Synthetic Biology: The Intellectual Property Puzzle

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Synthetic biology takes as its mission the construction, and "reconstruction," of life at the genetic level.[1] The scale and ambition of synthetic biology efforts go well beyond traditional recombinant DNA technology. Rather than simply transferring a preexisting gene from one species to another, synthetic biologists aim to make biology a true engineering discipline.[2] In the same way that electrical engineers rely on standard circuit components, or computer programmers rely on reusing modular blocks of code, synthetic biologists wish to create an array of standard, modular[3] gene "switches" or "parts" that can be readily synthesized and mixed together in different combinations.[4] The Massachusetts Institute of Technology (MIT) has a "Registry of Standard Biological Parts [that] supports this goal by recording and indexing biological parts that are currently being built and offering synthesis and assembly services to construct new parts, devices, and systems."[5] Systems, devices, parts, and DNA represent descending levels of complexity—systems consist of devices, and devices consist of parts composed of DNA.[6]

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1. *See, e.g.*, Drew Endy, *Foundations for Engineering Biology*, 438 NATURE 449, 449 (2005) (observing that the era of synthetic biology has been described as an era in which significantly new gene arrangements can be constructed and evaluated).

2. *See id.* (arguing that the recent interest in synthetic biology is driven in part by engineers who want to develop foundational technologies that make the design and construction of engineered biological systems easier).

3. Modularity involves "breaking up a complex system into discrete pieces—which can then communicate with one another only through standardized interfaces within a standardized architecture . . . ." Richard N. Langlois, *Modularity in Technology and Organization*, 49 J. ECON. BEHAV. & ORG. 19, 19 (2002).

4. *See* Endy, *supra* note 1, at 450 (asserting that the biological engineering community would benefit from the promulgation of standards for basic biological parts, as well as standards for using the parts in combination).

5. Help: About the Registry, http://parts.mit.edu/registry/index.php/Help:About_the_Registry (last modified Apr. 5, 2006).

6. Abstraction Hierarchy - Registry, http://parts.mit.edu/registry/index.php/Abstraction_Hierarchy (last modified June 7, 2006).

The idea behind the Registry of Standard Biological Parts (Registry) is that these parts can, and should, be recombined in different ways to produce many different types of devices and systems.[7] Although the Registry currently contains physical DNA, its developers believe that, as DNA synthesis technology becomes capable of generating ever-longer sequences, the Registry will be composed largely of information and specifications that can readily be fabricated in DNA synthesizers.[8] The fabricated, DNA-based functions would then be "executed" in a cell.

Synthetic biology's long-term goals encompass such far-reaching possibilities as constructing an entirely artificial programmable genome from standard parts. Scientists in the closely allied field of synthetic chemistry are working on artificial RNA and proteins with added amino acids, presumably linked through an artificial genetic code.[9] More immediately, synthetic biology "systems"—that is, organisms engineered with artificial metabolic pathways composed of a number of different standard parts—have produced important concrete results, including the possibility of unlimited supplies of previously expensive drugs for malaria.[10] Proponents hope to use synthetic organisms for economical production of not only medically relevant chemicals but also a large variety of industrial materials.[11] The possibility of low-cost production of "green" fuels such as cellulosic ethanol has particularly caught the attention of prominent venture capitalists.[12] Even more apparently whimsical applications, such as programming bacteria to take photographs[13] or to form visible patterns[14] may be useful for detection of environmental pollutants. Similarly, programming cells to implement digital logic could have large numbers of medical and computational applications.[15]

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7. Help: About the Registry, *supra* note 5.

8. *See* David Baker et al., *Engineering Life: Building a Fab for Biology*, SCI. AM., June 2006, at 44, 46 (2006) ("[The] combination of technology and methodology for designing and fabricating semiconductor chips . . . is a valuable model for another nascent technology sector: fabrication of biological systems.").

9. Steven A. Benner, *Act Natural*, 421 NATURE 118, 118 (2003).

10. *See* Vincent J.J. Martin et al., *Engineering a Mevalonate Pathway in* Escherichia Coli *for Production of Terpenoids*, 21 NATURE BIOTECHNOLOGY 796, 800 (2003) (reporting the development of an *Escherichia coli* (*E. coli*) microbial host to facilitate large-scale development of an antimalarial drug).

11. *See generally* BIO-ECONOMIC RESEARCH ASSOCIATES, GENOME SYNTHESIS AND DESIGN FUTURES: IMPLICATIONS FOR THE U.S. ECONOMY 71–91 (2007) (assessing the impact of bio-based technologies on the chemical industry).

12. *See, e.g.*, Michael S. Rosenwald, *Tackling the World's Energy Problems*, WASH. POST, Feb. 27, 2006, at D1 (reporting the founding of Synthetic Genomics, Inc. to use microorganisms to produce alternative fuels, with the venture capital backing of a prominent Mexican billionaire).

13. Anselm Levskaya et al., *Engineering* Escherichia Coli *to See Light*, 438 NATURE 441, 441 (2005).

14. Subhayu Basu et al., *A Synthetic Multicellular System for Programmed Pattern Formation*, 434 NATURE 1130, 1130 (2005).

15. *See* Endy, *supra* note 1, at 449 (discussing applications of synthetic biology, such as programmed cells that can "count up to 256 in response to a generic input signal" and could be used in "the study and control of cell division").

At the same time, synthetic biology has engendered numerous policy concerns. From its inception, commentators have raised issues ranging from bioethical and environmental worries to fears of bioterrorism. The successful *in vitro* creation of a complete polio virus genome "using mail-order segments of DNA and a viral genome map that is freely available on the Internet" provided a focal point for these concerns.[16] The worry has been sufficiently great that the synthetic biology community recently released a declaration publicly committing itself to improving the software that checks DNA synthesis orders for sequences encoding hazardous biological systems.[17]

There is, however, one area that has been largely unexplored by legal scholars until this point—the relationship of synthetic biology to intellectual property law. Nonetheless, scientists working in this area are sufficiently concerned about the possible impact of intellectual property that they are actively thinking about the applicability of "open source"-type strategies to parts and devices.[18] Three key issues deserve further attention.

First, synthetic biology, which operates at the intersection of biotechnology, software, and electronics, presents a particularly revealing example of the challenge that arises when a new technology has to be assimilated into existing intellectual property law. The manner in which the law has handled software on the one hand and biotechnology on the other may not bode well for synthetic biology. Already we are beginning to see problematic foundational patents that could impede the potential of the technology. Moreover, even assuming appropriate enforcement of foundational patents, a proliferation of patents on basic parts and devices could create transaction-cost-heavy thickets or "anticommons." Both foundational patents and patent thickets are likely to be particularly problematic to the extent they cover standards that synthetic biologists would like to establish.

Second, synthetic biology illustrates a tension between different methods of creating "openness." On the one hand, we have intellectual property law's insistence that certain types of material remain in the public domain, outside the world of property. On the other, we have the attempt by individuals to *use* intellectual property rights to create a "commons," just as developers of free and open-source software use the leverage of software copyrights to impose requirements of openness on future programmers—requirements greater than those attaching to a public domain work. Intellectual property policy specifies items, such as abstract ideas or

16. Phillip Ball, *Starting from Scratch*, 431 NATURE 624, 624 (2004).

17. Declaration of the Second International Meeting on Synthetic Biology (May 29, 2006) (revised public draft), http://dspace.mit.edu/bitstream/1721.1/32982/1/SB.v5.pdf.

18. *See* Matthew Herper, *Architect of Life: Drew Endy Aims to Reinvent the Biotechnology Industry*, FORBES, Oct. 2, 2006, at 63, 63 (reporting that Drew Endy, a leader in the synthetic biology field, advocates that scientists voluntarily place biological components in a freely accessible registry).

compilations of unoriginal facts,[19] that cannot be covered by intellectual property rights precisely in order to leave them open to all. Yet many of the techniques of open source *require* property rights so that future users and third parties will be bound by the terms of the license.[20] Should we rethink the boundary lines between intellectual property and the public domain as a result?

Third, synthetic biology illustrates a potentially symbiotic relationship between open and proprietary innovation models. Several of the firms that are prominent in the area of large-scale gene synthesis have significant proprietary positions. Notably, these proprietary positions are likely to be enhanced, not diminished, by the widespread availability of the information necessary for making parts, devices, and systems. For example, once the parts collected in the MIT Registry begin to be disseminated as pure information, widespread dissemination of this information will likely increase demand for the various proprietary DNA synthesis platforms. Whether this symbiosis is beneficial from a social welfare standpoint may depend on whether large-scale gene synthesis remains a competitive enterprise or falls under monopoly control.

