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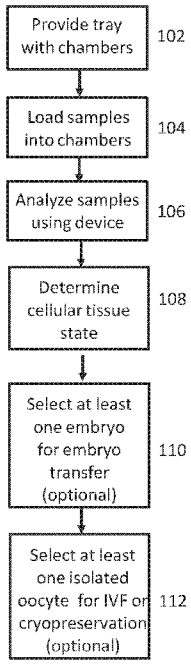
(54) Title: CELLULAR TISSUE ANALYSIS METHOD AND DEVICE

Fig. 1



(57) Abstract: A system for analyzing samples, for example for IVF, including: a tray comprising at least two chambers shaped and sized to store biological samples, each of said at least two chambers is configured to hold a single sample; an analyzer, comprising: a tray holder, shaped and sized to hold said tray; an identification (ID) reader configured to read one or more ID codes associated with said tray and/or with one or more samples in said tray; a memory; a control circuitry electrically connected to said ID reader, wherein said control circuitry is configured to identify said tray or said one or more samples in said tray according to signals received from said ID reader and one or more indications stored in said memory.

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CELLULAR TISSUE ANALYSIS METHOD AND DEVICE

RELATED APPLICATION

This application claims the benefit of priority under 35 USC §119(e) of U.S. Provisional Patent Application No. 62/714,806 filed 6 August 2018, the contents of which are incorporated herein by reference in their entirety.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a device and method for analyzing cellular tissue and, more particularly, but not exclusively, to a device and methods for analyzing samples related to in-vitro fertilization (IVF)-related cellular tissue.

SUMMARY OF THE INVENTION

The following describe some examples of embodiments of the invention. Other embodiments are within the scope of the description, including embodiments in which only some of the features from one example are used.

Example 1. A method for scoring in-vitro fertilization (IVF) related cellular tissue, comprising:

loading a tray having a plurality of chambers into a measuring device, wherein said tray comprises one or more samples related to a selected IVF-related cellular tissue;

automatically measuring values of at least one parameter in said one or more samples in said tray;

scoring said IVF-related cellular tissue based on results of said automatically measuring.

Example 2. A method according to example 1, comprising:

identifying said one or more samples after said loading.

Example 3. A method according to any one of examples 1 or 2, wherein said loading comprises loading a tray comprising said one or more samples and at least one reference sample into said measuring device and wherein said measuring comprises measuring values of said at least one parameter in said at least one reference sample.

Example 4. A method according to example 3, comprising calibrating said measured values of said at least one parameter to said measured values of said at least one reference sample.

Example 5. A method according to any one of the previous examples, wherein said IVF-related cellular tissue comprises an in-vitro cultured oocyte.

Example 6. A method according to example 5, wherein said one or more samples comprise follicular fluid (FF).

Example 7. A method according to any one of examples 5 or 6, comprising:

selecting at least one in-vitro cultured oocyte for cryopreservation and/or at least one in-vitro cultured oocyte for IVF based on the results of said scoring.

Example 8. A method according to any one of examples 1 to 4, wherein said IVF-related cellular tissue comprises an in-vitro cultured embryo.

Example 9. A method according to example 8, wherein said one or more samples comprise culture media samples.

Example 10. A method according to example 9, comprising:

selecting an in-vitro cultured embryo for embryo transfer based on the results of said scoring.

Example 11. A method according to any one of the previous examples, wherein said automatically measuring comprises automatically measuring values of at least one parameter related to oxidative state.

Example 12. A method according to example 11, comprising:

determining an oxidative state of said IVF-related cellular tissue based on said automatically measuring, and wherein said scoring comprises scoring said IVF-related cellular tissue according to said determined oxidative state.

Example 13. A method according to any one of the previous examples, comprising:

drying said one or more samples prior to said measuring.

Example 14. A method according to example 13, comprising:

heating said dried samples prior to and/or during said measuring.

Example 15. A method according to example 14, wherein said measuring comprises counting photons released from said dried samples during and/or after said heating.

Example 16. A method according to any one of the previous examples, wherein said one or more samples are one or more liquid samples.

Example 17. A method according to example 16, wherein said one or more liquid samples comprise tissues in suspension.

Example 18. A method according to any one of the previous examples wherein said one or more samples comprises at least two samples.

Example 19. A method according to example 1, comprising calculating, based on said scoring, a survival rate of a cryopreserved embryo to undergo freezing and thawing.

Example 20. A system for analyzing samples, comprising:

a tray comprising at least two chambers shaped and sized to store biological samples, each of said at least two chambers is configured to hold a single sample;

an analyzer, comprising:

a tray holder, shaped and sized to hold said tray;

an identification (ID) reader configured to read one or more ID codes associated with said tray and/or with one or more samples in said tray;

a memory;

a control circuitry electrically connected to said ID reader, wherein said control circuitry is configured to identify said tray or said one or more samples in said tray according to signals received from said ID reader and one or more indications stored in said memory.

Example 21. A system according to example 20, wherein said analyzer comprises an optical sensor configured to count photons emitted from said one or more samples in said chambers.

Example 22. A system according to any one of examples 20 or 21, wherein said analyzer comprises a vacuum assembly configured to apply vacuum on said one or more samples in said at least two chambers, sufficient to dry said biological samples.

Example 23. A system according to example 22, wherein said vacuum assembly comprises an adaptor which is shaped and sized to separately attach an opening of said vacuum assembly around each chamber of said tray.

Example 24. A system according to any one of examples 20 to 23, wherein said analyzer comprises at least two temperature sensors connected to said control circuitry.

Example 25. A system according to example 24, wherein said analyzer comprises a heater electrically connected to said control circuitry, wherein said heater is configured to heat at least a base layer of said chambers.

Example 26. A system according to example 25, wherein said heater is shaped and sized to match a surface of said base layer.

Example 27. A system according to example 25, wherein at least one temperature sensor of said at least two temperature sensors is configured to measure temperature levels of said chamber through an opening in said heater.

Example 28. A system according to example 27, wherein at least one temperature sensor of said at least two temperature sensors is configured to measure temperature levels of said heater.

Example 29. A system according to any one of examples 20 to 28, wherein said analyzer comprises a user interface electrically connected to said control circuitry, wherein said user interface is configured to deliver an alert signal to a user of said system.

Example 30. A system according to example 29, wherein said control circuitry signals said user interface to deliver said alert signal if said read ID code does not match said stored one or more indications.

Example 31. A system according to any one of examples 29 or 30, wherein said user interface is configured to receive sample and/or tray identification input from a user of said system.

Example 32. A system according to any one of examples 20 to 31, wherein said one or more samples comprise a FF sample and/or a culture media sample.

Example 33. A method for validating an ID of a sample and/or a tray, comprising:

loading a tray having a plurality of chambers into a measuring device, wherein said tray comprises one or more samples related to a selected IVF-related cellular tissue;

reading at least one ID code associated with said one or more samples and/or with said tray;

validating an ID of said one or more samples and/or said tray based on said read ID code and on one or more indications stored in a memory of said measuring device.

Example 34. A method according to example 33, comprising:

delivering an alert signal if said read ID code does not match said on or more indications stored in said memory.

Example 35. A method according to any one of examples 33 or 34, comprising:

removing said tray from said measuring device if said read ID code does not match said one or more indications stored in said memory.

Example 36. A method according to any one of examples 33 to 35, wherein said one or more samples are one or more liquid samples.

Example 37. A method for selecting one or more chambers of a tray used for optical analysis of biological samples within the one or more chambers, comprising:

providing one or more chambers shaped and sized to hold a sample;

heating said one or more chambers to a selected temperature value;

measuring photon emission from said one or more chambers in a timed relationship to said heating;

selecting a chamber based on the results of said measuring;

assembling said selected chamber in a tray comprising a plurality of chambers.

Example 38. A method according to example 37, wherein said selecting comprises discarding a chamber of said tray whose measured photon emission is higher than a predetermined value according to said measuring.

Example 39. A method according to any one of examples 37 or 38, wherein said selecting comprises treating said chamber if said measured photon emission is higher than a predetermined value according to said measuring.

Example 40. A method according to any one of examples 37 to 39, wherein said predetermined value comprises photon counts per second (CPS) higher than 40.

Example 41. A method according to any one of examples 37 to 39, wherein said predetermined value comprises photon counts per second (CPS) higher than 30.

Example 42. A method according to any one of examples 37 to 41, wherein said one or more chambers are made at least partly from Aluminum or Aluminum-containing alloy.

Example 43. A method according to any one of examples 37 to 42, wherein said heating comprises heating said one or more chambers to a temperature higher than 50 Celsius degrees.

Example 44. A system for analyzing samples, comprising: a tray defining at least one chamber in which a cuvette containing a biological sample is received; an analyzer, comprising: a tray holder, shaped and sized to hold said tray; a vacuum assembly which applies vacuum on said sample, sufficient to dry said biological sample; said vacuum assembly comprising a seal shaped and sized to seal an interface between said cuvette and said vacuum assembly.

Example 45. A system according to example 44, wherein said seal is configured to maintain said cuvette inside said chamber of said tray under a vacuum of between 1-5 mbar applied by said vacuum assembly distally in a direction of said cuvette.

Example 46. A system for analyzing samples, comprising: a tray defining at least one chamber in which a cuvette containing a biological sample is received; an analyzer, comprising: an optical sensor configured to detect emitted light; a tray holder, shaped and sized to hold said tray with respect to said optical sensor such that light emitted by said sample is detected by said optical sensor; and a heater comprising a surface area of between 80%-120% of a bottom surface area of said cuvette, said heater aligned beneath said bottom surface of said cuvette.

Example 47. A system according to example 46, wherein said surface of said heater is circular and wherein a diameter of said heater is between 80%-120% a diameter of said bottom surface of said cuvette.

Example 48. A system according to example 46, wherein said analyzer comprises a shutter assembly for controlling the passing of light to said optical sensor, said shutter assembly including an aperture shaped and sized to match said bottom surface of said cuvette; said aperture

positioned to overlap said bottom surface of said cuvette on a plane parallel to a plane of said bottom surface of said cuvette.

Example 49. A system according to example 46, wherein a layer which blocks the passage of light emitted from the material of the tray is layered on a top surface of said tray, without covering said cuvette.

Example 50. A method for evaluating embryo quality or oocyte quality by detection of photon emission, comprising:

providing a sample comprising biological fluid associated with an in-vitro grown embryo or with an in-vitro cultured oocyte; analyzing said sample by detecting photon emission from said sample to measure at least one of oxidative stress parameters and oxidative stress-derived factors in said sample; scoring said sample based on said analyzing; and evaluating embryo quality or oocyte quality according to said scoring.

Example 51. A method according to example 50, wherein said detection of photon emission is by Thermochemiluminescence (TCL) techniques.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

As will be appreciated by one skilled in the art, some embodiments of the present invention may be embodied as a system, method or computer program product. Accordingly, some embodiments of the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, etc.) or an embodiment combining software and hardware aspects that may all generally be referred to herein as a “circuit,” “module” or “system.” Furthermore, some embodiments of the present invention may take the form of a computer program product embodied in one or more computer readable medium(s) having computer readable program code embodied thereon. Implementation of the method and/or system of some embodiments of the invention can involve performing and/or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of some embodiments of the method and/or system of the invention, several selected tasks could be implemented by

hardware, by software or by firmware and/or by a combination thereof, e.g., using an operating system.

For example, hardware for performing selected tasks according to some embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to some embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to some exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

Any combination of one or more computer readable medium(s) may be utilized for some embodiments of the invention. The computer readable medium may be a computer readable signal medium or a computer readable storage medium. A computer readable storage medium may be, for example, but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, or device, or any suitable combination of the foregoing. More specific examples (a non-exhaustive list) of the computer readable storage medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a hard disk, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, a portable compact disc read-only memory (CD-ROM), an optical storage device, a magnetic storage device, or any suitable combination of the foregoing. In the context of this document, a computer readable storage medium may be any tangible medium that can contain, or store a program for use by or in connection with an instruction execution system, apparatus, or device.

A computer readable signal medium may include a propagated data signal with computer readable program code embodied therein, for example, in baseband or as part of a carrier wave. Such a propagated signal may take any of a variety of forms, including, but not limited to, electro-magnetic, optical, or any suitable combination thereof. A computer readable signal medium may be any computer readable medium that is not a computer readable storage medium and that can communicate, propagate, or transport a program for use by or in connection with an instruction execution system, apparatus, or device.

Program code embodied on a computer readable medium and/or data used thereby may be transmitted using any appropriate medium, including but not limited to wireless, wireline, optical fiber cable, RF, etc., or any suitable combination of the foregoing.

Computer program code for carrying out operations for some embodiments of the present invention may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the "C" programming language or similar programming languages. The program code may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider).

Some embodiments of the present invention may be described below with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems) and computer program products according to embodiments of the invention. It will be understood that each block of the flowchart illustrations and/or block diagrams, and combinations of blocks in the flowchart illustrations and/or block diagrams, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

These computer program instructions may also be stored in a computer readable medium that can direct a computer, other programmable data processing apparatus, or other devices to function in a particular manner, such that the instructions stored in the computer readable medium produce an article of manufacture including instructions which implement the function/act specified in the flowchart and/or block diagram block or blocks.

The computer program instructions may also be loaded onto a computer, other programmable data processing apparatus, or other devices to cause a series of operational steps to be performed on the computer, other programmable apparatus or other devices to produce a computer implemented process such that the instructions which execute on the computer or other

programmable apparatus provide processes for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

Some of the methods described herein are generally designed only for use by a computer, and may not be feasible or practical for performing purely manually, by a human expert. A human expert who wanted to manually perform similar tasks, such as scoring in-vitro grown embryos might be expected to use completely different methods, e.g., making use of expert knowledge and/or the pattern recognition capabilities of the human brain, which would be vastly more efficient than manually going through the steps of the methods described herein.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings and images. With specific reference now to the drawings and images in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

Fig. 1 is a general flow chart describing a process for analysis of a sample out of a group of samples, according to some embodiments of the invention;

Fig. 2 is a detailed flow chart describing a process for determining a state of a cellular tissue, according to some embodiments of the invention;

Fig. 3 is a flow chart describing the operation of a device for analysis of a group of samples, according to some embodiments of the invention;

Fig. 4 is a block diagram of a system for analysis of a group of samples, according to some embodiments of the invention;

Fig. 5A is a block diagram of a tray comprising a plurality of storage compartments, according to some embodiments of the invention;

Figs. 5B-5G are schematic illustrations of a tray comprising a plurality of storage compartments, according to some embodiments of the invention;

Figs. 6A-6E are schematic illustrations of a system and a device, according to some embodiments of the invention;

Figs. 7A-7F are schematic illustrations of a tray locking mechanism, according to some embodiments of the invention;

Fig. 7G-7H are schematic illustrations of a mechanism for moving a drawer of the device, according to some embodiments of the invention;

Figs. 8A-8E are schematic illustrations of a tray rotation mechanism, according to some embodiments of the invention;

Figs. 9A-9G are schematic illustrations of a heating assembly, according to some embodiments of the invention;

Fig. 10 is an image of a ring-shaped heater, according to some embodiments of the invention;

Fig. 11 is a schematic illustration of a movable heater-calibrator stage, according to some embodiments of the invention;

Figs. 12A-12C are schematic illustrations of a vacuum assembly, according to some embodiments of the invention;

Fig. 13A is a schematic illustration of an optical sensor assembly, according to some embodiments of the invention;

Fig. 13B is a schematic cross-section showing air flow from the heating assembly to the optical assembly through cuvette, according to some embodiments of the invention;

Figs. 13C-13F are schematic illustrations of a shutter mechanism, according to some embodiments of the invention;

Fig. 14 is a schematic illustration showing a relative position of the vacuum assembly and the optic assembly within a device, according to some embodiments of the invention;

Figs. 15A-15E are schematic illustration of tray identification using Barcode and/or RFID readers of the device, according to some embodiments of the invention;

Figs. 16A-16B images demonstrating sample spreading, according to some embodiments of the invention;

Fig. 17 is an image of a spreading stick, according to some embodiments of the invention;

Fig. 18 is a flow diagram showing flow of analysis results, according to some embodiments of the invention;

Fig. 19 is a flow chart of a process for selecting low self-emission cuvettes, according to some embodiments of the invention;

Fig. 20A is a graph showing changes in embryo quality between different groups in a verification study, according to some exemplary embodiments of the invention;

Fig. 20B is a graph showing changes in implantation rate between different groups in a verification study, according to some exemplary embodiments of the invention;

Fig. 20C is a schematic diagram of a scoring algorithm, according to some exemplary embodiments of the invention;

Fig. 21A is a graph showing changes in implantation rate between different groups in a second verification study, according to some exemplary embodiments of the invention; and

Fig. 21B is a graph showing changes in oxidation potential between groups in a second verification study, according to some exemplary embodiments of the invention;

Fig. 22A is a diagram listing various methods for increasing a signal to noise ratio upon detection of emitted photons by an optical sensor, such as a PMT, in accordance with some embodiments;

Fig. 22B schematically illustrates a system for analyzing a sample in which detection of light emitted by sources other than the sample is reduced or eliminated, according to some embodiments;

Fig. 23A illustrates, at a cross section, a PMT tube positioned atop a cuvette seated in a tray, according to some embodiments;

Fig. 23B is an enlarged view of a distal portion of FIG. 23A, according to some embodiments;

Fig. 24A illustrates, at a cross section, a vacuum chamber comprising a seal shaped and positioned to prevent the cuvette from being sucked proximally by the applied vacuum, according to some embodiments; and

Fig. 24B is an enlarged view of a distal portion of FIG. 24A, according to some embodiments.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a device and method for analyzing cellular tissue and, more particularly, but not exclusively, to a device and methods for analyzing in-vitro fertilization (IVF) related cellular tissue.

An aspect of some embodiments relates to determining a state of cellular tissue by automatically analyzing at least one sample, for example at least one liquid sample related to the cellular tissue. In some embodiments, the at least one liquid sample comprises a culture media sample, a follicular fluid sample, a liquid sample comprising suspension tissue, a seminal fluid sample or any other biological and/or physiological liquid sample. In some embodiments, the cellular tissue comprises seminal fluid and/or IVF-related cultured cells, for example harvested oocytes, cryopreserved oocytes, thawed oocytes and/or in-vitro grown embryos. In some embodiments, a group of liquid samples related to the cellular tissue is automatically analyzed.

According to some embodiments, samples, for example culture media samples, where each of the samples relates to a different embryo in a group of in-vitro grown embryos or to a different oocyte, for example cryopreserved or thawed oocyte, are loaded together in separate chambers into a device for analysis. Alternatively or additionally, samples, for example follicular fluid (FF) samples are loaded together in separate chambers into a device for analysis. In some embodiments, analysis of each sample of the loaded samples initiates automatically after the analysis of a previous sample. In some embodiments, at least one sample is loaded within a tray comprising a plurality of chambers into a device for analysis. In some embodiments, the at least one sample is loaded in one of the chambers of the tray, for example, prior to insertion of the tray into the device for analysis.

According to some embodiments, the cellular tissue is scored based on the analysis results of the sample, for example the liquid sample. In some embodiments, scoring in-vitro cultured embryos allows, for example, to select one or more in-vitro cultured embryos out of a group of embryos for transfer into the uterus. Alternatively or additionally, scoring oocytes, for example, to select one or more oocytes out of a group of isolated oocytes for an IVF process. In some embodiments, scoring oocytes, for example scoring isolated oocytes allows, for example, to select one or more isolated oocytes out of a group of isolated oocytes for cryopreservation.

According to some embodiments, the at least one sample or the group of samples are analyzed using TCL Thermochemiluminescence (TCL) technology, which is used, for example, for determining a state of cellular tissue, for example an in-vitro cultured embryo and/or an oocyte. Alternatively or additionally, the group of samples is analyzed using TCL technology for selection of an oocyte or an embryo in IVF procedures. In some embodiments, the results of the samples analysis assist an expert, for example a physician or an embryologist to advise in each IVF cycle which and how many embryos will be transferred to the uterus, which embryos should be frozen for future trials and which embryos should be discarded. Alternatively or additionally, the results of the samples analysis assist an expert, for example a physician or an embryologist to advise which oocyte in a group of oocytes, for example oocytes isolated from the same subject, to freeze and/or to use for IVF. In some embodiments, TCL analysis is used to measure oxidative stress parameters and/or oxidative stress-derived factors in body fluids and biological fluids as well as in-vitro culture media.

An aspect of some embodiments relates to calibrating TCL analysis results of a group of samples, for example culture media samples or FF samples using at least one reference. In some embodiments, an external reference is added to each of the culture media samples. Alternatively or additionally, the reference sample is analyzed as part of the group of samples.

According to some embodiments, a tray which contains each sample in a separate cuvette includes an additional cuvette which is used for calibration in the tray level. In some embodiments, the calibration cuvette includes a tablet, optionally from proprietary material, that is unified and returns equal signals for each tablet. In some embodiments, the tablet comprises selected bio-agents, for example lipids and/or proteins, optionally to imitate the nature of tested fluids. Alternatively or additionally, at least one light source, for example an electric light source or a chemical light source is used for calibration. In some embodiments, the light source is part of the tray, for example on the tray or in the tray. Alternatively or additionally, the light source is positioned within the device.

According to some embodiments, the device, for example the TCL analyzer device comprises a calibration module that will enable to test the response of a light sensor, for example a Photomultiplier (PMT) response over time. In some embodiments, the PMT is tested when activating the analysis device. In some embodiments, the PMT calibration module comprises a fixed, stable light source, optionally with controlled temperature. In some embodiments, the light source consistently emits light with fixed parameter values and the PMT response to the emitted light is measured. In some embodiments, if the PMT response is not a desired response, then correction of the PMT reading is performed, for example using software. In some embodiments, if entry of light from the outside affects photon counting by the PMT, the photon counting is corrected using software or an algorithm.

According to some exemplary embodiment, the tray is a round tray and optionally a disposable tray. In some embodiments the tray comprises two or more chambers, for example cuvettes which are shaped and sized to include biological samples. In some embodiments, the tray is used to analyze embryos of a specific patient, for example without mixing embryos of different female subjects in one dish. In some embodiments, the tray comprises 4 cuvettes, 6 cuvettes, 8 cuvettes, 12 cuvettes or any number of cuvettes.

According to some embodiments, culture media from each in-vitro grown embryo is fed into the cuvettes, for example in sterile conditions in a laboratory hood. In some embodiments, the media sample is taken by a pipette from a tissue culture well, optionally under a microscope control. In some embodiments, a volume of the culture media sample loaded into the cuvette is in a range of 2 µl-500 µl, for example 5 µl, 10 µl, 15 µl or any intermediate, smaller or larger volume.

According to some embodiments, when the device finalizes the analysis of samples related to a single patient, the device displays the analysis results. In some embodiments, the

device displays a score, optionally for each analyzed sample which grades a related in-vitro grown embryo.

According to some embodiments, a score for each analyzed embryo medium is calculated using an algorithm that uses CPS (counts per second) counted in each second for a period of up to 7 minutes, for example 2 minutes, 3 minutes, 5 minutes or any intermediate, shorter or longer time period. In some embodiments, based on the generated score the chances for pregnancy are higher.

According to some embodiments, the algorithm used for scoring each culture medium sample comprises the CPS counts and at least one additional parameter related to the type of culture media used, a parameter related to the in-vitro culturing period of each in-vitro grown embryo, and/or parameter related to the oxidation state of follicular fluid derived with an isolated oocyte. A possible advantage of including at least one parameter related to the in-vitro culturing conditions, for example culturing duration and/or culturing media type is that it allows to compare analysis results from different laboratories in different locations, for example to generate a unified database of results.

In some embodiments, the scoring algorithm weighs in the CPS counts and one or more other factors, for example factors associated with timing, factors associated with in-vitro conditions, factors associated with the type of sample being analyzed, factors related to the in-vitro grown embryo or oocyte associated with the sample (e.g. size, motility, symmetry, cell number, degree of cell fragmentation, presence of vacuoles, and/or other morphological features) and/or other factors.

In some embodiments, the scoring algorithm is sensitive enough to calculate a score based on culture media measurements performed at the 2^{nd} day of culturing, at the 3^{rd} day of culturing, at the 4^{th} day of culturing and/or at the 5^{th} day of culturing, for example at the blastocyst stage of the embryo. A possible advantage of generating a score at the 4^{th} day or earlier, is that it allows to transfer embryos to the uterus by the 5^{th} day, without spending time on testing processes during the embryo transfer day.

According to some embodiments, the scoring algorithm, is used to calculate a success probability of frozen embryos to survive after thawing and/or to resume embryonic development, for example using post-factum data of the outcome after thawing. In some embodiments, the scoring algorithm is used to calculate a survival rate of a cryopreserved embryo to undergo freezing and thawing.

In some embodiments, the sample is collected from a frozen embryo's culture media, optionally without thawing. In an example, the fluid sample is scraped and/or partitioned before

thawing. Optionally, a decision whether to thaw is made based on the analysis of the collected sample.

According to some exemplary embodiments, the scoring algorithm comprises measuring oxidative state values of samples related to cellular tissue. In some embodiments, oxidative state is combined with additional parameters, for example as shown in fig. 20C.

An aspect of some embodiments relates to avoiding identification mistakes of IVF embryos samples or FF samples analyzed as a group by identification of at least one ID tag associated with the group. In some embodiments, a tray containing the samples comprises a tag, for example a barcode or an RFID tag comprising identification information of the group of samples and/or identification information of the tray. Optionally, the tag is a sticker, for example a barcode sticker is attached to the tray surface. In some embodiments, the information on the sticker is compared to information stored in the device memory or to information typed in into the memory of the device.

According to some embodiments, the tray comprises an RFID tag, which includes identification information related to the group of samples. In some embodiments, a list of all the RFID numbers of trays supplied to a clinic is stored in a memory of the analysis device, for example to make sure that only authenticated trays are used.

According to some embodiments, information related to the tray and/or samples in the tray is inserted into a memory of the device. In some embodiments, identification information in a barcode or in the RFID tag is compared to the stored information, for example to verify that the samples on the tray match selected entries in the device memory.

According to some embodiments, the analysis device counts and stores the number of actual tests performed for each tray. In some embodiments, the number of tests performed is used for billing/charge of the patients by the clinic and/or for charging of the clinic by the distributor or by the supplier of the trays. Alternatively, or additionally, the number of tests performed is used for inventory management of the quantity of trays in the clinic, and/or for delivery of alert when the quantity is lower than a predefined level.

An aspect of some embodiments relates to reducing or eliminating noise upon detection of light emitted from a biological liquid sample by blocking light emitted from the sample surroundings and/or by reducing or preventing unintentional heating of the sample surroundings, thereby potentially reducing emission of light by the surroundings.

In some embodiments, one or more components of the system are positioned, shaped and/or sized to match a shape and/or size of a heated surface (e.g. a bottom surface) of a cuvette containing the sample. In an example, a heater configured to heat the bottom surface is shaped

and size according to the shape and/or size of the bottom surface of the cuvette. Optionally, when the heater is positioned with respect to the cuvette to heat the sample (e.g. positioned underneath the cuvette), a surface of the heater does not extend beyond a perimeter of the cuvette bottom surface. In some embodiments, a surface of heater and/or a heater dimension (e.g. diameter) are within the range of 80%-120% of the cuvette bottom surface area and/or dimension (e.g. diameter), respectively. A heater shaped and sized according to the cuvette bottom surface may be advantageous for reducing or preventing undesired heating of the cuvette surroundings, such as heating of the material of the tray in which the cuvette is placed, thereby potentially reducing photon emission from the tray material. Optionally, an intermediate heat-conducting element is placed between the heater and the cuvette bottom surface, where the intermediate element is shaped to match the bottom surface. In another example, an aperture of an analyzer device (such as a PMT) through which light passes is shaped and/or sized similarly to the bottom surface of the cuvette, so that when the aperture is positioned with respect to the cuvette (e.g. above the cuvette, overlapping the cuvette bottom surface), light emitted by sources other than sample (e.g. from the tray in which the cuvette is placed) substantially does not pass through the aperture. A shutter aperture shaped and sized according to the cuvette bottom surface may be advantageous for reducing erroneous light detection (e.g. erroneous counting of photons) emitted by sources other than the sample.

In some embodiments, a light blocking layer or cover is used, for example placed on an upper surface of the tray and around the cuvette, to block light emitted by the cuvette surroundings. The layer may be placed on tray portions surrounding the cuvette.

In some embodiments, unintentional heating of the cuvette surroundings is reduced or avoided, for example by applying cooling to the cuvette surroundings, e.g. to the tray or portions thereof. In some embodiments, unintentional heating is reduced or avoided by keeping a contact surface between the outer walls of the cuvette and the tray to a minimum, for example by loosely placing the cuvette in a chamber defined by the tray, without a direct attachment, e.g. a welding between the cuvette and the tray. In embodiments including such construction, in which the cuvette is not firmly attached to the tray, a seal may be used during applying of vacuum onto the sample, such as to allow the applying of vacuum through and prevent the cuvette from being sucked in the direction of the vacuum tube due to the applied vacuum. In some embodiments, the seal is configured to maintain the cuvette in place under a vacuum of 1-5 mbar, 2-3 mbar, 2-7 mbar or intermediate, higher or lower ranges.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Exemplary general process for determining a state of cellular tissue

According to some exemplary embodiments, a state of cellular tissue, for example a state of a group of oocytes and/or a state of embryos is determined. In some exemplary embodiments, oocytes isolated from a female subject are in-vitro fertilized or are cryopreserved for in-vitro fertilization in the future. In some embodiments, during oocytes isolation, FF is isolated, for example FF from a follicle from which the oocyte was isolated. In some embodiments, at least some of the isolated oocytes are cryopreserved and/or at least some of oocytes are used for in-vitro fertilization. In some embodiments, the oocytes, for example oocytes isolated from the same female subject are scored. In some embodiments, the oocytes are scored by analyzing FF, for example FF derived from the same follicle as the oocyte.

According to some exemplary embodiments, after in-vitro fertilization, at least some of the fertilized oocytes are developed into embryos, that are in-vitro cultured until one or more of the embryos are transferred into the uterus for further development. In some embodiments, the in-vitro grown embryos are scored, for example to allow classification of the embryos. In some embodiments, scoring and/or classification of the in-vitro grown embryos allows transferring to the uterus embryos that have a higher potential to continue their embryonic development in-vivo. Reference is now made to fig. 1 depicting a general process for selection of one or more embryos for embryo transfer, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a tray, for example a disposable tray, comprising one or more chambers is provided at 102. In some embodiments, the one or more chambers comprise one or more cuvettes. Optionally, the one or more cuvettes are configured to be used in a TCL analysis of a material, for example a FF sample or a culturing media sample.

According to some exemplary embodiments, at least one sample, for example a liquid sample is loaded into the one or more chambers for example into the cuvettes at 104. In some embodiments, at least two samples are loaded into the chambers of the tray. In some embodiments, each sample is loaded into a different chamber of the tray. In some embodiments, the at least one sample comprises seminal fluid sample, FF sample, culture media for example culture media sample of oocytes or in-vitro grown embryos, or any other sample related to an

IVF process. In some embodiments, each of the cuvettes contains a sample related to a single in-vitro grown embryo or oocyte. In some embodiments, the cuvettes are loaded with culture media samples of embryos that originate from oocytes of the same female subject. Alternatively, at least some of the culture media samples of embryos originate from different female subjects. In some embodiments, the cuvettes are loaded with FF samples isolated from the same female subject. In some embodiments, each of the FF sample is associated with a single isolated oocyte.

According to some exemplary embodiments, the samples are loaded together into a device for analysis at 106. In some embodiments, at least some of the samples are analyzed automatically by the device. In some embodiments, at least one sample loaded in a tray comprising a plurality of chambers is analyzed. In some embodiments, the analysis comprises TCL analysis. In some embodiments, in the TCL analysis, photon emission of each of the analysed samples is counted during and/or after each of the samples is heated.

According to some embodiments, the analysis comprises measuring values of at least one parameter related to the oxidative state of the at least one sample or the group of samples. In some embodiments, the at least one analyzed parameter related to the oxidative state of the samples is the number of photon emitted from the sample, for example as described in "modifications and oxidation of lipids and proteins in human serum detected by thermochemiluminescence" by Reznick AZ. et al., Luminescence 2003, and in the paper "Thermochemiluminescence (TCL) Oxidizability Assay - Clinical and Laboratory studies" page 40 by Shnizer S.V. (2004) Frontiers in Neurodegenerative Disorders and Aging: Fundamental Aspects, Clinical Perspectives and New Insights. Published by IOS Press, NATO Science Series.

According to some exemplary embodiments, a state of cellular tissue, for example a state of at least some of the in-vitro grown embryos or a state of at least some of the isolated oocytes is determined at 108. In some embodiments, the state of the cellular tissue is determined based on the results of the TCL analysis, for example based on the photon counts of each of the samples. Alternatively, the state of the cellular tissue is determined based on a combination between the TCL analysis results and at least one additional parameter, for example a parameter associated with the morphology of the cellular tissue. Optionally, the determined state is used for scoring at least some of the cellular tissue.

According to some exemplary embodiments, at least one in-vitro grown embryo is selected for embryo transfer at 110. In some embodiments, the at least one in-vitro grown embryo is selected according to the state of the cellular tissue, for example the state of the in-vitro grown embryos determined at 108.

According to some exemplary embodiments, at least one isolated oocyte is selected for IVF or cryopreservation at 112. In some embodiments, the at least one isolated oocyte is selected according to the state of the cellular tissue, for example to the state of isolated oocytes determined at 108.

Exemplary detailed process for determining a state of cellular tissue

Reference is made to fig. 2, depicting a detailed process for determining a state of cellular tissue, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a device for measuring at least one parameter of a sample related to IVF-related cells, for example an in-vitro grown embryos and/or isolated oocytes is calibrated at 200. In some embodiments, a tray comprising a plurality of chambers, for example a plurality of cuvettes is inserted into the device. In some embodiments, the device is calibrated, for example by heating one or more of the cuvettes, for example a calibration cuvette and counting photons emission from the cuvettes. In some embodiments, the calibration cuvette includes material or a device that has a known emission value. Alternatively, the device is calibrated using a fixed light source, for example a fixed light source within the device. In some embodiments, the cuvettes are made from an oxidized material and optionally comprise an oxidized surface, for example an oxidized bottom surface. Alternatively or additionally, the cuvettes are optionally made from aluminum or any other heat conducting material. In some embodiments, the cuvettes are heated to a temperature in a range of 50-100°C, for example 50°C, 60°C, 80°C or any intermediate, smaller or larger value. In some embodiments, cuvettes that self-emitted a large amount of photons which is higher than a predetermined value are marked or tagged by the device. Optionally, one or more cuvettes that self-emit a large amount of photons are marked and/or tagged before the tray is inserted into the device. Alternatively, the device identifies the position of the cuvettes, for example to avoid the identified cuvettes during samples analysis. According to some exemplary embodiments, the tray is ejected from the device once calibration ends.

According to some exemplary embodiments, a light sensor of the device, for example a PMT is calibrated at 200. In some embodiments, the PMT is calibrated using a reference light source within the device that emits light with known parameter values towards the PMT.

According to some exemplary embodiments, a tray comprising a plurality of chambers, for example cuvettes, is tagged at 202. In some embodiments, the tray is tagged to associate the samples in the tray with a selected female subject. Alternatively or additionally, the tray is tagged, for example to associate the tray with a selected plate, or a group of wells in a plate, for

example wells used for in-vitro growth of one or more embryos or one or more isolated oocytes. In some embodiments, the tray tag is selected from a group comprising a color coded tag, a barcode, a QR code or any other graphical code and/or a RFID tag. In some embodiments, the tray tag includes information about a female subject from which the Oocytes used for in-vitro fertilization, were harvested. In some embodiments, a patient ID number or any patient ID indication is written on the tray. Alternatively or additionally, a barcode sticker with the patient ID number or any patient ID indication is attached to the tray at 200.

According to some exemplary embodiments, the tray tag comprises information coded during the manufacture of the tray, for example manufacture day, company-related information, manufacturer-related information, batch number or any information related to the manufacturing process or the manufacturer of the tray. In some embodiments, the tray tag information is used to make sure that only a tray approved by the manufacturer of the analyzer device and/or that only a tray manufactured by the manufacturer of the analyzer is used, for example due to regulatory and/or safety considerations.

According to some exemplary embodiments, at least one sample, for example a liquid sample is loaded into one or more of the chambers of the tray at 204. In some embodiments, a plurality of samples, for example at least two samples are loaded into the chambers of the tray at 204. In some embodiments, each of the loaded samples is associated with a single in-vitro grown embryo and/or a single isolated oocyte. In some embodiments, each of the samples comprises a sample of the culture media of the in-vitro grown embryo. Alternatively, each of the samples comprises a sample of FF associated with a single isolated oocyte. In some embodiments, the sample volume loaded into each chamber of the tray is identical between all samples. Alternatively, the sample volume loaded into each chamber is different for at least some of the samples. In some embodiments, the sample volume is in a range of 1-500 µl, for example in a range of 1-100 µl, 50-250 µl, 150-350 µl, 250-500 µl or any intermediate, smaller or larger range of values.

According to some exemplary embodiments, a different parameter of the samples is identical when the volume of at least some of the loaded samples is different, for example to allow normalization between the loaded samples. In some embodiments, the different parameter comprises total protein level and/or a level of a specific protein or a mix of protein and/or any other biological and/or chemical compounds. In some embodiments, the protein, the mix of proteins, the biological and/or the chemical compounds are endogenous. Alternatively, the protein, the mix of proteins, the biological and/or the chemical compounds are added to the culture media, for example to serve as a reference.

According to some exemplary embodiments, each of the chambers that were loaded with samples is tagged at 206. In some embodiments, the chambers are tagged, for example to allow association of the sample within the chamber with a selected in-vitro grown embryo or with a selected isolated oocyte. In some embodiments, the chambers are marked by a written annotation, a barcode, a QR code or any other graphical code. In some embodiments, the chambers tag includes information about one or more of position of the in-vitro grown embryo or an isolated oocyte in the culture plate, ID information of the female subject from which the Oocytes were isolated, and/or culturing day. Alternatively, the chambers tag includes a code which relates to an entry in a database. Optionally, each chamber code is identical to an embryo code, to an isolated oocyte code and/or to a well code of a tissue culture plate. In some embodiments, an embryo ID number, an oocyte ID number, an embryo ID indication or an oocyte ID indication is written at a designated write pad next on the tray, optionally next to the cuvette. In some embodiments, the ID number or indication is written with a permanent ink. Alternatively, a sticker with the embryo or oocyte ID information is attached to the tray surface next to the cuvette.

According to some exemplary embodiments, the samples within the chambers are spread within the chambers and/or on a surface of the chambers, for example an internal surface of the chambers at 208. In some embodiments, a liquid sample within a chamber is spread, for example to distribute the liquid sample as uniformly as possible on the bottom surface of the chamber. Alternatively or additionally, the tray is tilted, twisted or turned to distribute the liquid sample as even as possible on the bottom surface of the chamber.

According to some exemplary embodiments, tray and/or samples identification information are loaded into the device at 209. In some embodiments, a user enters the ID number of each sample and/or the ID number of the tray into a memory of the device. In some embodiments, the identification number of each sample is assigned to a cuvette number in the memory of the device, for example as entries in a new analysis session that includes an entry for the samples group or a tray entry, and an entry for each sample assigned to a specific cuvette number.

According to some exemplary embodiments, the tray is placed inside a device for measuring at least one parameter of the samples at 210. In some embodiments, the tray is carried out from a biological laminar flow hood to the device. Alternatively, the device is small enough to be placed within the biological laminar flow hood. In some embodiments, the tray is positioned in a desired orientation within the device.

According to some exemplary embodiments, authentication procedure of the tray and/or samples is performed at 211. In some embodiments, the device, optionally automatically,

compares the ID information on the tray and/or the ID information next to each cuvette on the tray to information stored in the memory of the device. In some embodiments, the device verifies that the tray ID and the samples ID indicated on the surface of the tray match the entries loaded for the specific analysis session.

According to some exemplary embodiments, the analysis protocol is initiated at 212. In some embodiments, the device is a TCL analyzer and is used for TCL analysis of the loaded samples, and a selected analysis protocol comprises a TCL analysis protocol. In some embodiments, a user adjusts values of at least one parameter, for example heating level, heating duration. Optionally, when activating the device, a user selects to perform a calibration process of the optic sensor, for example according to an internal reference in the loaded tray. In some embodiments, the internal reference comprises a culture media sample or a liquid FF reference sample.

According to some exemplary embodiments, the analysis results are received at 214. In some embodiments, the user receives the analysis results are received on a screen of the device. Alternatively or additionally, the analysis results are received in a mobile device and/or a remote computer. In some embodiments, the analysis results are received in a database, for example a remote database and/or a cloud-based database. In some embodiments, the analysis results comprise TCL analysis results. Alternatively, or additionally, the analysis results comprise a score value for each of the analysed samples.

According to some exemplary embodiments, a state of cellular tissue, for example a state of at least some of the in-vitro grown embryos or the isolated oocytes is determined at 216. In some embodiments, the state of the cellular tissue, for example the embryos or the oocytes is determined based on the analysis results of a sample associated with the cells. In some embodiments, the state of the embryos is determined based on the analysis results of a sample derived from the culture media of the embryo. In some embodiments, the state of the isolated oocyte is determined based on the analysis results of a FF sample or culture media sample associated with the isolated oocyte. In some embodiments, the embryo state or the isolated oocyte state are determined based on the analysis results and/or a score value of the sample. Optionally, the score value is calculated based on the analysis results and at least one additional parameter, for example a morphological parameter, morphology score, culture medium type, embryo day, FF analysis score, and/or an embryoscope™ score.

According to some exemplary embodiments, at least one isolated oocyte is selected for IVF or for cryopreservation at 217. Alternatively, none of the isolated oocytes of a female subject are selected for IVF or cryopreservation. In some embodiments, the at least one isolated oocyte is

selected or not selected based on the analysis results and/or based on the calculated score of the oocyte.

According to some exemplary embodiments, at least one in-vitro grown embryo is selected for embryo transfer at 218. Alternatively, none of the in-vitro grown embryos are selected at 218. In some embodiments, the at least one in-vitro grown embryo is selected or not selected based on the analysis results and/or based on the calculated score of the embryo.

Exemplary device operation process

Reference is now made to fig. 3, depicting an operation process of a device for TCL analysis, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a tray with chambers, for example cuvettes, is received within the device at 302. In some embodiments, the device comprises a tray base that is configured to align the inserted tray in a desired orientation within the device. Optionally, the tray is locked in the desired orientation within the device.

According to some exemplary embodiments, the device reads an ID tag of the tray at 304. In some embodiments, an ID reader for example a barcode reader and/or a RFID reader read an ID tag of the tray. Optionally, the ID reader reads an ID tag of each of the chambers, for example the cuvettes.

According to some exemplary embodiments, the device determines if the ID tag read at 304 is a correct ID tag at 306. In some embodiments, the device compares the read ID tag to information entered by a user of the device, for example to determine if the read ID tag is the correct ID tag. Alternatively or additionally, the device compares the read ID tag to information stored in a memory of the device. In some embodiments, determining if the ID tag of the inserted tray and/or chambers is a correct ID tag is important, for example to prevent errors when relating analysis results generated by the device to in-vitro grown embryos.

According to some exemplary embodiments, if the read ID tag is a wrong ID tag, an alert is delivered by the device at 307. In some embodiments, the alert is a human detectable alert, for example an alert delivered by sound and/or light.

According to some exemplary embodiments, the tray is ejected from the device at 309. In some embodiments, the tray is ejected if the ID tag is incorrect and/or is not compatible with a stored ID tag.

According to some exemplary embodiments, vacuum is applied at 308 inside the device. In some embodiments, vacuum is applied on each of the chambers, for example on each of the cuvettes. In some embodiments, vacuum is applied, for example to dry a liquid sample within

each of the cuvettes. In some embodiments, vacuum is separately applied on each of the cuvettes. Alternatively, vacuum is applied within the device, simultaneously on all of the samples within the cuvettes. In some embodiments, the device examines if the liquid sample is dry, for example with a humidity sensor. In some embodiments, vacuum is applied for sufficient time and optionally while using a vacuum sensor to monitor vacuum levels, for example to make sure that the sample is dry.

According to some exemplary embodiments, the chambers are heated at 310. In some embodiments, heating is separately applied on each chamber, for example on each cuvette in the tray. Alternatively, heating is simultaneously applied on at least some of the cuvettes of the tray. In some embodiments, the cuvettes are heated to a temperature in a range of 40-100°C, for example 40°C, 55°C, 60°C, 75°C or any intermediate, smaller or larger value.

According to some exemplary embodiments, photon emission is detected at 312. In some embodiments, the device detects photons emitted from each of the cuvettes before, during and/or after the cuvettes are heated. In some embodiments, the cuvettes heating causes the samples within the cuvettes to emit photons. In some embodiments, an optical sensor of the device senses photons emitted from the cuvettes. Alternatively, the optical sensor detects photons emitted from the samples only. Optionally, the sensor detects photons emitted from the samples within the cuvettes and photons emitted from the cuvettes themselves. In some embodiments, the device measures photons emission in counts-per-second (CPS). In some embodiments, measured CPS values from each cuvette represent the number of photons emitted in a second from the cuvette.

According to some exemplary embodiments, the device detects emitted photons from at least one reference sample, for example using an optic sensor of the device, at 314. In some embodiments, the device detects photons emitted from a reference sample, for example a sample that contains on or more biological and/or chemical agents. Alternatively, or additionally, the device detects photons emitted from a reference cuvette. In some embodiments, the device detects photons emitted from the cuvette material during and/or after heating the cuvette. In some embodiments, each tray includes at least one reference sample and/or at least one reference cuvette.

According to some exemplary embodiments, the device calibrates measurements results of detected photons according to the results of the reference measurements at 316. In some embodiments, the device subtracts the CPS values measured from the reference sample from the CPS values measured from each sample in the same tray.

According to some exemplary embodiments, the measurement results are analyzed at 318. In some embodiments, the CPS count results are analyzed, for example using at least one

algorithm, look-up table, and/or any other formula stored in a memory of the device. In some embodiments, the photon measurement values, for example CPM values, are analyzed at 318.

According to some exemplary embodiments, a score is generated at 320. In some embodiments, the score is generated for each of the samples in the tray. Alternatively or additionally, a score is generated for each of the in-vitro grown embryos from which a sample was analyzed by the device. In some embodiments, the score is generated based on the analysis of photon measurement values performed at 318. Alternatively or additionally, the score is generated by combining the photon measurement values and at least one additional parameter, for example a morphological parameter, a biological parameter, a chemical parameter related to the in-vitro grown embryos.

According to some exemplary embodiments, the generated score is stored at 322. Alternatively, or additionally, the analysis results are stored at 322. In some embodiments, the generated score and/or the analysis results are stored in a memory of the device. Alternatively, or additionally, the generated score and/or the analysis results are stored in an external database, optionally a remote database or a cloud-based database.

According to some exemplary embodiments, the generated score is displayed at 324. Alternatively, or additionally, the analysis results are displayed at 324. In some embodiments, the generated score and/or the analysis results are displayed on a display of the device. In some embodiments, the generated score and/or the analysis results transmitted to a remote device and are optionally displayed on a display of the remote device.

According to some exemplary embodiments, the generated score and/or the analysis results are marked next to each of the analyzed cuvettes. In some embodiments, generated score indications and/or analysis results indications are marked next to each of the analyzed cuvettes.

Exemplary device

Reference is now made to fig. 4, depicting a device for measuring at least one parameter of a sample related to an in-vitro grown embryo, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a device 400 comprises a tray drawer 404, optionally a movable tray drawer configured to move in and out from a housing 402 of the device 400. In some embodiments, the movable tray drawer 404 is mechanically connected to at least one actuator, for example actuator 408 which moves the tray drawer 404 in and out from the housing 402. In some embodiments, actuator 408 comprises an electrical motor. In some embodiments, the tray drawer 404 is shaped and sized to accommodate a tray comprising a

plurality of chambers. Optionally, the tray drawer 404 includes at least one aligning element that allows, for example the placement of the tray in a desired orientation within the tray drawer 404.

According to some exemplary embodiments, the tray drawer 404 comprises at least one reversible locking mechanism, configured to lock the tray in the specific orientation, for example to prevent undesired movement of the tray during the analysis process. In some embodiments, the at least one reversible locking mechanism comprises at least one interference lock, for example a snap-fit lock. In some embodiments, the reversible locking mechanism is configured to allow release of the tray from the tray drawer, for example when the analysis is completed. In some embodiments, the locking mechanism comprises at least one manual and optionally a mechanical lock. Alternatively, or additionally, the locking mechanism comprises at least one electrical or magnetic lock.

According to some exemplary embodiments, the device comprises at least one control circuitry, for example control circuitry 406. In some embodiments, the control circuitry 406 is electrically connected to the actuator 408. In some embodiments, the control circuitry 406 signals the actuator 408 to move the tray drawer 404, for example to allow placement of a new tray within the tray drawer and/or at the end of the analysis. Optionally, the control circuitry 406 signals the actuator 408 to eject the tray drawer when an identification process of the tray fails.

According to some exemplary embodiments, the device comprises at least one ID reader, for example ID reader 422 electrically connected to the control circuitry 406. In some embodiments, the ID reader comprises an RFID reader, a barcode reader and/or an optical sensor configured to identify a pattern or a color tag. In some embodiments, the ID reader 422 detects a code on a tray placed within the tray drawer 404. Optionally, the tray code includes information on a tissue culture plate in which the embryos are grown, and/or information regarding a female subject from which oocytes used in the IVF procedure were isolated, for example an ID number of the female subject

According to some exemplary embodiments, the ID reader 422 detects codes that were assigned to each of the chambers, for example cuvettes in the tray. In some embodiments, a cuvette code includes information about a selected in-vitro grown embryo, for example an ID number, IVF date, culturing day, embryo day or any other data related to the selected in-vitro grown embryo.

According to some exemplary embodiments, the device 400 comprises a user interface, for example a user interface 424 electrically connected to the control circuitry 406. In some embodiments, the user interface 424 comprises a display and/or at least one speaker, for example

to provide a human detectable indication. Additionally, the user interface 424 comprises at least one input element, for example a keyboard. Optionally, the keyboard is presented on the display.

According to some exemplary embodiments, the device 400 comprises a memory, for example memory 428. In some embodiments, memory 428 stores at least one analysis protocol and/or parameters thereof. Additionally, the memory 428 stores information inserted by the device using the user interface 424 and/or log files related to the operation of the device. In some embodiments, the memory 428 stores information related to the samples, the in-vitro grown embryos and/or to the female subject, for example assigned ID information.

According to some exemplary embodiments, the user interface receives information regarding the in-vitro grown embryos, the samples and/or the female subject, for example ID information. In some embodiments, the control circuitry 406 compares the ID information read by the ID reader 422 and the ID information stored in the memory 428. In some embodiments, if the ID information read by the ID reader 422 does not match the stored information, then the control circuitry 406 signals the user interface 424 to generate an alert signal. Optionally, if the ID information read by the ID reader 422 does not match the stored information, then the control circuitry 406 signals the actuator 408 to eject the tray drawer.

According to some exemplary embodiments, the device 400 comprises a vacuum assembly, for example vacuum assembly 410, electrically connected to the control circuitry 406. In some embodiments, the vacuum assembly 410 is functionally connected to a vacuum source, for example vacuum pump 412. Optionally, the vacuum source is an external vacuum source. In some embodiments, the vacuum assembly comprises a seal, optionally a round seal shaped and sized to seal a connection between the vacuum assembly and chamber of the tray. In some embodiments, the seal external diameter is larger than the diameter or the maximal width of the chamber.

According to some exemplary embodiments, when the tray is positioned within the device 400, the control circuitry 406 signals an electric motor functionally connected to the tray to rotate the tray, for example to align a chamber of the tray with the vacuum assembly. In some embodiments, the chamber and the vacuum assembly are pushed against each other, for example by moving the tray and/or by moving the vacuum assembly 410. In some embodiments, the vacuum seal contacts the tray surface and vacuum is applied by the vacuum assembly on a sample located within the chamber. In some embodiments, vacuum I applied until the sample is dehydrated. In some embodiments, a vacuum sensor 414 electrically connected to the control circuitry 406 senses the applied vacuum levels. In some embodiments, the control circuitry 406

signals the vacuum assembly to apply vacuum with levels and for a pre-determined time period, for example according to at least one parameter of the analysis protocol.

According to some exemplary embodiments, the device 400 comprises a heating assembly, for example a heating assembly 416. Optionally, the heating assembly 416 is electrically connected to the control circuitry 406. In some embodiments, the heating assembly 416 is configured to heat a chamber, for example a cuvette of the tray. In some embodiments, the heating assembly 416 comprises a round shaped heater, optionally having a ring shape, sized to heat a cuvette having a round-shaped bottom. In some embodiments, the control circuitry 406 is configured to signal the heating assembly 416 to heat the cuvette to a temperature in a range of 50-100°C, for example 50°C, 55°C, 70°C, 80°C or any intermediate, smaller or larger value.

According to some exemplary embodiments, the device 400 comprises at least one heat sensor, for example a heat sensor 418. In some embodiments, the at least one heat sensor measures the heat of the cuvette during the cuvette heating, for example to make sure that the heat levels of the cuvette do not exceed a pre-determined heat level. Additionally, the device comprises at least one additional heat sensor, configured to measure the heat level of the heating assembly 416 during cuvette heating.

According to some exemplary embodiments, the device 400 comprises at least one optical sensor, for example optical sensor 420, electrically connected to the control circuitry 406. In some embodiments, the optical sensor 420 is configured to detect photons emission from the chambers of the tray. Alternatively, or additionally, the optical sensor 420 is configured to detect photons emission from samples within the chambers. In some embodiments, the optical sensor 420 detects photons emission when the cuvettes are heated, for example by the heating assembly 416. In some embodiments, the at least one optical sensor comprises at least one photomultiplier (PMT). In some embodiments, the control circuitry 406 counts the number of photons emitted from the cuvette, optionally when the cuvette is heated, based on signals received from the optical sensor 420. In some embodiments, the control circuitry calculates a CPS value for each cuvette, based on signals received from the optical sensor 420. In some embodiments, the control circuitry 406 stores the photons count and/or the calculated CPS values in the memory 428.

According to some exemplary embodiments, the device 400 comprises at least one cooling assembly, for example a cooling assembly 420. In some embodiments, the cooling assembly 420 is electrically connected to the control circuitry 406. In some embodiments, the control circuitry 406 activates the cooling assembly 420 when a temperature level inside the device 400 is higher than a pre-determined value, for example during the analysis of the samples. In some embodiments, the cooling assembly comprises at least one fan for actively evacuating

hot air from within the device. In some embodiments, when air is evacuated from device, fresh air enters through openings in the device housing 402.

According to some exemplary embodiments, the device 400 comprises at least one communication circuitry, for example communication circuitry 426. In some embodiments, the communication circuitry is configured to transmit wireless signals, for example Wi-Fi, Bluetooth, radiofrequency signals or any other wireless signal. In some embodiments, the communication circuitry transmits wireless signals and or wires signals to a remote computer and/or to a mobile device. Alternatively or additionally, the communication circuitry is configured to transmit wireless signals and/or wired signals to a remote database, for example to a cloud-based database.

Exemplary tray

According to some exemplary embodiments, in order to analyze a large number of samples, optionally automatically, a tray which includes a plurality of chambers, for example cuvettes, is used. Reference is now made to fig. 5A depicting a tray with a plurality of chambers, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a tray, for example tray 500, comprises a plate with one or more openings shaped and sized to include a chamber in each opening. In some embodiments, the plate is planar, optionally flat. In some embodiments, at least an upper surface of the tray is planar, optionally flat. In some embodiments, the tray is round or oval. Alternatively, the tray is shaped as a polygon, for example as a square.

According to some exemplary embodiments, a tray, for example tray 500 comprises two or more chambers, for example cuvettes 502. In some embodiments, cuvettes 502 are shaped and sized to contain biological samples, for example samples derived from in-vitro cultured embryos. In some embodiments, the cuvettes have an oval shape, a rectangular shape or a round shape. In some embodiments, at least part of the cuvettes, for example the cuvettes bottom surface is made from a heat-conducting material. In some embodiments, the heat conducting material comprises Aluminum or an Aluminum alloy. Alternatively or additionally, the cuvettes are made at least partly from Pyrex®, or Quartz glass.

According to some exemplary embodiments, the tray 500 comprises at least one tray tag 508. In some embodiments, the tray tag 508 is configured to allow identification of the tray, optionally an automatic identification of the tray by an analysis device, for example device 400. In some embodiments, a user of the analysis device loads one or more identification details into a memory of the device, for example to register the tray and/or the samples. In some embodiments, the device automatically verifies that a tray loaded into the device matches the loaded

identification details inserted by the device, for example by reading the chamber tag 504 and comparing the information in the tray tag 508 to the registration information in the memory of the device.

According to some exemplary embodiments, the tray tag 508 comprises an RFID tag, a barcode tag, a QR code tag, and/or a color coded tag. In some embodiments, the tray tag 508 includes identification information, for example information regarding a female subject from which oocytes were harvested, information regarding an analysis batch or a culturing batch, and/or information regarding a tissue culture plate which contains in-vitro grown embryos.

According to some exemplary embodiments, the tray 500 comprises at least one chamber tag for each chamber of the tray. In some embodiments, the chamber tag is located near the chamber. In some embodiments, the chamber tag includes identification information related to a sample and/or a sample origin placed inside the chamber. In some embodiments, if the sample comprises a culture media sample taken from culture media of a specific in-vitro grown embryo, then the chamber tag includes identification information regarding the in-vitro grown embryo. Optionally, the chamber tag is identical to a tag positioned next to a tissue culture well of the specific embryo. In some embodiments, an analysis device, for example device 400, reads optionally automatically the chamber tag, for example during an analysis procedure. In some embodiments, the analysis device automatically reads each of the chamber tags and compares the chamber tags to registration information inserted into the memory of the device. In some embodiments, the chamber tag comprises a barcode, a QR code or any other visible code.

According to some exemplary embodiments, the tray 500 comprises at least one alignment marking, for example alignment marking 510. In some embodiments, the alignment marking 510 is used to align the tray according to a pre-determined alignment or a pre-determined orientation within the analysis device. Optionally, the alignment marking 510 of the tray 500 is aligned according to an alignment marking in the device, for example according to at least one alignment marking in a tray drawer, for example tray drawer 404 of the device

According to some exemplary embodiments, the tray 500 comprises at least one tray lock, for example tray lock 506. In some embodiments, the tray lock 506 is configured to lock the tray 500 within the device in a pre-determined orientation. In some embodiments, the tray lock 506 is a reversible lock configured to lock and unlock the tray. Optionally, the tray lock 506 comprises an interference lock.

According to some exemplary embodiments, the tray 500 comprises a least one write pad 512. In some embodiments, the tray 500 comprises a plurality of write pads, for example a write pad next to each chamber 502 of the tray 500. In some embodiments, the write pad contains

information related to the tray, one or more of the chambers, one or more of the samples and/or one or more of the embryos, for example an ID number of the embryo.

Reference is now made to figs. 5B-5F depicting a round tray comprising a plurality of round cuvettes, according to some exemplary embodiments of the device.

According to some exemplary embodiments, for example as shown in figs. 5B and 5D, a round tray, for example round tray 520 comprises a plurality of cuvettes 522, optionally round cuvettes, distributed along the circumference of the tray. In some embodiments, the cuvettes 52 are made at least partly from a heat conducting material, for example aluminum or aluminum alloys.

According to some exemplary embodiments, the tray 520 comprises a cuvette index 524 next to each of the cuvettes. In some embodiments, the cuvette index includes identification information for each of the cuvettes.

According to some exemplary embodiments, the tray 520 comprises a write pad 526 next to each of the cuvettes. In some embodiments, the write pad includes identification information about each of the samples, for example the embryo number from which the sample was taken.

According to some exemplary embodiments, the tray 520 comprises at least one guiding mark 534. In some embodiments, the guiding mark 534 is shaped and sized to indicate a direction for inserting the tray 520 into the device and/or for aligning the tray 520 inside the device. Optionally, the guiding mark comprises a line and/or an arrow.

According to some exemplary embodiments, the tray 520 comprises at least one sticker pad 536. In some embodiments, the sticker pad is shaped and sized to allow attachment of a sticker to the tray 520, for example a sticker which contains identification information of a female subject, a tissue culture plate and/or an analysis batch.

According to some exemplary embodiments, the tray 520 comprises at least one homing slot 530, for example for aligning the tray 520 within the analysis device.

According to some exemplary embodiments, the tray 520 comprises at least one calibration socket 532. In some embodiments, the calibration slot includes a reference culture medium sample, for example a sample of culture medium taken prior to incubation, or a sample of culture medium from a culturing well without cells. Optionally, the analyzer comprises a calibration module configured to generate a fixed light signal, for example to allow calibration of the PMT.

According to some exemplary embodiments, the tray 520 comprises at least one reference cuvette, for example reference cuvette 528. In some embodiments, a liquid sample within the reference cuvette serves a reference in the analysis of samples found in the rest of the cuvettes. In

some embodiments, if the samples contain culture media samples taken from embryo cultures, the reference sample includes fresh culture media taken from a fresh culture media storage. Optionally, the fresh culture media reference sample is from the same manufacturer batch as the rest of the samples.

According to some exemplary embodiments, the tray 520 comprises at least one gripping member for holding the tray. In some embodiments, the gripping member comprises a central gripping member 538 shaped and sized to allow gripping of the tray 520 with at least two fingers. In some embodiments, the gripping member 538 is positioned at the center of the tray 520, and optionally is a round gripping member. In some embodiments, the gripping member allows to hold the tray with the fingers of one hand, for example to move the tray into the device.

According to some exemplary embodiments, the tray 520 comprises two or more openings in the surface of the tray, for example openings 540. In some embodiments, the openings 540 are positioned in proximity to the gripping member 538, and are shaped and sized to allow at least a partial penetration of fingers, for example the fingers used for gripping, through the openings. In some embodiments, the diameter or the width of the openings 540 is larger than the width of the fingers.

