Claiming Pitfalls in Bioinformatics Patent Applications

By Christopher Mitchell and Mehdi Ganjeizadeh

Among the types of IP protection, patents offer the "greatest assistance in protecting most forms of IP associated with bioinformatics."[1] However, analyzing by category patent data from the United States Patent and Trademark Office (USPTO) shows that the number of patents issued in the relevant subclasses is relatively low, and downward trends for bioinformatics-related patents have been observed in the past.[2] One explanation offered for this decline is "the relative difficulty of patenting bioinformatics innovations."[3] This article provides practical suggestions to overcome this difficulty and thus to obtain meaningful IP protection for inventions in bioinformatics.

To identify the difficulty facing applicants for patents in bioinformatics, we looked at the prosecution histories of 46 patents in subclasses 382/129, 702/19 to 702/21, 703/11, and 702/21 recently issued to top-ranking assignees. Our examination revealed that rejections under 35 U.S.C. section 101, alleging nonstatutory subject matter, and section 112, alleging indefinite claim language, were disproportionately higher in bioinformatics-related applications than in most other fields.[4] Thus, we focus in this article on these two areas of rejection as pitfalls in preparing and prosecuting patent applications in bioinformatics.

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The authors thank Mr. Craig Redinger, a third-year associate at Young Basile et al., P.C., for his contribution to the research for this article.

Pitfall No. 1: Nonstatutory Subject Matter

For a patent claim to contain eligible subject matter, it must recite a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[5]

Although the Supreme Court has stated that section 101 includes "anything under the sun that is made by man," and this expansive language is regularly quoted by practitioners, courts have limited its interpretation to exclude abstract ideas, laws of nature, and natural phenomena. So the USPTO requires examiners to determine whether the claimed invention falls within an enumerated statutory category; namely, a process, machine, manufacture, or composition of matter. The federal courts have embraced this determination as a threshold requirement:

> A transitory, propagating signal like Nuijten's is not a "process, machine, manufacture, or composition of matter." Those four categories define the explicit scope and reach of subject matter patentable under 35 U.S.C. § 101; thus, such a signal cannot be patentable subject matter. [6]

However, even if the claimed invention is within one of the four categories, the inquiry does not end. Consistent with case law, the USPTO obliges the examiner to consider whether the claimed invention falls within a judicial exception to section 101 (i.e., abstract ideas, laws of nature, and natural phenomena) or constitutes "a practical application thereof." Specifically, the MPEP states that "[w]hile a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of a scientific truth may be." A claimed invention is considered such a practical application of it: "(A) "transforms" an article or physical object to a different state or thing; or (B) otherwise produces a useful, concrete and tangible result, based on a balance of factors."[7] Regarding (A), if the examiner finds that the claim provides a transformation or reduction of an article to a different state or thing, the statutory subject matter inquiry under section 101 shall end, and the requirement deemed satisfied.[8]

Absent such a transformation under (A), application of (B) results. Based on our review, determinations of a useful, concrete, and tangible result under (B) are quite mixed. "Concreteness" appears to be the least controversial, and the guidelines indicate that an invention is concrete, if it has a "reproducible" or "predictable" result. The usefulness determination is more problematic. The guidelines indicate that, for an invention to be "useful" in light of current case law, it must have a "specific" and "substantial" utility. They also indicate that "if the specification discloses a practical application of a Section 101 judicial exception, but the claim is broader than the disclosure such that it does not require a practical application, then the claim must be rejected."[9]

The tangibility determination is particularly difficult for process claims. In this regard, the USPTO indicates that there is no requirement that "a claim must either be tied to a particular machine or apparatus or must operate to

change articles or materials to a different state or thing." However, to produce a real-world result, the process claim "must set forth a practical application of [the relevant] judicial exception [(e.g., law of nature or mathematical formula)]"; and, it is "for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted."[10] The USPTO places emphasis on the word "some" in the preceding sentence. A process claim is not patentable of it comprises "every 'substantial practical application' of an abstract idea." And, relative especially to certain bioinformatics applications, "a claim that recites a computer that solely calculates a mathematical formula or a . . . disk that solely stores a mathematical formula" is not patentable.[11]