Part I of this Article introduces the background law against which patenting in the area of synthetic biology operates. Part II discusses the current landscape of proprietary rights in the area of synthetic biology. Specifically, we focus on foundational patents, patents on DNA-binding proteins, and proprietary rights relevant to large-scale DNA synthesis. With respect to each set, we address possible benefits and costs. Part III identifies the obstacles that might be faced by those who might wish to use property rights to create openness. Part IV examines interactions between open information about parts and the highly proprietary business model of gene synthesis firms.

I. Synthetic Biology: Difficulties in Background Law

Intellectual property law has already had some difficulty incorporating two of the technologies from which synthetic biology draws inspiration—biotechnology and software. In certain areas of biotechnology, the U.S.

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19. It bears emphasis, however, that within patent law, the scope of the "abstract ideas" exception to patentability has progressively been narrowed by the Court of Appeals for the Federal Circuit. *See* Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 126 S. Ct. 2921, 2928 (2006) (per curiam) (Breyer, J., dissenting) (pointing out that the Federal Circuit has held inventions patentable if they produce a "useful, concrete, and tangible result," although the Supreme Court has "never made such a statement, and if taken literally, the statement would cover instances where this court has held the contrary"). Although the Supreme Court was poised to decide this question in *Laboratory Corp.*, a majority of the Court subsequently decided that the issue had not been squarely presented. *Id.* at 2921.

20. *See* Andrés Guadamuz González, *Open Science: Open Source Licenses in Scientific Research*, 7 N.C. J.L. & TECH. 321, 327 (2006) (describing open-source freedoms such as access to software source codes as "protected by the adoption of a restrictive licensing model that makes use of existing copyright legislation").

Court of Appeals for the Federal Circuit, which hears most patent appeals, has tended not to enforce the patent law requirement that inventions be "nonobvious" to the ordinary scientist working in the area.[21] Years after methods for cloning genes became routine and widely known, the Federal Circuit continues to treat the gene products of such methods as patentable.[22] On the Federal Circuit's reasoning, what matters is not whether a practicing biologist would find a particular invention obvious but, rather, rules about nonobviousness developed for chemical inventions in the mid-twentieth century.[23] Moreover, although economic arguments can be made for the low nonobviousness standard with respect to certain genetic sequences (for example, genetic sequences that represent therapeutic proteins), a per se rule of minimal nonobviousness in such technology is far from optimal economically.[24] So one major part of the technological terrain into which synthetic biology must fit—biotechnology—has already proven difficult for intellectual property law to manage.

While biotechnology has mainly posed difficulties for patent law, software has posed both copyright and patent problems. Copyright covers original works of expression.[25] It explicitly excludes works that are functional.[26] Patent law covers inventions that are useful, novel, and nonobvious—functionality is a requirement, not an impediment.[27] However, it had traditionally been understood to exclude formulas and algorithms.[28] Thus, software seemed to fit neither the copyright nor the patent box. It was too functional for copyright; too close to a collection of algorithms and ideas for patent. Additionally, certain economic aspects of software, including its high propensity to display network effects that militate in favor of standardization, led scholars to believe that neither copyright nor patent was well suited for encouraging innovation without unduly discouraging

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21. *See* Arti K. Rai, *Intellectual Property Rights in Biotechnology: Addressing New Technology*, 34 WAKE FOREST L. REV. 827, 834 (1999) (noting that under the court's logic, "DNA sequences can be nonobvious no matter how easy or routine it is to isolate the sequences").

22. *See In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("The fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious.").

23. *See* Rai, *supra* note 21, at 835 (noting that the court's argument is "based on its view that DNA-based technology is simply a subset of chemical technology generally," making the structural similarity test apply equally well to biotechnology); *see also In re* Fisher, 421 F.3d 1365, 1382 (Fed. Cir. 2005) (Rader, J., dissenting) ("Unfortunately this court has deprived the Patent Office of the obviousness requirement [of 35 U.S.C. § 103] for genomic inventions.").

24. *See* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1070–73 (2003) (discussing problems created by a nonobviousness standard that is uniformly low).

25. 17 U.S.C. § 102(a) (2000).

26. *Id.* § 102(b).

27. 35 U.S.C. §§ 101–103 (2000).

28. *See* Rai, *supra* note 24, at 1104 ("With respect to algorithms, this prior precedent suggested that algorithms were patentable only to the extent that they were embodied in a physical element, in the case of a product patent, or applied to a physical process, in the case of a process patent.").

competition; various *sui generis* intellectual property regimes were proposed as an alternative.[29]

Ultimately, as a result of actions by Congress and by the Federal Circuit, software ended up being covered by both copyright and patent.[30] Moreover, the historical refusal of some members of the Federal Circuit to allow patent examiners to use unwritten common knowledge in the field to determine that prior art references could be combined to render a patent application obvious[31] may have had a significant impact on software. As in other fields, it may have been difficult for a patent examiner to find specific written references testifying to information that is generally known.[32] Additionally, although the Supreme Court's recent decision in *KSR International Co. v. Teleflex Inc.*[33] rejects a formalistic requirement of a written "suggestion to combine,"[34] potential infringers bear the burden of challenging patents issued under the prior standard. Scholars have also argued that the Federal Circuit has allowed unduly broad patents to issue in the area of software.[35]

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29. *See, e.g.*, Peter S. Menell, *Tailoring Legal Protection for Computer Software*, 39 STAN. L. REV. 1329, 1331 (1987) (arguing that economics analysis militates in favor of protection specific to software); Pamela Samuelson et al., *A Manifesto Concerning the Legal Protection of Computer Programs*, 94 COLUM. L. REV. 2308, 2312 (1994) (suggesting a *sui generis* approach to legal protection of computer programs).

30. *See* Computer Software Copyright Act of 1980, Pub. L. No. 96-517, 94 Stat. 3028 (codified as amended at 17 U.S.C. §§ 101, 117) (extending in a formal way copyright protection to software); State St. Bank & Trust Co. v. Signature Fin. Group, Inc., 149 F.3d 1368, 1373 (Fed. Cir. 1998) (holding that software is considered patentable if it involves some practical application and "it produces 'a useful, concrete and tangible result'"); *In re* Alappat, 33 F.3d 1526, 1545 (Fed. Cir. 1994) (designating software that turns a general purpose computer into a special purpose computer as patentable subject matter).

31. *In re* Sang-Su Lee, 277 F.3d 1338, 1343–44 (Fed. Cir. 2002).

32. Various groups now focus on documenting software-related information. *See, e.g.*, Open Source as Prior Art, http://www.osapa.org (developing practices for electronic publication of software prior art to make it more available to developers and patent examiners); The Software Patent Institute, Mission and Endorsements, http://www.spi.org/missendo.htm (describing its mission as "assisting the United States Patent and Trademark Office and others by providing technical support in the form of educational and training programs and providing access to information and retrieval resources concerning software prior art").

33. 127 S. Ct. 1727 (2007).

34. *See id.* at 1741 ("The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

35. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1171 (2002) ("[T]he Federal Circuit has proven remarkably unwilling to require software patentees to disclose details. As a result, we should expect the first programmer to implement a new idea in software to claim the entire category of software . . . ."). One recent panel opinion, *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344–47 (Fed. Cir. 2005), suggests that at least some members of the Federal Circuit are not inclined to give all software patents broad scope. The extent to which future Federal Circuit opinions will follow *LizardTech* remains to be seen. In contrast, the Federal Circuit has generally required patents in the biopharmaceutical area to be narrower. *See, e.g.*, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 924–28 (Fed. Cir. 2004) (detailing the level of specificity required in a patent specification in "the chemical arts"). It is not clear, however, how assiduously the PTO is following

II. The Proprietary Landscape: Content and Implications

How does this history of intellectual property law's struggles to deal with software and biotechnology bear on synthetic biology? As a threshold matter, it bears emphasis that more than 5,000 granted U.S. patents currently cover ordinary DNA sequences.[36] This large number is a consequence, at least in part, of the low nonobviousness standard established by the Federal Circuit. In contrast, in the European Union, where the nonobviousness standard is higher, there are only about one-seventh as many patents on DNA sequences.[37] Just as many types of gene-related research may infringe at least some DNA sequence patents, so too may research in synthetic biology.

