UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OXFORD NANOPORE TECHNOLOGIES, INC.
Petitioner,

v.

PACIFIC BIOSCIENCES OF CALIFORNIA, INC.
Patent Owner.

Case IPR2018-00789
Patent 9,546,400 B2

Before ZHENYU YANG, JAMES A. WORTH, and
MICHAEL G. McMANUS *Administrative Patent Judges.*

McMANUS, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. BACKGROUND

Oxford Nanopore Technologies, Inc. ("Petitioner") filed a Petition, Paper 1 ("Pet."), to institute an *inter partes* review of claims 1–15 (the "challenged claims") of U.S. Patent No. 9,546,400 B2 ("the '400 patent"). 35 U.S.C. § 311. Pacific Biosciences of California, Inc. ("Patent Owner") timely filed a Preliminary Response, Paper 7 ("Prelim. Resp."), contending that the petition should be denied as to all challenged claims. We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the Petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Having considered the arguments and the associated evidence presented in the Petition and the Preliminary Response, for the reasons described below, we decline to institute *inter partes* review of claims 1–15.

II. REAL PARTIES IN INTEREST

The Petition identifies Oxford Nanopore Technologies, Inc. as the real party-in-interest. Pet. 6. The Petition further identifies Oxford Nanopore Technologies, Ltd., the parent company of Oxford Nanopore Technologies, Inc., and Metrichor Ltd., a corporate affiliate of Oxford Nanopore Technologies Inc. *Id.* Patent Owner indicates that it is the real party-in-interest. Paper 5.

III. PENDING LITIGATION

The Petition states that the ’400 patent is asserted in the following litigation: *Pacific Biosciences of California, Inc. v. Oxford Nanopore Technologies, Inc.*, 1:17-cv-00275-LPS and 1:17-cv-01353-LPS (D. Del.). Pet. 6.

IV. THE ’400 PATENT (EXHIBIT 1001)

The ’400 Patent, titled “Nanopore Sequencing Using N-Mers,” concerns the sequencing of polymeric molecules such as nucleic acids. Ex. 1001, 1:54–57. The disclosure of the ’400 Patent generally relates to a device for, and method of, sequencing a polymeric molecule, for example single-stranded DNA (“ssDNA”), where the polymer is passed through a nanoscopic opening (nanopore) while an electrical signal is monitored. *Id.* at 1:27–30. As the polymeric molecule passes through the nanopore, differences in the chemical and physical properties of the monomeric units are translated into characteristic electrical signals. *Id.* at 1:33–37. The general structure of the device used to practice the method taught by the ’400 Patent is shown in Figure 1A below.

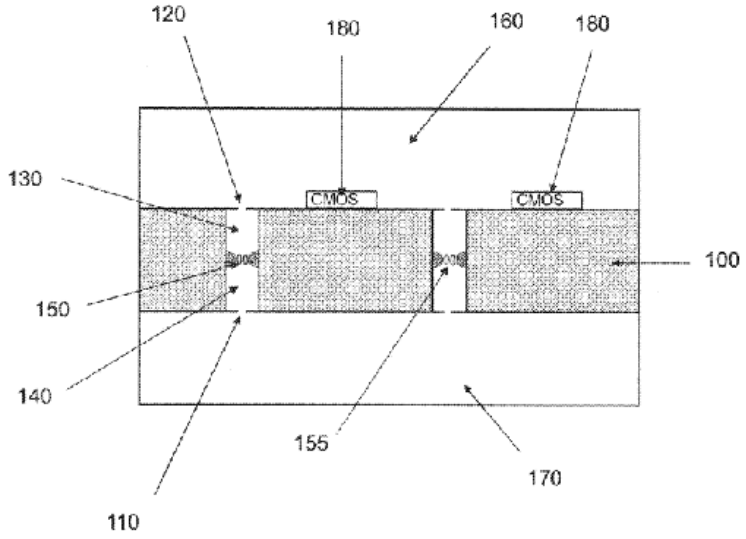
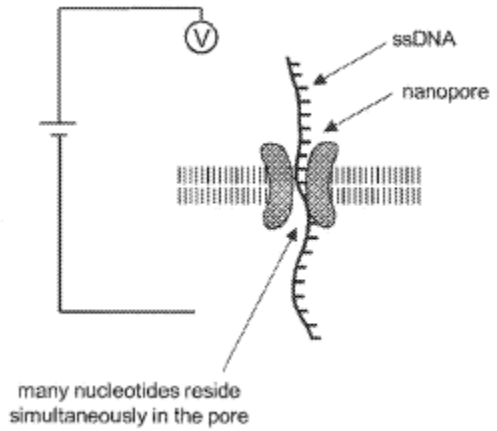


Figure 1A "shows a cross section of an exemplary multiplex nanopore sequencing device of the invention comprising resistive openings." *Id.* at 8:45–47. Figure 1A depicts substrate 100 in which nanopores 150 and 155 are formed. *Id.* at 8:45–9:38. It further shows electrical circuit 180 which "can be used to measure, process, and store electronic data and signals related to the sequencing measurements." *Id.* at 9:19–21.