The prosecution histories of several cases we examined are illustrative of the foregoing principles. U.S. Patent No. 7,197,400 includes claims directed to methods, systems, and software products for analyzing gene expression. During prosecution, the claims were amended to recite "using [a] normalization factor for gene analysis and outputting the result of said analysis." The USPTO argued that "using" is still a form of data manipulation (in this case converting probe array intensities), and that "outputting" may simply be the transference of data from one hard drive to another. Thus, as manipulation of data without any physical transformation, the claimed subject matter was deemed nonstatutory. The applicants' appeal brief argued that, as supported in the specification, the normalization factor can, for example, adjust signals from probe arrays (e.g., intensity values) to compensate for variations from array to array. And the result of the analysis can, for example, determine whether the expression of a gene is increased in one sample in comparison with another. Such a determination may lead to the development of new drugs and new diagnostic tools. Applicants offered further arguments supporting the proposition that performance of a result outside the computer, or any physical transformation outside the computer, is not required.

A host of prosecution histories include rejections directed to nonfunctional descriptive matter. These rejections may present under the tangibility requirement for a "useful, tangible, and concrete result" discussed above. Examiners often accompany these rejections with a suggestion to change the claim language so that nonfunctional descriptive material stored in a computer-readable medium is not claimed.[12] For example, the method claim of U.S. Patent No. 7,269,517 was amended to include the phrase "storing [a] plurality of profiles in a memory, a storage device, or a computer" as the final step. A software claim originally specifying "a data structure comprising" was amended to include the preamble phrase "[a] computer program product that comprises a computer program mechanism embedded in a computer readable storage medium, the computer program mechanism comprising," as well as recitation of "instructions for storing said plurality of profiles in a memory, a storage device, or a computer." Such amendments ensure that the claims include a limitation that the material has a functional relationship to a computer, which permits a computer's functionality to be realized.

To minimize section 101 rejections, applicants are well advised to assert practical utility for their claimed inventions. If possible, asserted utilities should include a commercially significant utility and should vary in scope (e.g., usefulness for analysis of gene expression, of genes involved in cancer, of genes involved in metastatic carcinomas, and of genes having the biological activity of inducing blastoma formation when actively expressed in a nerve cell, etc.). This approach strengthens one's position in future litigation. That is, even if the machine and manufacture claims receive allowance more easily than the process claims, for example, when the examiner suggests the addition of a disc or display monitor as a claim limitation, allowance of process claims comprehends the possibility that the machine and manufacture claims can be attacked by allegations of unpatentability of the process itself coupled with the allegation that the physical components are means for storing or displaying an otherwise unpatentable formula.

Pitfall No. 2: Indefiniteness

Novelty[13] and nonobviousness[14] are the most widely recognized requirements for patentability under U.S. law. However, they are not the only ones. Far less well recognized, and encountered infrequently even among practitioners, is the requirement that a patent's claims be definite. The definiteness requirement derives from section 112 of the Patent Act (35 U.S.C.), which provides that a patent must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The significance of this statutorily mandated clarity cannot be understated. A patent's claims define the scope of a patentee's exclusive rights, so they must "provide to others clear warning of what constitutes infringement of the patent."[15] Nor can practitioners ignore the definiteness requirement in drafting patent applications. For, while the Patent and Trademark Office (USPTO) reviews applications for compliance with section 112, thereby providing the opportunity to correct at least the definiteness issues identified on examination, resolution is not always straightforward or achieved at low cost. In far too many cases, rejections for indefiniteness come from protracted debate between the USPTO and the applicant's attorneys, as the two sides cannot agree either on the propriety of the rejection or, given the vagaries of language, an amendment to the claim that resolves the issue. The stakes attending these debates have increased in the wake of the Supreme Court's decision in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*,[16] since claim amendments for any reason related to patentability, including compliance with section 112, may give rise to a claim-narrowing estoppel in future litigation. And, of course, the opportunity for correction supposes that a problem of definiteness was identified by the USPTO in the first place. With distressing frequency this is not the case, as many patentees discover only after their patents' claims have been invalidated in litigation for indefiniteness.[17]

While USPTO rejections on section

112 grounds arise only occasionally in other technical fields, our research indicates they appear with alarming frequency in bioinformatics-related applications. While it is difficult to ascertain precisely why this is the case, it is at least possible, with the law and case study as a guide, to answer more particularly the question: How can the number of these rejections be minimized?

Section 112's definiteness mandate does not oblige practitioners to write claims at the limit of linguistic perfection nor to employ only terms of precision. The definiteness inquiry does not revolve around whether claims could be made *more* definite by alternate language.[18] Nor does section 112 preclude the use of all relative language.[19] Instead, section 112 requires that a claim's scope, to be definite, must be understandable to one skilled in the art (to which the invention pertains) when that person reads the claim in light of the patent's written specification.[20] Necessarily, this makes the inquiry one of fact unique to each set of circumstances, though the issue of compliance with section 112 is nominally one of law as a matter of claim construction.[21] And, though this inquiry is, as a general rule, confined to the patent document itself (and particularly the specification and claims), "the determination of the perspective of one of skill in the art may involve reference to evidence extrinsic to the patent, such as prior art and witness testimony."[22]

Our review of select cases in the bioinformatics art suggests that a number of the indefiniteness rejections imposed by the USPTO arise from the examiner's lack of familiarity with the subject matter and, in some cases, the examiner's simple failure to read the written specification carefully. Given the backlog of applications in the USPTO, failure to read each specification with care is explicable if not easily forgiven. Also explicable is the lack of familiarity with the subject matter, in view of the relatively recent advent of bioinformatics. The USPTO is still apparently laboring to adequately assign bioinformatics-related applications to personnel with the multidisciplinary training required to understand them, as evidenced by the fact that those cases we reviewed in researching this article were assigned to technology groups as diverse as the "image analysis" section of the communications technology unit, the "measuring and testing" section of the semiconductors, electrical, and optical systems technology unit, and the "recombinant enzymes" and "bioinformatics" sections of the biotechnology and organic chemistry unit. In these cases, rejections for indefiniteness were relatively easily traversed by evidencing to the USPTO definitive support (usually in the written specification) for the word or phrase at issue in the claim.

While many of the rejections were attributable to USPTO error, at least an equal number we reviewed of rejections for indefiniteness appear to have risen from the applicant's adoption of clearly questionable claim language. The following catalogs some of the problematic language we encountered.

- U.S. Patent No. 7,124,034 describes a method for analyzing the data structure of a nucleic acid-sequence target array. In the application as filed, however, the claim recited simply an "array." The USPTO found this to lack section 112 definiteness since "array" could refer to a *micro*array as well as a "data structure."

- U.S. Patent No. 7,286,970 describes a computational method for kinetically tailoring multidrug chemotherapy to individuals. In that case, the claims as filed created a host of definiteness problems for the applicant through employment of, inter alia, the following language:

  1. "*Providing* a mathematical model which models rates of population change . . . *using* cell kinetics and evolution of resistance" where "providing" and "using" rendered uncertain whether the method step was the *generation of* a mathematical model incorporating the subsequently recited elements or the *provision of* such a model comprising these elements.
  2. "Resistance of diseased cell" where the type of resistance was unspecified.
  3. "Applying" cell kinetic parameters to a mathematical model "to solve for" a plurality of treatment regimens" where the relationship between the acts of "applying" and "solving" was not particularized.
  4. "A plurality of treatment regimens having a quantitative *efficacy value*" where the target of the efficacy value was unspecified.
  5. "Treatment regimens *based on* the efficacy value" where "based on" failed to define a clear relationship between the treatment regimen and the efficacy value.
  6. "*Modeling* rates of population change . . . *using* cell kinetics and evolution of resistance" as failing to specify if the cell kinetics and evolution of resistance elements were "used" in building a model or in performing the modeling.

- U.S. Patent No. 7,167,819 describes a method for determining the three-dimensional shape of a macromolecule. The claims of the issued patent recite the steps of imposing constraints of physical distance between residues of the protein by cross-linking the protein; fragmenting the cross-linked protein into molecular fragments; subjecting the fragments to mass spectrometric analysis to identify sequences of the fragments and analyzing the information obtained to identify cross-linked fragments in the protein; providing a set of candidate three-dimensional conformations for the protein's primary sequence; applying constraints of physical distance associated with the cross-linking of the identified fragments to the candidate three-dimensional conformations to rank them, and selecting one or more of them based on the ranking. In the application as filed, however, the foregoing claim language—which sets forth definitive parameters for the method steps—was preceded by use of the relative terms "*smaller*" and "*best fit*" without identifying any criteria for making the relative judgments as to what was "smaller" or "larger" and which fit was "best."

At the end of the day, evaluating claim language for bioinformatics-related inventions is no different from any other inventive subject matter. What has distinguished bioinformatics, however, is the apparent lack of a precise lexicon for specific applications, the variable and relativist aspects of many manipulations of data, and the occasional failure of patent drafters to define more carefully language that they should recognize as facially uncertain. Or, alternatively, for drafters to avoid using altogether language that can be construed as facially uncertain. Where possible, drafters should use particularized language that conveys the same essential meaning. Herein lies the challenge for applicants.

Special care must be taken in bioinformatics applications to ensure that the written specification clearly defines claim terms that: (1) have no established meaning in the prior art, including the bioinformatics literature (e.g., "efficacy value"); (2) are facially relative (e.g., "best fit," "smaller"); or (3) are capable of multiple, inconsistent, or confusing interpretations in the claim (e.g., "array"). The applicant is well advised to canvas carefully the relevant literature where there is any doubt about the definiteness of a term in a claim and the specification does not define its meaning. If the term is not defined in multiple third-party sources, the applicant must either avoid it or define it in the specification. Equally advisable is a review of the prosecution histories and allowed claims of the most relevant prior art patents (such as those uncovered in a prefiling novelty search). Patent applicants should not hesitate to learn from the mistakes of others or adopt from issued patents claim language that bears the imprimatur of USPTO review. In short, more due diligence in preparing an application should bear fruit in reducing both pendency and the costs of prosecution and in eliminating the creation of unwanted estoppel. ◆

Endnotes

1. Bruce Rasmussen, *Commercialization Processes in Bioinformatics: Analysis of Bioinformatics Patents* (CSES Working Paper No. 26, 2005, at 3), *available at* www.cfses.com/documents/wp26.pdf.

2. *Id*. at 11.

3. *Id*. at 10 and 11.

4. However, we note that rejections for non-statutory subject matter are more common in the computer-related and business method arts.

5. 35 U.S.C. § 101.

6. *See In re* Nuijten, Fed. Cir. Sept. 20, 2007, at 18.

7. For example, *see* Diamond v. Diehr and Lutton, 450 U.S. at 199; and MPEP § 2106.IV.C.1 to § 2106.IV.C.2 .

8. MPEP § 2106.IV.C.2(1).

9. *See* footnote 5, *supra*; and MPEP § 2106.IV.C.2(1)a) and § 2106.IV.C.2(1)c).

10. *See Diehr*, *supra*, at 187; and Corning v. Burden 56 U.S. (15 How.) at 268; and MPEP § 2106.IV.C.2(1)b).

11. Gottschalk v. Benson et al., 409 U.S. at 71–72 and MPEP § 2106.IV.C.3.

12. *See*, *e.g., In re* Sarkar, 588 F.2d 1330, 1333; *In re* Abele, 684 F.2d at 907.

13. *See* 35 U.S.C. § 102.

14. *See* 35 U.S.C. § 103.

15. Donald Chisum, *in* 3 CHISUM ON PATENTS § 8.03, p. 8–18 (2002) (citing, e.g., United Carbon Co. v. Binney Co., 317 U.S. 228 (1942); McClain c. Ortmayer, 141 U.S. 419 (1891); Solomon v. Kimberly-Clark Corp., 55 USPQ 2d 1279 (Fed. Cir. 2000); Mycogen Plant Science, Inc. v. Monsanto Co., 61 F.Supp.2d 199 (D. Del. 1999); and Austin Powder Co. v. Atlas Powder Co., 219 USPQ 707 (D. Del. 1983)).

16. 535 U.S. 722 (2002).

17. *See, e.g.,* the numerous cases collected in Chisum, *supra*, at § 8.03[3][a][ii]–8.03[3][a][iii].

18. *See, e.g.,* Bausch & Lomb, Inc. v. Alcon Laboratories, Inc., 53 USPQ 2d 1353 (W.D. N.Y. 1999); *see also* MPEP § 2173.02.

19. *See* Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 13 USPQ 2d 1737 (D. Mass. 1989).

20. *See, e.g.,* Exxon Research & Eng'g Co. v. U.S., 66 USPQ 2d 1272 (Fed. Cir. 2001).

21. *Id.; see also* Markman v. Westview Instruments, Inc., 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc), *aff'd* 517 US 370 (1996).

22. Solomon v. Kimberly-Clark Corp., 55 USPQ 2d at 1282, n.4.