We also considered patent activity in three research contexts specific to synthetic biology.[38] These three contexts are foundational patents on the basic science of synthetic biology, patents on DNA-binding proteins, and patents on large-scale gene synthesis. In general, because the field of synthetic biology is quite new (and has not, in contrast to nanotechnology, caught the attention of the U.S. Patent and Trademark Office (PTO)[39]), patent classification categories are quite unsuited to the identification of synthetic biology patents. Thus, finding patents in each of these areas represented a search challenge. Below we describe our search strategy in each area and analyze the patents that we found.

A. Foundational Patents

We categorized as foundational those patents with broad claims that appeared important to a large percentage of work in the area. We identified such patents through discussions with members of the synthetic biology community and through our patent searches in the area of DNA-binding proteins and large-scale gene synthesis. Because synthetic biology is in a relatively inchoate state, the identification of foundational patents is

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the Federal Circuit's mandate. *See* Christopher M. Holman, *Is* Lilly *Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of* Eli Lilly *and its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. (forthcoming 2007) (manuscript at 63–64), *available at* http://ssrn.com/abstract=937374 (concluding that the Board of Patent Appeals and Interferences rarely denies claims for lack of a written description).

36. Michael M. Hopkins et al., *DNA Patenting: The End of an Era?*, 25 NATURE BIOTECHNOLOGY 185, 185 (2007).

37. *See id.* at 185 (noting that only 750 DNA patent families contain granted European Patent Office (EPO) patents and attributing the difference in part to the higher patentability bar in the EPO).

38. We focused on synthetic biology that relies upon existing bases and the existing genetic code, and thus, has relatively near-term application. Thus, for example, we do not include in our list of foundational patents U.S. Patent No. 6,617,106, which appears to cover a broad array of "methods for preparing oligonucleotides containing non-standard nucleotides." U.S. Patent No. 6,617,106 col.1 ll.1–3 (filed Mar. 29, 2000).

39. The nanotechnology field now has a PTO classification. *See* U.S. Patent and Trademark Office, US Classes by Number with Title, http://www.uspto.gov/go/classification/selectnumwithtitle.htm (last modified Feb. 28, 2007) (showing nanotechnology as Class 977 in the PTO classification system).

necessarily speculative. Nonetheless, we believe that patents of the general type discussed below are likely to be considered foundational.

One group of arguably foundational patents covers the use of cellular machinery for information-processing tasks. One of these, assigned to the University of Tennessee, encompasses applying electrical or chemical stimuli to genetically engineered cells for purposes of producing at least one detectable output protein.[40] Another patent issued to the U.S. Department of Health and Human Services (HHS) covers using the combination of any nucleic-acid-binding protein and any nucleic acid to set up data storage as well as certain types of logic gates that perform basic Boolean algebra.[41] As the patent document notes, the invention could be used not only for computation but also for complex ("digital") control of gene expression.[42] Finally, a patent held by Stanford University claims the use of a computer system to simulate the operation of a biochemical network, at least for a specified period of time.[43]

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40. U.S. Patent No. 7,020,560 (filed Sept. 6, 2001). Claim 1 reads:

> A method comprising the steps of:
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> providing a plurality of genetically engineered cells, said genetically engineered cells having at least one transcriptional unit, said transcriptional unit comprising a gene and a promoter, wherein application of a stimulus to said promoter results in the expression of a gene product;
>
> applying a plurality of independent input signals via nanofibers to said plurality of genetically engineered cells, said input signals being an energetic or chemical stimulus to activate said promoter, and
>
> detecting for the presence of at least one output signal, said output signal being related to a presence of said gene product.

Id. at col.17 ll.26–39. It is possible that the "nanofibers" limitation could narrow the scope of this patent.

41. U.S. Patent No. 6,774,222 (filed Feb. 17, 1999). Claim 1 reads:

> A system comprising
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> an isolated nucleic acid having a length of at least 5 base pairs and having a nucleotide sequence that comprises a first protein binding site and a second protein binding site, where said first and second protein binding sites specifically bind the same nucleic acid binding protein, and where said first and second protein binding sites are spaced in proximity to each other such that:
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> when said first protein binding site is specifically bound by the nucleic acid binding protein, said second binding site cannot be bound by a second molecule of the protein that otherwise specifically recognizes and binds said second binding site; and
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> when said second binding site is specifically bound by the nucleic acid binding protein, said first binding site cannot be bound by a second molecule of the protein that otherwise specifically recognizes and binds said first binding site; and
>
> the nucleic acid binding protein that specifically binds said first protein binding site or said second protein binding site.

Id. at col.45 ll.26–46.

42. *Id.* at col.24 l.3.

43. U.S. Patent No. 5,914,891 (filed Jan. 19, 1996). Claim 1 reads:

> A method of simulating the operation of a biochemical network, said method comprising the steps of:
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> (A) receiving and storing in a computer memory a list of objects, each object representing a biochemical mechanism in said biochemical network;

What is the likelihood that these foundational patents, or patents similar to such patents, would hold up in court? Given the low nonobviousness threshold that the Federal Circuit has set in the area of genetics, there is some possibility that the court would apply a similarly low threshold here.[44] Moreover, to the extent that these patents were viewed as software, they might not be considered too broad.

Considerable historical evidence, including evidence from many important industries of the twentieth century, suggests that the transaction costs associated with developing broad patents on foundational research can slow growth in the industry.[45] In this regard, it is instructive to contrast the proprietary situation in the nascent area of synthetic biology with that of computer hardware, computer software, and biotechnology in their infancy. In the area of computer hardware, the specter of broad patents loomed large until government action forced licensing of the AT&T transistor patent as well as patents obtained by Texas Instruments and Fairchild Instruments on integrated circuits.[46] As for software, it was already a robust industry before software patents became available, at least in any widespread fashion.[47]

(B) for each of at least a subset of said objects, associating one or more signals with said each object; a first subset of said signals representing quantities or concentrations of associated proteins; designating a second subset of said signals as output signals;

(C) associating a set of methods with each object in said list of objects; for each of at least a subset of said objects, said associated methods including one or more probability determination methods for determining one or more reaction probabilities for one or more biochemical reactions associated with said object, and one or more reaction simulation methods for simulating performance of one or more associated biochemical reactions;

(D) for a specified simulation time period, simulating operation of said biochemical network, including executing at least a subset of said probability determination methods to determine reaction probabilities for at least a subset of said biochemical reactions associated with said objects, selecting ones of said reaction simulation methods to execute in accordance with said determined reaction probabilities, and executing said selected ones of said reaction simulation methods; wherein execution of said selected ones of said reaction simulation methods causes associated ones of said signals to be updated;

(E) generating output data representing signal values of at least a subset of said output signals during said specified simulation time period.

Id. at col.21 ll.61–67 to col.22 ll.1–27.

44. Fortunately, because of the Supreme Court's recent decision in *KSR v. Teleflex International Co.*, 127 S. Ct. 1727 (2007), a challenger to one of these patents would not necessarily have to bring forward written evidence of information widely known in the field at the time the inventions at issue were made.

45. Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 884–909 (1990).

46. *See id.* at 893–94 (arguing that the existence of an antitrust consent decree with regard to AT&T and pressure from the Department of Defense with regard to Texas Instruments and Fairchild Instruments led to increased licensing of AT&T's transistor patent and cross licensing of Texas Instruments' and Fairchild Instruments' integrated circuit patents).

47. A few patents on software that claimed a process analogous to a manufacturing process appear to have been issued in the 1960s and 1970s; however, patent protection was quite rare. *See* MARTIN CAMPBELL-KELLY, FROM AIRLINE RESERVATIONS TO SONIC THE HEDGEHOG: A HISTORY

Many of biotechnology's foundational technologies—including monoclonal antibodies and Maxam–Gilbert sequencing—were not patented.[48] Synthetic biology appears to be coming of age under different circumstances.

