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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Emil P. KARTALOV and examiner information for NEGIN, RUSSELL SCOTT.

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):

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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 (i.e., changing from AIA to pre-AIA) 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.

Claims 1-30 are pending and examined in the instant Office action.

Information Disclosure Statements

The IDS filed on 2/1/2024 has 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.

The following rejection is reiterated:

Claims 3 and 19 are 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 applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claims 3 and 19 recite the equation $M=C*\log_2(F+1)$ wherein M is the number of analytes, C is the number of channels, and F is the number of fluorophores. It is unclear as to the meets and bounds of M being an integer when F+1 is not a power of 2.

Claim 20 is not rejected under this statute because when F=3, F+1 is 4 (a power of 2).

Response to arguments:

Applicant's arguments filed 1 February 2024 have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill in the art would know to choose F such that M is a positive integer. This argument is not persuasive because the claims only limit F to be a positive integer, and not a positive integer such that F+1 is a power of two. Amending the claims such that M is a positive integer does not limit F+1 to be a positive integer that is a power of two.

Claim Rejections - 35 USC § 112(a) - Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection is reiterated:

Claims 3 and 19 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for providing a positive integer when $F+1$ is a power of 2, does not reasonably provide enablement for providing a positive integer when $F+1$ is not a power of 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

1. Claims 3 and 19 recite the equation $M=C*\log_2(F+1)$ wherein M is the number of analytes, C is the number of channels, and F is the number of fluorophores. It is not understood as to how M is an integer when $F+1$ is not a power of 2.

Claim 20 is not rejected under this statute because when $F=3$, $F+1$ is 4 (a power of 2).

2. The specification is silent on how to determine M (a positive integer) when $F+1$ is not a power of 2.

3. The document of Han et al. [Nature Biotechnology, volume 19, 2001, pages 631-635; on IDS] teaches a system wherein each of the numbers of fluorophores, channels, and analytes are positive integers.

4. The claims recite an equation wherein the result (number of analytes) is not always a positive integer. The claims, specification, and prior art give no guidance on

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how to determine the number of analytes when $F+1$ is not a power of 2. Consequently, it is unpredictable as to determining the number of analytes (as positive integer) when $F+1$ is not a power of 2. Such unpredictability yields UNDUE EXPERIMENTATION.

In view of the above, it is the Examiner's position that with the insufficient guidance and working examples and in view of unpredictability and the state of art, one of skill in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments:

Applicant's arguments filed 1 February 2024 have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill in the art would know to choose F such that M is a positive integer. This argument is not persuasive because the claims only limit F to be a positive integer, and not a positive integer such that $F+1$ is a power of two. Amending the claims such that M is a positive integer does not limit $F+1$ to be a positive integer that is a power of two.

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

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matter pertains. Patentability shall not be negated 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).

The following rejection is reiterated:

35 U.S.C. 103 Rejection #1:

Claims 1-2, 5-14, 17-18, 20, 22-24, 27, and 29-30 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Han et al. [Nature Biotechnology, volume 19, 2001, pages 631-635; on IDS] in view of Sagner et al. [WO 2004/087950 A2; on IDS].

Claim 1 is drawn to a system comprising a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores. The system comprises a multi-channel detector. This detector detects first, second, third, and fourth electromagnetic signals from first, second, third, and fourth wavelengths, respectively, from the sample chamber. The first, second, third, and fourth electromagnetic signals are generated by excitement of the first, second, third, and fourth fluorophores, respectively of the multiple fluorophores.

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The system comprises a processor controlled analyzer to receive, from the multi-channel detector, a cumulative signal based on the electromagnetic signals and apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of each of M analytes by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal. Each first value is an intensity or range of intensities, and each second value is a wavelength or range of wavelengths. The second values comprise the first, second, third, and fourth wavelengths, and the determination is made without mass spectrometry or melting curve analysis. The analysis requires that M is greater than the number of second values used to encode the analytes, the multi-channel detector comprises C channels, and M and C are positive integers.

Claim 2 is further limiting wherein the analysis is extended to fifth and sixth electromagnetic signals from fifth and sixth fluorophores.

Claim 20 is drawn to similar subject matter as claim 2, except claim 20 is drawn to a reaction mixture.

Claim 30 is drawn to similar subject matter as claim 20, except claim 30 is drawn to a kit.

The document of Han et al. studies quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules [title]. Figure 1 on page 632 of Han et al. teaches that there are ten distinguishable colors of quantum dots that emit light at the ten listed wavelengths. Figures 5 and 6 of Han et al. use microbeads and hybridization to detect the presence of three of the quantum dot fluorophores. The spectral data of Figures 5 and 6 of Han et al. illustrates a matrix of intensity values of the fluorophores

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as a function of wavelength of light. The number of analytes in Figure 1 of Han et al. (10) is greater than the numbers of second values in each of Figures 5 and 6 Han et al. (3).

Han et al. does not teach all of the channel/apparatus limitations of the claims.

The document of Sagner et al. studies an improved system for multicolor real-time PCR [title]. The cover figure of Sagner et al. illustrates the detection unit with six different detectors that measure signals at six different channels of wavelength. Page 9 of Sagner et al. lists the fluorophores. Page 10 of Sagner et al. lists wavelengths analyzed.

With regard to claim 5, Figures 5-6 of Han et al. illustrates blue, green, and red fluorophores.

With regard to claims 6 and 22, page 9 of Sagner et al. teaches use of the cyanine fluorophores.

With regard to claims 7-14, 17-18, 23-24, and 27, Figures 5-6 of Han et al. illustrates blue, green, and red fluorophores attached to hybridization probes. The spectral data of Figures 5-6 of Han et al. illustrate plots of the first and second values. Figure 1 of Han et al. lists the wavelengths of all ten possible quantum dots. The cover figure of Sagner et al. lists the wavelengths of each of the six channels/filters/photodetectors where blue, green, and red are a subset of the colors that are detected.

With regard to claim 29, Figures 5-6 of Han et al. illustrate different hybridization probes at different concentrations in a mixture.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quantum dot analysis of Han et al. by use of the apparatus to analyze fluorophores of Sagner et al. wherein the motivation would have been that Sagner et al. teaches additional equipment to facilitate analysis of spectral data [cover figure of Sagner et al.]. There would have been a reasonable expectation of success to combine Han et al. and Sagner et al. because both studies are analogously applicable to analyzing spectral data relates to labeled biomolecules, either by quantum dots or fluorophores.

Response to arguments:

Applicant's arguments filed 1 February 2024 have been fully considered but they are not persuasive.

Applicant argues that the analysis of Han et al. does not apply to a cumulative signal. Absent a limiting description of the term "cumulative" in the disclosure, Han et al. is interpreted to measure the cumulative signal of a single bead.

Applicant argues that Han et al. involves immobilization of the particles. However, claims 1 and 19 do not exclude immobilization. In addition, in this obviousness prior art rejection, Sagner et al. does not involve immobilization.

The following rejection is reiterated:

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

Claims 15-16, 21, 25-26, and 28 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Han et al. in view of Sagner et al. as applied to claims 1-2, 5-14, 17-18, 20, 22-24, 27, and 29-30 above, in further view of Vogelstein et al. [PNAS, volume 96, 1999, pages 9236-9241; on IDS].

Claims 15 and 21 are further limiting wherein the sample comprises a droplet. Claim 16 is further limiting wherein the droplets are housed in a dynamic array.

Claims 25-26 constrain ratios of probe concentrations and hybridization procedures.

Claim 28 is further limiting wherein a probe comprises a quencher.

Han et al. and Sagner et al. make obvious analyze of labeled biomolecules using a multichannel apparatus, as discussed above.

Han et al. and Sagner et al. do not teach the droplet, array, ratio of concentrations, quenchers, and hybridization procedures in the instantly rejected claims.

The document of Vogelstein et al. studies digital PCR [title]. Figure 1 on page 9237 of Vogelstein et al. illustrates droplets in a dynamic array and probe attached to a quencher. The Methods section on pages 9236-9237 of Vogelstein et al. teaches the hybridization procedures. A subset of the cells in Figure 5 on pages 9240 of Vogelstein et al. illustrates the recited ratios of hybridization probes.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quantum dot analysis of Han et al. and the apparatus to analyze fluorophores of Sagner et al. by use of the digital PCR of Vogelstein et al. wherein the motivation would have been that Sagner et al. teaches additional empirical techniques to facilitate analysis of experimental data [Figure 1 of Vogelstein et al.]. There would have been a reasonable expectation of success to combine Han et al., Sagner et al., and Vogelstein et al. because all three studies are analogously applicable to analyzing spectral data relates to labeled biomolecules, either by quantum dots or fluorophores.

Response to arguments:

Applicant's arguments filed 1 February 2024 have been fully considered but they are not persuasive.

Applicant argue that the prior art does not teach four or more electromagnetic signals from four or more fluorophores. This argument is not persuasive because Figure 1 on page 632 of Han et al. teaches that there are ten distinguishable colors of quantum dots that emit light at the ten listed wavelengths.

