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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

CHROMACODE, INC., AND CALIFORNIA INSTITUTE OF TECHNOLOGY, Plaintiffs and Counter-Defendants, v. BIO-RAD LABORATORIES, INC., Defendant and Counter-Plaintiff.	Case No. 5:23-cv-06360-EJD **PLAINTIFFS AND COUNTER-DEFENDANTS CHROMACODE, INC. AND CALIFORNIA INSTITUTE OF TECHNOLOGY'S REPLY CLAIM CONSTRUCTION BRIEF** Date: August 28, 2024 Time: 10:00 a.m. Department: Courtroom 4 – 5th Floor Judge: Hon. Edward J. Davila

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I. INTRODUCTION

Bio-Rad's brief confirms that its proposed constructions suffer from three major flaws.

First, Bio-Rad has gone in search of ways to try to read the Caltech Asserted Patents that make them internally contradictory and nonsensical. Having seized on such readings, Bio-Rad declares two claims indefinite. But the claim language, specification, and Bio-Rad's own positions and expert testimony in its related IPR petitions confirm that the claims make perfect sense. For example, Bio-Rad here argues that one of the claims contains a "logical impossibility" that could never exist. But its own expert had no difficulty understanding it and claimed to find that element very much in existence in the prior art under "any reasonable construction."

Second, Bio-Rad twists the law and prosecution history in a transparent attempt to read a key limitation out of *both* the body and the preamble of a claim. Bio-Rad misleadingly argues that the examiner treated a wherein clause in the body as non-limiting during prosecution. Bio-Rad ignores that the examiner did so because the clause at that time was framed as stating a *capability*, and that the applicant in response revised the claim to state the clause as a positive *requirement*—after which the claim was allowed over the prior art. Bio-Rad also argues that because the antecedent basis for the limitation in the body can be found in the preamble, both should be non-limiting—stating the rule exactly backwards.

Third, Bio-Rad seeks to introduce confusion and complexity into a host of straightforward terms like "is present" or "each of said at least five hybridizing probes." In each case, there is no real dispute that the term is clear on its face under the plain language of the patent, but Bio-Rad wants to add more words in order to read in additional limitations found in other claims or other parts of the claim, or rule out phantom arguments that no one is making—with the net effect that the claims would be *more* difficult to understand, not less.

II. CONSTRUCTION OF THE DISPUTED TERMS

A. Bio-Rad's Indefiniteness Arguments Rest on Erroneous Constructions

Bio-Rad's two indefiniteness constructions fail for the same reason. Rather than reading the claims as its own expert does, Bio-Rad searches out any possible way to misunderstand the claims so as to render them non-sensical. That is not how claims are construed.

1. "providing a sample solution volume … comprising at least seven hybridization probes" and "contacting …" ('051 Claim 1)

Bio-Rad feigns confusion about the meaning of steps (a) and (b) of claim 1 of the '051 Patent. Step (a) requires "providing a sample solution volume comprising or potentially comprising at least one of at least seven polynucleotide analytes, and comprising at least seven hybridization probes," so the referenced sample solution volume already includes the hybridization probes and may also include analytes. Step (b) requires "contacting said sample solution volume with the plurality of hybridization probes and exciting the hybridization probes to generate the cumulative intensity signal(s) if one or more of the at least seven polynucleotide analytes is present in the sample solution volume." Bio-Rad misconstrues "contacting said sample solution volume with the plurality of hybridization probes" in step (b) to mean *add the probes that are already in the sample solution volume to the sample solution volume*. That is impossible, Bio-Rad argues, and a person of ordinary skill is left confused as to whether the probes are added to the sample the solution volume at step (a) or step (b).

Bio-Rad provides no support for its assumption that a person of ordinary skill would read "[c]ontacting" in step (b) to mean "adding" the hybridization probes to the sample solution. The Court should reject Bio-Rad's attempt to re-write the claim term and then claim that this re-write renders the claim indefinite. As the patent, Bio-Rad, and its expert all confirm, there is a much more reasonable and sensible way to read the claim: Because the "said sample solution volume" may comprise other things besides probes (most importantly, analytes), contacting the said sample solution volume with the probes includes contacting these other things (namely, the analytes), if they are present, with the probes. That is not only possible, it is key to how the claim describes the process of detection. Bio-Rad achieves the asserted impossibility only by misreading the claim in a way deliberately designed to render it nonsensical.

We begin with the claim language itself. Step (a) makes clear that the sample solution volume provided includes at least seven hybridization probes, and that it "potentially" also includes one or more of at least seven analytes. Step (a) also makes clear, through a wherein clause, what "contact" within the sample solution volume matters: "wherein each hybridization

probe, when *excited and* ***when contacted with its corresponding polynucleotide analyte****, generates a cumulative intensity signal*." (All emphasis in quotations is added.) This wherein clause describes a capability: if the analytes are present in the sample solution volume, and if the probes are allowed to contact their corresponding analytes in the sample solution volume, and if the probes are excited, then the probes will generate a cumulative intensity signal.

Step (b) uses similar language to say that the claimed method must actually use this capability: it must actually bring about the contact (if the analytes are present) and the excitement, and thus generate the signal:

Step (a)	Step (b)
Providing a sample solution volume comprising or potentially comprising at least one of at least seven polynucleotide analytes, and comprising at least seven hybridization probes, … wherein each hybridization probe, when excited and when contacted with its corresponding polynucleotide analyte, generates a cumulative intensity signal	contacting said sample solution volume with the plurality of hybridization probes and exciting the hybridization probes to generate the cumulative intensity signal(s) if one or more of the at least seven polynucleotide analytes is present in the sample solution volume

The act of "contacting" in step (b) is clearly a reference to facilitating the "contact" described in step (a)—contact between the analytes (if they are present in the sample solution volume) and the probes (which are also contained within the sample solution volume). As step (a) explains, that contact between probes and analytes in the sample solution volume, plus "exciting" the probe, is what generates the cumulative intensity signal in step (b). In other words, "contacting said sample solution volume with the plurality of hybridization probes" in step (b) includes contacting the *other contents* of the sample solution volume—namely the analytes—with the hybridization probes. There is nothing impossible about that.

This contacting step is important. Although the probes and analytes may both be present in the sample volume at step (a), they may not come into contact on their own. The

polynucleotide analyte is typically a strand of DNA, and two complementary strands of DNA are generally bound to each other in the classic double-helix arrangement. *See, e.g.*, '051 Patent, 25:45-50. The probe is designed also to be complementary to one of the strands of the analyte DNA so that it can bind (or "hybridize") to it. But to actually bring the probe into contact with the strand and hybridize them generally requires an amplification step where the DNA strands are split and copied. As the specification explains, the "sequence of the oligonucleotide probe is designed to be complementary to a polynucleotide sequence present in an analyte, and therefore ***capable*** of hybridizing to the polynucleotide sequence present in the analyte." *Id.* at 10:34-37. But the actual "[h]ybridization of the oligonucleotide probe is performed in a nucleic acid amplification reaction … (e.g., a polymerase chain reaction)." *Id*. at 10:37-40. This is reinforced by dependent claim 4, in which a "polymerase chain reaction" is claimed as one means of facilitating the contact and thus generating the cumulative intensity signals. In other words, even if probes and analytes are both present in the provided sample volume, a contacting step (such as amplification through polymerase chain reaction) must be taken so that the probes hybridize to the analytes. Step (b) includes that "contacting" step.