Another figure from the '400 Patent depicts a nucleotide (ssDNA) passing through the nanopore.



Id., Fig. 28 (excerpt). As shown in Figure 28, there are multiple monomers in the nanopore as the strand transits the nanopore. In this regard, the Specification provides as follows:

> [T]he amplitude of electric current passing through the nanopore (which constitutes the signal) depends on the identity of the several bases that reside in the pore throughout the duration of the current measurement. Thus, rather than there being 4 distinct current levels (for A, G, C, T) when the ssDNA translocates through the nanopore, there are 4 to the N levels (N=the number of bases that affect the current measurement). Some of which may be degenerate (see FIG. 28). Furthermore, the bases residing in the center of the nanopore likely affect the current measurement more than those near the entrance or exit.

Id. at 39:52–62. The '400 Patent further teaches that, "[f]or example, if one knows that only 3 contiguous bases on the ssDNA strand determine the current measurement at any given time, then there are $4^3 = 64$ possible current levels." *Id.* at 40:2–5. The '400 Patent additionally teaches that one may synthetically create "64 different ssDNA strands with all the possible 3-base combinations, and then pre-calibrat[e] the system by measuring the current blockage levels from each of these ssDNA strands." *Id.* at 40:6–9. One may then compare subsequent measures of current blockage associated with unknown ssDNA to the pre-calibrated values. *Id.* at 40:9–12.

V. ILLUSTRATIVE CLAIM

Claim 1 of the '400 Patent is illustrative:

1. A method for sequencing a nucleic acid template comprising:

a) providing a substrate comprising a nanopore in contact with a solution, the solution comprising a template nucleic acid above the nanopore;

b) providing a voltage across the nanopore;

c) measuring a property which has a value that varies for N monomeric units of the template nucleic acid in the pore, wherein the measuring is performed as a function of time, while the template nucleic acid is translocating through the nanopore, wherein N is three or greater; and

d) determining the sequence of the template nucleic acid using the measured property from step (c) by performing a process including comparing the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations.

Ex. 1001, 47:37–48:6.

VI. ART CITED IN PETITIONER'S CHALLENGES

Petitioner cites the following references in its challenges to patentability:

Reference	Designation	Exhibit No.
US 2008/0041733 A1, "Controlled Translocation of a Polymer in an Electrolytic Sensing System," Hibbs et al.	Hibbs	1007
US 2006/0063171 A1, "Methods and Apparatus for Characterizing Polynucleotides," Akeson et al.	Akeson	1008
Stephen Winters-Hilt, *Machine Learning Methods for Channel Current Cheminformatics, Biophysical Analysis, and Bioinformatics*	Winters-Hilt	1013
Grigori Sigalov et al., *Detection of DNA Sequences Using an Alternating Electric Field in a Nanopore Capacitor*, Nano Lett. 8:56-63 (2008)	Sigalov	1017

Grigori Sigalov et al., *Supporting information to the manuscript "Detection of DNA sequences Using an Alternating Electric Field in a Nanopore Capacitor"*	Sigalov	1019
US 6,446,198 B1, "Vectorized Table Lookup," Sazegari	Sazegari	1022
Jong-Sen Lee, *Digital Image Smoothing and the Sigma Filter*, Computer Vision, Graphics, and Image Processing 24, 255-269 (1983)	Lee	1023

VII. CHALLENGES ASSERTED IN PETITION

Ground	Claims	Statutory Basis	References
1	1–9, 12–15	35 U.S.C. § 103(a)[1]	Winters-Hilt, Hibbs
2	4, 5	35 U.S.C. § 103(a)	Winters-Hilt, Hibbs, Akeson
3	10	35 U.S.C. § 103(a)	Winters-Hilt, Hibbs, Sazegari
4	11	35 U.S.C. § 103(a)	Winters-Hilt, Hibbs, Lee
5	1–3, 6, 7, 12–15	35 U.S.C. § 103(a)	Sigalov
6	4, 5, 8	35 U.S.C. § 103(a)	Sigalov, Akeson
7	9	35 U.S.C. § 103(a)	Sigalov, Winters-Hilt
8	10	35 U.S.C. § 103(a)	Sigalov, Sazegari
9	11	35 U.S.C. § 103(a)	Sigalov, Lee

[1] We apply pre-AIA 35 U.S.C. § 103 because the effective filing date of the '400 Patent precedes the March 16, 2013, effective date for changes to 35 U.S.C. § 103. *See* MPEP § 2159 (Rev. 08.2017).

