Responsibility and intellectual property in synthetic biology

A proposal for using Responsible Research and Innovation as a basic framework for intellectual property decisions in synthetic biology

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Synthetic biology (SynBio) is an engineering view of biotechnology that has the potential to increase the number and industrial utility of biotechnological applications by implementing engineering principles such as standardization and modularity. The boundaries between SynBio, biotechnology, and metabolic engineering are not always clear, but assessing SynBio in a wider sense—that of modeling-based biotechnology and/or “sophisticated” metabolic engineering—we find that a significant number of applications and research articles have been generated in the past few years [1]. One of the best-known examples is that of a synthetic pathway for producing artemisinic acid, a precursor to the anti-malarial drug artemisinin, which has been engineered in yeast to produce commercially relevant concentrations of artemisinic acid. This impressive accomplishment can be easily adapted for the development of biofuels, biomaterials, new drugs, or fine chemicals [1].

“The concept of RRI has gained increasing relevance for policy in the EU and has become a cross-cutting leitmotiv in the Horizon 2020 strategy”

Two of the authors of this essay (PD and MP) attended the so-called Giant Jamboree

of the international Genetically Engineered Machine (iGEM) competition in Boston, as members of the Valencia Biocampus team, and presented a project, supported by the EU-funded SYNENERGENE initiative (<http://www.synenergene.eu>), on Intellectual Property (IP) in SynBio (http://2014.igem.org/Team:Valencia_Biocampus/). The project included an attempt to develop a common language for practitioners, from lawyers to scientists and engineers. Moreover, the team developed an attempt to quantify IP issues by including a “patentability index” (PI), with values ranging from 0 to 10 based on parameters including novelty, inventive step, and industrial application. An additional parameter, “responsibility” (R), was introduced in such a way that the PI can only be greater than zero when R is not zero. In other words, lack of “responsibility” could lead an otherwise-patentable SynBio invention to fail the test. Inspired by this somehow provocative idea, we describe here a proposal to link the concept of Responsible Research and Innovation (RRI) to IP (Fig 1). In particular, we try to elucidate whether IP schemes and the RRI concept could be mutually beneficial to foster innovation in SynBio, which may be required to provide solutions to the grand societal challenges we face.

RRI and its cognate expressions “responsible innovation” and “responsible development” have evolved over at least ten years, both in Europe and in the USA [2]. They are based on using applied ethics, science and technology studies (STS), and technology assessment

(TA) to shape research and development (R&D) processes to address the so-called societal goals: global health, sustainable development, protection of biodiversity and so on. The concept of RRI has gained increasing relevance for policy in the EU and has become a crosscutting *leitmotiv* in the Horizon 2020 strategy.

“... it is more important how patents and property rights are applied when it comes to fostering the development – and accessibility – of innovations for social benefits”

A first working definition proposed by Von Schomberg [3] describes RRI as: “[...] a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society).” What this could mean in practice has remained rather vague, however. A more integrated conceptual framework for “responsible innovation” (RI) has been proposed recently to translate the concept into practice and referring to specific initiatives. Defining “responsible innovation” somewhat more broadly as “[...] taking

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Figure 1. Responsible Research and Innovation (RRI) as the fulcrum for choosing an appropriate IP scheme in synthetic biology.

care of the future through collective stewardship of science and innovation in the present,” this framework suggests to integrate four dimensions: reflexivity (to reflect on the underlying purposes, motivations, and potential impacts); anticipation (describing and analyzing possible impacts to create appropriate solutions or policies); inclusiveness/deliberation (listening to perspectives from publics and stakeholders); and responsiveness (using the previous dimensions to set the direction of research and innovation) [2]. In summary, the notion of RRI is that research and development interact with society to ensure that the outcomes of research meet societal needs.

In biotechnology and SynBio, the most relevant forms of IP are patents that provide exclusive rights for a fixed period

of time in exchange for public disclosure of the inventions. However, other forms exist and are being used in practice: utility models, industrial designs, trademarks, trade secrets, know-how, plant breeders’ or plant variety protection rights, copyright and so on. Referring to one of synthetic biology’s key concepts—namely the use of standardized biological parts that should be freely available and exchanged via repositories—open-source-like approaches have been proposed to foster the development of SynBio. Within this vast array of possibilities, a diverse ecology of open and proprietary exist, as metaphorically referred to as a Diverse Ecology Scenario, a concept introduced by Drew Endy and further developed by Jane Calvert [4].

The concept of RRI requires that the impacts of science and innovation should go beyond merely economic or financial gains.