Bio-Rad's own arguments confirm this is what the "contacting" step means. As Bio-Rad concedes, it "is undisputed that 'hybridization or binding' refers to the interaction of the probes with the targets." Resp. Br. 7:18-19. That is key to the "contacting" step (b). The relevant contact made by the hybridization probes, as Bio-Rad says, is with the analytes. *See also id.* at 7 n.3 ("the claim already recites the probes used to perform the method are 'hybridization probes,' which bind to corresponding polynucleotide analytes").

Most importantly, Bio-Rad's own expert confirms that a person of ordinary skill would read the claim the way Plaintiffs do. Bio-Rad asserts in this case that a "skilled artisan" would not understand what is meant by "'contacting' the 'sample solution volume'" because that step is "impossible." Resp. Br. 4:20-5:1. Notably, it puts forward no evidence in this case of what a skilled artisan would understand. But it ***did*** put forth such evidence in its IPR petition. There, it submitted a declaration from its expert Carl Batt, Ph.D. Dr. Batt did ***not*** opine that that the step of "contacting the sample solution volume with the plurality of hybridization probes" is impossible.

To the contrary, he opined that this step is disclosed in a purported prior art reference because that reference "disclos[es] a sample having a volume comprising polynucleotide analytes and probes that hybridize to them" and "teaches contacting analytes in the sample solution volume with hybridization probes"—i.e., it "teaches hybridizing probes to their targets and exciting the probes to generate a signal." Tuttle Decl., Ex. A, ¶¶ 186-89. That is indeed the plain meaning of the contacting step (b) as Plaintiffs argue here.

Bio-Rad weakly responds that a claim can be both indefinite and disclosed in the prior art. Resp. Br. 8. But as Bio-Rad's own case explains, that is not true when the purported indefiniteness renders it "logically impossible" for the claim to be disclosed by prior art. *Nichia Corp. v. DSS, Inc.*, 2023 WL 7211097, at *3 (Fed. Cir. Nov. 2, 2023). It is one thing to say that a skilled artisan would not know the outer bounds of a claim limitation (rendering it indefinite), but that an example of something that clearly falls within it is present in the prior art (rendering it obvious). It is quite another to say that a claim term is both ***logically impossible*** *and* present in the prior art, as Bio-Rad is attempting to do here. A logically impossible claim term cannot be present in the prior art because it can't exist. If Bio-Rad's expert understood "contacting" to impossibly mean "adding" probes to the volume that are already in it, as Bio-Rad asserts, he could not have found it in the prior art. Instead, he claimed he *could* find it in the prior art because he read the term reasonably and consistent with its plain meaning. Bio-Rad tries to weasel out of its expert's opinion by asserting that its IPR petition was "based on Patent Owner's apparent interpretation in view of its infringement contentions." Resp. Br. 8:15-18. But Dr. Batt testified that "the prior art teaches and/or discloses the claim limitations under ***any reasonable construction***." Tuttle Decl., Ex. A, ¶ 130. That precludes impossibility.

Ultimately, Bio-Rad's argument is that the applicant could have written this claim term differently to say more clearly that the contacting step is about bringing the probes into contact with the analytes if they are present. Resp. Br. 7. That is beside the point. A patentee is not required to use the formulation deemed clearest by its litigation adversary. It need only inform, with reasonable certainty, those skilled in the art about the scope of the invention when read in light of the specification and prosecution history. The term at issue here does so, even if it is

phrased more awkwardly than other phrasing Bio-Rad can imagine. Bio-Rad must show the claim language is ***impossible***, not merely awkward. It has not met that standard.

2. "corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample" ('170 Claim 1)

Bio-Rad similarly misreads claim 1 of the '170 Patent to manufacture purported confusion about the location at which the detection of analytes takes place: Is it in the droplets, or is it in the sample as a whole? There is no genuine confusion. The claim language makes clear that the detection takes place in the droplets, as Bio-Rad largely concedes.

We begin with the preamble, which describes the claim as a whole: "A method of unambiguously detecting any unique combination of presence or absence of at least five polynucleotide analytes ***in a plurality of droplets***." Steps (a) and (b) explain that we start with "a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes," to which are added "at least five hybridization probes" to form a "mixture." Step (c) explains that we "partition[]" that mixture "into said plurality of droplets." The antecedent basis for "said plurality of droplets" is the "plurality of droplets" in the preamble, confirming that the requirement in the preamble that the detection take place "in a plurality of droplets" is limiting. *See Bio-Rad Labs., Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1369-72 (Fed. Cir. 2020) (reliance on preamble phrases for antecedent basis renders preamble limiting). Step (d) further reinforces that detection of analytes takes place in the droplets. As the patent explains, detection of analytes occurs by detecting light signals that are emitted by fluorophores on probes when (1) the probe binds (or "hybridizes") to an analyte and (2) the fluorophore is "excited" (e.g., with a laser). *See, e.g.*, '170 Patent, 10:31-45. Step (d) accordingly requires exciting the fluorophores to generate signals "if one or more of said at least five polynucleotide analytes is present ***in said plurality of droplets***." Thus, the generation of the signal that enables detection occurs on a droplet basis.

Bio-Rad concedes that the preamble and everything through step (d) relate to detection in the droplets. But Bio-Rad attempts to generate mischief with steps (e) and (f).

Step (f) relates to "determining whether each of said [at] least five polynucleotide analytes is present." Bio-Rad argues that, because step (f) doesn't expressly repeat that detection of

presence occurs in the droplets, the step is unclear. There is no lack of clarity, however, because the limiting preamble and the rest of the claim make clear that detecting the presence or absence of analytes takes place "in a plurality of droplets"; it is not necessary to repeat that in every step.

As to step (e), Bio-Rad misreads it. Step (e) requires:

> measuring said one or more signals to generate a cumulative intensity measurement, wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of *said at least five polynucleotide analytes* ***in said sample***.

Bio-Rad argues that the phrase "in said sample" at the end of this step must modify the phrase "presence or absence," i.e., must be saying where the presence or absence is determined. Bio-Rad's interpretation conflicts with the preamble and the rest of the claim, however, which are clear that the presence or absence of the analytes is detected "in a plurality of droplets," not in the sample as a whole as Bio-Rad contends this step requires.

Bio-Rad is misreading step (e) by ignoring the intervening words, i.e., the entire phrase "said at least five polynucleotide analytes in said sample." In this phrase, "in said sample" modifies "said at least five polynucleotide analytes." This is a reference back to step (a), where "a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes" is provided. The phrase "said at least five polynucleotide analytes in said sample" is making clear that the analytes at issue are the ones in the sample provided at step (a). The phrase "in said sample" says nothing about where the presence or absence is detected. That, as we know from the preamble and the rest of the claim, takes place in the droplets—which was the whole point of partitioning the sample into droplets, as step (d) confirms. There is thus no conflict.

This is a perfectly natural way to read the claim as a whole in light of the specification; under this reading, step (e) is consistent with the preamble and the claims make perfect sense and describe an invention consistent with the specification. That is how a person of ordinary skill would understand it. We know that because it's how Bio-Rad's own expert read step (e) in support of Bio-Rad's IPR petition. Dr. Batt claimed that step (e)'s requirement of "measuring said one or more signals to generate cumulative intensity measurement" could be found in purported prior art that disclosed "measur[ing] intensities of different signals ***in droplets***." Tuttle Decl., Ex.

D ¶ 178; *see also id.* ¶¶ 179-80 (opining that reference discloses this limitation because it shows signals that "correspond[] to the cumulative intensity signal generated by ***droplets*** containing [particular analytes or combinations of analytes]" as well as "***droplets*** with no polynucleotide present," and depicts "measured cumulative intensity signals of each ***droplet***"). Once again, Bio-Rad offers no evidence in support of its assertion that "a skilled artisan would not understand with reasonable certainty the location that one must assess for the 'presence or absence' of the claimed 'analytes.'" To the contrary, Bio-Rad submitted testimony with its IPR petition from an expert who had no trouble understanding step (e) and who located the cumulative signal measurements ***in the droplets*** because they correspond to the presence or absence of analytes ***in the droplets***.

Indeed, Bio-Rad acknowledges that the rest of the claim language and the specification confirms that the determination is made on a droplet basis rather than on a whole-sample basis. *See* Resp. Br. 22 (arguing claim does not require the entire mixture be partitioned or measuring signals from all droplets, and has no steps for equating presence or absence in droplets to the presence or absence in the sample); *id.* (arguing the specification does not explain how the plurality of droplets may be used as a proxy for the sample). That Bio-Rad can come up with a different way to misread a step that is inconsistent with the specification, the rest of the claim, and its own expert's analysis—so as to manufacture a conflict—does not make it indefinite. Bio-Rad's attempts to render the claims non-sensical should be rejected.

B. Bio-Rad's "Non-Limiting" Constructions Contradict the Prosecution History

Bio-Rad's "non-limiting" constructions make even less sense than its indefiniteness constructions. Bio-Rad dissects the "wherein" clause into two portions, concedes that one is limiting, but argues the other is merely an "intended purpose." Resp. Br. 20. Far from an intended purpose, the "wherein" clause goes to the heart of the invention, requiring that non-degenerate detection of any combination of analytes occur in a "single sample solution volume." Bio-Rad seeks to elide this requirement in service of its unsupported and erroneous arguments that its own Asserted Patents describe the methods claimed in the Caltech Asserted Patents. *Id.* at 2-3.

Bio-Rad's argument relies on a false and misleading characterization of the prosecution history. Bio-Rad falsely states that the examiner found a wherein clause "essentially the same" as

the one at issue here to recite a non-limiting intended use, and so the applicant added the second part of the clause to distinguish the prior art. Resp. Br. 20:16-26. In fact, the wherein clause at the time of the examiner's comment (which Bio-Rad misrepresents in its brief) was different in a key respect. The clause at the time said: "wherein said method ***is capable of*** non-degenerately detecting … in a single sample volume." Reply Decl. of Eric Tuttle ("Reply Decl."), Ex. 1 at 4. The examiner's conclusion was expressly tied to this "capability" phrasing:

> The capability of "non-degenerately detecting the presence or absence of at least seven analytes in a single sample volume, in any combination of presence or absence" is interpreted to be an intended use that does not differentiate the recitations of the claims from the prior art.

Reply Decl., Ex. 2 at 5. In response, the applicant rewrote the clause to change the "capable of" limitation into one expressly reciting the action of detection, as well as adding the second piece:

> wherein said method ~~is capable of~~ non-degenerately detects~~ing~~ the presence or absence of at least seven analytes in a single sample volume, in any combination of presence or absence, without immobilization of said analytes, physical separation of said analytes, or mass spectometry.

Tuttle Decl., Ex. B at 4-5; *see also id*. at 8-9 ("In response" to examiner's interpretation that "capability" was an "intended use," applicant "has replaced the expression 'capable of detecting' with 'detects.'"). The clause was then further amended to refer back to the "said single sample solution volume" in the preamble, reinforcing the intent to make the preamble limiting and the importance of the single sample solution volume requirement (Tuttle Decl., Ex. C at 5):

> wherein said method non-degenerately detects the presence or absence of the at least seven polynucleotide analytes in [[a]]said single sample solution volume, in any combination of presence or absence, without requiring any step of immobilization of said polynucleotide analytes, physical separation of said polynucleotide analytes, or mass ~~spectometry~~spectrometry.

This history confirms that the "wherein" clause language is not merely a statement of capability or intended use, but a hard requirement. The plain language of the claim is not satisfied unless the detection of the presence or absence of the at least seven polynucleotide analytes takes

place in said single sample solution volume. Bio-Rad's weak attempts to jettison this patentably significant feature of the claim body should be rejected.

Bio-Rad further argues the "wherein" clause in the body of the claim should be ignored because it refers back to the preamble, which it argues is non-limiting because the body recites a structurally complete invention. Resp. Br. 20. But Bio-Rad's cases do not support its proposal to make a portion of the wherein clause non-limiting because antecedent basis for that portion is found in the preamble. Bio-Rad's argument turns the case law on its head. The preamble is limiting *because* it provides antecedent basis for a requirement in the body of the claim. The wherein clause is part of the body of the claim, and on its face it limits how the method steps are performed. It does not simply express an intended result. Construing the wherein clause as non-limiting because its antecedent basis is found in the preamble gets the analysis exactly backward.

C. Bio-Rad's Attempts to Interject Complexity and Confusion into the Claims Should Be Rejected

Bio-Rad's remaining proposed claim constructions are incorrect, unjustified, and interject unnecessary complexity and confusion into the claims. They should be rejected.

1. "cumulative intensity signal(s)" ('051 Claims 1, 4)

Bio-Rad provides no justification for removing "cumulative" and "intensity" from its proposed definition of "cumulative intensity signal." It even admits that they should probably be added back by inserting "total intensity" somewhere (unspecified) in its proposed construction. Resp. Br. 11 n.4. Bio-Rad's argument that its construction "encompasses 'intensity'" through use of the word "signal(s)," *id.*, is self-defeating. The claim term *requires* intensity, and Bio-Rad admits that "signal" allows for intensity but does not require it. Bio-Rad's argument that its construction "refers to … a collection of probes—which reflects the 'cumulative' concept," *id.*, makes no sense. Bio-Rad's construction does *not* refer to a "collection of probes," but rather "*a signal or collection of signals* from the probes that contact the present analytes." Bio-Rad omits the requirement that the signal be *cumulated* (i.e., added into a total), and its reference to "signal or collection of signals" does not explain how the signals may or may not be "collected" together.

Bio-Rad also fails to provide any meaningful justification for the different language it

seeks to add into the claims. It argues that the definition of "cumulative intensity signal" must specify that each probe can generate a cumulative intensity signal, that each probe corresponds to a specific analyte, and that the probe is contacted with its analyte. Resp. Br. 9-11. But these requirements are expressly addressed elsewhere in the claim. Step (a) recites "each hybridization probe corresponding to one of the at least seven polynucleotide analytes." Step (a) also recites "wherein *each hybridization probe*, when excited and when contacted with its corresponding polynucleotide analytes, *generates a cumulative intensity signal*."[1] Step (b) recites the contacting step, as discussed above. Both parties agree that these elements are limiting requirements of the claims, despite Bio-Rad's assertion that some other "wherein" clauses are non-limiting.

There is no reason to redefine the term "cumulative intensity signal" to repeat requirements of the claim that are addressed elsewhere and that bring no clarity to the meaning of "cumulative intensity signal." Bio-Rad's construction should therefore be rejected.

2. "cumulative [signal/intensity] measurement" ('051 Claim 1; '170 Claim 1)

Bio-Rad effectively concedes that Plaintiffs' construction is the plain and ordinary meaning because it "adds no additional substantive meaning." Resp. Br. 11. Bio-Rad's proposed construction, on the other hand, adds unnecessary complexity and confusion. Bio-Rad's purported justification is that the "additional substantive meaning" it seeks to add to the claims is allegedly "supported by the intrinsic record, most notably the claim language." *Id.* But the claim language Bio-Rad emphasizes plainly supports Plaintiffs' construction, not Bio-Rad's:

> c) ***measuring the cumulative intensity signal(s), thereby generating a cumulative signal measurement***, wherein the cumulative signal measurement non-degenerately indicates the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence,

[1] Bio-Rad falsely characterizes Plaintiffs' position as reading "cumulative intensity signal" to refer to signals from multiple probes for "***different*** analytes." Resp. Br. 10:9-12. Plaintiffs' proposal is a "signal representing the total intensity of the light emitted ***by a given probe***." Bio-Rad misreads Table 4, in which each row (labeled "Cumulative Assay Result") corresponds to a cumulative intensity ***measurement*** (which combines signals across multiple probes/analytes).

Resp. Br. 11:17-21 (quoting '051 Patent, cl. 1). As the language Bio-Rad itself emphasized shows, the cumulative signal measurement is a measurement of the cumulative intensity signal(s). Nothing in this claim language requires that the cumulative signal measurement be "the signal or collection of signals from the probes that contact the present analytes," as Bio-Rad wants. Moreover, Bio-Rad has once again managed to read out both the concepts of "cumulative" and (in the case of the '170 Patent) "intensity."

Bio-Rad's construction is also problematic because it turns a ***measurement of signals*** into something that is itself a "signal." The claims clearly distinguish between the "cumulative intensity *signal(s)*" ('051 Patent) or "*signals*" ('170 Patent), on the one hand, and the "cumulative signal *measurement*" ('051 Patent) or "cumulative intensity *measurement*" ('170 Patent) on the other. But Bio-Rad's construction collapses them. The "cumulative signal *measurement*" is "generat[ed]" by "*measuring* the cumulative intensity signals" ('051 Patent, cl. 1, step (e)), and the "cumulative intensity *measurement*" is "generate[ed]" by "*measuring* said one or more signals" ('170 Patent, cl. 1, step (e)). By conflating a measurement of signals with the signals themselves, Bio-Rad changes the claim language in a way that introduces confusion and adds new limitations not present in the claims. Bio-Rad argues that, because the cumulative intensity measurement is based on cumulative intensity signals, that means the "'measurement' is a ***signal*** corresponding to the collection of probes that contact the analytes." Resp. Br. 12:4-6. That is a non-sequitur. Nothing about the signals that the measurement is measuring requires the measurement itself be a "signal or collection of signals," as Bio-Rad proposes. Its flawed construction should be rejected.

3. "each [of said at least 5] hybridization probe[s]" ('051 Claim 1; '170 Claim 1)

Bio-Rad's proposed construction purports to solve a problem that does not exist. Bio-Rad argues that it is necessary to construe "each hybridization probe" to mean "each collection of hybridization probes specific for a polynucleotide analyte" to avoid the misunderstanding that the claim term "probes" refers to "individual probe molecules"—a misunderstanding that Bio-Rad falsely attributes to Plaintiffs. Resp. Br. 15. Bio-Rad admits that the claim language does not recite individual molecules. *Id*. Plaintiffs agree. No one has asked the Court to construe "at least

[five/seven] probes" to mean at least five/seven molecules of a probe. No one is advocating that, when the Caltech Asserted Patents refer to the number of probes or analytes, they are talking about the number of molecules of the same probe or analyte, or that the claims refer to each molecule of analyte or probe as a different analyte or probe. The terms "probe" and "analyte" are used consistently throughout the claims, and yet Bio-Rad for some unexplained reason wants to treat the particular phrases "each hybridization probe" and "each of said at least five hybridization probes" differently from all other references to "probe" or "analyte"; namely, Bio-Rad seeks to add complexity and confusion by construing those phrases (and only those) to refer to "each *collection* of hybridization probes specific for a polynucleotide analyte." Resp. Br. 15.

This makes no sense. Bio-Rad apparently concedes, for example, that it is unnecessary to construe the phrase "at least five hybridization probes" in step (b) of claim 1 of the '170 Patent to mean "at least five collections of hybridization probes specific for a polynucleotide analytes." If the phrase "at least five collections of hybridization probes" is clear enough to merit no construction, why does "*each of said* at least five hybridization probes" need construction?[2] It is at minimum confusing to replace the phrase "hybridization probes" with "collection of hybridization probes" only when preceded by the word "each," but leave it as "hybridization probes" otherwise. That introduces a difference not present in the claim language or specification. For example, under Bio-Rad's proposal, the jury will be instructed that "each *collection* of hybridization probes" must comprise a fluorophore, but that mixture must contain "at least five hybridization *probes*." '170 Patent, cl.1, step (b). This suggests each "collection of probes" could include two or more of the five probes, so that there could be only one or two "collections of probes." A "probe" should mean a "probe" everywhere it is used in the claim, and only mischief results from interpreting "probe" to sometimes mean "collection of probes."

In its brief, Bio-Rad pivots away from the phrase "collection of probes" and to yet another

[2] Nor has Bio-Rad asked to construe "at least five polynucleotide analytes" as "at least five *collections* of polynucleotide analytes," or "each of said at least five polynucleotide analytes" to mean "each collection of polynucleotide analytes with the same polynucleotide sequence."

new phrase: "***types*** of probes." Resp. Br. 15:19-21, 16:18-22. But the claim language doesn't use the phrase "types of probes" or "types of analytes." It just uses "probes" and "analytes." Bio-Rad argues that "a skilled artisan would understand" the phrase "at least seven[/five] analytes" to means at least seven/five "different ***types*** of analytes" (as opposed to seven or five molecules of analyte), and would likewise understand the phrase "'at least [seven/five] hybridization probes' to refer to at least seven or five ***types*** of hybridization probes." Bio-Rad believes this is so clear that it hasn't even sought a construction on that point. Given that position, the terms "probe" and "analyte" are clear enough and there is no justification for confusingly introducing the concept of "type" or "collection" only when later referring to *each probe*. That will simply confuse the jury about what a "type" or "collection" of probes is and how it is different from the "at least [five/seven] probes" referred to earlier in the claims.

4. "exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes *is present* in said plurality of droplets" ('170 Claim 1)

Bio-Rad's proposed construction is an unnecessary attempt to rewrite a straightforward claim term—"is present"—in a way that makes it seem confusingly technical and introduces unnecessary hurdles for the jury. Bio-Rad fails to explain why the jury would have difficulty understanding the words "is present" in this claim term, but needs no guidance when that same term and other similar words like "presence or absence" are used elsewhere throughout the claims. Bio-Rad argues that, unless the jury is told "present" means "contacts at least one probe," the claim doesn't require that probes contact the analyte as part of identifying whether an analyte is present. Resp. Br. 17-19. It is unclear what Bio-Rad is concerned about. Bio-Rad concedes that the patent teaches how probes work and how presence or absence is determined. The claims need not recite the physical mechanics of that process for the jury to understand what it means when something "is present." Bio-Rad's attempt to interject unnecessary jargon into the claim term "is present" should be rejected.

5. "Non-degenerately," "degenerate" or "degeneracy" ('051 Claim 1; '921 Claim 4, 13, 14)

Bio-Rad says the specification uses the phrase "generally describe" to provide "one

meaning" (Resp. Br. 13) for the claim terms "degenerate" and "degeneracy," but never explains how the alleged singular meaning might be applied to both an adjective and a noun. Bio-Rad relies on *Uniloc 2017, LLC v. Paychex, Inc.*, *BMC Software, Inc. v. ServiceNow, Inc.*, and *Opal Run, LLC v. C & A Mktg., Inc.* to argue that the phrase "generally describes" constitutes an express definition. Resp. Br. 14. Those cases, which involve the phrase "generally refers to" or "may refer to," are of no help to Bio-Rad. *See* Resp. Br. 14:3-10 (quoting cases). As Plaintiffs pointed out (Op. Br. 23-24), the Caltech Asserted Patents use that same phrase—"refers to" or "generally refers to"—when providing definitions in the "Definitions" part of the specification. *See* '051 Patent, 9:58-11:44. The deviation from that "linguistic formula," and the use of the different phrase "generally *describes*," indicates that the *description* given for "degenerate" and "degeneracy" is *not* strictly definitional in the same way. *See Medicines Co. v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017). Bio-Rad fails to grapple with this difference, or the caselaw ascribing meaning to it, and provides no basis to convert "generally describes" into "means."

Bio-Rad argues that instructing the jury with the actual language used in the specification leaves these terms "with no meaning at all." Resp. Br. 13. But Bio-Rad never explains why the specification's general description of "degeneracy" and "degenerate" would not help the jury understand those terms. And Bio-Rad's concession that the language used in the specification is "open-ended" (*id.*) proves why Bio-Rad is wrong to treat it as a strict definition of two grammatically-different words. The patent's description of "degenerate" and "degeneracy" provides useful guidance to the jury; it just doesn't provide one all-purpose definition for these two claim terms.

With respect to the *opposite* concept of "non-degenerately" (an adverb), Bio-Rad never addresses how its proposed construction can or should be applied, nor does it respond to Plaintiffs' argument that doing so would be confusing and unnecessary (Op. Br. 24). Bio-Rad has thus abandoned its construction of this term.

III. CONCLUSION

For all the foregoing reasons, Bio-Rad's constructions should be rejected, and Plaintiffs' proposed constructions should be adopted where appropriate.

Dated: August 9, 2024

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

By: */s/ Amy H. Candido*

Amy H. Candido
Eric P. Tuttle

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Dated: August 9, 2024

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By: */s/ Jesse A. Salen*

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FILER'S ATTESTATION

I, Amy H. Candido, attest that all other signatories listed, and on whose behalf the filing is submitted, concur in the filing's content and have authorized the filing.

Dated: August 9, 2024

By: */s/ Amy H. Candido*

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

CHROMACODE, INC., Plaintiff and Counter-Defendant, v. BIO-RAD LABORATORIES, INC., Defendant and Counter-Plaintiff.	Case No. 5:23-cv-06360-EJD **DECLARATION OF ERIC P. TUTTLE IN SUPPORT OF PLAINTIFFS AND COUNTER-DEFENDANTS CHROMACODE, INC. AND CALIFORNIA INSTITUTE OF TECHNOLOGY'S REPLY CLAIM CONSTRUCTION BRIEF**

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I, Eric P. Tuttle, declare as follows:

1. I am a partner with the law firm Wilson Sonsini Goodrich & Rosati P.C., counsel of record for Plaintiff and Counter-Defendant ChromaCode, Inc. ("ChromaCode") in the above captioned matter. I submit this declaration in support of the Plaintiffs and Counter-Defendants ChromaCode, Inc. and California Institute of Technology's Reply Claim Construction Brief. I have personal knowledge of the facts stated herein, and if called as a witness I could and would testify competently thereto.

2. Attached hereto as **Exhibit 1** is a true and correct copy of the November 3, 2016 Response to Restriction Requirement from the file history of U.S. Patent No. 10,068,051.

3. Attached hereto as **Exhibit 2** is a true and correct copy of the November 23, 2016 Non-Final Office Action from the file history of U.S. Patent No. 10,068,051 (signed on November 17, 2016).

I declare under penalty of perjury that the foregoing is true and correct.

Dated: August 9, 2024

/s/ Eric P. Tuttle
Eric P. Tuttle

FILER'S ATTESTATION

I, Amy H. Candido, attest that Eric P. Tuttle, on whose behalf the filing is submitted, concurs in the filing's content and has authorized the filing.

Dated: August 9, 2024

By: */s/ Amy H. Candido*
Amy H. Candido

EXHIBIT 1

Electronically Filed on: November 3, 2016

PATENT
Attorney Docket No.: 38075-716.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1065
Inventor(s): Kartalov, Emil P., et al.	Examiner: Russell Scott Negin
Application No.: 14/451,876	Art Unit: 1631
Filed: August 5, 2014	Customer No.: 21971
For: SIGNAL ENCODING AND DECODING IN MULTIPLEXED BIOCHEMICAL ASSAYS	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Dear Sir:

This communication is in response to the Restriction Requirement mailed on May 12, 2016 ("Restriction Requirement"). Reconsideration of the above-referenced application is respectfully requested in view of the following remarks.