VIII. ORDINARY SKILL IN THE ART

Petitioner does not set forth any standard for the level of skill of a person of ordinary skill in the art in the Petition. Petitioner's expert, however, states that a person of ordinary skill in the art at the time of the invention of the '400 patent would have "an advanced degree, such as a masters or Ph.D. degree in bioinformatics, biostatistics, computational biology, or another field related to molecular analysis." Ex. 1005 ¶ 32. Petitioner's expert further asserts that "[t]he person of ordinary skill in this art area, a cross-disciplinary field spanning bioinformatics and molecular biology, would have experience in both the computational and biological sciences or experience in one of those disciplines with access to those with experience in the other." *Id.*

Patent Owner argues that "the skilled artisan would have been a researcher or professional scientist with an interest in nanopore sequencing and would have had at least a bachelor's degree in a hard science combined with experience working in the DNA sequencing field." Prelim. Resp. 28.

The parties' proposed levels of skill to be attributed to one of ordinary skill in the art are, in essence, substantially similar. Neither party has shown how the proposed level of skill would (or should) affect the present outcome. Both proposals imply technical education and knowledge of the relevant prior art. For purposes of the present determination, we need not decide more. *See, e.g., In re Huston*, 308 F.3d 1267, 1279 n. 8 (Fed. Cir. 2002) (affirming Board where "Appellants contend that the Board erred by not more precisely identifying the level of ordinary skill in the art . . . . But appellants have not shown how a different, more precise definition of the pertinent art would have changed the result").

IX. CLAIM CONSTRUCTION

We interpret claims of an unexpired patent using the broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). In applying a broadest reasonable construction, claim terms generally are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asks that we construe the term "calibration information produced by measuring such property for 4 to the N sequence combinations" as used in claim 1. Pet. 26–27. Petitioner argues that such term should be construed to mean "calibration information produced by measuring each of the 4 to the N sequence combinations, wherein N is the total number of bases within the pore that contribute to the signal." *Id.* at 27.

Petitioner argues that the Specification defines "N" to mean "the number of bases that affect the current measurement." *Id.* at 26 (citing Ex. 1001, 39:58–59). Petitioner further cites to a statement made by Patent Owner during the course of prosecution that "[t]he instant inventors discovered . . . , one first has to understand how many bases within the pore are contributing to the signal (N). . . . [and] 4 to the power of N calibration measurements must be carried out to produce calibration information for sequence determination." *Id.* at 27 (citing Ex. 1006, 388 [emphasis omitted]).

In contrast, Patent Owner argues that the Petitioner does not identify "any relevant controversy or dispute regarding the scope of this term." Prelim. Resp. 29. Accordingly, Patent Owner argues, there is no need to construe the term.

Claim construction is for "resolution of disputed meanings." *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997). Thus, "only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy." *Vivid Tech, Inc., v. Am. Science & Eng, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Here, it is not apparent that the designated term is relevant to the resolution of any dispute. Accordingly, we will not construe such term for purposes of the present determination.

X. ANALYSIS OF PETITIONER'S PRIOR ART CHALLENGES

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A. Asserted Grounds of Unpatentability

1. Obviousness of Claims 1–9 and 12–15 Over Winters-Hilt and Hibbs

Petitioner argues that claims 1–9 and 12–15 would have been unpatentable as obvious over the combined teachings of Winters-Hilt and Hibbs. Pet. 27–53.

a. Winters-Hilt

Winters-Hilt is a doctoral dissertation titled "Machine Learning Methods for Channel Current Cheminformatics, Biophysical Analysis, and Bioinformatics." Ex. 1013. Winters-Hilt states that the "major theme of this thesis is application of statistical analysis tools from machine learning to signal analysis and pattern recognition on stochastic sequential data. Application areas for the statistical tools include cheminformatics, biophysics, and bioinformatics." *Id.*, Abstract. In relevant part, it teaches as follows:

> DNA sequencing with a channel is currently being explored using two paradigms . . . .
>
> In the second sequencing paradigm, DNA sequencing is accomplished during translocation through the nanopore. . . . This is the paradigm that most of the solid-state efforts are beginning to explore. In work using α-hemolysin, DNA-hairpins with ssDNA overhangs have been used to probe the channel's limiting aperture. One of the goals of the latter effort is to explore another complication with the translocation-based paradigm: the base deconvolution problem. Suppose a stretched strand of ssDNA crosses the 5nm neck of the pore channel with 7 bases, this leads to a difficult deconvolution task in order to determine the sequence: $4^7 = 16{,}384$ patterns to discriminate (in very noisy environment with decoys). It may be that the α-hemolysin nanopore only has short "pinches" upon entering and exiting its transmembrane region, however, in effect requiring deconvolution on only 3 bases (64 patterns), which is probably

> manageable with the current device sensitivity. Likewise, for synthetic pores the goal is to engineer the constriction zone at the neck to be only a few bases across (picture an hourglass shaped pinch). In the end, an outgrowth of the translocation based paradigm may be successful, but only because the difficult base-calling task is decoupled from the single-molecule handling and left to some external, possibly florescence based, method.