Applicant reiterates the argument that the analysis of Han et al. does not apply to a cumulative signal. Absent a limiting description of the term "cumulative" in the disclosure, Han et al. is interpreted to measure the cumulative signal of a single bead. Assuming (*en arguendo*) that a cumulative signal relies on a plurality of signals from different particles, the analysis in Figure 5 of Vogelstein et al. relies on the cumulative signal of the relative combination of a red and green set of fluorophores.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Double Patenting Rejection #1:

Claim 19 is rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 8,838,394 B2 [on IDS] in view of Sagner et al.

Both claims are drawn to detecting the presence and absence of analytes using signals from fluorophores. However, the claim of '394 does not teach all of the apparatus limitations of the instantly rejected claim.

The document of Sagner et al. studies an improved system for multicolor real-time PCR [title]. The cover figure of Sagner et al. illustrates the detection unit with six different detectors that measure signals at six different channels of wavelength.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fluorophore analysis of the claim of '394 by use of the apparatus to analyze fluorophores of Sagner et al. wherein the motivation would have been that Sagner et al. teaches additional equipment to facilitate analysis of spectral data [cover figure of Sagner et al.]. There would have been a reasonable expectation of success to combine the claim of '394 and Sagner et al. because both studies are analogously applicable to analyzing spectral data relates to fluorophore labeled biomolecules.

Response to arguments:

Applicant requests that the double patenting rejections be held in abeyance.

Double Patenting Rejection #2:

Claim [1 or 20] is rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 10,068,051 B2 [on IDS] in view of Sagner et al.

Both sets of claims are drawn to detecting the presence and absence of analytes using signals from fluorophores. However, the claim of '051 does not teach all of the apparatus limitations of the instantly rejected claims.

The document of Sagner et al. studies an improved system for multicolor real-time PCR [title]. The cover figure of Sagner et al. illustrates the detection unit with six different detectors that measure signals at six different channels of wavelength.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fluorophore analysis of the claim of '051 by use of the apparatus to analyze fluorophores of Sagner et al. wherein the motivation would have been that Sagner et al. teaches additional equipment to facilitate analysis of spectral data [cover figure of Sagner et al.]. There would have been a reasonable expectation of success to combine the claim of '051 and Sagner et al. because both studies are analogously applicable to analyzing spectral data relates to fluorophore labeled biomolecules.

Response to arguments:

Applicant requests that the double patenting rejections be held in abeyance.

Double Patenting Rejection #3:

Claims [1, 15, 20, or 21] are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 10,770,170 B2 [on IDS] in view of Sagner et al.

Both sets of claims are drawn to detecting the presence and absence of analytes using signals from fluorophores. However, the claim of '170 does not teach all of the apparatus limitations of the instantly rejected claims.

The document of Sagner et al. studies an improved system for multicolor real-time PCR [title]. The cover figure of Sagner et al. illustrates the detection unit with six different detectors that measure signals at six different channels of wavelength.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fluorophore analysis of the claim of '170 by use of the apparatus to analyze fluorophores of Sagner et al. wherein the motivation would have been that Sagner et al. teaches additional equipment to facilitate analysis of spectral data [cover figure of Sagner et al.]. There would have been a reasonable expectation of success to combine the claim of '170 and Sagner et al. because both studies are analogously applicable to analyzing spectral data relates to fluorophore labeled biomolecules.

Response to arguments:

Applicant requests that the double patenting rejections be held in abeyance.

Double Patenting Rejection #4:

Claim [1 or 20] is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 22 of copending Application No. 16/937,464 in view of Sagner et al.

Application '464 has been issued.

Both sets of claims are analogously drawn to detecting the presence and absence of analytes using signals from fluorophores. However, the claim of '464 does not teach all of the apparatus limitations of the instantly rejected claims.

The document of Sagner et al. studies an improved system for multicolor real-time PCR [title]. The cover figure of Sagner et al. illustrates the detection unit with six different detectors that measure signals at six different channels of wavelength.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fluorophore analysis of the claim of '464 by use of the apparatus to analyze fluorophores of Sagner et al. wherein the motivation would have been that Sagner et al. teaches additional equipment to facilitate analysis of spectral data [cover figure of Sagner et al.]. There would have been a reasonable expectation of success to combine the claim of '464 and Sagner et al. because both studies are analogously applicable to analyzing spectral data relates to fluorophore labeled biomolecules.

Response to arguments:

Applicant requests that the double patenting rejections be held in abeyance.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The prior art does not teach the equation in the claim, and more specifically, the prior art does not teach the equation with the specific values of M, C, and F.

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.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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 8 am to 3 pm and variable hours on Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Larry Riggs, Supervisory Patent Examiner, can be reached at (571) 270-3062.

/RUSSELL S NEGIN/
Primary Examiner, Art Unit 1672
3 February 2024