

Parts, property and sharing

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Synthetic biology should look to other industries' models for ownership and open sharing.

Synthetic biologists have spent the past decade trying to recast genetic engineering in the image of electronics. Today's microprocessors are universally assembled from libraries of reusable modules, which are composed in turn of standard parts. The premise behind synthetic biology is that this same approach can be used to design the most complex devices of all—living organisms. But the standard parts agenda is much more than a technological choice. As in Silicon Valley, standardization will also help determine the new industry's structure and economics. These social arrangements will, in turn, have a profound impact on the rate at which synthetic biology generates new products, the affordability of those products and (through affordability) the number of human beings whose lives are actually improved.

We discuss here how the parts agenda is likely to shape commercial synthetic biology, the pitfalls this new industry could encounter and what governments and firms can do to address them. The first set of issues stems from synthetic biology's reliance on large numbers of patented parts. As with earlier 'complex technologies', this suggests that intellectual property (IP) rights will often be hard to identify, fragmented across many owners and sometimes overly broad. All of these factors will make it harder for would-be innovators to obtain the licenses they need to go forward. The second set of issues arises from synthetic biology's defining emphasis on standardization. In the electronics and software industries, the need for common standards has repeatedly produced a 'tipping dynamic' in which one solution quickly

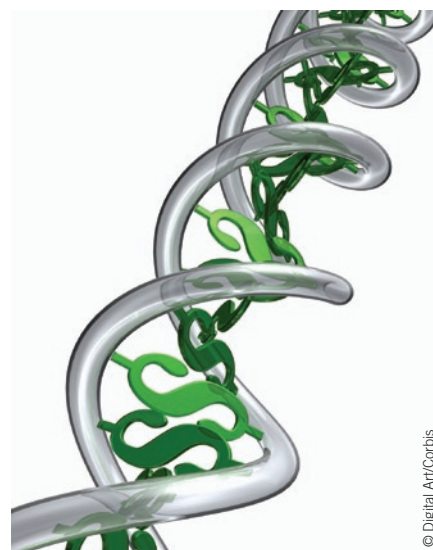
comes to dominate the rest. In principle, the dominant parts can be owned by one firm (as is true of Windows, for example), fragmented across many owners (mobile telephony standards), or owned by no one (Linux). We argue that Linux-style openness in synthetic biology is desirable and, to a significant extent, feasible.

Complex technologies

Commercial applications of the life sciences (for example, biotech R&D) have traditionally involved 'discrete technologies' that generate new products seldom consisting of more than a few individual inventions. In contrast, synthetic biology—with its emphasis on assembling organisms from dozens and eventually hundreds of standard biological parts—is a 'complex technology' similar to those found in the electronics and software industries. This makes it natural to think that the new synthetic biology companies will often resemble Microsoft at least as much as Pfizer.

This complexity has important implications for the management of IP. For example, no mobile phone manufacturer owns all the patents that cover its products. This forces the industry to share technology through cross-licensing instead of using IP to exclude competitors, as commonly occurs, for example, in pharmaceuticals. We expect something similar to happen in synthetic biology. The more complex the systems designed by synthetic biologists become, the less likely it is that any company will own all of the IP rights needed for each R&D project.

Scholars have documented various problems where IP ownership is very fragmented^{1,2}. First, firms can encounter an 'anticommons' scenario³, in which follow-on research is hampered by the high cost and difficulty of negotiating contracts with very large numbers of IP owners. This is aggravated by each individual owner's incentive to



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Synthetic biology's future will depend on who owns its most popular parts.

overcharge for its IP. Second, many types of cross-licenses (for example, per-unit royalties) tend to generate higher prices for consumers. This is because higher royalties push up each company's costs and therefore prices. This can happen even where payments cancel out so that no firm earns a net royalty.