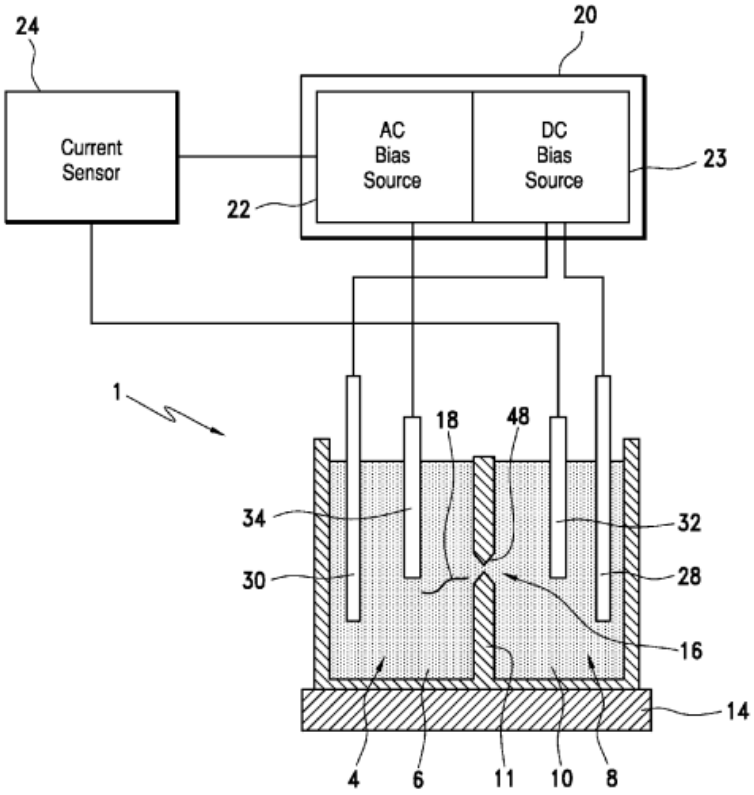
Id. at 103–105.

b. Hibbs

Hibbs is a United States Patent titled "Controlled Translocation of a Polymer in an Electrolytic Sensing System." Ex. 1016.[2] It was cited by the Examiner during prosecution of the application that matured into the '400 Patent. Pet. 23; Prelim. Resp. 30.

Hibbs generally relates to a system and method of providing controlled translocation of a polymer, such as ssDNA, through a fluid channel, and of measuring a channel blocking signal. Ex. 1007 ¶ 12. An apparatus used to practice the method of Hibbs is shown below.

[2]At certain points in the pleadings, the parties use "Hibbs" to refer to Ex. 1007 (US Pat. App. No. 11/839,793, Pub. No. 2008/0041733) and at other points Ex. 1016 (US 7,731,826 B2, issued June 8, 2010, to Hibbs et al.). We will refer to Ex. 1016.



Id., Fig. 1(a). Figure 1(a) depicts two fluid chambers separated by barrier 11. *Id.* at 4:8–14. Polymer 18 translocates through channel 16. *Id.* at 4:19–21. Current sensor 24 measures the AC current through the channel. *Id.* at 4:23–25. Signals detected by current sensor 24 are processed in order to calculate the monomer sequence of polymer 18. *Id.* at 4:26–29.

Hibbs teaches comparison of a blocking signal (resulting from the presence of the polymer in the nanopore) to "calibrated values" as follows:

> After a polymer enters the channel, a sensor detects blocking signals produced by the polymer's monomers as they move through the channel. The signals undergo filtering and demodulation before a preliminary estimate is projected of the blocking signal as a function of distance along the polymer. The amplitude of the signal is then compared to calibrated values to project the nature of the monomers present.

Id. at 3:13–20. Hibbs similarly teaches that, after certain filtering and demodulation steps,

> [t]he conductance of the blocked channel can then be compared to calibrated values to project the nature of the molecular unit present in channel **16**, as indicated at **56**. Calibrated values may be derived from previously measured signals as known simple polymer sequences translocate through channel **16**.

Id. at 6:36–41. Hibbs additionally teaches to use "empirical measurements of known polymer sequences." *Id.* at 10:8–9. Specifically, Hibbs teaches that

> [f]or instance, the signal can be measured from a ssDNA segment comprised of a long length of identical bases (e.g. adenine (A) bases) with a single differing base (e.g. cytosine(C)) in the middle. . . . As the strand moves through channel **16**, the single C base will produce a differing signal characteristic of having the C at each specific position along the length of the channel. Such a measurement can be repeated many times to allow this signal to be determined very accurately. Similar measurements can be done for the other possible combinations of repeated bases (eleven others in the case of DNA's four unique bases) with single differing bases in the middle.

