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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN ZACHARY SANBORN and DAVID HAUSSLER

Appeal 2018-003683
Application 15/167,507
Technology Center 1600

Before ERIC B. GRIMES, ULRIKE W. JENKS, and RYAN H. FLAX, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims directed to a computer-based sequence analysis system. Examiner rejected the claims as directed to patent ineligible subject matter, indefinite, and obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as Regents of the University of California. Appeal Br. 1.

STATEMENT OF THE CASE

The Specification "provides methods for generating databases that may be used to determine an individual's risk" for developing a disease, disorder, or condition. Spec. ¶ 5, *see also id.* ¶ 48. BamBam is a software tool "that enables a rapid comparison of tumor (somatic) and germline matched sequencing datasets." *Id.* ¶ 73.

> "BamBam" is a computationally efficient method for surveying large sequencing datasets to produce a set of high-quality genomic events that occur within each tumor relative to its germline. These results provide a glimpse into the chromosomal dynamics of tumors, improving our understanding of tumors' final states and the events that led to them.

Id. ¶ 54.

> BamBam takes in two short read sequencing datasets, one from the tumor and the other a matched normal ("germline") from the same patient, and the reference genome, and reads these datasets such that all sequences in both datasets overlapping the same genomic position are available to be processed at the same time.

Id. ¶ 76. Because "each dataset is processed by itself, and results are only merged afterwards" this creates efficiency as opposed to applying a traditional analysis. *Id.*

Claims 1–19 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is representative of the claims on appeal, and reads as follows:

> 1. A computer-based genomic sequence analysis system comprising:
> a memory storing at least two genomic sequence datasets including:
> a tumor sequence dataset comprising genomic sequence strings of a tumor tissue sample of a patient; and

a matched normal dataset comprising genomic sequence strings of a normal tissue sample of the same patient; and

a sequence analysis engine coupled with the memory and configured to:

simultaneously and synchronously read a tumor sequence string from the tumor sequence dataset and a matched normal sequence string from the matched normal sequence dataset;

wherein the tumor sequence string is *incrementally synchronized* with the matched normal sequence string based on a given genomic position;

identify a genomic alteration associated with the given genomic position according to a probability derived from reads of the tumor sequence string and of the matched normal sequence string; and

store the genomic alteration in a device memory.

Appeal Br. 28 (Claims Appendix) (emphasis added).

Appellant requests review[2] of the following grounds of rejection[3] made by Examiner:

I. Claims 1–19 under 35 U.S.C. § 112, second paragraph[4] as indefinite.

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[2] Appellant requests reversal of Examiner's objections to the Specification and claims. We cannot grant the relief Appellant seeks (*see* Appeal Br. 5–13) because doing so is not within our jurisdiction. Objections or other requirements imposed by an Examiner are reviewed by way of petition to the Director. *See* MPEP 1201. We, therefore, express no opinion regarding the propriety of the objections expressed by Examiner in the Final Rejection.

[3] Appellant does not address the obviousness-type double patenting rejections of claims 1–19 made by Examiner. *See* Final Act. 10–29, Ans. 6. We therefore summarily affirm these rejections. *See* MPEP § 1205.02 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it, unless the examiner subsequently withdrew the rejection in the examiner's answer.").

[4] Examiner applies pre-AIA provisions. Final Act. 2.

II. Claims 1–19 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

III. Claims 1–10, 12, and 14–17 under 35 U.S.C. § 103(a) as unpatentable over Sjöblom[5] and Swindells.[6]

IV. Claims 1, 9, and 11 under 35 U.S.C. § 103(a) as unpatentable over Sjöblom, Swindells, and Stratton.[7]

V. Claims 1 and 13 under 35 U.S.C. § 103(a) as unpatentable over Sjöblom, Swindells, and Kuhn.[8]

I. Indefiniteness

a. incrementally synchronized

Examiner finds that claims 1–19 are indefinite because the phrase "incrementally synchronized . . . based on a given genomic position" is not defined in the Specification. Final Act. 9.

