

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.
Petitioner,

v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner

IPR2024-01451
U.S. PATENT NO. 11,827,921

DECLARATION OF CARL A. BATT, PH.D. IN SUPPORT OF
PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

1. I, Carl Batt, declare as follows:

2. This declaration responds to Dr. Kevin Struhl's opinions regarding the patentability of U.S. Patent No. 11,827,921 (the "'921 patent").

II. RESPONSE TO DR. STRUHL'S OPINIONS REGARDING THE LEVEL OF ORDINARY SKILL

3. In this declaration, I apply the same definition of a person of ordinary skill in the art ("POSA") as in my original declaration. EX1002 at ¶¶ 66–69. I understand that Dr. Struhl adopted that definition for the purposes of his declaration. EX2018 at ¶ 18 ("Therefore, I adopt Petitioner's definition of POSA for the purposes of this declaration."). Dr. Struhl confirmed this in his deposition:

Q. So there was nothing you disagreed with in Petitioner's definition?

A. Of this thing, I don't remember particularly agreeing or disagreeing, but ***I adopted it.***

Q. You were comfortable with adopting it?

A. Yes. Obviously, I put it up for – ***I wouldn't have written that I adopted it if I wasn't comfortable adopting it.***

EX1044 at 16:8–17.¹

4. Importantly, Dr. Struhl made his opinions with the understanding that a POSA would be familiar with (1) multiplex PCR and its application in detecting

¹ All emphasis is added unless otherwise stated. For simplicity, I have also removed deposition objections and court reporter questions throughout.

and measuring polynucleotide analytes, (2) the design and use of fluorescent-labeled oligonucleotide probes in conjunction with multiplex PCR, (3) the quantitative detection and measurement of polynucleotide analytes using fluorescent-labeled oligonucleotide probes in multiplex applications, (4) techniques for labeling probes and detecting multiple targets using fewer differently colored fluorophores than the number of polynucleotide targets, and (5) quantitative PCR (qPCR) and digital PCR (dPCR) and their application in detecting and measuring polynucleotide analytes, including in multiplex applications. EX1002 at ¶ 69.

5. Dr. Struhl further admitted that he knew of these techniques as early as 2002:

Q. Okay. So let me ask this question: At what point in time would you have said that you would have understood the competencies that are part of Petitioner's definition of the level of ordinary skill in the art?

A. I would say that *I would be a Person of Ordinary Skill in the Art in like 2002, 2003.*

Q. Okay. That's when you would have understood the competencies that are listed in Petitioner's—

A. Yeah. We were doing it.

EX1044 at 38:5–15.

6. Dr. Struhl acknowledged during his deposition that multiplex PCR was routine and obvious:

Q. Now, were other researchers besides you and your coworkers in your lab also performing multiplex PCR in the 2005 time frame?

A. Probably.

Q. Can you say one way or the other?

A. Well, I don't think we invented the technique, but *it's a pretty obvious technique*, actually. There's a lot of techniques that are conceptually similar to that, even if they don't develop PCR.

Id. at 41:2–11; *see also id.* at 40:8–19; 42:5–9.

III. CLAIM CONSTRUCTION

A. Response to Dr. Struhl's Opinion that " $F \geq 2$ and $M \geq 3$ "

7. I disagree with Dr. Struhl's interpretation that the '921 patent claims require that "in all cases, $F \geq 2$ and $M \geq 3$." EX2018 at ¶ 48. The text of the claims clearly allows for $F=1$. Take, for example, the plain text of claim 1, which expressly states:

wherein said fluorescent signal comprises F wavelength components, and
wherein said assay is capable of unambiguously detecting the presence or
absence of each of said at least M analytes, in any combination of presence
or absence, in a single sample volume, based on detection of said F
wavelength components, when M is greater than F .

EX1001 at 67:14–21. Per the text of claim 1, F is not limited to greater than 1.