Id. at 10:8–21. As a result of such measurements, Hibbs teaches, "these empirical data sets will allow the blockage signal characteristics of each possible base at every position within channel **16** to be known. Once such convolution functions are known, then any given measured signal can be deconvolved." *Id.* at 10:26–30.

c. Analysis

Claim 1 includes a preamble and four subparts, designated as elements [a] through [d]. Ex. 1001, 47:37–48:6. Petitioner asserts that both Winters-Hilt and Hibbs teach the preamble as well as elements 1[a] – [c].

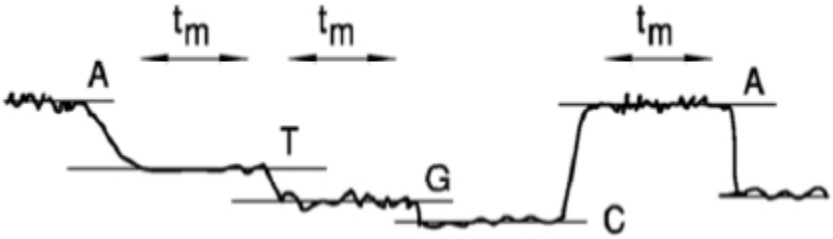
Pet. 30–37. Patent Owner does not meaningfully dispute these assertions (*see* Prelim. Resp., 38 n.5) nor do we discern error therein.

Claim element 1[d] requires "determining the sequence of the template nucleic acid using the measured property from step (c) by performing a process including comparing the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations." Ex. 1001, Pet. 37. Petitioner argues that this limitation is taught by the combination of Winters-Hilt and Hibbs. *Id.* at 37–43.

Petitioner asserts that Winters-Hilt teaches that multiple bases contribute to the channel current and the channel current must be measured for each of the 4^N combinations. *Id.* at 38. In support, Petitioner cites to Winters-Hilt's teaching that if "a stretched strand of ssDNA crosses the 5nm neck of the pore channel with 7 bases, this leads to a difficult deconvolution task in order to determine the sequence: 4^7 = 16,384 patterns to discriminate (in very noisy environment with decoys)." *Id.* (citing Ex. 1013, 105). Petitioner further cites to Winters-Hilt's teaching that "[i]t may be that the α-hemolysin nanopore only has short 'pinches' upon entering and exiting its transmembrane region, however, in effect requiring deconvolution on only 3 bases (64 patterns), which is probably manageable with the current device sensitivity." Ex. 1013, 105. Petitioner argues that this teaches "measuring all possible combinations of a 3-mer." Pet. 38. Petitioner then concedes that "[w]hile Winters-Hilt teaches the need to generate calibration information by measuring each of the 4^N combinations, it arguably does not expressly disclose a means of generating such calibration information." *Id.* For a

teaching regarding generating such data, Petitioner looks to Hibbs. *Id.* at 38–39.

Hibbs teaches to compare the conductance of a blocked channel (that is, a nanopore through which a strand of ssDNA translocates) to "calibrated values." Ex. 1016, 6:36–39. These "[c]alibrated values may be derived from previously measured signals as known simple polymer sequences translocate through channel **16**." *Id.* at 6:39–41. Petitioner cites to a figure from Hibbs, reproduced below.



Hibbs, Figure 7 is described as an "idealized base-by-base measurement of DNA." *Id.* at 12:32–33. Petitioner asserts that "a POSA could compare a measured signal to these calibrated values to determine the bases in the measured signal." Pet. 39 (citing Ex. 1005 (Settles Report) ¶ 80).

Hibbs further teaches that "[a] measured signal at any particular time can be considered a convolution between all the monomers in any portion of channel **16** with a convolution function that depends on the geometry and/or chemical properties of each position within channel **16**," Ex. 1016, 9:48–52, and that one may "directly probe[]" the convolution function "by empirical measurements on known polymer sequences," *id.* at 10:5–9.

Hibbs describes specific empirical measurements made on "a long length of identical bases (e.g. adenine (A) bases) with a single differing base

(e.g. cytosine (C)) in the middle." *Id.* at 10:11–12. Hibbs further describes as follows:

> As the strand moves through channel **16**, the single C base will produce a differing signal characteristic of having the C at each specific position along the length of the channel. Such a measurement can be repeated many times to allow this signal to be determined very accurately.

Id. at 10:15–19. Hibbs indicates that this was repeated with a single base of each of the four nucleotides within a longer strand of each type of nucleotide, thus (omitting homopolymers) 12 different strands would be assessed:

> Similar measurements can be done for the other possible combinations of repeated bases (eleven others in the case of DNA's four unique bases) with single differing bases in the middle.