Appellant contends that the Specification at paragraphs 92 and 100 provides support for this phrase. Appeal Br. 15. A review of paragraph 92 of the Specification describes that "[t]he aggregation process consists of grouping together the unique reads that overlap other reads on both sides of the putative breakpoint." Spec. ¶ 92. Paragraph 100 of the Specification states, "a large intra-chromosomal deletion-type rearrangement should have

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[5] Sjöblom et al., *The Consensus Coding Sequences of Human Breast and Colorectal Cancers*, 314 Science 268–274 in conjunction with the supporting online material (2006) ("Sjöblom"). *See* Final Act. 15.
[6] Swindells et al., US 2004/0015298 A1, published Jan. 22, 2004 ("Swindells").
[7] Stratton et al., *The Cancer Genome*, 458 Nature 710–24 (2009)("Stratton").
[8] Kuhn et al., *The UCSC Genome Browser Database: update 2009*, 37 Nucleic Acids Research D755–61 (2009) ("Kuhn").

a concordant drop in copy number in the region between the breakpoints." Both paragraphs 92 and 100 recite breakpoints. What is not clear from the Appeal Brief, however, is how the breakpoint defines "incrementally synchronized."

Examiner acknowledges that "incrementally synchronizing" appears in the Specification at paragraphs 6, 15, 24, and 25. Ans. 4. There is no dispute that the Specification contains the phrase "incrementally synchronized." The dispute lies with the lack of information from which to articulate a definition for this phrase. Directing our attention to areas in the Specification that recite the words does not in and of itself provide insight as to whether and how one of ordinary skill in the art would have understood what is meant by "incrementally synchronized" in the context of the remainder of the disclosure. This board serves as a board of review, not a de novo examination tribunal. *See* 35 U.S.C. 6(b) ("The [board] shall, on written appeal of an applicant, review adverse decisions of examiners upon applications for patents.").

On this record, we find that Examiner has the better position and agree that, without more, the meaning of "incrementally synchronized" is indefinite. Accordingly, we affirm the rejection of claim 1 as being indefinite. As claims 2–19 have not been separately argued, they fall with claim 1.

b. simultaneously and synchronously read

Examiner finds that claims 1–19 are indefinite because the phrase "simultaneously and synchronously read [two sequences]" is not defined in the Specification. Final Act. 9. Examiner explains that it is "not clear how

data can be inputted and aligned simultaneously because alignment of sequences requires comparison to two previously inputted sequences." *Id.* at 10.

Appellant contends that the Specification provides support for this phrase. Appeal Br. 18 (citing Spec. ¶¶ 2, 6–8, 15, 16, 22–25, 38, 39, 41, 42, 49, 51–53, 73, 76, and 78).

We find that Appellant has the better position. The Specification provides that "synchronizing comprises aligning at least one of the plurality of sub-strings based on a known reference string comprising known locations for the at least one of the plurality of sub-strings." Spec. ¶ 7. BamBam is a software tool that allows for simultaneous analyses at "each genomic position from a patient's tumor and germline genomes using the aligned short-read data contained in SAM/BAM-formatted files." *Id.* ¶ 39 (citing Li et al., *The Sequence Alignment/Map format and SAMtools*. 25 Bioinformatics 2078–79 (2009)).

> BamBam reads from two files at the same time, constantly keeping each BAM file in synchrony with the other and piling up the genomic reads that overlap every common genomic location between the two files. For each pair of pileups, BamBam runs a series of analyses listed above before discarding the pileups and moving to the next common genomic location. By processing these massive BAM files with this method, the computer's RAM usage is minimal and processing speed is limited primarily by the speed that the filesystem can read the two files. This enables BamBam to process massive amounts of data quickly, while being flexible enough to run on a single computer or across a computer cluster. Another important benefit to processing these files with BamBam is that its output is fairly minimal, consisting only of the important differences found in each file. This produces what is essentially a whole-genome diff[erentiation] between the patient's tumor

> and germline genomes, requiring much less disk storage than it would take if all genome information was stored for each file separately.

Id. ¶ 42. The Specification explains that short reading sequence datasets are aligned to a reference genome, which is "a natural way of organizing sequence data from multiple, related samples." *Id.* ¶ 76. These genome alignments allow the BamBam software to take tumor datasets and normal ("germline") datasets from the same patient that overlap the same genomic position for processing at the same time. *Id.* "Because BamBam keeps the sequence data in the pair of files in sync across the genome, a complex mutation model that requires sequencing data from both tumor and germline BAM files as well as the human reference can be implemented easily." *Id.* ¶ 78.