According to some exemplary embodiments, the tray 520 comprises one or more locking pads, for example locking pads 542. In some embodiments, for example as shown in fig. 5B, the tray 520 comprises three locking pads 542. In some embodiments, each of the locking pads is shaped and sized to fit a complementary locker of the device, for example to allow locking of the tray 520 within the device.

According to some exemplary embodiments, for example as shown in fig. 5C, a tray 544 comprises at least one homing bump, for example homing bump 548. In some embodiments, the at least one homing bump allows, for example, to align the tray within the device, optionally according to a pre-determined or a desired orientation.

According to some exemplary embodiments, the tray is a round tray, for example as shown in figs. 5B-5F. In some embodiments, the round tray has a diameter 550 in a range of 10cm-25cm, for example 10cm, 15cm, 17 cm 20 cm or any intermediate, smaller or larger diameter.

According to some exemplary embodiments, a tray, for example tray 552 shown in fig. 5E comprises at least one RFID tag, for example RFID tag 554. In some embodiments, the RFID tag comprises identification information related to the samples, the tray, a female subject from which oocytes were derived for the IVF process. In some embodiments, the information is loaded into the RFID tag by a user of the tray, for example prior to loading samples into the tray chambers. In

some embodiments, the device compares the information inserted into the RFID tag with information stored in the device memory, for example to make sure that there is no mismatch between the RFID information and the information in the memory of the device, for example registration information of the tray and/or registration information of the samples.

According to some exemplary embodiments, for example as shown in fig. 5F, a tray, for example tray 568 comprises at least one protrusion, for example protrusion 572 configured to verify the locking of the tray inside the device. In some embodiments, when the tray is locked within the device, the protrusion is located in a position that allows a sensor of the device to verify the locking of the tray.

According to some exemplary embodiments, for example as shown in fig. 5F, a tray, for example tray 568 comprises one or more air flow openings sized and shaped to allow flow of air through the tray, for example to cool the tray during an analysis process. Alternatively or additionally, the tray comprises one or more airways 570, optionally located around the circumference of the tray, for example to allow flow of air through the tray optionally during the analysis process.

Exemplary cuvette

Reference is now made to fig. 5G depicting a cuvette, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a cuvette, for example cuvette is a round cuvette, having an internal diameter in a range of 10 mm- 15 cm, for example 10 mm, 15 mm, 2 cm, 5 cm, 10 cm, 15 cm or any intermediate, smaller or larger value. In some embodiments, the cuvette has a height 584 of at least 2 mm, for example 2 mm, 2.5 mm, 3 mm, 5 mm, 10 mm, 20 mm or any intermediate, smaller or larger value.

According to some exemplary embodiments, at least part of the cuvette, for example cuvette 522 is made from a heat conducting material, for example aluminum, aluminum alloys or any material with low TCL emission.

Exemplary desktop device

According to some exemplary embodiments, the analysis device is small enough to be positioned on a desk, and to be connected to an external electrical source and/or to an external vacuum source. Reference is now made to figs 6A-6D depicting a desktop device, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a device, for example device 600 comprises a housing 602 which is shaped and sized to be positioned on a desk. In some embodiments, a base of the housing 602 has a length 604 in a range of 30 cm- 55 cm, for example 35 cm, 40 cm, 47 cm, or any intermediate, smaller or larger value. In some embodiments, a base of the housing 602 has a width 606 in a range of 30 cm – 45 cm, for example 30 cm, 35 cm, 40 cm or any intermediate, smaller or larger value. In some embodiments, a height 608 of the housing is in a range of 30 cm- 50 cm, for example 30cm, 38 cm, 40 cm or any intermediate, smaller or larger value.

According to some exemplary embodiments, for example as shown in fig. 6B, the device 600 is connected to an external vacuum source 610, for example a portable vacuum pump station (PPS) via tubing 612.

According to some exemplary embodiments, the device 600 comprises at least one speaker, for example speaker 614. In some embodiments, the speaker 614 delivers one or more indications or alert signals to a user of the device. In some embodiments, the device 600 comprises an operation panel, for example operation panel 620 that comprises an activation switch of the device. In some embodiments, the device 600 comprises at least one fan configured to remove air from within the device, which optionally leads to circulation of air and cooling of the device, for example during a TCL analysis process. In some embodiments, the fan is located under a fan cover 616 positioned at the back of the device. In some embodiments, the fan removes air from within the device 600 via one or more air outlets, for example air outlet 618. In some embodiments, for example as shown in fig. 6C, the device 600 comprises one or more absorb pads mounted to the external surface of the device base, for example to dampen vibrations caused during the operation of the deice 600. Alternatively or additionally, the pads are height adjustable pads and are configured to horizontally level the device when placed on a surface.

According to some exemplary embodiments, for example as shown in fig 6D, the device 600 comprises a display, for example a display 624. In some embodiments, the display 624 is used to display information to a user of the device. Alternatively or additionally, the display is used as an input device for inserting information into the device. Optionally, the display is an LCD display and/or a touch screen display.

According to some exemplary embodiments, the device 600 comprises a movable tray drawer 628. In some embodiments, the movable tray drawer 628 includes an indentation in the surface of the tray drawer 628 which is shaped and sized to accommodate a tray, for example round tray 520, round tray 552 or round tray 568. In some embodiments, the indentation has a round shape with a diameter larger than the diameter of a round tray 626.

Exemplary air flow

According to some exemplary embodiments, during an analysis procedure, for example a TCL analysis procedure, heat levels increases within the analysis device. In some embodiments, the device includes a cooling assembly, for example to allow removal of excess heat from within the device. Reference is now made to fig. 6E, depicting air flow pathways within an analysis device, according to some exemplary embodiments.

According to some exemplary embodiments, the device 600 comprises at least one fan 618, for example an electric fan located at the back end of the device. In some embodiments, the housing 602 comprises one or more openings, for example openings 630 and 632 for allowing introduction of fresh air into the device 600. Additionally, the housing 602 comprises one or more openings behind the fan 618 to allow removal of air from within the device.

According to some exemplary embodiments, activation of the fan 618 circulates air within the device, while air enters into the device through openings 630 and 632, optionally located at the front face of the device 600, and exits through openings behind the fan 618. In some embodiments, in order to minimize light entry into the device, the entry and exit of air through openings in the housing 602 is through directing channels that allow free passage of air but minimize light entry into the device 600, for example into the housing 602 of the device 600. In some embodiments, hot air exits through one or more air outlets, for example air outlets 640 in the fan cover 616. Optionally, the air outlets 640 direct the hot air towards the base of the device. In some embodiments, air flows along air flow paths, for example air flow paths 634 and 636 from one or more air inlets, for example openings 630 and 632 towards the air outlet 640, for example when the fan 618 is activated. Optionally, the fan is activated when a temperature sensor indicates that a temperature within the device is higher than a pre-determined value.

Exemplary tray locking

According to some exemplary embodiments, in order to prevent movement of the tray and chambers during the analysis procedure the tray position within the device is fixed during the analysis process. In some embodiments, fixing the tray position allows, for example, to make sure that the analysis results are related to a correct chamber and sample in the tray. Reference is now made to figs. 7A-7G depicting a tray locking mechanism, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a tray comprises a gripping member, for example gripping member 702. In some embodiments, the gripping member is a ring-shaped gripping member 702 that surrounds a lumen, for example lumen 709. In some embodiments, the

ring-shaped gripping member comprises one or more indentations, for example indentations 706 and 704 shaped for fingers gripping. In some embodiments, the indentations 706 and 704 ate located on the circumference of the ring-shaped gripping member 702.

According to some exemplary embodiments, one or more locking slots, for example locking slots 708, 710 and 712 are positioned in the central lumen 709. In some embodiments, the locking slots are located on protrusions that protrude from the ring-shaped gripping member 702 into the central lumen 709. In some embodiments, for example as shown in figs. 7B and 7C, a tray 700 is shaped and sized to be positioned on a tray drawer base 714 within the device. In some embodiments, the tray drawer base 714 comprises a tray connector 716, optionally positioned in the center of the tray drawer base 714. In some embodiments, a width of the tray connector 716 is smaller than an internal width of the central lumen 709 that the gripping member 702 surrounds. In some embodiments, the tray connector 716 has one or more slots that optionally fit the shape and/or the size of the locking slots protrusions.

According to some exemplary embodiments, for example as shown in fig. 7B, the tray connector 716 comprises one or more lockers, for example a plunger ball spring bolt 715 that fit at least partly through the locking slot 712. In some embodiments, a spring of the locker, pushes the locker at least partly through the locking slot, for example when the locking slot is aligned with the locker.

According to some exemplary embodiments, for example as shown in fig. 7D, the tray 700 is positioned within the tray drawer, in a way that a tray connector 716 of the tray drawer base penetrates through central lumen 709. In some embodiments, the locking slots protrusions are introduced between the tray connector slots.

According to some exemplary embodiments, for example as shown in fig. 7E, the tray 700 is rotated clockwise or counterclockwise in one direction, for example to lock the tray position within the tray drawer. In some embodiments, rotation of the tray 700 in one direction, aligns one or more locking slots 712 of the tray 700 with one or more lockers of the tray connector 716, which locks the tray position. In some embodiments, rotation of the tray in a second opposite direction, releases the one or more lockers from the locking slots, and allows removal of the tray 700 from the tray drawer.

Exemplary tray drawer movement mechanism

Reference is made to figs. 7G and 7H depicting a movement mechanism of a tray drawer of the device, according to some exemplary embodiments.

According to some exemplary embodiments, a tray drawer, for example a tray drawer 628 comprises at least one linear rail attached to a tray drawer side. In some embodiments, a motor 742, for example an electric motor or a stepper electric motor rotates a pinion 744 that fits into indentations of a linear rack 746 attached to at least one side of the tray drawer 628. In some embodiments, the motor 742 is configured to move the tray in a speed in a range of 10 mm/sec – 250 mm/sec, for example in a speed of 100 mm/sec, 120 m/sec, 130 m/sec, 150 mm/sec, or any intermediate, smaller or larger value.

According to some exemplary embodiments, the device comprises at least one sensor switch, for example an optical switch, for controlling the movement of the tray drawer.

Exemplary tray rotation mechanism

According to some exemplary embodiments, once a tray comprising a plurality of chamber is positioned within the device, the tray moves by the device, for example to sequentially analyze samples positioned in the tray chamber.

Reference is now made to figs. 8A-8E depicting a tray rotation mechanism, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, an electric motor, for example an electric stepper motor 802 is positioned underneath the tray drawer 628. In some embodiments, the stepper motor 802 is positioned in a central notch of a tray drawer stage 808. Optionally, the tray drawer stage 808 comprise one or more springs 810, to allow up and down movement of the stage 808, for example when a tray is pushed down onto the tray drawer base 714.

According to some exemplary embodiments, the stepper motor 802 is mechanically connected through a shaft to the tray drawer base 714. In some embodiments, an encoder for example a magnetic encoder 806 surrounds at least partly the tray drawer base 714, and is used to monitor the rotation of the tray drawer base. In some embodiments, the magnetic encoder 806 is an incremental magnetic encoder. Alternatively, the magnetic encoder 806 is an absolute magnetic encoder.

Exemplary cuvette heater

According to some exemplary embodiments, during the analysis of samples within the chambers, for example cuvettes of the tray, the cuvettes are heated by a heater of the device. In some embodiments, the heating of the cuvettes is monitored in order to receive accurate and repeatable analysis results of all the samples in the tray.

Reference is now made to figs. 9A-9G depicting a heater and a heating sensing mechanism of the device, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a heating assembly 902 of an analysis device comprises an external heating housing 906 and a heater 904 positioned at an upper notch 905 of the external heating housing 906. In some embodiments, an elongated movable bar, for example a plunger 912 comprises a cuvette thermometer 908 at an upper end of the plunger. In some embodiments, the plunger passes through an internal channel within the heating housing 906. In some embodiments, the cuvette thermometer comprises one or more resistance thermometers, for example one or more resistance thermometer detectors (RTDs).

According to some exemplary embodiments, at least one heater thermometer, for example heater thermometers 910 and 911 are functionally connected to the heater 904, and are configured to measure the temperature of the heater 904. In some embodiments, the at least one heater thermometer comprises a thermistor, for example a negative temperature coefficient (NTC) thermistor.

According to some exemplary embodiments, for example as shown in figs. 9C-9E, a heater spring 920 is configured to push the heater 904 against the external surface of the cuvette 522, for example to allow efficient heating of the cuvette 522. In some embodiments, a plunger spring 922 is configured to push the cuvette thermometer against the external surface of the cuvette 522 at a different location from the heater, optionally at the center of the cuvette 522, for example to measure the temperature of the cuvette 522 during the heating process.

According to some exemplary embodiments, for example as shown in fig. 9F, in a first step the heater 904, for example a ring-shaped heater, is pushed first against the external surface of the cuvette 522. In some embodiments, in a second step the plunger 912 pushes the cuvette thermometer through the center of the ring-shaped heater, against the cuvette external surface to measure the cuvette temperature level.

Reference is now made to fig. 10, depicting a ring-shaped heater according to some exemplary embodiments of the inventions.

According to some exemplary embodiments, a ring-shaped heater, for example ring-shaped heater 1000 is connected via electrical wiring 1002 to an electric source. In some embodiments, the diameter of the ring-shaped heater is smaller than the diameter of a cuvette, for example 0.5 mm, 1 mm, 2 mm smaller or any intermediate, smaller or larger value. Alternatively, the diameter of the ring-shaped heater is larger than the diameter of the cuvette, for example 0.5 mm, 1 mm, 2 mm or any intermediate smaller or larger value. In some embodiments, a central opening of the ring-shaped heater is larger than a temperature sensor configured to measure the

temperature of the cuvette through the central opening. In some embodiments, a temperature sensor 1004, for example a thermistor, is connected to the surface of the ring-shaped heater 1000, optionally the surface of the heater that contacts the cuvette surface. In some embodiments, the temperature sensor 1004 is electrically connected to a control circuitry of the device, for example control circuitry 406 shown in fig. 4 via electrical wiring 1006.

Exemplary Calibrator-Heater stage

Reference is now made to fig. 11, depicting a Calibrator-Heater stage, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a calibrator and the heater 902 are connected to a movable stage, for example to allow the attachment of either the calibrator or the heater 902 to different cuvettes of the tray. In some embodiments, the calibrator-heater stage comprises at least one motor, for example a stepper motor 1104. In some embodiments, the stepper motor 1104 is configured to axially move the stage underneath the tray. Alternatively, the stepper motor 1104 elevates and lowers the calibrator and/or the heater 902, for example when approaching a selected cuvette.

Exemplary vacuum assembly

According to some exemplary embodiments, in order to dry liquid samples placed in the cuvettes, vacuum is applied on each cuvette. In some embodiments, vacuum is applied for a pre-determined time period. In some embodiments, a user determines a time period for vacuum application, for example according to the amount of liquid placed in the cuvettes. Reference is now made to figs. 12A-12C depicting a vacuum assembly of the device, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a vacuum assembly 1202 is attached to a chamber, for example a cuvette of the tray 520. In some embodiments, a seal between the vacuum assembly and the cuvette is formed, for example to allow application of vacuum on a liquid sample found inside the cuvette. In some embodiments, a sealing between the vacuum assembly 1202 and the tray 520 is formed, for example by lowering the vacuum assembly 1202 to the surface of the tray 520 with sufficient force. Alternatively, the sealing between the vacuum assembly and the tray is formed by elevating the tray 520 towards the vacuum assembly 1202.

According to some exemplary embodiments, for example as shown in fig. 12B, the vacuum assembly 1202 comprises a vacuum pressure transmitter 1204 which is connected via a vacuum tube 1206 to an external vacuum source. In some embodiments, the vacuum pressure

transmitter is connected through a vacuum spacer 1208 to a vacuum chamber 1210. In some embodiments, the vacuum chamber has a volume in a range of 5-30 cm^3, for example 10 cm^3, 15 cm^3, 20 cm^3 or any intermediate, larger or smaller volume.

According to some exemplary embodiments, a sealing ring, for example sealing ring 1212 is connected to the lower end of the vacuum chamber 1210 by a seal connector 1214. In some embodiments, the vacuum assembly 1202 comprises at least one pressure sensor positioned inside the vacuum pressure transmitter unit 1204. In some embodiments, the vacuum sensor is configured to measure pressure levels inside the vacuum assembly 1202 and/or pressure levels applied on the sample within the cuvette. In some embodiments, vacuum levels applied on the sample are in a range of 1 mbar (millibar)- 10 mbar, for example 1 mbar, 3 mbar, 5 mbar or any intermediate, smaller or larger value.

According to some exemplary embodiments, for example as shown in fig. 12C, the vacuum chamber 1210 is pressed against the tray 520 surface. In some embodiments, a ring seal 1212, optionally a u-shaped seal contacts the tray surface surrounding the cuvette 520. In some embodiments, the inner diameter of the ring seal 1212 is in a range of 25mm-50mm, for example 25 mm, 30 mm, 38.8 mm, 40 mm or any intermediate, smaller or larger inner diameter.

Exemplary optical assembly

According to some exemplary embodiments, the device comprises at least one optical sensor assembly which comprises at least one light sensor, for example a PMT. In some embodiments, the PCT is configured to detect photons emitted from a cuvette and/or a sample within the cuvette, for example during a TCL analysis process. In some embodiments, the PMT detect emitted photons during and/or after the heating of the cuvette. Optionally, the PMT detects emitted photons prior to heating the cuvette, for example during a calibration process. According to some exemplary embodiments, the device comprises a photon counting head, which is optionally an integrated unit which includes one or more of a PMT, a high voltage shield, and a control circuitry configured to calculate CPS values. Alternatively or additionally, the device comprises a CCD or any other optical or light sensor configured to sense emission of photons. Reference is now made to figs. 13A and 13B depicting an optical sensor assembly, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, the optical sensor assembly 1302 comprises a PMT 1304 which is placed at least partly within an insulator 1306, In some embodiments, one or more thermal pads 1308 are positioned between the PMT 1304 and a cooler, for example a thermoelectric cooler (TEC) 1310. In some embodiments, a cooling surface of the TEC 1310

contacts a heat conducting adapter 1312. In some embodiments, a heat emitting surface of the TEC contacts a heatsink 1314, configured to dissipate heat. In some embodiments, an electric fan 1316 is connected or positioned next to the heatsink 1314 and draws heat from the TEC 1310 through the heatsink 1314.

According to some exemplary embodiments, for example as shown in fig. 13B, heat flows from the heating assembly 902 and through a cuvette, for example cuvette 520. In some embodiments, activation of fan 1316 draws the heat through the TEC 1310 into the heatsink 1314, which is configured to dissipate the heat.

According to some exemplary embodiments, the temperature of the PMT 1304 is maintained at a temperature range of 20-25°C, for example at 20°C, 22°C, 22.5°C, 23°C or any intermediate, smaller or larger temperature. In some embodiments, the PMT temperature is monitored by at least one temperature sensor located on the body of the PMT 1304, and is optionally electrically connected to a control circuitry of the device, for example control circuitry 406 shown in fig. 4. Additionally or alternatively, at least one additional temperature sensor is located on a heat conducting surface of the TEC 1310. Optionally the TEC temperature sensor is electrically connected to the control circuitry 406. In some embodiments, the TEC temperature sensor and/or the PMT temperature sensor are thermistors, for example NTC thermistors.

According to some exemplary embodiments, in order to prevent entry of light into the light sensor, for example between samples analysis and/or calibration, a shutter mechanism covers the light passage into the light sensor. Reference is now made to figs. 13D-13F depicting a shutter assembly, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, a shutter assembly 1330 is positioned between the optical assembly 1302 and a cuvette, for example to control the passage of light into the light sensor. In some embodiments, for example as shown in figs. 13D-13F, a shutter assembly comprises a movable shutter 1334, which is configured to move, optionally pivotally move, between at least two states, an open aperture state and a closed aperture state. In some embodiments, an electric motor, for example a stepper motor 1332 is mechanically connected to the movable shutter 1334 and is configured to control the movement of the shutter.

According to some exemplary embodiments, for example as shown in figs. 13E and 13F, at least two sensors, for example switch sensors 1336 configured to monitor the movement of the movable shutter between an open aperture state and a closed aperture state. In some embodiments, in an open aperture state for example as shown in fig. 13E, the movable shutter does not block passage of light through the aperture and the aperture 1340 is open. In some

embodiments, for example as shown in fig. 13F the movable shutter 1334 covers the aperture 1340 and block the passage of light into the light sensor.

According to some exemplary embodiments, the switch sensors 1336 comprise optical switch sensors, and are configured to determine the state of the movable shutter 1334. In some embodiments, the switch sensors 1336 stop the activation of the electric motor 1332 when reaching a desired state.

Exemplary device rearrangement

Reference is now made to fig. 14, depicting the rearrangement of the vacuum assembly and the optical assembly within the device, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, the tray 520 is positioned within the device on a movable stage. In some embodiments, rotation of the tray 520 aligns each of the cuvettes with a stationary vacuum assembly 1202. In some embodiments, when a sample is dry, the tray 520 rotates to align the cuvette with an optical assembly 1302, for example to detect emitted photons during and/or after the cuvette is heated.

According to some exemplary embodiments, the position of both the vacuum assembly 1202 and the optical assembly is fixed relative to each other, for example by bar 1402 which comprises openings with width that fits the vacuum assembly 1202 and the optical assembly 1302.

Exemplary tray and/or samples identification

According to some exemplary embodiments, the device verifies that the inserted tray and/or the inserted samples comply with registration entries inserted into the device memory, for example by a user. In some embodiments, identity verifications of the tray and/or the samples in the tray are important, for example to prevent confusion and mixed-up between different samples and/or samples from different batches or between samples which relate to different female subjects. Reference is now made to figs. 15A-15E depicting identification mechanisms of the device, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, each tray inserted into the device is tagged, for example by a code, barcode, RFID tag or any other electronically-readable tag. In some embodiments, the tray tag comprise information related to the group of samples loaded in the tray, for example culturing batch of the embryos, identification info of a female that donated the

oocytes for the IVF process and/or identification information of a plate that is used to culture the embryos, optionally a 6-well plate or a 12-well plate.

According to some exemplary embodiments, a tray, for example tray 1500 comprises at least one tag, for example an RFID tag 1502. In some embodiments, the RFID tag 1502 was loaded with the identification information listed above, or indications of the identification information. In some embodiments, the device comprises at least one RFID reader, for example RFID reader 1504 shown in figs. 15B and 15C. In some embodiments, the RFID reader 1504 reads the information on the RFID tag 1502, optionally automatically, when the tray is positioned within the device. In some embodiments, the RFID reader 1504 reads the information on the RFID tag 1502 before starting an analysis of the samples, for example a TCL analysis.
In some embodiments, the RFID reader 1504 is positioned below the tray1500.

According to some exemplary embodiments, a tag, for example a code or a barcode is assigned to each sample in a cuvette, and is located next to each cuvette on the surface of the tray. In some embodiments, the cuvette tag includes information on a sample loaded into the tray, for example embryo ID number, embryo identification details or any other identification information related to the sample and/or to the embryo. Optionally, the cuvette tag comprises a sticker attached to the tray. In some embodiments, the cuvette tag is already present on the tray surface, and a user assigns information to the tag using a tag reader.

According to some exemplary embodiments, the device comprises at least one tag reader, for example a camera 1506 shown in figs. 15D and 15E, configured to read the cuvette tag. In some embodiments, the device reads and verifies that the cuvette tags comply with identification information stored in a memory of the device, for example prior to analysis initiation. Alternatively or additionally, the device reads and verifies the cuvette tag of a selected cuvette prior to vacuum application and/or heating of the selected cuvette.

According to some exemplary embodiments, the camera 1506 is positioned above the tray 1500 at an angle that allows a clear view of the tag on the surface of the tray. Optionally, for example as shown in fig. 15E, the camera 1506 is positioned at an angle in a range of 15°- 90° relative to the surface of the tray 1500 and/or relative to the cuvette 1510.

Exemplary sample spreading

According to some exemplary embodiments, in order to efficiently dry a liquid sample inside the cuvette, for example a culture media sample, the sample is distributed or spread on the surface of the cuvette prior to vacuum application and/or analysis. Reference is now made to figs.

16A-16B depicting sample spreading, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, liquid sample 1704 is placed inside a cuvette 1702, for example as shown in fig. 16A. In some embodiments, the sample is spread on the surface of the cuvette, for example to form a layer of the liquid sample on the cuvette's surface, as shown in fig. 16B.

According to some exemplary embodiments, for example as shown in fig. 17, a spreading stick 1706 is used. In some embodiments, the spreading stick 1706 comprises a ball-shaped end 1708 and/or a ring-shaped end 1710 that are used for spreading the liquid sample on top the cuvette surface.

Exemplary analysis results usages

Reference is now made to fig. 18, depicting different usages of the analysis results, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, the samples are analyzed by the device, and analysis results are generated. Optionally, the analysis results are used for scoring the in-vitro grown embryos, optionally in combination with additional parameters, for example morphological and/or genetic parameters, culturing medium type, embryo day, culturing day, morphology score, and/or Embryoscope, for example time-lapse analysis score.

According to some exemplary embodiments, the analysis results 1802, for example TCL analysis results are delivered to an expert, for example a physician 1804. In some embodiments, based on the results, the physician decided which of the in-vitro grown embryos to transfer into a uterus for further embryonic development. Alternatively or additionally, based on the analysis results, the physician 1804 determines if additional in-vitro culturing is needed and/or which of the in-vitro grown embryos to cryopreserve.

According to some exemplary embodiments, the analysis results 1802, for example TCL analysis results, are used to update entries in a database 1806. In some embodiments, the analysis results are used to update entries related to isolated oocytes and/or in-vitro grown embryos inserted into the database 1806.

According to some exemplary embodiments, the analysis results 1802 are used to update or to generate an algorithm, for example a machine learning algorithm, used for scoring oocytes and/or in-vitro grown embryos.

According to some exemplary embodiments, analysis log files 1802 are transmitted, optionally automatically, to a billing system 1808. In some embodiments, the device records the

number of trays used for a subject and/or number of analysed samples. In some embodiments, based on the number of trays used for an analysis or the number of analysed samples, a billing system 1808 calculates the cost per subject, and optionally sends a report, for example to a medical insurance company. Alternatively, the log files are delivered to a billing system of the disposable trays manufacturer for example, for billing the clinic for the used trays.

Exemplary cuvettes and/or tray selection

According to some exemplary embodiments, the cuvettes are made at least partly from a heat conducting material, for example aluminum or aluminum alloys. In some embodiments, the heat conducting material emits photons when heated and therefore self-emitted photons mask photons emitted from a sample in the cuvette. In some embodiments, in order to reduce the risk of self-emitted photons, the cuvettes and/or a tray containing a plurality of cuvettes are selected. Reference is now made to fig. 19, depicting a process for selecting cuvettes, according to some exemplary embodiments of the invention.

According to some exemplary embodiments, cuvettes are formed at 1902. In some embodiments, the cuvettes are formed at least partly from aluminum or aluminum alloys.

According to some exemplary embodiments, the cuvettes are warmed at 1902. In some embodiments, the cuvettes are warmed, for example to a temperature used in a TCL analysis at 1904. Optionally, the cuvettes are warmed to a maximal temperature of 95°C, for example 60°C, 70°C, 80°C or any intermediate, lower or higher temperature level.

According to some exemplary embodiments, photons emission is measured at 1906. In some embodiments, the emission of photons is measured after and/or during the cuvettes heating. In some embodiments, the photons emission from the cuvettes is measured using the same measurement parameter values of a TCL analysis, for example for a similar time period and/or using the same detection threshold of the light sensor, for example a PMT.

According to some exemplary embodiments, cuvettes that emitted photons below a pre-determined threshold value are selected at 1908. In some embodiments, cuvettes that emitted photons with a counts-per-second (CPS) value lower than 50, 40, 30 or any intermediate, smaller or larger value are selected to be included in an analysis tray. In some embodiments, cuvettes that emitted photons with a CPS value equal or higher than 30, 40, 50 or any intermediate, smaller or larger value, are discarded or treated.

According to some exemplary embodiments, selected cuvettes are cleaned, for example in an ultrasonic bath, optionally using a detergent. In some embodiments, the cleaned cuvettes are analyzed again, for example to measure CPV values post cleaning.

According to some exemplary embodiments, the selected cuvettes are assembled into the tray at 1110.

According to some exemplary embodiments, an analysis device, for example device 400 shown in fig. 4, performs a tray test. In some embodiments, the device performs a tray test on a new tray prior to loading samples into the tray cuvettes. In some embodiments, the tray is inserted into the device, and the device heats the cuvettes to a pre-determined temperature, for example as described at 1904. In some embodiments, the device measures photon emission during and/or following the heating. In some embodiments, if one of the cuvettes in the tray emitted photons with a CPS value higher than a pre-determined value indicating that this cuvette cannot be used due to high self-emission values, then an indication is delivered to a user of the device, for example by generating an alert signal. Optionally, the device marks the cuvette with the high CPS value, for example to indicate not to use this cuvette during the analysis. Alternatively, the tray is discarded, and a new tray is analyzed.

Exemplary experiments

Study I

A retrospective cohort study was performed with a total of 505 spent embryo culture media, including 205 single-embryo transfers (SET) with known implantation, from 390 IVF cycles. Embryos were cultured and monitored in independent-well slides in the time-lapse system incubator Embryoscope® (Vitrolife) and were subsequently transferred at blastocyst stage. Implantation potential and embryo quality at day 5 (Transferred + Vitrified vs. Discarded embryos) were considered, in terms of oxidation, to find a predictive profile of pregnancy success.

Oxidative status of 15 µl/embryo of Blastocyst medium (Cook) samples were assessed by the TCL, based on the heat-induced oxidation of biological fluids, leading to the production of light energy counted as photons emitted per second (cps). TCL parameters recorded were cps amplitude after 55 seconds (H1), 155 seconds (H2) and 255 (H3), in a 300-second period. Oxidative data was normalized with a smoothing algorithm (sm) and analyzed by the statistical test ANOVA.

Reference is now made to figs. 20A and 20B containing graphs depicting changes in embryo quality and implantation rate, respectively, between different groups in the experiment.

Regarding day 5 embryo quality, transferred and vitrified embryos showed significantly higher values (sig. <0.05) for the oxidative parameters H1sm, H2sm and H3sm. In addition, out of 205 transferred embryos, 54.1% succeeded at implantation showing again higher significant

values (sig. <0.05) in the oxidative parameters. This therefore implies high quality embryos have a more extensive oxidative metabolism exerting an oxidative load on their surrounding media.

Reference is now made to fig. 20C depicting an exemplary assessment algorithm, according to some exemplary embodiments of the invention.

A combined assessment algorithm, including morphology, morphokinetics and the embryo's culture media oxidative status was subsequently developed as a predictive clinical tool of embryo selection, prior to transfer. Motato et al. (2016) morphokinetic model based on blastocyst expansion (tEB; optimal range $\leq$ 112.9 hours) and timing of transition from 5-blastomere embryo until 8-blastomere embryo (t8–t5; optimal range $\leq$ 5.67) was combined with TCL parameter H2sm (optimal range $\leq$ 92.96). A hierarchical classification was generated with six embryo categories (A - F) according to their implantation potential (76.5 - 29.2%).