RRI is based on cooperative shaping or steering research and innovation by involving stakeholders and the public, toward societal beneficial outcomes and societal needs, as a prerequisite for sustainable economic growth. These outcomes and needs include the ethical acceptability of innovations, increasing the quality of life and contributions toward economically, socially, and environmentally sustainable development [3]. To foster RRI, IP schemes should not only increase innovation and its economic exploitation, but they should also have the potential to encourage and drive innovations toward addressing societal needs to yield “broader” societal benefits. A prerequisite would be that IP schemes could modify the application of technologies and innovation, and influence research at earlier stages of the innovation process. But is there evidence that this may be the case?

Empirical studies of scientific publications and citations linked to patented inventions suggest that patent rights can in fact impede research in biomedicine and human genomics. Similarly, recent data on causal effects of removing patent rights by US court invalidation confirm patents can affect the trajectory of later innovations [5]. Negative effects on research can strongly vary across different fields. They are mostly concentrated in complex technologies with highly fragmented patent ownership, such as electronics or medical instruments, but not in the pharmaceutical or chemical industries. The extent of such effects also depends on the size of patent-owning companies [5]. Additionally, data from history suggest that patent laws may affect the direction of technological development: It appears that, in countries without patent law, innovation tends to concentrate on a narrow range of industries in which secrecy is effective [6]. However, these data hardly provide specific evidence that patent rights can be used to drive public or private R&D toward societal needs/benefits that go beyond market profitability and macroeconomic considerations—as aimed at by RRI.

A better example may be combinatorial schemes, such as the US Orphan Drug Act, to promote the development of treatments for rare “orphan” diseases. These include, in addition to tax credits for certain development costs, lower hurdles for approval and longer market exclusivity rights. Such schemes are considered highly successful and have increased the number of molecules and approved drugs to treat orphan diseases [7]. By promoting market profitability for drugs or therapies, these schemes have also fostered R&D on issues that are not of “macroeconomic importance,” but are desirable for ethical and societal reasons.

“... RRI could play a more constructive role by choosing IP schemes that could guide research and innovation processes towards desirable goals and needs”

Owing to the composite nature of the schemes, however, the specific role of the IP

part, longer market exclusivity, is difficult to judge. Data on investments into clinical trials of cancer drugs suggest that longer protection/exclusivity rights may indeed change or broaden R&D efforts toward more “societal desirable” applications. Clinical trials are costly and may take several years, and—because patents are filed at the time of drug discovery—shorten the time for a patent to yield revenues before cheaper generic products can enter the market. This so-called effective patent term therefore depends on the length of trials, which have to prove that drugs positively affect survival time. Clinical trials tend to be longer and thus shorten the effective patent terms for drugs against milder or localized tumors compared to later-stage metastatic cancer. A recent study based on data of 80 cancer types and associated R&D investment in clinical trials suggests fewer investments by firms in patient groups that require longer clinical trials [8]. Longer protection or market exclusivity rights, as granted for orphan diseases, might change cancer R&D directions: from lucrative R&D for late-stage cancer to more R&D efforts targeting curable early-stage cancer as well as cancer prevention [8].

“iGEM may therefore provide an ideal testing ground for experimentation on open and proprietary IP schemes...”

Instead, it is more important how patents and property rights are applied when it comes to fostering the development—and accessibility—of innovations for social benefits. This can include “humanitarian licensing” including clauses in patent licenses to support research or uses that meet the needs of developing countries. Generally, patents allow or license academic, nonprofit-oriented research on the patented technology. Some licenses specifically allow the generic production of drugs in developing countries, such as Yale University’s license with Bristol-Myers Squibb Co. for stavudine (Zerit®), a widely used HIV/AIDS drug. Other patents explicitly allow further development of royalty-free inventions, as in the case of the vitamin-A-enriched Golden Rice. Similarly, a royalty-free license to produce the artemisinin precursor for antimalarial drugs has

been donated to the nonprofit organization iOWH/PATH and its industrial partner Sanofi (<http://news.berkeley.edu/2013/04/11/launch-of-antimalarial-drug-a-triumph-for-uc-berkeley-synthetic-biology/>).

There are also potential pitfalls with patents that could conversely hinder RRI in synthetic biology and might restrain further research and innovation or restrict access to innovation: “broad” patents on basic biological parts or techniques; a large number of patents (the so-called patent thickets) that might be connected to complex functions; or the concentration of patents with a few companies. It is therefore important to determine the roles that different IP schemes—as well as “open-source” approaches—could play in reaching RRI’s goals, and conversely, how RRI may help to choose among IP schemes or even to improve them.

