

REMARKS

I. Status of the Application

Claims 9-38 were pending prior to entry of the amendments. Claim 18 has been cancelled herein without prejudice or disclaimer. Claims 9-17 and 19-38 have been amended. New claims 39-45 have been added. Support for the claim amendments can be found in the claims and specification of the originally filed application. No new matter is added by any of these amendments. Accordingly, upon entry, claims 9-17 and 19-45 will be pending.

Reconsideration and allowance of this application are respectfully requested in light of the abovementioned amendments and the following remarks.

II. Obviousness-type Double Patenting

Claims 9-38 stand rejected under obviousness-type double patenting over claims 18-30 of U.S. Patent No. 11,118,220 in view of U.S. Patent Publication No. 2011/0216953 (Callahan). Without conceding in the basis of rejection, Applicant submits a terminal disclaimer over this patent. In view of the terminal disclaimer, the Applicant believes that the rejection has been rendered moot. The Applicant respectfully requests that the rejection of claims 9-38 be withdrawn.

Claims 9-38 stand rejected under obviousness-type double patenting over claims 1-14 of U.S. Patent No. 10,266,888 in view of Callahan. Without conceding in the basis of rejection, Applicant submits a terminal disclaimer over this patent. In view of the terminal disclaimer, the Applicant believes that the rejection has been rendered moot. The Applicant respectfully requests that the rejection of claims 9-38 be withdrawn.

III. Claim Objections

Claim 30 stands objected for lacking a connecting term. Without conceding in the basis

of the objection, Applicant has amended claim 30 to recite “wherein said light source comprises one or more lasers.” Applicant respectfully submits that the objection of claim 30 is overcome, and respectfully requests that the objection be withdrawn.

IV. Claim Rejections - 35 U.S.C. § 103

A. Claims 9 and 14-38 are not obvious over Keller in view of Callahan

Claims 9 and 14-38 stand rejected under 35 U.S.C. § 103 over U.S. Patent Publication No. 2015/0098126 (Keller) in view of Callahan.

Without conceding in the basis of rejection and solely to expedite prosecution of this application, Applicant has amended claim 9 to further clarify certain differences between the claimed subject matter and the cited art. Applicant submits that claim 9 is not obvious over the asserted combination of Keller and Callahan, because these references, alone or in any combination, do not meet all of the elements of claim 9.

Nothing in Keller teaches or discloses “at least one processor to perform a method comprising: determining a plurality of optically-encoded signals from a plurality of light signals, wherein said plurality of light signals is obtained from a plurality of read-out cycles, wherein said plurality of optically-encoded signals is associated with one or more nucleic acid molecules within said volume; and determining three-dimensional positional information of said one or more nucleic acid molecules using said plurality of optically-encoded signals,” as is recited in claim 9.

Callahan does not cure the above-mentioned deficiencies of Keller.

Accordingly, Applicant respectfully requests that the § 103 rejection of claim 9 be withdrawn.

Claims 14-17 and 19-38 depend from and include all of the elements of claim 9, and recite additional elements of particular advantage and utility. The asserted combination of Keller

and Callahan does not meet all of the elements of claim 9, much less the combination of elements of claims 14-17 and 19-38. Accordingly, Applicant respectfully requests that the §103 rejections of claims 14-17 and 19-38 also be withdrawn.

Without conceding in the basis of rejection, Applicant submits that the § 103 rejection of claim 18 is moot in view of the cancellation of this claim.

B. Claims 10-13 are not obvious over Keller in view of Callahan and further in view of Frisen

Claims 10-13 stand rejected under 35 U.S.C. § 103 over Keller in view of Callahan and further in view of U.S. Patent Publication No. 2019/0203275 (Frisen).

Without conceding in the basis of rejection, Applicant submits that claim 103 is not obvious over the asserted combination of Keller, Callahan, and Frisen for at least the reason that this claim depends from and includes all of the elements of claim 9, and recite additional elements of particular advantage and utility. Keller does not teach or disclose all of the elements of claim 9, much less the combination of claims 10-13, and Callahan and Frisen do not cure the abovementioned deficiencies of Keller.