Study II

Embryos were cultured in independent well slides (Embryoslides) in the Embryoscope Incubator (Vitrolife, Denmark). TCL device was able to analyzed 368 samples of the 400 obtained. A minimum of 15 µl/embryo of CCM medium (Vitrolife) were necessary for measurements. Two groups were formed according to embryo destiny: transferred+vitrified (T+V group) and discarded (D group), 159 vs. 83 embryos respectively. The photons emitted per second (cps) were measured during oxidation process in a 300-second period. The oxidative parameters recorded were: TCL amplitude after 50 seconds (H1), 100 seconds (H2) and 280 seconds (H3).

TCL (thermochemiluminescence) is an oxidative stress (OS) determination technique of biological samples. It is based on heat oxidation induction, which generates the formation of electronically Excited Species (EES). A retrospective study focused on the search for novel indicators of embryo quality was performed based on that OS analysis concept. The study included a total of 400 embryo spent culture media samples. All the embryo transfers were at blastocysts stage.

Differences were found when the oxidation parameters results were related with implantation rate, for example as shown in fig. 21A. These values were obtained from 76 transferred embryos, retrospectively analyzed. From a total of 49 implanted embryos, the 69% of them showed H1> 77 cps, H2> 90 cps values were collected from the 70% of the implanted embryos and H3> 88 cps was registered in 76% of them.

A consistent difference was also found when the average of TCL's settings between T+V and D group were compared, for example as shown in fig. 21B. The results were distributed as follows: H1 95.17:cps vs. 90.51 cps; H2: 94.05 vs. 88.82 cps; H3:112.64 vs.88.06 cps, belonging

to T+V and D group, respectively. The Embryos that presented highest oxidation potential, showed a higher implantation than the rest of cohort's embryos.

FIG. 22A is a diagram listing various methods for increasing a signal to noise ratio upon detection of emitted photons by an optical sensor, such as a PMT, in accordance with some embodiments.

At 2201, in some embodiments, increasing the signal to noise ratio includes reducing or preventing sources other than the sample being measured from affecting the reading. Some examples of external sources which may affect measurement accuracy include sources which emit photons (optionally as a byproduct of the heating that is applied to the cuvette). These sources may include the material forming the cuvette; the material forming the tray (e.g. plastic such as Delrin, Makrolon and/or other polycarbonate materials); external light entering the device; and/or other sources which may emit photons that are detected and optionally erroneously counted by the PMT. The following list describes examples of methods and/or structural system features which may improve the signal to noise ratio of the PMT reading:

At 2203, in some embodiments, a shutter assembly aperture (for example aperture 1340 as shown in FIGs. 13E-13F) is sized to overlap only a surface of the cuvette which is heated by the heater (e.g. directly heated by the heater), for example a bottom surface of the cuvette. A potential advantage of sizing and/or shaping the shutter assembly aperture to match a size (e.g. diameter) and/or shape (e.g. circular shape) of the cuvette surface being heated may include reducing exposure of the PMT sensor to light emitted by sources other than the sample being analyzed, which is spread or otherwise placed in the cuvette, overlying the heated surface.

At 2205, in some embodiments, a heater (for example heater 904, FIGs. 9A-9G) is shaped and/or sized to match (e.g. overlap) only the heatable surface of the cuvette, for example, the heater does not extend beyond a perimeter of the cuvette bottom surface. For example, the heater does not contact the tray material surrounding the cuvette. In some embodiments, the heater is aligned under the cuvette bottom surface, optionally parallel to the cuvette bottom surface. In some embodiments, a surface area of the heater is between 80%-120%, between 70%-110%, between 100%-110%, between 90%-100% or intermediate, larger or smaller percentage of the bottom surface area of the cuvette. In some embodiments, the heater is circular, e.g. ring shaped, having a diameter of between 80%-120%, between 70%-110%, between 100%-110%, between 90%-100% or intermediate, larger or smaller percentage of a diameter of the bottom surface of the cuvette. Optionally, the heater comprises more than one surface, for example, a plurality of small surfaces shaped and/or sized and/or positioned to heat the cuvette.

A potential advantage of sizing and/or shaping the heater to match a size (e.g. diameter) and/or shape (e.g. circular shape) of the cuvette surface being heated may include reducing or preventing unintentional heating of other system components, such as the tray, thereby potentially reducing light emission from those components (since the emission of light by the tray material may increase due to the tray material being unintentionally heated). In some embodiments, an intermediate heat-conducting element such as a heat conductive ring shaped and sized to match the cuvette bottom surface is placed intermediate the cuvette bottom surface and the heater, transferring heat from the heater to the cuvette. Use of an intermediate heat conducting element may be advantageous when the heater surface is shaped and/or sized differently from the cuvette bottom surface, for example, the heater surface being larger than the cuvette bottom surface and extending beyond the cuvette bottom perimeter.

At 2207, in some embodiments, undesired heating of the tray material may be reduced or prevented by minimizing a contact surface between the cuvette the tray material, for example a contact surface between the cuvette rim and the tray. Referring now to **FIGs. 23A-B**, illustrating, at a cross section, a PMT tube 2301 positioned atop a cuvette 2303 seated in a tray 2305 (FIG. 23B is an enlarged view of the cuvette being engaged by a distal portion of the PMT tube), it can be observed that a contact area between the cuvette 2303 and the tray 2305 is limited, for example contact with tray material exits only between the side walls 2307 of the cuvette and shoulder portions 2309 (see FIG. 23B) extending radially outwardly from the cuvette. In some embodiments, the cuvette is simply placed in the tray, such that the cuvette bottom is seated against the tray. Optionally, there is no or only a loose attachment between the cuvette and the tray material (e.g. no welded attachment and/or other tight engagement between the cuvette and the tray).

At 2209, in some embodiments, to eliminate or reduce detection of photons emitted by sources other than the measured sample, for example by sources in the cuvette surroundings, a cover or layer that blocks the emitted light is applied. In some embodiments, such light-blocking layer is placed on the top surface of the tray, potentially reducing or blocking photons emitted by the tray material (e.g. plastic) from passing into the PMT tube. Optionally, the light blocking layer is blackened. Optionally, the light blocking layer is made of a heat-resistant material. Optionally, the light blocking layer does not comprise plastic. In some embodiments, as can also be observed in the example of FIG. 23B, a window 2311 (e.g. a protective glass window) of the PMT tube is brought into an approximated position with the cuvette, optionally contacting shoulder portions 2309 of the cuvette. Alternatively, window 2311 does not contact the cuvette, but is lowered to a distance of less than 3 mm, less than 5 mm, less than 7 mm, less than 10 mm

or intermediate, shorter or longer distance above the cuvette shoulders; or a distance of less than 3 mm, less than 5 mm, less than 7 mm, less than 10 mm or intermediate, shorter or longer distance above the surface of the liquid sample contained in the cuvette.

In some embodiments, there is little or no contact between the tray 2305 and the window 2311, which may potentially reduce detection of light emitted by the tray material, if any, by the PMT sensor.

At 2211, in some embodiments, cooling of the tray is performed. Optionally, the tray (or portions thereof, such as portions around the cuvette) is actively cooled, for example by a thermoelectric cooler (TEC). In some embodiments, the tray is cooled by a cooling assembly, for example by a fan 618, see FIG. 6E. A potential advantage of cooling the tray may include reducing or eliminating light emission by the tray material.

Additional noise reduction methods may include cooling the PMT to reduce thermal background noise (e.g. dark count), for example using a thermoelectric cooler (TEC), such as TEC 1310 described above in FIGs. 13A-B. Optionally, the PMT is cooled to a temperature of 22°C, 20°C, 25°C or intermediate, higher or lower temperatures. In some embodiments, cooling of the PMT is to an extent set by a tradeoff between improving the sensitivity of photon detection while maintaining background noise (e.g. dark count) under a selected, acceptable threshold.

In some embodiments, a TEC may be used for the dual purpose of cooling and heating. For example, heat from a heat emitting surface of the TEC can be conducted, e.g. via a heat transfer device such as a heat pipe, to the bottom surface of the cuvette and/or to one or more portions of the tray underlying the cuvette to heat the sample.

FIG. 22B schematically illustrates a system for analyzing a sample in which detection of light emitted by sources other than the sample is reduced or eliminated, according to some embodiments.

In some embodiments, at least some of the system components are shaped and/or sized to match a heated surface 2231 of the cuvette 2233 including the sample 2235. In some embodiments, a heater 2237 is shaped and sized to apply heat to surface 2231, optionally without extending beyond the perimeter of surface 2231. In some embodiments, an aperture 2239 of the analyzer's shutter assembly (the assembly not shown) is shaped and sized to overlap heated surface 2231. Optionally aperture 2239 is located directly above surface 2231 and the aperture plane is parallel to that of surface 2231.

In some embodiments, during use, sample 2235 is heated by the heater 2237. Photons 2243 emitted by the sample in correlation with the heating pass via aperture 2239 to be detected by optical sensor 2241.

A potential advantage of a system including a heater shaped and sized to match the heated surface of the cuvette may include preventing or reducing heating of the cuvette surroundings, thereby potentially reducing photon emission by the surroundings (e.g by the tray material, not shown).

A potential advantage of a system including a shutter assembly aperture shaped and sized to match the heated surface of the cuvette may include reducing or eliminating light emitted by sources other than the sample to be detected by optical sensor 2241.

FIGs. 24A-B illustrate, at a cross section, a vacuum chamber comprising a seal shaped and positioned to prevent the cuvette from being sucked proximally by the applied vacuum, according to some embodiments.

In some embodiments, a seal 2401 is configured at a lower end of the vacuum chamber 2403 (the lower end shown in an enlarged view in FIG. 24B). In some embodiments, seal 2401 (such as a rubber seal, a silicon seal) is shaped and/or sized to fit onto the cuvette 2407, for example onto the cuvette shoulder portions 2409. Optionally, seal 2401 is pressed onto the cuvette such that shoulder portions 2409 of the cuvette are pushed against the tray 2411. Optionally, when vacuum is applied through vacuum chamber 2403, seal 2401 provides a tight enough enclosure of the cuvette 2407 to enable the application of the vacuum suction through, while maintaining the cuvette in its position in the tray, preventing the cuvette from being drawn proximally by the vacuum suction and/or for otherwise moving with respect to the tray, e.g. moving laterally within the tray chamber in which the cuvette is placed.

In some embodiments, seal 2401 is configured to prevent pulling of the cuvette under vacuum suction in the range of 1-5 mbar, 2-3 mbar, 2-10 mbar or intermediate, higher or lower ranges.

In some embodiments, an inner diameter 2405 of seal 2401 matches an inner diameter of the cuvette, for example a diameter measured between inner sides of the opposing shoulder portions of the cuvette, ranging between, for example, 12-25 mm, such as 15 mm, 18.5 mm, 20 mm or intermediate, longer or shorter diameter.

As used herein, the term "light" may refer to visible wavelengths, non-visible wavelengths, electromagnetic radiation and its elementary particles, photons.

The term "cuvette" as used herein in accordance with some embodiments should not be considered as limiting, and other types of containers suitable to hold a sample are also contemplated. Some examples may include test tubes, slides, dishes and/or other containers structured to hold a sample.

It is expected that during the life of a patent maturing from this application many relevant vacuum, heating and optical assemblies will be developed; the scope of the terms vacuum assembly, heating assembly and optical assembly is intended to include all such new technologies *a priori*.

As used herein with reference to quantity or value, the term "about" means "within ± 10 % of".

The terms "comprises", "comprising", "includes", "including", "has", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, embodiments of this invention may be presented with reference to a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as "from 1 to 6" should be considered to have specifically disclosed subranges such as "from 1 to 3", "from 1 to 4", "from 1 to 5", "from 2 to 4", "from 2 to 6", "from 3 to 6", etc.; as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein (for example "10-15", "10 to 15", or any pair of numbers linked by these another such range indication), it is meant to include any number (fractional or integral) within the indicated range limits, including the range limits, unless the context clearly dictates otherwise. The phrases "range/ranging/ranges between" a first indicate number and a second indicate number and "range/ranging/ranges from" a first indicate number "to", "up to", "until" or "through" (or another such range-indicating term) a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numbers therebetween.

Unless otherwise indicated, numbers used herein and any number ranges based thereon are approximations within the accuracy of reasonable measurement and rounding errors as understood by persons skilled in the art.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

In addition, any priority document(s) of this application is/are hereby incorporated herein by reference in its/their entirety.

WHAT IS CLAIMED IS:

1. A method for scoring in-vitro fertilization (IVF) related cellular tissue, comprising:

loading a tray having a plurality of chambers into a measuring device, wherein said tray comprises one or more samples related to a selected IVF-related cellular tissue;

automatically measuring values of at least one parameter in said one or more samples in said tray;

scoring said IVF-related cellular tissue based on results of said automatically measuring.

2. A method according to claim 1, comprising:

identifying said one or more samples after said loading.

3. A method according to claim 1, wherein said loading comprises loading a tray comprising said one or more samples and at least one reference sample into said measuring device and wherein said measuring comprises measuring values of said at least one parameter in said at least one reference sample.

4. A method according to claim 3, comprising calibrating said measured values of said at least one parameter to said measured values of said at least one reference sample.

5. A method according to claim 1, wherein said IVF-related cellular tissue comprises an in-vitro cultured oocyte.

6. A method according to claim 5, wherein said one or more samples comprise follicular fluid (FF).

7. A method according to claim 5, comprising:

selecting at least one in-vitro cultured oocyte for cryopreservation and/or at least one in-vitro cultured oocyte for IVF based on the results of said scoring.

8. A method according to claim 1, wherein said IVF-related cellular tissue comprises an in-vitro cultured embryo.

9. A method according to claim 8, wherein said one or more samples comprise culture media samples.

10. A method according to claim 9, comprising:

selecting an in-vitro cultured embryo for embryo transfer based on the results of said scoring.

11. A method according to claim 1, wherein said automatically measuring comprises automatically measuring values of at least one parameter related to oxidative state.

12. A method according to claim 11, comprising:

determining an oxidative state of said IVF-related cellular tissue based on said automatically measuring, and wherein said scoring comprises scoring said IVF-related cellular tissue according to said determined oxidative state.

13. A method according to claim 1, comprising:

drying said one or more samples prior to said measuring.

14. A method according to claim 13, comprising:

heating said dried samples prior to and/or during said measuring.

15. A method according to claim 14, wherein said measuring comprises counting photons released from said dried samples during and/or after said heating.

16. A method according to claim 1, wherein said one or more samples are one or more liquid samples.

17. A method according to claim 16, wherein said one or more liquid samples comprise tissues in suspension.

18. A method according to claim 1, wherein said one or more samples comprises at least two samples.

19. A method according to claim 1, comprising calculating, based on said scoring, a survival rate of a cryopreserved embryo to undergo freezing and thawing.

20. A system for analyzing samples, comprising:

a tray comprising at least two chambers shaped and sized to store biological samples, each of said at least two chambers is configured to hold a single sample;

an analyzer, comprising:

a tray holder, shaped and sized to hold said tray;

an identification (ID) reader configured to read one or more ID codes associated with said tray and/or with one or more samples in said tray;

a memory;

a control circuitry electrically connected to said ID reader, wherein said control circuitry is configured to identify said tray or said one or more samples in said tray according to signals received from said ID reader and one or more indications stored in said memory.

21. A system according to claim 20, wherein said analyzer comprises an optical sensor configured to count photons emitted from said one or more samples in said chambers.

22. A system according to claim 20, wherein said analyzer comprises a vacuum assembly configured to apply vacuum on said one or more samples in said at least two chambers, sufficient to dry said biological samples.

23. A system according to claim 22, wherein said vacuum assembly comprises an adaptor which is shaped and sized to separately attach an opening of said vacuum assembly around each chamber of said tray.

24. A system according to claim 20, wherein said analyzer comprises at least two temperature sensors connected to said control circuitry.

25. A system according to claim 24, wherein said analyzer comprises a heater electrically connected to said control circuitry, wherein said heater is configured to heat at least a base layer of said chambers.

26. A system according to claim 25, wherein said heater is shaped and sized to match a surface of said base layer.

27. A system according to claim 25, wherein at least one temperature sensor of said at least two temperature sensors is configured to measure temperature levels of said chamber through an opening in said heater.

28. A system according to claim 27, wherein at least one temperature sensor of said at least two temperature sensors is configured to measure temperature levels of said heater.

29. A system according to claim 20, wherein said analyzer comprises a user interface electrically connected to said control circuitry, wherein said user interface is configured to deliver an alert signal to a user of said system.

30. A system according to claim 29, wherein said control circuitry signals said user interface to deliver said alert signal if said read ID code does not match said stored one or more indications.

31. A system according to claim 29, wherein said user interface is configured to receive sample and/or tray identification input from a user of said system.

32. A system according to claim 20, wherein said one or more samples comprise a FF sample and/or a culture media sample.

33. A method for validating an ID of a sample and/or a tray, comprising:

loading a tray having a plurality of chambers into a measuring device, wherein said tray comprises one or more samples related to a selected IVF-related cellular tissue;

reading at least one ID code associated with said one or more samples and/or with said tray;

validating an ID of said one or more samples and/or said tray based on said read ID code and on one or more indications stored in a memory of said measuring device.

34. A method according to claim 33, comprising:

delivering an alert signal if said read ID code does not match said on or more indications stored in said memory.

35. A method according to claim 33, comprising:

removing said tray from said measuring device if said read ID code does not match said one or more indications stored in said memory.

36. A method according to claim 33, wherein said one or more samples are one or more liquid samples.

37. A method for selecting one or more chambers of a tray used for optical analysis of biological samples within the one or more chambers, comprising:

providing one or more chambers shaped and sized to hold a sample;

heating said one or more chambers to a selected temperature value;

measuring photon emission from said one or more chambers in a timed relationship to said heating;

selecting a chamber based on the results of said measuring;

assembling said selected chamber in a tray comprising a plurality of chambers.

38. A method according to claim 37, wherein said selecting comprises discarding a chamber of said tray whose measured photon emission is higher than a predetermined value according to said measuring.

39. A method according to claim 37, wherein said selecting comprises treating said chamber if said measured photon emission is higher than a predetermined value according to said measuring.

40. A method according to claim 37, wherein said predetermined value comprises photon counts per second (CPS) higher than 40.

41. A method according to claim 37, wherein said predetermined value comprises photon counts per second (CPS) higher than 30.

42. A method according to claim 37, wherein said one or more chambers are made at least partly from Aluminum or Aluminum-containing alloy.

43. A method according to claim 37, wherein said heating comprises heating said one or more chambers to a temperature higher than 50 Celsius degrees.

44. A system for analyzing samples, comprising:

a tray defining at least one chamber in which a cuvette containing a biological sample is received;

an analyzer, comprising:

a tray holder, shaped and sized to hold said tray;

a vacuum assembly which applies vacuum on said sample, sufficient to dry said biological sample; said vacuum assembly comprising a seal shaped and sized to seal an interface between said cuvette and said vacuum assembly.

45. A system according to claim 44, wherein said seal is configured to maintain said cuvette inside said chamber of said tray under a vacuum of between 1-5 mbar applied by said vacuum assembly distally in a direction of said cuvette.

46. A system for analyzing samples, comprising:

a tray defining at least one chamber in which a cuvette containing a biological sample is received;

an analyzer, comprising:

an optical sensor configured to detect emitted light;

a tray holder, shaped and sized to hold said tray with respect to said optical sensor such that light emitted by said sample is detected by said optical sensor; and

a heater comprising a surface area of between 80%-120% of a bottom surface area of said cuvette, said heater aligned beneath said bottom surface of said cuvette.

47. A system according to claim 46, wherein said surface of said heater is circular and wherein a diameter of said heater is between 80%-120% a diameter of said bottom surface of said cuvette.

48. A system according to claim 46, wherein said analyzer comprises a shutter assembly for controlling the passing of light to said optical sensor, said shutter assembly including an aperture shaped and sized to match said bottom surface of said cuvette; said aperture positioned to overlap said bottom surface of said cuvette on a plane parallel to a plane of said bottom surface of said cuvette.

49. A system according to claim 46, wherein a layer which blocks the passage of light emitted from the material of the tray is layered on a top surface of said tray, without covering said cuvette.

50. A method for evaluating embryo quality or oocyte quality by detection of photon emission, comprising:

providing a sample comprising biological fluid associated with an in-vitro grown embryo or with an in-vitro cultured oocyte;

analyzing said sample by detecting photon emission from said sample to measure at least one of oxidative stress parameters and oxidative stress-derived factors in said sample;

scoring said sample based on said analyzing; and

evaluating embryo quality or oocyte quality according to said scoring.

Fig. 1

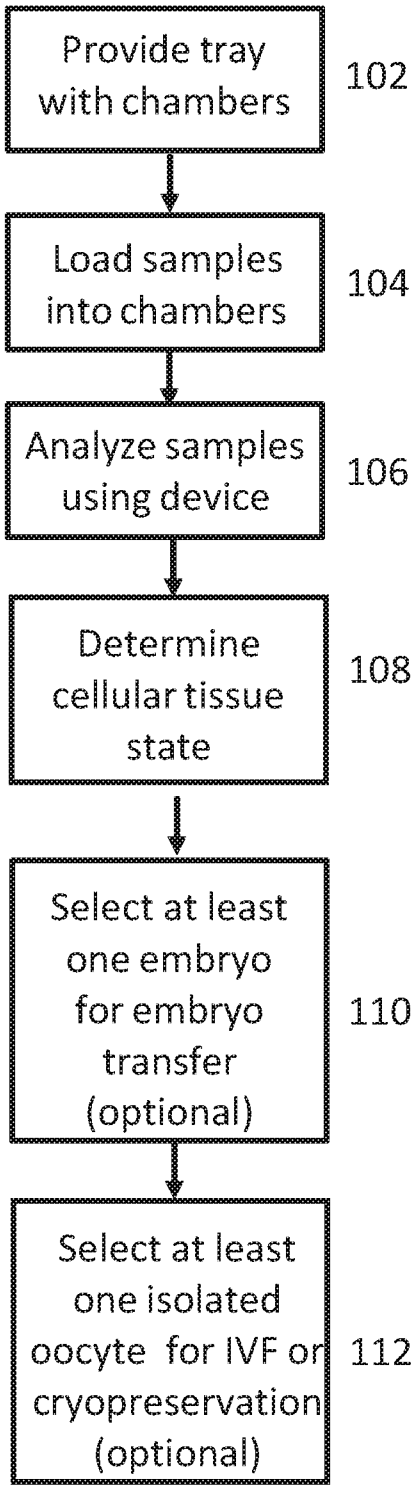

Provide tray with chambers
102
Load samples into chambers
104
Analyze samples using device
106
Determine cellular tissue state
108
Select at least one embryo for embryo transfer (optional)
110
Select at least one isolated oocyte for IVF or cryopreservation (optional)
112

Fig. 2

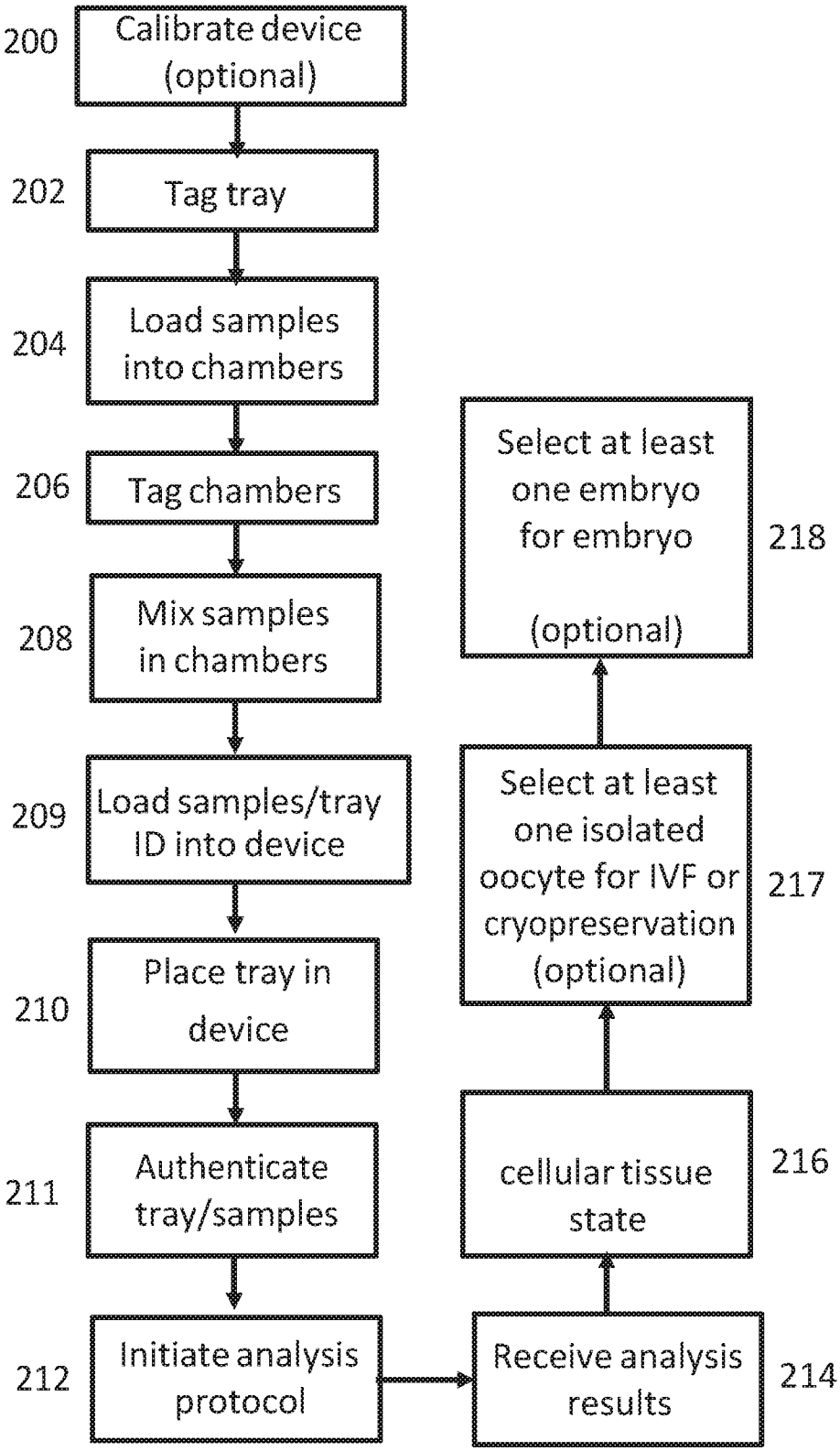

200
Calibrate device (optional)
202
Tag tray
204
Load samples into chambers
206
Tag chambers
208
Mix samples in chambers
209
Load samples/tray ID into device
210
Place tray in device
211
Authenticate tray/samples
212
Initiate analysis protocol
214
Receive analysis results
216
cellular tissue state
217
Select at least one isolated oocyte for IVF or cryopreservation (optional)
218
Select at least one embryo for embryo (optional)

Fig. 3

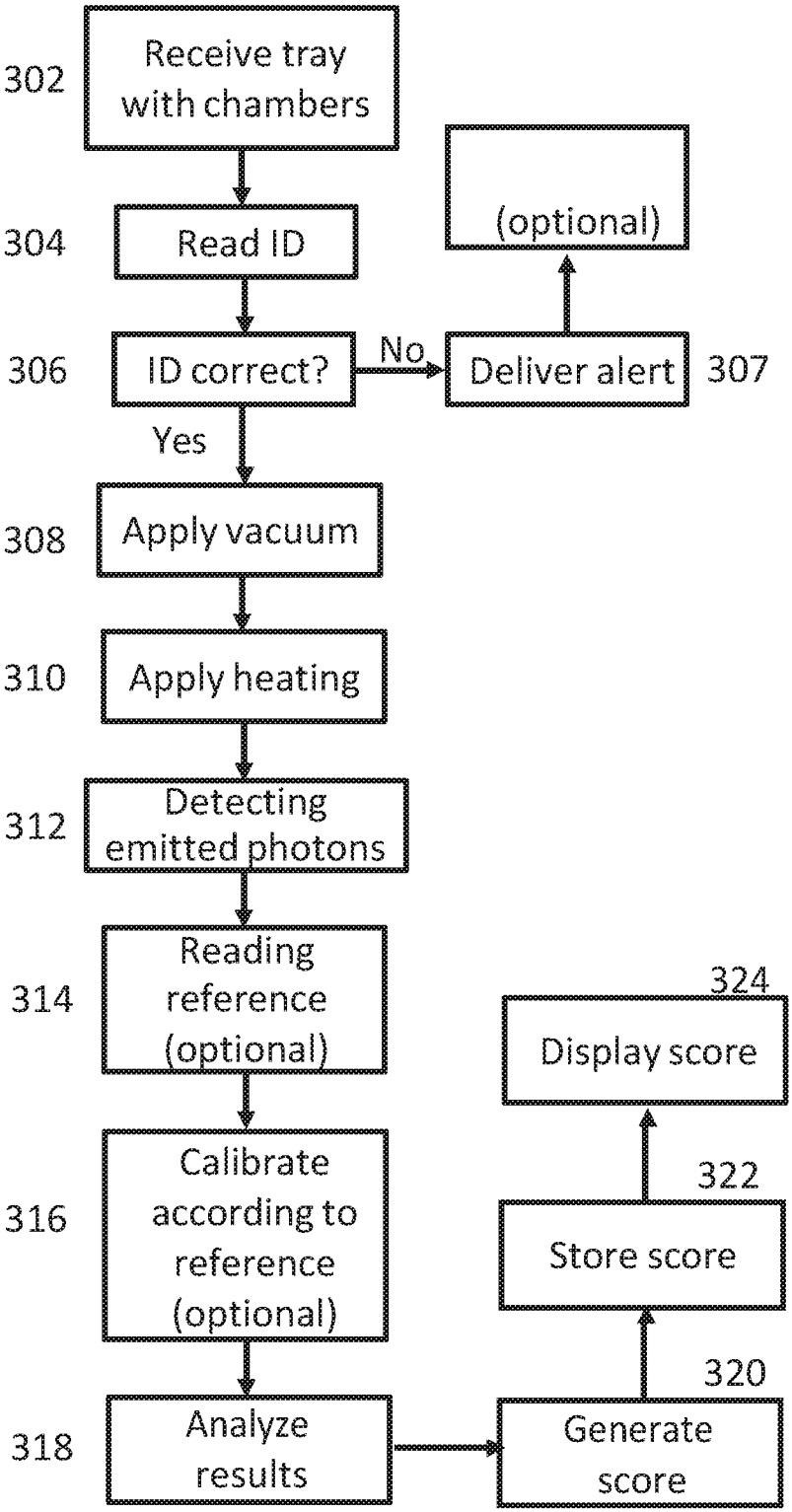

302
Receive tray with chambers
304
Read ID
306
ID correct?
No
(optional)
Deliver alert
307
Yes
308
Apply vacuum
310
Apply heating
312
Detecting emitted photons
314
Reading reference (optional)
316
Calibrate according to reference (optional)
318
Analyze results
320
Generate score
322
Store score
324
Display score