To what extent open-source approaches—in analogy to open-source software models which rely on copyright—may contribute to innovations in biotechnology or biomedicine, and thus fulfill RRI’s goals, remains to be seen. First, whether or under which conditions copyright will be applicable to biotechnological approaches is unclear, mainly because copyright laws do not cover functional articles or aspects but rather require the so-called expressive choices; that is, how a functionality is implemented (<https://softwarefreedom.org/resources/2007/originality-requirements.html>). Whether any approach based on the existing gene sequence data would meet this requirement seems far from clear [9]. In addition, open-source schemes might only work well in certain segments of the innovation process, such as data mining or finding early-stage drug targets or compounds, or where relatively weak open-source incentives are not in competition with profitable royalties from IP rights, as in the development of treatments for neglected tropical diseases. It is unclear whether open-source schemes can work in downstream processes—including “wet” laboratory work or drug approval—where development costs are higher, or in areas that promise high returns. A further issue is the role that patents play in research evaluation and in financial markets, especially to allow small companies to find venture capital. Finally, it is arguable whether open-source schemes can be “truly” innovative and produce new or “better” products, or just “cheaper” versions.

Nonetheless, in areas such as neglected diseases, open-source approaches may be able to contribute to one of the key goals of RRI: fostering innovations that are not merely driven by market profitability.

“The dogma that scientific advance must lead, per se to more societal benefit has been seriously challenged”

In summary, various IP schemes—including open source and the way in which intellectual property rights are applied—might contribute to RRI by guiding research and development toward socially desirable outcomes. This raises the question of the extent to which RRI concepts could, in turn, contribute to the ecology of open and proprietary schemes. And what might responsibility within RRI actually mean in terms of the main form of IP in biotechnology: patents?

The contribution of RRI to IP should go beyond “merely” preventing unethical inventions or abuse—as, for example, the European Directive on the “Legal Protection of Biotechnological Inventions” that prohibits patenting inventions that would be contrary to *ordre public* or morality, such as processes for cloning human beings (<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31998L0044>). Instead, RRI could play a more constructive role by choosing IP schemes that could guide research and innovation processes toward desirable goals and needs. For researchers or inventors, this may imply specifying appropriate licensing or not seeking a patent at all. They could also help to mitigate the problem of vague and overly broad patents and the so-called patent trolls. Such “nonpracticing entities” acquire patents without any intention to develop commercial products and make profit by suing companies that (allegedly) infringe their patents. Very broad patents, which are a problem for instance in software development, make it difficult for companies to determine whether they infringe such patents and often result in costly lawsuits or out-of-court agreements. Broad patents might indeed become a problem in synthetic biology, and patent trolling has already affected biotechnology (<http://www.nature.com/news/congress-seeks-to-quash-patent-trolls-1.17578>). Thus, “responsibility” in the sense of RRI could foster social benefits from R&D independent of court decisions, which are usually based on technical rather than ethical, social, or “moral” criteria, such as in US Supreme Court’s decisions on the non-patentability of isolated genomic DNA (www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf); or that may be largely ineffective, like the various bills that the US Congress introduced in recent years to curb patent trolling (<http://www.nature.com/news/congress-seeks-to-quash-patent-trolls-1.17578>).

If we regard RRI as a means to contribute to the redesign of IP schemes or policies, it is worth considering that the current concept is largely based on “constructive” notions in the sense of shaping regulatory frameworks or guiding R&D toward socially desirable and acceptable outcomes. Involving stakeholders and the public should contribute to reflection by all SynBio players—including researchers and policy makers—on possible consequences, and to envision and design solutions in an anticipatory manner. Although these elements are certainly important to reach RRI’s objective, they might not be sufficient on their own. The reasons are complexity, “unknowables,” or statistical limits, which make forecasting—and sometimes even envisioning—or, modeling or “directing” economic, societal and political developments impossible. Yet, such developments are interconnected to both innovation outcomes and societal needs.

The benefits and costs of different IP solutions depend on a complex array of innovation policies and social factors, such as R&D tax credits, governmental research grants, regulations, contracts, education, or social norms. Thus, the social and economic implications have largely remained elusive, despite much theoretical work and empirical correlations [10]. A way to deal with these issues could be to complement the largely reflection- and anticipation-based approach to responsibility by experimentation. Experimentation here is not only meant to explore new ways to include stakeholders or the public, but also additional laboratory or social experiments on IP. Laboratory “experiments” that evaluate the performance and behavior of participants in games or tasks have become a valuable tool in recent years, for instance, to identify factors that affect creativity or licensing, or to develop alternative IP

schemes [10]. Randomized “real-world” experiments are a reasonable tool to evaluate alternative policy options in specific contexts. For example, it has been proposed to use such experiments to improve orphan drug incentives by testing alternative schemes with minor variations in the length of market exclusivity rights and tax credit rates [10]. Such experimentation could add an additional “dimension of responsibility” to the process of finding IP and open-source schemes.

