3D MOLECULAR STRUCTURES: PATENTABLE SUBJECT MATTER UNDER 35 U.S.C. § 101?

Ben Quarmby[1]
Duke University School of Law
Benoit.quarmby@law.duke.edu

With the advent of protein engineering, the determination of a protein's 3D structure has taken on a whole new importance. This has prompted some to call for the United States Patent and Trademark Office [USPTO] to break with tradition and allow patents on the three-dimensional structural information of proteins. This iBrief will discuss whether such information would constitute patentable subject matter under 35 U.S.C. § 101, and how much protection patents on this information could actually confer.

INTRODUCTION

The Biotechnology Industry

¶1 The combination of new gene sequencing technologies, protein engineering and 3D molecular structure determination has recently revolutionized the biotechnology industry by allowing the development of a host of new proteins and drugs.

¶2 "[T]he properties of a protein are largely determined by its three dimensional structure":[2] information on the three-dimensional shape and structure of proteins is therefore crucial. Many research groups now rely heavily on structural biology to design further proteins or drugs. And yet this structural information cannot be protected. Should patent law evolve to accommodate these concerns?

Proposals for Structural Patents

¶3 Alicia Russo, an associate with Fitzpatrick, Cella, Harper & Scinto Baker Botts,[3] recently summarized the current situation as follows: "The USPTO's trend has not been toward a grant of patents that adequately protect structural genomics inventions. Rather, the trend has been to issue patents for methods for rational drug design using the information obtained from the three-dimensional structure of a protein."[4]

---

[1] Ben Quarmby - J.D., Duke School of Law, expected 2004; B.Sc. Biochemistry, University of Bristol, U.K., 2001.
[2] DONALD VOET & JUDITH G. VOET, BIOCHEMISTRY 141 (2d ed.1995).
[3] In 2002, when Ms. Russo's article came to publication, she was still an associate with Baker Botts, L.L.P.
[4] Alicia Russo, *Patent Protection for Three-Dimensional Protein Structure May Be Within Reach*, 3 No. 2 PATENT STRATEGY & MGMT. 1 (2002); *see also, e.g.,* U.S. Patent No. 6,490,588 (issued Dec. 3, 2002) (claiming "A Method of searching one or more ligand compound to a target biopolymer from a three-dimensional structure database"); U.S. Patent No. 5,856,116 (issued Jan. 5, 1999) (claiming "1. A method for identifying a potential inhibitor for an interleukin-1.beta. converting enzyme, comprising the steps of: : a. using a three-dimensional structure of said enzyme as defined by atomic coordinates of interleukin-1.beta. converting enzyme according to FIG. 5; b. employing said three-dimensional structure to design or select said potential inhibitor; c. synthesizing said potential

¶4 Ms. Russo and many others feel that the current system is inadequate. Patents provide poor protection for a researcher's work product because "atomic coordinates may be used in many ways for drug design, making infringement of the patents avoidable."[5]

¶5 These are grave concerns. Without adequate patent protection, researchers cannot obtain the legally-sanctioned monopoly enabling them to derive profit from licensing, and thus cannot recoup their investment. Without that monopoly, there is little incentive to fund any new research. The consequences for the biotechnology industry could be dire.

¶6 Some say patent law should adapt to meet these concerns. Ms. Russo suggests that pharmaceutical companies in particular need "the ability to claim the atomic coordinates themselves, which would cover any use of the coordinates."[6] At present, these firms have to rely on "method" patents, which disclose the molecule's 3D structural information but "do not cover the drug molecules themselves, which are the real revenue source for companies."[7]

¶7 Such a change would presumably be welcomed by many in the industry. But questions remain. Would this structural information constitute patentable subject matter under 35 U.S.C. § 101? Wouldn't this violate the ban on patents over "laws of nature" and "physical phenomena"? And provided these obstacles can be overcome, would the scheme really provide the extra protection advocated by Ms. Russo?

DISCUSSION

Patentable Subject Matter: 35 U.S.C. § 101

¶8 The "patentable subject matter" requirement for the allocation of a patent is enunciated in section 101 of the Patent Act: "[w]hoever invents or discovers any new and useful *process, machine, manufacture, or composition of matter*, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[8]

Is Structural Information "Patentable Subject Matter" Under § 101?

a. Broad interpretation of patentable subject matter requirement

---

inhibitor; and d. contacting said potential inhibitor with said enzyme in the presence of a substrate to determine the ability of said potential inhibitor to inhibit said enzyme.")