Id. at 10:19–22. Petitioner asserts that "[f]or a pore with a signal affected by three nucleotides, a total of 40 different three nucleotide combinations would be measured. In the case where two nucleotides affect the signal, the example method disclosed in Hibbs would measure the signal produced from all $4^N = 16$ possible combinations of two nucleotides." Pet. 41 (internal citations omitted).

Petitioner argues that "[a]lthough Hibbs does not explicitly disclose the direct measurement of all 4 to the N sequence combinations when N is 3 or greater, it does disclose how to determine the blockage characteristics for all such combinations by performing direct measurements on a significant fraction of the sequence combinations." *Id.* at 42 (citing Ex. 1005 ¶ 87). Petitioner then concludes as follows:

> It would be trivial for a POSA to modify the method of Hibbs to directly measure additional sequence combinations. For example, instead of including only a single nucleotide in a chain of monomers, one could include all combinations of two nucleotides within the chain. Such a method would provide direct measurement of all sequence combinations where N is 3. *Id.* A POSA, recognizing the importance of knowing the "blockage signal characteristic of each possible base at every position," and the difficulty in predicting such blockage signal characteristics as disclosed by Winters-Hilt, would have been motivated to extend the methods disclosed by Hibbs to directly measure each of the possible 4 to the N sequence combinations.

Id. at 42. As a result, Petitioner argues, claim 1 of the '400 Patent would have been obvious over the combined teachings of Winters-Hilt and Hibbs. *Id.* at 43.

Patent Owner contests such argument on several bases. Prelim. Resp. 29–53. First, Patent Owner argues that Petitioner's First Asserted Ground of Unpatentability (and Grounds 2–4) relies principally on Hibbs which was thoroughly considered by the Examiner during the course of prosecution. *Id.* at 30–38. Second, Patent Owner argues that neither Hibbs nor Winters-Hilt teaches the claimed calibration information. *Id.* at 38–46. Third, Patent Owner argues that Petitioner has not shown that one of skill in the art would have had a reason to combine or a reasonable expectation of success. *Id.* at 46–53. We begin with Patent Owner's second argument.

Patent Owner asserts that Petitioner concedes that neither Winters-Hilt nor Hibbs explicitly discloses the generation of "calibration information" by measuring all "4 to the N sequence combinations" as required by claim element 1[d]. *Id.* at 38. Indeed, Patent Owner argues that Hibbs teaches away from measuring all 4^N sequence combinations. *Id.* at 39–42.

With respect to teaching away, Patent Owner contends that Hibbs teaches that the best method to interpret nanopore signals is to understand the contribution of individual bases at every position in the nanopore. *Id.* at 41. In support, Patent Owner cites to Hibbs' teaching that "[a]s the strand moves through the channel **16**, the single base will produce a differing signal characteristic of having the C at each specific position along the length of the channel." Ex. 1007 ¶ 46. Patent Owner contends that this method of calibration is "fundamentally incompatible" with the measurement of all 4^N sequence combinations, Prelim. Resp. 41, and that introducing additional bases would run counter to Hibbs' method to distinguish "a differing signal characteristic" of each base at each position in the channel, *id.* at 42.

Similarly, Patent Owner argues that Winters-Hilt does not teach the use of any calibration information determined by the measurement of a characteristic (such as blocking signal) for 4^N sequence combinations. *Id.* at 42–46. Patent Owner cites Petitioner's statement that Winters-Hilt "does not expressly disclose a means of generating calibration information." *Id.* at 42 (citing Pet. 38). Patent Owner further contends that Petitioner goes beyond the reference in asserting that Winters-Hilt teaches that "multiple bases contribute to the channel current and the channel current must be measured for each of the 4^N combinations." *Id.* at 44.

Patent Owner argues that Winters-Hilt's teaching that the α-hemolysin nanopore may have only short "pinches" that require deconvolution of "only 3 bases (64 patterns), which is probably manageable with the current device sensitivity" should be interpreted as "focused on techniques for achieving single-base resolution." Prelim. Resp. 45.

Additionally, Patent Owner argues that the portion of Winters-Hilt relied upon by Petitioner is mere speculation regarding the course of future research. *Id.* Patent Owner cites to Winters-Hilt's statement that "[i]n the end, an outgrowth of the translocation based paradigm may be successful, but only because the difficult base-calling task is decoupled from the single molecule handling and left to some external, possibly florescence based, method" as evidence that it does not teach calibration information based on 4^N sequence combinations (emphasis omitted). *Id.*

We find Patent Owner's arguments to be persuasive. The thrust of Hibbs is to measure the blockage signal for a "long length of identical bases . . . with a single differing base." Ex. 1016, 10:10–12. In doing so, Hibbs teaches to determine the blockage signal associated with that single differing base in various positions. There is no indication of any intent to make 4^N measurements (64 where N = 3) so as to capture the signal associated with each possible trimer (or longer oligomer) for comparison to unknown DNA strands. Rather, the Hibbs strategy is to identify the blockage characteristics of each type of base and use such data to sequence a strand of bases. *See, e.g.*, Ex. 1016, 10:25–27 ("these empirical data sets will allow the blockage signal characteristic of *each possible base* at every position within channel **16** to be known"), 4:4–8 ("the present invention is directed to a method and electrolytic sensing system for controlling the translocation of a molecule or polymer through a channel, *in order to measure blocking signals corresponding to individual monomers*") (emphasis added).