8. A POSA would understand that the only limitation placed on the value of F is that it be less than M . Moreover, the claim language does not limit the number of analytes, M , which can be detected. This makes clear that the '921 patent claims assays where one wavelength can be used to detect two analytes, *i.e.*, $F=1$ and $M=2$.

9. Dr. Struhl's interpretation is not based on the claim language. During his deposition, Dr. Struhl acknowledged that his opinion that $F \geq 2$ and $M \geq 3$ was based on examples from the specification. EX1044 at 196:24–197:4 (“Yes, because all of the examples in there have F -- in the patent are all F, at least 2.”); *see also id.* at 197:5–14. I understand from counsel that examples from the specification do not limit otherwise unambiguous claim language.

10. More importantly, the '921 patent describes examples using a single color, meaning $F=1$. For example, the '921 patent describes that “a single color coding scheme encoding all 16 analytes may assign the values 1, 2, 4, 8, 16, 32, 64, 128, 256, 512, 1024, 2048, 4096, 8192, and 16384 to analytes A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P.” EX1001 at 23:43–47.

11. In his deposition, Dr. Struhl agreed that the coding schemes described in the '921 patent can be used where $F=1$, specifically in the case of two analytes.

Q. Well, I'm asking you about the approach set forth in Column 22, Lines 18 to 37 that I just had you review.

A. Yeah.

Q. And my question to you is a simple one. Could you use that for just two analytes. Did you give the first analyte an intensity of 1 and the second analyte an intensity of 2; would you do that? Would that work? Do you know?

A. ***If you only had two analytes, and you had them at different levels—if you—if you followed the way the patent is done, if you did what the patent does, it would work.*** If you—if you—if you did it that way, if you did what—if you basically did what the patent did.

EX1044 at 69:19–70:10.

B. Single Sample Volume

12. I have been informed that Patent Owner has changed its interpretation of the phrase “single sample volume.” Under its new construction, Patent Owner contends “single sample volume” is limited to a single partition from an original sample solution, *i.e.*, a single droplet. Paper 17 at 26. Originally, Patent Owner argued that the claimed “single sample volume” is a portion of an original sample solution that may be partitioned into sub-volumes, *i.e.*, droplets, later for amplification. EX1002 at ¶ 318.

13. Patent Owner’s new interpretation is contradicted by the text of the ’921 patent. The claim language requires detecting “M analytes” in a “single sample volume,” with amplification occurring in that same volume. EX1001 at 67:9–26. However, the ’921 patent specifies that a “single sample volume” is not limited to a droplet, and may be any volume, such as a “tube or a bottle.” *Id.* at 38:63–65.

14. The claims and specification do not prohibit analytes from being compartmentalized or separated for analysis. This can be done using a widely used technique called “droplet-based microfluidics,” which involves separating a single sample volume into uniform droplets ranging from picoliters to nanoliters, all of which are then suspended in an immiscible fluid and analyzed *en masse*. The ’921 specification describes both separated and non-separated scenarios, stating “the invention **could** be used with separation ... if desired.” *Id.* at 36:4–6.

15. Moreover, during prosecution, the claims were amended to remove a requirement that the assay be performed “in a single sample volume *without ... separation.*” The final claim language requires only that amplification occur in the “single sample volume.” EX1029.002. Notably, when Patent Owner intended to exclude “separation” or limit claims to “droplets” in other related patents, it did so. *See* Paper 9 at 2 (citing IPR2024-01177, EX1001; IPR2024-01178, EX1001).

16. A POSA would therefore understand that the term “single sample volume” encompasses situations in which a portion of an original sample solution is separation into droplets for later amplification.

IV. RESPONSE TO DR. STRUHL’S CHARACTERIZATION OF THE PRIOR ART

A. Larson

17. It is my opinion that Dr. Struhl mischaracterizes the key teachings of Larson, and his description of Larson is deficient. I disagree with Dr. Struhl’s description of Larson for at least two reasons. First, I disagree with Dr. Struhl’s suggestion that Larson focuses solely on a single target per droplet. *See e.g.*, EX2018 at ¶ 76 (“Larson is replete with examples of how to identify a single analyte molecule within a droplet, repeats this as a key inventive concept throughout the reference, and indeed I believe that a POSA reasonably would have considered identifying a single analyte molecule within a droplet to be Larson’s principle of

operation.”). Second, I disagree with Dr. Struhl’s opinion that Larson’s “solution” to multiple occupancy is excluding droplets containing multiple analytes. *See* EX2018 at ¶¶ 64–75.

1. Larson Teaches Multiple Occupancy

18. As discussed in my original declaration, Larson expressly contemplates situations with multiple targets per droplet. *See* EX1002 at ¶¶ 321, 332, 370; *see also* EX1017 at ¶ 141 (“However, methods of the invention can accommodate these complications arising from multiple occupancy.”). Larson’s methods are capable of detecting the presence or absence of multiple targets in a sample.

19. Specifically, Larson recognizes the likelihood of multiple occupancy. EX1017 ¶ 6. Larson teaches a Poisson distribution, which necessarily results in some droplets having multiple analytes. *Id.*; *see also* EX1002 at ¶ 187. Following the Poisson distribution, “at so called ‘limiting dilution,’ some reactions contain zero [target] molecules, some reactions contain one molecule, and *frequently some other reactions contain multiple molecules.*” EX1017 at ¶ 6. Moreover, Larson teaches the use of limiting dilution. *Id.* at ¶ 52 (“[T]he invention is compatible with all distributions of DNA loading that conform to *limiting* or terminal *dilution.*”). Despite the fact that droplets at limiting dilution “frequently” contain multiple molecules, Larson’s methods “can accommodate ... complications arising from multiple occupancy.” *Id.* at ¶ 141. A POSA reading Larson would understand that

Larson contemplates multiple analytes per droplet and discloses methods that accommodate analyzing droplets with multiple analytes.

20. Several sections of Larson teach the detection of multiple targets in a single droplet. For example, Larson describes a method where “a single droplet might contain four different probes for measuring three different targets” (T1, T2, T3). *Id.* at ¶ 140; *see also id.* at ¶¶ 141–142. Notably, as discussed above, Dr. Struhl admits that a POSA would be familiar with techniques for detecting targets in such a droplet. *See supra* Section.II. In Larson’s three target example, two probes are labeled with different intensities of color A (A1, A2) and two with different intensities of color B (B1, B2). EX1017 at ¶ 140. T1 is detected by A1 (color A at the first intensity level), T2 by B1 (color B at the first intensity level), and T3 by both A2 and B2 (colors A and B together at the second intensity level). *Id.* During his deposition, Dr. Struhl admitted that this is an example in Larson of the “situation where multiple targets get loaded into the droplet at the same time.” EX1044 at 134:25–135:4. Larson further teaches that the intensity of signals can be adjusted to prevent ambiguous results, thus unambiguously distinguishing multiple targets in a single droplet. EX1017 at ¶¶ 35, 146, 150.

21. Another example of the detection of multiple targets can be found in Larson Figure 11a, reproduced below. Figure 11a teaches distinguishing droplets containing three different combinations of two target genes—BCKDHA and SMN2.

The figure shows a histogram of droplet fluorescence intensities for three template DNA samples: a no template control (dotted line), BCKDHA only (solid line), and a 1:1 mixture of BCKDHA and SMN2 (dashed line). *Id.* at ¶ 131. In the 1:1 BCKDHA to SMN2 scenario, Larson reports that “three populations were readily apparent,” with peaks at 0.08 V, 0.27 V, and 0.71 V. *Id.* The peak at 0.08 V corresponds to droplets that do not contain any target. *Id.* The peak at 0.71 V corresponds to droplets containing only BCKDHA. *Id.* And the peak at 0.27 V corresponds to droplets containing only SMN2. *Id.* Additionally, Larson discloses that “a very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a that corresponded to ***droplets occupied by both genes.***” *Id.* A POSA would understand that Larson Figure 11a discloses an example of Larson teaching the unambiguous detection of multiple analytes in a single droplet.