Accordingly, Applicant respectfully requests that the §103 rejection of claims 10-13 be withdrawn.

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.

V. Conclusion

Having addressed all outstanding issues, Applicant respectfully requests reconsideration and allowance of this case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below. The Commissioner is authorized to apply any additional charges or credits to Deposit Account No. 19-0733.

Respectfully submitted,

Dated: June 3, 2022

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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Evan R. Daugharthy	)	Examiner: David C. Thomas
	)	
Serial No.: 17/395,534	)	Art Unit: 1637
	)	
Filed: August 6, 2021	)	Conf. No.: 5147
	)	
Title: Method and Apparatus for Volumetric Imaging	)	
of a Three-Dimensional Nucleic Acid	)	
Containing Matrix	)	

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

AMENDMENT AND RESPONSE

Dear Commissioner:

This is in response to the non-final office action dated March 4, 2022. Kindly reconsider the above-referenced application in view of the following amendments and remarks. The Commissioner is hereby authorized to charge such extension fee or credit any overpayment of fees for this submission to Deposit Account No. 19-0733.

Amendments to the Claims are reflected in the Listing of Claims, which begin at page 2 of this paper.

Remarks begin at page 10 of this paper.

Amendments to the Claims

The following claim listing replaces all prior claim listings in the subject application.

Listing of Claims:

1. – 8. (Cancelled)

9. (Currently Amended) A system device, comprising:

(a) a stage₁ comprising:

(i) a sample holder, ~~wherein said sample holder is configured to receive a~~ ₁ ~~[[solid]]~~ substrate comprising a ~~biological sample having a volume,~~

(ii) a temperature control heating or cooling apparatus ~~programmable for a time and temperature parameter, wherein said heating or cooling apparatus is operatively coupled operationally connected to~~ said sample holder₁; ~~[[,]]~~ and

(iii) an XY multi-axis motion control system ~~programmable for XY motion control of said stage;~~

(b) a fluidics system ~~comprising configured to dispense one or more reagents to said sample holder, wherein said fluidics system comprises:~~

(i) one or more reservoirs configured to ~~for containing~~ contain ₁ ~~[[said]]~~ one or more fluid reagents; ~~and~~

(ii) a ~~fluidics~~ fluid dispenser operationally coupled to a pump, which pump is configured to dispense provide said one or more fluid reagents from said one or more reservoirs ₁ ~~[[into]]~~ to said sample holder₁; ~~wherein said fluidics dispenser is fluidically connected to said one or more reservoirs;~~

~~—————~~ (iii) a pump that facilitates the dispensation of a programmed volume of fluid from at least one reservoir of said one or more reservoirs to said sample holder, and

(c) an optical system ~~configured for volumetric imaging of said biological sample, wherein said optical system comprises~~ comprising:

(i) an objective₁; ~~[[,]]~~

(ii) a ~~Z-axis motion control system operatively connected to one or more components~~

of said optical system, wherein said Z-axis motion control system is configured for Z-motion of an objective focal plane through said biological sample,

————— (iii) ~~one or more light source sources~~, wherein each light source of said one or more light sources is configured to deliver light to said ~~biological sample~~ volume; [[.]] and

[[(iv)]] (iii) one or more detectors configured to receive light signals from said volume; and positioned in light receiving communication with said sample holder, wherein said one or more detectors receives light intensity signals which are processed into a three dimensional volumetric image of said biological sample

(d) a Z-axis motion control system configured for Z-motion of an objective focal plane through said volume; and

(e) a computing system comprising at least one computer readable storage medium having program instructions stored thereon, which program instructions are executable by at least one processor of said computing system to cause said at least one processor to perform a method comprising:

determining a plurality of optically-encoded signals from a plurality of light signals, wherein said plurality of light signals is obtained from a plurality of read-out cycles, wherein said plurality of optically-encoded signals is associated with one or more nucleic acid molecules within said volume; and

determining three-dimensional positional information of said one or more nucleic acid molecules using said plurality of optically-encoded signals.