Further, Petitioner's argument that Winters-Hilt teaches the need to generate calibration information by measuring each of the 4^N combinations (Pet. 38) goes beyond the evidence. Winters-Hilt's conjecture that

deconvolution of three bases may be sufficient to determine a sequence (Ex. 1013, 104) does not imply any particular method of deconvolution.

Petitioner asserts that modification of Hibbs so as to measure the current (or other property) associated with 4^N sequence combinations would be "trivial" and argues as follows:

> Such a method would provide direct measurement of all sequence combinations where N is 3. A POSA, recognizing the importance of knowing the "blockage signal characteristic of each possible base at every position," and the difficulty in predicting such blockage signal characteristics as disclosed by Winters-Hilt, would have been motivated to extend the methods disclosed by Hibbs to directly measure each of the possible 4 to the N sequence combinations.

Pet. 42 (internal citation omitted).

This is not persuasive. Hibbs teaches that the measurements described therein (of a homopolymer with a single varied nucleotide) "will allow the blockage signal characteristic of each possible base at every position within channel **16** to be known." Ex. 1016, 10:26–28. Petitioner then cites to Winters-Hilt teaching of "the difficulty in predicting such blockage signal characteristics" without accounting for Hibbs' teaching regarding the very same subject.

More importantly, Winters-Hilt's recognition of the "difficult deconvolution task" offers no clear support for Petitioner's proposed modification. The thrust of Winters-Hilt is to recognize a single unknown nucleotide in a known strand. Winters-Hilt ultimately concludes that, in dealing with unknown sequences, "the difficult base-calling task" should be "left to some external, possibly florescence-based method." Ex. 1013, 105.

Thus, Petitioner provides no clear analytical path from statements

regarding the difficulty of multinucleotide deconvolution to the obviousness of using three-base trimer calibration information.

Accordingly, we determine that Petitioner has not shown that there is a reasonable likelihood that it would prevail with regard to establishing that claim 1 would have been unpatentable as obvious over the combined teachings of Winters-Hilt and Hibbs or that claims 2–9 and 12–15, which ultimately depend from claim 1 would have been unpatentable as obvious over the combined teachings of Winters-Hilt and Hibbs.

2. Obviousness of Claims 4, 5, 10, and 11 Over Winters-Hilt, Hibbs, and Akeson, Sazegari, and/or Lee

For its second asserted ground of unpatentability, Petitioner asserts that claims 4 and 5 are obvious over the combined teachings of Winters-Hilt, Hibbs, and Akeson. Pet. 53–56. For its third asserted ground of unpatentability, Petitioner asserts that claim 10 is obvious over the combined teachings of Winters-Hilt, Hibbs, and Sazegari. *Id.* at 56–58. For its fourth asserted ground of unpatentability, Petitioner asserts that claim 11 is obvious over the combined teachings of Winters-Hilt, Hibbs, and Lee. *Id.* at 58–59.

Each of these claims depends directly or indirectly from claim 1 and, therefore, includes the requirements of claim element 1[d]. For each of Grounds 2–4, Petitioner relies upon the combined teachings of Winters-Hilt and Hibbs as described above to teach claim element 1[d]. As we have found Petitioner's arguments not persuasive in this regard, we determine that Petitioner has not shown that there is a reasonable likelihood that it would prevail with regard to the asserted obviousness of the challenged claims in grounds 2–4.

3. Obviousness of Claims 1–3, 6, 7, and 12–15 Over Sigalov

a. Sigalov

Sigalov is a journal article titled "Detection of DNA Sequences Using an Alternating Electric Field in a Nanopore Capacitor." Ex. 1017.[3]

The authors describe a system with a nanopore in a silicon membrane submerged in an electrolyte solution. *Id.* at 56. An external electric bias is applied across the membrane to drive an ssDNA strand back and forth across the pore while the electric potential near the pore is recorded. *Id.*

The authors indicate that they have demonstrated "that back-and-forth motion of DNA in a 1 nm diameter pore has a sequence-specific hysteresis that results in a detectable change of the electrostatic potential at the electrodes of the nanopore capacitor." *Id.*

Sigalov teaches that "the chemical identity of the bases affects the induced potential." *Id.* at 59. As a result, "the ensuing differences in the potential are base type-specific and can be employed for DNA sequencing upon careful design and calibration of the device." *Id.* Sigalov further teaches that "successful implementation of the nanopore-sequencing device will likely require calibration using DNA homopolymers and repeat copolymers." *Id.* at 62.