Of course, broad patents held by universities and the federal government—the University of Tennessee, HHS, and Stanford—may not necessarily impede progress. It may be that these owners are willing to tolerate substantial infringement, not only by other academics but also by commercial firms. Alternatively, where a single owner controls the foundational patent(s), the owner may recognize the profit potential of licensing the patent nonexclusively on standard terms, on the model of Stanford's licensing of its patented Cohen–Boyer recombinant DNA technology.[49] On the other hand, universities have not always licensed their foundational patents nonexclusively. A prominent, and controversial, recent case of exclusive licensing involves a broad patent held by Harvard University and MIT on mechanisms for modulating the NF-kB cell signaling pathway.[50] This patent has been exclusively licensed to a small firm, Ariad Pharmaceuticals, which is apparently aiming to extract large "holdup" rents by asserting the patent against a number of pharmaceutical firms that have already invested in the manufacture and sale of allegedly infringing drugs.[51] Moreover, at least in the software arena, universities—which are nonmanufacturing entities, and thus not necessarily subject to retaliatory infringement lawsuits by the manufacturer defendants they sue—have been quite active in asserting their patents for purposes of extracting rents from holdup.[52]

OF THE SOFTWARE INDUSTRY 107 (2003) (discussing a successful software patent application by ADR but noting that "there were complex public policy issues regarding the validity of software patents, insofar as patents were designed to protect tangible artifacts rather than 'ideas'"). Not until 1981 did the U.S. Supreme Court make it clear that software could be patented as part of a tangible physical process. *See* Diamond v. Diehr, 450 U.S. 175, 185 (1981) (declaring that the Court's conclusions regarding whether a process fell within the statutory categories of patentable subject matter were "not altered by the fact that in several steps of the process a mathematical equation and a programmed digital computer are used").

48. *See* Joe Fore Jr. et al., *The Effects of Business Practices, Licensing, and Intellectual Property on Development and Dissemination of the Polymerase Chain Reaction: Case Study*, J. BIOMEDICAL DISCOVERY & COLLABORATION, July 3, 2006, at 1:7, ¶ 15 (noting that Maxam–Gilbert sequencing is not patented); Timothy A. Springer, *César Milstein, the Father of Modern Immunology*, 3 NATURE IMMUNOLOGY 501, 503 (2002) ("[M]onoclonal antibodies were never patented.").

49. *See* Maryann Feldman, Rotman School of Management, University of Toronto, Commercializing Cohen-Boyer 1980–1997 (Sept. 29, 2005), http://www.kauffman.org/pdf/tt/Feldman_Maryann.pdf.

50. Ariad Pharms., Inc. v. Eli Lilly & Co., No. Civ. A. 02-11280-RWZ, 2004 WL 413262 (D. Mass. Mar. 3, 2004).

51. *See, e.g.*, Andrew Pollack, *Lilly Loses Patent Case to Ariad*, N.Y. TIMES, May 5, 2006, at C6 (discussing the holding by the Federal District Court of Massachusetts that Eli Lilly had infringed a patent licensed to Ariad Pharmaceuticals).

52. Arti Rai et al., University Software Ownership: Technology Transfer or Business As Usual? (unpublished manuscript under submission to the Journal of Legal Studies, on file with the Texas Law Review) (discussing university lawsuits against successful commercializers). In a somewhat similar vein, Mark Lemley suggests that the significant university position in nanotechnology

In any event, not all of the foundational patents in synthetic biology are held by nonprofit players. One of the more aggressive firms in the field, Sangamo Biosciences, has several broad patents on arguably foundational technologies.[53] These include a broad patent on an iterative technique for optimizing the binding specificity of nucleic-acid-binding proteins[54] as well as a patent on methods for selecting DNA-binding proteins that bind with greater specificity in the presence of a DNA-binding ligand.[55] Sangamo also

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patenting may be problematic because universities are not in a symmetric relationship with other patentees and may therefore be more inclined to assert their patents aggressively than to cross license. Mark Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601, 626 (2005).

53. For a list of Sangamo's U.S. patents as of December 31, 2006, see Sangamo Biosciences, Inc., Annual Report (Form 10-K), at 17–18 (Mar. 1, 2007).

54. U.S. Patent No. 6,794,136 (filed Nov. 20, 2000). Claim 1 reads:

> A method of enhancing the binding specificity of a DNA-binding protein for its target sequence, the method comprising:
>
> (a) providing the DNA-binding protein;
>
> (b) determining the specificity of binding of the DNA-binding protein with respect to each residue in the target sequence;
>
> (c) identifying one or more residues in the target sequence for which the DNA-binding protein does not possess requisite specificity;
>
> (d) substituting one or more amino acids at positions in the DNA-binding protein that affect the specificity of the DNA-binding protein for the residues identified in (c), to make a modified DNA-binding protein;
>
> (e) determining the specificity of binding of the modified DNA-binding protein with respect to each residue in the target sequence;
>
> (f) identifying any residues in the target sequence for which the modified DNA-binding protein does not possess requisite specificity; and
>
> (g) repeating steps (d), (e) and (f) until the modified DNA-binding protein evaluated in step (f) demonstrates the requisite specificity for each residue in the target sequence,
>
> thereby obtaining a DNA-binding protein with enhanced binding specificity for its target sequence.

Id. at col.51 ll.2–28.

55. U.S. Patent No. 6,706,470 (filed Nov. 28, 2001). Claim 1 reads:

> A method of selecting a gene switch, which gene switch comprises (i) a target DNA molecule; (ii) a non-naturally occurring DNA binding molecule which binds to the target DNA molecule in a manner modulatable by a DNA binding ligand; and (iii) the DNA binding ligand, which method comprises:
>
> (a) contacting one or more candidate target DNA molecule(s) with one or more candidate, non-naturally occurring DNA binding molecules, in the presence of one or more DNA binding ligands;
>
> (b) selecting a complex comprising a candidate target DNA, a non-naturally occurring DNA binding molecule and a DNA binding ligand;
>
> (c) isolating and/or identifying the unknown components of the complex;
>
> (d) comparing the binding of the DNA binding molecule component of the complex to the target DNA component of the complex in the presence and absence of the DNA binding ligand component of the complex; and
>
> (e) selecting complexes wherein the DNA binding molecule component has a higher affinity for the target DNA in the presence of the DNA binding ligand component than in the absence of the DNA binding ligand component.

Id. at col.83 ll.2–25.

owns several dozen broad patents involving so-called zinc finger proteins[56] and has exclusive licenses to many others.[57] Although none of these individually is necessarily a foundational patent, Sangamo's collection of patents on zinc finger proteins is quite powerful, particularly because zinc finger proteins are perhaps the most versatile of the DNA-binding proteins.[58] Unlike other DNA-binding proteins, which tend to bind only to very specific nucleotide sequences, zinc finger proteins can be engineered to bind to virtually any nucleotide sequence.[59]

Already various potential infringers in the area of zinc finger nuclease technology (which joins zinc finger proteins with nucleases for gene "repair") are voicing discontent over Sangamo's assertion of its zinc finger protein "monopoly."[60] For example, Sangamo appears to have warned academics who are working on developing public domain zinc finger protein technology of potential patent infringement.[61] While these difficulties may ultimately prove only a minor impediment—Sangamo may forbear from actually suing academic researchers and may ultimately be able to negotiate reasonable licenses with private sector users[62]—Sangamo's role is well worth watching.

B. Thickets and Anticommons

Broad patents on foundational technology do not represent the only potential difficulty. There is the possibility of a plethora of narrower patents on individual parts, some of which may fall within the scope of the

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56. *E.g.*, U.S. Patent No. 7,070,934 (filed June 5, 2003); U.S. Patent No. 7,045,304 (filed Apr. 10, 2003); U.S. Patent No. 6,989,269 (filed Apr. 10, 2003); U.S. Patent No. 7,013,219 (filed Sept. 16, 2002); U.S. Patent No. 7,163,824 (filed Aug. 15, 2002); U.S. Patent No. 6,933,113 (filed Aug. 28, 2001).

57. *See* Sangamo Biosciences, Inc., *supra* note 53, at 18 (listing patents that Sangamo has exclusively licensed from universities, most of which pertain to the "design, selection, and use of [zinc finger DNA-binding proteins (ZFPs)], [ZFP transcription factors], and [ZFP nucleases] for gene regulation and modification").

58. *See* Willemijn M. Gommans et al., *Engineering Zinc Finger Protein Transcription Factors: The Therapeutic Relevance of Switching Endogenous Gene Expression On or Off at Command*, 354 J. MOLECULAR BIOLOGY 507, 509 (2005) (explaining that the properties of zinc finger proteins make them "extremely promising and flexible devices for the targeted regulation of . . . genes").

59. *See id.* (explaining the structural advantages that zinc finger proteins have over most other DNA-binding proteins that make them "very suitable for targeting virtually any DNA sequence").

60. *See* Jocelyn Kaiser, *Putting the Fingers on Gene Repair*, 310 SCIENCE 1894, 1896 (2005) (relating the concerns of researchers and biotech entrepreneurs that Sangamo's assertion of its intellectual property rights is hindering the progress of research on zinc finger proteins); Christopher Thomas Scott, *The Zinc Finger Nuclease Monopoly*, 23 NATURE BIOTECHNOLOGY 915, 915 (2005) ("Sangamo's proprietary database of zinc fingers has academic experts both excited and nervous.").

61. *See* Kaiser, *supra* note 60, at 1896 (describing the reluctance of various academics to undertake research they believe would infringe on Sangamo's patents).

62. *See* Fore et al., *supra* note 48, ¶ 78 (arguing that in the case of the foundational PCR patents, "rational forbearance" with respect to academic researchers and the negotiation of largely reasonable licensing terms for commercial actors led to broad dissemination of the technology).

foundational patents. At least in the area of information technology,[63] there is considerable evidence that patent thickets[64] or anticommons[65] create difficulties for subsequent researchers above and beyond those created by foundational patents. This is because many products in information technology represent combinations of dozens, if not hundreds, of patented components.

In the biopharmaceutical arena, where patents often cover "research tools" that are not necessarily a component of the final marketed product, firms may be able to circumvent anticommons difficulties through secret infringement that does not come to light (if at all) until after the six-year statute of limitations has run. Indeed, some empirical evidence suggests that in biotechnology, secret infringement is a common mechanism for evading patent liability.[66] However, this strategy may not work as well in synthetic biology. Some of the patents discussed above may be infringed not only at the research stage but also by the marketed product.

Additionally, to the extent that the aim of synthetic biology is to achieve a newfound level of standardization in biology, secret infringement may not be an option. In order to serve their purpose, standards need to be developed and disseminated openly. In the case of synthetic biology, standardization might involve not only parts that perform particular functions but, perhaps even more importantly, the interfaces used to assemble parts. As MIT synthetic biologist Tom Knight has noted, synthetic biology must establish "a set of standard and reliable engineering mechanisms to remove much of the tedium and surprise during assembly of genetic components into larger systems."[67] Standards governing the interaction between parts and the host

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63. The situation in biotechnology is less clear. *Compare* John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCIENCE 2002 (2005) (finding that academic researchers ignore patents) *and* John P. Walsh et al., *Working Through the Patent Problem*, 299 SCIENCE 1021, 1021 (2003) [hereinafter Walsh et al., *Patent Problem*] (observing that a proliferation of biotechnology patents creates the preconditions for an anticommons but arguing, based on interviews, that industry players have adopted "working solutions" to circumvent patents), *with* Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis* 31 (Nat'l Bureau of Econ. Research, Working Paper No. 11465, 2005), *available at* http://www.nber.org/papers/w11465 (finding that the existence of patents has a small, but statistically significant, negative impact on scientific research).

64. *See* Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY 119, 120 (Adam B. Jaffe et al. eds., 2001) (noting the concern among "thoughtful observers" that "a dense web of overlapping intellectual property rights" hinders companies from commercializing new technologies).

65. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698 (1998).

66. Walsh et al., *Patent Problem*, *supra* note 63, at 1021.

67. Tom Knight, Idempotent Vector Design for Standard Assembly of BioBricks 2 (2003) (unpublished manuscript), *available at* http://dspace.mit.edu/bitstream/1721.1/21168/1/biobricks.pdf.

cell or "chassis" may also be needed. The establishment of such standards will be necessary to make such interactions reasonably predictable.[68]

Of course, for patents that are not foundational, noninfringing alternatives may be available. However, even such designing around is inefficient if the patent in question is likely to be invalid (and yet won't be challenged because of the collective action problems associated with patent challenge[69]). Additionally, a crowded patent landscape creates the possibility of "holdup" by a previously unknown patent holder who emerges only after others have invested large sums of money.[70] These problems are only exacerbated when the patent covers a standard that can not be readily altered. Additionally, to the extent that patent rights holders rely upon reach-through royalties to secure revenue, standard economic theory predicts that product output by the improver will be suboptimal.[71]

In the next subpart, we examine the possibility of patent thickets covering one particularly important technology—the DNA-binding proteins that can be used to switch genes on and off.[72] Such binding proteins are likely to be a component of many different parts and devices, including parts and devices that become standards. To be sure, patents on DNA-binding proteins do not represent the only types of patents that might contribute to a thicket. Patents on specific parts or devices—such as those held by Boston University on the use of DNA to produce specific gene regulation mechanisms, such as a multistate oscillator;[73] a genetic toggle switch;[74] and an adjustable threshold switch[75]—might also contribute. But the patent cluster surrounding DNA-binding proteins can be identified somewhat more clearly than other patent clusters. Thus, for illustrative purposes in this Article, we focus on DNA-binding proteins.

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68. *See* Ernesto Adrianantoandro et al., *Synthetic Biology: New Engineering Rules for an Emerging Discipline*, MOLECULAR SYS. BIOLOGY, May 16, 2006, at 1, 8–9, *available at* http://www.nature.com/msb/journal/v2/n1/pdf/msb4100073.pdf (explaining the need to standardize the interaction between host cells and engineered, modular additions to them).

69. For a discussion of these collective action problems, see for example, Joseph Scott Miller, *Building a Better Bounty: Litigation-Stage Rewards for Defeating Patents*, 19 BERKELEY TECH. L.J. 667 (2004).

70. Mark A. Lemley & Carl Shapiro, *Patent Holdup and Royalty Stacking*, 85 TEXAS L. REV. 1991, 1993 (2007). Lemley and Shapiro particularly emphasize the power that the threat of injunctive relief can give the patent holder. To some extent, the Supreme Court's recent decision in *eBay v. MercExchange, L.L.C.*, 126 S. Ct. 1837 (2006), may mitigate this power by making injunctive relief less than fully automatic.

71. The classic reference is AUGUSTIN COURNOT, RESEARCHES INTO THE MATHEMATICAL PRINCIPLES OF THE THEORY OF WEALTH 99–116 (Nathaniel T. Bacon trans., Augustus M. Kelley Publishers 1971) (1838).

72. As a technical matter, these DNA-binding proteins alter the conformation of DNA so as to make it easier or more difficult for the enzymes necessary for transcription to do their work. *See generally* Andrew A. Travers, *DNA Conformation and Protein Binding*, 58 ANN. REV. BIOCHEMISTRY 427 (1989).

73. U.S. Patent No. 6,737,269 (filed June 21, 2001).

74. U.S. Patent No. 6,841,376 (filed May 1, 2001).

75. U.S. Patent No. 6,828,140 (filed June 1, 2001).

C. Patents on DNA-Binding Proteins

A search of the Delphion database for all patents with the term "DNA-binding protein" in their claims identified 178 patents with 112 different owners. A more focused investigation that attempted to isolate those patents that claimed DNA-binding proteins in the context of synthetic biology found fifty-two patents with twenty-eight different owners.[76] These preliminary investigations suggest a fair number of patents as well as a pattern of dispersed ownership that might yield substantial transaction costs. Notably, a search for DNA-binding proteins is probably quite underinclusive: for example, only one of Sangamo's plethora of patents on zinc finger proteins shows up in this search.

Firms that work in information technology have sometimes succeeded in pooling patents, particularly patents around industry standards.[77] But efforts at patent pooling do not always succeed in addressing problems of inefficient royalty stacking.[78] Such efforts have also been stymied by failure on the part of firms with relevant patents to bring holdup actions after failing to disclose such patents.[79]

A prominent argument often made in favor of upstream patents is that such patents provide necessary protection against misappropriation for small firm start-ups that market technology inputs.[80] To the extent that market-based arrangements may be more innovative than large, vertically integrated firms[81] (or at least disseminate information more widely than vertically integrated firms), promoting these small firms could be a valuable goal. In biotechnology, the limited empirical evidence is somewhat supportive of this "small firm" argument in favor of patents: small biotechnology firms often have patents and those firms with patents tend to fare significantly better in terms of attracting financing than firms without patents.[82] But the obvious

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76. For this more focused investigation, we searched the LEXIS patents database for patents that: (1) claimed DNA-binding protein, (2) discussed the concept of a DNA-binding protein in their abstracts, and (3) included some mention of the term "synthetic" in their specification. We then reviewed these patents by hand and discarded those that referred to DNA-binding protein only in a dependent claim; included DNA-binding protein as one of a group of options; or used the term "synthetic" in a context other than synthetic biology.

77. Lemley & Shapiro, *supra* note 70, at 2028–29.

78. *Id.* at 2029.

79. *See In re* Rambus, Inc., No. 9302, Opinion of the Commission, at 16, 70–71 (F.T.C. Aug. 2, 2006) (noting that Rambus did not disclose its computer memory technology patents to an industry-wide standard-setting organization of which it was a member). In this case, the FTC determined that Rambus's actions had violated § 5 of the FTC Act. *Id.* at 3. Breach of contract and patent misuse might also be used to deter the possibility of holdup in standard-setting contexts.

80. ASHISH ARORA ET AL., MARKETS FOR TECHNOLOGY: THE ECONOMICS OF INNOVATION AND CORPORATE STRATEGY 164–66 (2001); Ashish Arora & Robert P. Merges, *Specialized Supply Firms, Property Rights and Firm Boundaries*, 13 INDUS. & CORP. CHANGE 451, 459 (2004).

81. The empirical evidence on this question is mixed.

82. Ronald J. Mann & Thomas W. Sager, *Patents, Venture Capital, and Software Start-ups*, 36 RES. POL'Y 193, 197 (2007). This evidence is limited by the fact that the authors could only

difficulty with vertical "disintegration" is that it creates the potential for large transaction costs, including holdup. Moreover, patents do not appear to be nearly as important in promoting software start-ups.[83] Thus, to the extent that at least certain areas of synthetic biology research and development (R&D) have an economic structure similar to that of software, extensive patenting does raise concerns.

D. Proprietary Rights on Large-Scale Gene Synthesis

A third set of proprietary rights relevant to our analysis are rights, including patents, that encompass large-scale genetic and genomic synthesis. Large-scale gene synthesis is a relatively new technology. For the last thirty years, gene synthesis has primarily involved the creation of individual oligonucleotides—short (200 base pairs or less) DNA strands that can be used as primers to copy natural DNA.[84] Even now, most gene synthesis companies produce DNA strands that are only a few thousand base pairs long.[85] However, a few prominent companies—such as Codon Devices and Blue Heron—have prominently advertised their quest to produce longer DNA sequences.[86] Moreover, this type of large-scale synthesis is likely to be quite important for producing the devices and systems that synthetic biology ultimately aims to produce.

A review of the technology used by the major players suggests some similarity in approach. For example, Codon Devices and Blue Heron both appear to generate double-stranded oligonucleotides and use computer-assisted design to ensure that these oligonucleotides can be linked to each other to form longer sequences.[87] Nonetheless, the firms both emphasize the unique and proprietary nature of their synthesis platforms.[88] Indeed, Codon

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tabulate patents owned outright by the small biotechnology firms. They could not determine the number of patents exclusively licensed from universities.

83. *See id.* (noting that most venture-backed software firms did not acquire any patents during the period of the study).

84. Hans Bügl et al., A Practical Perspective on DNA Synthesis and Biological Security (Dec. 4, 2006), http://pgen.us/PPDSS.htm.

85. *See* Charlie Schmidt, *Synthetic Gene Firms Evolve Toward Sustainable Business?*, 24 NATURE BIOTECHNOLOGY 1304, 1304 (2006) (noting that although some companies are pushing the limits of production, "[t]he vast bulk of what people need now are DNA stretches in the 500 to 10,000 base pair range").

86. *See, e.g.*, Press Release, Blue Heron Biotechnology, Blue Heron Biotechnology, Inc. Awarded a $2.4 Million SBIR Grant (Feb. 5, 2003), *available at* http://www.blueheronbio.com/company/press/feb5-03.html ("GeneMaker has built hundreds of full-length genes and thousands of gene fragments with perfect accuracy, including sequences with 98% G-C content or with sizes exceeding 10,000 base pairs.").

87. *See GeneMaker Gene Synthesis, Blue Heron Bio*, DRUG DISCOVERY NEWS, Jan. 2005, http://www.drugdiscoverynews.com/index.php?newsarticle=83 (describing the GeneMaker genetic synthesis device); Codon Devices, The BioFAB Platform, http://www.codondevices.com/science.aspx?id=114 (discussing the BioFAB genetic construction platform).

88. *See* Codon Devices, *supra* note 87 ("The BioFAB platform combines advanced informatics with proprietary algorithms, sophisticated high-capacity automation, and an arsenal of chemical and biochemical protocols that collectively represent the most advanced genetic construction platform in

Devices asserts a "front-runner" position based in part on its aggressive pursuit of patent protection for its technology.[89]

A LEXIS search of U.S. patents and applications assigned to Codon Devices revealed three patent applications.[90] These patent applications broadly cover methods for making polynucleotide products with nucleotide alterations;[91] methods for using oligonucleotides to "seamlessly" join polynucleotide constructs;[92] and methods for assembly of "high-fidelity" polynucleotides.[93] The Web site for Codon Devices indicates that the company also has exclusive licenses to technology generated at Harvard, MIT, Duke University, and the University of Wisconsin.[94] These exclusive licenses most likely attach to relevant patents held by academic scientists who are on the Codon Scientific Advisory Board, including George Church of Harvard, Francesco Cerrino of the University of Wisconsin, and Paul Modrich of Duke.[95] Such patents include a host of patents on microarray

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the world."); Blue Heron Biotechnology: GeneMaker Gene Synthesis, http://www.blueheron bio.com ("GeneMaker is a proprietary, automated, high throughput gene synthesis platform . . . . Through years of experience making thousands of perfectly accurate genes, Blue Heron Bio has emerged as the leader in gene synthesis.").

89. *See* Codon Devices, Intellectual Property, http://www.codondevices.com/science.aspx? id=118 ("Protecting our position as the front-runner . . . is important to Codon Devices. We aggressively pursue patent protection for most of our proprietary technology, and protect other aspects of our proprietary technology as trade secrets.").

90. Interestingly, the Web site for Codon Devices states that the firm's patent portfolio consists of thirty-five patent applications and ten issued patents in the United States. *Id.*

91. Hierarchical Assembly Methods for Genome Engineering, U.S. Patent Application Publication No. US 2007/0004041 (filed Jan. 12, 2006). Claim 4 of this application appears particularly broad. It reads:

> A method for introducing a plurality of predetermined nucleotide changes throughout a polynucleotide product, comprising:
>
> modifying one or more nucleotides on each of a plurality of polynucleotide segments from a genome to form a plurality of polynucleotide constructs; and
>
> incorporating said plurality of polynucleotide constructs into said genome thereby introducing a plurality of nucleotide changes throughout said polynucleotide product.

Id. at 30.

92. Accessible Polynucleotide Libraries and Methods of Use Thereof, U.S. Patent Application Publication No. US 2006/0281113 ¶ [0007] & ¶ [0012] (filed May 17, 2006).

93. Methods for Assembly of High Fidelity Synthetic Polynucleotides, U.S. Patent Application Publication No. US 2006/0194214 (filed Feb. 28, 2005).

94. Codon Devices, *supra* note 89.

95. *See* Codon Devices, Scientific Advisory Board, http://www.codondevices.com/aboutus. aspx? id=98 (listing members of the Codon Scientific Advisory Board).

technology (apparently for oligonucleotide synthesis)[96] and on DNA error correction and repair.[97]

Meanwhile, Blue Heron has a broad patent that claims software for "decomposing" a designated target molecule into potential fragments; adjusting the fragment definitions sufficiently to ensure that the fragments satisfy a plurality of synthesis criteria; and then generating an output that indicates an order for combining the adjusted fragments.[98] Blue Heron also has a patent on error correction in gene synthesis.[99]

Although the details of the processes used by Blue Heron and Codon Devices no doubt differ in many respects (both companies emphasize, for example, that certain aspects of their assembly processes are protected by trade secrecy[100]), their patents and patent applications do overlap to some extent. A third firm, Egea Biosciences (now wholly owned by Johnson & Johnson) also has several patents on gene synthesis that claim computer-directed assembly of oligonucleotides.[101] In some information industries, such overlap deters lawsuits—firms compete within a framework of "mutual assured destruction" if any firm asserts its patents against any other. Whether competition will ultimately survive in the context of large-scale gene synthesis is less clear. Codon Devices appears to be sufficiently confident of the superiority of its patent position that it recently sued Blue Heron for infringement of five patents, four licensed exclusively from Duke and one licensed exclusively from MIT.[102] We discuss concerns that might be raised by possible monopoly dominance of large-scale gene synthesis in Part IV.