The existence of these problems suggests the importance of cutting the number of licensing transactions that firms face wherever possible. In principle, this could be done by making standard biological parts unpatentable. Legislatures and courts, however, are highly unlikely to do this. Furthermore, this would also reduce incentives to innovate^{2,4}. Traditional private-sector solutions based on patent pools—perhaps with zero royalties—seem more promising^{5–9}. Here, the main difficulties are getting contributors to agree on terms and writing agreements that do not exclude competitors in violation of the anti-trust laws¹⁰. An ASCAP-style clearinghouse

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for patents would go further by providing licenses to any company that requested one^{11–13}. Alternatively, where royalties are much smaller than the expected transaction cost, companies may decide that it is simpler to share their IP in the style of open source collaborations^{14,15}. We return to this point below.

But there are other issues beyond licensing. Complex technologies are also more prone to inadvertent IP infringement. This problem is particularly pronounced when patents are overly broad or so numerous that they create webs of overlapping rights or ‘patent thickets’ that are so dense that infringement becomes almost inevitable^{2,5}. In the electronics industry, even large firms find it difficult to identify each and every patent that potentially covers their products. This is due both to complexity of the technology and to the fact that many patents are so vaguely written that they can no longer reliably fulfill their ‘notice function’¹⁶. Genetic engineering already faces significant problems in finding out whether parts are patented or not¹⁷, despite attempts, for example by Cambia’s Patent Lens project, to increase transparency. It is reasonable to think that the same problem will similarly affect synthetic biology as designs become more complex. The problem is already evident in the Registry of Standard Biological Parts, where it is seldom clear which parts are or are not patented.

To make matters worse, the increasing risk of inadvertent infringement encourages ‘patent trolls’: that is, firms that acquire patents not because they want to make products but because they hope to extract extortionate payments from companies that do^{18,19}. We expect this problem to become increasingly relevant also for synthetic biology, especially if patent trolls start to acquire patents from bankrupt biotech firms. Industry initiatives to buy up patents are a natural way to mitigate this threat. The Open Invention Network already does this for Linux-related patents in the software industry.

Network effects

IP ownership and royalties are not the only issues. Other criteria may prove even more important in selecting a part for a specific application. Characterizing a new part requires considerable time and effort, and so researchers have a strong preference for parts that have been used before. After all, the only way to learn about parts is to use them. Researchers estimate that the cost of using parts falls 20%–30% each time they are used, so the information obtained by using a part is significant²⁰.

All else equal, a firm will tend to become locked in to those parts it has used before. If, however, parts information is shared, a firm may find it advantageous to switch to a part that is already widely used across the industry. This preference for widely used parts is an instance of what economists call a ‘network effect’. Where network effects are strong, individual lock-in tends to be replaced by global, industry-wide lock-in. Network effects are not new to biology. Indeed, researchers in various biology disciplines focus disproportionately on a half-dozen cell lines out of the many thousands that could be used in principle²¹. The fact that these lines are widely used makes it easier to find out how to maintain and culture them, compare experiments with earlier published work, and acquire them in the first place^{21,22}.

Economists already know a great deal about network effects from studying the electronics and software industry. Software markets in particular have demonstrated how network effects produce a runaway dynamic in which whichever product starts with the biggest user base attracts still more users until it eventually dominates the industry. Crucially, this dynamic does not depend on whether the dominant standard is owned by one company, several, or no one at all (that is, ‘open’). At the same time, ownership matters very much to the price that consumers and follow-on innovators must pay to use or improve the product. This suggests that early interventions to create and promote open standards will often yield important benefits to society.

It is reasonable to think that a similar dynamic will operate in synthetic biology so that popular parts become steadily more entrenched over time. Crucially, such dominant parts could be open or proprietary. If a popular part is open and costs nothing to use, well and good. But if not, researchers will be willing to pay for a proprietary part that comes with a large experience base, so long as license fees are less than the cost of characterizing and learning to work with a substitute part. More generally, the same argument should apply not just to individual parts but also to families of parts that are routinely used together.