Fig. 4

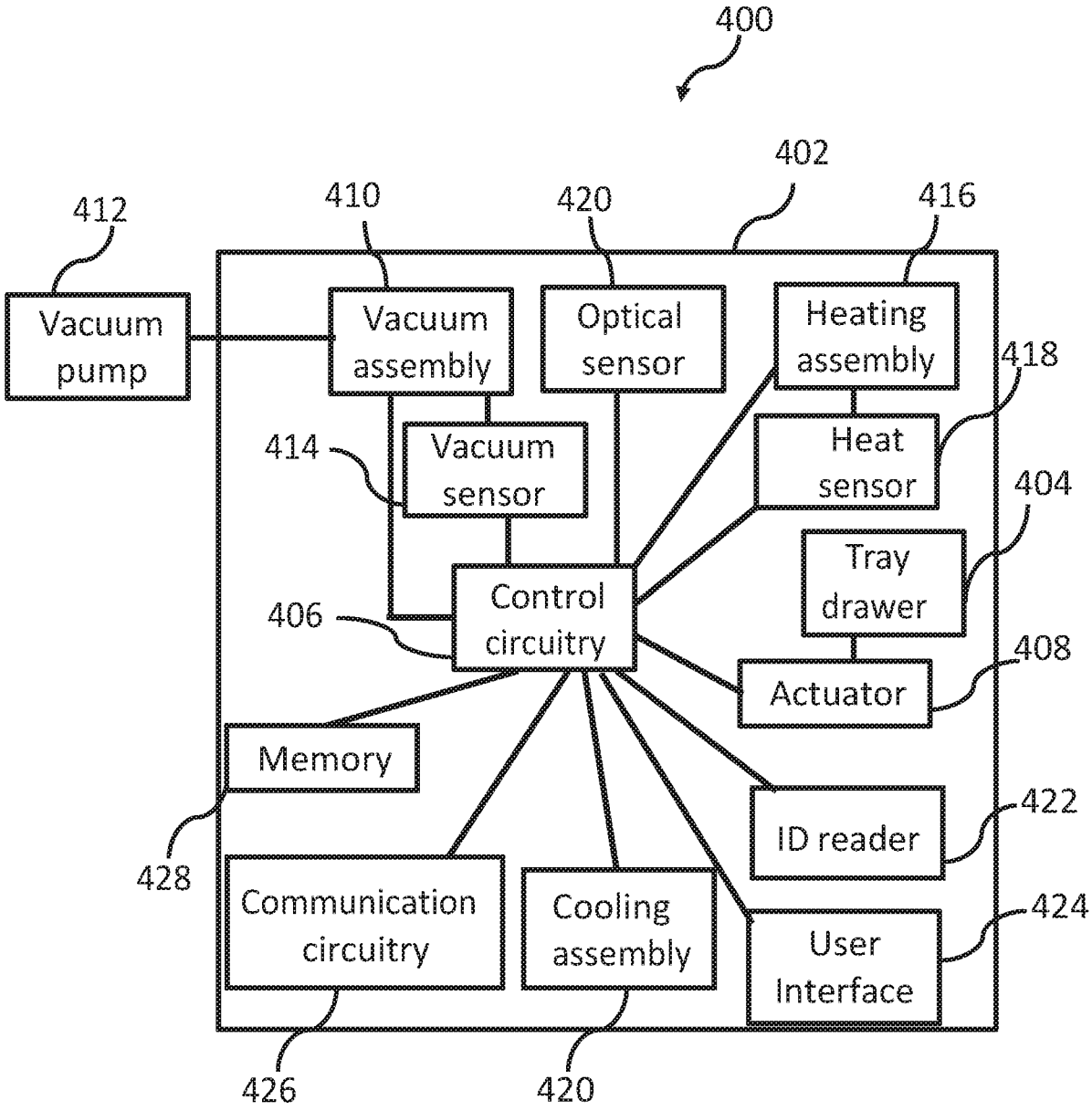

400
402
412
410
420
416
Vacuum pump
Vacuum assembly
Optical sensor
Heating assembly
418
414
Vacuum sensor
Heat sensor
404
Tray drawer
406
Control circuitry
408
Actuator
Memory
422
ID reader
428
Communication circuitry
Cooling assembly
424
User Interface
426
420

Fig. 5A

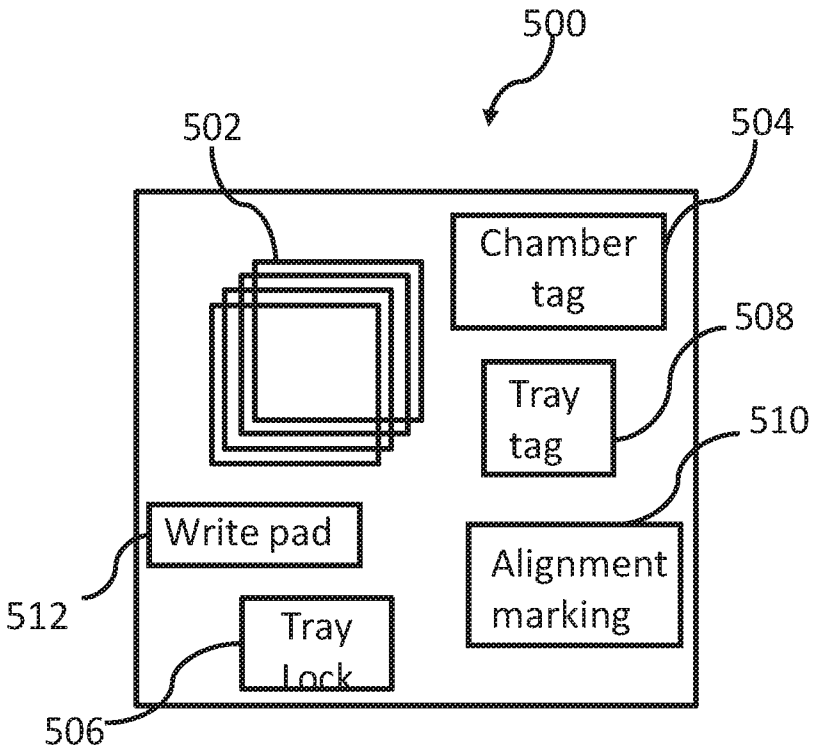

500
502
504
Chamber tag
508
Tray tag
510
Write pad
512
Alignment marking
Tray Lock
506

Fig. 5B

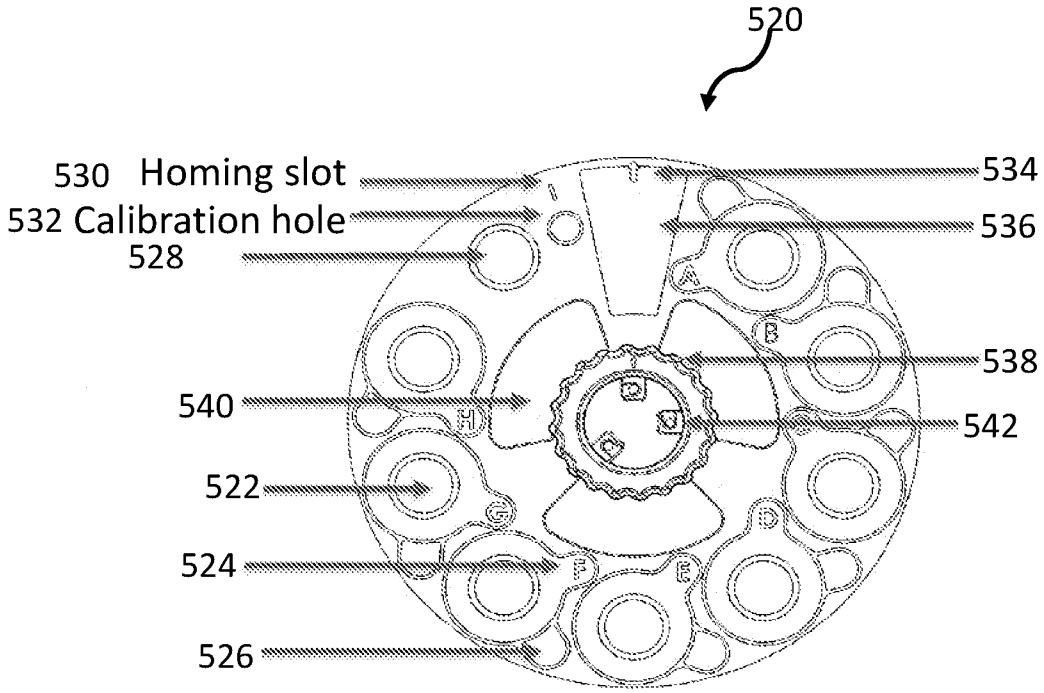


Fig. 5C

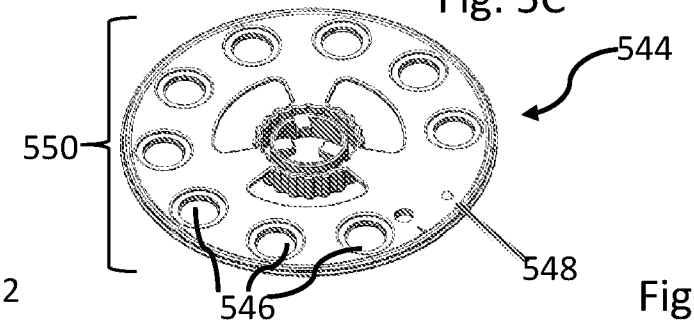


Fig. 5D

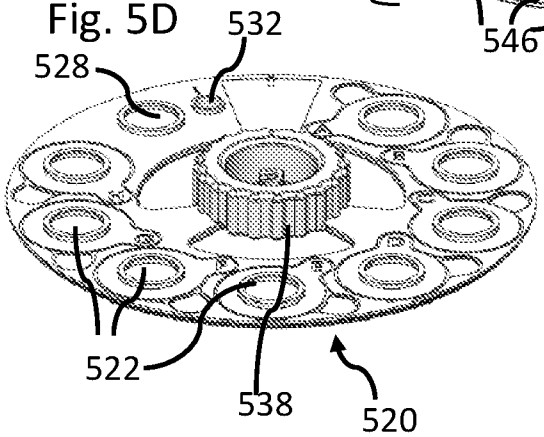


Fig. 5E

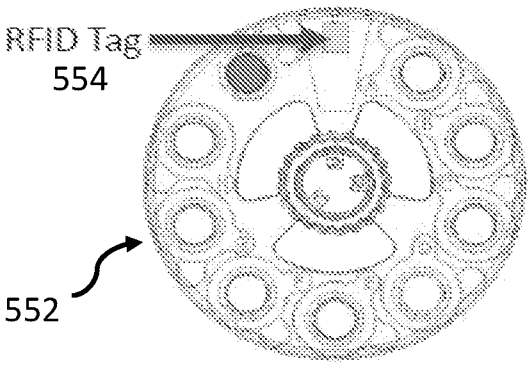


Fig. 5F

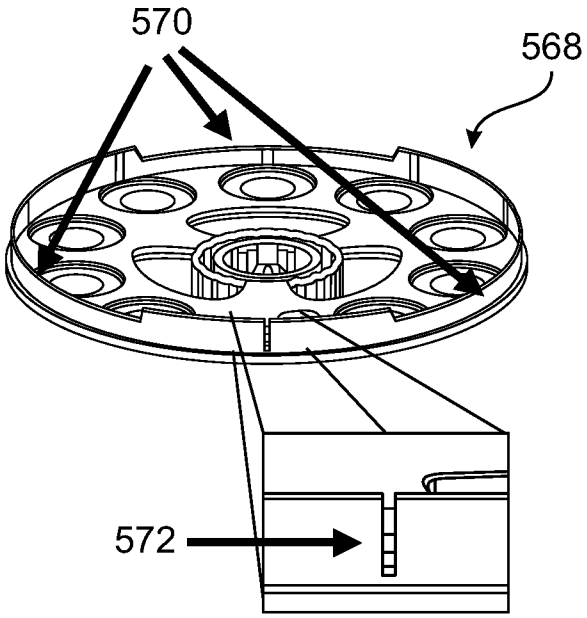


Fig. 5G

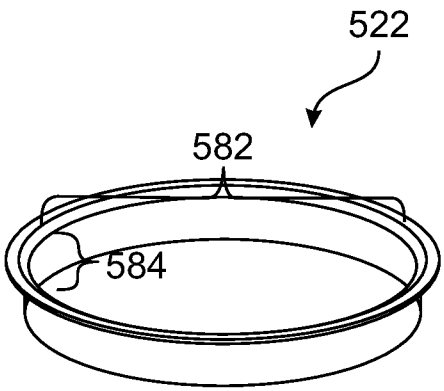


Fig. 6A

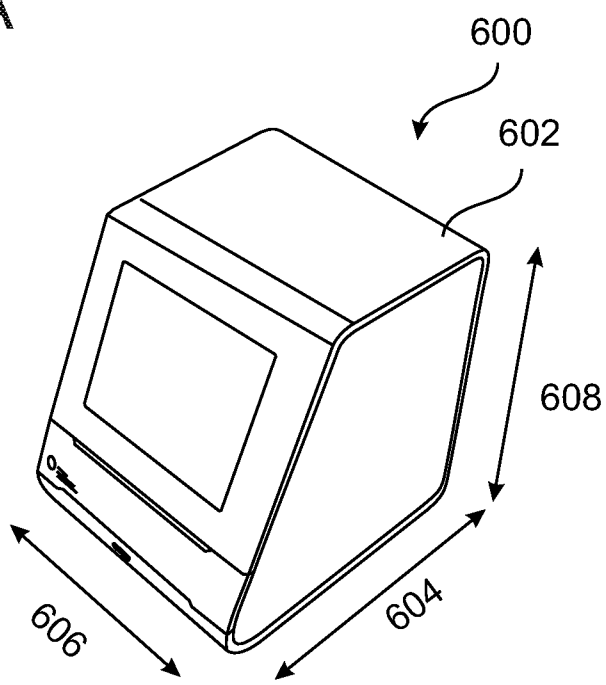


Fig. 6B

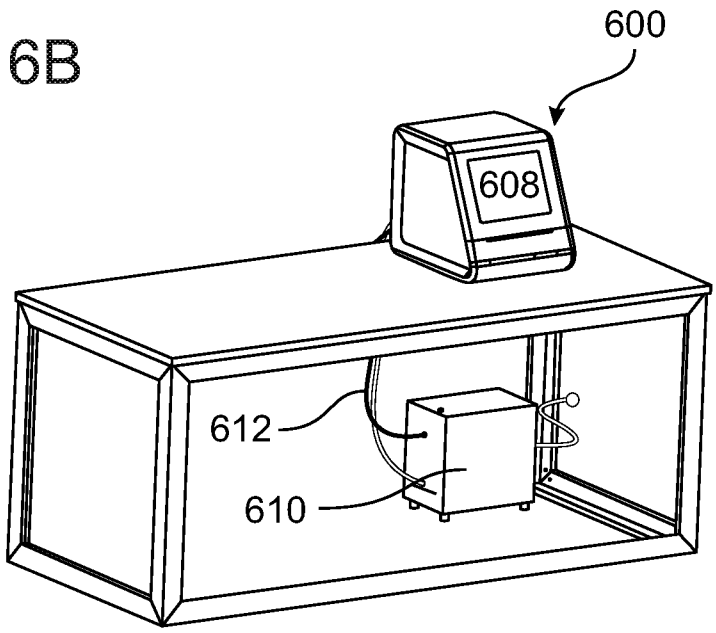


Fig. 6C

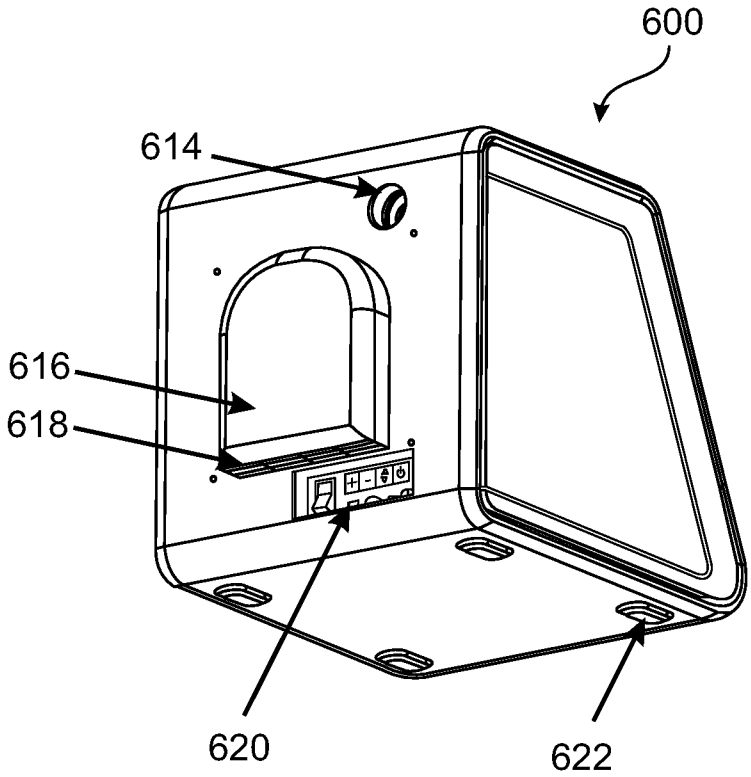


Fig. 6D

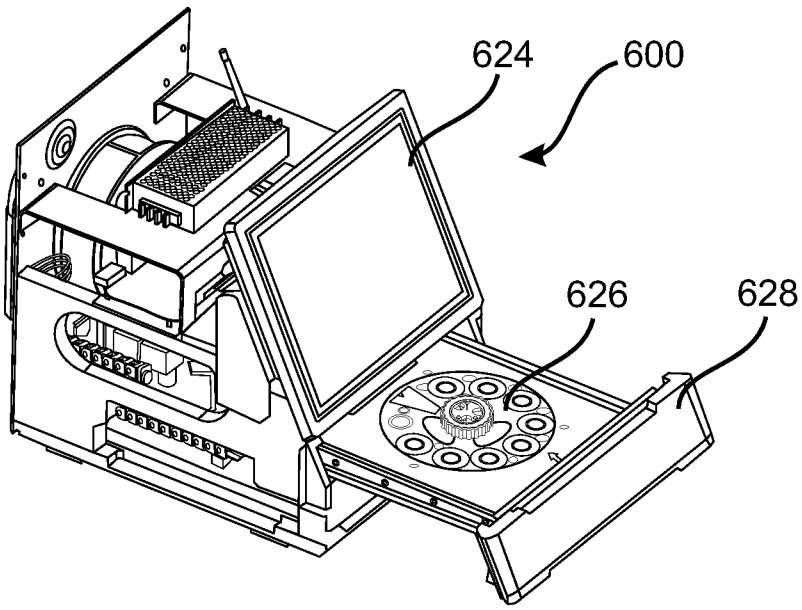


Fig. 6E

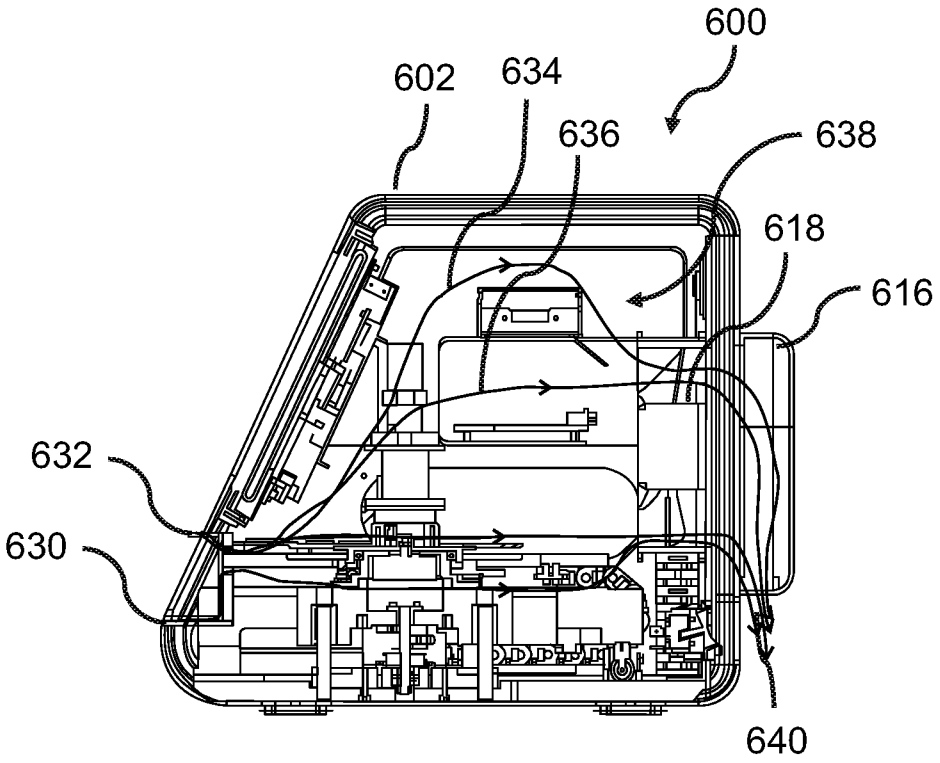


Fig. 7A

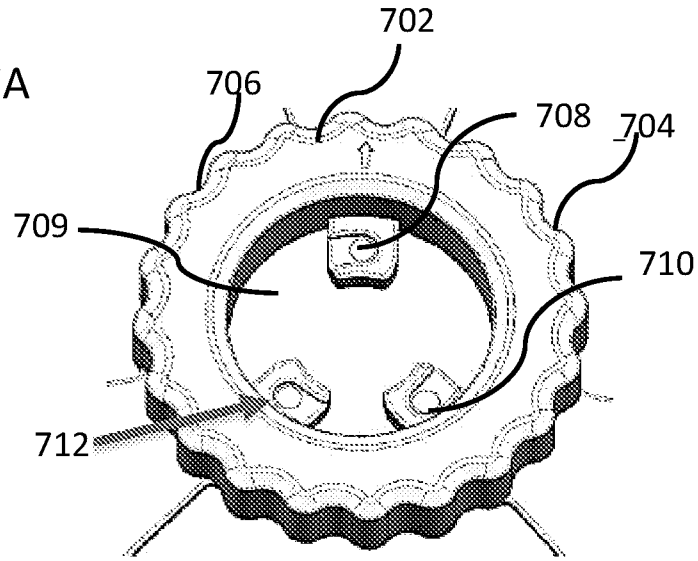
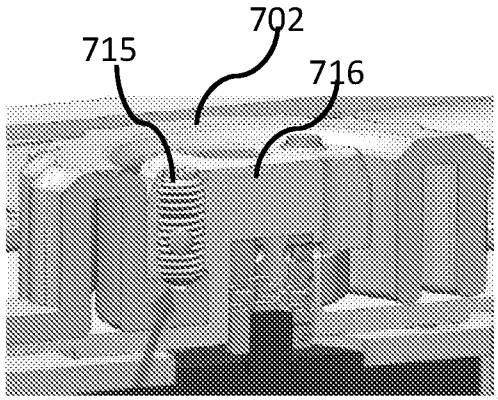