Sigalov additionally teaches that "the nucleotide closest to the electrode contributes ~50% of the total potential. The two nearest neighbors contribute further ~40%, and the two next-nearest neighbors contribute the remaining ~10% of the total potential." Ex. 1019, 10; *see also* Ex. 1017, 61.

[3] The same authors published a supplement to the article. *See* Ex. 1019. Collectively, these exhibits are referred to as "Sigalov."

Because most of the total potential derives from the nucleotide closest to the electrode and the two adjacent nucleotides, "attribution of the measured potential to a triad of nucleotides may be possible." *Id.*

b. Analysis

Petitioner relies upon Sigalov's teaching that it may be possible to attribute the measured potential of the nucleotide in the nanopore to "a triad of nucleotides" closest to the electrode as motivation for a POSA to recognize the need to measure the potential for each possible triad (three nucleotide sequence). Specifically, Petitioner argues as follows:

> A POSA would recognize that to attribute a measured property to such a triad, one must first know the expected value of that property for the triad. Because Sigalov teaches that the system should be calibrated by using known monomers and copolymers, a POSA would understand that one should obtain the expected values for the triads by measuring the value for each possible triad. As there are four possible nucleotides, there are 4^N, or 64, possible nucleotide triads.

Pet. 64–65.

Patent Owner contests Petitioner's argument. Patent Owner contends that "[w]hat is critically missing from Sigalov is any suggestion that the 'attribution' can or should be done using calibration information based on 4^N sequence combinations where N is three or greater." Prelim. Resp. 56.

Patent Owner further points out that Sigalov's teaching immediately following the reference to the "triad of nucleotides" portion cited by Petitioner suggests a method of attribution. *Id.* Sigalov teaches that "[i]f the beginning of the DNA sequence is known," which can be controlled by grafting a known primer segment, "then only one unknown nucleotide must be identified at each step." Ex. 1019, 10.

Patent Owner has the better argument. Measurement of blocking characteristics of "homopolymers and repeat copolymers" as taught by Sigalov cannot produce calibration data relating to varied three nucleotide (or longer) sequences. Rather, it is directed at determining the potential of a single nucleotide at a given location. The same is true of the foregoing teaching regarding use of a known primer to permit identification of one unknown nucleotide at a time. Elsewhere, Sigalov (Ex. 1019) indicates an ability to differentiate blocks of four consecutive adenine nucleotides from blocks of four consecutive cytosine nucleotides. Ex. 1019, 3–4. This falls well short of an ability to discriminate one random three nucleotide sequence from another. In any case, Sigalov's disclosure lacks any clear teaching or suggestion to "compar[e] the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations" as required by claim element 1[d].

Accordingly, we determine that Petitioner has not shown that there is a reasonable likelihood that it would prevail with regard to establishing claim 1 would have been unpatentable as obvious over Sigalov or that claims 2, 3, 6, 7, and 12–15, which ultimately depend from claim 1 would have been unpatentable as obvious over Sigalov.

4. Obviousness of Claims 4, 5, and 8–11 over Sigalov and Akeson, Winters-Hilt, Sazegari, or Lee

For its sixth asserted ground of unpatentability, Petitioner asserts that claims 4, 5, and 8 are obvious over the combined teachings of Sigalov and Akeson. Pet. 68–71. For its seventh asserted ground of unpatentability, Petitioner asserts that claim 9 is obvious over the combined teachings of Sigalov and Winters-Hilt. *Id.* at 71–73. For its eighth asserted ground of unpatentability, Petitioner asserts that claim 10 is obvious over the combined teachings of Sigalov and Sazegari. *Id.* at 73–75. For its ninth asserted ground of unpatentability, Petitioner asserts that claim 11 is obvious over the combined teachings of Sigalov and Lee. *Id.* at 76–77.

Each of these claims depends directly or indirectly from claim 1 and, therefore, includes the requirements of claim element 1[d]. For each of Grounds 6–9, Petitioner relies upon the combined teachings of Sigalov as described above to teach such claim element. As we have found Petitioner's arguments not persuasive in this regard, we determine that Petitioner has not shown that there is a reasonable likelihood that it would prevail with regard to establishing claims 4, 5, and 8–11 would have been unpatentable as obvious over Sigalov and the additional references cited by Petitioner set forth in Grounds 6–9.

SUMMARY

For the reasons discussed above, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that it would succeed on any of the foregoing challenges to patentability.

ORDER

Accordingly, it is ORDERED that the Petition challenging the patentability of claims 1–15 of United States Patent No. 9,546,400 B2 is denied and *inter partes* review is not instituted.

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