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page **8** of this paper.

AMENDMENTS TO THE CLAIMS

1. **(Withdrawn)** An assay that is capable of unambiguously detecting the presence or absence of each of at least seven (7) analytes, in any combination of presence or absence, in a single sample volume without immobilization of said analytes, physical separation of said analytes, melting curve analysis, or mass spectrometry.
2. **(Withdrawn)** The assay of claim 1, wherein each of said analytes is encoded as a value of one component of a signal.
3. **(Canceled)**
4. **(Withdrawn)** The assay of claim 2, wherein each of said analytes is encoded as at least one first value in a first component of said signal and at least one second value in a second component of said signal.
5. **(Withdrawn)** The assay of claim 2, wherein each of said analytes is encoded as a first value in a first component of said signal at each of a plurality of second values in a second component of said signal.

6.-8. **(Canceled)**

9. **(Withdrawn)** The assay of claim 4, wherein said first value is an intensity or range of intensities and said second value is a wavelength or range of wavelengths.

10.-12. **(Canceled)**

13. **(Withdrawn)** The assay of claim 2, wherein said signal is an electromagnetic signal.

14.-16. **(Canceled)**

17. **(Withdrawn)** The assay of claim 1, wherein said detecting is performed with reagents comprising hybridization probes.

18. **(Withdrawn)** The assay of claim 1, wherein said detecting is performed with a plurality of hybridization probes, comprising an identical fluorophore, wherein said plurality of hybridization probes are specific for different analytes.

19. **(Withdrawn)** The assay of claim 1, wherein said detecting is performed with a plurality of hybridization probes comprising different fluorophores, wherein said plurality of hybridization probes are specific for different analytes.

20.-21. **(Canceled)**

22. **(Withdrawn)** The assay of claim 2, wherein said signal is generated during a polymerase chain reaction.

23.-26. **(Canceled)**

27. **(Withdrawn)** The assay of claim 4, further comprising constructing a diagram.

28. **(Withdrawn)** The assay of claim 27, wherein said diagram is constructed by plotting possible combinations of said first values and said second values for positive control samples.

29. **(Withdrawn)** The assay of claim 1, wherein at least one of said analytes comprises a polynucleotide.

30.-33. **(Canceled)**

34. **(Withdrawn)** The assay of claim 1, further comprising transmitting information concerning the presence or absence of said analyte through a computer network.

35. **(Withdrawn)** The assay of claim 1, further comprising providing information concerning the presence or absence of said analyte to a health care professional, wherein the health care professional makes a clinical decision based on said information.

36. **(Canceled)**

37. **(Withdrawn)** The assay of claim 1, wherein at least one step of said assay is performed using a computer.

38. **(Withdrawn)** The assay of claim 37, wherein said computer is located on a remote server.

39. **(Withdrawn)** The assay of claim 37, wherein said computer is located on a thermal cycler.

40.-41. **(Canceled)**

42. **(Withdrawn)** The assay of claim 2, wherein said coding is innately non-degenerate.

43. **(Withdrawn)** The assay of claim 42, wherein said coding is designed to be non-degenerate by enumerating legitimate results that can be obtained from said encoding, identifying legitimate results that are degenerate, and eliminating at least one potential analyte code from

said encoding to eliminate degeneracy.

44. **(Canceled)**

45. **(Withdrawn)** The assay of claim 1, wherein said assay is an end-point assay.

46. **(Canceled)**

47. **(Withdrawn)** The assay of claim 1, wherein said assay is a liquid phase assay.

48. **(Canceled)**

49. **(Currently Amended)** A method of detecting the presence or absence of each analyte of a plurality of analytes, comprising:

    a. encoding each of said analytes as a first value of a signal, thereby generating a coding scheme, wherein each of said analytes is represented in said coding scheme by said first value, wherein said encoding is performed in a manner that reduces or eliminates degeneracy;

    b. providing a sample comprising, or potentially comprising, at least one of said analytes;

    c. contacting said sample with analyte-specific reagents that generate said first value, as represented in said coding scheme, when each of said analytes is present;

    d. cumulatively measuring said first values of said signal within said sample, thereby providing a cumulative measurement; and

    e. determining whether each of said analytes is present or absent based on said cumulative measurement and said coding scheme;
    wherein said method is capable of non-degenerately detecting the presence or absence of at least seven analytes in a single sample volume, in any combination of presence or absence.

50. **(Canceled)**

51. **(Original)** The method of claim 49, wherein said first value is an intensity or range of intensities.

52. **(Canceled)**

53. **(Previously Presented)** The method of claim 49, wherein said first value is incremented in said coding scheme to an amount greater than the sum of said preceding first values.

54. **(Canceled)**

55. **(Currently Amended)** A method of detecting the presence or absence of each analyte of a plurality of analytes, comprising:

a.[[f.]] encoding each of said analytes as at least one first value and at least one second value, wherein said first value is a value from a first component of a signal and said second value is a value from a second component of said signal, thereby generating a coding scheme, wherein each of said analytes is represented in said coding scheme by said at least one first value and said at least one second value, wherein said encoding is performed in a manner that reduces or eliminates degeneracy;

b.[[g.]] providing a sample comprising, or potentially comprising, at least one of said analytes;

c.[[h.]] contacting said sample with analyte-specific reagents that generate said at least one first value and at least one said second value, as represented in said coding scheme, when each of said analytes is present;

d.[[i.]] cumulatively measuring said first values and said second values within said sample, thereby providing a cumulative measurement; and

e.[[j.]] determining whether each of said analytes is present or absent based on said cumulative measurement and said coding scheme,

wherein, when degeneracy is eliminated, said method is capable of ~~unambiguously~~ non-degenerately detecting the presence or absence of each of at least six analytes in a single volume, in any combination of presence or absence, when each of said reagents generates only one second value.

56. **(Original)** The method of claim 55, wherein each of said analytes is encoded as a first value in a first component of said signal at each of a plurality of second values in a second component of said signal.

57.-74. **(Canceled)**

75. **(New)** The method of claim 49, wherein each of said analytes is encoded as said first value of one component of said signal.

76. **(New)** The method of claim 75, wherein each of said analytes is encoded as at least one first value in said first component of said signal and at least one second value in a second

component of said signal.

