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Synthetic Biology: Role of open source approaches

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Abstract

Synthetic biology strives to take a leap beyond classical genetic engineering approach by attempting to engineer important life processes in order to come up with modified processes which are capable of performing functions which are generally not found in nature. Therefore, it possesses immense potential in spite of being in its initial stages. There exist two contrasting approaches, namely strict regulation and open source approaches in synthetic biology governance. However, the construction of pathogenic organisms such as infectious poliovirus from published DNA sequence information and reconstruction of influenza virus (which was extinct for around 5 million years) exploiting similar technologies have highlighted serious concerns associated with open source approach. At the same time open source approach offer promises for the encouragement and expansion of the synthetic biology community. This review article discusses the role of open source approaches in synthetic biology.

Keywords: Systems Biology, synthetic biology, intellectual property rights, open source

Introduction

Synthetic biology aims to develop 'modular' biological parts following the engineering principles of standardization, decoupling and abstraction to create novel organisms or redesign the existing ones. Synthetic biology is receiving increased attention not only from research laboratories, venture capitalists and major corporations but also from artists (Reardon, 2011) and do-it-yourself biologists (Kean, 2011) due to its potential to deliver less expensive lifesaving new drugs and innovative biofuels to address health and energy problems of the world. The potential of the field can be estimated by the fact that the Biotechnology and Biological Sciences Research Council (BBSRC) had invested £20 million for synthetic biology research in UK in 2012. An advisory firm Lux Research has estimated that by 2015 one-fifth of the chemical industry (approximately $2 trillion) could be relying on synthetic biology.

Synthetic biology is in nascent stage, however, issues related to open access to research versus the intellectual property rights have already started raising concerns. In 2002, the synthesis of the world's first synthetic pathogen, poliovirus, using mail-order DNA segments and genome map of virus had further fuelled these concerns (Ball, 2004). It is likely that monopolistic intellectual property regime may impede the

growth of field by limiting access to the technology necessary for complete realization of the inherent potential of the field whereas open sources are likely to raise several biosafety concerns. However, proponents of the open source approach believe that apart from securing common benefits, it would bring scientific community together through reliability and security (Saukshmya and Chugh, 2010). In this article, first part briefly describes the open source approaches in IT industry and synthetic biology, and then compares the two. Later half highlights the implications of intellectual property rights to the field, and finally discusses the proposed roles for open source approaches.

Open source approach in Information Technology

The goal of open source movement in information technology was to restore the cooperative spirit prevalent initially in computing world by removing the obstacles imposed by proprietary software. Open source approach in systems and synthetic biology is adopted from information technology. Since the nature of technology differs, the minimal regulations suitable for IT may not suit synthetic biology. Bioengineered virus has been analogized to computer virus; however, the analogy is flawed as "computer viruses can't kill people, at least not directly" (Bennett et al, 2009).

The open-source movement in IT was primarily based on the presumption that it is destructive to extract money from the users of a program by restricting their use as it leads to the reduction in the amount and the way a program can be used. The Free Software Foundation aims to provide a free operating system and a variety of application software. The users are allowed to copy, modify and distribute modified versions, but are not permitted to impose restrictions of their own because of distribution terms in the General Public License (GPL), thus preventing the conversion of free software into proprietary. It is worth noting that free software is copyrighted so that programmers have the right to stop others from restricting the use of the software.

Open source approach in synthetic biology

Synthetic biologists hope to combine biological parts in the same manner that Linux modules are now combined to make software (Maurer, 2009) suggests that it models itself upon the open source; however, it does not imply exclusion from the intellectual property regime. In fact, it depends on open source licenses such as 'copyleft' to enforce sharing of intellectual property by inventors. Contrary to software in IT industry, the products of synthetic biology are not regarded as copyrightable because copyright does not cover functionality and demands expressive choices. Thus, it is difficult to use copyright for developing open source licenses in synthetic biology (Rai and Boyle, 2007). The Biological Innovation for Open Society (BIOS) uses patent-based open source license for the non-assertion of IP rights by its members (Skipper, 2005).

The Registry of Standard Biological Parts, established in 2003 by Massachusetts Institute of Technology (MIT), represents open source movement in synthetic biology. It is an open access repository of increasing collection of 'Biobricks', namely standardized biological parts and associated functional information. The Registry provides its services for free via web similar to Free Software Foundation's approach. Both oppose to 'dysfunctional community polarization', enabling an open technical standards process to support the development of a community of contributors and users of free-to-use parts. The Registry has the BioBrick public agreement which compel contributors to make irrevocable

promise of non-assertion of IP rights against use of their contributed parts by subsequent users.

Parallels between open source approaches in IT industry and synthetic biology

The BioBrick public agreement differs from the General Public License in few aspects. According to agreement, the user needs to agree once in order to get access to all genetic parts. The Registry does not maintain records of agreement and validation is done only when required, also, users are not allowed to remove or alter any BioBrick identification tag in the parts. The users and contributors are obligated to comply with regulations applicable to parts, including regulations governing export control and safety. However, the agreement does not put any encumbrance on the users by not putting give-back or share like clauses (Smolke, 2009).

These differences are mainly attributed to the nature of objects covered under agreement. The open source software relies on copyright which arises automatically upon creation of software for free to the programmer whereas patents which usually protect genetic parts are expensive (Henkel and Maurer, 2009). Due to progress in DNA sequencing and synthesis technology the genetic material can be readily sequenced or vice versa rendering genetic material transfer agreement less useful. The biological part received by a user may differ from the one described in the agreement because of spontaneous mutation.

Proposed roles for open source approaches in Synthetic Biology

Synthetic biology is a complex technology as it emphasizes on designing/constructing novel biological organisms from several standard biological parts. Ownership of individual parts by multiple IP owners leads to the 'anticommons scenario' where downstream research is hampered by high cost (Heller and Eisenberg, 1998). Foundational patents and presence of numerous patents create 'patent thickets' that leads to inadvertent infringement of intellectual property rights encouraging 'patent trolls' i.e. firms acquire patents solely in the hope to extract royalties from the serious researchers. Regarding standardization process, concerns have been raised that excessive intellectual property rights may negatively impact the progress of the field. How synthetic biology community tackle the situation where patented parts were to be adopted as standards? In the light of these implications for the management of intellectual property rights in synthetic biology, open source approach emerges as a promising option which may help in the realization of the full potential of this field. The possible roles that open source approaches might play in the field of systems and synthetic biology can be discussed as follows.

1. Pragmatic: More Innovations

It has been argued that aggressive patenting and licensing, though, put many desirable biological parts off limits to downstream researchers but they are required to stimulate the private sector investment for developing the products (Nature Biotechnology, 2007). This suggests that strong intellectual property rights are likely to hinder the innovation rather than promoting it. The purpose of patents is to let inventors recover the initial investment in R&D and also to provide incentives for their invention. Nonetheless, in synthetic biology the value of a biological part depends more on the subsequent use of that part by other researchers than the initial investment in developing that part. Follow on innovators not only have to bear the burden of high costs but also the difficulty to negotiate with multiple IP owners of the biological parts. Unlike restrictive approach, by putting the biological parts in public domain would not

only avoid situation like 'patent thickets' and 'patent trolls' but would also make these parts freely available to the downstream researchers facilitating more innovations that will result in the development and commercialization of downstream applications.

2. Promote Establishment of Standards

The conscious reliance of synthetic biology on engineering approaches has led to the consideration of standards for characterization, manufacture and information sharing about the 'modular' biological parts (Arkin, 2008). Many institutions, such as BioBricks Foundation (BBF), The Registry of Standard Biological Parts ('Registry'), the international Genetically Engineered Machine Foundation ('iGEM'), the Synthetic Biology Engineering Research Center ('SynBERC'), the Synthetic Biology Open Language ('SBOL'), the International Association of Synthetic Biology ('ISAB') have been created with an important goal of setting standards in synthetic biology. Several relevant standards have been proposed including those pertaining to biosafety and biosecurity. However, only biosecurity related standards for screening DNA synthesis orders have been widely adopted due to infancy of the principles of design and predictability of product in the field and its rapid technical evolution. It has been argued that there is an 'important connection between openness and pressures of standardization' (Calvert, 2012). A patented standard biological part cannot be adopted as a standard across the industry due to transaction cost associated with it. Thus, patents on standard biological parts would hinder the establishment of common standards required for synthetic biology to flourish. This can be avoided by putting these standards in open. The wide use of open parts would lead to 'interoperability' which is required for parts based approach to synthetic biology.

3. Monitor Bioterrorism

The synthesis of complete genome of Poliovirus, reconstruction of the Spanish influenza virus genome responsible for the pandemic in 1918 and resurrection of an extinct human endogenous retrovirus have shown the potential of synthetic biology to engineer harmful pathogens (Wimmer and Paul, 2011). The CIA 2003 report suggests that some "engineered biological agents could be worse than any disease known to man" and that the traditional methods of monitoring weapons would be inadequate due to rapid progress in genomics (Balmer and Martin, 2008). The easy availability of biological parts and the online publications such as 'Primer for Synthetic Biology' encourages not only biohacking (Ledford, 2010) but also invites bioterrorism. Realizing the potential risks associated with such research the synthetic biology community released a declaration publicly reiterating its commitment to check the hazardous DNA synthesis orders. However, restricting access to these tools would not help much as keeping them open. The quote by Linus Torvalds which is quite famous in IT sector, 'Given enough eye balls, all bugs are shallow' has been aptly rephrased by synthetic biologists as 'our best defense against biological threats is to create and maintain open networks of researchers at every level, thereby magnifying the number of eyes and ears keeping track of what is going on in the world' (Carlson, 2010). It is suggested that constant monitoring and strict regulations applicable to open resources would be great measures to avoid their malicious use.

4. Prevent Monopolization of the Field

Synthetic biology is a 'tipping market' and thus prone to monopoly. The broad patents, such as the one filed by JCVI claiming a set

of essential genes and the cellular chassis to host them, pose threat that the group might become the 'Microbesoft' of the synthetic biology. Amyris (Emeryville, CA, USA), a leading company in synthetic biology industry, has protected all its research through patents (Maurer, 2009). These instances are indicative of attempts made to dominate the industry. Nevertheless, it has been suggested that the transparency conferred by open resources would help in preventing the field from being dominated and monopolized by a research group or large corporations, like GM technology by Monsanto (Calvert, 2012).

5. Foster Network Effects

Researchers strongly prefer parts that have been already used since characterizing a new part requires considerable time and efforts. It has been estimated that the cost of using parts decreases by up to 30% every time it is used indicating the significance of information obtained by using a part (Henkel and Maurer, 2007). The preference for widely used parts is referred to as 'network effect' by economists (Easley and Kleinberg, 2010). It is likely that popular open parts would attract large user base fostering network effects which would be beneficial for the growth of synthetic biology industry community.

Conclusions

Patents may bring incentives to innovators but for the industry which is still in its infancy, and has not started harvesting profits, efforts are required to enable it to realize its inherent potential. Being open would help start-up companies to catch up with industry frontrunners and academics to get acquainted or experimental with the subject. Open source approaches are the need of the hour not only to spur more innovations and help in establishing standards but also to address issues like bioterrorism and monopoly through fostering network effects.

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