[5] Russo, *supra* note 4.

[6] *Id*.

[7] *Id*.; *see also, e.g.,* U.S. Patent No. 6,329,184 (issued Dec. 11, 2001) (claiming "1. A crystalline form of mammalian TRAP (tartrate-resistant and purple acid phosphatase), activated by cleavage prior to crystallization with a protease, wherein the crystalline form of the mammalian TRAP is capable of being used for X-ray studies, and wherein the crystalline form of the mammalian TRAP has a crystal structure with atomic structural coordinates as given in Table 2, or with coordinates having a root mean square deviation therefrom, with respect to conserved backbone atoms of the listed amino acid sequence, of not more than 1.5 Å")

[8] 35 U.S.C. § 101 (2001) (emphasis added).

¶9 "The plain and unambiguous meaning of § 101 is that any invention falling within one of the four stated categories of statutory subject matter may be patented, provided it meets the other requirements for patentability set forth in Title 35."[9] At first glance, it would seem that the structural coordinates of a protein could not qualify as patentable subject matter. Structural information is neither a process, a machine, a manufacture nor a composition of matter.

¶10 However, many cases and commentators recommend a broad interpretation of the patentable subject matter clause of § 101. In *Chakrabarty*, the Supreme Court expressed its belief that Congress intended for "anything under the sun that is made by man" to be patentable under the statute.[10] "In choosing such expansive terms as "manufacture" and "composition of matter," modified by the comprehensive "any," Congress plainly contemplated that the patent laws would be given wide scope."[11]

¶11 But while the Court is prepared to read § 101 broadly, there are limits to its scope. "[L]aws of nature, physical phenomena, and abstract ideas[, for example] have been held not patentable,"[12] because they are in essence "the basic tools of scientific and technological work,"[13] "free to all men and reserved exclusively to none."[14]

¶12 Would the spatial configuration and structural coordinates of a protein or other molecule found in nature be considered "manifestations of nature," or "physical phenomena," and as such, unpatentable subject matter? An overview of the methods used to obtain the structural data will help answer this difficult question.

b. The "law of nature" bar to patentability

¶13 The two most widely used methods to determine the 3D structure of proteins and other molecules are X-ray Crystallography and Nuclear Magnetic Resonance (NMR).

¶14 X-ray crystallography, as its name suggests, requires the studied molecule to be crystallized, an unnatural state for a protein.[15] Protein crystals are highly hydrated, and are less rigid and ordered than crystals of small molecules such as NaCl or Glycine. The electron density map of a protein crystal, as a result, tends to be less accurate.[16]

¶15 Indeed, in order to precisely determine the structure of a protein, an electron density map alone is not enough. Only by studying the amino acid sequence of the protein and using mathematical refinement techniques can one "reduce the errors in the crystal structure's atomic positions to around 0.1 Å."[17] Bearing

---

[9] State Street Bank & Trust Co. v. Signature Fin. Group, Inc., 149 F.3d 1368, 1372 (Fed. Cir. 1998).
10 Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).
11 *Id*. at 308.
12 *Id*. at 309; *see also* Parker v. Flook, 437 U.S. 584, 589 (1978); Gottschalk v. Benson, 409 U.S. 63, 67 (1972).
13 *Parker*, 437 U.S. at 589.
14 *Diamond*, 447 U.S. at 309.
[15] VOET & VOET, *supra* note 2, at 77. (Note: This may not work for all proteins; some cannot be crystallized at all.).
[16] *Id*. at 164.
[17] *Id*.

in mind that "[a]t 1.5 Å resolution, . . . individual atoms become partially resolved,"[18] and that "[a]t 1.1 Å resolution, atoms are clearly visible,"[19] this represents a very accurate structural map.

¶16 But while the level of accuracy reached may be considerable, the form of the resolved protein will still depend to a large extent on the conditions under which the protein was crystallized[20] and as a general rule, will differ from the form which the protein would adopt under natural conditions.

¶17 The structural determination of proteins using NMR, on the other hand, differs fundamentally from X-ray crystallography in that the protein being studied is analyzed in a liquid solution. However, the protein is not in its natural state in this situation either, as "low salt and low pH conditions are [generally] required for NMR, and such conditions compromise the structure of the protein in the solution."[21] The resolution in NMR, in the most favorable cases, "is roughly comparable to that of an X-ray crystal structure."[22] In NMR, as in X-ray crystallography, additional steps are then required to refine the picture of the protein obtained.

¶18 The differences between the data obtained using each method of structure determination tend to be minimal. Indeed, "crystalline proteins assume very nearly the same structures that they have in solution,"[23] and "in the several cases that both the X-ray crystal structure and the solution NMR structure of the same protein have been determined, the two structures are, for the most part, identical to within experimental error."[24] However, in both processes, the structural information obtained does not exactly reflect the protein's structure under natural conditions.

¶19 Thus, a patent protecting information obtained through either X-ray crystallography or NMR would probably not be considered as a patent over a "manifestation of nature" or a "physical phenomenon." Where a product is different from that found in nature, the product may be patentable.[25] Here, the snapshot of the protein structure obtained through either method would probably not accurately reflect the structure of the protein in its natural state, as discussed above.

¶20 Moreover, proteins in their natural environment are not rigid, fixed structures, but dynamic, flexible ones. They can and do take on a variety of three dimensional-conformations. Can a patent on the structural data obtained from a crystallized protein then really be considered a patent on a "law of nature"? It seems unlikely. A case-by-case analysis focusing on the degree of structural difference between the protein in its natural state and under NMR or crystallized conditions would seem more appropriate than a blanket ban on these types of patents.

---

[18] *Id*.
[19] *Id*.
[20] *Id*. at 165.
[21] Russo, *supra* note 4.
[22] VOET, *supra* note 2, at 166.
[23] *Id*. at 164.
[24] *Id*. at 165.
[25] *See* Merck & Co. v. Chase Chem. Co., 273 F. Supp. 68 (D.C.N.J. 1967).

¶21 In sum, if the image of the protein obtained is not an accurate picture of the protein in its natural state, the structural data might still qualify as patentable subject matter under § 101, escaping the bar on patents claiming phenomena of nature. But feasability and usefulness do not necessarily go hand in hand: the practical value of such patents is still very much open to debate.

How Much Protection Would Such Patents Confer?

¶22 While structural information may be considered patentable subject matter under 35 U.S.C. § 101, it is far from certain that patents on such information would achieve the greater protection for biotechnological products prophesized by Ms. Russo.

¶23 First of all, as discussed above, the structural information protected by the patents might have to relate to "non-natural" structures to qualify as patentable subject matter. How valuable would a patent over a protein in a conformation differing from that in which it will be marketed really be? It is still difficult to say. But there seems little doubt that the door would be open for competitors to exploit the differences between the natural structure of a protein and the protected structure, thereby avoiding infringement.

¶24 The doctrine of equivalents might provide some sort of protection for the holders of such patents. The doctrine of equivalents was "[d]esigned to protect a patentee from an infringer who appropriates the invention but avoids the literal language of the claims,"[26] i.e., a competitor using minor structural variations to avoid infringement. Under the doctrine of equivalents, "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claims elements of the patented invention."[27]

¶25 This seems a promising line of thought, but it is one fraught with danger. The perils of applying the doctrine of equivalents too broadly should not be understated. A broad patent on a chemical structure could completely shield a protein, or a structural component of a protein, from widespread use, thus potentially blocking off entire areas of research. On the other hand, interpreting the protection offered by a patent too narrowly would render it worthless.

¶26 Proteins are not fixed, rigid entities. They stretch and contract, fold and unfold. Attempting to protect a rigid conformation of a protein, with precisely determined spatial coordinates, seems inappropriate. The potential for imitation without infringement is most likely too great for such a scheme to provide the protection sought by Ms. Russo.

---

[26] Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1579 (Fed.Cir.1984).

[27] Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997); *see also* Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 609 (1950).

CONCLUSION

¶27 Allowing patents on the three dimensional coordinates of proteins is a fascinating concept, and one which may hold great promise for some in the biotechnology industry.

¶28 However, even assuming that 3D coordinates were held to constitute patentable subject matter under 35 U.S.C. § 101, it remains doubtful whether such patents would provide any real degree of protection for the proteins at issue. Fearful of blocking off entire branches of research, the USPTO and the courts might choose to read the scope of protection afforded by these patents narrowly, allowing other parties to circumvent the patents with minor modifications to similar products.

¶29 All in all, patent law seems ill-adapted to satisfy the very real need for protection of this information, and while a major overhaul of the patent system could be contemplated, a more promising avenue might be to venture into the realm of copyright law to meet these concerns.