Fig. 7B



Plunger Ball Spring Bolt
712

Fig. 7C

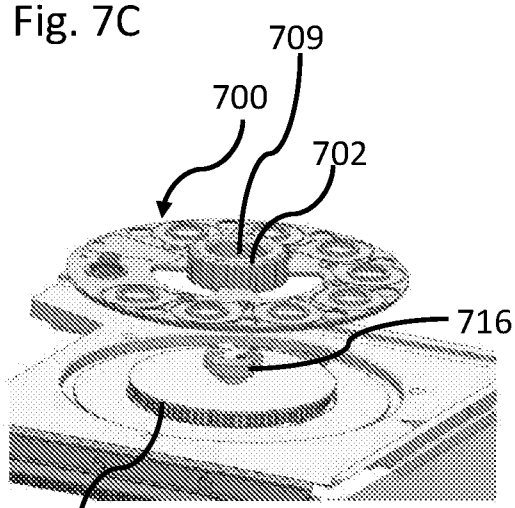


Fig. 7D

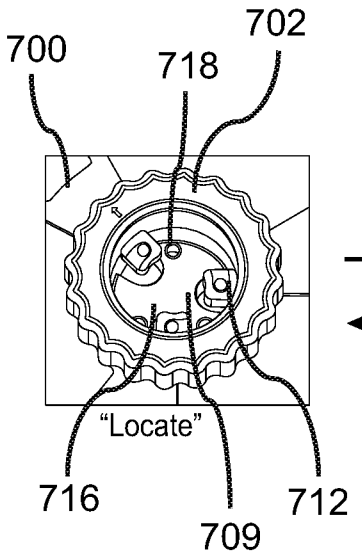


Fig. 7E

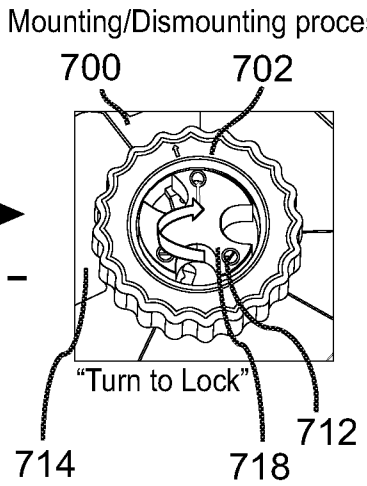


Fig. 7F

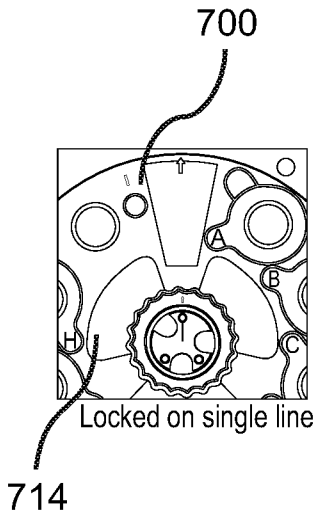


Fig. 7G

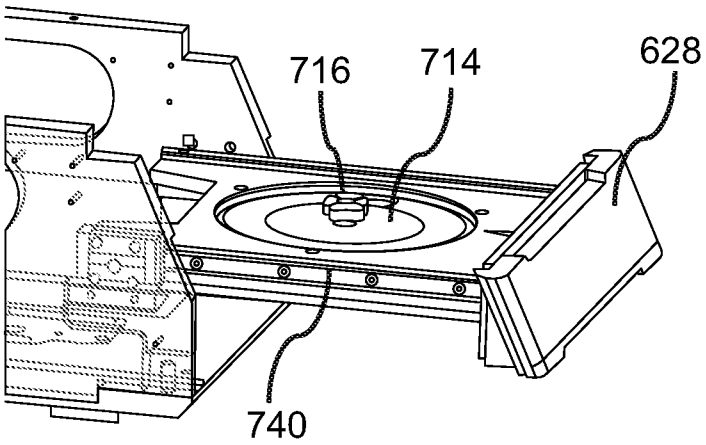


Fig. 7H

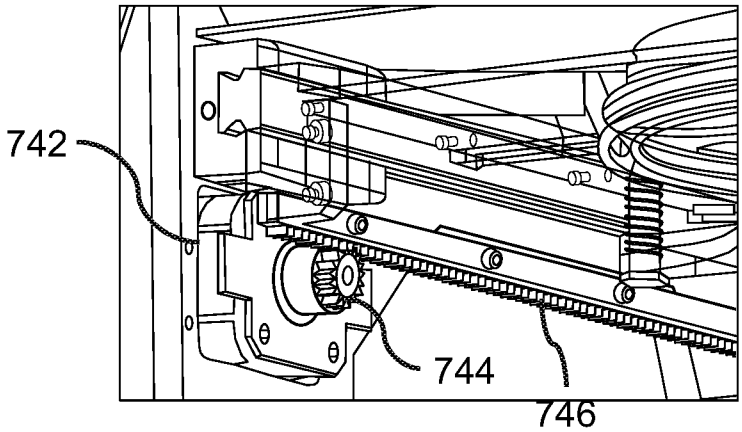


Fig. 8A

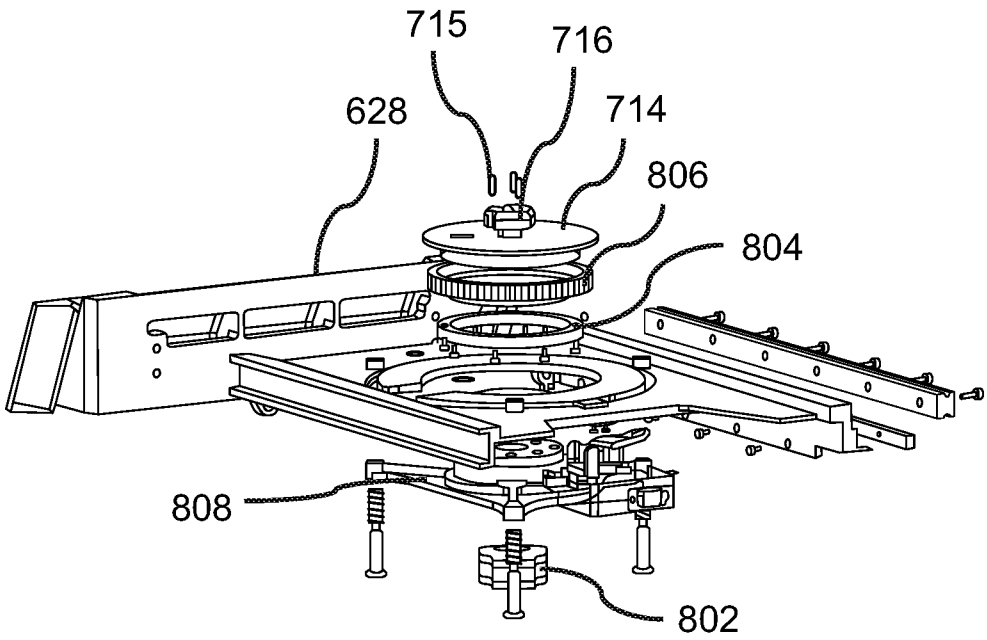


Fig. 8B

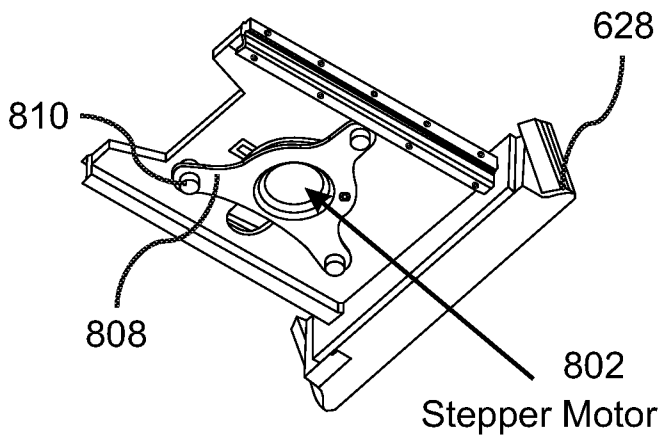


Fig. 8C

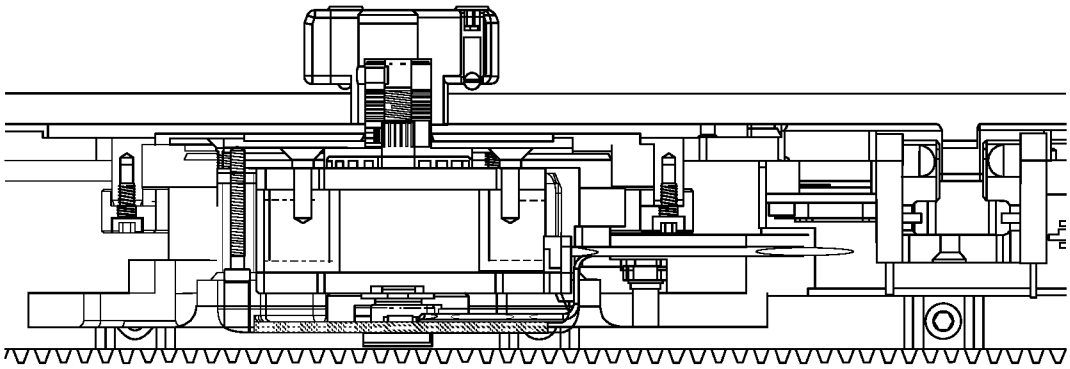


Fig. 8D

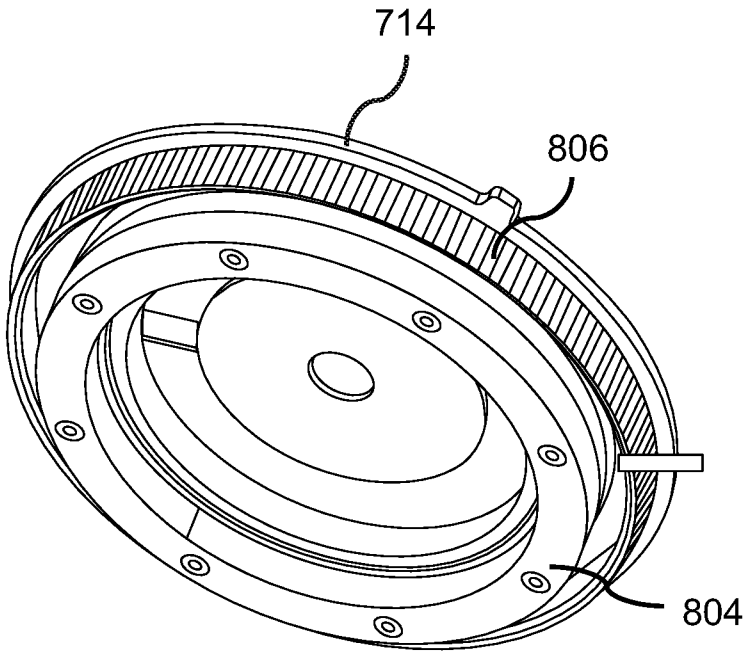


Fig. 8E

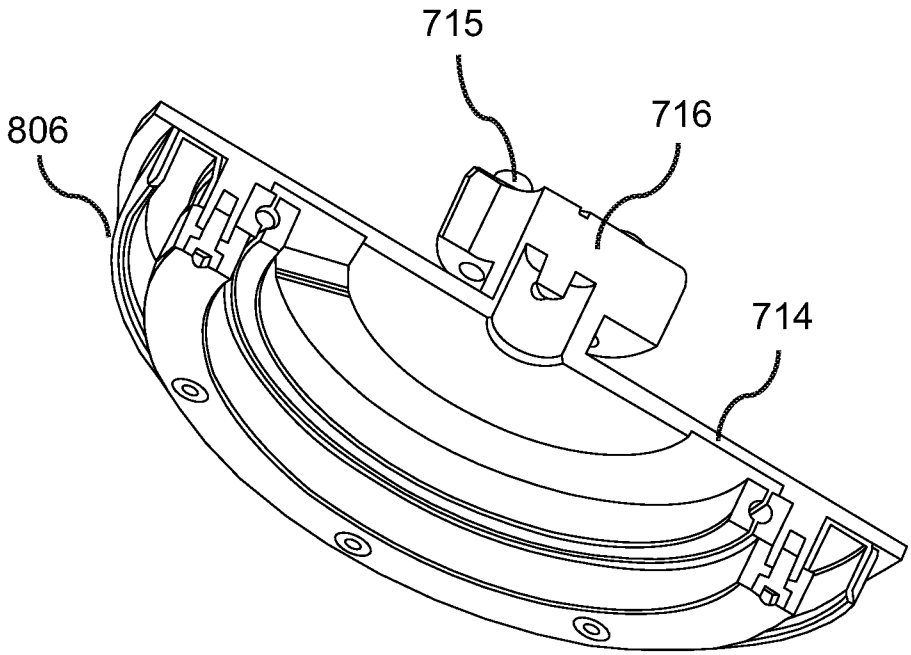


Fig. 9A

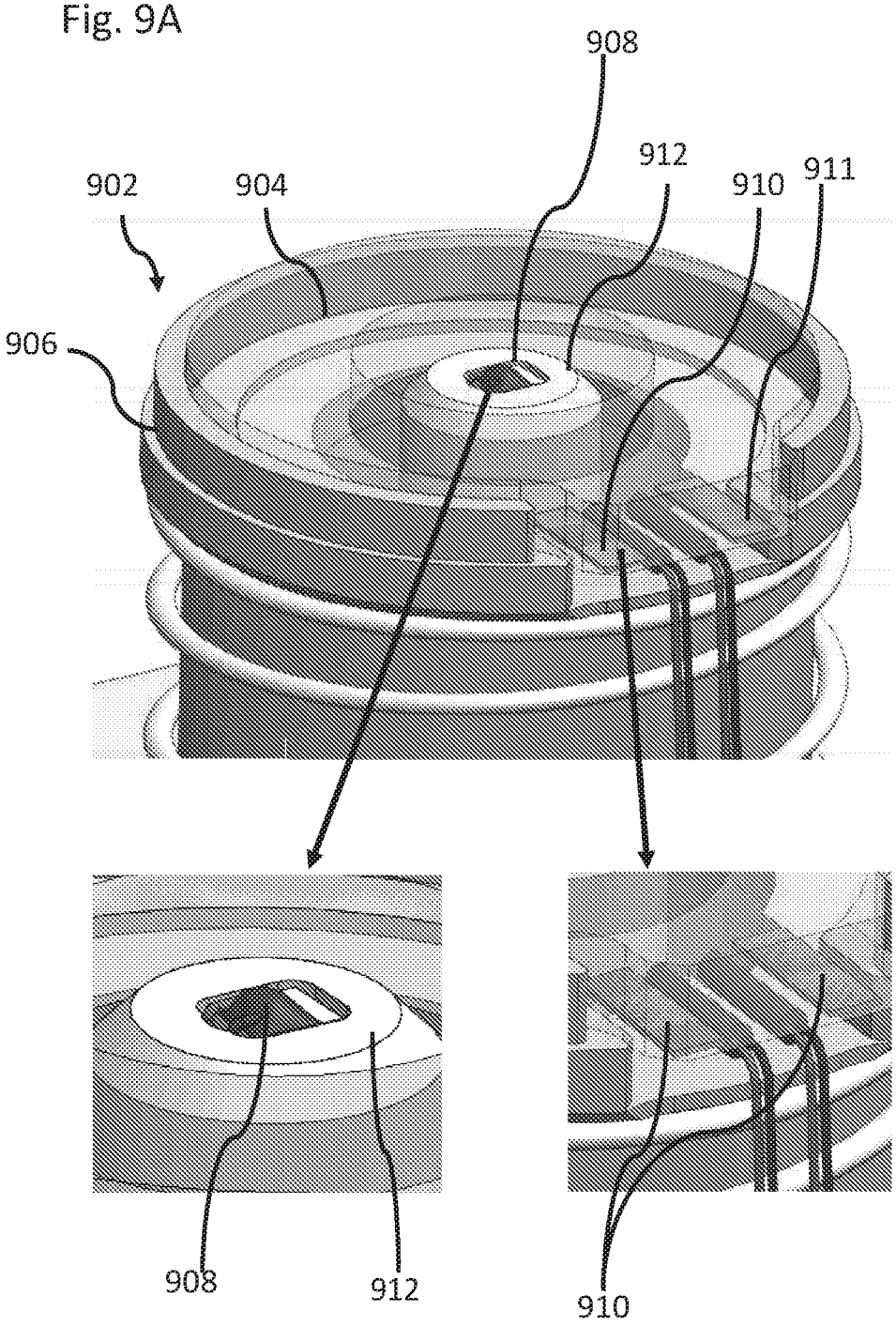


Fig. 9B

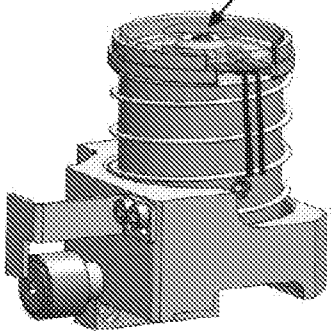


Fig. 9C

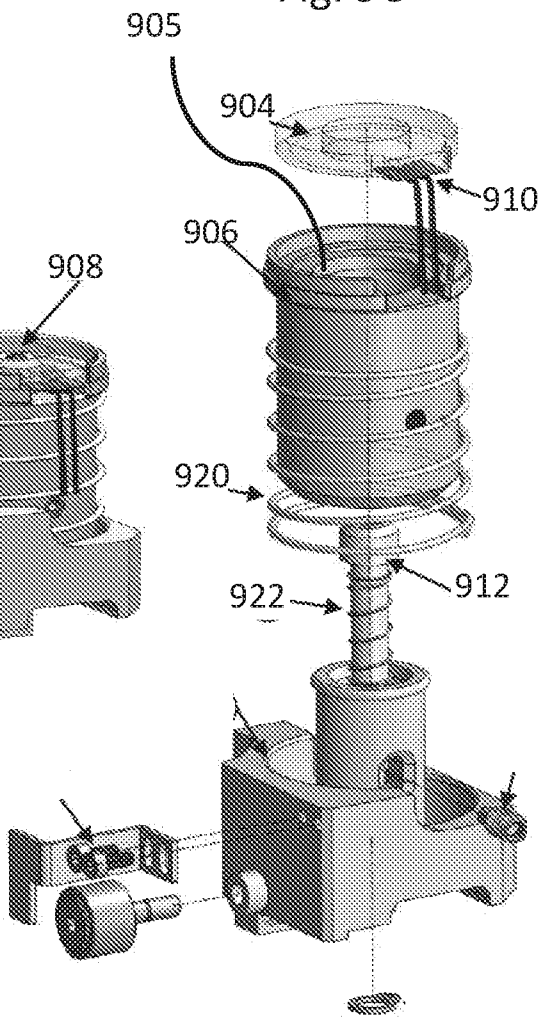


Fig. 9D

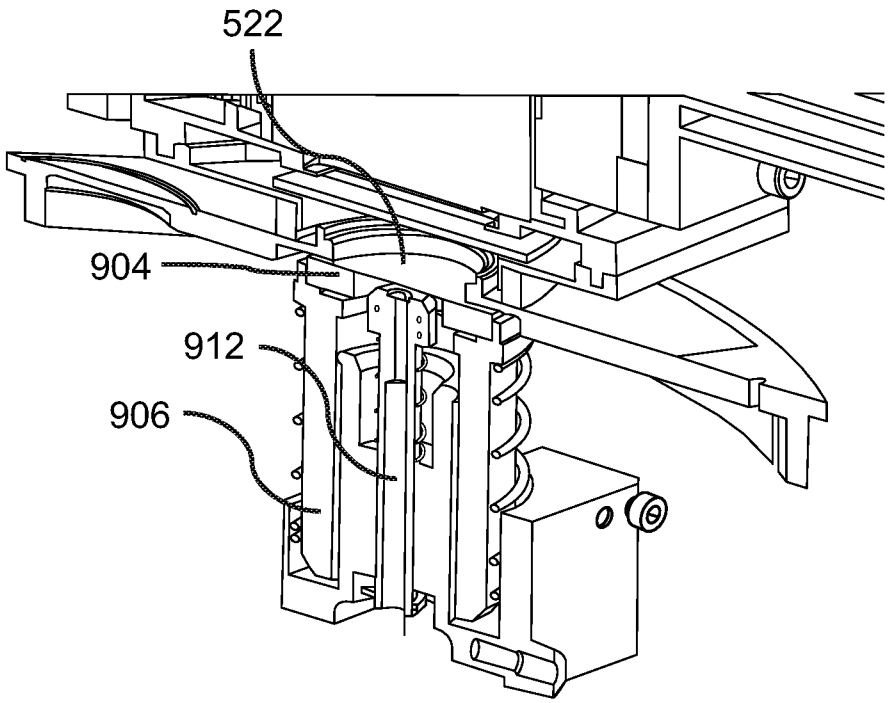


Fig. 9E

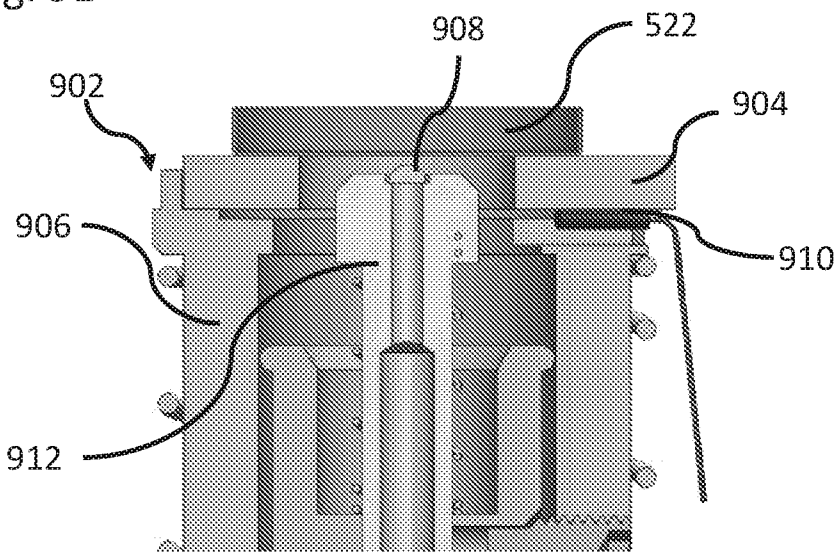


Fig. 9F

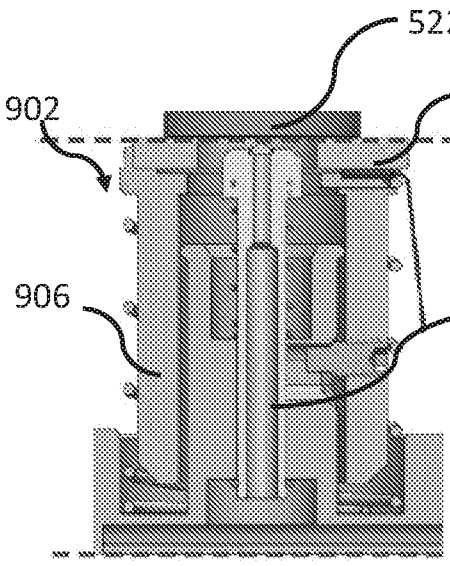


Fig. 9G

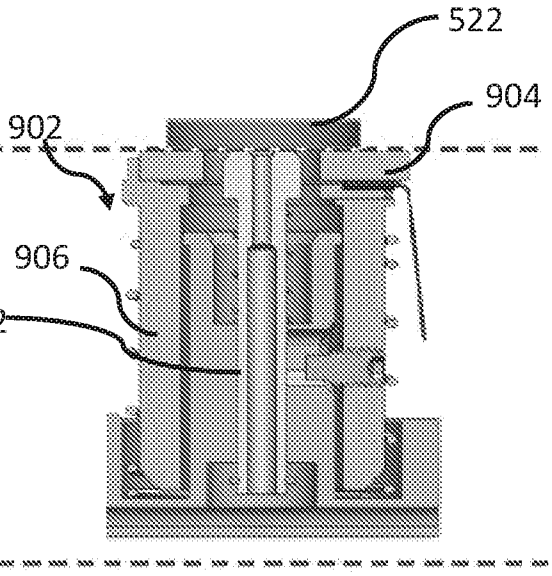


Fig. 10

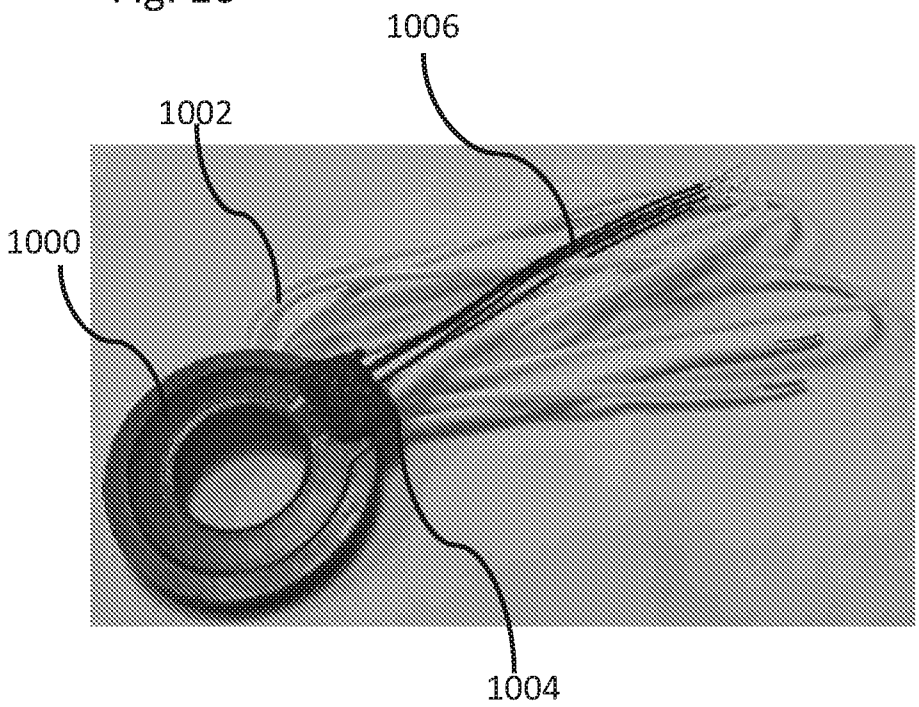


Fig. 11

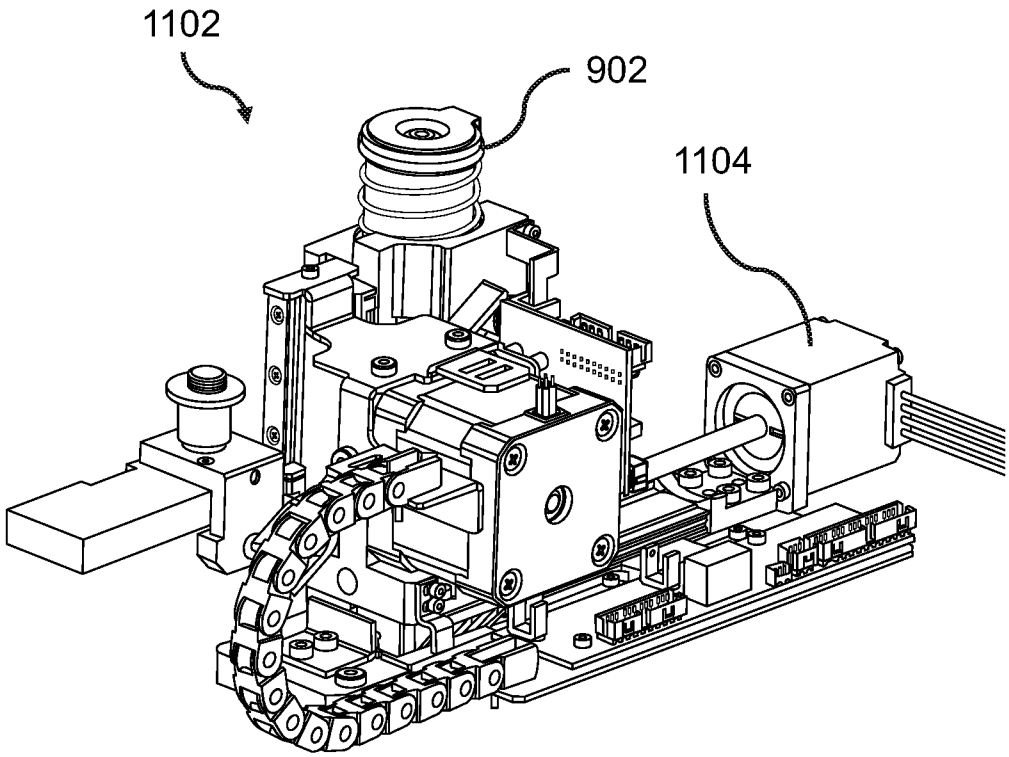


Fig. 12A

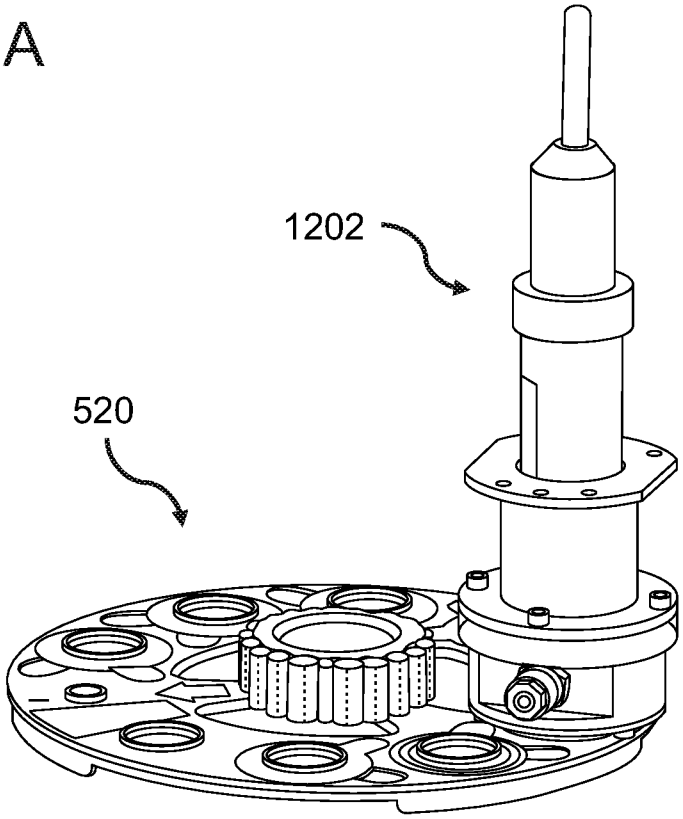


Fig. 12B

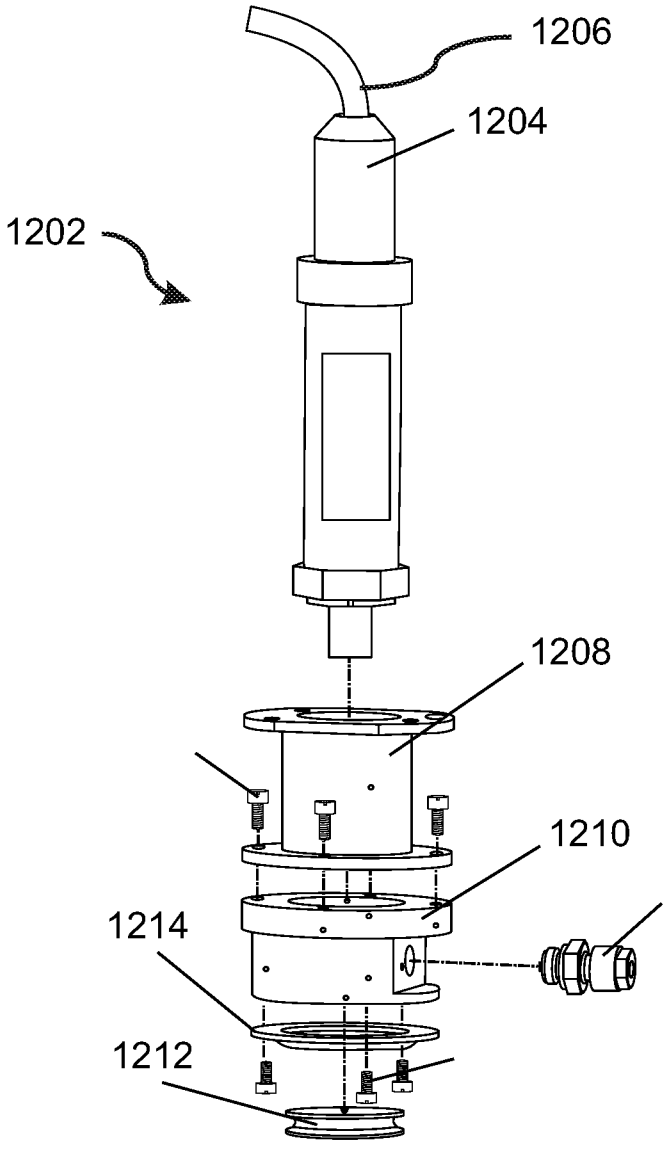


Fig. 12C

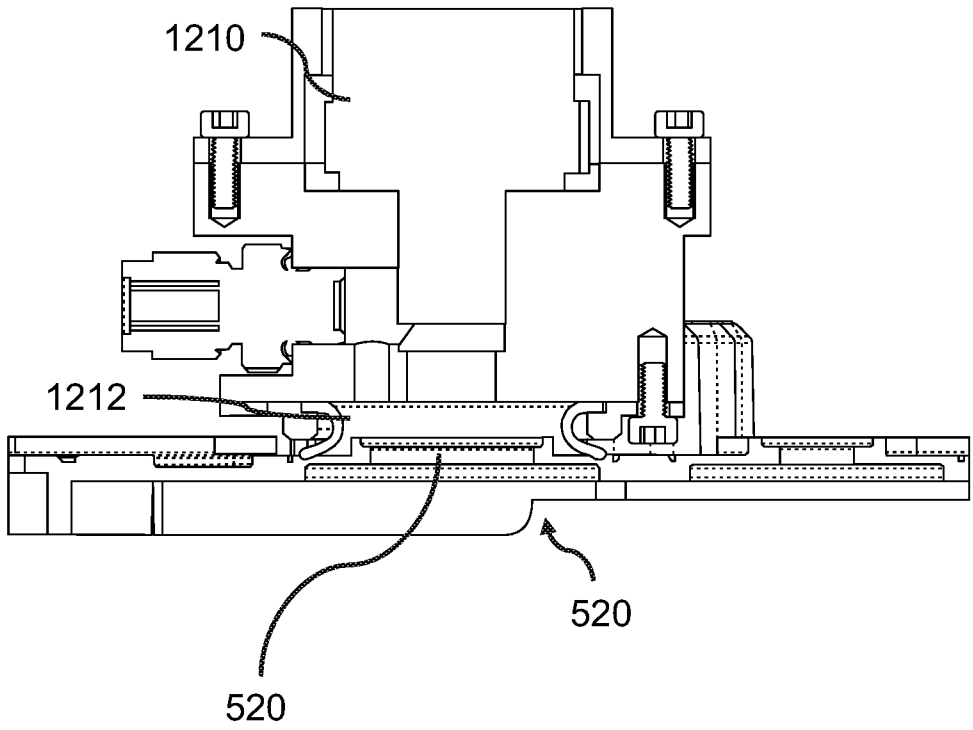


Fig. 13A

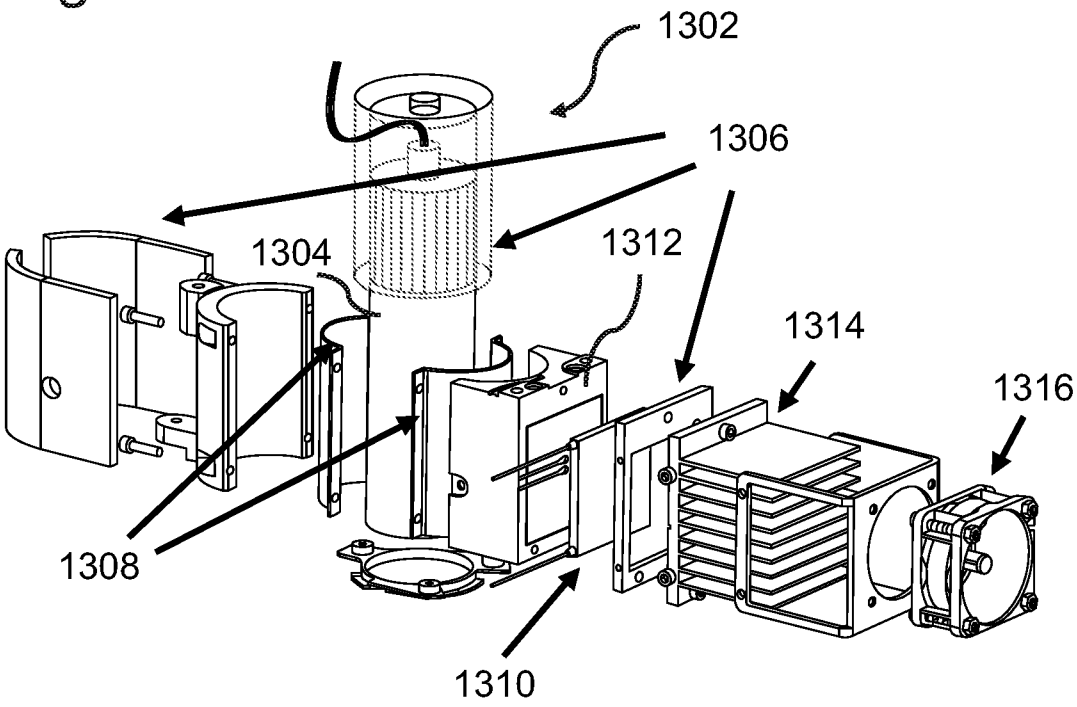


Fig. 13B