77. **(New)** The method of claim 75, wherein each of said analytes is encoded as said first value in a first component of said signal at each of a plurality of second values in a second component of said signal.
78. **(New)** The method of claim 76, wherein said first value is an intensity or range of intensities and said second value is a wavelength or range of wavelengths.
79. **(New)** The method of claim 49, wherein said signal is an electromagnetic signal.
80. **(New)** The method of claim 49, wherein said detecting is performed with reagents comprising hybridization probes.
81. **(New)** The method of claim 49, wherein said detecting is performed with a plurality of hybridization probes, comprising an identical fluorophore, wherein said plurality of hybridization probes are specific for different analytes.
82. **(New)** The method of claim 49, wherein said detecting is performed with a plurality of hybridization probes comprising different fluorophores, wherein said plurality of hybridization probes are specific for different analytes.
83. **(New)** The method of claim 49, wherein said signal is generated during a polymerase chain reaction.
84. **(New)** The method of claim 49, further comprising constructing a diagram.
85. **(New)** The method of claim 84, wherein said diagram is constructed by plotting possible combinations of said first values and said second values for positive control samples.
86. **(New)** The method of claim 49, wherein at least one of said analytes comprises a polynucleotide.
87. **(New)** The method of claim 49, further comprising transmitting information concerning the presence or absence of said analyte through a computer network.
88. **(New)** The method of claim 49, further comprising providing information concerning the presence or absence of said analyte to a health care professional, wherein the health care professional makes a clinical decision based on said information.
89. **(New)** The method of claim 49, wherein said encoding is innately non-degenerate.
90. **(New)** The method of claim 89, wherein said encoding is designed to be non-degenerate by enumerating legitimate results that can be obtained from said encoding, identifying legitimate

results that are degenerate, and eliminating at least one potential analyte code from said encoding to eliminate degeneracy.

91. **(New)** The method of claim 49, wherein said method does not comprise immobilization of said analytes.

92. **(New)** The method of claim 55, wherein said method does not comprise immobilization of said analytes.

REMARKS

Claims 1-2, 4-5, 9, 13, 17-19, 22, 27-29, 34-35, 37-39, 42-43, 45, 47, 49, 51, 53, 55, and 56 were pending prior to the entry of the above-mentioned amendments. Claims 1-2, 4-5, 9, 13, 17-19, 22, 27-29, 34-35, 37-39, 42-43, 45, and 47 are withdrawn. Claims 3, 6-8, 10-12, 14-16, 20-21, 23-26, 30-33, 36, 40-41, 44, 46, 48, 50, 52, 54, and 57-74 are canceled.

Claims 75-92 are new. Support for new claims 75-92 can be found at least in the originally filed claims and paragraphs [0003]-[0023], [00119], and [00179] of the filed specification.

Claims 49 and 55 are amended. Support for amended claims 49 and 55 can be found at least in paragraphs [0003], [0023], [0059], and [0084]-[0085] of the filed specification. Claim 55 has also been amended to correct typographical errors.

No new matter has been added. Accordingly, claims 49, 51, 53, 55-56, and 75-92 are currently pending.

Reconsideration of this application is respectfully requested in light of the following remarks.

Election/Restrictions

The Office has required an election of an invention under 35 U.S.C. § 121 to one of the following species.

I. Claims 1-2, 4-5, 9, 13, 17-19, 22, 27-29, 34-35, 37-39, 42-43, 45 and 47 drawn to an assay that does not use immobilization of analytes, separation of analytes, melting curve analysis, or mass spectrometry.

II. Claims 49, 51, 53, and 55-56 drawn to using cumulative measurements to determine the presence or absence of each analyte in a plurality of analytes.

Applicant elects, without traverse, invention II, encompassing claims 49, 51, 53, and 55-56 and new claims 75-92.

The Office is also requiring an election of a single patentably distinct species from each of the following sets of species:

I. Species A: the plurality of fluorescent probes comprise an identical fluorophore (claim 18)

II. Species B: the plurality of fluorescent probes comprise different fluorophores (claim 19)

Applicant elects, without traverse, Species A, encompassing claims 18, 49, 51, 53, and 55-56 and new claims 75-92.

Applicant reserves the right, pursuant to 35 U.S.C. § 121, to file one or more divisional applications directed to the non-elected inventions during the pendency of the present application.

Applicant respectfully submits that upon the allowance of a generic claim, Applicant shall be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or canceled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

Applicant submits that this paper fully addresses the Office Action mailed May 12, 2016. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 23-2415, Attorney Docket No. 38075-716.301.

Respectfully submitted,

Dated: November 3, 2016

By: /Andrew L. Chang/
Andrew L. Chang
Reg. No. 75,298

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EXHIBIT 2

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/451,876	08/05/2014	Emil Kartalov	38075-716.301	1065

21971 7590 11/23/2016
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EXAMINER
NEGIN, RUSSELL SCOTT

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
11/23/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 14/451,876	Applicant(s) KARTALOV ET AL.	
	Examiner Russell S. Negin	Art Unit 1631	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3 November 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

5a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *49,51,53,55,56,75-81 and 83-92* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *5 August 2014* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *See Continuation Sheet*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,5,9,13,17-19,27-29,34,35,37-39,42,43,45,47,49,51,53,55,56 and 75-92.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,2,4,5,9,13,17-19,27-29,34,35,37-39,42,43,45,47, and 82.

Continuation of Attachment(s) 2). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/2/2014; 1/25/2016; 8/12/2016.

DETAILED ACTION

Comments

The present application is being examined under the pre-AIA first to invent provisions. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Election/Restrictions

Applicant's election without traverse of Group II and Species A in the reply filed on 3 November 2016 is acknowledged.

Claims 1-2, 4-5, 9, 13, 17-19, 27-29, 34-35, 37-39, 42-43, 45, 47, and 82 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group or Species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3 November 2016.

Claims 1-2, 4-5, 9, 13, 17-19, 27-29, 34-35, 37-39, 42-43, 45, 47, 49, 51, 53, 55-56, and 75-92 are pending in the instant application.

Claims 49, 51, 53, 55-56, 75-81, and 83-92 are examined in the instant Office action.

Information Disclosure Statements

The IDSs filed on 12/2/2014, 1/25/2016, and 8/12/2016 have been considered.

Claim Rejections - 35 USC § 112(b) - Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 89 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The term "innately" in claim 89 is a relative term which renders the claim indefinite. The term "innately" is not defined by the claim, 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. It is unclear as to the metes and bounds of what makes encoding non-degenerate versus innately non-degenerate. For the purpose of examination, it is interpreted that any non-degenerate encoding is innately non-degenerate.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 49, 51, 53, 55-56, 75-81, and 83-92 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more. According to Step 1 of the 2014 Interim Subject Matter Eligibility Guidelines, claim(s) 49, 51, 53, 55-56, 75-81, and 83-92 is/are directed to methods. According to Step 2A of the 2014 Interim Subject Matter Eligibility Guidelines, claim(s) 49, 51, 53, 55-56, 75-81, and 83-92 is/are directed to the abstract idea of encoding signals in a manner that reduces or eliminates degeneracy. The signal processing is a manner of mathematical manipulation analogous to the Arrhenius equation of *Diamond v. Diehr*, 450 U.S. 175 (1981), which was also found to be abstract. The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception (i.e. Step 2B of the Guidelines) because providing samples, performing assays, and determine presence/absence patterns of analytes is routine and conventional in the prior art. This rejection has been made in view of the U.S. Supreme Court Decision in *Alice Corporation Pty. Ltd. V. CLS Bank International, et al.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 49, 51, 53, 55-56, 75-81, 84-85, and 88-92 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Nie et al. [US PGPUB 2003/0148544 A1; on IDS].