III. A Synthetic Biology Commons?

Thus far, synthetic biology patents do not appear to have created significant problems. However, as commercial applications for the

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96. George Church invented many of these technologies. *E.g.*, U.S. Patent No. 6,511,803 (filed Mar. 10, 2000); U.S. Patent No. 6,485,944 (filed Mar. 12, 1999); U.S. Patent No. 6,432,360 (filed Aug. 28, 1998); U.S. Patent No. 6,548,021 (filed Aug. 11, 1998); U.S. Patent No. 6,326,489 (filed Aug. 5, 1997). Francesco Cerrina invented others. *E.g.*, U.S. Patent No. 7,072,500 (filed May 7, 2004); U.S. Patent No. 7,083,975 (filed Feb. 1, 2002).

97. Paul Modrich was responsible for developing many of these patented technologies. *E.g.*, U.S. Patent No. 6,008,031 (filed June 17, 1997); U.S. Patent No. 5,922,539 (filed Dec. 13, 1996); U.S. Patent No. 5,858,754 (filed Feb. 13, 1996); U.S. Patent No. 5,861,482 (filed June 2, 1995); U.S. Patent No. 5,702,894 (filed June 2, 1995); U.S. Patent No. 5,679,522 (filed June 2, 1995); U.S. Patent No. 5,556,750 (filed Nov. 1, 1993).

98. U.S. Patent No. 7,164,992 (filed Mar. 22, 2002).

99. U.S. Patent No. 6,664,112 (filed June 1, 2001).

100. *See* Blue Heron Biotechnology, GeneMaker Technology, http://www.blueheronbio.com/genemaker/technology.html (mentioning use of a "proprietary algorithm"); Codon Devices, *supra* note 89 ("[We] protect other aspects of our proprietary technology as trade secrets.").

101. *E.g.*, U.S. Patent No. 6,670,127 (filed Aug. 2, 2001); U.S. Patent No. 6,521,427 (filed Sept. 16, 1998).

102. *Codon, Duke, MIT Sue Blue Heron for Allegedly Infringing IP to Synthesize DNA*, GENOMEWEB DAILY NEWS, Mar. 15, 2007, http://www.genomeweb.com/issues/news/138956-1.html.

technology develop further, and a need for standards emerges, future prospects are less clear. The MIT scientists involved with the Registry of Standard Biological Parts are sufficiently concerned that they have created a "BioBricks Foundation" that might serve to coordinate a synthetic biology commons.[103] The idea of a synthetic biology commons draws inspiration, in part, from the prominence of the open-source software model as an alternative to proprietary software. Like software, synthetic biology aims to be information based and modular. Indeed, the synthetic biologist might argue that what she does is comparable to software programming—the only difference is that synthetic biologists program with four bases (As, Ts, Cs, and Gs) while software programmers ultimately use 0s and 1s. So the analogy to open-source software is hardly farfetched.

Unlike proprietary software developers, open-source software producers make their source code available for improvement, modification, and redistribution.[104] Certain types of open-source licenses also have a "commons-expanding" aspect: these "copyleft" licenses not only make source code available, but they also require those who distribute improvements to the source code to make the improvements available on the same terms.[105] Copylefted software relies heavily on the existence of property rights—specifically, copyright in the source code. Because of this copyright, users of the copylefted software necessarily use it subject to the terms of the license.

Synthetic biologists might argue that strings of DNA bases are comparable to source code and that DNA strings could therefore also be covered by copyright.

Unlike software, however, the products of synthetic biology are not discussed as copyrightable subject matter in the statute.[106] Thus, a court that wished to find that material copyrightable would have to do so by analogy. Additionally, even if courts were willing to make such an analogy, there are the internal restrictions of copyright law. Copyright does not cover functionality or methods of operation, and it requires expressive choices.[107]

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103. *See* BioBricks Foundation Home Page, http://www.biobricks.org (advocating the use of BioBrick standard DNA parts, for which sequence information and other characteristics are freely available).

104. *See generally* Bruce Perens, The Open Source Definition, http://perens.com/OSD.html (explaining and evaluating the creation and use of open-source software).

105. *See* Robert W. Gomulkiewicz, *How Copyleft Uses License Rights to Succeed in the Open Source Software Revolution and the Implications for Article 2B*, 36 HOUS. L. REV. 179, 185–89 (1999) (describing the licensing principles embodied in the GNU General Public License and other copyleft licenses); Free Software Foundation, What is Copyleft? – GNU Project, http://www.gnu.org/copyleft/copyleft.html (defining "copyleft" as "a general method for making a program or other work free, and requiring all modified and extended versions of the program to be free as well").

106. *See* 17 U.S.C. § 101 (2000) (including a definition of "computer program" but not of "synthetic biology" as part of the chapter pertaining to subject matter and scope of copyright).

107. *See* 17 U.S.C. § 102(b) (excluding from copyright protection any "idea, procedure, process, system, [or] method of operation").

For this reason, courts have determined that copyright protection of software is relatively thin. Although source code is generally protected against verbatim copying, higher level features of software that are driven by functional considerations are not protectable.[108] Even source code may become unprotectable if it represents a method of operation.[109]

The construction of DNA sequences using base pairs that do not exist in nature might allow significant room for expressive choice. Such DNA sequences might be protected by copyright, at least against verbatim copying. However, most synthetic biologists working today, including those at MIT, are working within the confines of the existing genetic code. This code constrains the expressive choices that they make, making copyright protection less likely.

Beyond formal legal doctrine lies a set of policy concerns. With patent rights clearly available, courts and Congress might be reluctant to layer on an entirely new kind of property right, for fear that such rights would hurt rather than help innovation. The fact that the question of copyrightability arises in the attempt to create a research commons should not change the conclusion. While the goal is a laudable one, the boundaries of the public domain should not be altered to enable a particular initiative.

Thus, in the case of synthetic biology, the ability to invoke copyright is by no means clear. An obvious alternative is patents. One example of a patent-based commons is that created by the group Biological Innovation for Open Society (BIOS). BIOS is using patent protection on a few key plant gene transfer technologies to force licensees to make patented improvements to these enabling technologies available to other commons members.[110] Although some have suggested that the BIOS approach could raise concerns about antitrust and patent misuse,[111] the concern should be relatively small given BIOS's mission to expand the commons[112] and the relatively permissive, rule-of-reason-based approach taken by contemporary antitrust law.[113] The more pressing problem for purposes of projects like the MIT

108. *See, e.g.*, Computer Assocs. Int'l, Inc. v. Altai, Inc., 982 F.2d 693, 714 (2d Cir. 1992) ("[F]unctional elements and elements taken from the public domain do not qualify for copyright protection.").

109. *See, e.g.*, Lotus Dev. Corp. v. Borland Int'l, Inc., 49 F.3d 807, 815 (1st Cir. 1995) (holding the software in question to be a method of operation and therefore unprotectable).

110. Biological Innovation for Open Society, Improvements and Technology Data, http://www.bios.net/daisy/PELicense/751/383.html.

111. Sara Boettinger & Dan L. Burk, *Open Source Patenting*, 1 J. INT'L BIOTECHNOLOGY L. 221, 230 (2004); Robin Feldman, *The Open Source Biotechnology Movement: Is It Patent Misuse?*, 6 MINN. J.L. SCI. & TECH. 117, 139–44 (2004).

112. *See* Biological Innovation for Open Society, BiOS Initiative, http://www.bios.net/daisy/bios/about/3.html ("The BiOS Initiative uses the communications tools of the Internet and open source to generate open access to capabilities for innovation.").

113. *See* Thomas A. Lambert, *Tweaking Antitrust's Business Model*, 85 TEXAS L. REV. 153, 167 (2006) (book review) (describing the rule of reason as the predominant approach taken by courts in antitrust analysis).

Registry—which contains more than two thousand standardized parts[114]—is that a patent-based approach may be quite expensive. A single patent can cost tens of thousands of dollars to secure.[115]

Of course, to the extent that a few broad patents might effectively cover many of the parts in the Registry, the patent option becomes more plausible. For example, a patent comparable in breadth to the HHS patent noted above[116] might cover many Registry parts. In this scenario, the Registry would essentially be exploiting flaws in the current patent system for commons-expanding purposes. The difficulty in this scenario would be to identify an area of inventive territory that was quite broad but nonetheless not suggested either by prior broad patents or by information already in the public domain.

Alternatively, the Registry might try to attract statements of nonassertion by other patentees, on the model of recent statements by IBM, Sun Microsystems, and other firms that they will not assert their patents against anyone working on open-source software.[117] Indeed, the fact that many synthetic biology patents are currently held by academic and government institutions may make such statements of assertion a real possibility. Nonassertion statements would certainly be useful in providing those who are working on the MIT Registry comfort in moving forward. More generally, to the extent that institutions with synthetic biology patents vowed not to assert their patents against academic researchers, such a move would be a salutary development. Nonassertion statements are not, however, a property right. In order to secure a property right, the owners of the MIT Registry would need a license with explicit permission to sublicense. Moreover, patents licensed to the Registry would have to cover, at least in some fashion, parts that were important for maintaining and expanding the commons.

Another alternative for securing an expanding commons might rely on some kind of contract, such as a "clickwrap" license over the BioBricks. This contractual alternative does not require an underlying property right. Instead, the contract simply imposes conditions as part of the price of access. One problem with such contracts is that they bind only those who receive the technology from the entity imposing the terms.[118] Attempts to prevent

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114. Help: About the Registry, *supra* note 5.

115. *See* Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495, 1498 (2001) ("[T]he general range of costs for prosecuting a patent from start to finish . . . appears to be $10,000 to $30,000 per patent.").

116. *See supra* notes 41–42 and accompanying text.

117. *See, e.g.*, IBM Statement of Non-Assertion of Named Patents Against OSS, http://www.ibm.com/ibm/licensing/patents/pledgedpatents.pdf; OASIS, Sun SAML Non-Assertion Covenant, http://www.oasis-open.org/committees/security/ipr.php.

118. *See* Rebecca S. Eisenberg & Arti K. Rai, *Harnessing and Sharing the Benefits of State-Sponsored Research: Intellectual Property Rights and Data Sharing in California's Stem Cell*

leakage to those not bound by the terms of the contract can require strict restrictions on information dissemination.[119] For example, for some time the publicly funded International HapMap project (a database of human genetic variation) used a clickwrap license.[120] This license required those who sought access to single nucleotide polymorphism (SNP) data to refrain from combining it with their own proprietary SNP data in order to seek product patents on haplotypes (collections of SNPs).[121] In order to prevent leakage of the data outside the confines of this clickwrap license, to those who would then have no obligation to the HapMap commons, the license required those who accessed the data to refrain from disseminating it to anyone who had not signed onto the license.[122] Conventional publication of the data was not possible. This condition is no longer imposed because it is believed that the database has reached a sufficient density to be self-sustaining and to defeat subsequent patent claims. But the old requirements indicate one of the difficulties of the clickwrap approach: the comparative weakness of the contractual restraints paradoxically requires extremely broad restrictions on dissemination.

Finally, it bears emphasis that a copyleft approach may be more suited to the economic structure of R&D in the software arena than to, at least certain applications of, synthetic biology. Although the uses of synthetic biology are by no means limited to biomedicine, at the end of some chains of innovation will lie the expensive development and commercialization of a drug. While taking a drug through FDA-mandated clinical trial may not cost as much as drug companies claim, it does cost hundreds of millions of dollars.[123] As our system of pharmaceutical innovation is currently constituted, patents are an important mechanism for appropriating returns to clinical R&D.[124] There is no direct equivalent in the world of free software. If a copyleft condition did attach to certain synthetic biology parts, care would have to be taken in the design of the system, lest the copyleft feature undermine patents on products like drugs. The BIOS licenses, which restrict the copyleft condition to improvements on the enabling technology and do

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Initiative, 21 BERKELEY TECH. L.J. 1187, 1208 (2006) ("[T]here is no property right that survives disclosure to those not bound by the license.").

119. *See id.* at 1207–08 (describing HapMap's experience with controlling dissemination of information).

120. *See id.* at 1208 (describing HapMap's access restrictions and noting that these restrictions were lifted in December 2004).

121. *Id.* at 1207.

122. *Id.* at 1208.

123. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 165–66 (2003).

124. *See* Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)* 2–3 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000), *available at* http://www.nber.org/papers/w7552 (observing that numerous empirical studies have found that in comparison to other industries, patents are particularly important in the pharmaceutical arena).

not constrain the patenting of transgenic plant products,[125] provide one model. But the distinction between enabling technology and product appears easier to make in a situation like that faced by BIOS, where the enabling technology in question has a relatively clear innovation trajectory, both in terms of improvement to the technology itself and in terms of end products.

In the meantime, the decision, already implemented by the MIT Registry, to place its parts in the public domain certainly provides some protection against excessive patenting. Placing parts into the public domain not only makes the parts unpatentable, but it calls into question patents on trivial improvements.

IV. The Interaction Between Openness and Patents

As currently envisioned by its proponents, a commons or public domain approach would be limited to parts and devices.[126] Proponents of a commons approach do not envision extending the commons to include gene synthesis technologies.[127] Indeed, some of those who have proposed a commons or public domain approach for components are also involved with Codon Devices.[128]

In the software arena, some firms have embraced vigorously what they perceive as a complementarity between open-source and proprietary models. For example, IBM embraces open-source software in part because widespread dissemination of software increases demand for its hardware products.[129] Similarly, in synthetic biology, a robust "component" commons or public domain is likely to increase demand for gene synthesis services.

From a social welfare perspective, this complementarity could be beneficial, particularly to the extent that large-scale gene synthesis firms are going to succeed only if their services are used by many customers. Widespread use, coupled with competition, could also lead to continued price reduction. On the other hand, it is possible that one or more of the nascent firms currently doing large-scale gene synthesis will fail. Relatedly, as suggested by the lawsuit recently brought by Codon Devices, a superior patent position held by one firm may help to drive other firms out of business. To the extent that a single firm ultimately dominates the large-scale gene synthesis space, widespread use will not necessarily result in price reduction. More importantly, because large-scale gene synthesis represents a technology

125. Biological Innovation for Open Society, The CAMBIA BiOS License for Plant Enabling Technology, http://www.bios.net/daisy/PELicense/751/1169.html.

126. Discussion at the Duke–MIT Conference, Synthetic Biology: The Intellectual Property Puzzle, in Durham, N.C. (March 2–3, 2007).

127. *Id.*

128. For example, Drew Endy is a Codon Devices cofounder who is currently on its scientific advisory board. Codon Devices, *supra* note 95.

129. Andrea Bonaccorsi & Cristina Rossi, *Why Open Source Software Can Succeed*, 32 RES. POL'Y 1243, 1249 (2003).

platform onto which many applications can be layered, a monopoly position in such a synthesis raises the same concerns as monopolies created by single-firm ownership of foundational patent platforms. Because of transaction-cost difficulties, or for a host of other reasons, the monopoly firm may use its market power in a manner that is detrimental to innovation.[130] In the case of large-scale gene synthesis in particular, a monopoly firm might have strategic reasons for seeking vertical integration into the applications space. For example, it could seek to integrate vertically into manufacturing, and patenting, standardized parts. To the extent such vertical integration fortified the monopoly over the firm's core synthesis technology, it could be quite detrimental to innovation.[131]

V. Conclusion

Even in its nascent state, the synthetic biology research space is filled with proprietary rights. These rights may offer benefits, particularly to the extent that venture financing in biotechnology appears to be linked to patents. But propertization also threatens familiar costs, costs that could be particularly great to the extent that synthetic biology ends up looking more like information technology than like biotechnology. Thus, attempts by scientists to establish a parallel unpatented space should be welcomed. Although this parallel space could operate as a public domain or a commons, a public domain approach may be simpler and cause fewer difficulties for important downstream proprietary rights. The obvious effect of a parallel unpatented space will be to constrain the effects of patenting (particularly if those who work in this space do not themselves get sued for patent infringement). Less obviously, a public domain or commons could be quite complementary to proprietary positions in the area of large-scale gene synthesis.

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130. For a lucid discussion of situations in which monopolies in platform technologies could impede innovation, see, for example, Joseph Farrell and Philip J. Weiser, *Modularity, Vertical Integration, and Open Access Policies: Towards a Convergency of Antitrust and Regulation in the Internet Age*, 17 HARV. J.L. & TECH. 85 (2003).

131. *Id.* at 109–10 ("[E]ven if a two-level monopoly may not yield more than one monopoly profit, it can protect the monopolist against entry in several ways.").