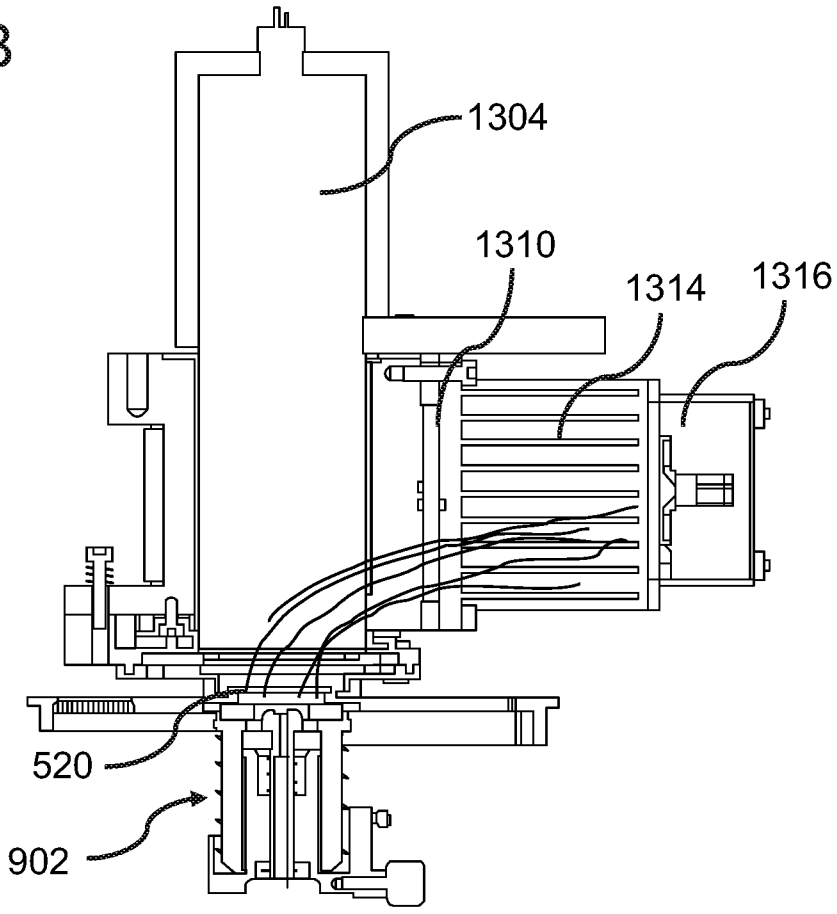


Fig. 13C

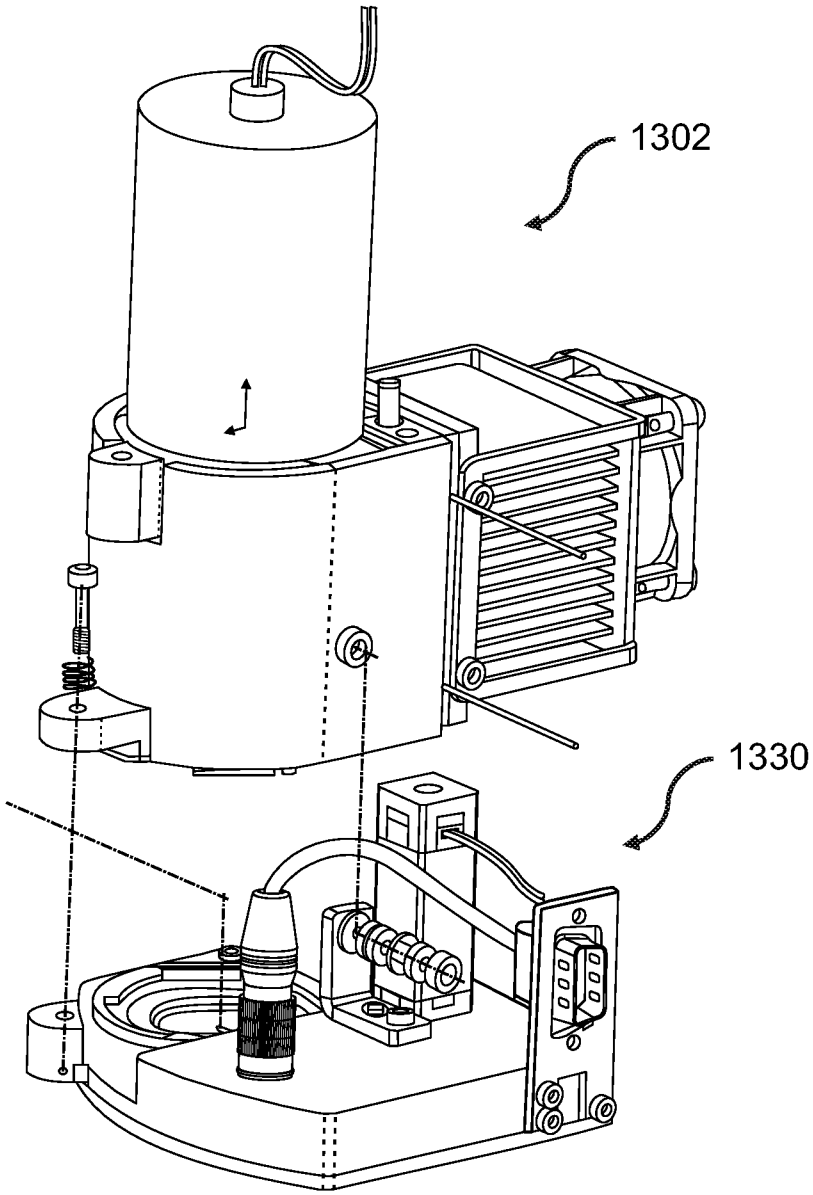


Fig. 13D

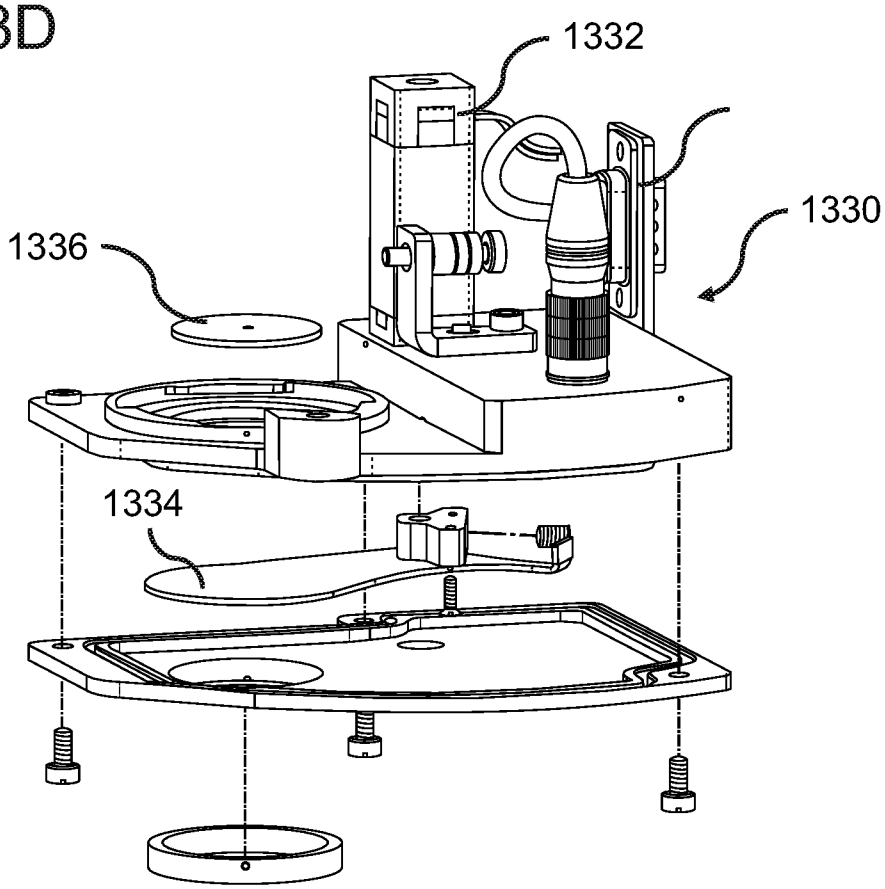


Fig. 13E

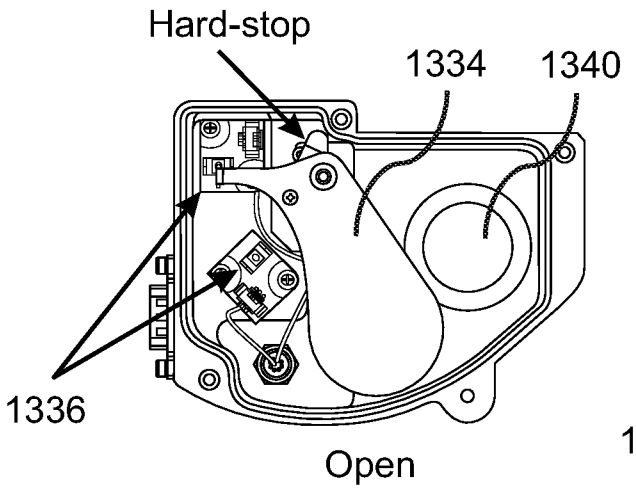


Fig. 13F

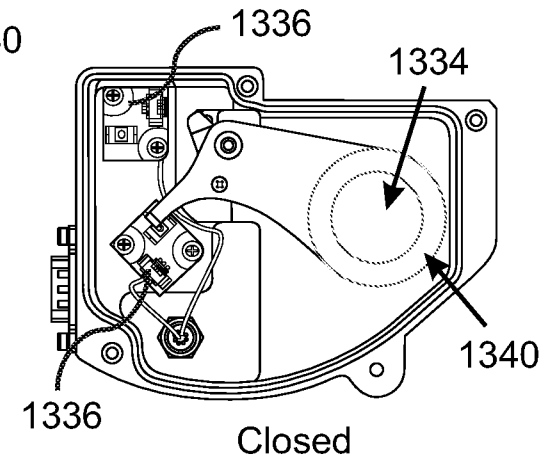


Fig. 14

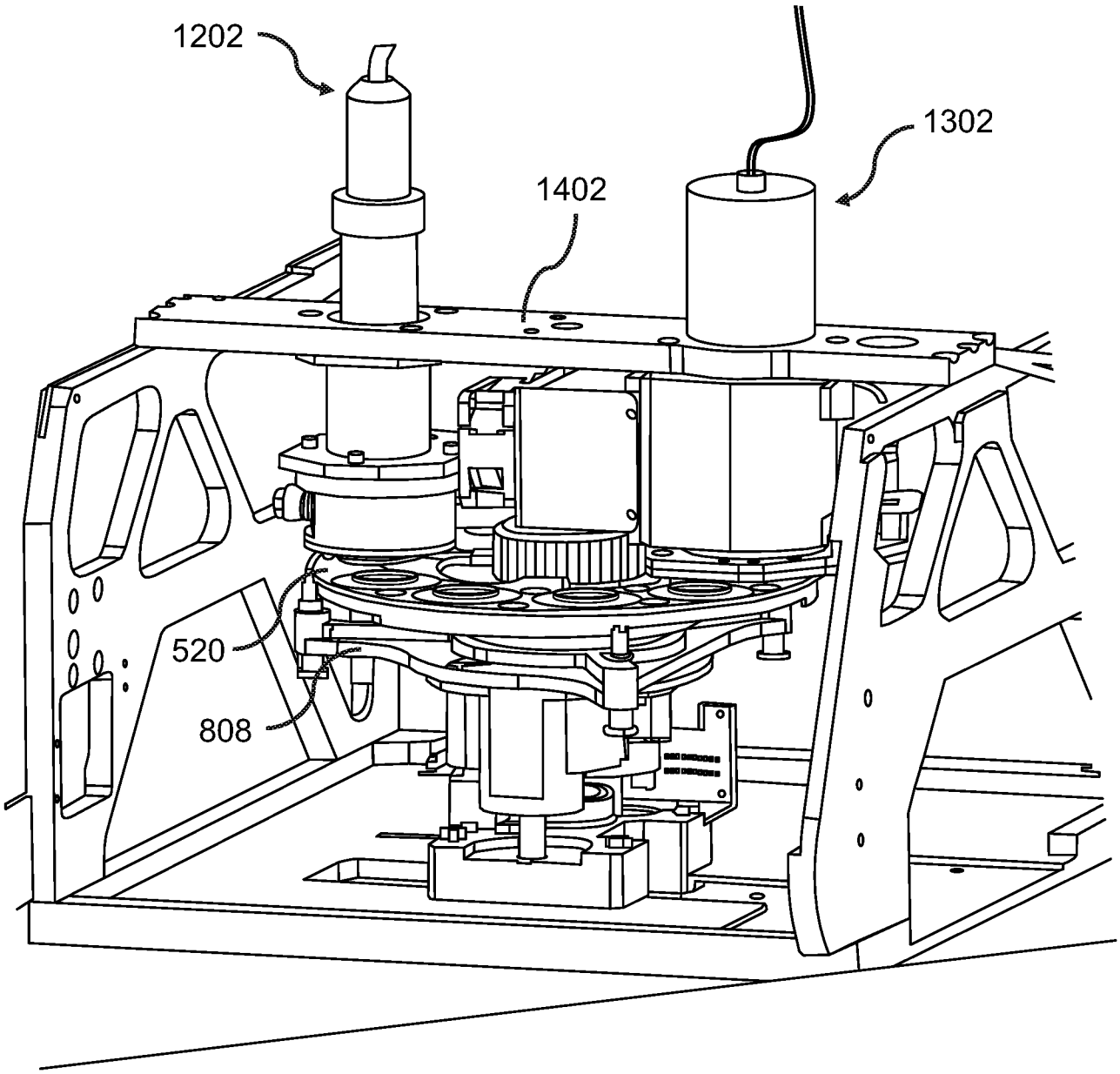


Fig. 15A

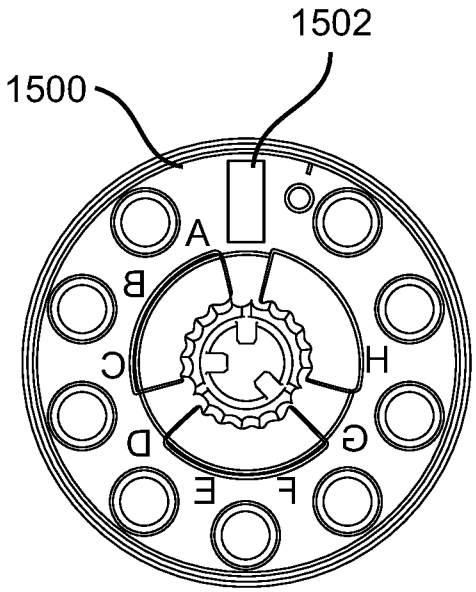


Fig. 15B

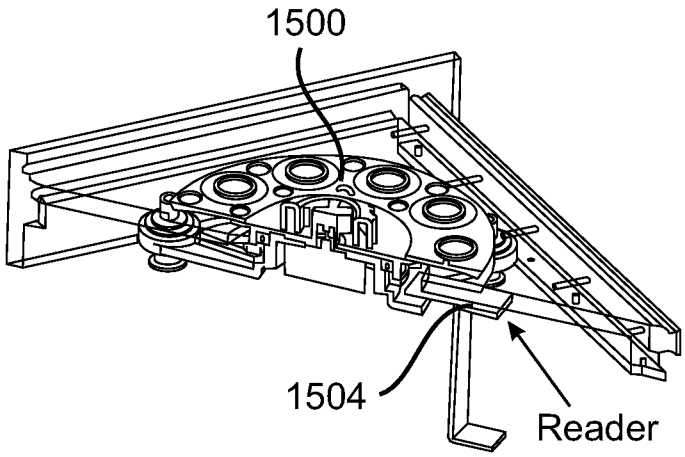


Fig. 15C

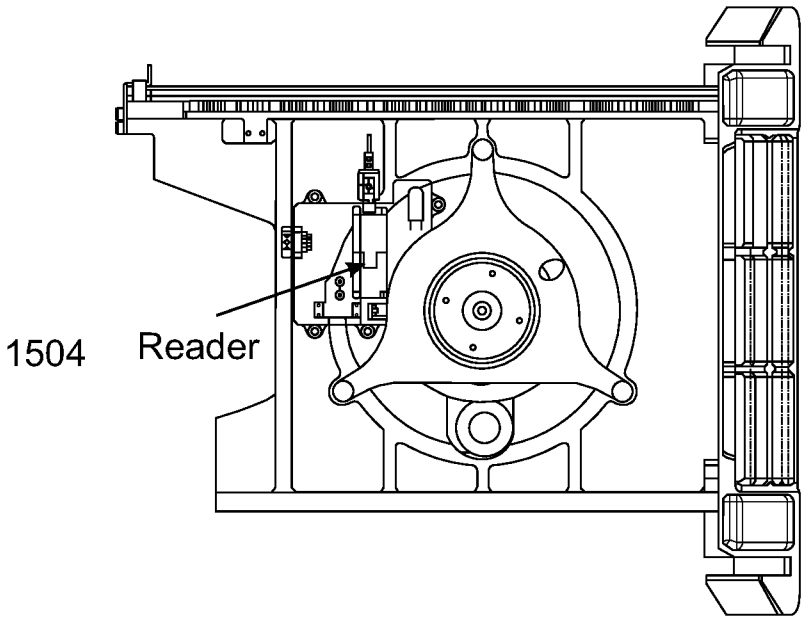


Fig. 15D

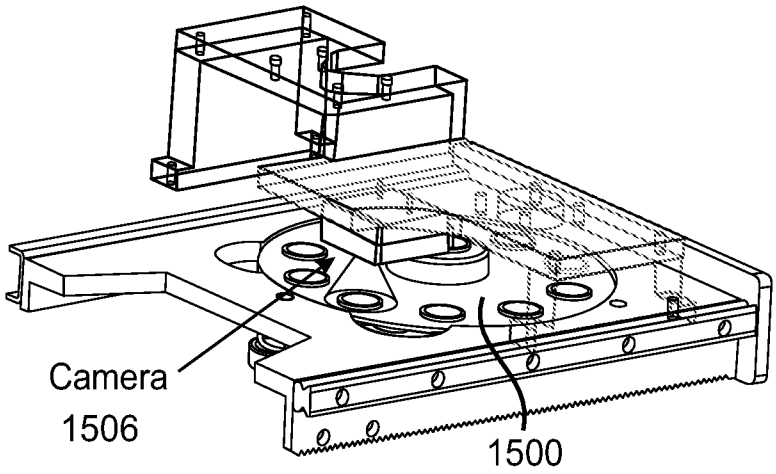


Fig. 15E

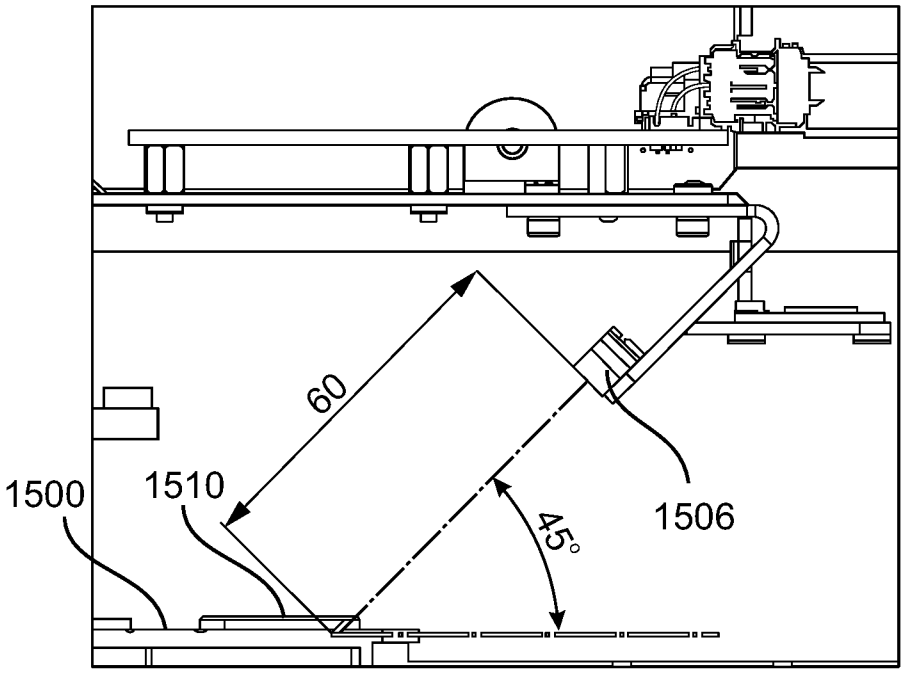


Fig. 16A

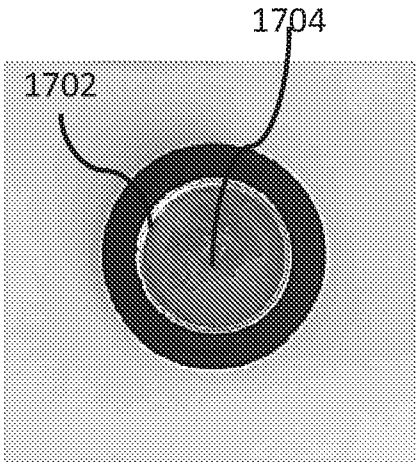


Fig. 16B

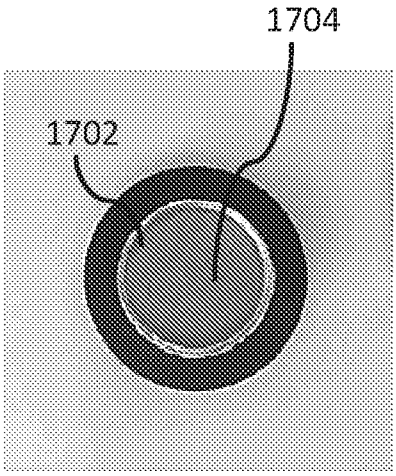


Fig. 17

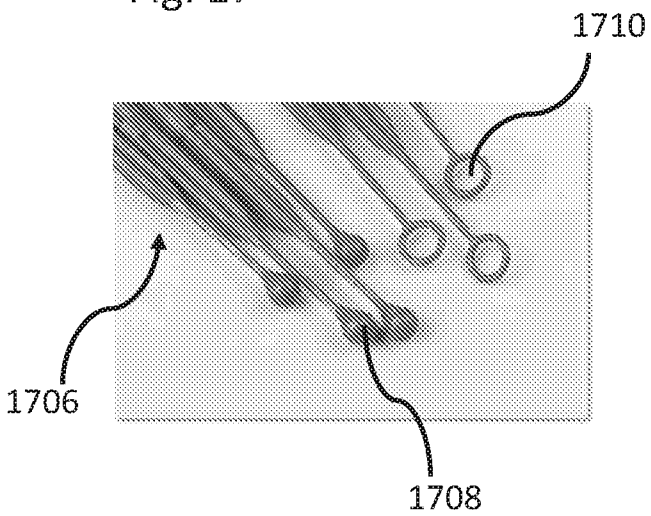


Fig. 18

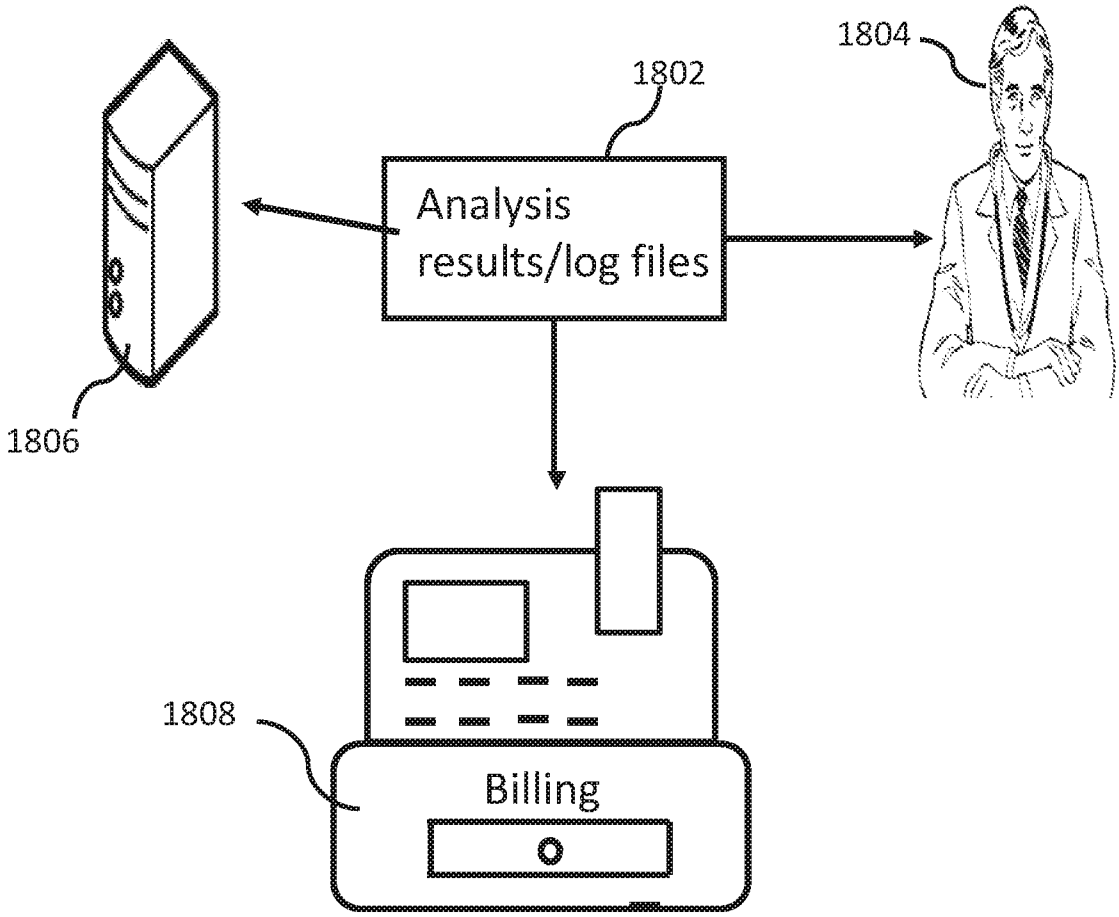


Fig. 19

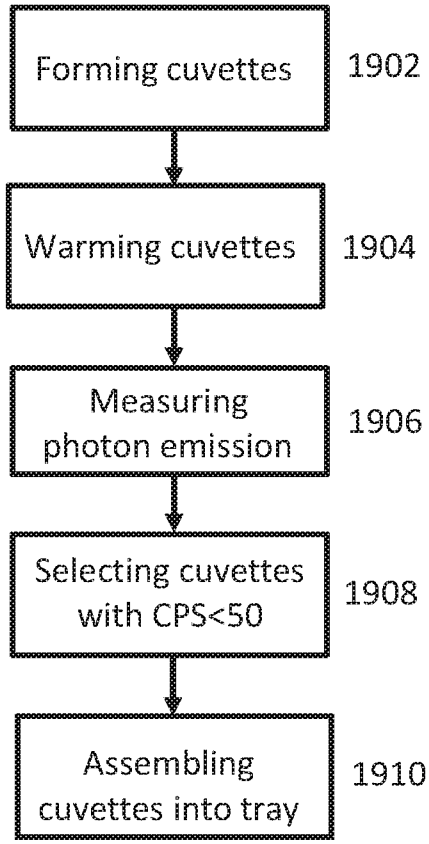

Forming cuvettes
1902
Warming cuvettes
1904
Measuring photon emission
1906
Selecting cuvettes with CPS<50
1908
Assembling cuvettes into tray
1910

Fig. 20A

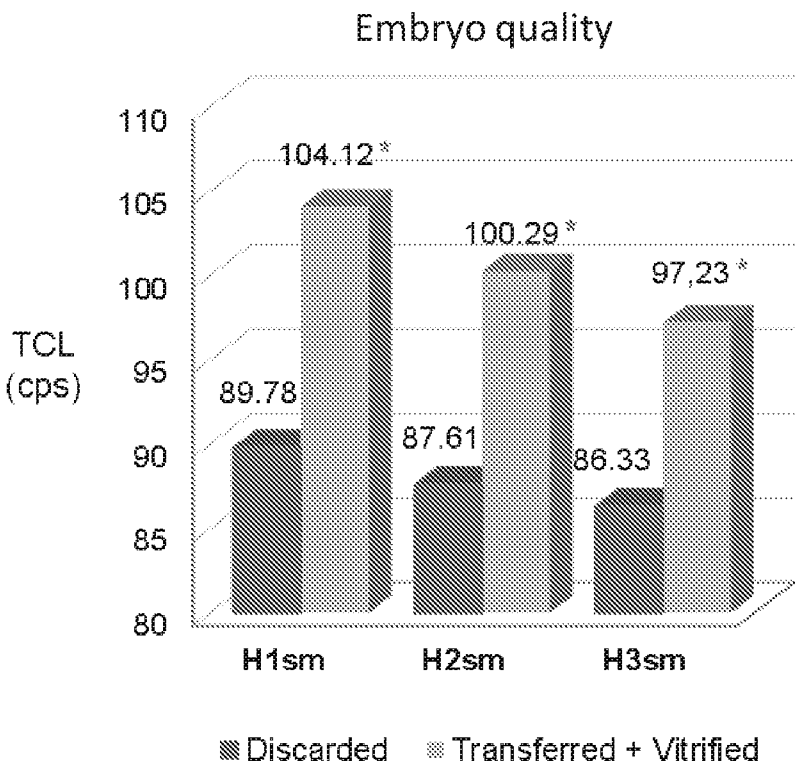


Fig. 20B

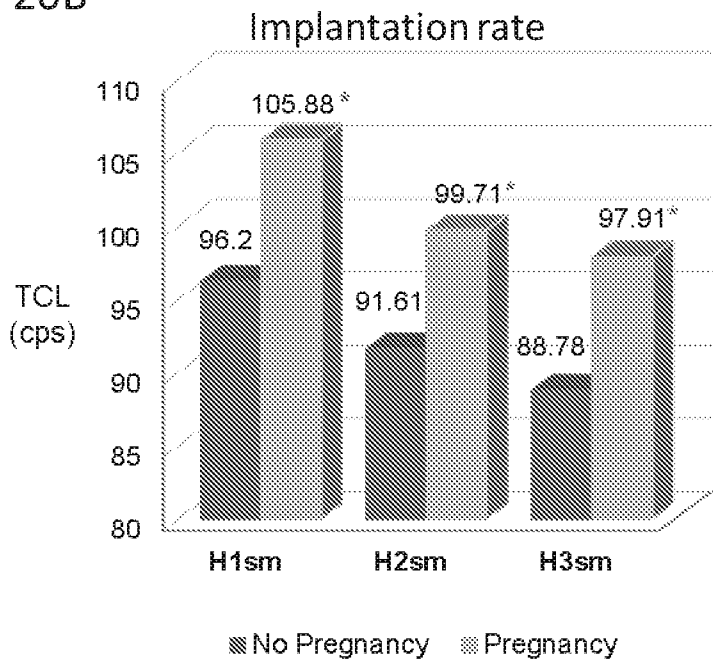


Fig. 20C

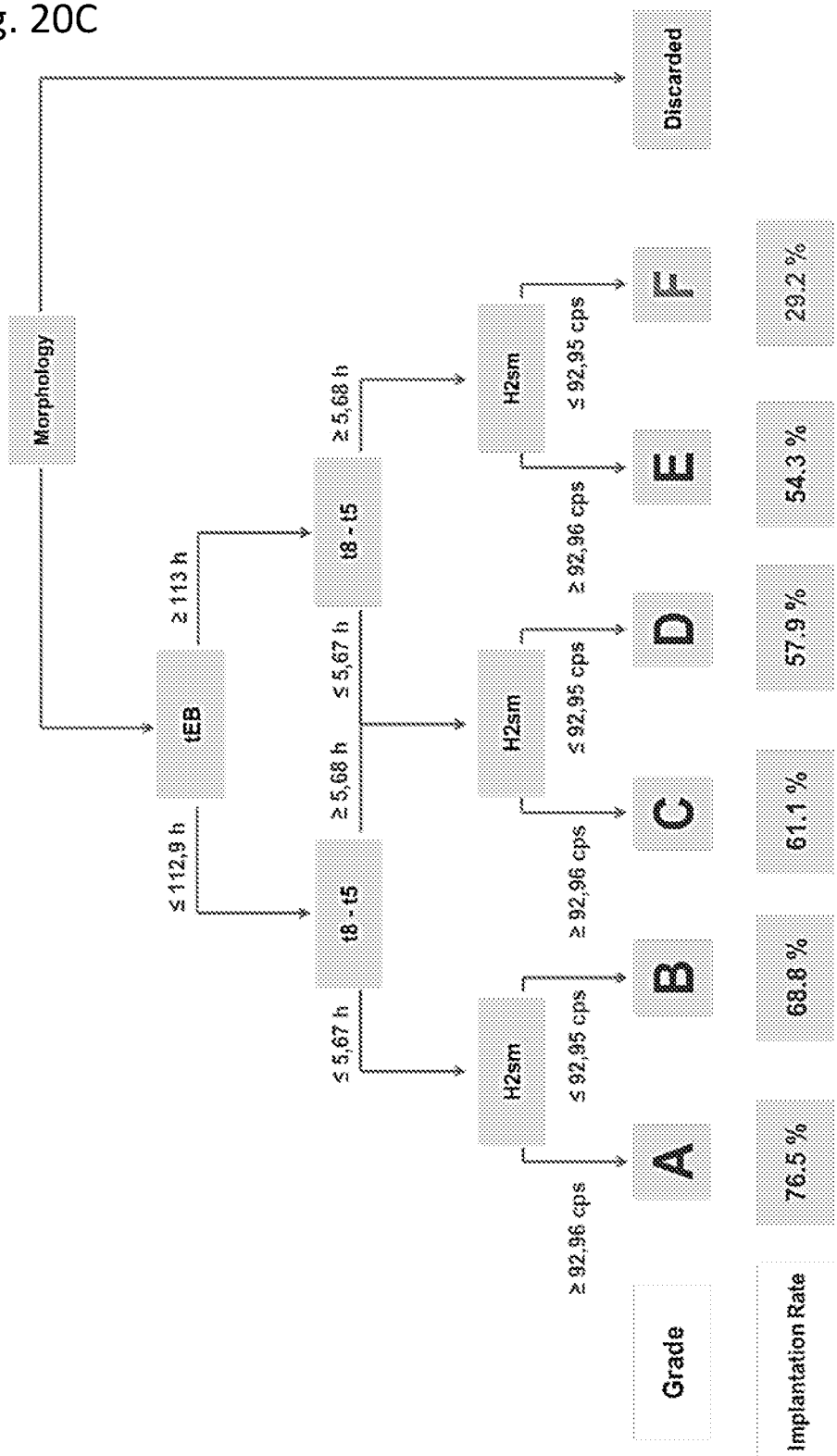

Morphology
Discarded
tEB
≥ 113 h
≤ 112,9 h
t8 - t5
≥ 5,68 h
≤ 5,67 h
H2sm
≤ 92,95 cps
≥ 92,96 cps
A
B
C
D
E
F
Grade
Implantation Rate
76.5 %
68.8 %
61.1 %
57.9 %
54.3 %
29.2 %

