such as the research project described by Blakely and Vohra in this issue on the development of vaccines against diarrhoea. Blakely and Vohra identify several relevant stakeholders, such as the final recipients of the vaccine, who need to play an important role in its development. In addition, they also outline some concerns and issues that need to be addressed, such as the possibility of public distrust. When considering an ILA process, these issues can explicitly be addressed and integrated in the innovation process.

Concluding remarks

Various applications of synthetic biology appear to be relevant to global health and there seems to be a growing potential of the field. Synthetic biology appears to have particular potential in the development of vaccines, drugs and diagnostics. However, history shows that translation of innovations into practical use is not straightforward. Mismatches between the development of applications and societal use can occur, and ethical and social issues may arise. Robust societal embedding of science and technology has been a hot topic in the field of Science, Technology and Society studies since the 1980s and various attempts have been made to improve this. Efforts to ensure fair and equal innovation in science and technology development by involving stakeholders from the beginning, an ambition shared by this paper, are currently often referred to as Responsible Research and Innovation (RRI) (see e.g. Douglas and Stemerding, this issue; Owen et al. 2012). RRI

[4] A 'frame of reference' can be viewed as a combined set of knowledge, norms, and values and (societal) background by which people weigh, value, and interpret new information.

receives much policy attention across the USA and the European Union.

In this paper, we have presented a specific RRI approach, namely ILA, as a strategy to involve society in the development of synthetic biology in the context of global health. Central to the ILA approach is the continuous involvement of stakeholders and end-users in a process where experiential knowledge is articulated, knowledge is co-created between science and society, and attention is paid to the embedding of this new knowledge, all requiring a careful process of facilitation. The ILA approach has been developed over the past two decades and has led to, among other outcomes, the development of new research areas, empowerment of vulnerable groups, the alignment of research agendas, and the discovery of win–win situations (Broerse and Bunders 2000; Caron-Flinterman et al. 2006; Kloet 2011; Roelofsen 2011; Swaans et al. 2006).

The ILA was developed in the context of innovations in developing countries and has been proven to address issues similar to the ones that are involved in synthetic biology. Thus, ILA could be well suited to contribute to the development of socially robust applications of synthetic biology for global health. In this article, we propose an ILA for this purpose, based on results of our recently initiated ILA project on synthetic biology; results from other interactive initiatives described in the literature; and examples of possible applications of synthetic biology for global health that are currently being developed.

Involving many different stakeholders from inside and outside the scientific community is acknowledged to be essential in synthetic biology, and continuous reflexivity and mutual learning are required, as also mentioned by Zhang (2012). Given its continuous, cyclic character and its emergent design, an ILA process could be of help in 'accommodating networks of stakeholders' as the development of synthetic biology continues and expands (Zhang 2012). Zhang also argues that the 'border-transcending characteristics' of synthetic biology call for a different mode of governance, namely trans-boundary governance. For the trans-boundary mode of governance, Zhang (2012) explains that, for example, instead of persisting in defining synthetic biology, it could be more effective to facilitate cross-border communication in which all stakeholders learn from other disciplines. This notion is also supported by, for example, the GAVI Alliance argues that the introduction of new vaccines can 're-energise other important aspects of pneumonia and diarrhoea control, such as safe drinking water and sanitation'.[5] The Alliance also highlights the importance of an *integrated approach* to pneumonia and diarrhoea control. This also requires transdisciplinary efforts in which stakeholders from multiple levels should be involved, including community leaders or local health service providers.

In addition to the potential of such an approach, executing an ILA process can be time-consuming and might seem complex for researchers in the field of synthetic biology. It highlights the importance of a transdisciplinary approach. Social scientists studying the relationship between science, technology and society have build up their expertise on interactive development strategies that have led to the development of ILA. This paper should therefore be seen as an invitation to be involved in the development of synthetic biology for global health.

We acknowledge that the successes referred to in this article are small-scale and that it is very difficult to induce structural change in a research system. As the main challenge in realizing RRI in the field of synthetic biology and global health, we would point at the difficulty in realizing a transition towards a more responsive research system; a research system that is demand-driven, takes societal responsibility as an important value, and considers the interaction with societal stakeholders and their experiential knowledge to enrich the research process. From the results of our evaluation studies, a mixed picture emerges. Increasingly—at least in the Netherlands—research agenda are set and research programmes are formulated using multi-stakeholder dialogue processes, such as the ILA approach. For example, about half of the Dutch charity funds on disease-related health research have developed a research agenda that explicitly includes the perspectives of patients and sometimes citizens. At the same time, we have established that relatively little research is actually taking place on the topics specifically identified by patients and citizens, even though money is made available. In addition, after the phase of agenda setting, the involvement of societal stakeholders is rarely sustained. They are not involved in the design, assessment or implementation of research projects or dissemination of outcomes (Pittens et al. 2013). This is likely to result in less attention for the interest and needs of these groups. Indeed, it is 'business-as-usual'. The current research system is much less responsive to needs of societal stakeholders than aimed for in RRI. Changing the thinking and conduct of research is by no means simple and straightforward, given the general resistance of societal systems to change. We therefore argue that RRI needs an explicit systems' perspective in which strategies are applied to facilitate system innovation. Here, we would like to refer to the growing body of knowledge on transition theory and system innovation studies. This will bring us an important step closer to reaching the potential of synthetic biology for global health.

5 See http://www.gavialliance.org/about/ghd/mdg/.

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