Based on these disclosures in the Specification, the phrase "simultaneously and synchronously read" (more than one sequence) is reasonably understood to mean that genetic information stored in two (or more) files can be directly compared at the same genomic position at the same time before moving on to the next genomic position. Accordingly, the phrase "simultaneously and synchronously read" takes into account more than just aligning the sequences to a reference genomic position but also informs that the analysis at a particular genomic position can encompass multiple datasets at the same time. We, therefore, are not persuaded by Examiner's contention that the phrase is indefinite and reverse the rejection of claims 1–19 under 35 U.S.C. § 112, second paragraph.

c. illegible formulas

Examiner rejects claims 18 and 19 because the text in the formulas are illegible. Final Act. 9; Ans. 4.

Appellant disagrees and asserts that the formulas are indeed legible. Appeal Br. 17; *see id.* at 8–13.

Section 112, second paragraph, requires the Specification to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." As our reviewing court has explained that claims are "to be cast in clear—as opposed to ambiguous, vague, indefinite—terms." *In re Packard*, 751 F.3d 1307, 1313 (Fed. Cir. 2014). The rationale for requiring such "reasonable precision" in claim language is because "[i]t is the claims that notify the public of what is within the protections of the patent, and what is not." *Id.*; *see also Ex parte McAward*, Appeal 2015-006416, 2017 WL 3669566, at *5 (PTAB Aug. 25, 2017) (precedential) (adopting the approach for assessing indefiniteness approved by the Federal Circuit in *Packard*).

We agree with Examiner that the formulas recited in the claims are not clear because certain elements of the formulas cannot be made out. Consultation with the Specification is not helpful because it contains the same illegible material. For example, the subscripts and superscripts found in the formulas of paragraph 80 could be any one of 1, 2, l, t, g, or m. *See* Spec. ¶ 80. Without clarity in the Specification, we agree with Examiner that the claims are indefinite. Accordingly, we affirm the rejection of claims 18 and 19 as being indefinite.

d. related sequencing data sets

Examiner finds that the metes and bound of the phrase "related sequencing datasets" as recited in the claims is unclear. Final Act. 10.

Appellant contends that the term is clear. Appeal Br. 20–21.

We find that Appellant has the better position. For example, the Specification explains that the

> method is easily extendible to more than two related sequencing datasets. For example, if three samples, matched normal, tumor, and relapse, were sequenced, this method could be used to search for changes specific to the tumor & the relapse sample, and changes specific only to the relapse, suggesting the relapse tumor has changed somewhat from the original tumor from which it had presumably derived.

Spec. ¶ 77. Based on this paragraph, "related sequencing datasets" is reasonably understood to mean sequences covering the same genomic region that can then be compared with each other. Accordingly, we reverse the rejection of claim 10 as being indefinite.

II. Patent Ineligible Subject Matter

Examiner finds that the claims are directed to "the abstract idea of comparing information of a sample or test subject to a control or target data." *Id.* at 12 (citing *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014)). Examiner finds that any additional elements such as the use of "[c]omputer memory, processors, and inputting and outputting data using computer memory are conventional computer processing components and activities." *Id.* Examiner finds that the process of comparing sequence data using a genome browser and computer interface are conventional activities engaged by artisans in the

field. *Id.* at 13 (citing Kuhn in support). Examiner concludes that these additional elements "when considered individually or as an ordered combination" do not transform the abstract idea into "a patent-eligible application of the judicial exception." *Id.*

Appellant contends that the claims are more than an abstract idea, because they show an improvement to the functioning of a computer by improving the efficiency. Appeal Br. 21–22. Specifically, "claim 1 limitations relating to the configuration of the sequence analysis engine, describe a computer-based genomic sequence analysis system that is more efficient than, and produces results more quickly than the known techniques described in paragraphs 41 and 76" of the Specification. *Id.* at 22.

The Supreme Court has established a two-step framework for "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014). The United States Patent and Trademark Office (PTO) issued the *2019 Revised Patent Subject Matter Eligibility Guidance* ("*Guidance*"), indicating how the PTO can analyze patent eligibility under the Supreme Court's two-step framework and the October 2019 Update to the Revised Guidance ("*Update*"), which provides further details regarding how the Patent Office is to analyze patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50−57 (Jan. 7, 2019); 84 Fed. Reg. 55,942 (Oct. 18, 2019). Following the *Guidance*, under Revised Step 2A, we first look to whether the claim recites the following:

> (1) any judicial exceptions, including certain groupings of abstract ideas (i.e., mathematical concepts, certain methods of

organizing human activity such as a fundamental economic practice, or mental processes); and

(2) additional elements that integrate the judicial exception into a practical application (*see* MPEP § 2106.05(a)-(c), (e)-(h)).