Fig. 21A

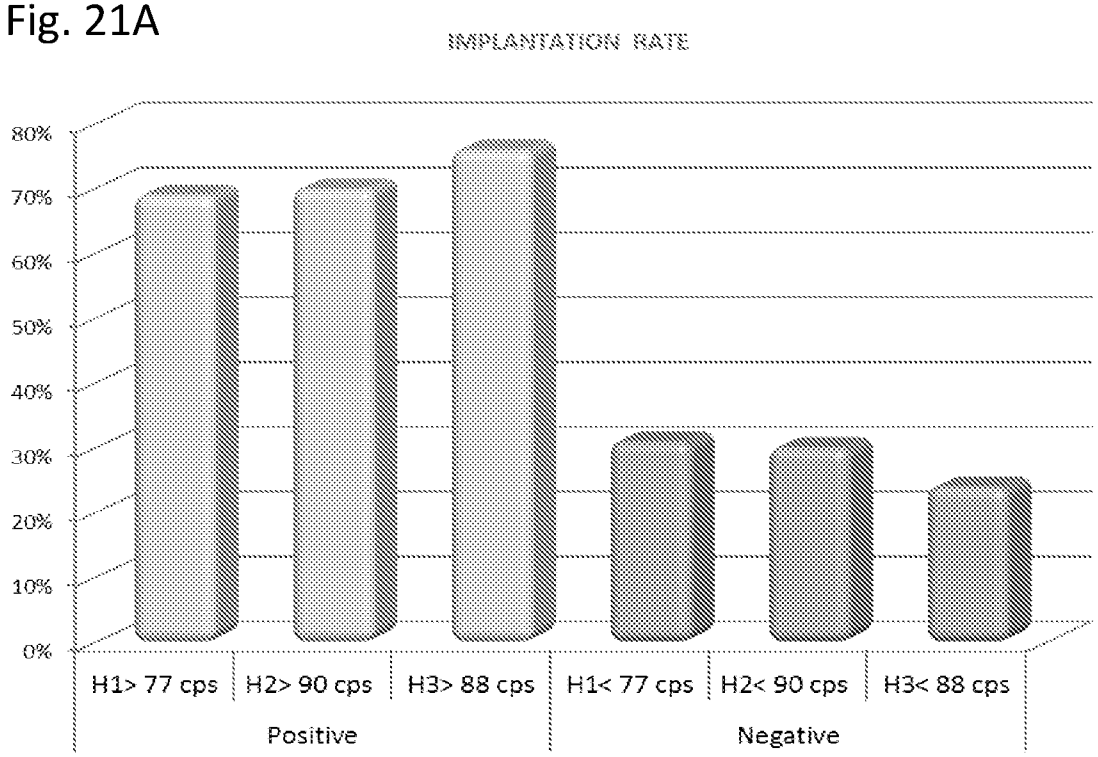
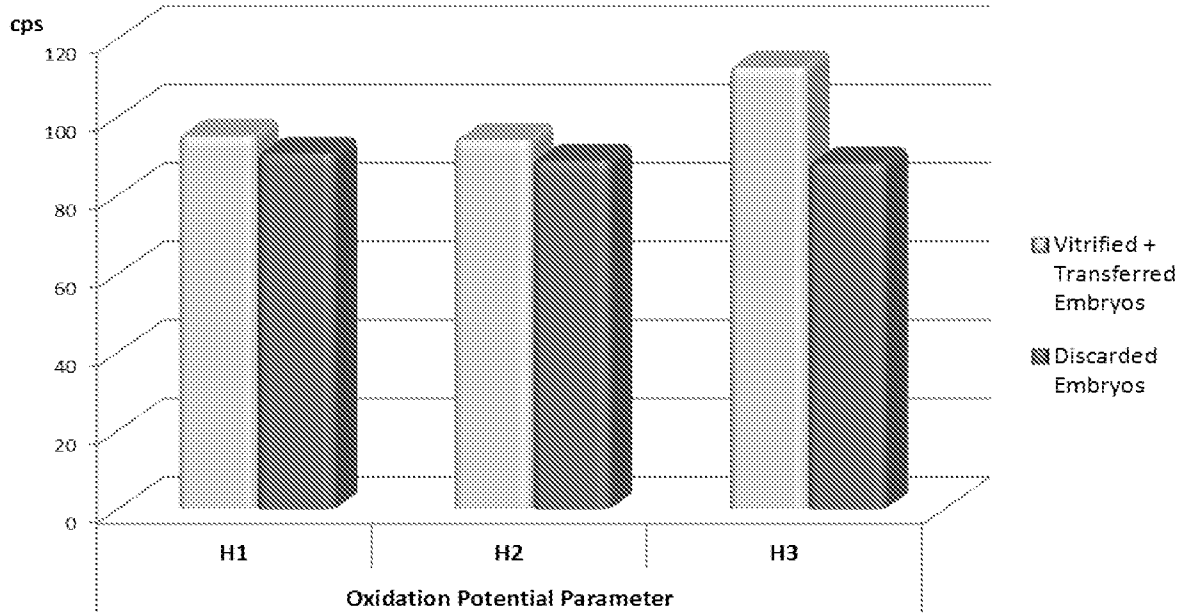


Fig. 21B



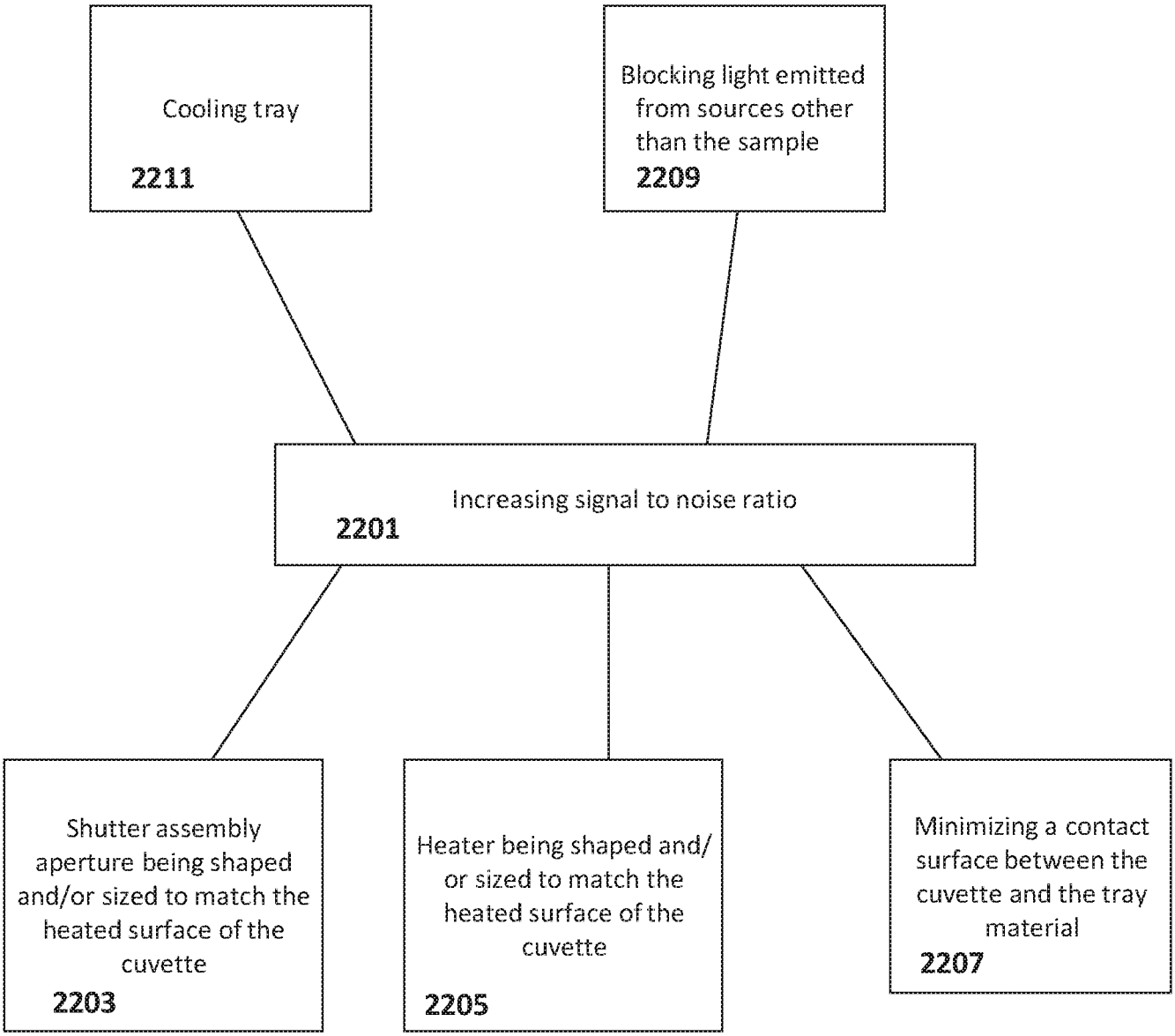

Cooling tray
2211
Blocking light emitted from sources other than the sample
2209
Increasing signal to noise ratio
2201
Shutter assembly aperture being shaped and/or sized to match the heated surface of the cuvette
2203
Heater being shaped and/or sized to match the heated surface of the cuvette
2205
Minimizing a contact surface between the cuvette and the tray material
2207

FIG. 22A

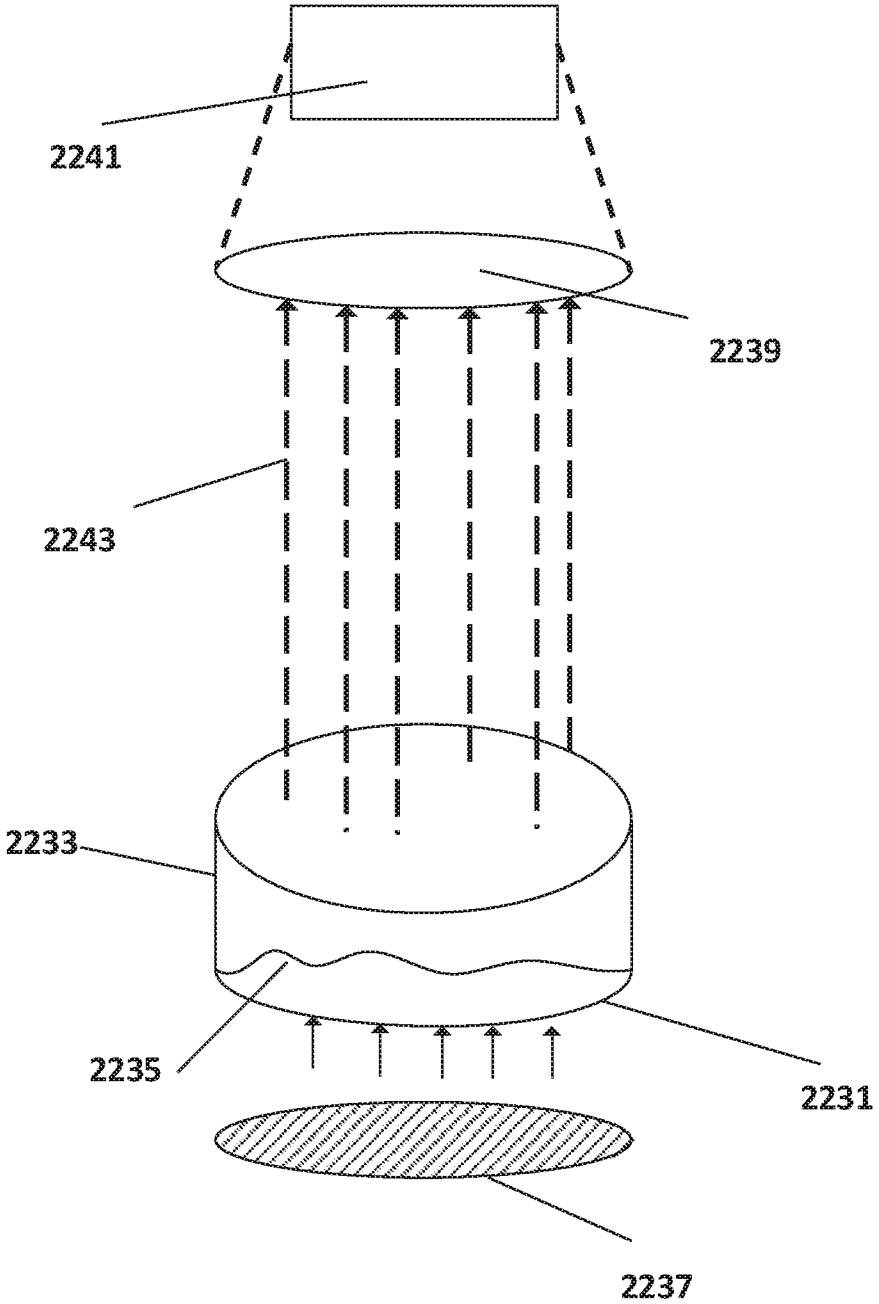


FIG. 22B

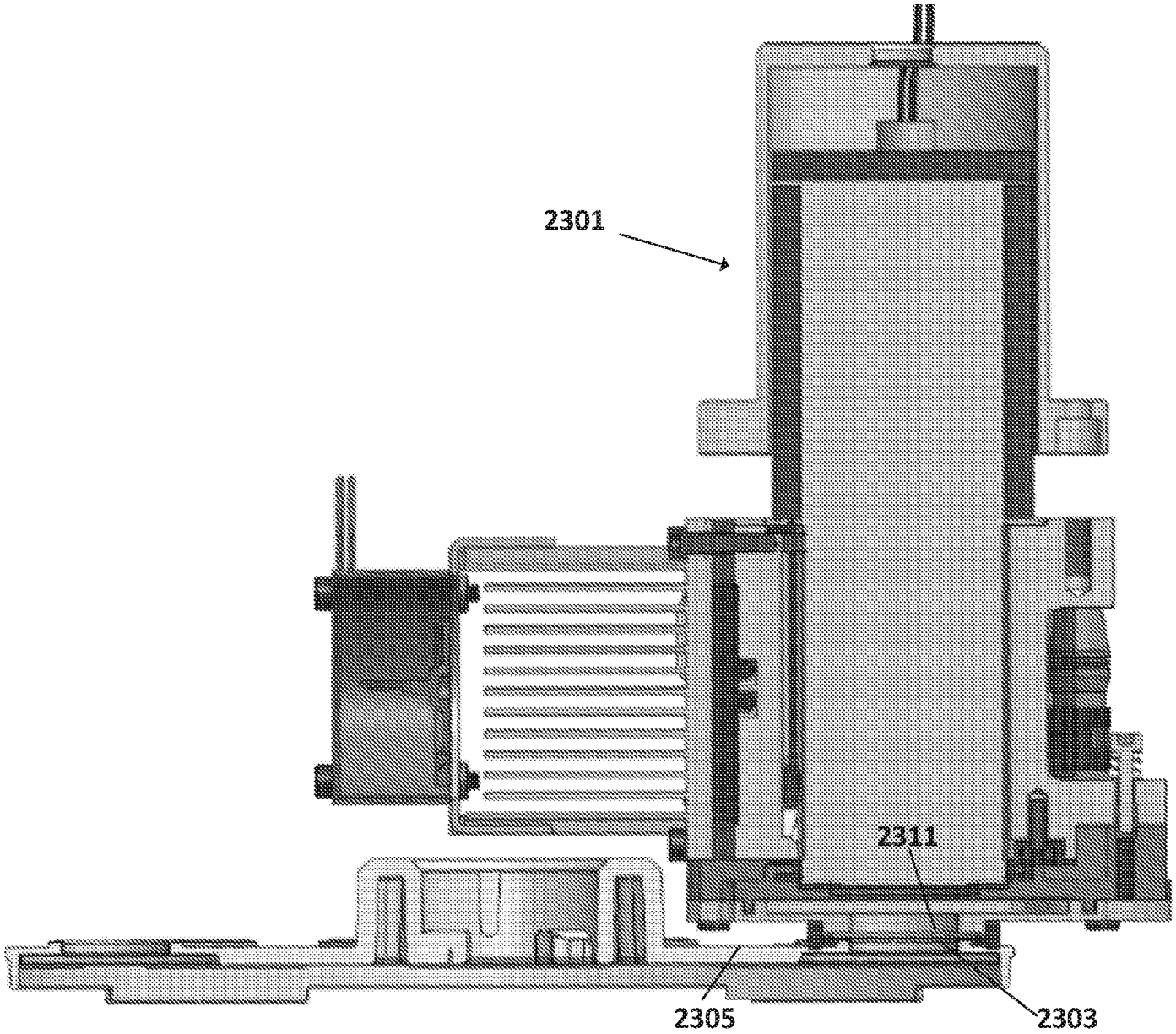


FIG. 23A

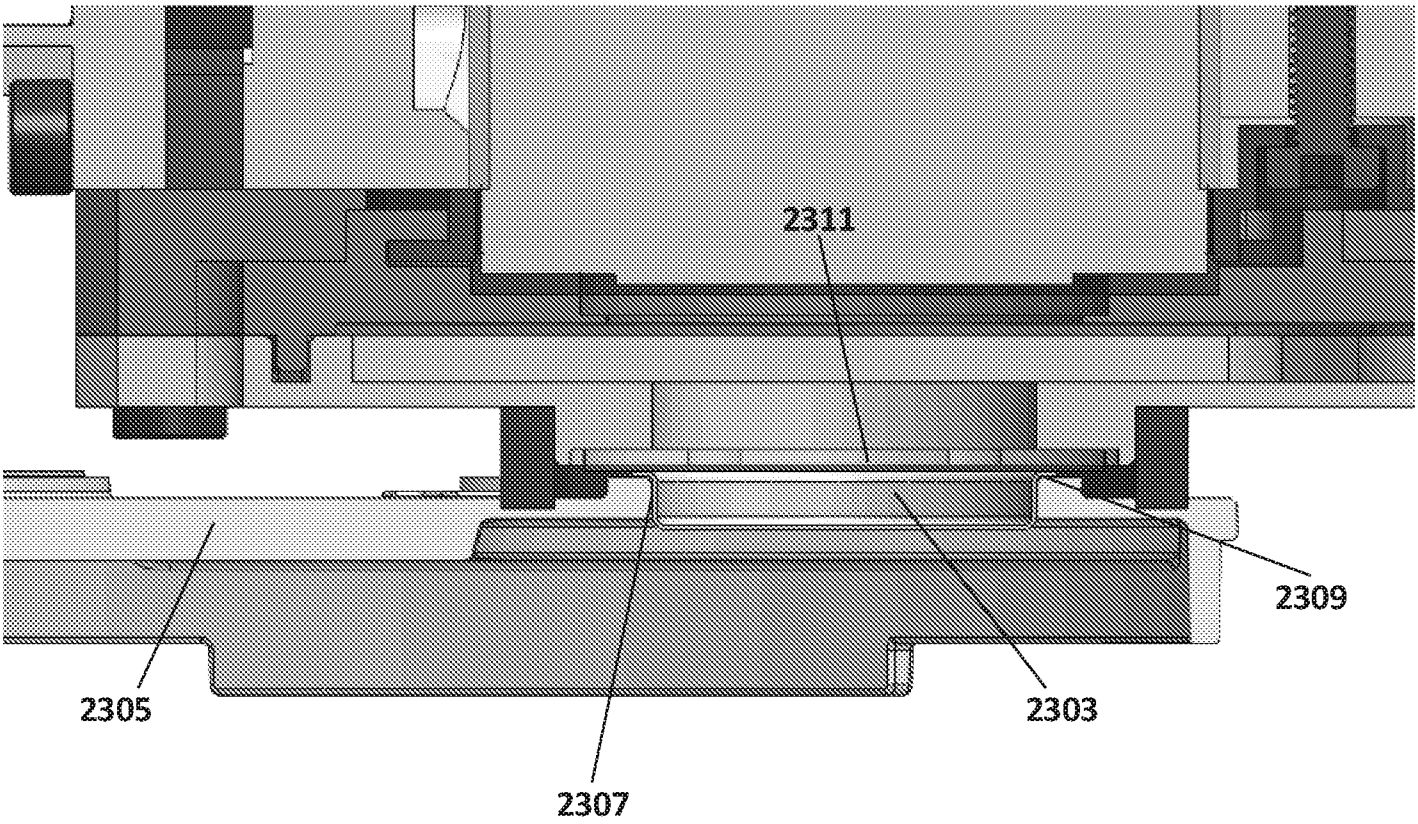


FIG. 23B

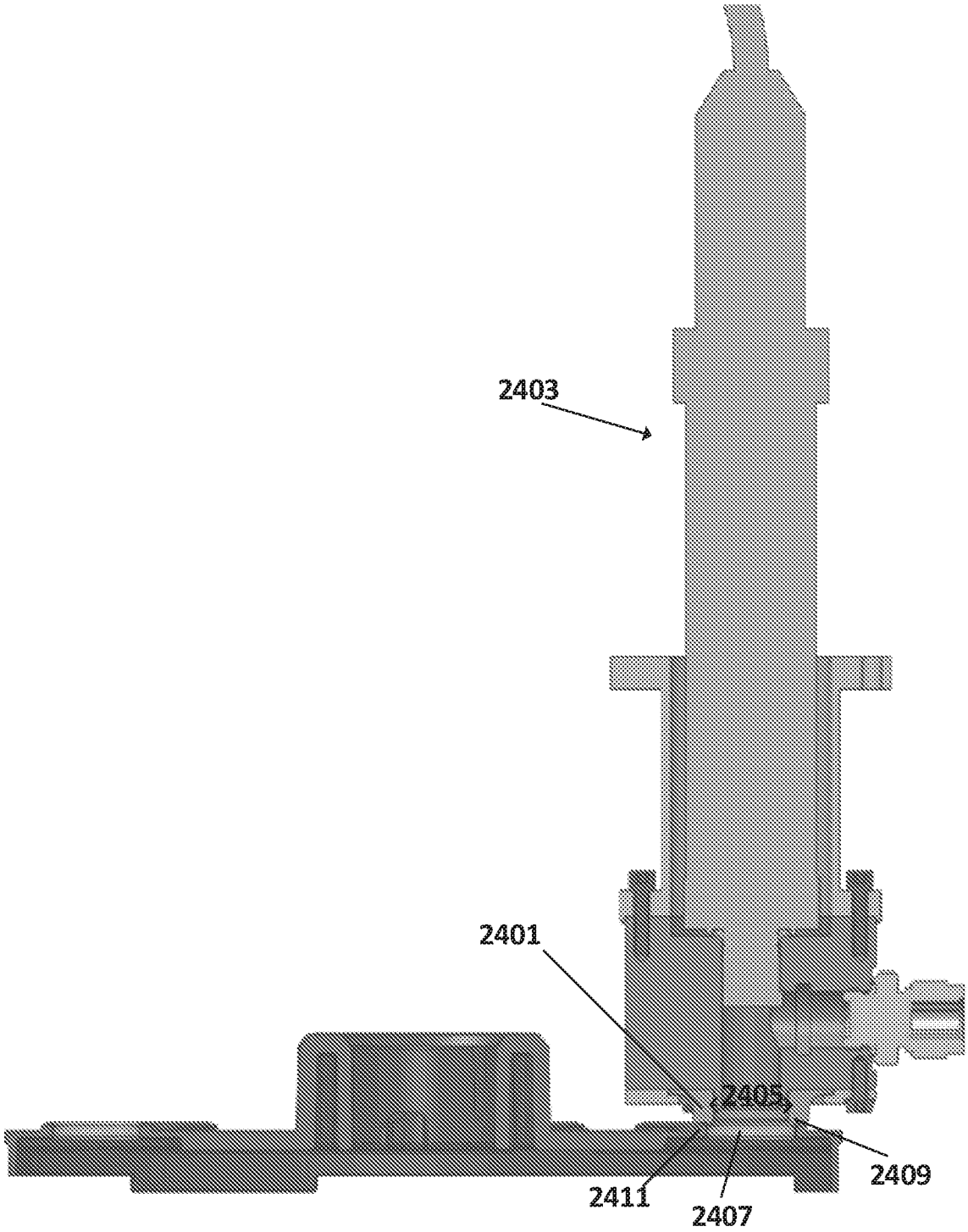


FIG. 24A

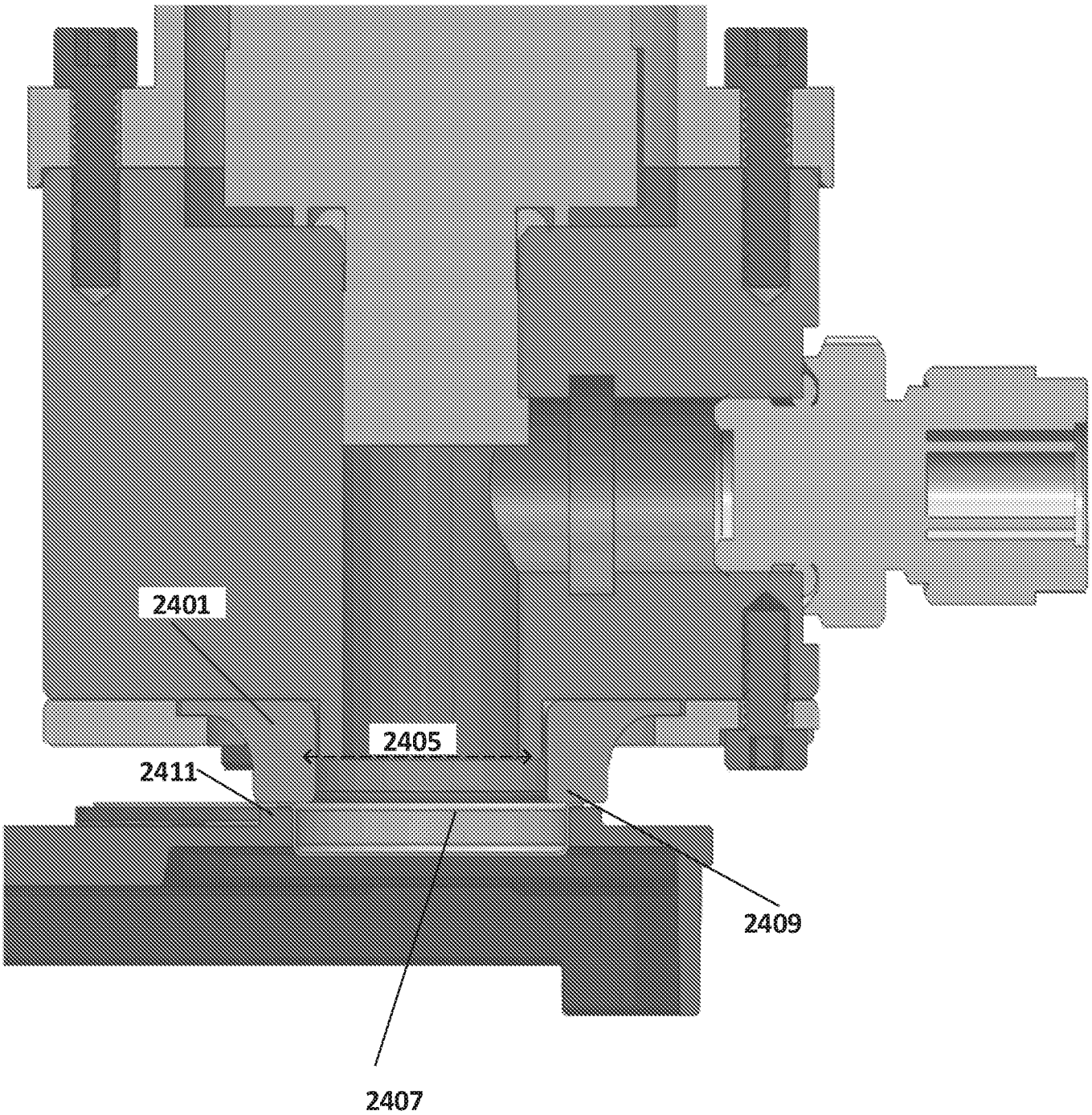


FIG. 24B