Making synthetic biology more open

We have already said that the tipping dynamic can produce dominant parts that are owned by one company, several companies or no one at all. Which regime should society hope for? For existing parts, the answer is simple: open parts are preferable, because they offer the lowest prices to consumers and follow-

on innovators. But what about incentives for creating new parts? Such innovative activity is costly, and patents are known to create incentives for innovation in the biotechnology and pharmaceutical industry. So, what can be done to support sharing in synthetic biology, while maintaining incentives for innovators? We see four viable measures.

Wherever possible, use unpatented parts.

Many parts are not, or are no longer, patented. Today, academic researchers often care little about the patent status of the parts they use. This is shortsighted because it may be expensive to replace patented parts if and when a project is later commercialized. Deliberately selecting open parts over ‘closed’ substitutes avoids this, and more generally increases the odds that open parts will become dominant. The problem for now is that researchers often find it difficult to tell which parts are patented and which are not. Extending platforms like the Registry of Standard Biological Parts to include ownership information would help boost open parts usage. Patent offices can also help by requiring applicants to do a better job of specifying claims. The increasing willingness of US, European and Japanese patent offices to deny patents to applicants who fail to disclose a specific gene sequence—that is, who only provide a functional definition without specifying the relevant structural elements—is a useful step in this direction.

Donate parts to the commons. Commercial software firms frequently donate code to public open source projects. They do this for a variety of reasons. These commonly include establishing a reputation, hoped-for reciprocity by others and the desire to build a user base²³. These incentives should similarly apply to synthetic biology firms. Some firms and universities already do this for parts that are not central to their business (W. Weber, personal communication).

Link public funding to the obligation to share. Many firms in the nascent field of synthetic biology receive public funding. This potentially lets governments adjust the balance between IP protection and sharing without changing existing patent law. In synthetic biology, the main issue is whether the full 20 years’ patent reward is needed to elicit investment, especially for companies that receive significant grant support. The problem, of course, will be figuring out how much patent duration these firms actually do need. We think that the best option is to ask firms to specify a desired patent duration as part of their grant applications. In this way,

competition for grants would provide a powerful incentive for companies to limit patent duration and maximize sharing.

Create open parts licenses. Commons models rely on firms' willingness to share information voluntarily. Open source licenses, such as the General Public License (GPL), provide an important additional incentive to share. They do so by requiring those who develop improvements to GPL code, or who merge GPL code with other code, to license the resulting software under the GPL. As a practical matter, this enormously increases the chances that developers will make their improvements public so that the original author can use them.

Commentators have talked about extending open source principles to biology since the late 1990s (refs. 15,24). Despite this, not much has happened. The best-known project, Cambia's 'Bioforge' initiative²⁵, seems to have elicited little shared research²⁶. Within synthetic biology, recent efforts by the Biobricks Foundation to write an open parts license have similarly stopped short of conferring a GPL-style obligation on the recipients to share their improvements²⁷. For this reason, researchers' incentives to donate parts are not significantly stronger than they would be in the commons schemes described above.

Ten years on, the absence of anything resembling an open parts regime in synthetic biology is striking. Most commentators (for example, ref. 28) explain it in two ways. First, they argue that biology research requires a much larger up-front investment than software. However, this could be addressed by writing licenses that let companies retain ownership of parts for a commercially reasonable period of time—say, several years—before sharing. The required period would almost always be far less than the 20 years specified by patent law. In fact, schemes that feature sharing after similarly short periods of exclusive ownership already exist and provide important incentives for the developers of the 'embedded Linux' software used in cell phones, machine controls and the like²³. Second, commentators argue that existing open source licenses rely on copyright protection, which attaches to software automatically at no cost to the author. By contrast, standard biological parts are usually protected by patents, and these are expensive—~\$10,000 per application in the United States²⁹. It is difficult to see how even the wealthiest open parts collaboration can obtain enough patents to protect its work.

However, copyrights and patents are not the only choices. Instead, all modern juris-

dictions recognize trade secret laws that let collaborators make binding agreements as to when and how to share confidential information. Commentators have long speculated that an open parts collaboration could be built around such agreements. Furthermore, trade secret protection, like copyright, costs nothing to acquire. Instead, the main drawback would be that trade secret agreements—unlike most open source software agreements—require "extremely broad restrictions on dissemination" to nonmembers³. Even so, this seems like a small price to pay provided that anyone who wanted to join the collaboration was truly able to do so. Large pharmaceutical companies, which already have long experience keeping and managing trade secrets, should find such collaborations particularly straightforward.

Legally, it is easy to see what such an agreement would look like. Members who joined the collaboration would receive access to a confidential database of parts and parts information. In return, they would promise to share whatever data they acquired in the course of using and/or improving the collaboration's parts after some short period of time. This simple bargain would be the same whether the collaboration consisted of two firms or an entire industry. A potential downside of trade secret protection is that, unlike patents or copyright, it could suddenly disappear if the underlying secret became public. A related and potentially more severe problem arises when a third party independently discovers the secret and patents it. However, these issues do not seem fatal. Instead, trade secrecy exists in all industries, and firms have invented various strategies to manage them both individually and in joint ventures. An open parts collaboration could similarly mitigate risk by allowing members to seek patent rights on the express condition that these could only be asserted against nonmembers. Alternatively, a collaboration could give members the right to make any information they supplied public at any time³⁰. This 'defensive publishing' would block third parties from obtaining patents as a matter of law³¹. A famous example of the latter strategy is the Merck Gene Index, a public domain database of expressed human gene sequences³².

Would companies that use synthetic biology approaches be willing to share information in return for a right that might suddenly evaporate? This kind of open parts model is obviously very different from life science firms' usual strategies for managing IP. In the short run, therefore, the new model will probably encounter a certain amount of cultural

resistance. Here, synthetic biology's status as a crossover discipline with deep roots in chemical engineering, electronics and software should predispose it toward sharing. More importantly, companies can be wonderfully receptive to new business models that help the bottom line. For every firm that earns a living by selling patented parts to others, we expect several who see themselves as net consumers with an interest in keeping parts prices as low as possible. This group notably includes the big pharmaceutical companies that have repeatedly used their deep pockets to bankroll projects (for example, The SNP Consortium) aimed at keeping the biology's basic building blocks as open as possible.

In the long run, then, the only real question is whether an open parts model makes economic sense. Will companies that use synthetic biology approaches really share information in return for trade secret protection that might suddenly evaporate? We are optimistic. In the real world, companies can and do routinely enter agreements to share and improve unpatented trade secrets. Extending this model from commercial joint venture agreements to open parts collaborations seems straightforward.

Conclusions

Synthetic biology is bound to change the rules of the game in genetic engineering. Its reliance on large numbers of parts turns the field into a complex technology, and the importance of shared learning implies network effects and makes winner-take-all outcomes likely. Both aspects are compounded by weaknesses of the IP system—in particular, its lack of transparency. Although these problems may seem modest today, they are likely to become much more serious once the synthetic biology industry starts to generate significant profits.

For these reasons—and even though the general usefulness of patents in the life sciences is beyond doubt—reasonable steps to grow the commons and support open sharing seem highly advisable. We have already argued that an embedded Linux-style open parts collaboration makes good legal and economic sense. Furthermore, the open parts idea enjoys widespread support, not just in the academic community but also, to a large extent, in industry. For every front-runner like Amyris (Emeryville, CA), there are several firms for whom sharing is the only way to catch up. Similarly, companies that sell synthetic genes and other support services know that cheap, abundant, high-quality parts are good for business. Open parts are the best way to deliver this result. Finally, government

has repeatedly intervened to promote open source-style sharing in software and, more recently, stem cell research. We think it will be similarly predisposed to support an open parts project. Yet no matter how synthetic biology is made more open, it needs to happen soon.

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