The goal of SynBio is often simplified as “making biology easier to engineer.” Indeed, one of the cofounders of the discipline, Drew Endy, postulated that undergraduate students should be able, under minor supervision, to achieve ambitious genetic modifications of living entities. This is the philosophy of the iGEM competition, a meeting of engineering ingenuity in the form of summer research projects carried out by undergraduate students (<http://igem.org/Competition>) and one of the most popular SynBio events. Despite a heterogeneous scientific level of the projects, we think that iGEM has some features that could make it a good laboratory for such experimentation. iGEM is a worldwide, media-savvy competition, in which not only students but also academia and companies are involved; it is a “mirror” of regular SynBio research, since it tends to focus on the same topics covered by academic research; focusing on students, iGEM may be more flexible and open to new, heterodox ideas; and there are attempts to reconcile research and biosafety, biosecurity, and legal aspects. These efforts include a special committee on biosafety; specialized judges for Human Practices/Policy issues; RRI-related awards; and an *ad hoc* IP framework for BioBrick™ parts, a “free-to-use legal tool that allows individuals, companies, and institutions to make their standardized biological parts free for others to use” (<https://biobricks.org/bpa/>).

Despite its open-source credo, iGEM leaves open the possibility of filing patents on applications and combinations of BioBricks (http://2014.igem.org/Team:Oxford/P&P_intellectual_property), which might be important to find investment for turning discoveries into social benefits. Similarly, humanitarian licensing and the analogies with open-source schemes in information technology are actually based on IP rights (licenses) to ensure that users adhere to the creator’s/inventor’s intentions to foster social

benefits. There are options to facilitate or expand IP options in the iGEM research frame. These include timely limited confidentiality clauses or license agreements that entitle contributors of BioBrick parts to a share of the profits should their contribution result in a commercial product (http://2014.igem.org/wiki/images/8/86/IP_REPORTWEBVER.pdf).

“RRI should be a guiding force during the brainstorming, not just an addendum”

iGEM may therefore provide an ideal testing ground for experimentation on open and proprietary IP schemes and could become a key element toward the overarching goal of achieving broader societal benefits from research and innovation. RRI is increasingly present in iGEM projects, but often as a separate notion and not necessarily connected with the research topic. By way of example, the iGEM website highlights four teams with particularly outstanding approaches (<http://2015.igem.org/Team:Example/Practices>). Respectively, they focused on transparency (Cornell 2013 team); the societal impact of their project (Manchester 2013 team); and the need, impact, and legal issues of the project (Dundee 2014 team). The Dundee team's project illustrates a particularly interesting approach by including experts in the initial part of the project “in order to ensure that our project is addressing a genuine need as defined by those who know best.”

We believe that RRI should be a key point, particularly at the beginning and at the end of each project. The dogma that scientific advance must lead, *per se*, to more societal benefit has been seriously challenged. The development of effective antiretroviral HIV/AIDS drugs has not been able to curb the spread of the disease globally, since most of the people living with HIV in sub-Saharan Africa do not have access to prevention, care, or

lifesaving drugs (<https://www.aids.gov/hiv-aids-basics/hiv-aids-101/global-statistics/>). Similarly, though malaria is widely considered an obstacle to economic development, R&D on malaria drugs/treatments—even if it led to eradication of the disease—would not solve the issue of lacking economic development of the affected countries owing to social and political issues, such as corruption, governance failures, or poverty and inequality (<http://www.worldbank.org/en/publication/global-monitoring-report/report-card/twin-goals/ending-extreme-poverty-cont>).

It would thus be wise to make clear to *igemites* that science cannot solve “just everything”: Research projects can provide useful tools in solving a wide range of problems, but beneficial solutions should never be taken as a direct, “unavoidable” outcome of research. Reflection in terms of critical exploration of the broader societal context and possible impacts should be a pivotal part of any iGEM—or any other research—project. RRI should be a guiding force during the brainstorming, not just an addendum. Teams should ask themselves why they are choosing a specific research project, and compare potential social and environmental implications. If successful, teams should again use an RRI perspective to make an informed and reflexive choice on whether or not protect their invention and, if so, under which IP form. Initiatives to foster collaboration between iGEM teams with institutions/researchers in the RRI field could contribute to such a process. Furthermore, judges could be key to foster a holistic RRI approach by appreciating a responsible strategy such as the one we propose here: focusing on RRI at both the onset of the project (decision point), and once the development has been achieved (responsible IP). This would imply a clear message to the next generation of biological engineers on the importance of combining one's interests with those of our society and the environment.

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Conflict of interest

The authors declare that they have no conflict of interest.

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