Claim 49 is drawn to a method of detecting the presence or absence of each analyte of a plurality of analytes. The method comprises encoding each of the analytes as a first value of a signal, thereby generating a coding scheme, wherein each of the analytes is represented in the coding scheme by the first value, wherein the encoding is performed in a manner that reduces or eliminates degeneracy. The method comprises providing a sample comprising at least one of said analytes. The method comprises contacting the sample with analyte-specific reagents that generate the first value, as represented in the coding scheme, when each of the analytes is present. The method comprises cumulatively measuring the first values of the signal within the sample, thereby providing a cumulative measurement. The method comprises determining whether each of the analytes is present or absent based on the cumulative measurement and the coding scheme. The method is capable of non-degenerately detecting the presence or absence of at least seven analytes in a single sample volume, in any combination of presence or absence.

The capability of "non-degenerately detecting the presence or absence of at least seven analytes in a single sample volume, in any combination of presence or absence" is interpreted to be an intended use that does not differentiate the recitations of the claims from the prior art.

Claim 55 is drawn to similar subject matter as claim 49, the additional limitation that each of the analytes corresponds to both a first value and a second value.

The document of Nie et al. studies methods of preparing multicolor quantum dot tagged beads [title]. The cover figure of Nie et al. teaches that different color quantum dots within microbeads. Each type of quantum dot emits light at a different wavelength. The histograms in the cover figure of Nie et al. illustrates how the quantum dot composition within each microbead encodes a non-degenerate spectral signature in the form of intensity versus wavelength histogram. In the cover figure of Nie et al., the quantum dots are the analytes in contact with the microbead to generate the optical wavelength used in the coding scheme. The height of each bar in each histogram represents the cumulative measurement of all of the quantum dots of a particular type within each microbead. The existence of a bar in each histogram indicates presence of a specific analyte emitting at a particular wavelength. The absence of a bar in each histogram indicates absence of a specific analyte emitting at a particular wavelength. It is interpreted that the first value corresponding to the analyte in the microbead is intensity, and the second value is the wavelength.

With regard to claims 51 and 75, the first value represents the fluorescent intensity value in the histograms of the cover figure of Nie et al. Each type of analyte in each microbead is encoded as a specific intensity value.

With regard to claim 53, the cover figure of Nie et al. comprises incrementing the first value in an amount greater than the sum of the preceding values.

With regard to claims 76-78, in the cover figure of Nie et al., it is interpreted that the first values corresponding to the analyte in the microbead are intensities, and the second values are the wavelengths.

With regard to claim 79, it is interpreted that the photons emitted from the quantum dots in the microbeads in the cover figure of Nie et al. to result in colored light comprises electromagnetic signaling.

With regard to claims 80-81, Figure 5 of Nie et al. teaches the use of hybridization probes to generate the probes wherein each combination of analytes within each microbead corresponds to a different hybridization probe. Each microbead in Figure 5 of Nie et al. comprises the three quantum dot analyte fluorophores.

With regard to claims 84-85, the cover figure of Nie et al. illustrates a diagram plotting possible combinations of first and second values for positive control samples.

With regard to claim 88, paragraph 4 of Nie et al. teaches an application of the optical signatures of Nie et al. is in clinical diagnostics.

With regard to claims 89-90, Figure 1 and 5 and Nie et al. illustrate non-degenerate, legitimate results. No results are eliminates because the data in Figures 1 and 5 of Nie et al. are non-degenerate.

With regard to claims 91-92, the analytes in Figures 1 and 5 of Nie et al. are in microbeads that are freely moving and not immobilized.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented 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. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

<u>35 U.S.C. 103 Rejection #1</u>:

Claim 86 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Nie et al. as applied to claims 49, 51, 53, 55-56, 75-81, 84-85, and 88-92 above in further view of Craig et al. [Nucleic Acids Research, volume 18, 1990, pages 2653-2660; on IDS].

Claim 86 is further limiting wherein at least one of the analytes comprises a polynucleotide.

Nie et al. teaches optical encoding of analytes in microbeads as a result of intensities and wavelengths of optical signals emitted from the analytes, as discussed above.

Nie et al. does not teach that the analytes comprise polynucleotides.

The document of Craig et al. studies ordering of cosmid clones covering Herpes simplex virus type I (HSV-I) genome for use in fingerprinting. Figure 1 of Craig et al. lists the 22 polynucleotide analytes used to encode presence/absence patterns for the purpose of differentiating genomes by hybridization.

It would have been obvious for someone of ordinary skill in the art at the time of the invention to modify the optical encoding of Nie et al. by use of the hybridization encoding of Craig et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, hybridization encoding is an alternative to optical encoding. There would have been a reasonable expectation of success in combining Nie et al. and Craig et al. because both studies are analogously applicable to using presence/absence patterns as signatures for analyte combinations.

35 U.S.C. 103 Rejection #2:

Claim 83 and 87 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Nie et al. in view of Craig et al. as applied to claims 49, 51, 53, 55-56, 75-81, 84-86, and 88-92 above in further view of Orpana et al.[WO 2010/128206 A1].

Claim 83 is further limiting wherein the signal is generated by PCR.

Claim 87 is further limiting comprising transiting information via a computer network.

Nie et al. and Craig et al. make obvious using presence/absence patterns of biomolecules in coding schemes, as discussed above.

Nie et al. and Craig et al. do not teach PCR or computer automation.

Orpana et al. studies a method, instrument, and computer program product for quantification of PCR products [title].

It would have been obvious for someone of ordinary skill in the art at the time of the invention to modify the optical encoding of Nie et al. and the hybridization encoding of Craig et al. by use of the computerized PCR of Orpana et al. wherein the motivation would have been that computer automate the analysis and PCR facilitates understanding of the experiment by amplifying the results of the experiment [title and abstract of Orpana et al.].

E-mail Communications Authorization

Per updated USPTO Internet usage policies, Applicant and/or applicant's representative is encouraged to authorize the USPTO examiner to discuss any subject

matter concerning the above application via Internet e-mail communications. See MPEP 502.03. To approve such communications, Applicant must provide written authorization for e-mail communication by submitting the following statement via EFS-Web (using PTO/SB/439) or Central Fax (571-273-8300):

> Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application by video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file.

Written authorizations submitted to the Examiner via e-mail are **NOT** proper. Written authorizations must be submitted **via EFS-Web** (using PTO/SB/439) **or Central Fax** (571-273-8300). A paper copy of e-mail correspondence will be placed in the patent application when appropriate. E-mails from the USPTO are for the sole use of the intended recipient, and may contain information subject to the confidentiality requirement set forth in 35 USC § 122. See also MPEP 502.03.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. This Examiner can normally be reached from Monday through Thursday from 10:30 am to 5 pm and variable hours on Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Peter Paras, Supervisory Patent Examiner, can be reached at (571) 272-4517.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

/Russell S. Negin/
Primary Examiner, Art Unit 1631
17 November 2016