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, do we then look, under Step 2B of the *Guidance*, to whether the claim:

(3) adds specific limitations beyond the judicial exception that are not "well-understood, routine, conventional" in the field (*see* MPEP § 2106.05(d)); or

(4) simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception.

See Guidance.

Appellant does not argue the claims separately. We analyze claim 1 as representative.

STEP 1:

We first find that claim 1 is directed to a "sequence analysis system." We therefore conclude that the claims are directed to a "manufacture" for carrying out the sequence analysis and thus falls into one of the broad categories of patentable subject matter under section 101. *See* MPEP 2106.03 ("because a microprocessor is generally understood to be a manufacture, a product claim to the microprocessor or a system comprising the microprocessor satisfies Step 1 regardless of whether the claim falls within any other statutory category (such as a machine)").

STEP 2A, Prong One:

Under the *Guidance*, in determining what concept a claim is "directed to" in step one of the Supreme Court's two-step framework, we first look to whether the claim recites any judicial exceptions to Section 101, such as an abstract idea, a law of nature, or a natural phenomenon. Guidance, 84 Fed. Reg. at 52, 54 (Step 2A, Prong One).

In *Mayo*, the Supreme Court found "mental processes and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 71 (2012) (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). Comparison between two gene sequences represents a mental process, i.e., an abstract idea. *See In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755, 762 (2014).

Claim 1 requires "identifying a genomic alteration" at any given genomic position between tumor tissue sequence and normal tissue sequence from the same patient. This "identifying" step of the sequence analysis system is a mental process, i.e., the comparison between a tumor sequence dataset and a normal sequence dataset. *See* Final Act. 12 ("comparing information of a sample or test subject to a control or target data"). Claim 1, therefore, recites an abstract idea.

STEP 2A, Prong Two:

Having made the determination that claim 1 recites an abstract idea, under the *Guidance*, we next examine whether there are additional elements *beyond* the abstract idea that integrate the judicial exception into a practical application. Under the *Guidance*, this is referred to as the "Prong Two"

inquiry under "Step 2A." Guidance, 84 Fed. Reg. at 54–55. Under the Prong Two analysis, we look to whether the claim as a whole "appl[ies], rel[ies] on, or use[s] the judicial exception in a manner that imposes a meaningful limit on the judicial exception." *Id.*

Examiner acknowledges that one way to overcome this rejection is to establish that the combination as claimed results in an improvement to the technology, and the improvement is a result of the additional elements. Final Act. 14. We consider whether the claim covers a particular solution to a problem or a particular way to achieve a desired outcome, as opposed to merely claiming the idea of a solution or outcome.

Appellant contends that the limitations of claim 1 relate to improving the sequence analysis to make the process more efficient. Appeal Br. 22. Appellant cites paragraphs 41 and 76 of the Specification as providing support that the use of BamBam software improves the sequence analysis. Paragraph 76 recites:

> BamBam takes in two short read sequencing datasets, one from the tumor and the other a matched normal ("germline") from the same patient, and the reference genome, and reads these datasets such that all sequences in both datasets overlapping the same genomic position are available to be processed at the same time. This is the most efficient method for processing such data, while also enabling complex analyses that would be difficult or impossible to accomplish in a serialized manner, where each dataset is processed by itself, and results are only merged afterwards.

Spec. 76.

The cited passages in the Specification do not provide a sufficiently detailed disclosure for one of ordinary skill in the art to recognize an improvement in technology. Binary Alignment/Map (BAM) is a generic

alignment format for storing read alignments against a reference. *See* Li 2078; *see* Spec. ¶ 39. The Specification explains that the "BamBam [software] reads from two files at the same time, constantly keeping each BAM file in synchrony with the other and piling up [i.e., gathering] the genomic reads that overlap every common genomic location between the two files." *Id.* ¶ 42. The art already recognizes the benefits of a BAM file, specifically, that it "is compact in size and supports fast retrieval of alignments in specified regions. Using positional sorting and indexing, applications can perform stream-based processing on specific genomic regions without loading the entire file into memory." Li 2079. Here, the claim relies on a computer as a tool for making comparisons between the sequences. The improvement, if any, is with the way the sequence files (i.e. the BAM file) is stored for later retrieval. However, this type of processing, storage, and retrieval was already known and practiced by ordinary artisans in the field. *See generally* Li. Thus, the claim lacks additional elements that establish an improvement in technology.