10. (Currently Amended) The ~~device system~~ of claim 9, wherein said [[solid]] substrate comprises [[is]] a flow cell.

11. (Currently Amended) The ~~system device~~ of claim 10, wherein said flow cell is a closed flow cell.

12. (Currently Amended) The ~~system device~~ of claim 11, wherein said closed flow cell comprises a fluid inlet and a fluid outlet, and wherein said fluid inlet is fluidically coupled to ~~comprises~~ said ~~fluidies fluid~~ dispenser.

13. (Currently Amended) The system~~device~~ of claim 10, wherein said flow cell is an open flow cell.

14. (Currently Amended) The system~~device~~ of claim 9, wherein said objective is a water immersion objective.

15. (Currently Amended) The system~~device~~ of claim 9, wherein said objective is a water dipping objective.

16. (Currently Amended) The system~~device~~ of claim 9, wherein said ~~heating or said cooling~~temperature control apparatus comprises a heat sink or a Peltier element.

17. (Currently Amended) The system~~device~~ of claim 9, ~~wherein said heating or said cooling apparatus comprises a temperature sensor for providing temperature feedback to a~~further comprising thermal control system.

18. (Cancelled)

19. (Currently Amended) The system~~device~~ of claim 9, wherein said pump is a syringe pump.

20. (Currently Amended) The system~~device~~ of claim 9, wherein said fluidics system further comprises one or more valves downstream of said one or more reservoirs and upstream of said ~~fluidics~~fluid dispenser, wherein, upon actuation, said one or more valves facilitate dispensation of ~~said programmed volume of~~ fluid to said sample holder.

21. (Currently Amended) The system~~device~~ of claim 20, wherein said one or more valves comprise a rotary valve.

22. (Currently Amended) The ~~system~~device of claim 20, wherein said one or more valves comprise a solenoid valve or a microfluidic valve.

23. (Currently Amended) The ~~system~~device of claim 13, wherein said fluidics system further comprises an aspiration system ~~configured to remove liquid from said open flow cell, wherein said aspiration system comprises comprising: (1) an aspiration tube that removes liquid~~configured to remove fluid from said open flow cell and a ~~pump or vacuum~~pressure source operatively coupled to said aspiration tube.

24. (Currently Amended) The ~~system~~device of claim 23, wherein said aspiration system ~~further comprises a motor~~ tube is operatively coupled to ~~a motor~~said aspiration tube, wherein said motor is configured to adjust a motion axis of said aspiration tube to control an interface between said aspiration tube and said open flow cell.

25. (Currently Amended) The ~~system~~device of claim 24, wherein said motor is a stepper motor.

26. (Currently Amended) The ~~system~~device of claim 9, wherein said Z-axis motion control system comprises a Z-axis linear motor configured for Z motion of said objective focal plane through said ~~biological sample~~volume.

27. (Currently Amended) The ~~system~~device of claim 26, further comprising a linear encoder configured to provide Z motion feedback to said Z-axis linear motor.

28. (Currently Amended) The ~~system~~device of claim 9, further comprising an objective wetting apparatus.

29. (Currently Amended) The ~~system~~device of claim 9, wherein said light source comprises one or more light emitting diodes (LEDs).

30. (Currently Amended) The systemdevice of claim 9, wherein said light source comprises one or more lasers.

31. (Currently Amended) The systemdevice of claim 9, wherein said optical system further comprises ~~one or more emission filters and one or more excitation filters~~ configured to selectively filter one or more ~~for directing certain wavelengths of light from said one or more light sources to said volume within said optical system.~~

32. (Currently Amended) The systemdevice of claim 31, wherein at least one excitation filter of said one or more excitation filters ~~[[are]]~~ is configured to selectively filter ~~provide~~ light having a wavelength of about 480 nm, about 530 nm, about 590 nm, or about 640 nm from said one or more light sources to said ~~biological sample~~ volume.

33. (Currently Amended) The systemdevice of claim ~~[[31]]~~9, wherein said optical system further comprises one or more emission filters ~~[[are]]~~ configured to ~~provide~~ selectively filter one or more wavelengths of light emitted from said volume ~~having a wavelength of about 510 nm, about 570 nm, about 620 nm, or about 680 nm~~ to said one or more detectors.

34. (Currently Amended) The systemdevice of claim 9, wherein said optical system is mechanically, electrically, or electromechanically coupled ~~[[with]]~~ to a controller system configured to synchronize one or more imaging events within said systemdevice.

35. (Currently Amended) The systemdevice of claim 9, ~~where said device~~ comprises ~~further comprising~~ a vibration control rigid foundation.

36. (Currently Amended) The systemdevice of claim 9, further comprising, ~~one or more microprocessors with software for~~ a fluidics controller operatively coupled to said fluid dispenser and configured to automate or control ~~automating or controlling said dispensation of said one or more fluid reagents [[into]]~~ to said sample holder.

37. (Currently Amended) The ~~system~~device of claim ~~[[9]]17~~, ~~further comprising, one or more microprocessors with software for automating or controlling said time and temperature parameter of said heating or cooling apparatus~~wherein said temperature control apparatus further comprises a temperature sensor configured to provide a feedback signal to said thermal control system.

38. (Currently Amended) The ~~device~~system of claim ~~[[9]]33~~, ~~wherein at least one of said one or more emission filters is configured to selectively filter light having a wavelength of about 510 nm, about 570 nm, about 620 nm, or about 680 nm to said one or more detectors from said volume to said one or more detectors~~further comprising, one or more microprocessors with software for automating or controlling image detection and acquisition of said optical system.

39. (New) The system of claim 9, wherein said one or more light sources comprises two or more light sources, wherein each light source of said two or more light sources is configured to excite fluorescence in a unique color channel.

40. (New) The system of claim 39, wherein each optically-encoded signal of said plurality of optically-encoded signals comprises at least one of said unique color channels.

41. (New) The system of claim 9, wherein at least one of the plurality of optically-encoded signals comprises two or more colors detected in series.

42. (New) The system of claim 39, wherein said two or more light sources comprise four light sources.

43. (New) The system of claim 9, wherein said optical system is configured for wide-field microscopy.

44. (New) The system of claim 9, wherein a numerical aperture of said objective is about 1.0.

45. (New) A system comprising:

- (a) a stage comprising:
 - (i) a sample holder configured to receive a substrate comprising a sample having a volume;
 - (ii) a temperature control apparatus operatively coupled to said sample holder; and
 - (iii) an XY motion control system;
- (b) a fluidics system comprising:
 - (i) one or more reservoirs configured to contain one or more fluid reagents; and
 - (ii) a fluid dispenser operationally coupled to a pump, which pump is configured to provide said one or more fluid reagents from said one or more reservoirs to said sample holder; and
- (c) an optical system comprising:
 - (i) an objective;
 - (ii) two or more light sources, wherein each light source of said two or more light sources is configured to deliver light to said volume, wherein said two or more light sources are configured to emit two or more colors of light; and
 - (iii) one or more detectors configured to receive light signals from said volume;
- (d) a Z-axis motion control system configured for Z-motion of an objective focal plane through said volume; and
- (e) a computing system comprising at least one computer readable storage medium having program instructions stored thereon, which program instructions are executable by at least one processor of said computing system to cause said at least one processor to perform a method comprising:
 - receiving a plurality of images of at least a portion of said volume from a plurality of read-out cycles, wherein said plurality of images comprises a plurality of light signals received from said volume during said plurality of readout cycles, wherein said plurality of light signals is associated with one or more nucleic acid molecules within said volume, wherein each light signal of said plurality of light signals has a three-dimensional spatial position within said volume;

determining a plurality of optically-encoded signals from said plurality of light signals obtained from said plurality of read-out cycles, wherein each optically-encoded signal is associated with a nucleic acid molecule of said one or more nucleic acid molecules, wherein said plurality of optically-encoded signals comprises said two or more colors of light detected by said one or more detectors in series;

identifying said one or more nucleic acid molecules based on said plurality of optically-encoded signals; and

determining three-dimensional positional information of said one or more nucleic acid molecules.