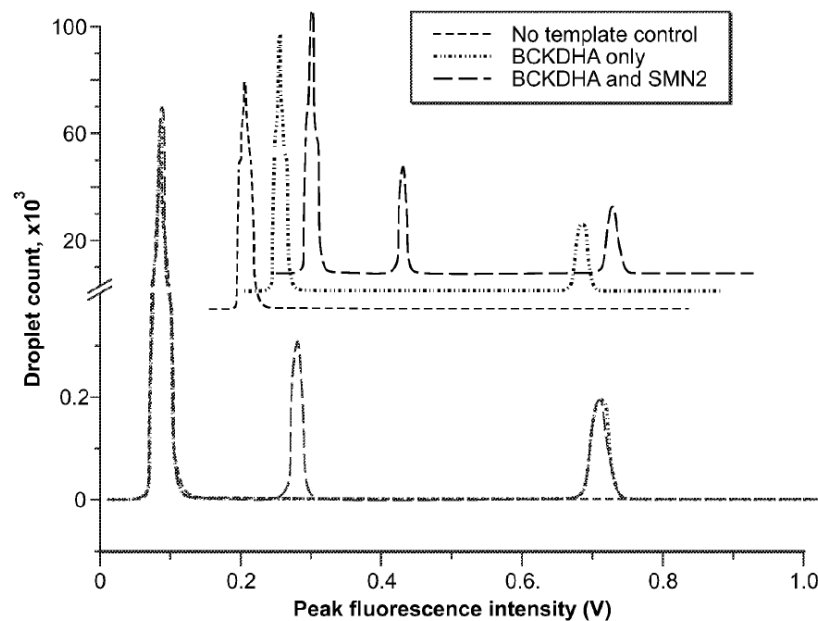


FIG. 11a

22. At his deposition, Dr. Struhl stated he did not consider Figure 11a in preparing his declaration. EX1044 at 136:1–6 (“I don’t remember this figure at all.”).

23. Additionally, paragraph 61 of Dr. Struhl’s declaration acknowledges that Larson contemplates multiple targets per droplet. EX2018 at ¶ 61 (“Larson teaches that in a duplex system (an assay for two analytes), the contribution from each probe can be recovered from *a droplet that contains both of the analytes.*”). According to Dr. Struhl, Larson even discloses how to distinguish between a droplet with both analytes and droplets with one analyte. *Id.* (“[B]ased on the increased intensity from such a droplet relative to droplets containing only a single analyte.”).

At his deposition, Dr. Struhl confirmed as much. EX1044 at 160:25–161:14 (“I think that’s pretty straightforward.... What’s written is written; that’s all I’m saying. I can’t add to it.”).

2. Larson Does Not Teach Discarding All Droplets with Multiple Occupancy

24. Dr. Struhl mischaracterizes Larson by opining that “[t]o the extent that any droplets nonetheless contain more than one analyte molecule before and during PCR, Larson expressly teaches excluding any such droplets from analysis after PCR, and before analyzing the droplets.” EX2018 at ¶ 64.

25. Larson teaches exclusion of *amplification products resulting from polymerase errors during PCR*, not droplets containing multiple targets resulting from the Poisson distribution under limiting dilution. Larson teaches that “[f]or applications requiring very high sensitivity” (EX1017 at ¶ 168)—such as the detection of rare genetic mutations in cancer diagnostics—“false positives greatly impact the validity and precision of digital PCR results.” *Id.* at ¶ 171. These applications are ones in which “each droplet contains only a single target nucleic acid, if any at all.” *Id.* at ¶ 168. Larson explains that false positives frequently occur due to the inherent error rate of DNA polymerase used during PCR amplification. *Id.* at ¶ 170. Polymerase errors occur when DNA polymerase incorporates an incorrect nucleotide into the target’s sequence during DNA amplification. These

polymerase errors produce a variant of the target, and a heterogeneous population in a droplet which is not representative of the original sample due to a false increase in mutant allele frequency. *Id.* at ¶ 171. Critically, Larson teaches methods to detect these droplets with heterogeneous populations, *i.e.*, droplets with multiple targets from polymerase errors during PCR amplification, in order to exclude these variants. *Id.* at ¶ 172. Identifying and removing these erroneous amplification products from the analysis ensures that only mutations in the original sample are detected, which enhances the reliability and specificity of mutation detection in highly sensitive applications. *Id.* at ¶¶ 15–18, 168–173. A POSA would therefore understand that Larson discloses methods for detecting droplets with multiple analytes and does not teach excluding those droplets for all applications.

B. Saxonov

26. Dr. Struhl does not address Saxonov in his declaration. *See* EX2018 at ¶ 77 (“I understand that the Board found that Petitioner did not establish Saxonov is § 102(e) prior art against the ’921 Patent for Grounds 3 and 4 in the Petition. *See* Paper 11, 26–29. I do not address this matter further herein.”). However, many portions of Saxonov are clearly found in the ’013 Provisional, which I understand from counsel are § 102(e) prior art as of the ’013 Provisional Application’s filing date of July 20, 2011. In fact, Dr. Struhl’s pre-institution declaration acknowledges

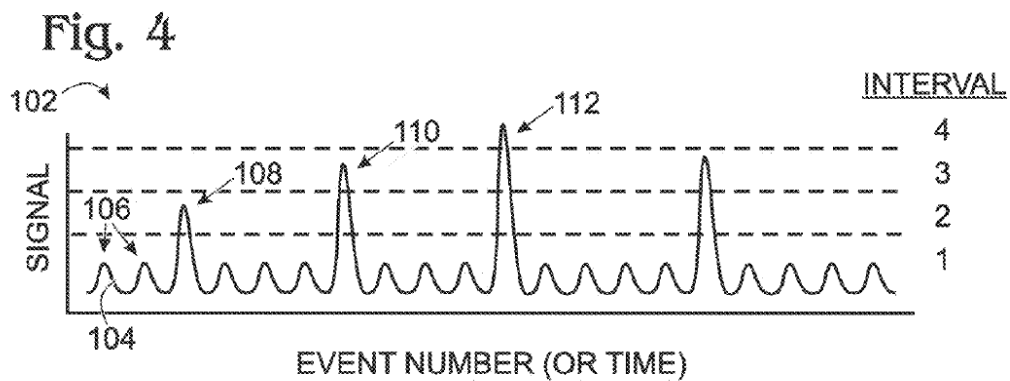
the prior art nature of those portions that are indisputably disclosed in the '013 Provisional. *See* EX2001 at ¶¶ 70–81; 88–89.

27. Saxonov, and the '013 Provisional, both teach detecting targets using color combinations and distinguishing between droplets containing “two, three, four, or more targets.” EX1007 at 9:14–15. Specifically, Saxonov teaches methods of using two colors to detect three targets. *Id.* at 5:19–6:3. This results in eight separate data clusters (populations) in a two-dimensional color/intensity space. *Id.* Saxonov clearly demonstrates that multiple targets per droplet yields eight unique populations based on color combinations, as seen in the table below.

	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	-	Intermediate
Population 6	+	-	+	Intermediate
Population 5	-	+	+	Intermediate
Population 4	+	-	-	Intermediate
Population 3	-	+	-	Intermediate
Population 2	-	-	+	Intermediate
Population 1	-	-	-	Lowest

Id. at 11:3.

28. Another portion of Saxonov that is carried over from the '013 Provisional is Saxonov Figure 4, depicted below. EX2001 at ¶¶ 88–89. Figure 4 depicts “an exemplary graph 102 of data corresponding to an exemplary digital PCR assay for Target 1 and Target 2 performed in droplets.” EX2007 at 15:12–17:3.



29. Saxonov Figure 4 illustrates a signal 104 corresponding to light collected within a “single channel,” which can be analyzed to determine “whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet.” *Id.* at 15:12–19 (emphasis added). In a dual-target system, Saxonov teaches that the “strength or intensity of the signal” can be divided into four distinct ranges, each corresponding to: “no Target (Interval 1[, Peak 106]), Target 1 alone (Interval 2[, Peak 108]), Target 2 alone (Interval 3[, Peak 110]), or **both** Targets 1 and 2 (Interval 4[, Peak 112]).” *Id.* at 15:19–16:20.

30. Most importantly, Saxonov Figure 4 depicts the exact scheme taught by Larson Figure 11a. A POSA would have understood to combine these references and would have done so with a reasonable expectation of success.

V. RESPONSE TO DR. STRUHL'S OPINIONS REGARDING OBVIOUSNESS

A. Ground 1: Claims 1–10 and 13–19 Are Anticipated by Larson

31. It is my opinion the claims of the '921 patent are anticipated by the clear disclosures of Larson. Dr. Struhl's arguments to the contrary are based on his misinterpretation of both Larson and the '921 patent, as described above.

32. Larson teaches an assay that is capable of unambiguously detecting the presence or absence of each of at least M analytes. As discussed above, Larson expressly contemplates samples containing multiple analytes. *See supra* Section.IV.A.1. Larson does not teach discarding these droplets. *Id.* Dr. Struhl's opinion to the contrary is a mischaracterization of Larson. *Id.*

33. A POSA would not read Larson to exclude droplets with multiple targets. Larson expressly discloses that its methods "can accommodate ... complications arising from multiple occupancy." EX1017 at ¶ 141. Larson Figure 11a teaches the unambiguous detection of two target genes in a single sample volume. *See supra* Section.IV.A.1.

34. Larson also teaches amplification within a "single sample volume," even under Patent Owner's construction of the term. This can be seen in Larson's description of droplet formation. *See* EX1017 at ¶¶ 78–79, 193. Larson describes taking a sample and separating the sample into droplets. *Id.* Following droplet

formation, Larson teaches “the droplets are *collected* off-chip as an emulsion in a *PCR thermal cycling tube*.” *Id.* at ¶ 79. This tube of droplets is thermocycled in a thermal cycler, where DNA amplification occurs. *Id.* By amplifying the collected droplets, Larson ultimately describes a method where amplification occurs within a “single sample volume,” *i.e.*, the original sample volume in collected, compartmentalized form.

B. Ground 3: Obviousness of Claims 1–10 and 12–19 in View of Larson and Saxonov

35. It is still my opinion that the claims of the '921 patent are obvious in view of Larson and Saxonov. As discussed above in my discussion of Ground 1, Larson teaches the unambiguous detection of the presence or absence of each of at least M analytes.

36. Saxonov similarly teaches detection of multiple targets per droplet and the use of color combinations. *See supra* Section.IV.B. It would be obvious to a POSA to apply the methods of Saxonov to the situations in Larson to arrive at the claims of the '921 patent.

37. A POSA would be motivated to combine Saxonov and Larson because, in part, Saxonov discloses the same scenarios taught in Larson. *Id.* A POSA would have a reasonable expectation of success because Saxonov and Larson both teach methods for unambiguous detection of multiple targets in a single droplet.

C. Grounds 2 and 4

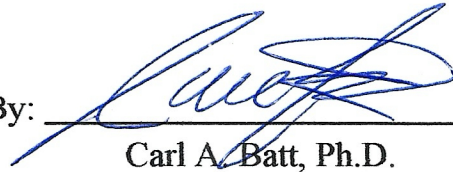
38. Dr. Struhl's opinions regarding Grounds 2 and 4 do not differ substantially from his opinion regarding Grounds 1 and 3. As such, I refer to my original declaration on both grounds. EX1002 at ¶¶ 286–317; 388–393.

DECLARATION

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are belief to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: September 11, 2025

By: _____



Carl A. Batt, Ph.D.