STEP 2B:

Step 2B requires that we look to whether the claim "adds a specific limitation beyond the judicial exception that [is] not 'well-understood, routine, conventional' in the field." *See* MPEP § 2106.05(d) (9th ed., rev. 08.2017 (Jan. 2018)). Examiner found that it is conventional to display lineups of genomic sequences on a computer interface based on results derived by comparing sequence data in a genome browser. Final Act. 13 (citing Kuhn). Additionally, storing the sequences in the particular BAM file format for later processing and analysis is conventional. *See* Li 2078 (BAM is a generic alignment format that "is compact in size and supports

fast retrieval of alignments in specified regions."). Thus, the steps of obtaining sequence datasets for storage in memory and comparing sequences are well-known conventional steps in assessing genome differences. Final Act. 13. When the additional steps of the claim are considered individually or as an ordered combination, they do not add an inventive concept and thus do not amount to significantly more than the judicial exception. Accordingly, the claim does not add a specific limitation beyond the judicial exception.

Based on the foregoing, therefore, we conclude that claim 1 is directed to a judicial exception without significantly more, and therefore, is not eligible for patent protection. Claims 2–19 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv) (2017).

III. Obviousness Sjöblom and Swindells

Examiner has rejected claims 1–10, 12, and 14–17 under 35 U.S.C. § 103(a) as being unpatentable over Sjöblom and Swindells.

Examiner relies on Sjöblom for teaching detecting genomic alterations associated with cancer. Final Act. 16. Examiner acknowledges that Sjöblom "shows use of a computer analysis but does not discuss inputting and exporting sequence data to memory or multiple sequence alignment." *Id.* at 17. Examiner relies on the teaching of Swindells for showing multiple sequence alignments. *Id.* Based on these teachings, Examiner concludes that it would be obvious to modify Sjöblom by "having a memory to store sequence data and to perform multiple sequence alignments" as shown in Swindells in order to allow analysis of more data at one time. *Id.*

Appellant contends that the combination of Sjöblom and Swindells is missing "the limitation[] of the configuration of the sequence analysis engine to 'simultaneously and synchronously read'" a sequence as recited in claim 1. Appeal. Br. 24.

On this record, we find that Appellant has the better position. Examiner, for the purpose of examination, interpreted each of the phrases "incrementally synchronized" and "simultaneously and synchronously read" as meaning to align sequences. *See* Final Act. 9–10. Although we agree with Examiner that "incrementally synchronized" is indefinite (*see above I.a*), we do not agree with Examiner's position that "simultaneously and synchronously read" a sequence is indefinite in light of the Specification (*see above I.b*). The phrase "simultaneously and synchronously read" takes into account more than just aligning a test sequence to a reference genomic position but also informs us that the analysis occurs at the same time for the same position across the various datasets. *See above I.b*. Because we do not agree with Examiner's interpretation that showing sequence alignments, including multiple alignments based on the disclosure of Sjöblom and Swindells, is sufficient to meet the limitation of "simultaneously and synchronously read," we do not find that Examiner has made out a prima facie case. The evidence does not support a conclusion that the cited references disclose or suggest the simultaneous aspect of the sequence read analysis of claim 1 such that a person of ordinary skill in the art would have considered it obvious. We therefore reverse the rejection of claim 1, as well as dependent claims 2–10, 12, and 14–17.

IV. Obviousness Sjöblom, Swindells, and Stratton

We reverse the rejection of claims 1, 9, and 11 under 35 U.S.C. § 103(a) based on Sjöblom, Swindells, and Stratton. Examiner has not pointed to any teaching in Stratton that makes up for the deficiency discussed above (*see III*).

V. Obviousness Sjöblom, Swindells, and Kuhn

We reverse the rejection of claims 1 and 13 under 35 U.S.C. § 103(a) based on Sjöblom, Swindells, and Kuhn. Examiner has not pointed to any teaching in Kuhn that makes up for the deficiency discussed above (*see III*).

SUMMARY

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/ Basis**	**Affirmed**	**Reversed**
1–19	112 (b)	indefiniteness	1–19	
1–19	101	Patent ineligible subject matter	1–19	
1–10, 12, 14–17	103	Sjöblom, Swindells		1–10, 12, 14–17
1, 9, 11	103	Sjöblom, Swindells, Staratton		1, 9, 11
1, 13	103	Sjöblom, Swindells, Kuhn		1, 13
Overall Outcome			1–19	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED