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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TIMOTHY HARRIS

Appeal 2017-008991¹
Application 11/496,063
Technology Center 1600

Before FRANCISCO C. PRATS, JEFFREY N. FREDMAN, and
RYAN H. FLAX, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of sequencing nucleic acids. The Examiner rejected the claims for indefiniteness, as lacking enablement, as failing to comply with the written description requirement, as being directed to subject matter ineligible for patenting, for obviousness, and for obviousness-type double patenting.

We have jurisdiction under 35 U.S.C. § 6(b)(1).

We reverse the indefiniteness rejection as to all but two claims.

We reverse the enablement and written description rejections.

¹ As to the real party in interest, Appellant identifies “Fluidigm, a corporation with head offices located in South San Francisco, California, being the successor in interest to Helicos Biosciences Corporation, to which this application was originally assigned by the inventors.” Br. 2.

We reverse the patent ineligibility rejection.

We affirm the obviousness and obviousness-type double patenting rejections.

STATEMENT OF THE CASE

The following rejections are before us for review:

(1) Claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 112, second paragraph, as being indefinite (Ans. 2–4);

(2) Claims 1–8, 13, and 50–65, under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement (*id.* at 4–13);

(3) Claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (*id.* at 13–19);

(4) Claims 1–8, 13–16, and 50–65,² under 35 U.S.C. § 101, because the claimed invention is not directed to patent eligible subject matter (*id.* at 19–27);

(5) Claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 103(a) as being unpatentable over Williams,³ Sklar,⁴ Fleming,⁵ and admitted prior art (*id.* at 28–38);

(6) Claims 1–8, 13–16, and 50–65, on the ground of nonstatutory double patenting over claims 1 and 8–20 of U.S. Patent No. 7,897,345 B2

² The Examiner’s inclusion of claim “665” among the claims subject to this rejection is clearly a typographical error. *See* Ans. 27 (summarizing rejection as being directed to “claims 1–8, 13–16, and 50–65”).

³ US 6,255,083 B1 (issued July 3, 2001).

⁴ US 2003/0232365 A1 (published Dec. 18, 2003).

⁵ US 6,090,593 (issued July 18, 2000)

(issued Mar. 1, 2011; “the ’345 patent”) in view of Williams, Sklar, and Fleming (*id.* at 38–41); and

(7) Claims 1–8, 13–16, and 50–53, on the ground of nonstatutory double patenting over claims 1, 11–13, and 15–17 of U.S. Patent No. 7,491,498 B2 (issued Feb. 17, 2009; “the ’498 patent”) in view of Williams, Sklar, and Fleming (*id.* at 41).⁶

Claim 1 is representative and reads as follows:

1. A method for single molecule nucleic acid sequencing, the method comprising:
 - (a) providing a plurality of duplexes, each comprising a nucleic acid template containing a known nucleotide sequence, a primer hybridized thereto, and a first label, wherein the duplexes are bonded to a surface so as to be optically resolvable;
 - (b) determining locations on the surface of the duplexes by detecting the first label;
 - (c) extending the primers by at least three consecutive nucleotides by a process that comprises multiple iterations of the following steps:
 - (i) contacting the duplex with a labeled nucleotide and a polymerase so as to extend the primers by adding the nucleotide if the labeled nucleotide is complementary to the next nucleotide on the template, wherein the labeled nucleotide contains a label that is different from the first label;
 - (ii) washing the duplexes to remove unincorporated nucleotides,
 - (iii) determining locations on the surface of

⁶ Although the Examiner included claim 9 among the claims subject to this ground of rejection (Ans. 41), claim 9 has been canceled. *See* Response to Notice of Non-Compliant Appeal Brief 13 (entered Aug. 29, 2016) (Claims App’x).

primers that were extended in step (i) by detecting the labeled nucleotides that were added;

(iv) comparing the locations of labeled nucleotides determined in step (iii) with the locations of the duplexes to determine which of the primers have been extended; and

(v) removing the label from the labeled nucleotides added to the primers in step (i) before the next iteration.

Response to Notice of Non-Compliant Appeal Brief 12 (“Claims App’x”).

STANDARD OF REVIEW

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

INDEFINITENESS

The Examiner’s Prima Facie Case

In rejecting claims 1–8, 13–16, and 50–65 for indefiniteness, the Examiner advance three rationales: (1) that the pending independent claims omit essential steps (Ans. 2–3); (2) that the scope of the recitation “using an alignment algorithm” in claims 55 and 65 is unclear (*id.* at 3); and (3) that the scope of the term “about” in claims 59 and 65 is unclear (*id.* at 3–4).

Analysis

A claim does not comply with 35 U.S.C. § 112, second paragraph, “when it contains words or phrases whose meaning is unclear.” *In re Packard*, 751 F.3d at 1310, 1314 (Fed. Cir. 2014) (approving, for pre-

issuance claims, the standard from MPEP § 2173.05(e)); *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*).

That is, “claims are required to be cast in clear—as opposed to ambiguous, vague, indefinite—terms.” *Packard*, 751 F.3d at 1313.

Lacking Essential Steps

We reverse the Examiner’s indefiniteness rejection of independent claims 1, 63, and 65 alleging the absence of essential steps in the claims.

While the Examiner alleges that claims 1, 63, and 65 lack a number of essential steps (*see* Ans. 2–3, 47–48), the Examiner identifies no unclear, ambiguous, or vague language in the claims. As Appellant contends, moreover, the Examiner does not advance any evidence suggesting that a skilled artisan would fail to understand what steps are encompassed by the nucleic acid sequencing processes recited in claims 1, 63, and 65.

Rather, the Examiner’s position, as we understand it, is that the alleged lack of detail as to the specific steps encompassed by claims 1, 63, and 65 renders them overly broad. It is well settled, however, that that “breadth is not to be equated with indefiniteness.” *In re Miller*, 441 F.2d 689, 693 (CCPA 1971).

Because the Examiner does not persuade us that a skilled artisan would consider the processes recited in claims 1, 63, and 65 to be unclear, ambiguous, or vague because the scope of the claimed processes is uncertain, we reverse the Examiner’s rejection of claims 1, 63, and 65 for indefiniteness.

Using an Alignment Algorithm

We reverse the Examiner's indefiniteness rejection of claims 55 and 65 based on their recitation of using an alignment algorithm.

The Examiner rejected claims 55 and 65 as indefinite, based on the assertion that it is unclear what alignment algorithms are encompassed by the claims, and also based on the assertion that it is unclear what it means to use an alignment algorithm. Ans. 3. In rejecting the claims, however, the Examiner provided no clear explanation *why* a skilled artisan would consider the claim language at issue unclear, ambiguous, or vague. *See id.* Nor did the Examiner advance any evidence suggesting that a skilled artisan would fail to understand what an alignment algorithm is, or what it means to use an alignment algorithm.

Indeed, consistent with Appellant's contentions that a skilled artisan would understand what it means to use an alignment algorithm, and directly contrary to the Examiner's own conclusion of indefiniteness, the Examiner cited prior art disclosing the use of an alignment algorithm to compare sequences, when rejecting the claims for obviousness. *See id.* at 33–34 (citing Fleming 12:21–27); *see also* Fleming 12:21–27 (“Sequencing was done by an automated unit and the obtained sequences were compared with Genbank archives *using the BLAST algorithm*. . . . Prior to computer analysis the automated readout was visually inspected for deletions. Both the BLASTN and BLASTX functions were used.” (emphasis added; citation omitted)).

That the rejected claims do not recite a particular alignment algorithm (*see* Ans. 49), establishes, at best, that the claims might be considered

relatively broad in that respect. Again, however, “breadth is not to be equated with indefiniteness.” *In re Miller*, 441 F.2d at 693.

In sum, because preponderant evidence does not support the Examiner’s conclusion that a skilled artisan would consider the processes recited in claims 55 and 65 to be unclear, ambiguous, or vague, to the extent that the scope of the claimed processes is uncertain, we reverse the Examiner’s rejection of claims 55 and 65 for indefiniteness.

“About”

The Examiner rejected claims 59 and 65 as indefinite because “[t]he term ‘about’ is not defined by the claim(s), the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.” Ans. 3.

As the Examiner points out (Ans. 50), Appellant advanced no argument explaining why the Examiner erred in determining that the use of the term “about” renders claims 59 and 65 indefinite. *See Br.*, generally.

We, therefore, summarily affirm the Examiner’s rejection of claims 59 and 65 for indefiniteness, based on the use of the term “about” in those claims. *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.”).

ENABLEMENT

The Examiner's Prima Facie Case

In rejecting claims 1–8, 13, and 60–65 as failing to comply with the enablement requirement, the Examiner determined that practicing the full scope of the claimed invention would require undue experimentation, based on the breadth of the claims, the alleged unpredictability in the art, and the alleged large quantity of experimentation required to practice the full scope of the claimed subject matter. Ans. 5–13. Although not presented in a particularly straightforward manner, as we understand it, the Examiner's rejection is based on the determination that the claims encompass using any prior-art-known or future-known nucleic acid sequence in a process of determining the sequences of any and all target nucleic acids, from any and all types of organisms. *See id.* at 9–12.

Therefore, the Examiner reasons, practicing the full scope of the claimed methods would take a significant amount of time and effort. *See id.* at 13 (“[T]he aspect of having to work for many tens of years just to provide the starting materials for [a] minute fraction of the scope of the claimed invention is deemed to constitute both an unreasonable length of time and undue experimentation.”).

Analysis

We agree with Appellant that preponderant evidence does not support the Examiner's conclusion of non-enablement.

As our reviewing court has explained, the Examiner “bears an initial burden of setting forth a reasonable explanation as to why [he or she] believes that the scope of protection provided by that claim is not adequately

enabled by the description of the invention provided in the specification of the application.” *In re Wright*, 999 F.2d 1557, 1561–62 (Fed. Cir. 1993).

“The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.” *National Recovery Technols. Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

Although the Specification must enable the skilled artisan to practice the full scope of the claimed subject matter, “[i]t is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.” *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). Moreover, a claim does not lack enablement merely because it encompasses inoperative embodiments. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Rather, as our reviewing court has noted:

[T]here must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

Vaeck, 947 F.2d at 496 (footnote omitted).

In the present case, each of Appellant’s independent claims is directed to a process of sequencing a single nucleic acid molecule. Claims App’x 12, 15, and 16. Each of the independent claims requires providing a plurality of labeled duplexes, the duplexes being bonded to a surface. *Id.*

Each surface-bonded duplex is composed of a template nucleic acid to be sequenced, and a primer hybridized thereto. *Id.* As noted by the

Examiner, in addition to the target nucleic acid molecule to be sequenced, the template component of the duplex includes a molecule having “a known nucleotide sequence” attached to it. *Id.*

As explained in the Specification, the known sequence attached to the template may be a poly(dA) tail, with the primer hybridized thereto being a poly(dT) oligonucleotide. *See* Spec. ¶ 35; *see also id.* ¶¶ 60–63 (working example describing polyadenylation of digested sample DNA to be sequenced and hybridization of a polydT(50) primer to the polyadenylated sample DNA).

As recited in claims 1, 63, and 65, the locations of the surface-bound duplexes are determined by detecting the label attached to the duplexes. Claims App’x 12, 15, 16. Claims 1, 63, and 65 then recite extending the hybridized primers by contacting the surface-bonded duplexes with a polymerase and a nucleotide having a second label, followed by washing, and if the labeled nucleotide is incorporated into the complement to the template, the label is detected. *Id.* Each of claims 1, 63, and 65 recites extending the primers by at least three consecutive nucleotides. *Id.*

As explained in the Specification, fluorescent labeling may be used, and detection of the location of the surface-bound duplexes, as well as the location of labeled nucleotides incorporated into the duplexes, may be performed by microscopy using an imaging system depicted in Figure 3. *See, e.g.,* Spec. ¶¶ 14, 45, and 52; *see also* Fig. 3 (showing imaging system); Fig. 2 (showing stack of images obtained after each successive labeled nucleotide incorporation event).

Thus, as is evident, by knowing the identity of each nucleotide consecutively added to the template, and the location of each nucleotide

added to the template, the sequence of each of the surface-bound templates may be determined. *See* Spec. ¶¶ 60–69 (working example showing sequencing of bacteriophage M13mp18 at about 99% accuracy).

Therefore, as Appellant contends, the Specification not only describes how to perform the claimed process, but also provides a working example.

We agree with the Examiner that, given their broadest reasonable interpretation consistent with the Specification, Appellant’s independent claims 1, 63, and 65 encompass sequencing numerous target nucleic acids in addition to the sequence exemplified in the Specification, using any known sequence and hybridizing complement that allows primer extension. The Examiner does not, however, advance specific persuasive evidence demonstrating that an ordinary artisan would have needed to experiment unduly to determine suitable primer and complementary sequences for practicing the claimed invention, particularly given the poly(dA) and poly(dT) sequences described in the Specification. And the existence of numerous as yet undiscovered and un-sequenced potential target sequences does not persuade us that a skilled artisan only would have been able to practice the methods *as claimed and described* by experimenting unduly.

We do not agree, moreover, with the Examiner’s implication that Appellant must draft the claims in a manner that excludes application of the claimed process to as yet undiscovered target sequences. *See* Ans. 6 (“[T]he claimed methods have been construed as encompassing that which will become ‘known’ at some point in the future.”).

As explained by our reviewing court’s predecessor, “[i]t is always possible to put something into a combination to render it inoperative. It is not the function of the claims to *exclude* all such matters but to point out

what the combination is.” *In re Anderson*, 471 F.2d 1237, 1242 (CCPA 1973). In the present case, the claims are not directed to methods of sequencing every known organism. Rather, the claims are simply directed to methods of single molecule nucleic acid sequencing by a primer extension that incorporates labeled nucleotides. As noted above, Appellant’s Specification describes how to perform the claimed process, and provides a working example.

Accordingly, for the reasons discussed, we agree with Appellant that a preponderance of the evidence does not support the Examiner’s conclusion that Appellant’s claims lack enablement. We, therefore, reverse the Examiner’s enablement rejection.

WRITTEN DESCRIPTION

The Examiner’s Prima Facie Case

In rejecting claims 1–8, 13, and 60–65 as failing to comply with the written description requirement, the Examiner applied a rationale similar to that applied above in relation to enablement. Specifically, as with the enablement rejection discussed above, the Examiner determined that the claims “encompass[] the sequencing of any and all nucleic acids, regardless of source” (Ans. 16), and also encompass using any and all primers capable of hybridizing with a nucleic acid having a known sequence (*see id.* at 16–17). As with the enablement rejection, the Examiner noted that the claims therefore encompass sequencing nucleic acids obtained from billions of organisms. *Id.* at 17.

Based on those determinations, the Examiner reasoned that the claimed subject matter lacks sufficient written description support because (1) the Specification does not describe sequencing a representative number

of nucleic acids of those encompassed by the claims, and (2) the Specification does not disclose common identifying properties allowing sequencing of any and all nucleic acids. *See id.* at 19 (“[T]he disclosure has not been found to satisfy either prong of the written description test . . .”).

Analysis

For reasons similar to those discussed above as to the Examiner’s enablement rejection, we also reverse the Examiner’s written description rejection.

Our reviewing court has directed:

A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)); *see also Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (“[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue.”).

In the present case, as discussed above, contrary to the Examiner’s determination that the Specification fails to provide any examples of known

sequences and primers complementary thereto, the Specification not only describes how to perform the claimed process, but also provides a working example. *See* Spec. ¶¶ 60–69 (working example describing polyadenylation of digested sample DNA to be sequenced, followed by hybridization of a polydT(50) primer to the polyadenylated sample DNA, followed by extension of primer with labeled oligonucleotides allowing sequence determination of target DNA at about 99% accuracy).

The Specification also discloses that the described and claimed sequencing processes may be applied to a variety of nucleic acids from a number of different sources. *Id.* ¶ 24.

We agree with the Examiner that the rejected claims are not limited to a particular template targeted for sequencing. We also agree with the Examiner that the claims are not limited to a particular known sequence as the hybridizing partner for the extended primer.

The Examiner, however, fails to identify persuasive evidence suggesting that it would be unpredictable whether the sequencing process as disclosed and claimed would be applicable to nucleic acids other than those exemplified and described in the Specification, to the extent that a skilled artisan would question whether Appellant was in possession of the claimed invention. Nor does the Examiner identify persuasive evidence suggesting that it would be unpredictable for a skilled artisan to determine a suitable known sequence and hybridizing partner for use in the process as disclosed and claimed, such that Appellant's possession of the claimed invention would be doubted by a skilled artisan.

Because we are not persuaded that preponderant evidence supports the Examiner's determination that claims 1–8, 13, and 60–65 lack sufficient

descriptive support, we reverse the Examiner's rejection of claims 1–8, 13, and 60–65 as failing to comply with the written description requirement.

ELIGIBILITY FOR PATENTING

The Examiner's Prima Facie Case

In rejecting claims 1–8, 13–16, and 50–65 as being directed to subject matter not eligible for patenting, the Examiner stated that the claimed “aspect of ‘determining’ and ‘comparing’ are deemed to be an abstract idea.” Ans. 19.

In particular, the Examiner concluded that the claimed determining and comparing steps encompass mental processes, as do a number of other steps recited in the claims. *Id.* at 19–22. The Examiner determined that the remaining “active, physically-transforming steps are deemed to be well understood and routine in the art and do not add significantly more than the judicial exception (Question 2B of the Interim Guidelines)” (*id.* at 22).

The Examiner cited a number of paragraphs from the Specification, as well as the Williams, Sklar, and Fleming references cited in the obviousness rejection discussed below, as evidence that the non-mental steps recited in the claims were well understood, routine, and conventional in the art. *Id.* at 22–27. The Examiner reasoned, therefore, that the non-mental steps recited in the rejected claims “do not add significantly more than the judicial exception.” *Id.* at 27.

Analysis

An invention is patent-eligible if it claims a “new and useful process, machine, manufacture, or composition of matter.” 35 U.S.C. § 101. The Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions, however: “[l]aws of nature, natural phenomena, and abstract

ideas” are not patentable. *Alice Corp. v. CLS Bank Int’l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court’s two-step framework, described in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012) and *Alice*, 573 U.S. at 217–18 (citing *Mayo*, 566 U.S. at 75–77). In accordance with that framework, we first determine what concept the claim is “directed to.” *See Alice*, 573 U.S. at 219 (“On their face, the claims before us are drawn to the concept of intermediated settlement, *i.e.*, the use of a third party to mitigate settlement risk.”).

Concepts determined to be abstract ideas, and thus patent ineligible, include certain methods of organizing human activity, such as fundamental economic practices (*Alice*, 573 U.S. at 219–20; *Bilski v. Kappos*, 561 U.S. 593, 611 (2010)); mathematical formulas (*Parker v. Flook*, 437 U.S. 584, 594–95 (1978)); and mental processes (*Gottschalk v. Benson*, 409 U.S. 63, 69 (1972)).

If the claim is “directed to” an abstract idea, we turn to the second step of the *Alice* and *Mayo* framework, where “we must examine the elements of the claim to determine whether it contains an ‘inventive concept’ sufficient to ‘transform’ the claimed abstract idea into a patent-eligible application.” *Alice*, 573 U.S. at 221 (quotation marks omitted).

The PTO recently published revised guidance on the application of § 101. USPTO, *2019 Revised Patent Subject Matter Eligibility Guidance*,

84 Fed. Reg. 50 (January 7, 2019) (“Memorandum” or “Office Guidance”).⁷

Under that guidance, 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 interactions 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 to whether the claim:

- (3) adds a specific limitation 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 Memorandum.

In the present case, the Examiner does not persuade us that Appellant’s claims recite subject matter that is ineligible for patenting.

Appellant’s independent claims 1, 63, and 65 are not directed to mathematical concepts or methods of organizing human interactions. We are not persuaded, moreover, that the Examiner has established that the claimed steps of determining the locations of the labeled surface-bound duplexes, and comparing the locations of the incorporated labeled nucleotides to the original locations of the surface-bound duplexes, could practicably be performed by the human mind alone, and, therefore, amount to mental processes.

⁷ Available at <https://www.govinfo.gov/content/pkg/FR-2019-01-07/pdf/2018-28282.pdf>.

As discussed above, Appellant's Specification discloses the use of a specific imaging system that involves the use of lasers and a microscope to determine the locations of the fluorescently labeled surface-bound duplexes, and the fluorescently labeled nucleotides added thereto. *See, e.g.*, Spec. ¶¶ 14, 45, and 52; *see also* Fig. 3 (showing imaging system); Fig. 2 (showing stack of images obtained after each successive labeled nucleotide incorporation event). The evidence of record, therefore, does not support the Examiner's determination that is practicable to perform the claimed determining and comparing steps solely by a mental process.

Even if it were practicable to perform the claimed determining and comparing steps solely by mental processes (which, as noted above, the evidence does not support), the claimed processes include critical steps which are actual physical steps that involve the use of non-abstract tangible components. Specifically, the claims all require preparing a product composed of a labeled nucleic acid duplex bonded to a surface, contacting that surface-bound duplex with labeled nucleotides and a polymerase, washing the surface-bound duplex with its incorporated nucleotide to remove unincorporated nucleotides, and removing the label from the incorporated nucleotide. Claims App'x 12, 15, and 16.

Thus, even if the evidence were to support the premise that the claimed determining and comparing steps could practicably be performed solely by mental processes, the claimed determining and comparing steps are nonetheless integrated into a practical application, demonstrated by the fact that steps critical to the claimed processes are actual physical steps that involve the use of non-abstract tangible components.

The fact that the physical steps recited in the claims might be described in the prior art does not persuade us that the claims are ineligible for patenting. *See* Office Guidance, 84 Fed. Reg. at 54 (“[A] claim that includes conventional elements may still integrate an exception into a practical application, thereby satisfying the subject matter eligibility requirement of Section 101.”).

In sum, for the reasons discussed, the Examiner does not persuade us that Appellant’s claims are directed to subject matter that is ineligible for patenting. We, therefore, reverse the Examiner’s rejection of claims 1–8, 13–16, and 50–65 on that ground.

OBVIOUSNESS

The Examiner’s Prima Facie Case

In rejecting claims 1–8, 13–16, and 50–65 over Williams, Sklar, Fleming, and admitted prior art, the Examiner cited Williams as disclosing a method of sequencing single nucleic acid molecules in which a polymerase incorporates fluorescently labeled nucleotides into a surface-bound template. Ans. 32–33.

The Examiner found that Williams’s process differs from the processes recited in Appellant’s claims in that, “[w]hile Williams has been found to teach using fluorescent labels in a sequencing reaction, it has not been found to teach using a primer that is labeled in combination with labeled nucleotides.” *Id.* at 33.

As evidence that a skilled artisan would have considered Appellant’s claimed processes obvious despite that difference, the Examiner cited Sklar as disclosing that it was known in the art of nucleotide sequencing to label

both the primer and added nucleotide as a FRET (fluorescent resonance energy transfer) pair. *Id.* (citing Sklar ¶ 63).

The Examiner cited Fleming as evidence it would have been obvious to use a sequence alignment algorithm in nucleic acid processes. *Id.* at 33–34. The Examiner cited a number of paragraphs from Appellant’s Specification as admitted prior art evidence that the elements of the claimed invention recited in the dependent claims would have been obvious features of a nucleic acid sequencing process. *See id.* at 34–37.

Based on the combined teachings in the cited prior art, the Examiner reasoned:

[I]t would have been obvious to one of ordinary skill in the art at the time of the invention to have modified the method of Williams with that of Sklar et al., therein allowing for the determination of polymorphisms by use of FRET, and to have further modified the methods of Williams and Sklar et al., with that of Fleming et al., whereby sequence alignments are performed either via automated means o[r] visually, wherein if via automated means, known algorithms are used. It would have also been obvious to said routineer in the art to have taken advantage of known polymerases, known methods and means of linking nucleic acids to supports, known blocking agents, known labels that, along with detection means, are not only known but commercially available.

Id. at 37–38.

Analysis

Having considered the arguments and evidence advanced by Appellant and the Examiner, Appellant does not persuade us that the Examiner’s conclusion of obviousness is not supported by a preponderance of the evidence.

As the Supreme Court explained in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), “when a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976)).

In the present case, as the Examiner found, and Appellant does not dispute, Williams discloses a process of single molecule nucleic acid sequencing that includes the steps, recited in Appellant’s claim 1, of providing a surface-bonded primer-template duplex, and using a polymerase to extend the template-hybridized primer with labeled nucleotides:

This invention provides for a method of . . . sequencing a target nucleic acid [NA] comprising the steps of: i. immobilizing . . . the target nucleic acid onto a solid support in a single molecule configuration; ii. contacting the solid support with a solution containing: . . . (a) . . . a polymerase; (b) a primer nucleic acid which complements a region of the target nucleic acid downstream of the region to be sequenced; (c) NTP where each type of base is differently labeled on the phosphate portion, where the labels provide a unique signal that is selectively detectable upon incorporation of NTP into the polymerase extension product; iii. permitting the polymerase to sequentially extend the primer incorporating the NTP creating a complement to the target nucleic acid; and, iv. determining extension of the primer by detecting the unique signal from the labeled NTP to genotype or to sequence the target nucleic acid.
. . .

It is preferred that the NTPs are labeled on the gamma phosphate with a fluorescent label that differentially fluoresces when the gamma phosphate is cleaved away from the nucleoside. The immobilized moieties can further comprise an array of locations each bearing a single molecule of . . . target nucleic acid.

Williams 2:17–42.

As the Examiner found, and Appellant does not dispute, Williams’s process differs from the process of Appellant’s claim 1 only in that Williams does not disclose that its surface-bound duplex includes a label. As the Examiner found, however, and Appellant does not dispute, Sklar discloses that when performing primer extension sequencing reactions, it was desirable to include a label on the extended primer as one partner of a FRET pair, such that incorporation a labeled nucleotide onto the extended primer would result in detectable fluorescence identifying the added nucleotide:

The labeled primer is hybridized to the locus, and single base extension of the labeled primer is performed with fluorescently labeled dideoxynucleotides (ddNTPs) in dye-terminator sequencing fashion, except that no deoxynucleotides are present. An increase in fluorescence of the added ddNTP in response to excitation at the wavelength of the labeled primer is used to infer the identity of the added nucleotide.

Sklar ¶ 63.

Appellant does not assert error in the Examiner’s finding that the combined teachings of Williams and Sklar would have suggested configuring Williams’s process to include a labeled primer that, using the FRET effect, would fluoresce upon incorporation of a labeled nucleotide into the extended primer. Nor does Appellant contend that the claimed process yields unexpected results.

Rather, Appellant contends that the Examiner erred by failing to consider the claimed invention as a whole, because the cited prior art does not teach or suggest:

- determining the positions of the duplexes *on the surface* by way of locations *on the surface* of the duplexes by detecting the first label – step (b) of claim 1;

- *comparing the locations* of labeled nucleotides determined in step (iii) with the locations of the duplexes – step (iv); or
- removing the label from the labeled nucleotides added to the primers in step (i) before the next iteration – step (v).

Br. 10.

In response, the Examiner cited the Braslavsky reference⁸ (cited in Appellant’s Specification (Spec. ¶ 7)) as evidence that when performing array-based sequencing reactions involving the extension of surface-bound primer-template complexes as recited in Appellant’s claim 1, it was well known in the art to determine the initial location of the surface-bound primer-template duplexes, and to determine location of the labeled nucleotides incorporate into the duplexes, by comparing the location of the incorporated nucleotides to the original location of the labeled primer-template duplexes:

When as here one is trying to determine the nucleotide sequence of a plurality of “DNA template oligonucleotides” (appellant’s “nucleic acid template”), and that these multiple templates are bound to different positions on a common support, it is essential that one be able to correlate a given position with a nucleotide having been incorporated into the elongating primer. To not be able to do so would not allow one to determine the nucleotide sequence of such hybridized and immobilized templates.

Ans. 61. Citing the Braslavsky reference as admitted prior art, the Examiner responds also that “performing multiple wash steps was admittedly well known in the art.” *Id.*

⁸ Ido Braslavsky et al., *Sequence information can be obtained from single DNA molecules*, 100 PNAS 3960–64 (2003).

We find that the preponderance of the evidence supports the Examiner's position. We first note that Appellant did not file a reply brief alleging error in the Examiner's determination that the claimed steps of determining the location of the surface-bound template-primer complex, comparing that location to the location of the incorporated labeled nucleotide, and removing the label from the labeled nucleotide after incorporation, were well known in the art.

We note also Braslavsky's disclosure that its primer-extension sequencing process involves determining the location of the surface-bound template-primer complex and comparing that location to the location of the incorporated labeled nucleotide:

DNA template oligonucleotides were hybridized to a fluorescently labeled primer and bound to the surface via streptavidin and biotin with a surface density low enough to resolve single molecules. The primed templates were detected through their fluorescent tags, their locations were recorded for future reference, and the tags were photobleached. Labeled nucleotide triphosphates and DNA polymerase enzyme were then washed in and out of the flow cell while the known locations of the DNA templates were monitored for the appearance of fluorescence.

Braslavsky 3960.

As noted above, Williams discloses that its sequencing process can involve the use of arrays. *See* Williams 2:40–42. Williams also discloses the importance of knowing the locations of the extended molecules at each array location. *See id.* at 3:14–17 (“The array members are optionally addressed so that the locations are defined and comparative information between sites can be generated and recorded by the optical reader.”).

Given the disclosures in Williams of using arrays of nucleic acid molecules of defined locations in its sequencing processes, we discern no error in the Examiner's determination that it would have been obvious in view of Williams to determine the location on the array of the initial template-primer complex, as well as the location (by comparison) of the incorporated labeled nucleotide, particularly in light of Braslavsky's disclosure of the usefulness of those determinations.

Moreover, given Williams's disclosure of using a nucleotide label that is liberated from the primer-template complex upon incorporation, we discern no error in the Examiner's determination that it would have been obvious to remove the label after nucleotide incorporation, particularly given Braslavsky's disclosure of photobleaching the incorporated label.

In sum, for the reasons discussed, Appellant does not persuade us that preponderant evidence fails to support the Examiner's conclusion of obviousness as to claim 1. We, therefore, affirm the Examiner's rejection of claim 1 over Williams, Sklar, Fleming, and admitted prior art. Because they were not argued separately, claims 2–8, 13–16, and 50–65 fall with claim 1.

DOUBLE PATENTING

The Examiner's Prima Facie Case

The Examiner's rejection of claims 1–8, 13–16, and 50–65 for obviousness-type double patenting over claims 1 and 8–20 of the '345 patent in view of Williams, Sklar, and Fleming applies a rationale similar to the rationale applied in the obviousness rejection, discussed above. *See* Ans. 39–41.

In particular, based on the teachings Williams, Sklar, and Fleming, the Examiner reasoned that “the prior art of record fairly teaches a method of

sequencing individual nucleic acid molecules which have been bound to a surface and wherein the primer and the nucleotides being added are both labeled.” *Id.* at 40. In addition, the Examiner reasoned, “as shown above, the aspect of aligning a determined sequence with that known, including the use of algorithms, was also known in the art.” *Id.* at 41.

In rejecting claims 1–8, 13–16, and 50–53 for obviousness-type double patenting over claims 1, 11–13, and 15–17 of the ’498 patent, the Examiner applied essentially identical reasoning. *See id.*

Analysis

In evaluating obviousness-type double patenting, the Federal Circuit has explicitly “endorsed an obviousness determination similar to, but not necessarily the same as, that undertaken under 35 U.S.C. § 103 in determining the propriety of a rejection for double patenting.” *In re Braat*, 937 F.2d 589, 592–93 (Fed. Cir. 1991).

Thus, in making an obviousness-type double patenting rejection, the Examiner must show that a claimed invention is “a mere variation of [the patented invention] . . . which would have been obvious to those of ordinary skill in the relevant art . . . [and] there must be some clear evidence to establish why the variation would have been obvious which can qualify as ‘prior art.’” *In re Kaplan*, 789 F.2d 1574, 1579–80 (Fed. Cir. 1986).

In the present case, as to the rejection based on the claims of the ’345 patent, Appellant contends that the Examiner “does not explain with particularity how these [cited] references suggest the combination of all the elements and steps of the claimed invention configured and utilized as stated in the claims.” Br. 10. Appellant does not, however, explain specifically which elements of representative rejected claim 1 are not taught or suggested

by the combination of claims 1 and 8–20 of the '345 patent, Williams, Sklar, and Fleming. *See id.* We are not persuaded, moreover, that the teachings cited by the Examiner fail to render obvious the process recited in rejected representative claim 1.

Appellant's claim 1 recites a process of single molecule nucleic acid sequencing that includes the steps of providing a plurality of surface-bonded primer-template duplexes, and using a polymerase to extend the template-hybridized primers by at least three consecutive nucleotides with labeled nucleotides. Claims App'x 12.

Appellant's claim 1 recites washing the duplexes to remove unincorporated nucleotides, determining the locations on the surface of the primers that were extended by detecting the labeled nucleotides that were added, comparing the locations of labeled nucleotides with the locations of the duplexes to determine which of the primers have been extended, and removing the label from the labeled nucleotides added to the primers before the next iteration of labeled nucleotide addition. *Id.*

Claims 1, 8, and 19 of the '345 patent, cited by the Examiner, read as follows:

1. A method for sequencing a nucleic acid template, the method comprising:
 - conducting a sequencing-by-synthesis reaction on a template nucleic acid/primer duplex, wherein the reaction is controlled such that on average no more than three nucleotides are added to the primer per incorporation cycle; and
 - determining a sequence of the template based upon order of incorporation of the nucleotides to the primer over multiple incorporation cycles, wherein the nucleotides are not chain terminating nucleotides, and wherein the template/primer duplexes are individually optically resolvable.

8. The method of claim 1, wherein the determining comprises optically identifying the incorporated nucleotide(s).

19. The method according to claim 1, wherein the duplexes are attached to a solid support.

The '345 patent, 22:59–24:18.

As is evident, claims 1, 8, and 19 of the '345 patent recite a similar sequencing process to that recited in rejected claim 1, including rejected claim 1's step of providing a plurality of surface-bonded primer-template duplexes, and using a polymerase to extend the template-hybridized primers by at least three consecutive nucleotides with labeled nucleotides. Moreover, as discussed above in relation to the Examiner's obviousness rejection, Williams discloses using arrays of nucleic acid molecules of defined locations in sequencing processes. *See* Williams 2:40–42, 3:14–17. We, therefore, discern no error in the Examiner's determination that it would have been obvious in view of Williams to use an array in a sequencing process as recited in the claims of the '345 patent, and to determine the location on the array of the initial template-primer complex, as well as the location (by comparison) of the incorporated labeled nucleotide.

Further, as also discussed above in relation to the Examiner's obviousness rejection, Williams discloses using a nucleotide label that is liberated from the primer-template complex upon incorporation. *See id.* at 2:37–40. Accordingly, we discern no error in the Examiner's determination that it would have been obvious in the process recited in the '345 patent claims to remove the label after nucleotide incorporation. Lastly, because the '345 patent claims recite the addition of up to three nucleotides to the template-bound primer, we discern no error in the Examiner's determination that the step of removing unincorporated nucleotides by washing recited in

rejected claim 1 would have been an obvious step in the process recited in the claims of the '345 patent.

In sum, for the reasons discussed, Appellant does not persuade us preponderant evidence fails to support the Examiner's conclusion that the process recited in representative rejected claim 1 would have been obvious over claims 1 and 8–20 of the '345 patent in view of Williams, Sklar, and Fleming. We, therefore, affirm the Examiner's rejection of claim 1 on that ground. Because they were not argued separately, claims 2–8, 13–16, and 50–65 fall with claim 1.

As the Examiner points out (Ans. 63), Appellant advanced no argument explaining why the Examiner erred in determining that the processes recited in claims 1–8, 13–16, and 50–53 under consideration herein would have been obvious over claims 1, 11–13, and 15–17 of the '498 patent in view of Williams, Sklar, and Fleming. *See Br.*, generally.

We, therefore, summarily affirm the Examiner's rejection of claims 1–8, 13–16, and 50–53 for obviousness-type double patenting over claims 1, 11–13, and 15–17 of the '498 patent in view of Williams, Sklar, and Fleming. *See* MPEP § 1205.02.

SUMMARY

For the reasons discussed, we reverse the Examiner's rejection of claims 1–8, 13–16, and 50–65, as being indefinite based on the absence of essential steps in the claims.

For the reasons discussed, we reverse the Examiner's rejection of claims 55 and 65, as being indefinite based on the language in those claims reciting the use of and algorithm.

For the reasons discussed, we affirm the Examiner's rejection of claims 59 and 65, as being indefinite based on the presence of the term "about" in those claims.

For the reasons discussed, we reverse the Examiner's rejection of claims 1–8, 13, and 50–65, under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

For the reasons discussed, we reverse the Examiner's rejection of claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

For the reasons discussed, we reverse the Examiner's rejection of claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 101, as not being directed to patent eligible subject matter.

For the reasons discussed, we affirm the Examiner's rejection of claims 1–8, 13–16, and 50–65, under 35 U.S.C. § 103(a) as being unpatentable over Williams, Sklar, Fleming, and admitted prior art.

For the reasons discussed, we affirm the Examiner's rejection of claims 1–8, 13–16, and 50–65, on the ground of nonstatutory double patenting over claims 1 and 8–20 of the '345 patent in view of Williams, Sklar, and Fleming.

For the reasons discussed, we affirm the Examiner's rejection of claims 1–8, 13–16, and 50–53, on the ground of nonstatutory double patenting over claims 1, 11–13, and 15–17 of the '498 patent in view of Williams, Sklar, and Fleming.

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED