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(54) **SYSTEMS AND METHODS FOR DETERMINING PHYSIOLOGICAL PARAMETERS USING MEASURED ANALYTE VALUES**

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Related U.S. Application Data

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(51) **Int. Cl.**
A61K 5/00 (2006.01)

(52) **U.S. Cl.** **600/310; 600/316; 600/324; 600/328**

(58) **Field of Classification Search** None
See application file for complete search history.

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(57) **ABSTRACT**

Systems and methods for determining a physiological parameter in a patient are provided. In certain embodiments, a system can include an analyte detection system configured to measure first analyte data in a fluid sample received from a patient, a medical sensor configured to measure second analyte data in the patient, and a processor configured to receive the first analyte data and the second analyte data and to determine a physiological parameter based at least in part on the first analyte data and the second analyte data. In certain such embodiments, the medical sensor may be a pulse oximeter, and the physiological parameter may include a cardiovascular parameter including, for example, cardiac output.

28 Claims, 42 Drawing Sheets

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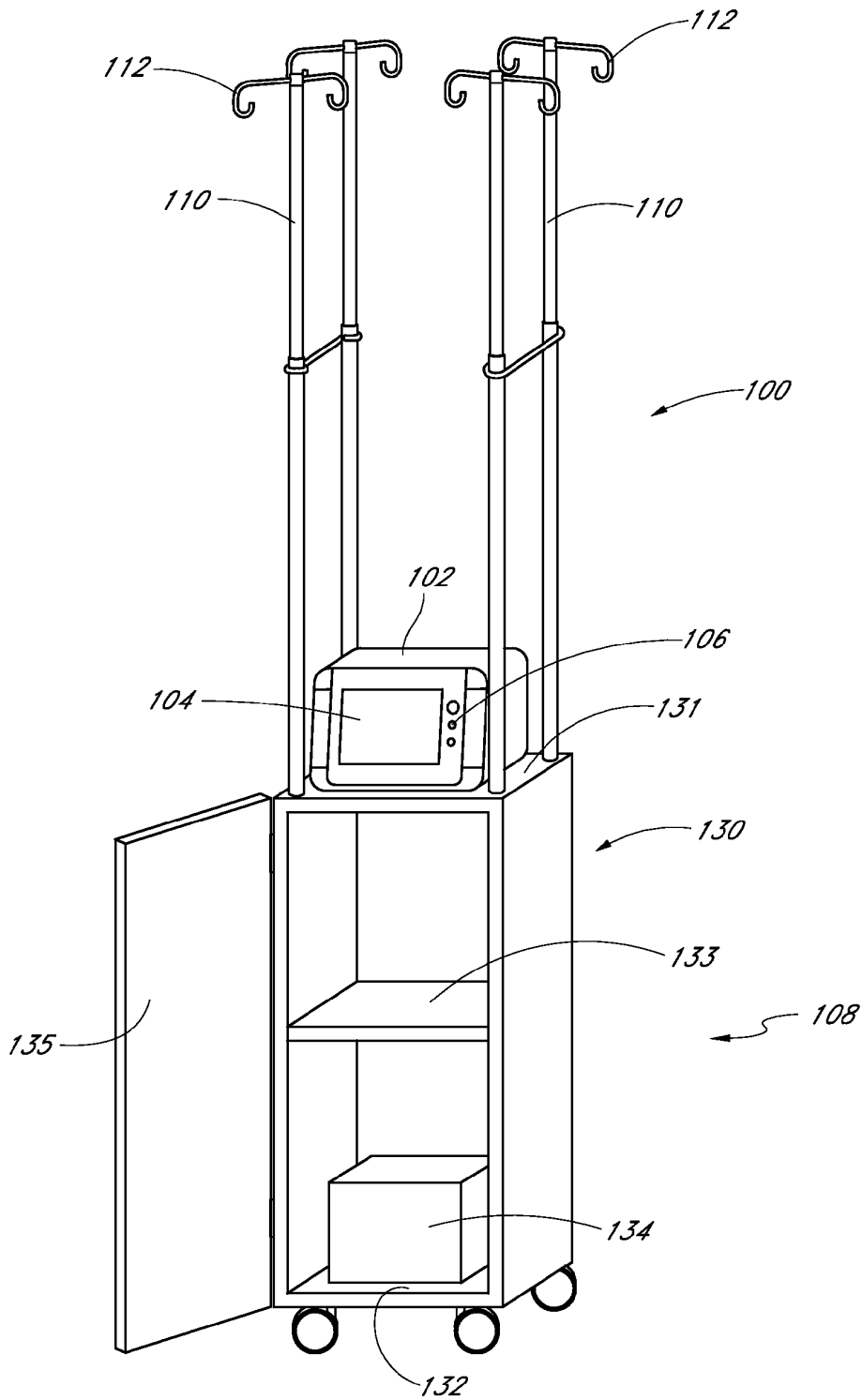


FIG. 1

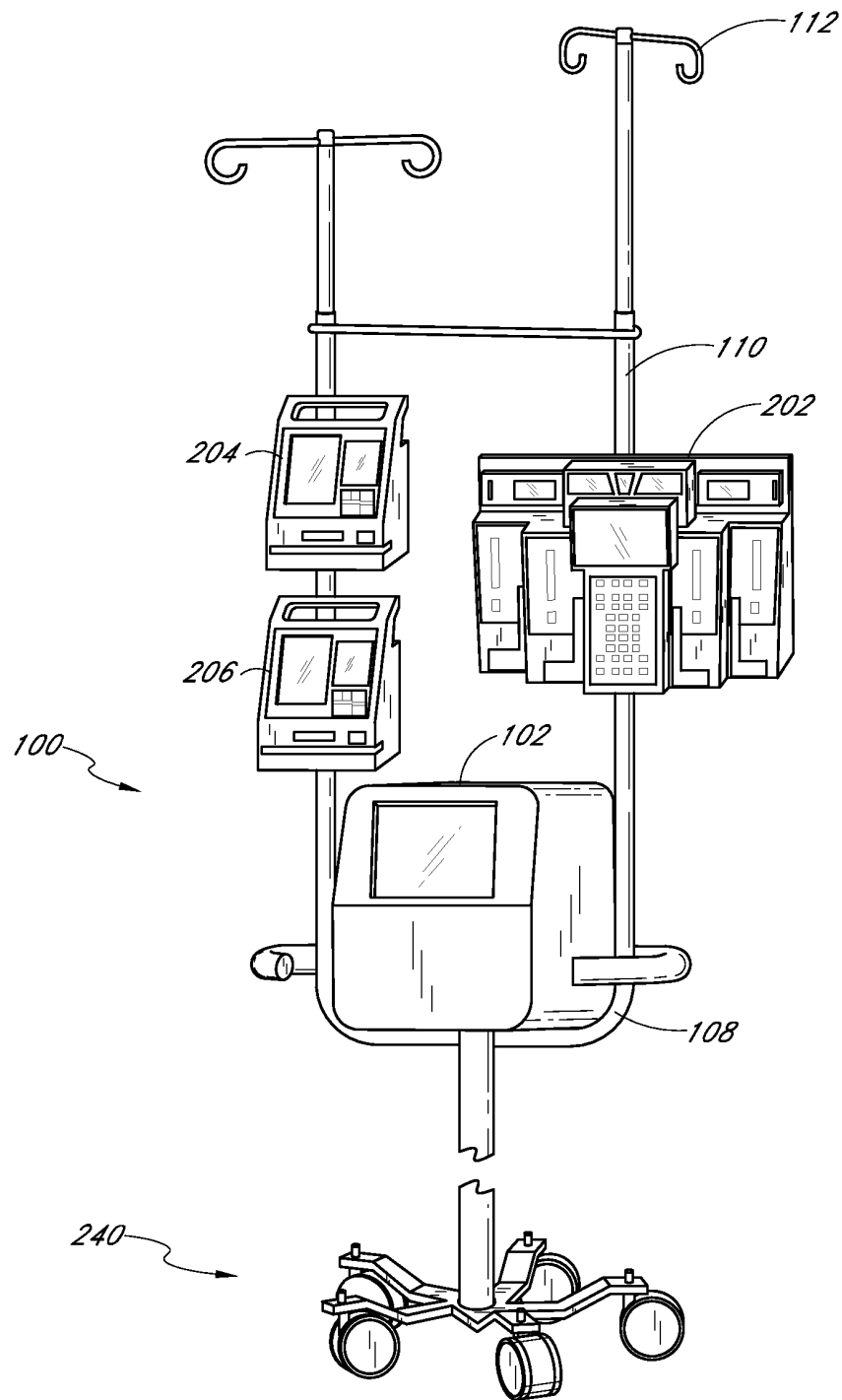


FIG. 2

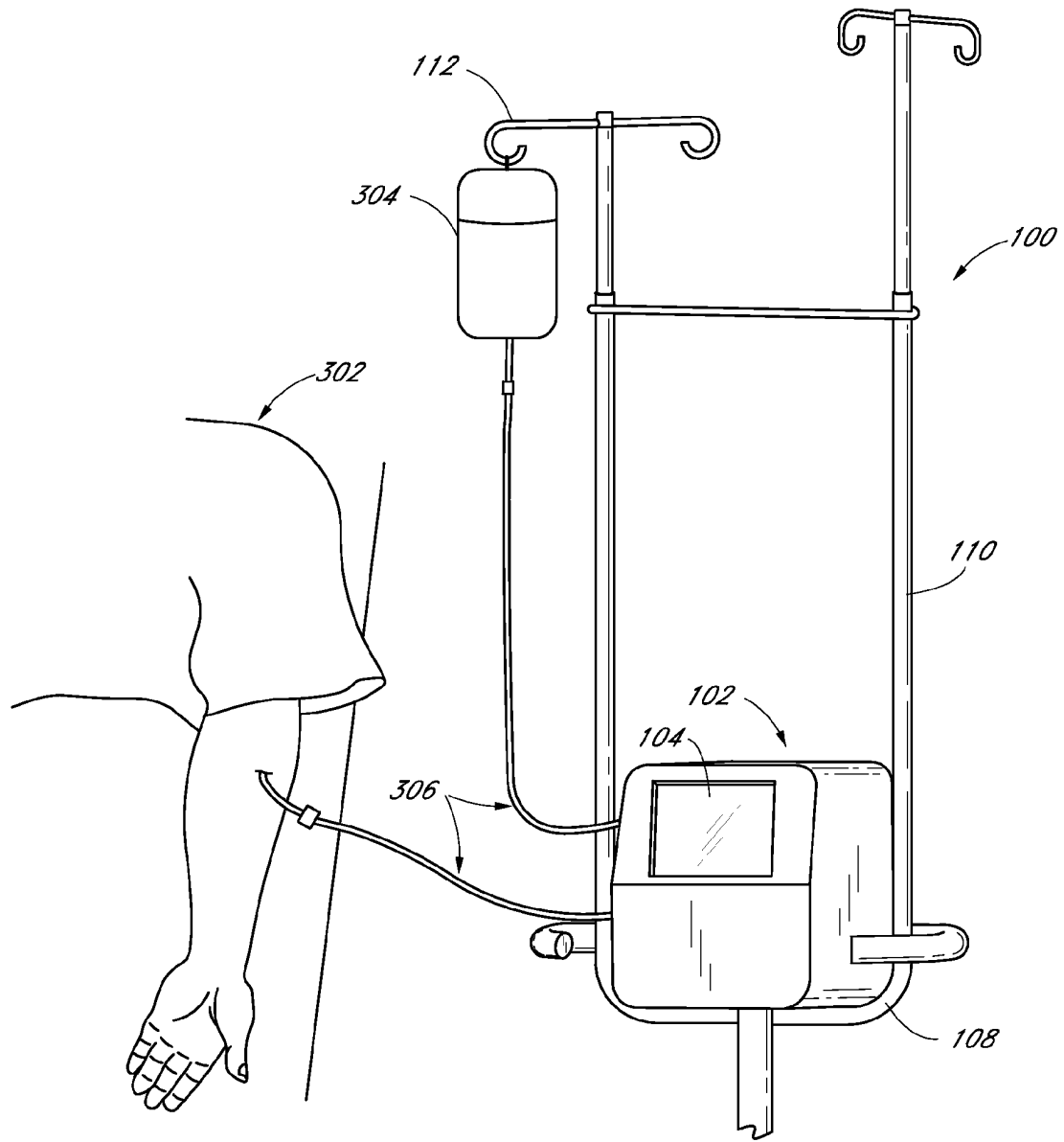


FIG. 3

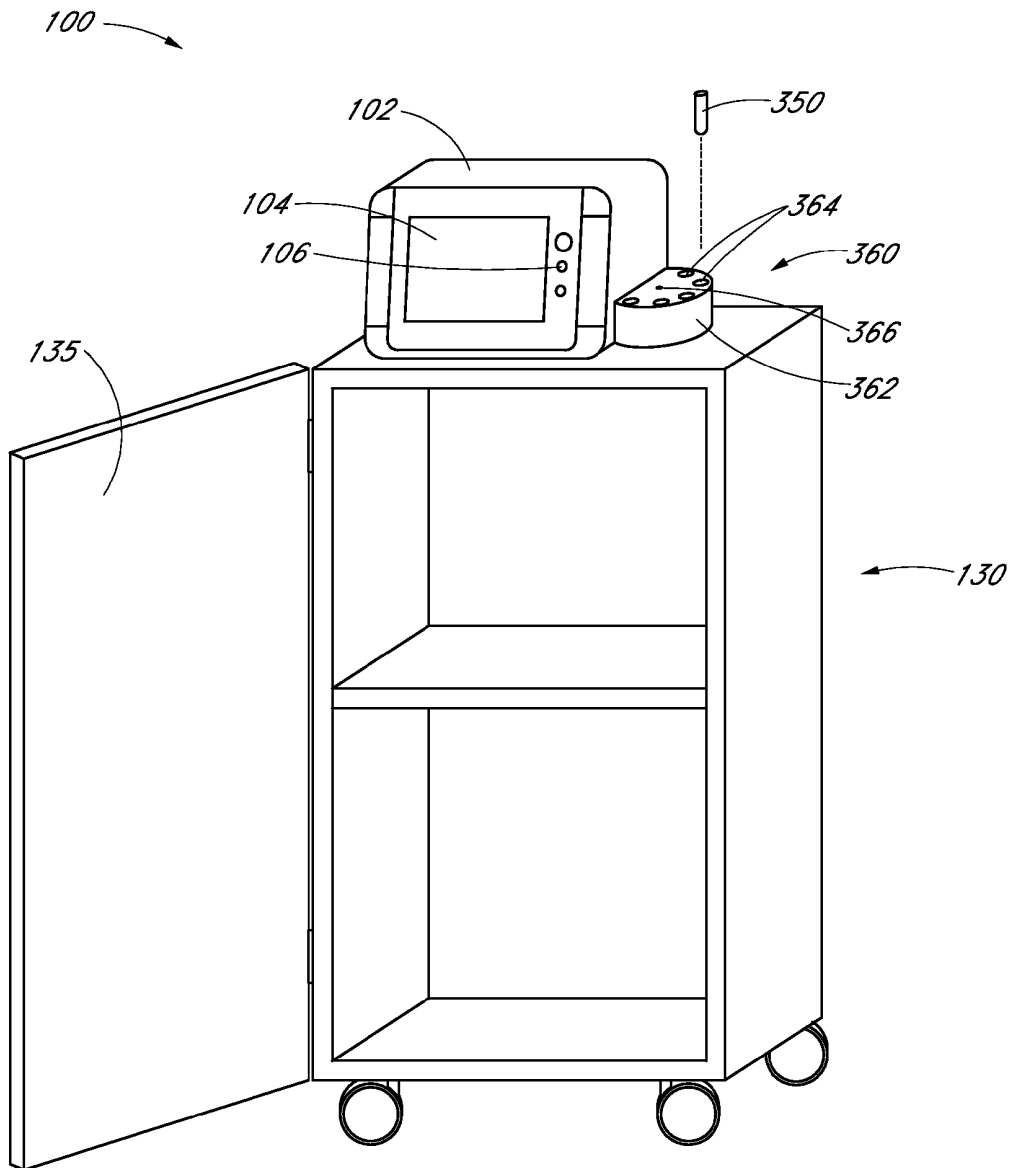


FIG. 3A

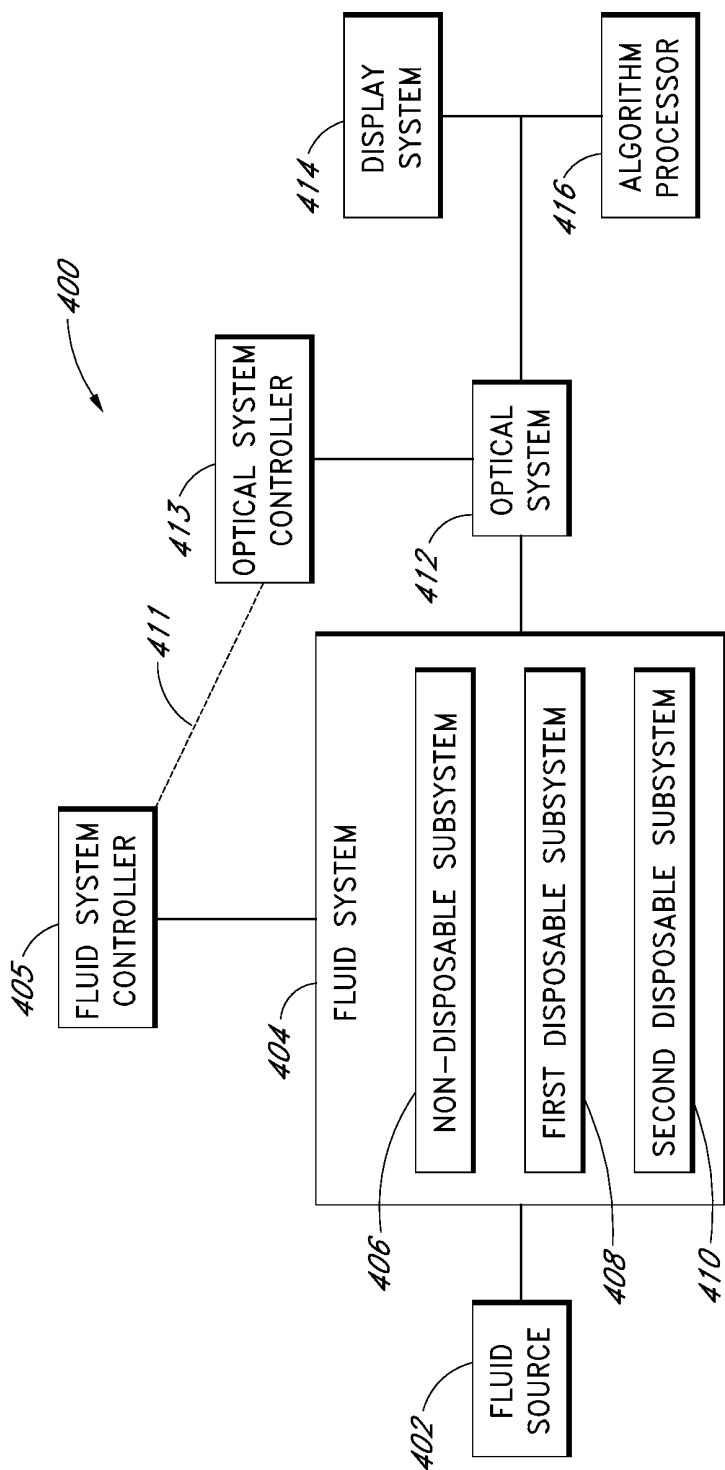


FIG. 4

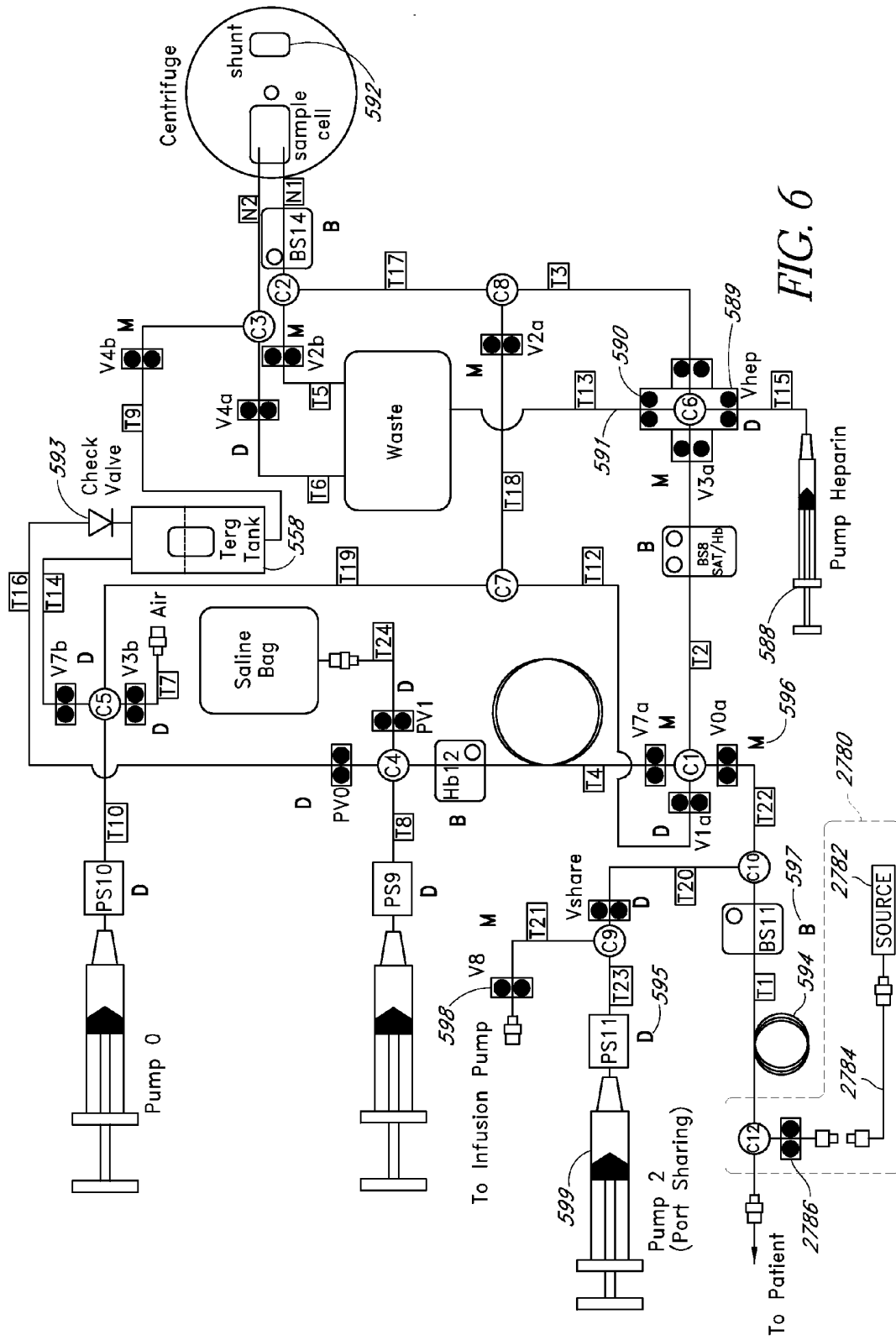


FIG. 6

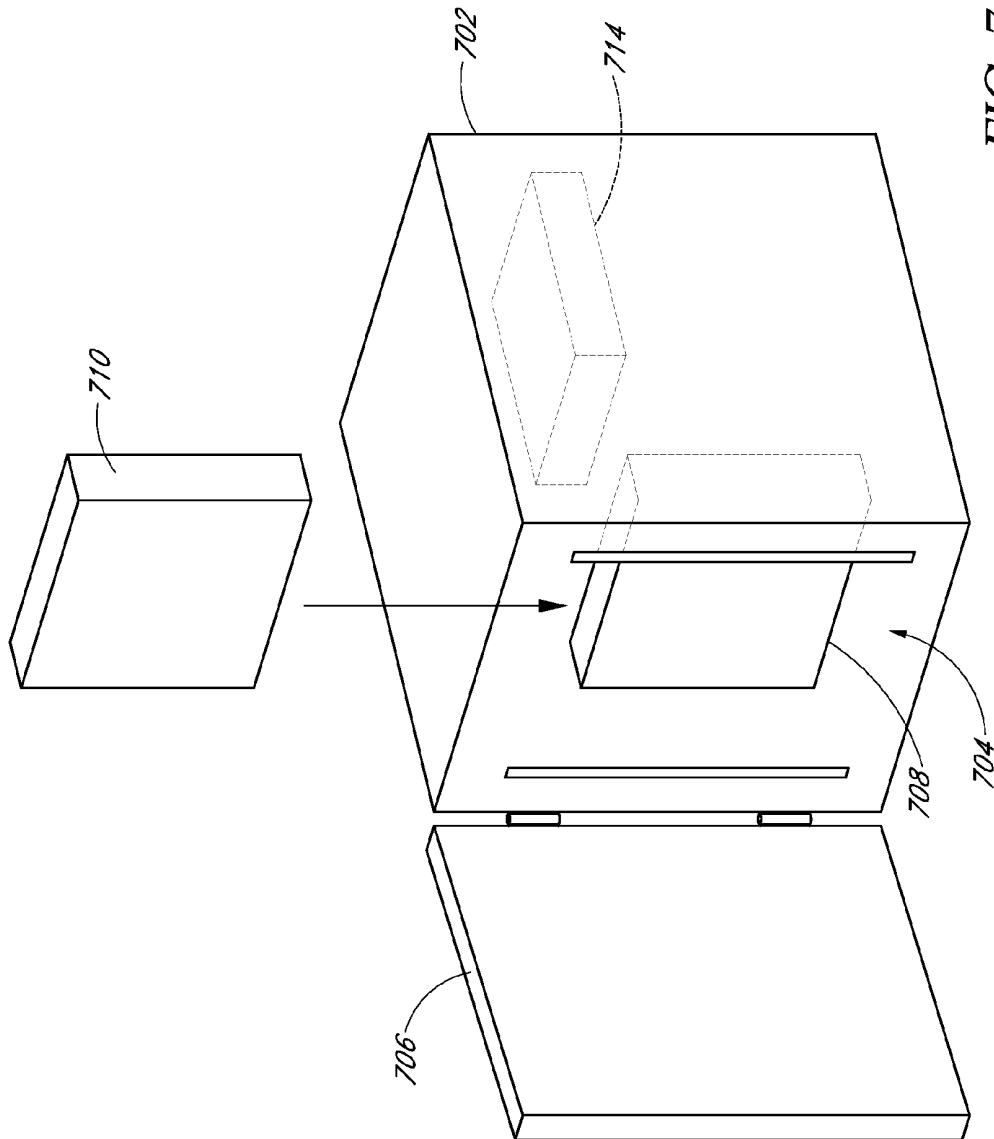


FIG. 7

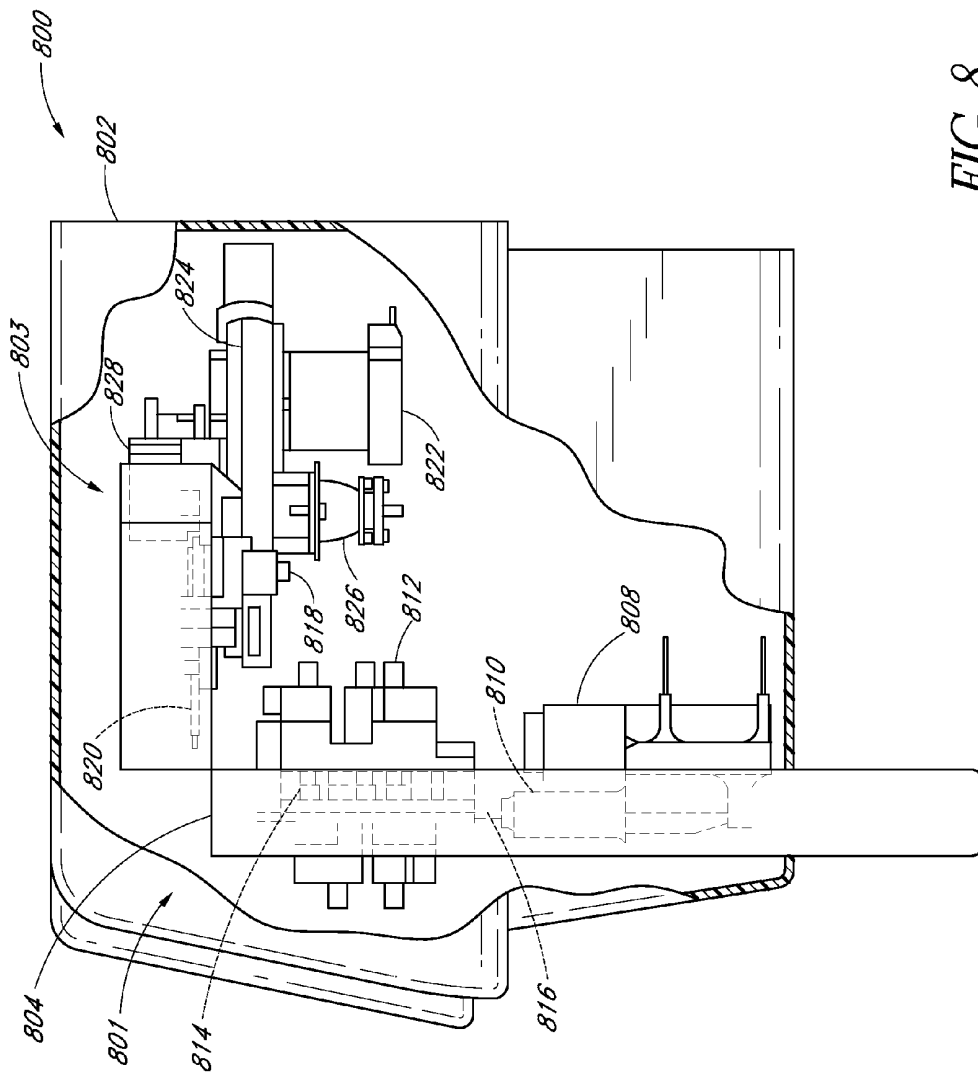


FIG. 8

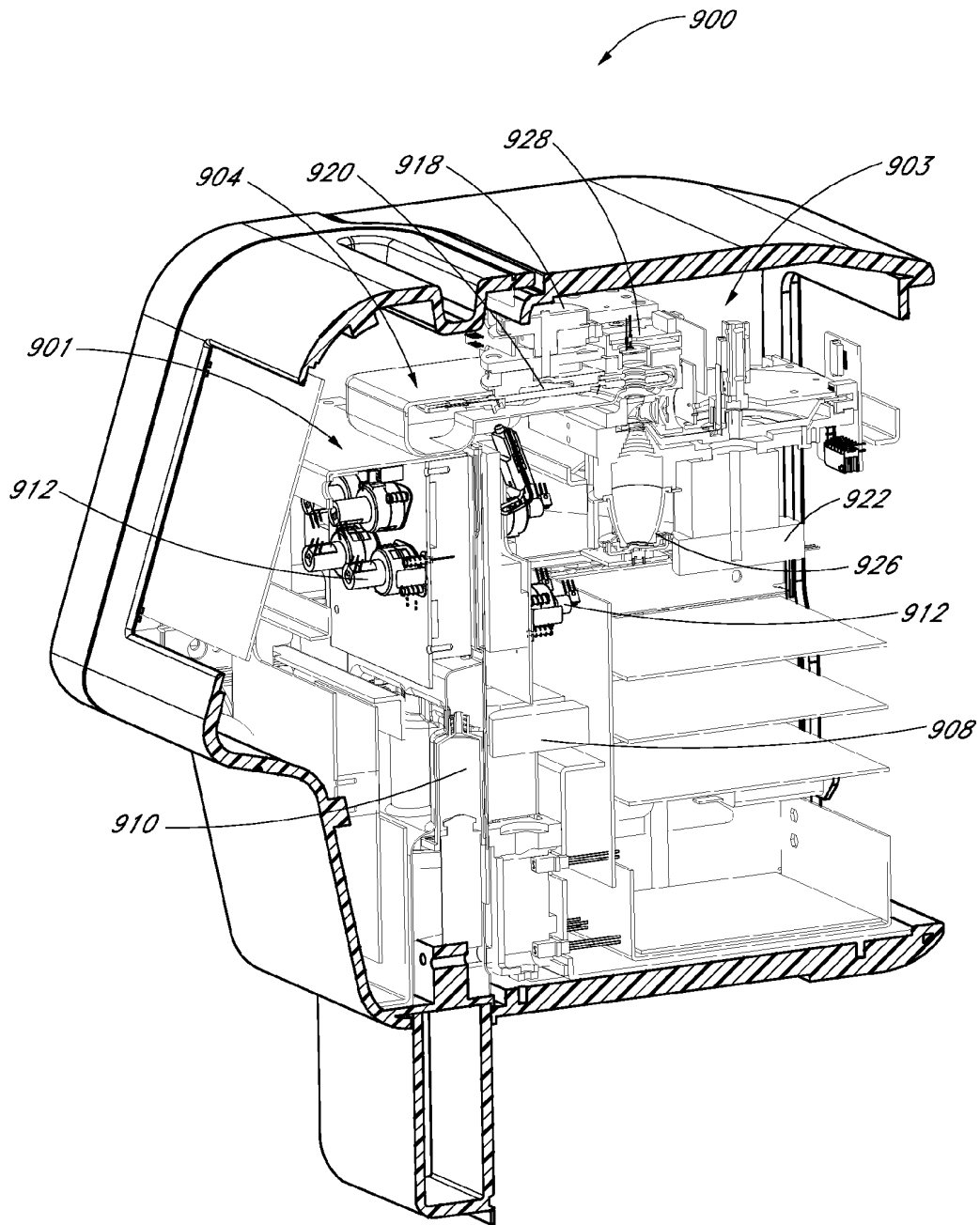


FIG. 9

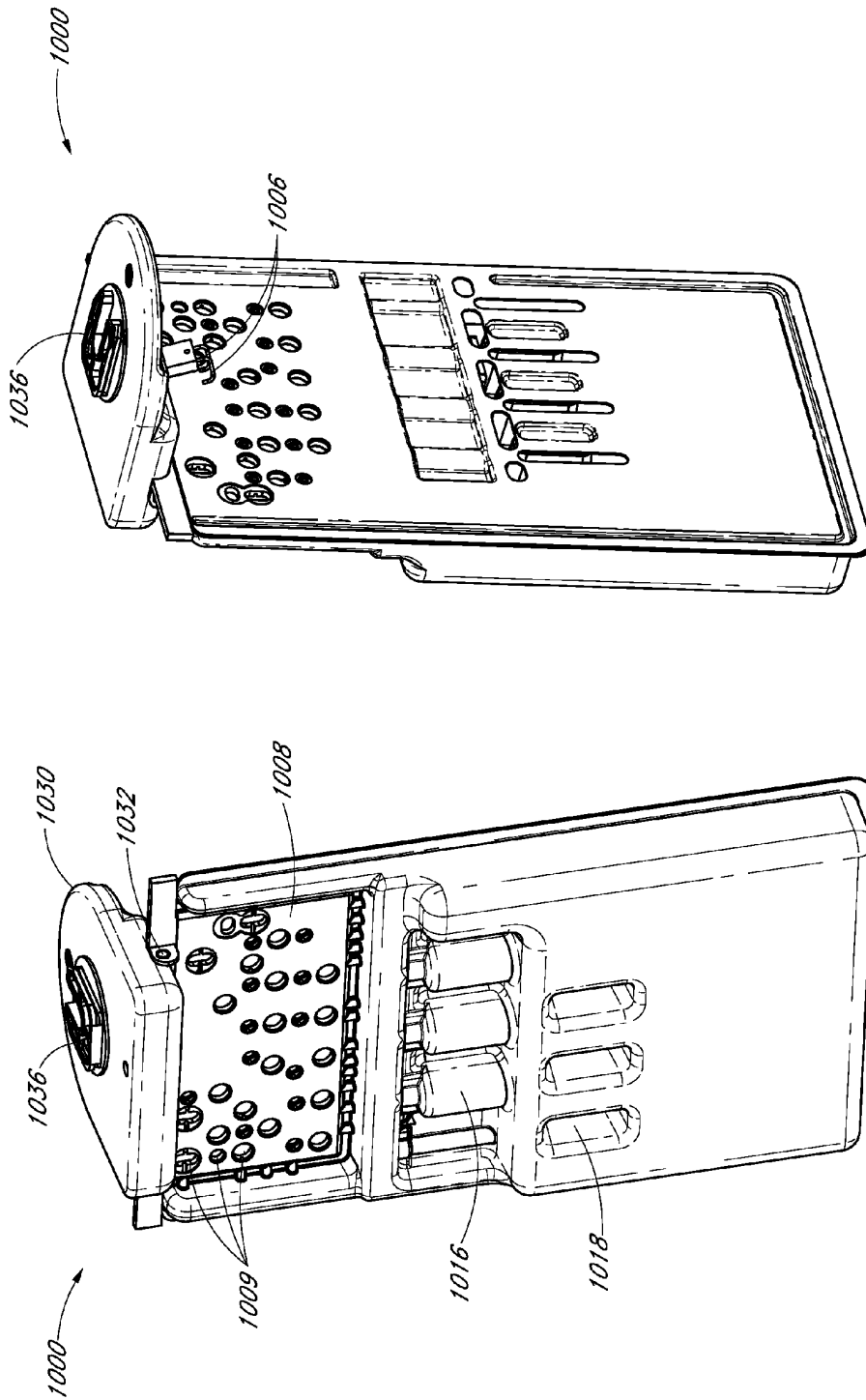


FIG. 10

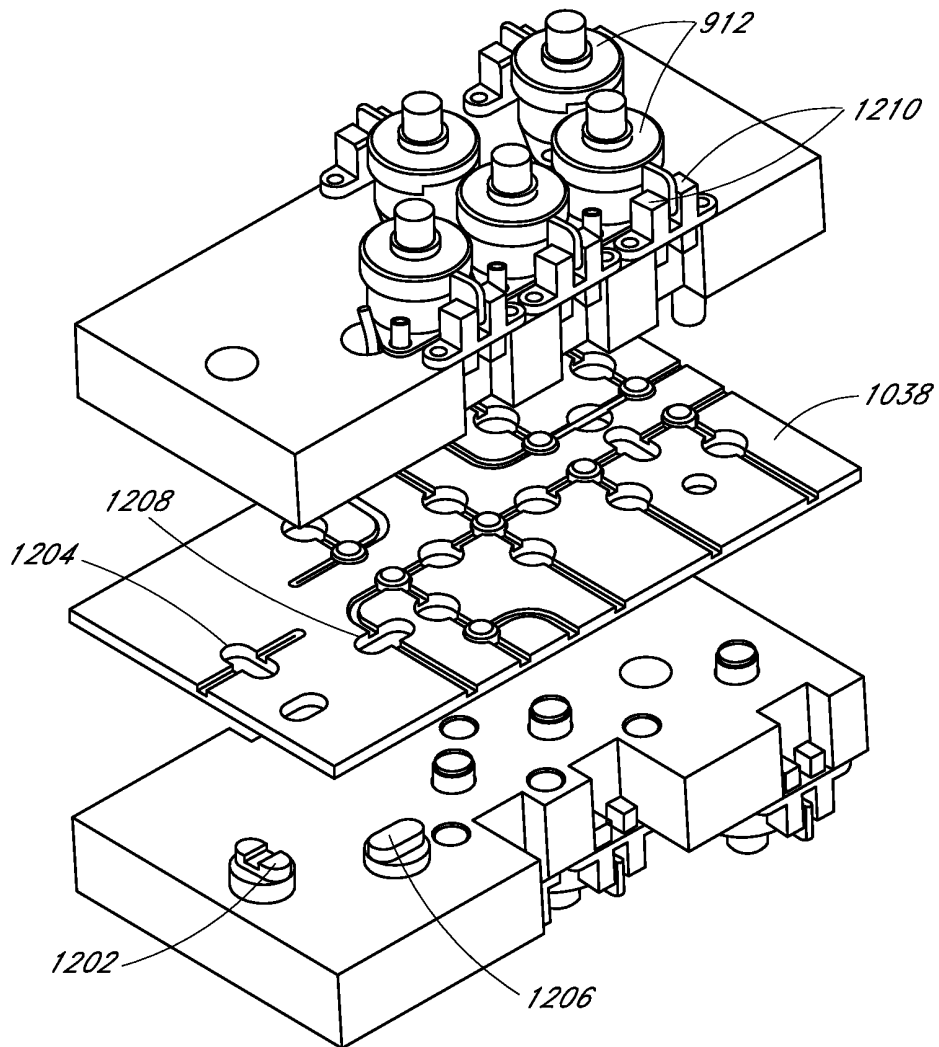


FIG. 12

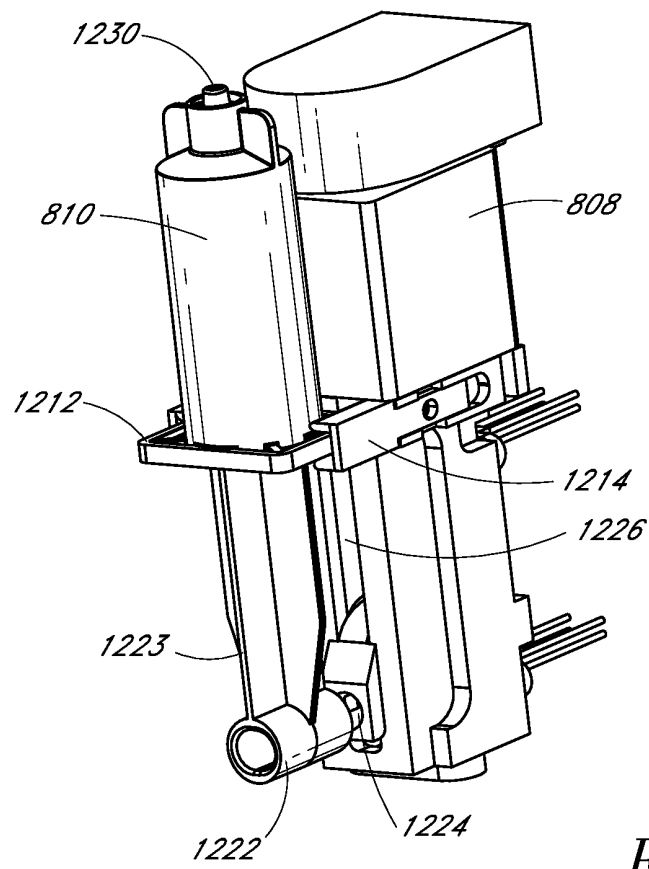


FIG. 13

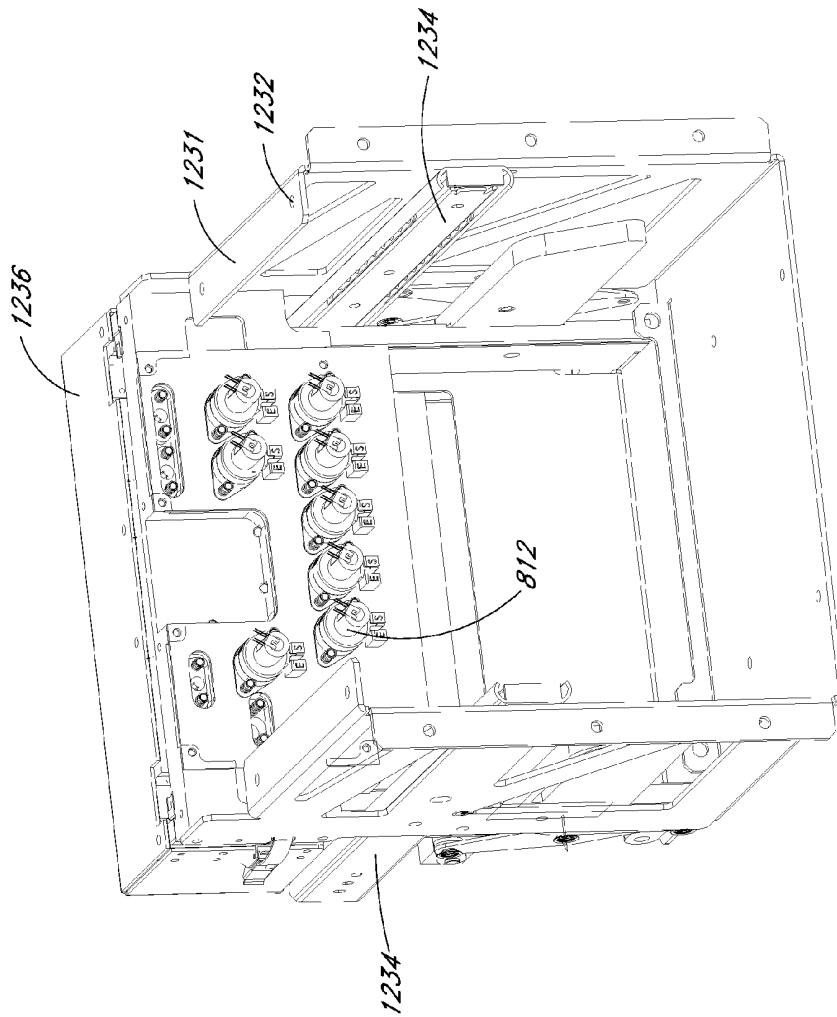


FIG. 14

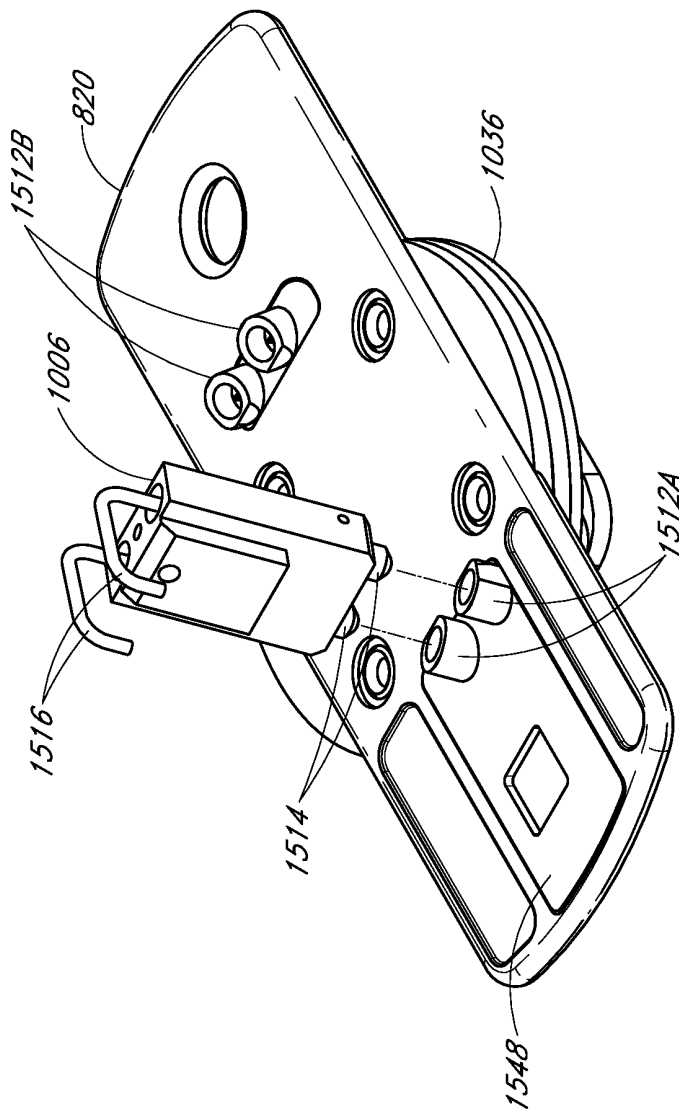


FIG. 15

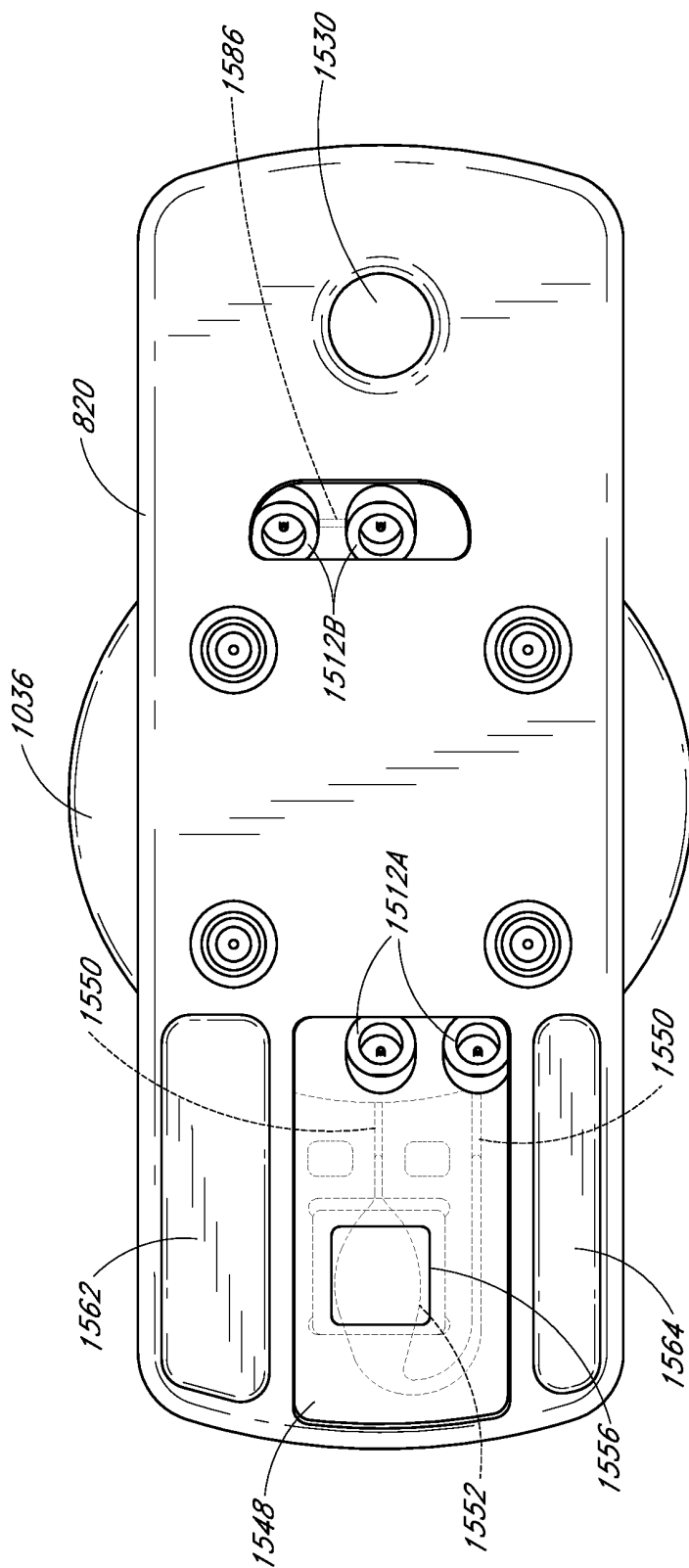


FIG. 16

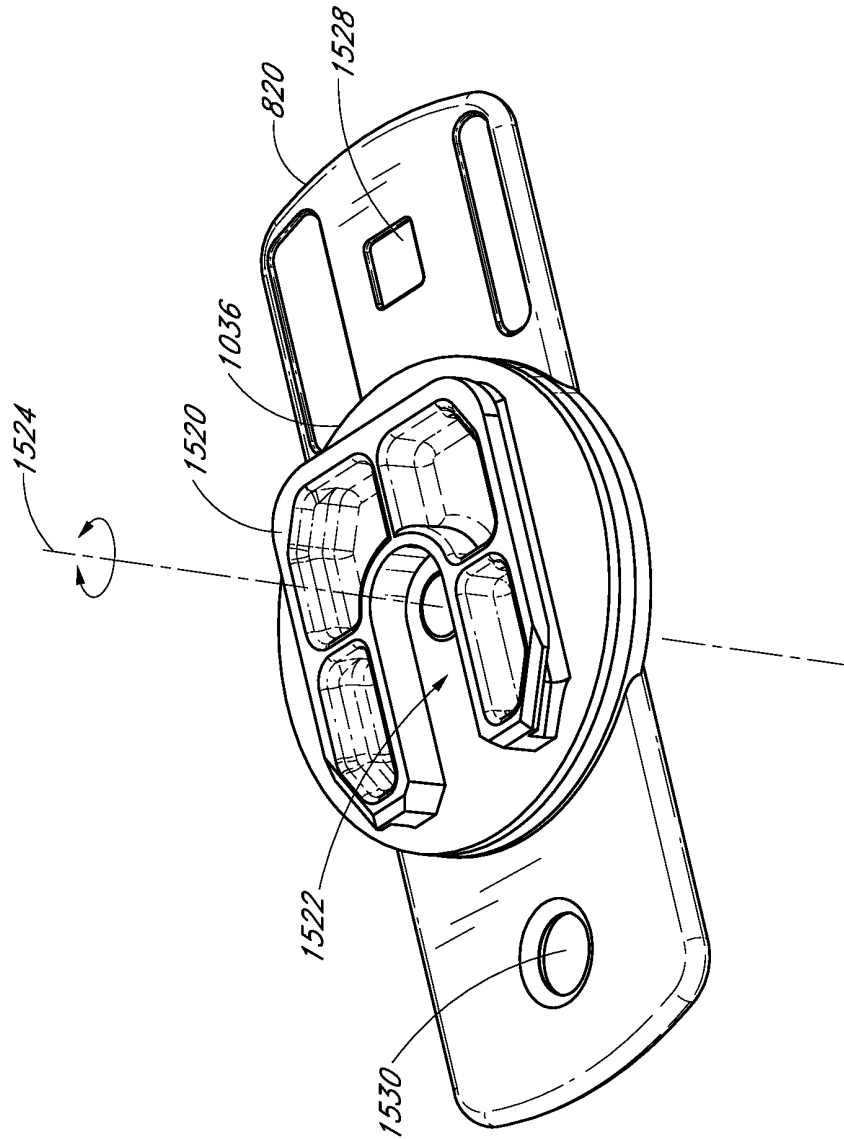


FIG. 17

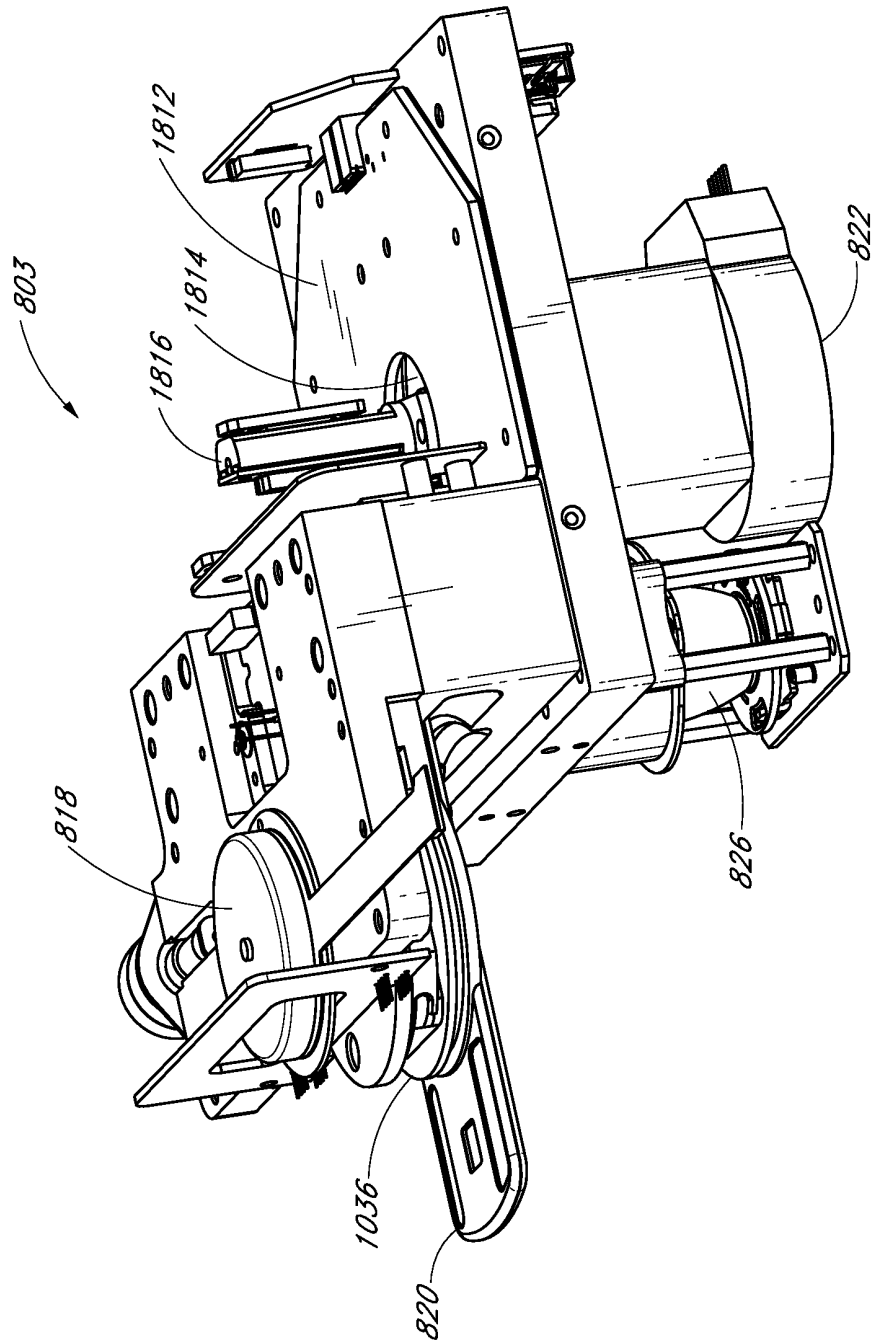


FIG. 18

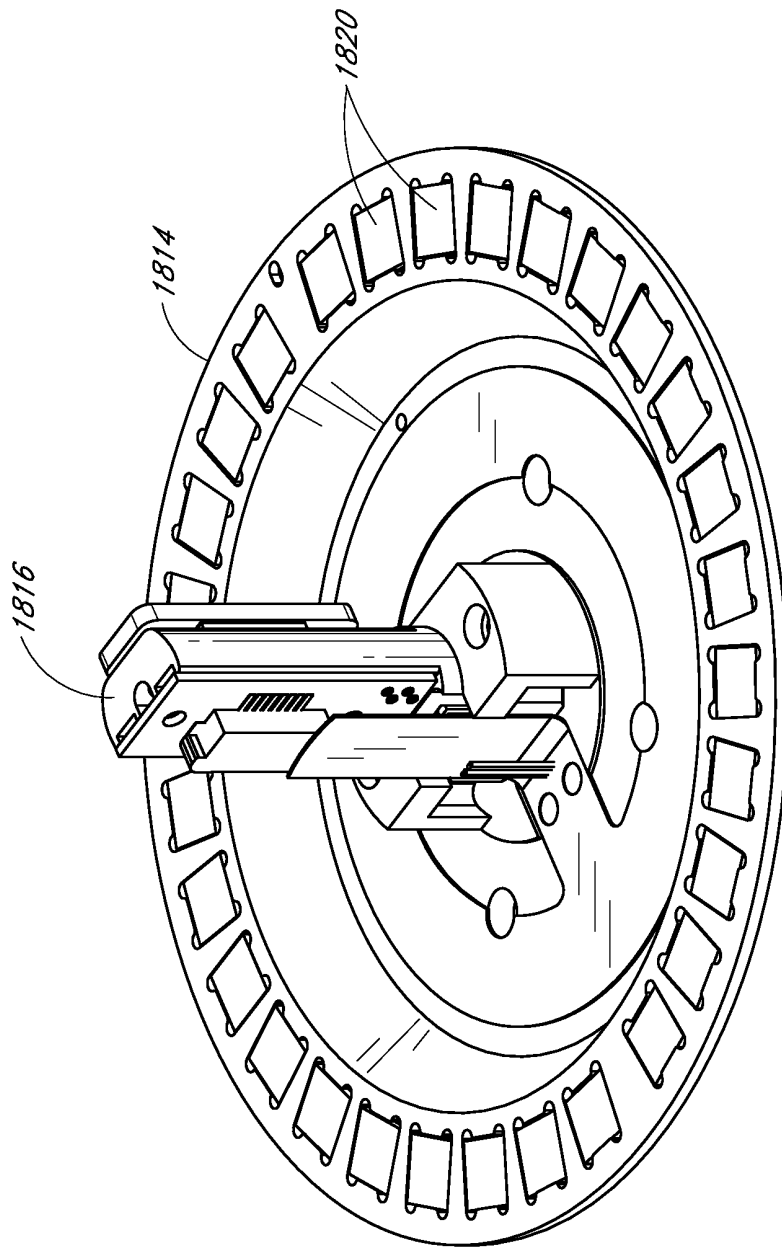


FIG. 19

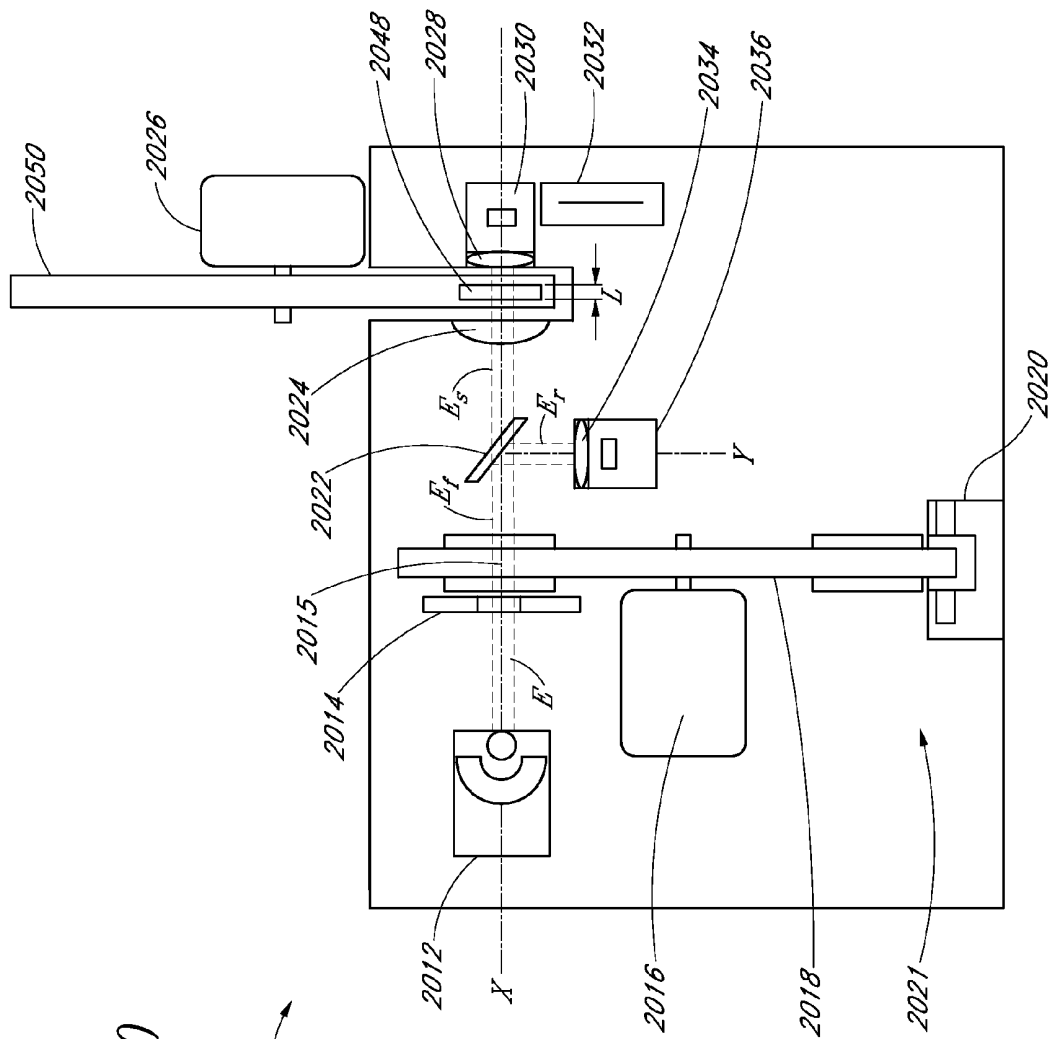
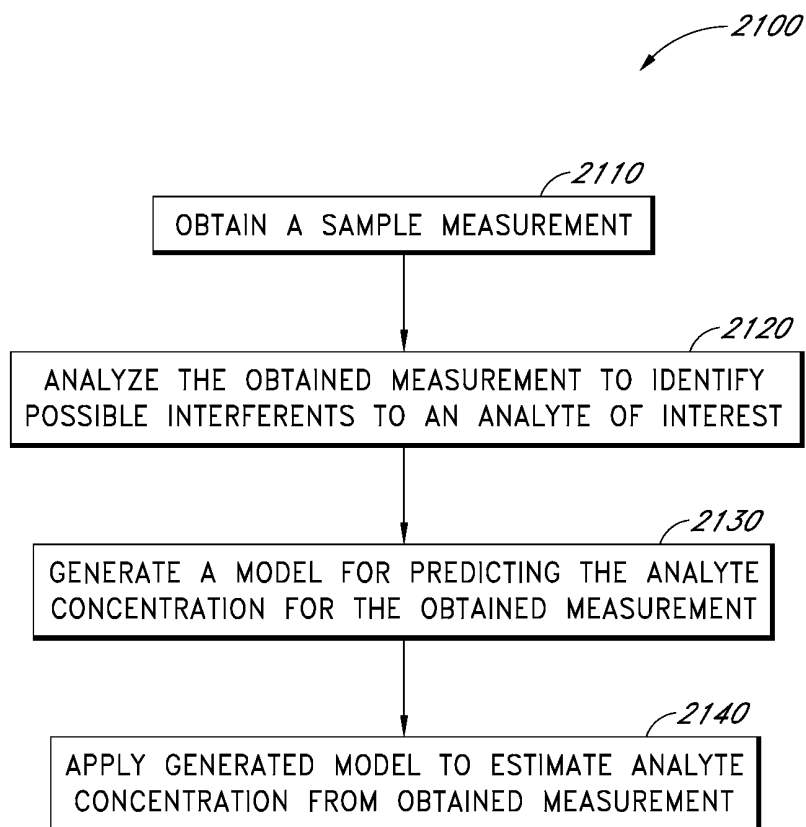


FIG. 20

2010

*FIG. 21*

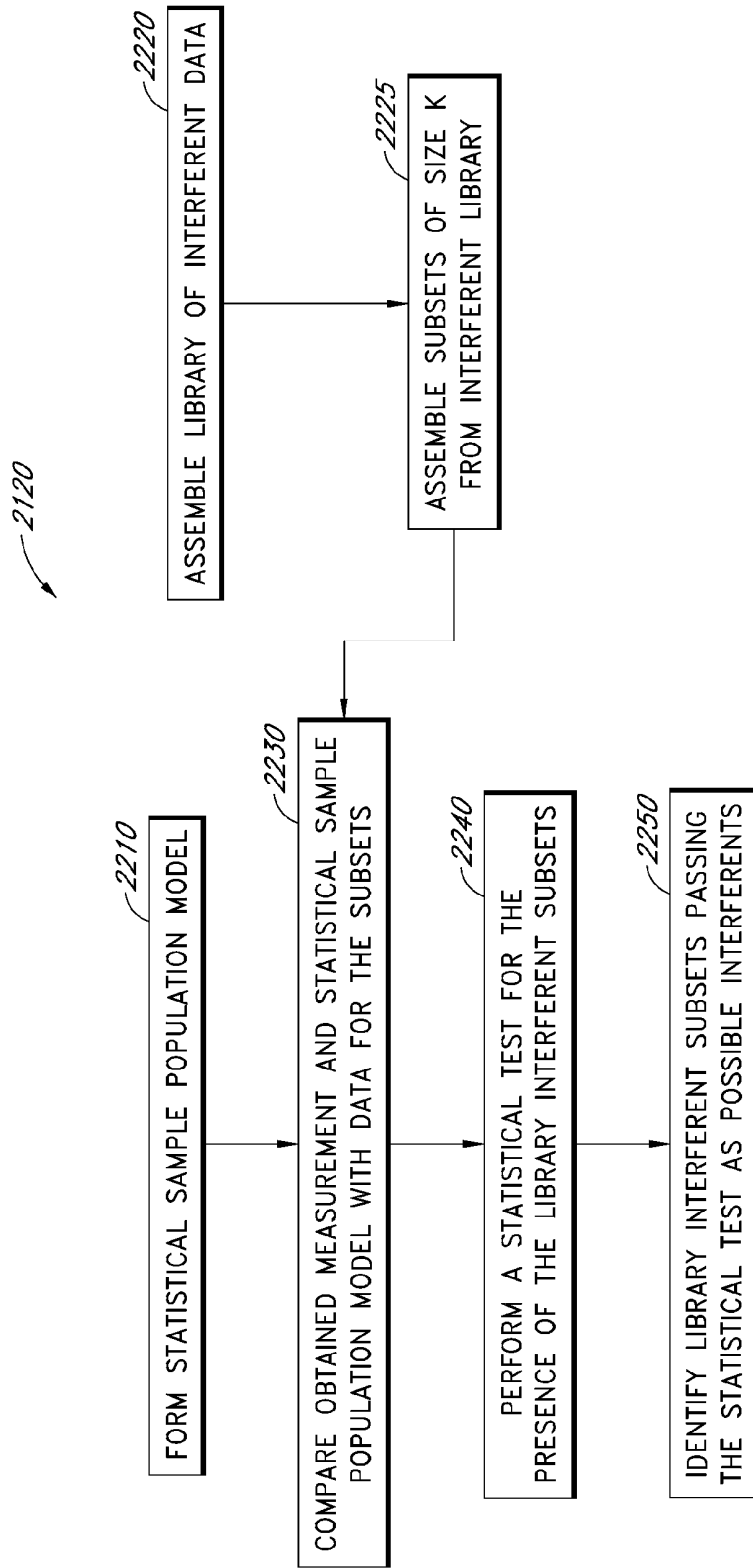


FIG. 22

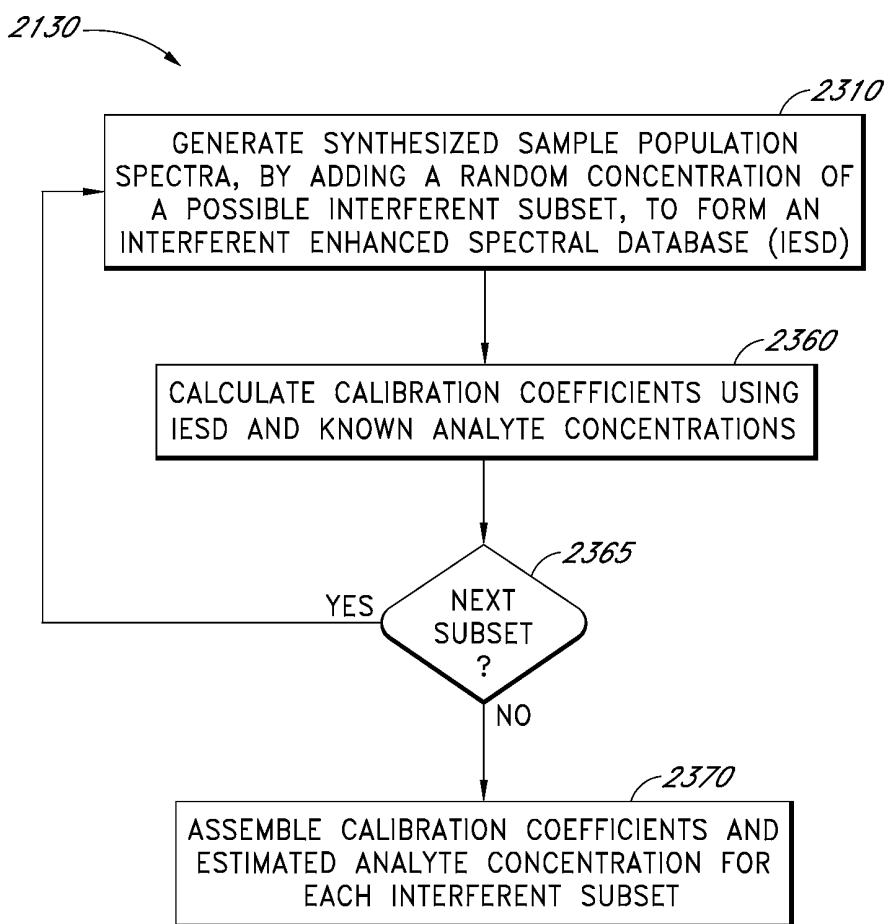


FIG. 23

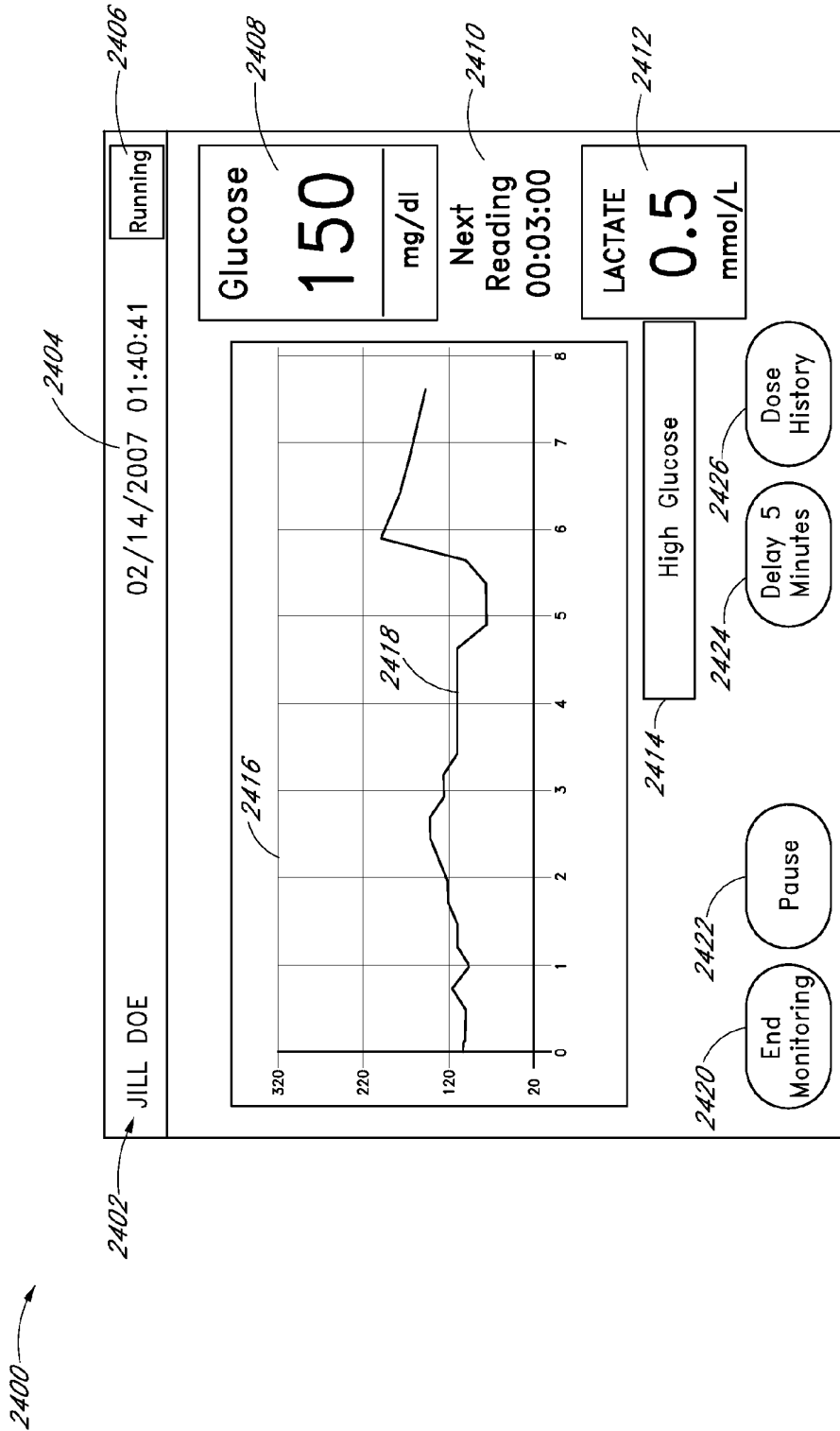


FIG. 24

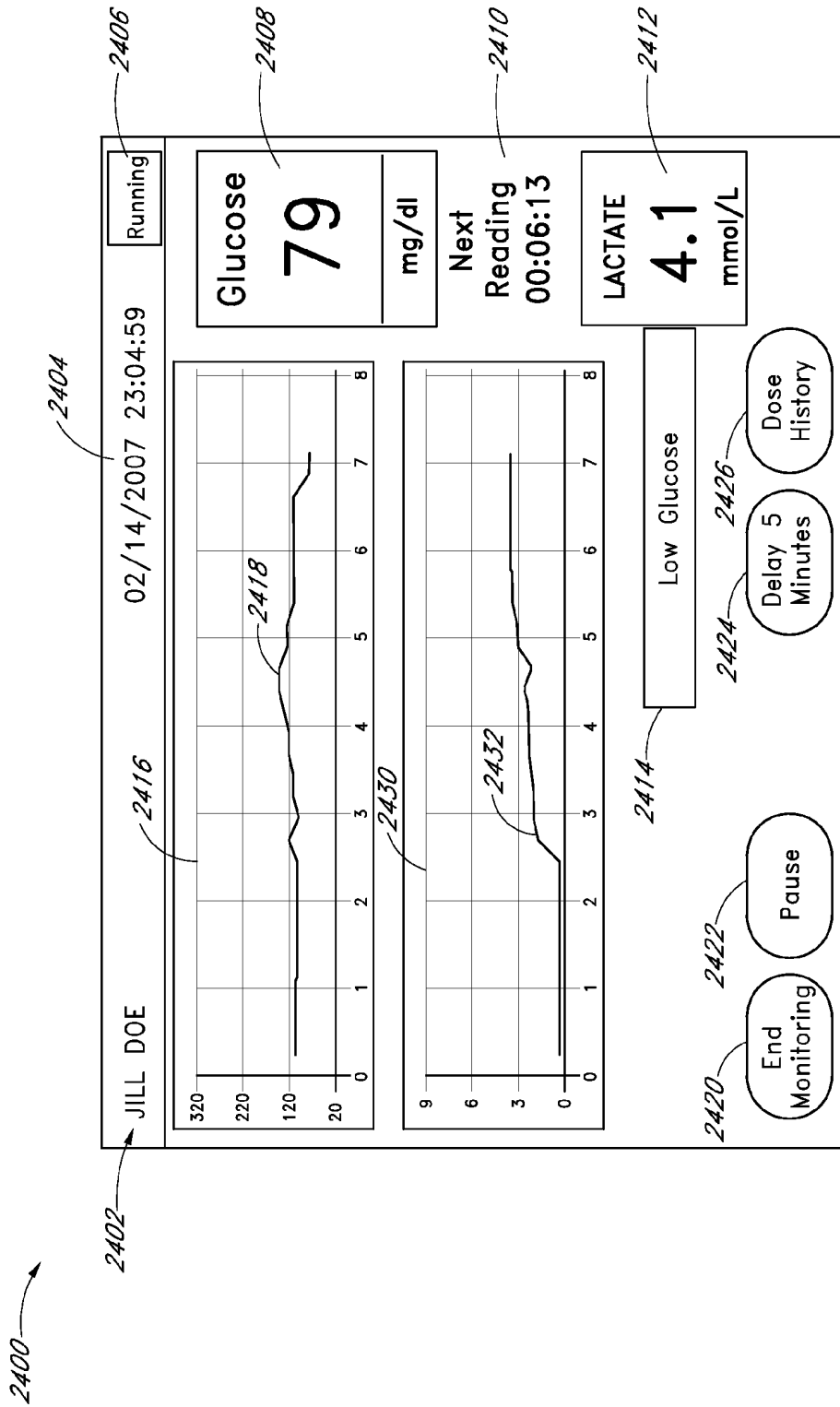


FIG. 25

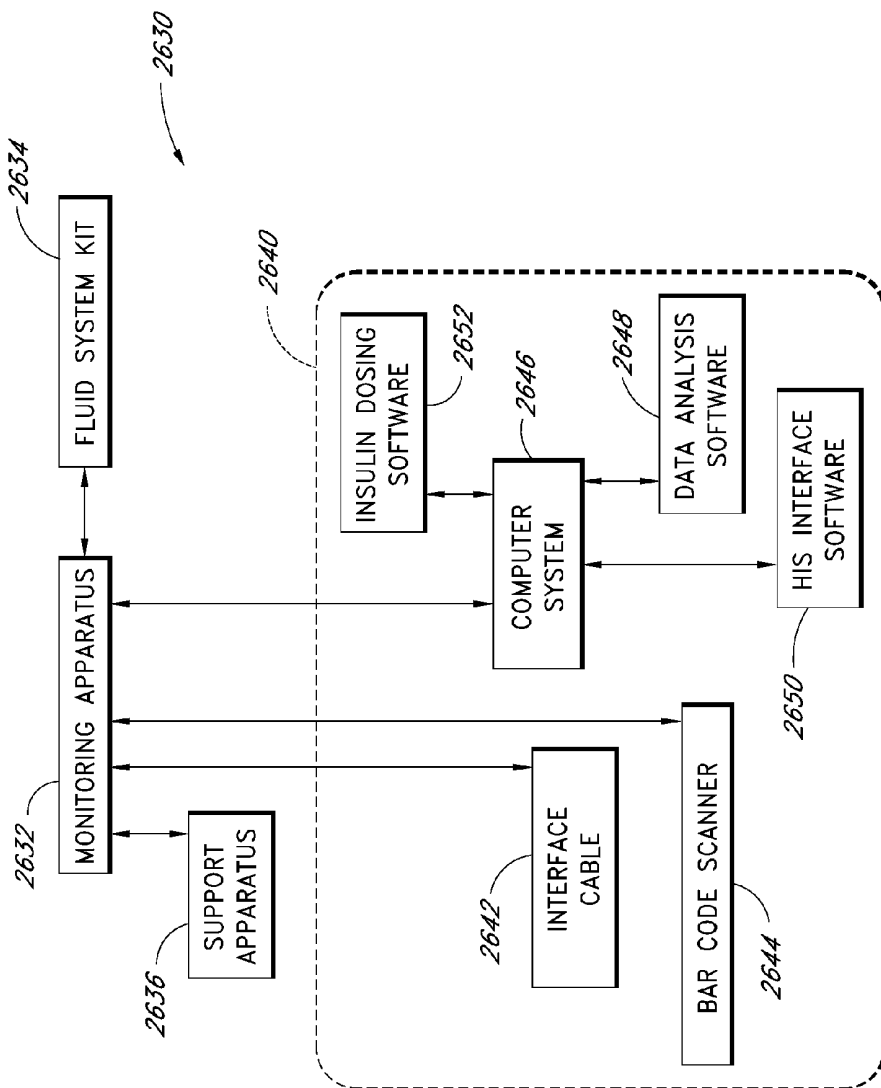


FIG. 26

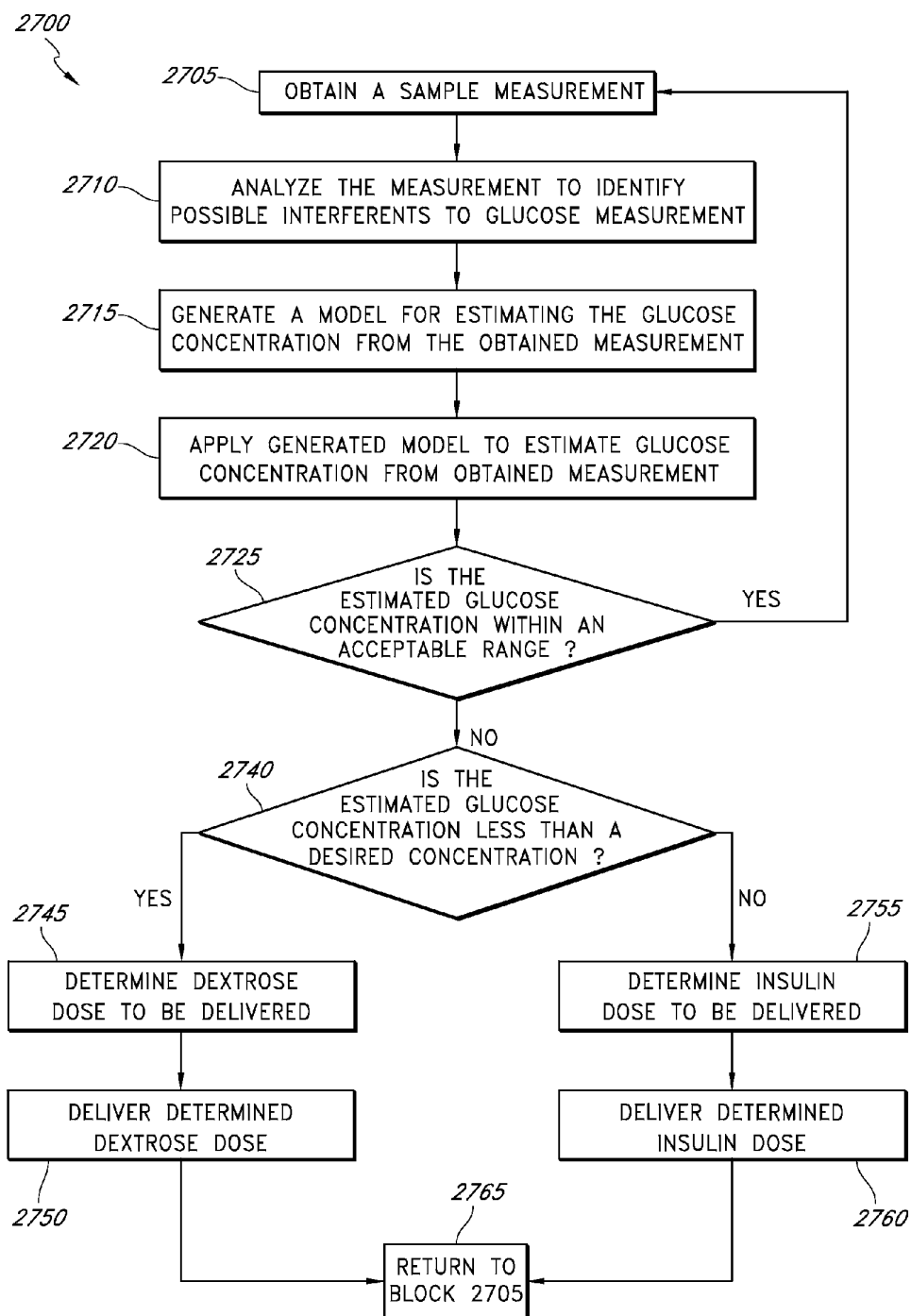
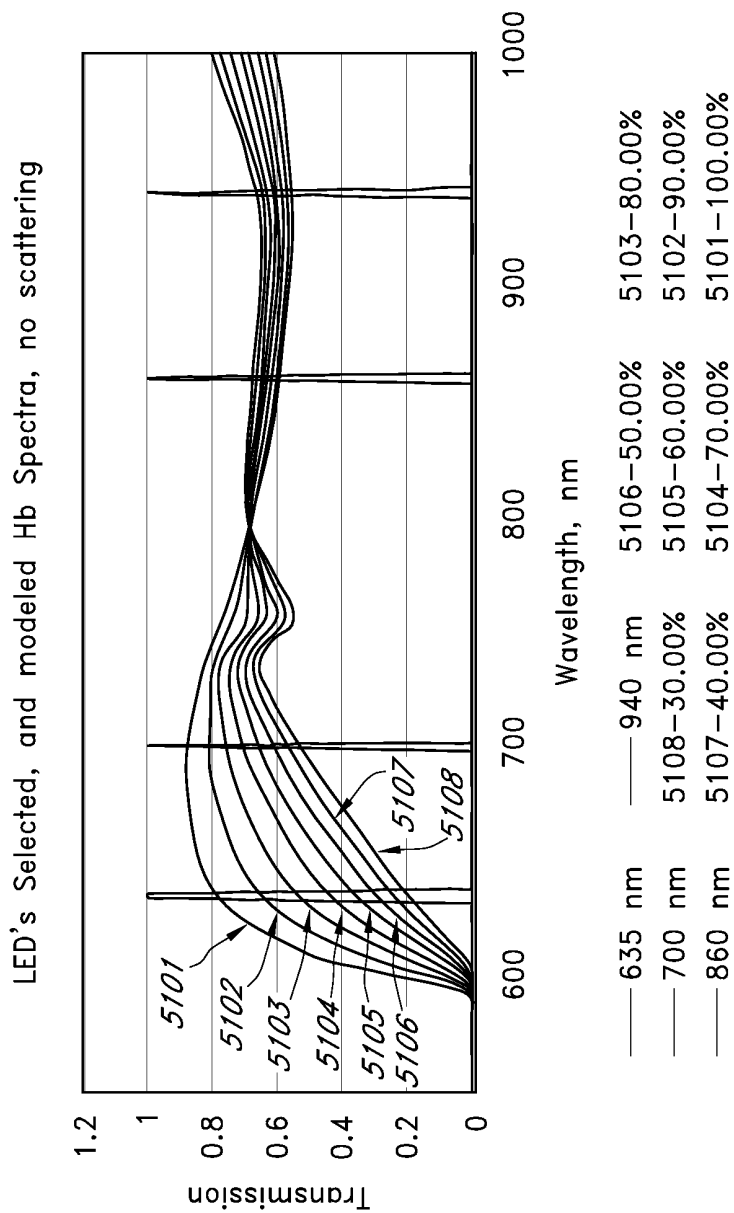


FIG. 27

FIG. 29



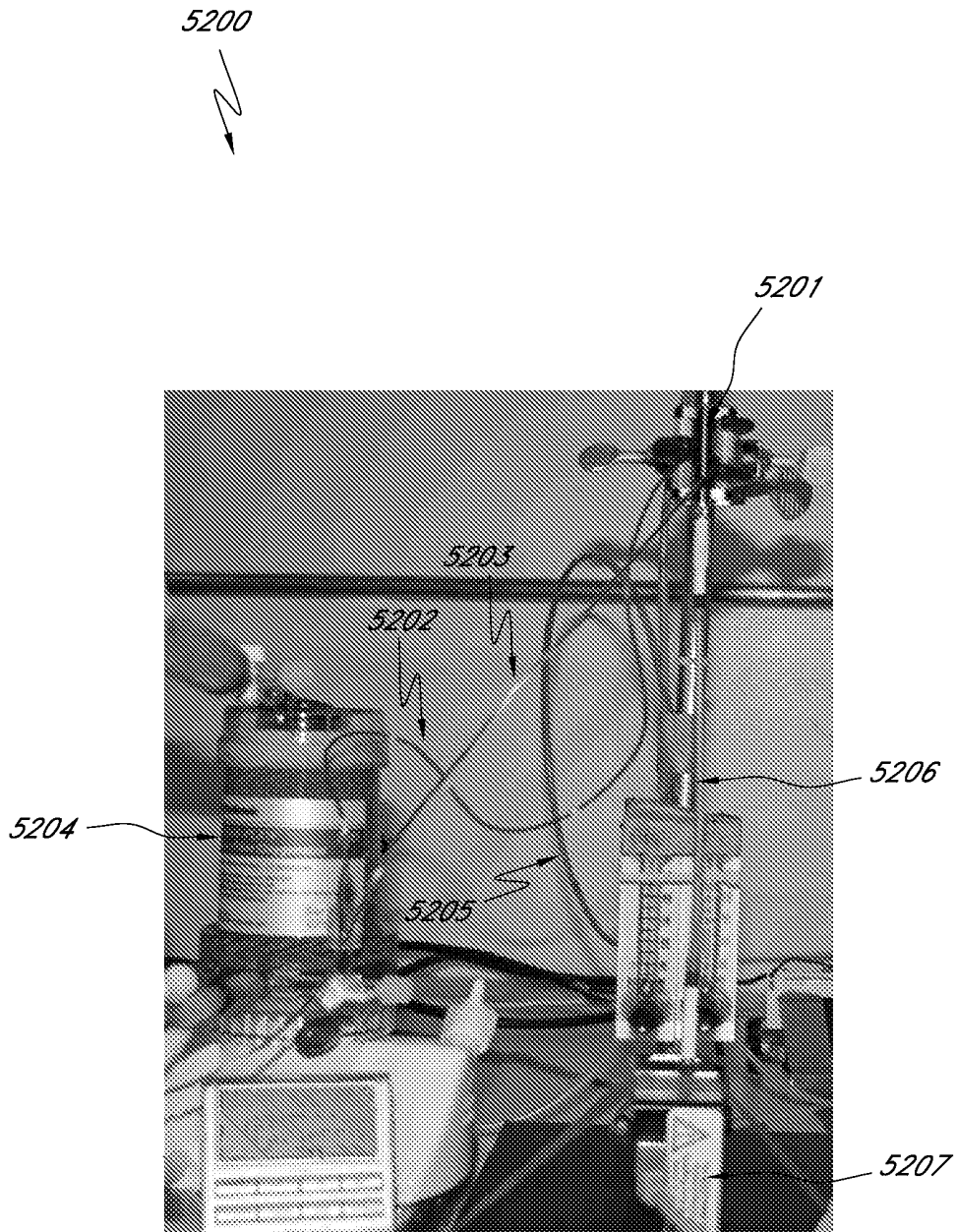


FIG. 30

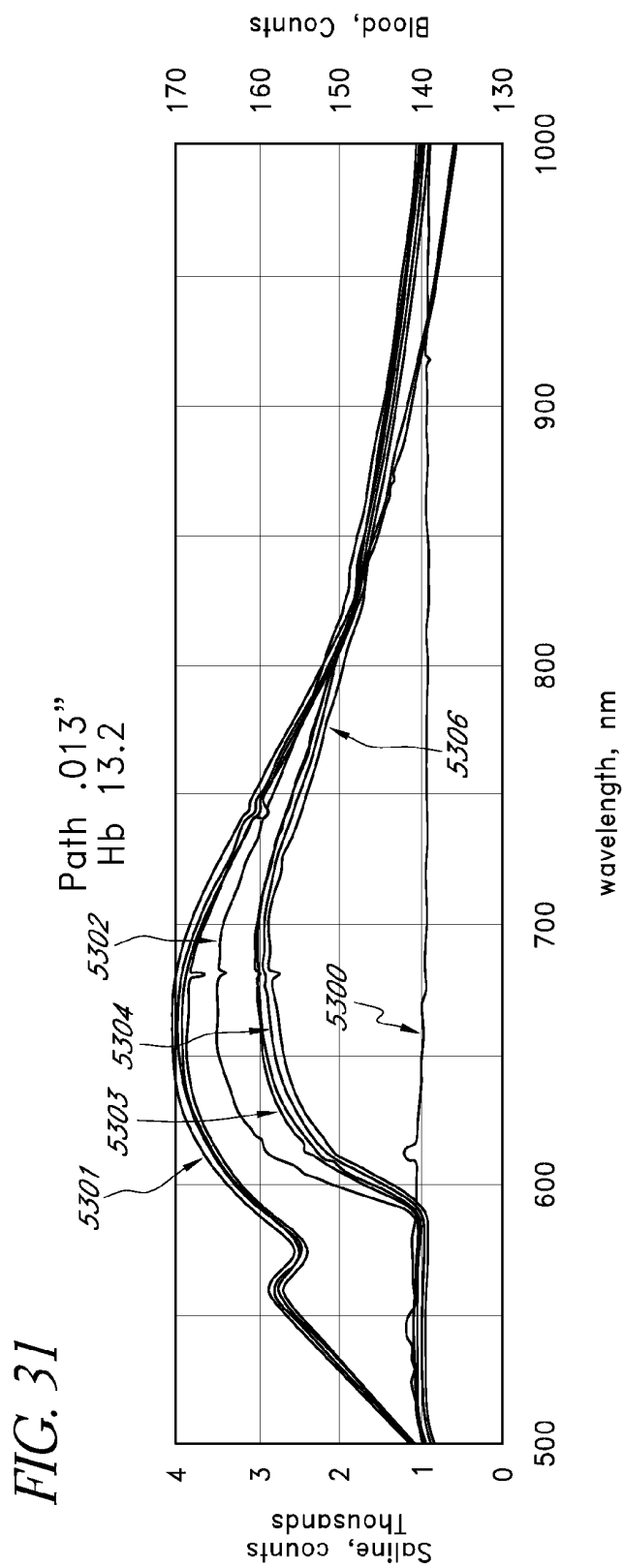
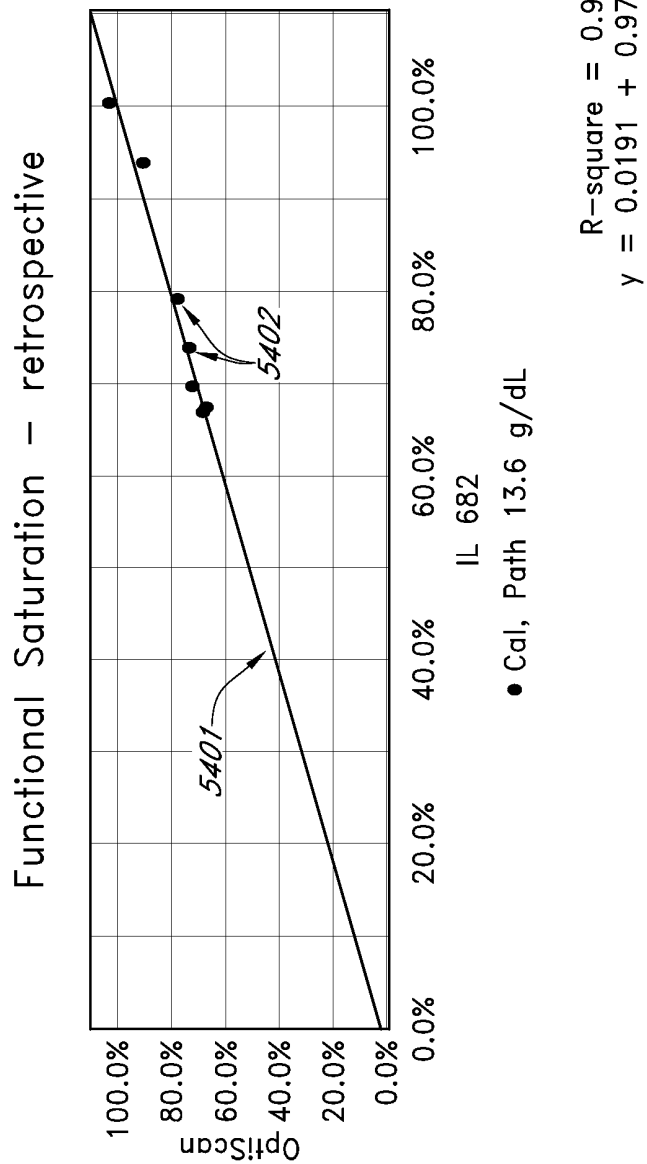
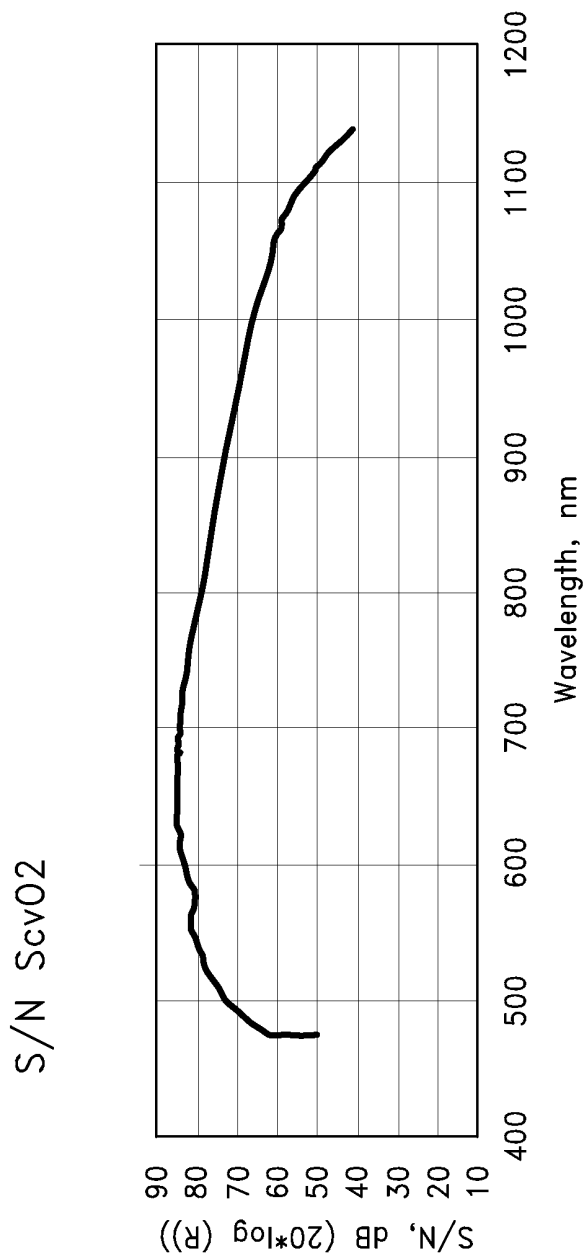


FIG. 32





Path .013", flat tube
Saline
ACQ; 3 mS, Avg 2000

FIG. 33

FIG. 34

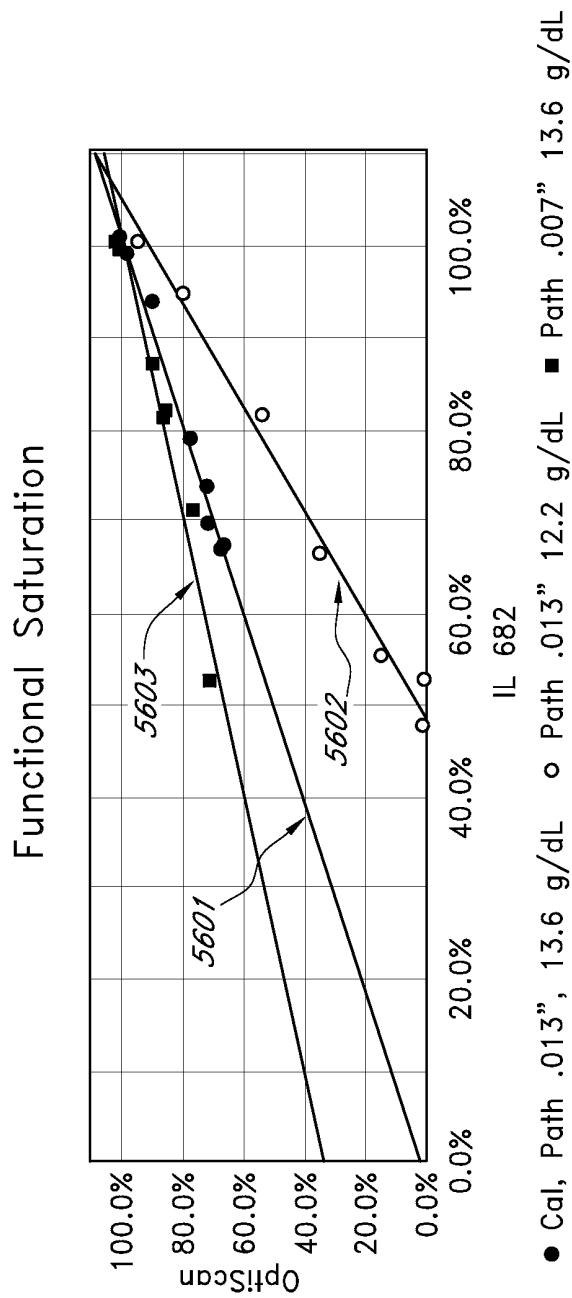


FIG. 35

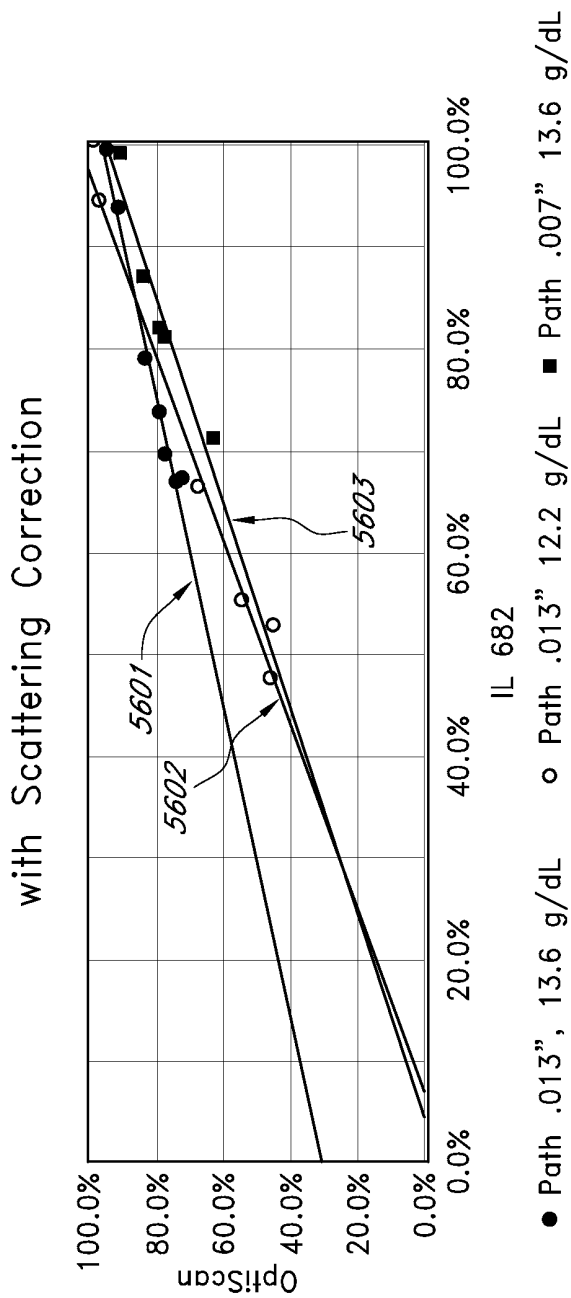


FIG. 36

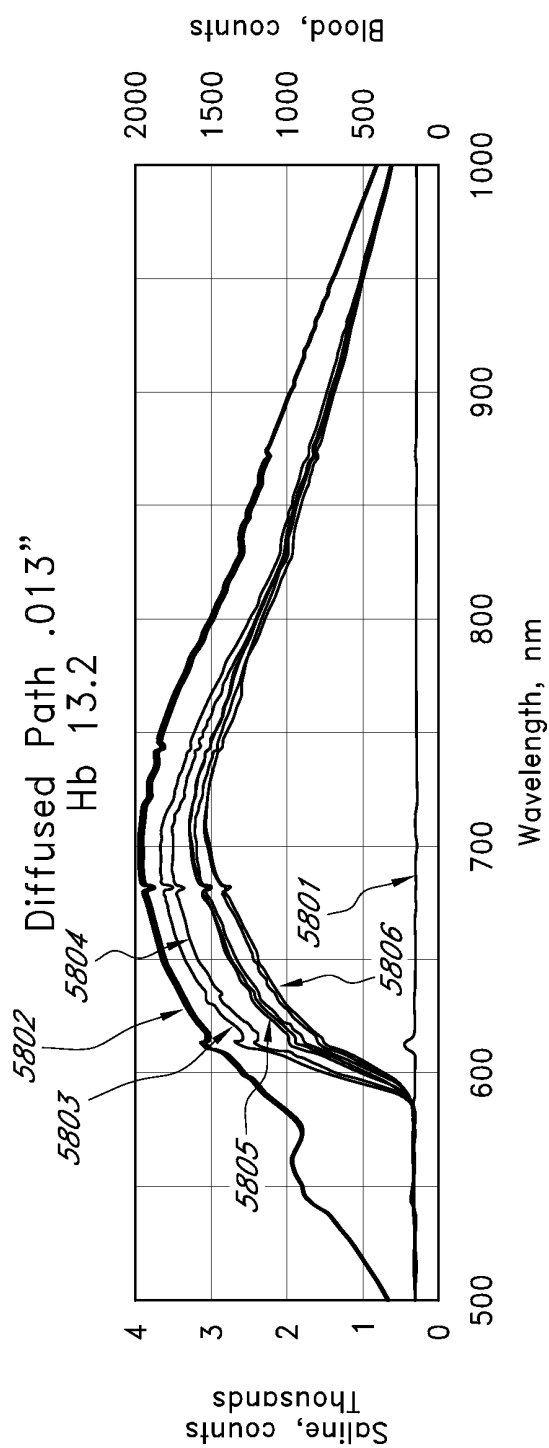
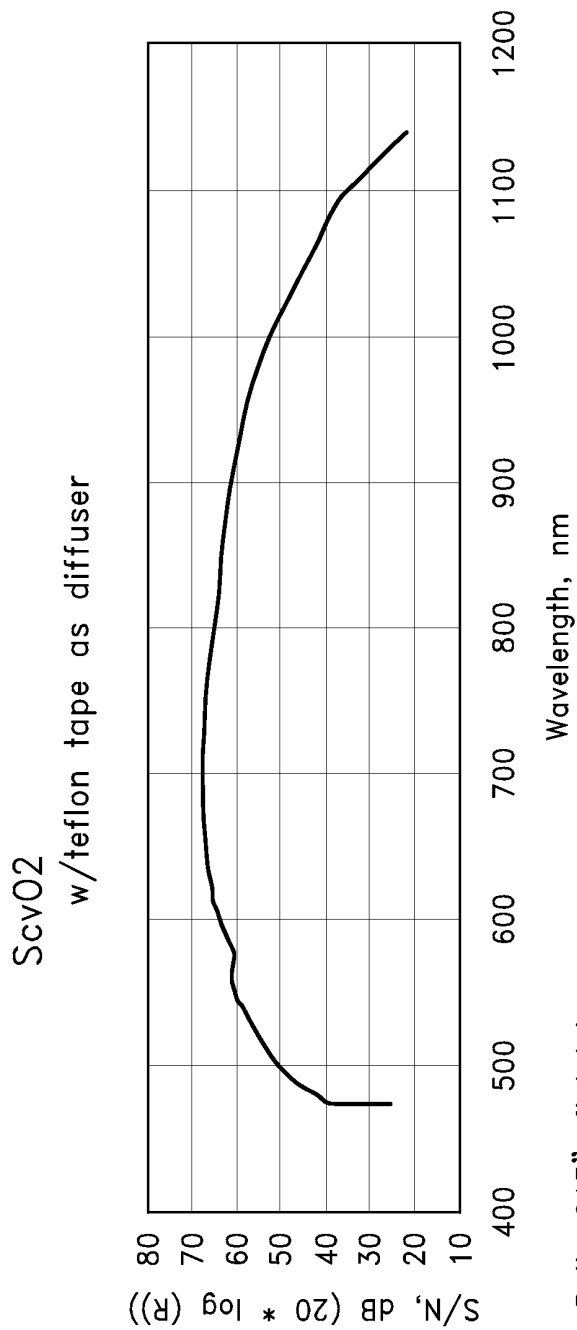


FIG. 37



Path .013", flat tube
Saline
Apert Full Open, ACQ 186 mS, Avg 100

FIG. 38

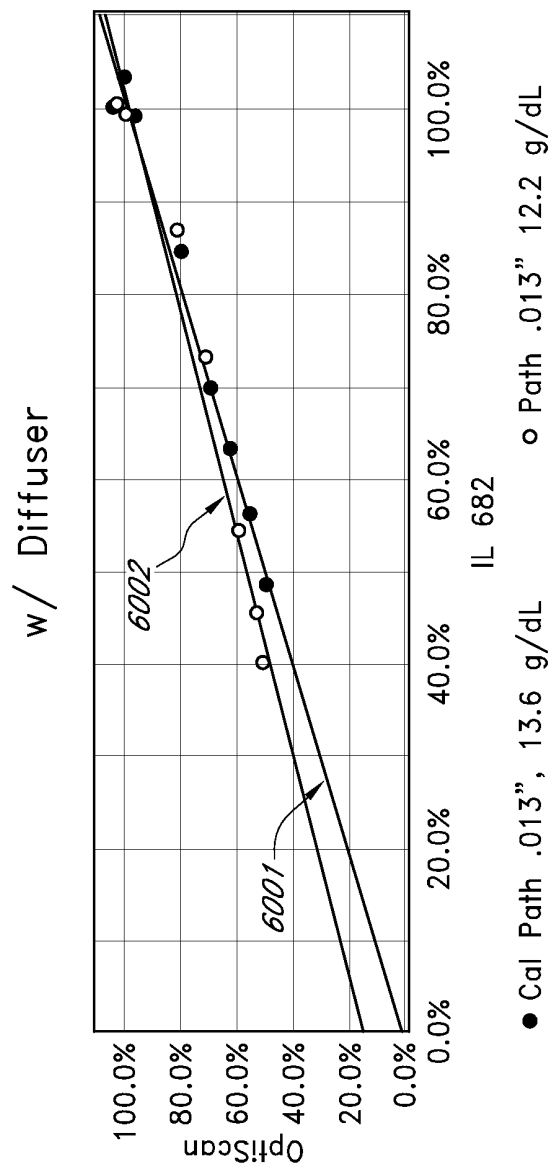
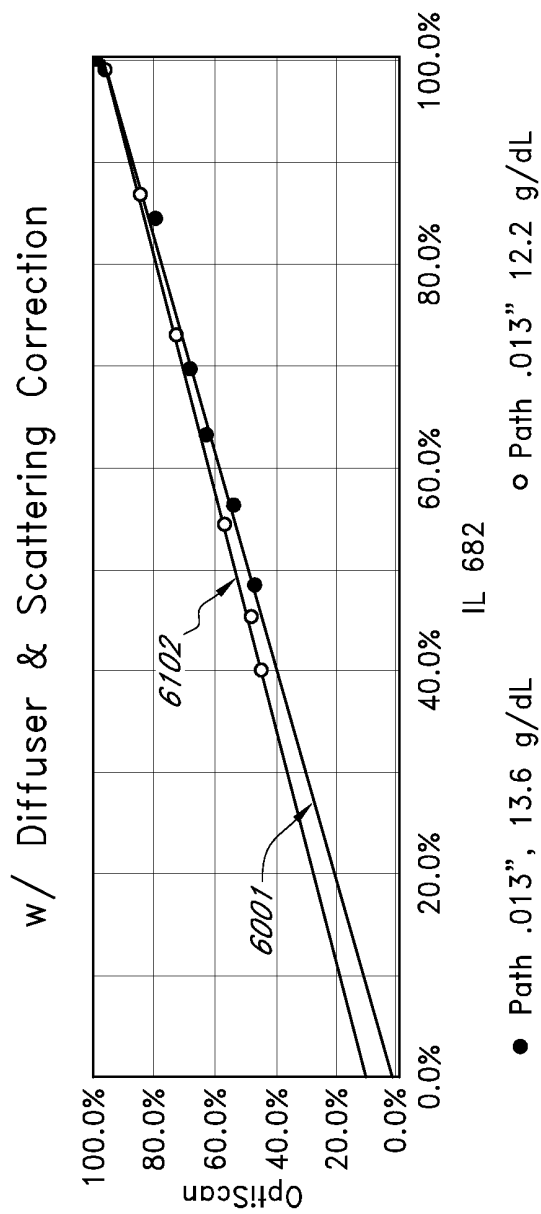
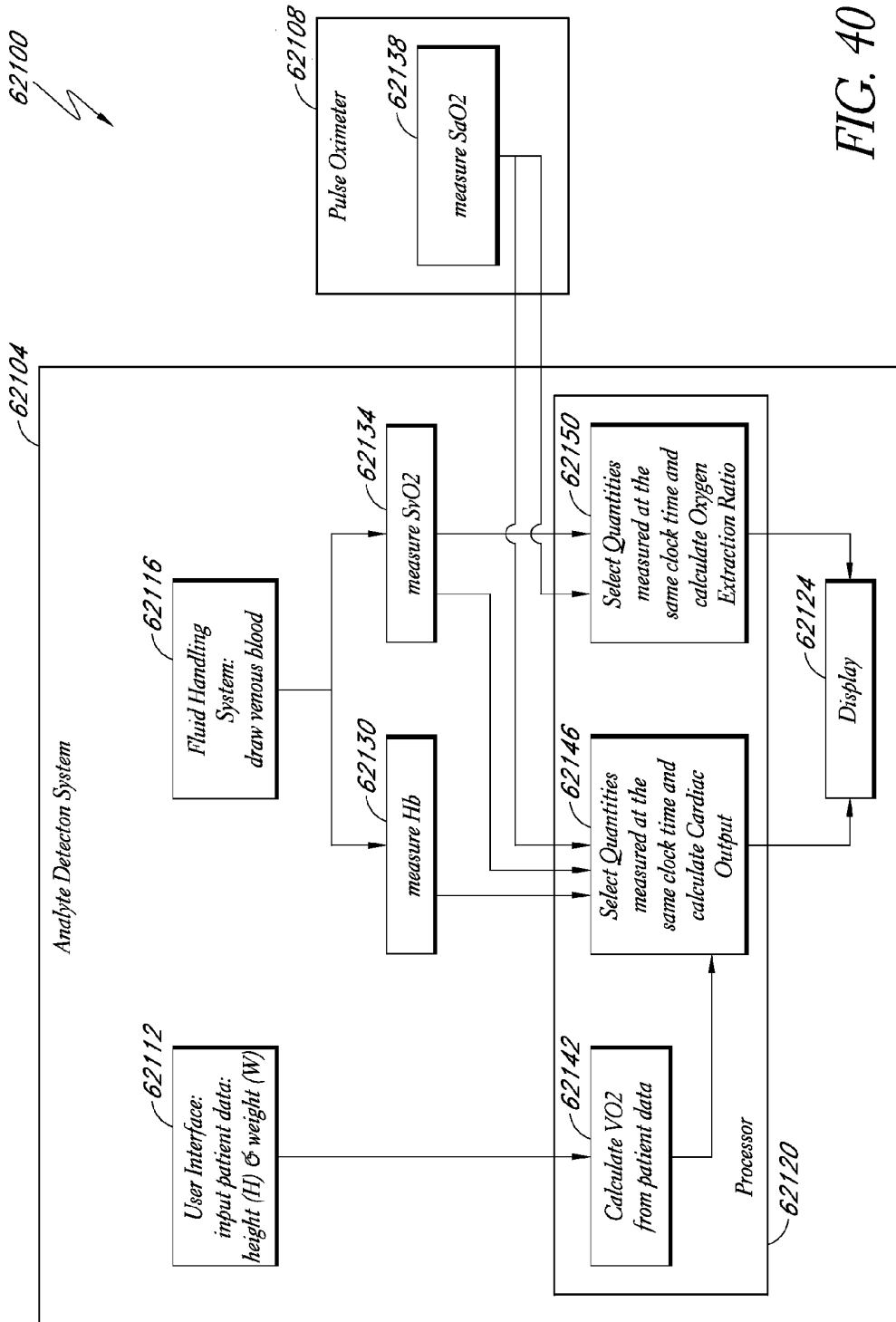


FIG. 39





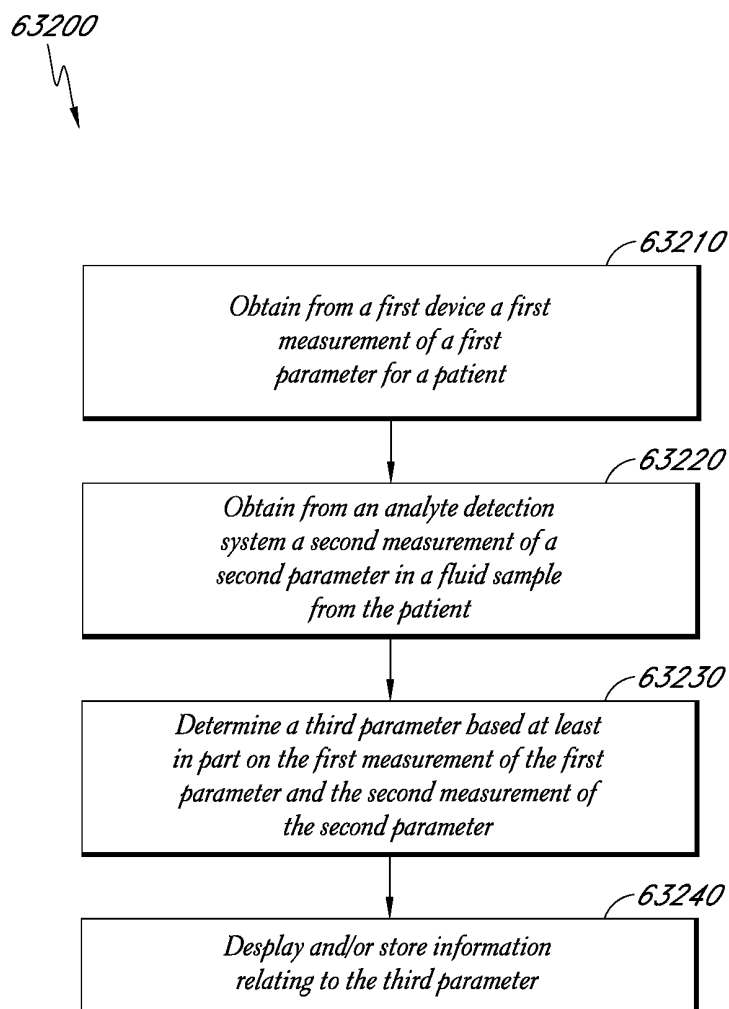


FIG. 41

**SYSTEMS AND METHODS FOR
DETERMINING PHYSIOLOGICAL
PARAMETERS USING MEASURED ANALYTE
VALUES**

CROSS-REFERENCE TO RELATED
APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 (e) of U.S. Provisional Patent Application No. 60/950,093, filed Jul. 16, 2007, entitled "ANALYTE MEASUREMENT SYSTEMS AND METHODS," the entire disclosure of which is hereby incorporated by reference herein and made part of this specification.

BACKGROUND

1. Field

Some embodiments of the disclosure relate generally to methods and devices for determining a concentration of an analyte in a sample, such as an analyte in a sample of bodily fluid, as well as methods and devices which can be used to support the making of such determinations. This disclosure also relates generally to determining physiological parameters (such as, e.g., cardiac output or metabolic functions.) based at least in part on one or more measured analyte values.

2. Description of Related Art

It is advantageous to measure the levels of certain analytes, such as glucose, in a bodily fluid, such as blood. This can be done, for example, in a hospital or clinical setting when there is a risk that the levels of certain analytes may move outside a desired range, which in turn can jeopardize the health of a patient. Currently known systems for analyte monitoring in a hospital or clinical setting suffer from various drawbacks.

SUMMARY

Embodiments described herein have several features, no single one of which is solely responsible or required for their desirable attributes. Without limiting the scope of the disclosure, some of the advantageous features will now be discussed briefly.

In various embodiments, systems and methods are provided for determining physiological parameters from one or more analyte measurements. For example, systems and methods for determining cardiac output may utilize, among other quantities, measurements of hemoglobin in a venous blood sample drawn from a patient and measurements of the patient's arterial hemoglobin saturation to estimate cardiac output, oxygen extraction ratio, and/or other physiologically interesting quantities.

In some embodiments, the measurements may be made by different instruments. For example, in an embodiment, an analyte detection system (such as, e.g., an OptiScanner® monitoring system available from OptiScan Biomedical Corporation, Hayward, Calif.) may be used to measure venous hemoglobin concentration, and a pulse oximeter may be used to measure arterial hemoglobin saturation. In some embodiments, the instruments may communicate information with each other (and/or with other instruments) via wired and/or wireless techniques. For example, in an embodiment, the analyte detection system communicates with the pulse oximeter over a wired and/or wireless network.

In certain embodiments, the rate at which measurements are taken may be different for different instruments. For example, in one embodiment, an analyte detection system may take measurements every fifteen minutes and an oxime-

ter may take measurements every second. In some embodiments, the measurements taken by one, some, or all of the instruments is stored in data storage for future retrieval and processing. For example, in one embodiment, a fluid sample (e.g., blood) is drawn from a patient at a sampling time and venous hemoglobin concentration in the fluid sample is determined by an analyte detection system at a measurement time. Cardiac output is estimated based at least in part on the determination of venous hemoglobin concentration and a determination of arterial oxygen saturation by a pulse oximeter at a third time. In some embodiments, the third time is approximately equal to the sampling time. In some embodiments, the arterial oxygen saturation determination at the third time is based on statistical estimation from a sequence of oxygen saturation measurements. In various embodiments, the statistical estimation may utilize techniques including, but not limited to, interpolation, extrapolation, averaging, filtering, or correlation.

In one embodiment, a method for determining a physiological parameter in a patient is provided. The method comprises receiving, in a first analyte detection system, a fluid sample from a patient, measuring, by the first analyte detection system, one or more analyte values in the fluid sample, measuring, by a second analyte detection system, one or more analyte values in the patient, and determining a physiological parameter in the patient based at least in part on the one or more analyte values measured by the first analyte detection system and the one or more analyte values measured by the second analyte detection system.

In one embodiment, a system for determining a physiological parameter in a patient is provided. The system comprises an analyte detection system configured to measure first analyte data in a fluid sample received from a patient, a medical sensor configured to measure second analyte data in the patient, and a processor configured to receive the first analyte data and the second analyte data and to determine a physiological parameter based at least in part on the first analyte data and the second analyte data.

In various embodiments, the systems and methods disclosed herein may use the Fick principle (e.g., the Fick equation) in the determination of cardiovascular parameters such as, for example, cardiac output or oxygen extraction ratio.

In one embodiment, a method of determining the concentration of one or more analytes in a sample is provided. The method comprises illuminating a sample with multiple wavelengths of pre-scattered radiation, measuring transmission spectra for the radiation, and taking the ratio of transmission spectra. The method further comprises providing a reference curve, comparing the ratio to the reference curve, and determining the analyte concentration from the comparison to the reference curve. The analyte may comprise hemoglobin.

In one embodiment, an apparatus for measuring the concentration of one or more analytes in a sample is provided. The apparatus comprises a source module configured to emit multiple wavelengths of radiation along an optical path, a flow cell in the optical path, a diffuser located in the optical path such that the radiation is diffused before passing through the flow cell, and a detector module configured to detect radiation that has passed through the diffuser and the flow cell. The analyte may comprise hemoglobin.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings and associated descriptions are provided to illustrate certain non-limiting, illustrative embodiments.

FIG. 1 shows an embodiment of an apparatus for withdrawing and analyzing fluid samples.

FIG. 2 illustrates how various other devices can be supported on or near an embodiment of apparatus illustrated in FIG. 1.

FIG. 3 illustrates an embodiment of the apparatus in FIG. 1 configured to be connected to a patient.

FIG. 3A illustrates an embodiment of the apparatus in FIG. 1 that is not configured to be connected to a patient but which receives a fluid sample from an extracorporeal fluid container such as, for example, a test tube. This embodiment of the apparatus advantageously provides in vitro analysis of a fluid sample.

FIG. 4 is a block diagram of an embodiment of a system for withdrawing and analyzing fluid samples.

FIG. 5 schematically illustrates an embodiment of a fluid system that can be part of a system for withdrawing and analyzing fluid samples.

FIG. 6 schematically illustrates another embodiment of a fluid system that can be part of a system for withdrawing and analyzing fluid samples.

FIG. 7 is an oblique schematic depiction of an embodiment of a monitoring device.

FIG. 8 shows a cut-away side view of an embodiment of a monitoring device.

FIG. 9 shows a cut-away perspective view of an embodiment of a monitoring device.

FIG. 10 illustrates an embodiment of a removable cartridge that can interface with a monitoring device.

FIG. 11 illustrates an embodiment of a fluid routing card that can be part of the removable cartridge of FIG. 10.

FIG. 12 illustrates how non-disposable actuators can interface with the fluid routing card of FIG. 11.

FIG. 13 illustrates a modular pump actuator connected to a syringe housing that can form a portion of a removable cartridge.

FIG. 14 shows a rear perspective view of internal scaffolding and some pinch valve pump bodies.

FIG. 15 shows an underneath perspective view of a sample cell holder attached to a centrifuge interface, with a view of an interface with a sample injector.

FIG. 16 shows a plan view of a sample cell holder with hidden and/or non-surface portions illustrated using dashed lines.

FIG. 17 shows a top perspective view of the centrifuge interface connected to the sample holder.

FIG. 18 shows a perspective view of an example optical system.

FIG. 19 shows a filter wheel that can be part of the optical system of FIG. 18.

FIG. 20 schematically illustrates an embodiment of an optical system that comprises a spectroscopic analyzer adapted to measure spectra of a fluid sample.

FIG. 21 is a flowchart that schematically illustrates an embodiment of a method for estimating the concentration of an analyte in the presence of interferents.

FIG. 22 is a flowchart that schematically illustrates an embodiment of a method for performing a statistical comparison of the absorption spectrum of a sample with the spectrum of a sample population and combinations of individual library interferent spectra.

FIG. 23 is a flowchart that schematically illustrates an example embodiment of a method for estimating analyte concentration in the presence of the possible interferents.

FIGS. 24 and 25 schematically illustrate the visual appearance of embodiments of a user interface for a system for withdrawing and analyzing fluid samples.

FIG. 26 schematically depicts various components and/or aspects of a patient monitoring system and the relationships among the components and/or aspects.

FIG. 27 is a flowchart that schematically illustrates an embodiment of a method of providing glycemic control.

FIG. 28A illustrates an example embodiment of a hemoglobin sensor comprising source module, flow cell and detector module.

FIG. 28B illustrates further details of the source module of FIG. 28A.

FIG. 28C illustrates further details of the flow cell of FIG. 28A.

FIG. 28D illustrates further details of the detector module of FIG. 28A.

FIG. 29 illustrates a graph of transmission through hemoglobin versus wavelength obtained by simulation.

FIG. 30 illustrates an exemplary apparatus that can be used to determine functional oxygen saturation.

FIG. 31 indicates a graph illustrating the transmission spectra through saline and sample containing hemoglobin with different saturation values.

FIG. 32 indicates a comparison between the reference Functional Oxygen Saturation and the Functional Oxygen Saturation determined by the method disclosed herein.

FIG. 33 shows a graph of signal-to-noise ratio of the apparatus of FIG. 30 versus wavelength.

FIG. 34 illustrates the effect of varying the optical path length and the total hemoglobin content in the sample on the correlation of the functional oxygen saturation obtained by the method disclosed herein and the functional oxygen saturation as measured by a standard instrument.

FIG. 35 illustrates the effect of including scattering correction in the method described herein.

FIG. 36 is a graph illustrating the transmission spectra through a sample containing hemoglobin with different levels of saturation when the apparatus of FIG. 30 comprises a diffuser.

FIG. 37 indicates the signal-to-noise ratio of the apparatus comprising a diffuser versus wavelength.

FIG. 38 shows a graph of the functional oxygen saturation obtained by using the method described herein and the apparatus of FIG. 30 comprising a diffuser.

FIG. 39 shows a graph of functional oxygen saturation obtained by employing scattering correction to FIG. 38.

FIG. 40 is a block diagram that schematically illustrates an embodiment of a system for determining cardiac output and oxygen extraction ratio.

FIG. 41 is a flowchart schematically illustrating an embodiment of a method for determining physiological parameters using measured analyte values.

These and other features will now be described with reference to the drawings summarized above. The drawings and the associated descriptions are provided to illustrate embodiments and not to limit the scope of any claim. Throughout the drawings, reference numbers may be reused to indicate correspondence between referenced elements. In addition, where applicable, the first one or two digits of a reference numeral for an element can frequently indicate the figure number in which the element first appears.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Although certain preferred embodiments and examples are disclosed below, inventive subject matter extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and to modifications and equiva-

lents thereof. Thus, the scope of the disclosure is not limited by any of the particular embodiments described below. For example, in any method or process disclosed herein, the acts or operations of the method or process may be performed in any suitable sequence and are not necessarily limited to any particular disclosed sequence. Various operations may be described as multiple discrete operations in turn, in a manner that may be helpful in understanding certain embodiments; however, the order of description should not be construed to imply that these operations are order dependent. Additionally, the structures, systems, and/or devices described herein may be embodied as integrated components or as separate components. For purposes of comparing various embodiments, certain aspects and advantages of these embodiments are described. Not necessarily all such aspects or advantages are achieved by any particular embodiment. Thus, for example, various embodiments may be carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other aspects or advantages as may also be taught or suggested herein.

The systems and methods discussed herein can be used anywhere, including, for example, in laboratories, hospitals, healthcare facilities, intensive care units (ICUs), or residences. Moreover, the systems and methods discussed herein can be used for invasive techniques, as well as non-invasive techniques or techniques that do not involve a body or a patient such as, for example, in vitro techniques.

Analyte Monitoring Apparatus

FIG. 1 shows an embodiment of an apparatus **100** for withdrawing and analyzing fluid samples. The apparatus **100** includes a monitoring device **102**. In some embodiments, the monitoring device **102** can be an "OptiScanner®" monitor available from OptiScan Biomedical Corporation of Hayward, Calif. In some embodiments, the device **102** can measure one or more physiological parameters, such as the concentration of one or more substance(s) in a sample fluid. The sample fluid can be, for example, whole blood from a patient **302** (see, e.g., FIG. 3) and/or a component of whole blood such as, e.g., blood plasma. In some embodiments, the device **100** can also deliver an infusion fluid to a patient.

In the illustrated embodiment, the monitoring device **102** includes a display **104** such as, for example, a touch-sensitive liquid crystal display. The display **104** can provide an interface that includes alerts, indicators, charts, and/or soft buttons. The device **102** also can include one or more inputs and/or outputs **106** that provide connectivity and/or permit user interactivity.

In the embodiment shown in FIG. 1, the device **102** is mounted on a stand **108**. The stand **108** may comprise a cart such as, for example, a wheeled cart **130** as shown in FIG. 1. In some embodiments, the stand **108** is configured to roll on a wheeled pedestal **240** (shown in FIG. 2). The stand **108** advantageously can be easily moved and includes one or more poles **110** and/or hooks **112**. The poles **110** and hooks **112** can be configured to accommodate other medical devices and/or implements, including, for example, infusion pumps, saline bags, arterial pressure sensors, other monitors and medical devices, and so forth. Some stands or carts may become unstable if intravenous (IV) bags, IV pumps, and other medical devices are hung too high on the stand or cart. In some embodiments, the apparatus **100** can be configured to have a low center of gravity, which may overcome possible instability. For example, the stand **108** can be weighted at the bottom to at least partially offset the weight of IV bags, IV pumps and medical devices that may be attached to the hooks **112** that are placed above the monitoring device **102**. Adding

weight toward the bottom (e.g., near the wheels) may help prevent the apparatus **100** from tipping over.

In some embodiments, the apparatus **100** includes the cart **130**, which has an upper shelf **131** on which the monitoring device **102** may be placed (or attached) and a bottom shelf **132** on which a battery **134** may be placed (or attached). The battery **134** may be used as a main or backup power supply for the monitoring device **102** (which may additionally or alternatively accept electrical power from a wall socket). Two or more batteries are used in certain embodiments. The apparatus **100** may be configured so that the upper and lower shelves **131**, **132** are close to ground level, and the battery provides counterweight. Other types of counterweights may be used. For example, in some embodiments, portions of the cart **130** near the floor (e.g., a lower shelf) are weighted, formed from a substantial quantity of material (e.g., thick sheets of metal), and/or formed from a relatively high-density metal (e.g., lead). In some embodiments the bottom shelf **132** is approximately 6 inches to 1 foot above ground level, and the upper shelf **131** is approximately 2 feet to 4 feet above ground level. In some embodiments the upper shelf **131** may be configured to support approximately 40 pounds (lbs), and the bottom shelf **132** may be configured to support approximately 20 lbs. One possible advantage of embodiments having such a configuration is that IV pumps, bags containing saline, blood and/or drugs, and other medical equipment weighing approximately 60 lbs, collectively, can be hung on the hooks **112** above the shelves without making the apparatus **100** unstable. The apparatus **100** may be moved by applying a horizontal force on the apparatus **100**, for example, by pushing and/or pulling the poles **110**. In many cases, a user may exert force on an upper portion of the apparatus **100**, for example, close to shoulder-height. By counterbalancing the weight as described above, the apparatus **100** may be moved in a reasonably stable manner.

In the illustrated embodiment, the cart **130** includes the bottom shelf **132** and an intermediate shelf **133**, which are enclosed on three sides by walls and on a fourth side by a door **135**. The door **135** can be opened (as shown in FIG. 1) to provide access to the shelves **132**, **133**. In other embodiments, the fourth side is not enclosed (e.g., the door **135** is not used). Many cart variations are possible. In some embodiments the battery **134** can be placed on the bottom shelf **132** or the intermediate shelf **133**.

FIG. 2 illustrates how various other devices can be supported on or near the apparatus **100** illustrated in FIG. 1. For example, the poles **110** of the stand **108** can be configured (e.g., of sufficient size and strength) to accommodate multiple devices **202**, **204**, **206**. In some embodiments, one or more COLLEAGUE® volumetric infusion pumps available from Baxter International Inc. of Deerfield, Ill. can be accommodated. In some embodiments, one or more Alaris® PC units available from Cardinal Health, Inc. of Dublin, Ohio can be accommodated. Furthermore, various other medical devices (including the two examples mentioned here), can be integrated with the disclosed monitoring device **102** such that multiple devices function in concert for the benefit of one or multiple patients without the devices interfering with each other.

FIG. 3 illustrates the apparatus **100** of FIG. 1 as it can be connected to a patient **302**. The monitoring device **102** can be used to determine the concentration of one or more substances in a sample fluid. The sample fluid can come from the patient **302**, as illustrated in FIG. 3, or the sample fluid can come from a fluid container, as illustrated in FIG. 3A. In some preferred embodiments, the sample fluid is whole blood.

In some embodiments (see, e.g., FIG. 3), the monitoring device 102 can also deliver an infusion fluid to the patient 302. An infusion fluid container 304 (e.g., a saline bag), which can contain infusion fluid (e.g., saline and/or medication), can be supported by the hook 112. The monitoring device 102 can be in fluid communication with both the container 304 and the sample fluid source (e.g., the patient 302), through tubes 306. The infusion fluid can comprise any combination of fluids and/or chemicals. Some advantageous examples include (but are not limited to): water, saline, dextrose, lactated Ringer's solution, drugs, and insulin.

The example monitoring device 102 schematically illustrated in FIG. 3 allows the infusion fluid to pass to the patient 302 and/or uses the infusion fluid itself (e.g., as a flushing fluid or a standard with known optical properties, as discussed further below). In some embodiments, the monitoring device 102 may not employ infusion fluid. The monitoring device 102 may thus draw samples without delivering any additional fluid to the patient 302. The monitoring device 102 can include, but is not limited to, fluid handling and analysis apparatuses, connectors, passageways, catheters, tubing, fluid control elements, valves, pumps, fluid sensors, pressure sensors, temperature sensors, hematocrit sensors, hemoglobin sensors, colorimetric sensors, gas (e.g., "bubble") sensors, fluid conditioning elements, gas injectors, gas filters, blood plasma separators, and/or communication devices (e.g., wireless devices) to permit the transfer of information within the monitoring device 102 or between the monitoring device 102 and a network.

In some embodiments, the apparatus 100 is not connected to a patient and may receive fluid samples from a container such as a decanter, flask, beaker, tube, cartridge, test strip, etc., or any other extracorporeal fluid source. The container may include a biological fluid sample such as, e.g., a body fluid sample. For example, FIG. 3A schematically illustrates an embodiment of the monitoring device 102 that is configured to receive a fluid sample from one or more test tubes 350. This embodiment of the monitoring device 102 is configured to perform in vitro analysis of a fluid (or a fluid component) in the test tube 350. The test tube 350 may comprise a tube, vial, bottle, or other suitable container or vessel. The test tube 350 may include an opening disposed at one end of the tube through which the fluid sample may be added prior to delivery of the test tube to the monitoring device 102. In some embodiments, the test tubes 350 may also include a cover adapted to seal the opening of the tube. The cover may include an aperture configured to permit a tube, nozzle, needle, pipette, or syringe to dispense the fluid sample into the test tube 350. The test tubes 350 may comprise a material such as, for example, glass, polyethylene, or polymeric compounds. In various embodiments, the test tubes 350 may be re-usable units or may be disposable, single-use units. In certain embodiments, the test tubes 350 may comprise commercially available low pressure/vacuum sample bottles, test bottles, or test tubes.

In the embodiment shown in FIG. 3A, the monitoring device 102 comprises a fluid delivery system 360 configured to receive a container (e.g., the test tube 350) containing a fluid sample and deliver the fluid sample to a fluid handling system (such as, e.g., fluid handling system 404 described below). In some embodiments, the fluid handling system delivers a portion of the fluid sample to an analyte detection system for in vitro measurement of one or more physiological parameters (e.g., an analyte concentration). Prior to measurement, the fluid handling system may, in some embodiments, separate the fluid sample into components, and a measurement may be performed on one or more of the components. For example, the fluid sample in the test tube 350 may com-

prise whole blood, and the fluid handling system may separate blood plasma from the sample (e.g., by filtering and/or centrifuging).

In the embodiment illustrated in FIG. 3A, the fluid delivery system 360 comprises a carousel 362 having one or more openings 364 adapted to receive the test tube 350. The carousel 362 may comprise one, two, four, six, twelve, or more openings 364. In the illustrated embodiment, the carousel 362 is configured to rotate around a central axis or spindle 366 so that a test tube 350 inserted into one of the openings 364 is delivered to the monitoring device 102. In certain embodiments, the fluid handling system of the monitoring device 102 comprises a sampling probe that is configured to collect a portion of the fluid sample from the test tube 350 (e.g., by suction or aspiration). The collected portion may then be transported in the device 102 as further described below (see, e.g., FIGS. 4-7). For example, in one embodiment suitable for use with whole blood, the collected portion of the whole blood sample is transported to a centrifuge for separation into blood plasma, a portion of the blood plasma is transported to an infrared spectroscope for measurement of one or more analytes (e.g., glucose), and the measured blood plasma is then transported to a waste container for disposal.

In other embodiments of the apparatus 100 shown in FIG. 3A, the fluid delivery system 360 may comprise a turntable, rack, or caddy adapted to receive the test tube 350. In yet other embodiments, the monitoring device 102 may comprise an inlet port adapted to receive the test tube 350. Additionally, in other embodiments, the fluid sample may be delivered to the apparatus 100 using a test cartridge, a test strip, or other suitable container. Many variations are possible.

In some embodiments, one or more components of the apparatus 100 can be located at another facility, room, or other suitable remote location. One or more components of the monitoring device 102 can communicate with one or more other components of the monitoring device 102 (or with other devices) by communication interface(s) such as, but not limited to, optical interfaces, electrical interfaces, and/or wireless interfaces. These interfaces can be part of a local network, internet, wireless network, or other suitable networks.

System Overview

FIG. 4 is a block diagram of a system 400 for sampling and analyzing fluid samples. The monitoring device 102 can comprise such a system. The system 400 can include a fluid source 402 connected to a fluid-handling system 404. The fluid-handling system 404 includes fluid passageways and other components that direct fluid samples. Samples can be withdrawn from the fluid source 402 and analyzed by an optical system 412. The fluid-handling system 404 can be controlled by a fluid system controller 405, and the optical system 412 can be controlled by an optical system controller 413. The sampling and analysis system 400 can also include a display system 414 and an algorithm processor 416 that assist in fluid sample analysis and presentation of data.

In some embodiments, the sampling and analysis system 400 is a mobile point-of-care apparatus that monitors physiological parameters such as, for example, blood glucose concentration. Components within the system 400 that may contact fluid and/or a patient, such as tubes and connectors, can be coated with an antibacterial coating to reduce the risk of infection. Connectors between at least some components of the system 400 can include a self-sealing valve, such as a spring valve, in order to reduce the risk of contact between port openings and fluids, and to guard against fluid escaping from the system. Other components can also be included in a system for sampling and analyzing fluid in accordance with the described embodiments.

The sampling and analysis system **400** can include a fluid source **402** (or more than one fluid source) that contain(s) fluid to be sampled. The fluid-handling system **404** of the sampling and analysis system **400** is connected to, and can draw fluid from, the fluid source **402**. The fluid source **402** can be, for example, a blood vessel such as a vein or an artery, a container such as a decanter, flask, beaker, tube, cartridge, test strip, etc., or any other corporeal or extracorporeal fluid source. For example, in some embodiments, the fluid source **402** may be a vein or artery in the patient **302** (see, e.g., FIG. 3). In other embodiments, the fluid source **402** may comprise an extracorporeal container **350** of fluid delivered to the system **400** for analysis (see, e.g., FIG. 3B). The fluid to be sampled can be, for example, blood, plasma, interstitial fluid, lymphatic fluid, or another fluid. In some embodiments, more than one fluid source can be present, and more than one fluid and/or type of fluid can be provided.

In some embodiments, the fluid-handling system **404** withdraws a sample of fluid from the fluid source **402** for analysis, centrifuges at least a portion of the sample, and prepares at least a portion of the sample for analysis by an optical sensor such as a spectrophotometer (which can be part of an optical system **412**, for example). These functions can be controlled by a fluid system controller **405**, which can also be integrated into the fluid-handling system **404**. The fluid system controller **405** can also control the additional functions described below.

In some embodiments, at least a portion of the sample is returned to the fluid source **402**. At least some of the sample, such as portions of the sample that are mixed with other materials or portions that are otherwise altered during the sampling and analysis process, or portions that, for any reason, are not to be returned to the fluid source **402**, can also be placed in a waste bladder (not shown in FIG. 4). The waste bladder can be integrated into the fluid-handling system **404** or supplied by a user of the system **400**. The fluid-handling system **404** can also be connected to a saline source, a detergent source, and/or an anticoagulant source, each of which can be supplied by a user, attached to the fluid-handling system **404** as additional fluid sources, and/or integrated into the fluid-handling system **404**.

Components of the fluid-handling system **404** can be modularized into one or more non-disposable, disposable, and/or replaceable subsystems. In the embodiment shown in FIG. 4, components of the fluid-handling system **404** are separated into a non-disposable subsystem **406**, a first disposable subsystem **408**, and a second disposable subsystem **410**.

The non-disposable subsystem **406** can include components that, while they may be replaceable or adjustable, do not generally require regular replacement during the useful lifetime of the system **400**. In some embodiments, the non-disposable subsystem **406** of the fluid-handling system **404** includes one or more reusable valves and sensors. For example, the non-disposable subsystem **406** can include one or more valves (or non-disposable portions thereof), (e.g., pinch-valves, rotary valves, etc.), sensors (e.g., ultrasonic bubble sensors, non-contact pressure sensors, optical blood dilution sensors, etc). The non-disposable subsystem **406** can also include one or more pumps (or non-disposable portions thereof). For example, some embodiments can include pumps available from Hospira. In some embodiments, the components of the non-disposable subsystem **406** are not directly exposed to fluids and/or are not readily susceptible to contamination.

The first and second disposable subsystems **408**, **410** can include components that are regularly replaced under certain circumstances in order to facilitate the operation of the system

400. For example, the first disposable subsystem **408** can be replaced after a certain period of use, such as a few days, has elapsed. Replacement may be necessary, for example, when a bladder within the first disposable subsystem **408** is filled to capacity. Such replacement may mitigate fluid system performance degradation associated with and/or contamination wear on system components.

In some embodiments, the first disposable subsystem **408** includes components that may contact fluids such as patient blood, saline, flushing solutions, anticoagulants, and/or detergent solutions. For example, the first disposable subsystem **408** can include one or more tubes, fittings, cleaner pouches and/or waste bladders. The components of the first disposable subsystem **408** can be sterilized in order to decrease the risk of infection and can be configured to be easily replaceable.

In some embodiments, the second disposable subsystem **410** can be designed to be replaced under certain circumstances. For example, the second disposable subsystem **410** can be replaced when the patient being monitored by the system **400** is changed. The components of the second disposable subsystem **410** may not need replacement at the same intervals as the components of the first disposable subsystem **408**. For example, the second disposable subsystem **410** can include a sample holder and/or at least some components of a centrifuge, components that may not become filled or quickly worn during operation of the system **400**. Replacement of the second disposable subsystem **410** can decrease or eliminate the risk of transferring fluids from one patient to another during operation of the system **400**, enhance the measurement performance of system **400**, and/or reduce the risk of contamination or infection.

In some embodiments, the sample holder of the second disposable subsystem **410** receives the sample obtained from the fluid source **402** via fluid passageways of the first disposable subsystem **408**. The sample holder is a container that can hold fluid for the centrifuge and can include a window to the sample for analysis by a spectrometer. In some embodiments, the sample holder includes windows that are made of a material that is substantially transparent to electromagnetic radiation in the mid-infrared range of the spectrum. For example, the sample holder windows can be made of calcium fluoride.

An injector can provide a fluid connection between the first disposable subsystem **408** and the sample holder of the second disposable subsystem **410**. In some embodiments, the injector can be removed from the sample holder to allow for free spinning of the sample holder during centrifugation.

In some embodiments, the components of the sample are separated by centrifuging for a period of time before measurements are performed by the optical system **412**. For example, a fluid sample (e.g., a blood sample) can be centrifuged at a relatively high speed. The sample can be spun at a certain number of revolutions per minute (RPM) for a given length of time to separate blood plasma for spectral analysis. In some embodiments, the fluid sample is spun at about 7200 RPM. In some embodiments, the sample is spun at about 5000 RPM. In some embodiments, the fluid sample is spun at about 4500 RPM. In some embodiments, the fluid sample is spun at more than one rate for successive time periods. The length of time can be approximately 5 minutes. In some embodiments, the length of time is approximately 2 minutes. Separation of a sample into the components can permit measurement of solute (e.g., glucose) concentration in plasma, for example, without interference from other blood components. This kind of post-separation measurement, (sometimes referred to as a "direct measurement") has advantages over a solute measurement taken from whole blood because the proportions of plasma to other components need not be known or estimated

in order to infer plasma glucose concentration. In some embodiments, the separated plasma can be analyzed electrically using one or more electrodes instead of, or in addition to, being analyzed optically. This analysis may occur within the same device, or within a different device. For example, in certain embodiments, an optical analysis device can separate blood into components, analyze the components, and then allow the components to be transported to another analysis device that can further analyze the components (e.g., using electrical and/or electrochemical measurements).

An anticoagulant, such as, for example, heparin can be added to the sample before centrifugation to prevent clotting. The fluid-handling system 404 can be used with a variety of anticoagulants, including anticoagulants supplied by a hospital or other user of the monitoring system 400. A detergent solution formed by mixing detergent powder from a pouch connected to the fluid-handling system 404 with saline can be used to periodically clean residual protein and other sample remnants from one or more components of the fluid-handling system 404, such as the sample holder. Sample fluid to which anticoagulant has been added and used detergent solution can be transferred into the waste bladder.

The system 400 shown in FIG. 4 includes an optical system 412 that can measure optical properties (e.g., transmission) of a fluid sample (or a portion thereof). In some embodiments, the optical system 412 measures transmission in the mid-infrared range of the spectrum. In some embodiments, the optical system 412 includes a spectrometer that measures the transmission of broadband infrared light through a portion of a sample holder filled with fluid. The spectrometer need not come into direct contact with the sample. As used herein, the term "sample holder" is a broad term that carries its ordinary meaning as an object that can provide a place for fluid. The fluid can enter the sample holder by flowing.

In some embodiments, the optical system 412 includes a filter wheel that contains one or more filters. In some embodiments, more than ten filters can be included, for example twelve or fifteen filters. In some embodiments, more than 20 filters (e.g., twenty-five filters) are mounted on the filter wheel. The optical system 412 includes a light source that passes light through a filter and the sample holder to a detector. In some embodiments, a stepper motor moves the filter wheel in order to position a selected filter in the path of the light. An optical encoder can also be used to finely position one or more filters. In some embodiments, one or more tunable filters may be used to filter light into multiple wavelengths. The one or more tunable filters may provide the multiple wavelengths of light at the same time or at different times (e.g., sequentially). The light source included in the optical system 412 may emit radiation in the ultraviolet, visible, near-infrared, mid-infrared, and/or far-infrared regions of the electromagnetic spectrum. In some embodiments, the light source can be a broadband source that emits radiation in a broad spectral region (e.g., from about 1500 nm to about 6000 nm). In other embodiments, the light source may emit radiation at certain specific wavelengths. The light source may comprise one or more light emitting diodes (LEDs) emitting radiation at one or more wavelengths in the radiation regions described herein. In other embodiments, the light source may comprise one or more laser modules emitting radiation at one or more wavelengths. The laser modules may comprise a solid state laser (e.g., a Nd:YAG laser), a semiconductor based laser (e.g., a GaAs and/or InGaAsP laser), and/or a gas laser (e.g., an Ar-ion laser). In some embodiments, the laser modules may comprise a fiber laser. The laser modules may emit radiation at certain fixed wavelengths. In some embodiments, the emission wavelength of the laser

module(s) may be tunable over a wide spectral range (e.g., about 30 nm to about 100 nm). In some embodiments, the light source included in the optical system 412 may be a thermal infrared emitter. The light source can comprise a resistive heating element, which, in some embodiments, may be integrated on a thin dielectric membrane on a micromachined silicon structure. In one embodiment the light source is generally similar to the electrical modulated thermal infrared radiation source, IRSource™, available from the Axetris Microsystems division of Leister Technologies, LLC (Itasca, Ill.).

The optical system 412 can be controlled by an optical system controller 413. The optical system controller can, in some embodiments, be integrated into the optical system 412. In some embodiments, the fluid system controller 405 and the optical system controller 413 can communicate with each other as indicated by the line 411. In some embodiments, the function of these two controllers can be integrated and a single controller can control both the fluid-handling system 404 and the optical system 412. Such an integrated control can be advantageous because the two systems are preferably integrated, and the optical system 412 is preferably configured to analyze the very same fluid handled by the fluid-handling system 404. Indeed, portions of the fluid-handling system 404 (e.g., the sample holder described above with respect to the second disposable subsystem 410 and/or at least some components of a centrifuge) can also be components of the optical system 412. Accordingly, the fluid-handling system 404 can be controlled to obtain a fluid sample for analysis by optical system 412, when the fluid sample arrives, the optical system 412 can be controlled to analyze the sample, and when the analysis is complete (or before), the fluid-handling system 404 can be controlled to return some of the sample to the fluid source 402 and/or discard some of the sample, as appropriate.

The system 400 shown in FIG. 4 includes a display system 414 that provides for communication of information to a user of the system 400. In some embodiments, the display 414 can be replaced by or supplemented with other communication devices that communicate in non-visual ways. The display system 414 can include a display processor that controls or produces an interface to communicate information to the user. The display system 414 can include a display screen. One or more parameters such as, for example, blood glucose concentration, system 400 operating parameters, and/or other operating parameters can be displayed on a monitor (not shown) associated with the system 400. An example of one way such information can be displayed is shown in FIGS. 24 and 25. In some embodiments, the display system 414 can communicate measured physiological parameters and/or operating parameters to a computer system over a communications connection.

The system 400 shown in FIG. 4 includes an algorithm processor 416 that can receive spectral information, such as optical density (OD) values (or other analog or digital optical data) from the optical system 412 and or the optical system controller 413. In some embodiments, the algorithm processor 416 calculates one or more physiological parameters and can analyze the spectral information. Thus, for example and without limitation, a model can be used that determines, based on the spectral information, physiological parameters of fluid from the fluid source 402. The algorithm processor 416, a controller that may be part of the display system 414, and any embedded controllers within the system 400 can be connected to one another with a communications bus.

Some embodiments of the systems described herein (e.g., the system 400), as well as some embodiments of each

method described herein, can include a computer program accessible to and/or executable by a processing system, e.g., a one or more processors and memories that are part of an embedded system. Indeed, the controllers may comprise one or more computers and/or may use software. Thus, as will be appreciated by those skilled in the art, various embodiments may be embodied as a method, an apparatus such as a special purpose apparatus, an apparatus such as a data processing system, or a carrier medium, e.g., a computer program product. The carrier medium carries one or more computer readable code segments for controlling a processing system to implement a method. Accordingly, various embodiments may take the form of a method, an entirely hardware embodiment, an entirely software embodiment or an embodiment combining software and hardware aspects. Furthermore, any one or more of the disclosed methods (including but not limited to the disclosed methods of measurement analysis, interferent determination, and/or calibration constant generation) may be stored as one or more computer readable code segments or data compilations on a carrier medium. Any suitable computer readable carrier medium may be used including a magnetic storage device such as a diskette or a hard disk; a memory cartridge, module, card or chip (either alone or installed within a larger device); or an optical storage device such as a CD or DVD.

Fluid Handling System

The generalized fluid-handling system **404** can have various configurations. In this context, FIG. 5 schematically illustrates the layout of an example embodiment of a fluid system **510**. In this schematic representation, various components are depicted that may be part of a non-disposable subsystem **406**, a first disposable subsystem **408**, a second disposable subsystem **410**, and/or an optical system **412**. The fluid system **510** is described practically to show an example cycle as fluid is drawn and analyzed.

In addition to the reference numerals used below, the various portions of the illustrated fluid system **510** are labeled for convenience with letters to suggest their roles as follows: T# indicates a section of tubing. C# indicates a connector that joins multiple tubing sections. V# indicates a valve. BS# indicates a bubble sensor or ultrasonic air detector. N# indicates a needle (e.g., a needle that injects sample into a sample holder). PS# indicates a pressure sensor (e.g., a reusable pressure sensor). Pump# indicates a fluid pump (e.g., a syringe pump with a disposable body and reusable drive). "Hb 12" indicates a sensor for hemoglobin (e.g., a dilution sensor that can detect hemoglobin optically).

The term "valve" as used herein is a broad term and is used, in accordance with its ordinary meaning, to refer to any flow regulating device. For example, the term "valve" can include, without limitation, any device or system that can controllably allow, prevent, or inhibit the flow of fluid through a fluid passageway. The term "valve" can include some or all of the following, alone or in combination: pinch valves, rotary valves, stop cocks, pressure valves, shuttle valves, mechanical valves, electrical valves, electro-mechanical flow regulators, etc. In some embodiments, a valve can regulate flow using gravitational methods or by applying electrical voltages or by both.

The term "pump" as used herein is a broad term and is used, in accordance with its ordinary meaning, to refer to any device that can urge fluid flow. For example, the term "pump" can include any combination of the following: syringe pumps, peristaltic pumps, vacuum pumps, electrical pumps, mechanical pumps, hydraulic pumps, etc. Pumps and/or

pump components that are suitable for use with some embodiments can be obtained, for example, from or through Hospira.

The function of the valves, pumps, actuators, drivers, motors (e.g., the centrifuge motor), etc. described below is controlled by one or more controllers (e.g., the fluid system controller **405**, the optical system controller **413**, etc.) The controllers can include software, computer memory, electrical and mechanical connections to the controlled components, etc.

At the start of a measurement cycle, most lines, including a patient tube **512** (T1), an Arrival sensor tube **528** (T4), an anticoagulant valve tube **534** (T3), and a sample cell **548** can be filled with saline that can be introduced into the system through the infusion tube **514** and the saline tube **516**, and which can come from an infusion pump **518** and/or a saline bag **520**. The infusion pump **518** and the saline bag **520** can be provided separately from the system **510**. For example, a hospital can use existing saline bags and infusion pumps to interface with the described system. The infusion valve **521** can be open to allow saline to flow into the tube **512** (T1).

Before drawing a sample, the saline in part of the system **510** can be replaced with air. Thus, for example, the following valves can be closed: air valve **503** (PV0), the detergent tank valve **559** (V7b), **566** (V3b), **523** (V0), **529** (V7a), and **563** (V2b). At the same time, the following valves can be open: valves **531** (V1a), **533** (V3a) and **577** (V4a). Simultaneously, a second pump **532** (pump #0) pumps air through the system **510** (including tube **534** (T3), sample cell **548**, and tube **556** (T6)), pushing saline through tube **534** (T3) and sample cell **548** into a waste bladder **554**.

Next, a sample can be drawn. With the valves **542** (PV1), **559** (V7b), and **561** (V4b) closed, a first pump **522** (pump #1) is actuated to draw sample fluid to be analyzed (e.g. blood) from a fluid source (e.g., a laboratory sample container, a living patient, etc.) up into the patient tube **512** (T1), through the tube past the two flanking portions of the open pinch-valve **523** (V0), through the first connector **524** (C1), into the looped tube **530**, past the arrival sensor **526** (Hb12), and into the arrival sensor tube **528** (T4). The arrival sensor **526** may be used to detect the presence of blood in the tube **528** (T4). For example in some embodiments, the arrival sensor **526** may comprise a hemoglobin sensor. In some other embodiments, the arrival sensor **526** may comprise a color sensor that detects the color of fluid flowing through the tube **528** (T4). During this process, the valve **529** (V7a) and **523** (V0) are open to fluid flow, and the valves **531** (V1a), **533** (V3a), **542** (PV1), **559** (V7b), and **561** (V4b) can be closed and therefore block (or substantially block) fluid flow by pinching the tube.

Before drawing the sample, the tubes **512** (T1) and **528** (T4) are filled with saline and the hemoglobin (Hb) level is zero. The tubes that are filled with saline are in fluid communication with the sample source (e.g., the fluid source **402**). The sample source can be the vessels of a living human or a pool of liquid in a laboratory sample container, for example. When the saline is drawn toward the first pump **522**, fluid to be analyzed is also drawn into the system because of the suction forces in the closed fluid system. Thus, the first pump **522** draws a relatively continuous column of fluid that first comprises generally nondiluted saline, then a mixture of saline and sample fluid (e.g., blood), and then eventually nondiluted sample fluid. In the example illustrated here, the sample fluid is blood.

The arrival sensor **526** (Hb12) can detect and/or verify the presence of blood in the tubes. For example, in some embodiments, the arrival sensor **526** can determine the color of the fluid in the tubes. In some embodiments, the arrival sensor

526 (Hb12) can detect the level of Hemoglobin in the sample fluid. As blood starts to arrive at the arrival sensor **526 (Hb12)**, the sensed hemoglobin level rises. A hemoglobin level can be selected, and the system can be pre-set to determine when that level is reached. A controller such as the fluid system controller **405** of FIG. 4 can be used to set and react to the pre-set value, for example. In some embodiments, when the sensed hemoglobin level reaches the pre-set value, substantially undiluted sample is present at the first connector **524 (C1)**. The preset value can depend, in part, on the length and diameter of any tubes and/or passages traversed by the sample. In some embodiments, the pre-set value can be reached after approximately 2 mL of fluid (e.g., blood) has been drawn from a fluid source. A nondiluted sample can be, for example, a blood sample that is not diluted with saline solution, but instead has the characteristics of the rest of the blood flowing through a patient's body. A loop of tubing **530** (e.g., a 1-mL loop) can be advantageously positioned as illustrated to help insure that undiluted fluid (e.g., undiluted blood) is present at the first connector **524 (C1)** when the arrival sensor **526** registers that the preset Hb threshold is crossed. The loop of tubing **530** provides additional length to the Arrival sensor tube **528 (T4)** to make it less likely that the portion of the fluid column in the tubing at the first connector **524 (C1)** has advanced all the way past the mixture of saline and sample fluid, and the nondiluted blood portion of that fluid has reached the first connector **524 (C1)**.

In some embodiments, when nondiluted blood is present at the first connector **524 (C1)**, a sample is mixed with an anticoagulant and is directed toward the sample cell **548**. An amount of anticoagulant (e.g., heparin) can be introduced into the tube **534 (T3)**, and then the undiluted blood is mixed with the anticoagulant. A heparin vial **538** (e.g., an insertable vial provided independently by the user of the system **510**) can be connected to a tube **540**. An anticoagulant valve **541** (which can be a shuttle valve, for example) can be configured to connect to both the tube **540** and the anticoagulant valve tube **534 (T3)**. The valve can open the tube **540** to a suction force (e.g., created by the pump **532**), allowing heparin to be drawn from the vial **538** into the valve **541**. Then, the anticoagulant valve **541** can slide the heparin over into fluid communication with the anticoagulant valve tube **534 (T3)**. The anticoagulant valve **541** can then return to its previous position. Thus, heparin can be shuttled from the tube **540** into the anticoagulant valve tube **534 (T3)** to provide a controlled amount of heparin into the tube **534 (T3)**.

With the valves **542 (PV1)**, **559 (V7b)**, **561 (V4b)**, **523 (V0)**, **531 (V1a)**, **566 (V3b)**, and **563 (V2b)** closed, and the valves **529 (V7a)** and **553 (V3a)** open, first pump **522 (pump #1)** pushes the sample from tube **528 (T4)** into tube **534 (T3)**, where the sample mixes with the heparin injected by the anticoagulant valve **541** as it flows through the system **510**. As the sample proceeds through the tube **534 (T3)**, the air that was previously introduced into the tube **534 (T3)** is displaced. The sample continues to flow until a bubble sensor **535 (BS9)** indicates a change from air to a liquid, and thus the arrival of a sample at the bubble sensor. In some embodiments, the volume of tube **534 (T3)** from connector **524 (C1)** to bubble sensor **535 (BS9)** is a known and/or engineered amount, and may be approximately 500 μL , 200 μL or 100 μL , for example.

When bubble sensor **535 (BS9)** indicates the presence of a sample, the remainder of the sampled blood can be returned to its source (e.g., the patient veins or arteries). The first pump **522 (pump #1)** pushes the blood out of the Arrival sensor tube **528 (T4)** and back to the patient by opening the valve **523 (V0)**, closing the valves **531 (V1a)** and **533 (V3a)**, and keep-

ing the valve **529 (V7a)** open. The Arrival sensor tube **528 (T4)** is preferably flushed with approximately 2 mL of saline. This can be accomplished by closing the valve **529 (V7a)**, opening the valve **542 (PV1)**, drawing saline from the saline source **520** into the tube **544**, closing the valve **542 (PV1)**, opening the valve **529 (V7a)**, and forcing the saline down the Arrival sensor tube **528 (T4)** with the pump **522**. In some embodiments, less than two minutes elapse between the time that blood is drawn from the patient and the time that the blood is returned to the patient.

Following return of the unused patient blood sample, the sample is pushed up the anticoagulant valve tube **534 (T3)**, through the second connector **546 (C2)**, and into the sample cell **548**, which can be located on the centrifuge rotor **550**. This fluid movement is facilitated by the coordinated action (either pushing or drawing fluid) of the pump **522 (pump #1)**, the pump **532 (pump #0)**, and the various illustrated valves. In particular, valve **531 (V1a)** can be opened, and valves **503 (PV0)** and **559 (V7b)** can be closed. Pump movement and valve position corresponding to each stage of fluid movement can be coordinated by one or more multiple controllers, such as the fluid system controller **405** of FIG. 4.

After the unused sample is returned to the patient, the sample can be divided into separate slugs before being delivered into the sample cell **548**. Thus, for example, valve **553 (V3a)** is opened, valves **566 (V3b)**, **523 (V0)** and **529 (V7a)** are closed, and the pump **532 (pump #0)** uses air to push the sample toward sample cell **548**. In some embodiments, the sample (for example, 200 μL or 100 μL) is divided into multiple (e.g., more than two, five, or four) "slugs" of sample, each separated by a small amount of air. As used herein, the term "slug" refers to a continuous column of fluid that can be relatively short. Slugs can be separated from one another by small amounts of air (or bubbles) that can be present at intervals in the tube. In some embodiments, the slugs are formed by injecting or drawing air into fluid in the first connector **546 (C2)**.

In some embodiments, when the leading edge of the sample reaches blood sensor **553 (BS14)**, a small amount of air (the first "bubble") is injected at a connector **C6**. This bubble helps define the first "slug" of liquid, which extends from the bubble sensor to the first bubble. In some embodiments, the valves **533 (V3a)** and **556 (V3b)** are alternately opened and closed to form a bubble at connector **C6**, and the sample is pushed toward the sample cell **548**. Thus, for example, with pump **532** actuated, valve **566 (V3b)** is briefly opened and valve **533 (V3a)** is briefly closed to inject a first air bubble into the sample.

In some embodiments, the volume of the tube **534 (T3)** from the connector **546 (C2)** to the bubble sensor **552 (BS14)** is less than the volume of tube **534 (T3)** from the connector **524 (C1)** to the bubble sensor **535 (BS9)**. Thus, for example and without limitation, the volume of the tube **534 (T3)** from the connector **524 (C1)** to the bubble sensor **535 (BS9)** can be in the range of approximately 80 μL to approximately 120 μL , (e.g., 100 μL), and the volume of the tube **534 (T3)** from the connector **546 (C2)** to the bubble sensor **552 (BS14)** can be in the range of approximately 5 μL to approximately 25 μL (e.g., 15 μL). In some embodiments, multiple blood slugs are created. For example, more than two blood slugs can be created, each having a different volume. In some embodiments, five blood slugs are created, each having approximately the same volume of approximately 20 μL each. In some embodiments, three blood slugs are created, the first two having a volume of 10 μL and the last having a volume of 20 μL . In some embodiments, four blood slugs are created; the first three blood slugs

can have a volume of approximately 15 μL and the fourth can have a volume of approximately 35 μL .

A second slug can be prepared by opening the valve 553 (V3a), closing the valve 566 (V3b), with pump 532 (pump #0) operating to push the first slug through a first sample cell holder interface tube 582 (N1), through the sample cell 548, through a second sample cell holder interface tube 584 (N2), and toward the waste bladder 554. When the first bubble reaches the bubble sensor 552 (BS 14), the open/closed configurations of valves 553 (V3a) and 566 (V3b) are reversed, and a second bubble is injected into the sample, as before. A third slug can be prepared in the same manner as the second (pushing the second bubble to bubble sensor 552 (BS 14) and injecting a third bubble). After the injection of the third air bubble, the sample can be pushed through system 510 until the end of the sample is detected by bubble sensor 552 (BS 14). The system can be designed such that when the end of the sample reaches this point, the last portion of the sample (a fourth slug) is within the sample cell 548, and the pump 532 can stop forcing the fluid column through the anticoagulant valve tube 534 (T3) so that the fourth slug remains within the sample cell 548. Thus, the first three blood slugs can serve to flush any residual saline out the sample cell 548. The three leading slugs can be deposited in the waste bladder 554 by passing through the tube 556 (T6) and past the tube-flanking portions of the open pinch valve 557 (V4a).

In some embodiments, the fourth blood slug is centrifuged for a given length of time (e.g., more than 1 minute, five minutes, or 2 minutes, to take three advantageous examples) at a relatively fast speed (e.g., 7200 RPM, 5000 RPM, or 4500 RPM, to take three examples). Thus, for example, the sample cell holder interface tubes 582 (N1) and 584 (N2) disconnect the sample cell 548 from the tubes 534 (T3) and 562 (T7), permitting the centrifuge rotor 550 and the sample cell 548 to spin together. Spinning separates a sample (e.g., blood) into its components, isolates the plasma, and positions the plasma in the sample cell 548 for measurement. The centrifuge 550 can be stopped with the sample cell 548 in a beam of radiation (not shown) for analysis. The radiation, a detector, and logic can be used to analyze a portion of the sample (e.g., the plasma) spectroscopically (e.g., for glucose, lactate, or other analyte concentration). In some embodiments, some or all of the separated components (e.g., the isolated plasma) may be transported to a different analysis chamber. For example, another analysis chamber can have one or more electrodes in electrical communication with the chamber's contents, and the separated components may be analyzed electrically. At any suitable point, one or more of the separated components can be transported to the waste bladder 554 when no longer needed. In some chemical analysis systems and apparatus, the separated components are analyzed electrically. Analysis devices may be connected serially, for example, so that the analyzed substance from an optical analysis system (e.g., an "OptiScanner[®]" fluid analyzer) can be transferred to an independent analysis device (e.g., a chemical analysis device) for subsequent analysis. In certain embodiments, the analysis devices are integrated into a single system. Many variations are possible.

In some embodiments, portions of the system 510 that contain blood after the sample cell 548 has been provided with a sample are cleaned to prevent blood from clotting. Accordingly, the centrifuge rotor 550 can include two passageways for fluid that may be connected to the sample cell holder interface tubes 582 (N1) and 584 (N2). One passageway is sample cell 548, and a second passageway is a shunt 586. An embodiment of the shunt 586 is illustrated in more detail in FIG. 16 (see reference numeral 1586).

The shunt 586 can allow cleaner (e.g., a detergent such as tergazyme A) to flow through and clean the sample cell holder interface tubes without flowing through the sample cell 548. After the sample cell 548 is provided with a sample, the interface tubes 582 (N1) and 584 (N2) are disconnected from the sample cell 548, the centrifuge rotor 550 is rotated to align the shunt 586 with the interface tubes 582 (N1) and 584 (N2), and the interface tubes are connected with the shunt. With the shunt in place, the detergent tank 559 is pressurized by the second pump 532 (pump #0) with valves 561 (V4b) and 563 (V2b) open and valves 557 (V4a) and 533 (V3a) closed to flush the cleaning solution back through the interface tubes 582 (N1) and 584 (N2) and into the waste bladder 554. Subsequently, saline can be drawn from the saline bag 520 for a saline flush. This flush pushes saline through the Arrival sensor tube 528 (T4), the anticoagulant valve tube 534 (T3), the sample cell 548, and the waste tube 556 (T6). Thus, in some embodiments, the following valves are open for this flush: 529 (V7a), 533 (V3a), 557 (V4a), and the following valves are closed: 542 (PV1), 523 (V0), 531 (V1a), 566 (V3b), 563 (V2b), and 561 (V4b).

Following analysis, the second pump 532 (pump #0) flushes the sample cell 548 and sends the flushed contents to the waste bladder 554. This flush can be done with a cleaning solution from the detergent tank 558. In some embodiments, the detergent tank valve 559 (V7b) is open, providing fluid communication between the second pump 532 and the detergent tank 558. The second pump 532 forces cleaning solution from the detergent tank 558 between the tube-flanking portions of the open pinch valve 561 and through the tube 562 (T7). The cleaning flush can pass through the sample cell 548, through the second connector 546, through the tube 564 (T5) and the open valve 563 (V2b), and into the waste bladder 554.

Subsequently, the first pump 522 (pump #1) can flush the cleaning solution out of the sample cell 548 using saline in drawn from the saline bag 520. This flush pushes saline through the Arrival sensor tube 528 (T4), the anticoagulant valve tube 534 (T3), the sample cell 548, and the waste tube 556 (T6). Thus, in some embodiments, the following valves are open for this flush: 529 (V7a), 533 (V3a), 557 (V4a), and the following valves are closed: 542 (PV1), 523 (V0), 531 (V1a), 566 (V3b), 563 (V2b), and 561 (V4b).

When the fluid source is a living entity such as a patient, a low flow of saline (e.g., 1-5 mL/hr) is preferably moved through the patient tube 512 (T1) and into the patient to keep the patient's vessel open (e.g., to establish a keep vessel open, or "KVO" flow). This KVO flow can be temporarily interrupted when fluid is drawn into the fluid system 510. The source of this KVO flow can be the infusion pump 518, the third pump 568 (pump #3), or the first pump 522 (pump #1). In some embodiments, the infusion pump 518 can run continuously throughout the measurement cycle described above. This continuous flow can advantageously avoid any alarms that may be triggered if the infusion pump 518 senses that the flow has stopped or changed in some other way. In some embodiments, when the infusion valve 521 closes to allow pump 522 (pump #1) to withdraw fluid from a fluid source (e.g., a patient), the third pump 568 (pump #3) can withdraw fluid through the connector 570, thus allowing the infusion pump 518 to continue pumping normally as if the fluid path was not blocked by the infusion valve 521. If the measurement cycle is about two minutes long, this withdrawal by the third pump 568 can continue for approximately two minutes. Once the infusion valve 521 is open again, the third pump 568 (pump #3) can reverse and insert the saline back into the system at a low flow rate. Preferably, the time between measurement cycles is longer than the measurement

cycle itself (for example, the time interval can be longer than ten minutes, shorter than ten minutes, shorter than five minutes, longer than two minutes, longer than one minute, etc.). Accordingly, the third pump 568 can insert fluid back into the system at a lower rate than it withdrew that fluid. This can help prevent an alarm by the infusion pump.

FIG. 6 schematically illustrates another embodiment of a fluid system that can be part of a system for withdrawing and analyzing fluid samples. In this embodiment, the anticoagulant valve 541 has been replaced with a syringe-style pump 588 (Pump Heparin) and a series of pinch valves around a junction between tubes. For example, a heparin pinch valve 589 (Vhep) can be closed to prevent flow from or to the pump 588, and a heparin waste pinch valve 590 can be closed to prevent flow from or to the waste container from this junction through the heparin waste tube 591. This embodiment also illustrates the shunt 592 schematically. Other differences from FIG. 5 include the check valve 593 located near the detergent tank 558 and the patient loop 594. The reference letters D, for example, the one indicated at 595, refer to components that are advantageously located on the door. The reference letters M, for example, the one indicated at 596, refer to components that are advantageously located on the monitor. The reference letters B, for example, the one indicated at 597, refer to components that can be advantageously located on both the door and the monitor.

In some embodiments, the system 400 (see FIG. 4), the apparatus 100 (see FIG. 1), or even the monitoring device 102 (see FIG. 1) itself can also actively function not only to monitor analyte levels (e.g., glucose), but also to change and/or control analyte levels. Thus, the monitoring device 102 can be both a monitoring and an infusing device. In some embodiments, the fluid handling system 510 can include an optional analyte control subsystem 2780 that will be further described below (see discussion of analyte control).

In certain embodiments, analyte levels in a patient can be adjusted directly (e.g., by infusing or extracting glucose) or indirectly (e.g., by infusing or extracting insulin). FIG. 6 illustrates one way of providing this function. The infusion pinch valve 598 (V8) can allow the port sharing pump 599 (compare to the third pump 568 (pump #3) in FIG. 5) to serve two roles. In the first role, it can serve as a "port sharing" pump. The port sharing function is described with respect to the third pump 568 (pump #3) of FIG. 5, where the third pump 568 (pump #3) can withdraw fluid through the connector 570, thus allowing the infusion pump 518 to continue pumping normally as if the fluid path was not blocked by the infusion valve 521. In the second role, the port sharing pump 599 can serve as an infusion pump. The infusion pump role allows the port sharing pump 599 to draw a substance (e.g., glucose, saline, etc.) from another source when the infusion pinch valve 598 is open, and then to infuse that substance into the system or the patient when the infusion pinch valve 598 is closed. This can occur, for example, in order to change the level of a substance in a patient in response to a reading by the monitor that the substance is too low. In some embodiments, one or more of the pumps may comprise a reversible infusion pump configured to interrupt the flow of the infusion fluid and draw a sample of blood for analysis.

Mechanical/Fluid System Interface

FIG. 7 is an oblique schematic depiction of a modular monitoring device 700, which can correspond to the monitoring device 102. The modular monitoring device 700 includes a body portion 702 having a receptacle 704, which can be accessed by moving a movable portion 706. The receptacle 704 can include connectors (e.g., rails, slots, protrusions, resting surfaces, etc.) with which a removable portion

710 can interface. In some embodiments, portions of a fluidic system that directly contact fluid are incorporated into one or more removable portions (e.g., one or more disposable cassettes, sample holders, tubing cards, etc.). For example, a removable portion 710 can house at least a portion of the fluid system 510 described previously, including portions that contact sample fluids, saline, detergent solution, and/or anticoagulant.

In some embodiments, a non-disposable fluid-handling subsystem 708 is disposed within the body portion 702 of the monitoring device 700. The first removable portion 710 can include one or more openings that allow portions of the non-disposable fluid-handling subsystem 708 to interface with the removable portion 710. For example, the non-disposable fluid-handling subsystem 708 can include one or more pinch valves that are designed to extend through such openings to engage one or more sections of tubing. When the first removable portion 710 is present in a corresponding first receptacle 704, actuation of the pinch valves can selectively close sections of tubing within the removable portion. The non-disposable fluid-handling subsystem 708 can also include one or more sensors that interface with connectors, tubing sections, or pumps located within the first removable portion 710. The non-disposable fluid-handling subsystem 708 can also include one or more actuators (e.g., motors) that can actuate moveable portions (e.g., the plunger of a syringe) that may be located in the removable portion F10. A portion of the non-disposable fluid-handling subsystem 708 can be located on or in the moveable portion F06 (which can be a door having a slide or a hinge, a detachable face portion, etc.).

In the embodiment shown in FIG. 7, the monitoring device 700 includes an optical system 714 disposed within the body portion 702. The optical system 714 can include a light source and a detector that are adapted to perform measurements on fluids within a sample holder (not shown). The light source may comprise a fixed wavelength light source and/or a tunable light source. The light source may comprise one or more sources including, for example, broadband sources, LEDs, and lasers. In some embodiments, the sample holder comprises a removable portion, which can be associated with or disassociated from the removable portion F10. The sample holder can include an optical window through which the optical system 714 can emit radiation for measuring properties of a fluid in the sample holder. The optical system 714 can include other components such as, for example, a power supply, a centrifuge motor, a filter wheel, and/or a beam splitter.

In some embodiments, the removable portion 710 and the sample holder are adapted to be in fluid communication with each other. For example, the removable portion 710 can include a retractable injector that injects fluids into a sample holder. In some embodiments, the sample holder can comprise or be disposed in a second removable portion (not shown). In some embodiments, the injector can be retracted to allow the centrifuge to rotate the sample holder freely.

The body portion 702 of the monitoring device 700 can also include one or more connectors for an external battery (not shown). The external battery can serve as a backup emergency power source in the event that a primary emergency power source such as, for example, an internal battery (not shown) is exhausted.

FIG. 7 shows an embodiment of a system having subcomponents illustrated schematically. By way of a more detailed (but nevertheless non-limiting) example, FIG. 8 and FIG. 9 show more details of the shape and physical configuration of a sample embodiment.

FIG. 8 shows a cut-away side view of a monitoring device **800** (which can correspond, for example, to the device **102** shown in FIG. 1). The device **800** includes a casing **802**. The monitoring device **800** can have a fluid system. For example, the fluid system can have subsystems, and a portion or portions thereof can be disposable, as schematically depicted in FIG. 4. As depicted in FIG. 8, the fluid system is generally located at the left-hand portion of the casing **802**, as indicated by the reference **801**. The monitoring device **800** can also have an optical system. In the illustrated embodiment, the optical system is generally located in the upper portion of the casing **802**, as indicated by the reference **803**. Advantageously, however, the fluid system **801** and the optical system **803** can both be integrated together such that fluid flows generally through a portion of the optical system **803**, and such that radiation flows generally through a portion of the fluid system **801**.

Depicted in FIG. 8 are examples of ways in which components of the device **800** mounted within the casing **802** can interface with components of the device **800** that comprise disposable portions. Not all components of the device **800** are shown in FIG. 8. A disposable portion **804** having a variety of components is shown in the casing **802**. In some embodiments, one or more actuators **808** housed within the casing **802**, operate syringe bodies **810** located within a disposable portion **804**. The syringe bodies **810** are connected to sections of tubing **816** that move fluid among various components of the system. The movement of fluid is at least partially controlled by the action of one or more pinch valves **812** positioned within the casing **802**. The pinch valves **812** have arms **814** that extend within the disposable portion **804**. Movement of the arms **814** can constrict a section of tubing **816**.

In some embodiments, a sample cell holder **820** can engage a centrifuge motor **818** mounted within the casing **802** of the device **800**. A filter wheel motor **822** disposed within the housing **802** rotates a filter wheel **824**, and in some embodiments, aligns one or more filters with an optical path. An optical path can originate at a source **826** within the housing **802** that can be configured to emit a beam of radiation (e.g., infrared radiation, visible radiation, ultraviolet radiation, etc.) through the filter and the sample cell holder **820** and to a detector **828**. A detector **828** can measure the optical density of the light when it reaches the detector.

FIG. 9 shows a cut-away perspective view of an alternative embodiment of a monitoring device **900**. Many features similar to those illustrated in FIG. 8 are depicted in this illustration of an alternative embodiment. A fluid system **901** can be partially seen. The disposable portion **904** is shown in an operative position within the device. One of the actuators **808** can be seen next to a syringe body **910** that is located within the disposable portion **904**. Some pinch valves **912** are shown next to a fluid-handling portion of the disposable portion **904**. In this figure, an optical system **903** can also be partially seen. The sample holder **920** is located underneath the centrifuge motor **918**. The filter wheel motor **922** is positioned near the radiation source **926**, and the detector **928** is also illustrated.

FIG. 10 illustrates two views of a cartridge **1000** that can interface with a fluid system such as the fluid system **510** of FIG. 5. The cartridge **1000** can be configured for insertion into a receptacle of the device **800** of FIG. 8 and/or the device **900** shown in FIG. 9. In some embodiments, the cartridge **1000** can comprise a portion that is disposable and a portion that is reusable. In some embodiments, the cartridge **1000** can be disposable. The cartridge **1000** can fill the role of the removable portion **710** of FIG. 7, for example. In some embodiments, the cartridge **1000** can be used for a system having only one disposable subsystem, making it a simple

matter for a health care provider to replace and/or track usage time of the disposable portion. In some embodiments, the cartridge **1000** includes one or more features that facilitate insertion of the cartridge **1000** into a corresponding receptacle. For example, the cartridge **1000** can be shaped so as to promote insertion of the cartridge **1000** in the correct orientation. The cartridge **1000** can also include labeling or coloring affixed to or integrated with the cartridge's exterior casing that help a handler insert the cartridge **1000** into a receptacle properly.

The cartridge **1000** can include one or more ports for connecting to material sources or receptacles. Such ports can be provided to connect to, for example, a saline source, an infusion pump, a sample source, and/or a source of gas (e.g., air, nitrogen, etc.). The ports can be connected to sections of tubing within the cartridge **1000**. In some embodiments, the sections of tubing are opaque or covered so that fluids within the tubing cannot be seen, and in some embodiments, sections of tubing are transparent to allow interior contents (e.g., fluid) to be seen from outside.

The cartridge **1000** shown in FIG. 10 can include a sample injector **1006**. The sample injector **1006** can be configured to inject at least a portion of a sample into a sample holder (see, e.g., the sample cell **548**), which can also be incorporated into the cartridge **1000**. The sample injector **1006** can include, for example, the sample cell holder interface tubes **582** (N1) and **584** (N2) of FIG. 5, embodiments of which are also illustrated in FIG. 15.

The housing of the cartridge **1000** can include a tubing portion **1008** containing within it a card having one or more sections of tubing. In some embodiments, the body of the cartridge **1000** includes one or more apertures **1009** through which various components, such as, for example, pinch valves and sensors, can interface with the fluid-handling portion contained in the cartridge **1000**. The sections of tubing found in the tubing portion **1008** can be aligned with the apertures **1009** in order to implement at least some of the functionality shown in the fluid system **510** of FIG. 5.

The cartridge **1000** can include a pouch space (not shown) that can comprise one or more components of the fluid system **510**. For example, one or more pouches and/or bladders can be disposed in the pouch space (not shown). In some embodiments, a cleaner pouch and/or a waste bladder can be housed in a pouch space. The waste bladder can be placed under the cleaner pouch such that, as detergent is removed from the cleaner pouch, the waste bladder has more room to fill. The components placed in the pouch space (not shown) can also be placed side-by-side or in any other suitable configuration.

The cartridge **1000** can include one or more pumps **1016** that facilitate movement of fluid within the fluid system **510**. Each of the pump housings **1016** can contain, for example, a syringe pump having a plunger. The plunger can be configured to interface with an actuator outside the cartridge **1000**. For example, a portion of the pump that interfaces with an actuator can be exposed to the exterior of the cartridge **1000** housing by one or more apertures **1018** in the housing.

The cartridge **1000** can have an optical interface portion **1030** that is configured to interface with (or comprise a portion of) an optical system. In the illustrated embodiment, the optical interface portion **1030** can pivot around a pivot structure **1032**. The optical interface portion **1030** can house a sample holder (not shown) in a chamber that can allow the sample holder to rotate. The sample holder can be held by a centrifuge interface **1036** that can be configured to engage a centrifuge motor (not shown). When the cartridge **1000** is

being inserted into a system, the orientation of the optical interface portion **1030** can be different than when it is functioning within the system.

In some embodiments, the cartridge **1000** is designed for single patient use. The cartridge **1000** may also be disposable and/or designed for replacement after a period of operation. For example, in some embodiments, if the cartridge **1000** is installed in a continuously operating monitoring device that performs four measurements per hour, the waste bladder may become filled or the detergent in the cleaner pouch depleted after about three days. The cartridge **1000** can be replaced before the detergent and waste bladder are exhausted. In some embodiments, a portion of the cartridge **1000** can be disposable while another portion of the cartridge **1000** is disposable, but lasts longer before being discarded. In some embodiments, a portion of the cartridge **1000** may not be disposable at all. For example, a portion thereof may be configured to be cleaned thoroughly and reused for different patients. Various combinations of disposable and less- or non-disposable portions are possible.

The cartridge **1000** can be configured for easy replacement. For example, in some embodiments, the cartridge **1000** is designed to have an installation time of only minutes. For example, the cartridge can be designed to be installed in less than about five minutes, or less than two minutes. During installation, various fluid lines contained in the cartridge **1000** can be primed by automatically filling the fluid lines with saline. The saline can be mixed with detergent powder from the cleaner pouch in order to create a cleaning solution.

The cartridge **1000** can also be designed to have a relatively brief shut down time. For example, the shut down process can be configured to take less than about fifteen minutes, or less than about ten minutes, or less than about five minutes. The shut down process can include flushing the patient line; sealing off the insulin pump connection, the saline source connection, and the sample source connection; and taking other steps to decrease the risk that fluids within the used cartridge **1000** will leak after disconnection from the monitoring device.

Some embodiments of the cartridge **1000** can comprise a flat package to facilitate packaging, shipping, sterilizing, etc. Advantageously, however, some embodiments can further comprise a hinge or other pivot structure. Thus, as illustrated, an optical interface portion **1030** can be pivoted around a pivot structure **1032** to generally align with the other portions of the cartridge **1000**. The cartridge can be provided to a medical provider sealed in a removable wrapper, for example.

In some embodiments, the cartridge **1000** is designed to fit within standard waste containers found in a hospital, such as a standard biohazard container. For example, the cartridge **1000** can be less than one foot long, less than one foot wide, and less than two inches thick. In some embodiments, the cartridge **1000** is designed to withstand a substantial impact, such as that caused by hitting the ground after a four foot drop, without damage to the housing or internal components. In some embodiments, the cartridge **1000** is designed to withstand significant clamping force applied to its casing. For example, the cartridge **1000** can be built to withstand five pounds per square inch of force without damage. In some embodiments, the cartridge **1000** can be designed to be less sturdy and more biodegradable. In some embodiments, the cartridge **1000** can be formed and configured to withstand more or less than five pounds of force per square inch without damage. In some embodiments, the cartridge **1000** is non pyrogenic and/or latex free.

FIG. **11** illustrates an embodiment of a fluid-routing card **1038** that can be part of the removable cartridge of FIG. **10**.

For example, the fluid-routing card **1038** can be located generally within the tubing portion **1008** of the cartridge **1000**. The fluid-routing card **1038** can contain various passages and/or tubes through which fluid can flow as described with respect to FIG. **5** and/or FIG. **6**, for example. Thus, the illustrated tube opening openings can be in fluid communication with the following fluidic components, for example:

Tube Opening Reference Numeral	Can Be In Fluid Communication With
1142	third pump 568 (pump #3)
1144	infusion pump 518
1146	Pressx
1148	air pump
1150	Vent
1152	detergent (e.g., tergazyme) source or waste tube
1154	Pressx
1156	detergent (e.g., tergazyme) source or waste tube
1158	waste receptacle
1160	first pump 522 (pump #1) (e.g., a saline pump)
1162	saline source or waste tube
1164	anticoagulant (e.g., heparin) pump (see FIG. 6) and/or shuttle valve
1166	detergent (e.g., tergazyme) source or waste tube
1167	Pressx
1168	Arrival sensor tube 528 (T4)
1169	tube 536 (T2)
1170	Arrival sensor tube 528 (T4)
1171	Arrival sensor tube 528 (T4)
1172	anticoagulant (e.g., heparin) pump
1173	T17 (see FIG. 6)
1174	Sample cell holder interface tube 582 (N1)
1176	anticoagulant valve tube 534 (T3)
1178	Sample cell holder interface tube 584 (N2)
1180	T17 (see FIG. 6)
1182	anticoagulant valve tube 534 (T3)
1184	Arrival sensor tube 528 (T4)
1186	tube 536 (T2)
1188	anticoagulant valve tube 534 (T3)
1190	anticoagulant valve tube 534 (T3)

The depicted fluid-routing card **1038** can have additional openings that allow operative portions of actuators and/or valves to protrude through the fluid-routing card **1038** and interface with the tubes.

FIG. **12** illustrates how actuators, which can sandwich the fluid-routing card **1038** between them, can interface with the fluid-routing card **1038** of FIG. **11**. Pinch valves **812** can have an actuator portion that protrudes away from the fluid-routing card **1038** containing a motor. Each motor can correspond to a pinch platen **1202**, which can be inserted into a pinch platen receiving hole **1204**. Similarly, sensors, such as a bubble sensor **1206** can be inserted into receiving holes (e.g., the bubble sensor receiving hole **1208**). Movement of the pinch valves **812** can be detected by the position sensors **1210**.

FIG. **13** illustrates an actuator **808** that is connected to a corresponding syringe body **810**. The actuator **808** is an example of one of the actuators **808** that is illustrated in FIG. **8** and in FIG. **9**, and the syringe body **810** is an example of one of the syringe bodies **810** that are visible in FIG. **8** and in FIG. **9**. A ledge portion **1212** of the syringe body **810** can be engaged (e.g., slid into) a corresponding receiving portion **1214** in the actuator **808**. In some embodiments, the receiving portion **1214** can slide outward to engage the stationary ledge portion **1212** after the disposable cartridge **804** is in place. Similarly, a receiving tube **1222** in the syringe plunger **1223** can be slide onto (or can receive) a protruding portion **1224** of the actuator **808**. The protruding portion **1224** can slide along a track **1226** under the influence of a motor inside the actuator

808, thus actuating the syringe plunger 1223 and causing fluid to flow into or out of the syringe tip 1230.

FIG. 14 shows a rear perspective view of internal scaffolding 1231 and the protruding bodies of some pinch valves 812. The internal scaffolding 1231 can be formed from metal and can provide structural rigidity and support for other components. The scaffolding 1231 can have holes 1232 into which screws can be screwed or other connectors can be inserted. In some embodiments, a pair of sliding rails 1234 can allow relative movement between portions of an analyzer. For example, a slidable portion 1236 (which can correspond to the movable portion 706, for example) can be temporarily slid away from the scaffolding 1231 of a main unit in order to allow an insertable portion (e.g., the cartridge 804) to be inserted.

FIG. 15 shows an underneath perspective view of the sample cell holder 820, which is attached to the centrifuge interface 1036. The sample cell holder 820 can have an opposite side (see FIG. 17) that allows it to slide into a receiving portion of the centrifuge interface 1036. The sample cell holder 820 can also have receiving nubs 1512A that provide a pathway into a sample cell 1548 held by the sample cell holder 820. Receiving nubs 1512B can provide access to a shunt 1586 (see FIG. 16) inside the sample cell holder 820. The receiving nubs 1512A and 1512B can receive and or dock with fluid nipples 1514. The fluid nipples 1514 can protrude at an angle from the sample injector 1006, which can in turn protrude from the cartridge 1000 (see FIG. 10). The tubes 1516 shown protruding from the other end of the sample injector 1006 can be in fluid communication with the sample cell holder interface tubes 582 (N1) and 584 (N2) (see FIG. 5 and FIG. 6), as well as 1074 and 1078 (see FIG. 11).

FIG. 16 shows a plan view of the sample cell holder 820 with hidden and/or non-surface portions illustrated using dashed lines. The receiving nubs 1512A communicate with passages 1550 inside the sample cell 1548 (which can correspond, for example to the sample cell 548 of FIG. 5). The passages widen out into a wider portion 1552 that corresponds to a window 1556. The window 1556 and the wider portion 1552 can be configured to house the sample when radiation is emitted along a pathlength that is generally non-parallel to the sample cell 1548. The window 1556 can allow calibration of the instrument with the sample cell 1548 in place, even before a sample has arrived in the wider portion 1552.

An opposite opening 1530 can provide an alternative optical pathway between a radiation source and a radiation detector (e.g., the radiation source 826 of FIG. 18) and may be used, for example, for obtaining a calibration measurement of the source and detector without an intervening window or sample. Thus, the opposite opening 1530 can be located generally at the same radial distance from the axis of rotation as the window 1556.

The receiving nubs 1512B communicate with a shunt passage 1586 inside the sample cell holder 820 (which can correspond, for example to the shunt 586 of FIG. 5).

Other features of the sample cell holder 820 can provide balancing properties for even rotation of the sample cell holder 820. For example, the wide trough 1562 and the narrower trough 1564 can be sized or otherwise configured so that the weight and/or mass of the sample cell holder 820 is evenly distributed from left to right in the view of FIG. 16, and/or from top to bottom in this view of FIG. 16.

FIG. 17 shows a top perspective view of the centrifuge interface 1036 connected to the sample cell holder 820. The centrifuge interface 1036 can have a bulkhead 1520 with a rounded slot 1522 into which an actuating portion of a cen-

trifuge can be slid from the side. The centrifuge interface 1036 can thus be spun about an axis 1524, along with the sample cell holder 820, causing fluid (e.g., whole blood) within the sample cell 1548 to separate into concentric strata, according to relative density of the fluid components (e.g., plasma, red blood cells, buffy coat, etc.), within the sample cell 1548. The sample cell holder 820 can be transparent, or it can at least have transparent portions (e.g., the window 1556 and/or the opposite opening 1530) through which radiation can pass, and which can be aligned with an optical pathway between a radiation source and a radiation detector (see, e.g., FIG. 20). In addition, a round opening 1530 through centrifuge rotor 1520 provides an optical pathway between the radiation source and radiation detector and may be used, for example, for obtaining a calibration measurement of the source and detector without an intervening window or sample.

FIG. 18 shows a perspective view of an example optical system 803. Such a system can be integrated with other systems as shown in FIG. 9, for example. The optical system 803 can fill the role of the optical system 412, and it can be integrated with and/or adjacent to a fluid system (e.g., the fluid-handling system 404 or the fluid system 801). The sample cell holder 820 can be seen attached to the centrifuge interface 1036, which is in turn connected to, and rotatable by the centrifuge motor 818. A filter wheel housing 1812 is attached to the filter wheel motor 822 and encloses a filter wheel 1814. A protruding shaft assembly 1816 can be connected to the filter wheel 1814. The filter wheel 1814 can have multiple filters (see FIG. 19). The radiation source 826 is aligned to transmit radiation through a filter in the filter wheel 1814 and then through a portion of the sample cell holder 820. Transmitted and/or reflected and/or scattered radiation can then be detected by a radiation detector.

FIG. 19 shows a view of the filter wheel 1814 when it is not located within the filter wheel housing 1812 of the optical system 803. Additional features of the protruding shaft assembly 1816 can be seen, along with multiple filters 1820. In some embodiments, the filters 1820 can be removably and/or replaceably inserted into the filter wheel 1814.

Spectroscopic System

As described above with reference to FIG. 4, the system 400 comprises the optical system 412 for analysis of a fluid sample. In various embodiments, the optical system 412 comprises one or more optical components including, for example, a spectrometer, a photometer, a reflectometer, or any other suitable device for measuring optical properties of the fluid sample. The optical system 412 may perform one or more optical measurements on the fluid sample including, for example, measurements of transmittance, absorbance, reflectance, scattering, and/or polarization. The optical measurements may be performed in one or more wavelength ranges including, for example, infrared (IR) and/or optical wavelengths. As described with reference to FIG. 4 (and further described below), the measurements from the optical system 412 are communicated to the algorithm processor 416 for analysis. For example, in some embodiments the algorithm processor 416 computes concentration of analyte(s) (and/or interferent(s)) of interest in the fluid sample. Analytes of interest include, e.g., glucose and lactate in whole blood or blood plasma.

FIG. 20 schematically illustrates an embodiment of the optical system 412 that comprises a spectroscopic analyzer 2010 adapted to measure spectra of a fluid sample such as, for example, blood or blood plasma. The analyzer 2010 comprises an energy source 2012 disposed along an optical axis X of the analyzer 2010. When activated, the energy source 2012

generates an electromagnetic energy beam E, which advances from the energy source **2012** along the optical axis X. In some embodiments, the energy source **2012** comprises an infrared energy source, and the energy beam E comprises an infrared beam. In some embodiments, the infrared energy beam E comprises a mid-infrared energy beam or a near-infrared energy beam. In some embodiments, the energy beam E can include optical and/or radio frequency wavelengths.

The energy source **2012** may comprise a broad-band and/or a narrow-band source of electromagnetic energy. In some embodiments, the energy source **2012** comprises optical elements such as, e.g., filters, collimators, lenses, mirrors, etc., that are adapted to produce a desired energy beam E. For example, in some embodiments, the energy beam E is an infrared beam in a wavelength range between about 2 μm and 20 μm . In some embodiments, the energy beam E comprises an infrared beam in a wavelength range between about 4 μm and 10 μm . In the infrared wavelength range, water generally is the main contributor to the total absorption together with features from absorption of other blood components, particularly in the 6 μm -10 μm range. The 4 μm to 10 μm wavelength band has been found to be advantageous for determining glucose concentration, because glucose has a strong absorption peak structure from about 8.5 μm to 10 μm , whereas most other blood components have a relatively low and flat absorption spectrum in the 8.5 μm to 10 μm range. Two exceptions are water and hemoglobin, which are interferents in this range.

The energy beam E may be temporally modulated to provide increased signal-to-noise ratio (S/N) of the measurements provided by the analyzer **2010** as further described below. For example, in some embodiments, the beam E is modulated at a frequency of about 10 Hz or in a range from about 1 Hz to about 30 Hz. A suitable energy source **2012** may be an electrically modulated thin-film thermoresistive element such as the HawkEye IR-50 available from Hawkeye Technologies of Milford, Conn.

As depicted in FIG. **20**, the energy beam E propagates along the optical axis X and passes through an aperture **2014** and a filter **2015** thereby providing a filtered energy beam E_f . The aperture **2014** helps collimate the energy beam E and can include one or more filters adapted to reduce the filtering burden of the filter **2015**. For example, the aperture **2014** may comprise a broadband filter that substantially attenuates beam energy outside a wavelength band between about 4 μm to about 10 μm . The filter **2015** may comprise a narrow-band filter that substantially attenuates beam energy having wavelengths outside of a filter passband (which may be tunable or user-selectable in some embodiments). The filter passband may be specified by a half-power bandwidth ("HPBW"). In some embodiments, the filter **2015** may have an HPBW in a range from about 0.1 μm to about 2 μm , or 0.01 μm to about 1 μm . In some embodiments, the bandwidths are in a range from about 0.2 μm to 0.5 μm , or 0.1 μm to 0.35 μm . Other filter bandwidths may be used. The filter **2015** may comprise a varying-passband filter, an electronically tunable filter, a liquid crystal filter, an interference filter, and/or a gradient filter. In some embodiments, the filter **2015** comprises one or a combination of a grating, a prism, a monochromator, a Fabry-Perot etalon, and/or a polarizer. Other optical elements may be utilized as well.

In the embodiment shown in FIG. **20**, the analyzer **2010** comprises a filter wheel assembly **2021** configured to dispose one or more filters **2015** along the optical axis X. The filter wheel assembly **2021** comprises a filter wheel **2018**, a filter wheel motor **2016**, and a position sensor **2020**. The filter wheel **2018** may be substantially circular and have one or

more filters **2015** or other optical elements (e.g., apertures, gratings, polarizers, mirrors, etc.) disposed around the circumference of the wheel **2018**. In some embodiments, the number of filters **2015** in the filter wheel **2016** may be, for example, 1, 2, 5, 10, 15, 20, 25, or more. The motor **2016** is configured to rotate the filter wheel **2018** to dispose a desired filter **2015** (or other optical element) in the energy beam E so as to produce the filtered beam E_f . In some embodiments, the motor **2016** comprises a stepper motor. The position sensor **2020** determines the angular position of the filter wheel **2016**, and communicates a corresponding filter wheel position signal to the algorithm processor **416**, thereby indicating which filter **2015** is in position on the optical axis X. In various embodiments, the position sensor **2020** may be a mechanical, optical, and/or magnetic encoder. An alternative to the filter wheel **2018** is a linear filter translated by a motor. The linear filter can include an array of separate filters or a single filter with properties that change along a linear dimension.

The filter wheel motor **2016** rotates the filter wheel **2018** to position the filters **2015** in the energy beam E to sequentially vary the wavelengths or the wavelength bands used to analyze the fluid sample. In some embodiments, each individual filter **2015** is disposed in the energy beam E for a dwell time during which optical properties in the passband of the filter are measured for the sample. The filter wheel motor **2016** then rotates the filter wheel **2018** to position another filter **2015** in the beam E. In some embodiments, 25 narrow-band filters are used in the filter wheel **2018**, and the dwell time is about 2 seconds for each filter **2015**. A set of optical measurements for all the filters can be taken in about 2 minutes, including sampling time and filter wheel movement. In some embodiments, the dwell time may be different for different filters **2015**, for example, to provide a substantially similar S/N ratio for each filter measurement. Accordingly, the filter wheel assembly **2021** functions as a varying-passband filter that allows optical properties of the sample to be analyzed at a number of wavelengths or wavelength bands in a sequential manner.

In some embodiments of the analyzer **2010**, the filter wheel **2018** includes 25 finite-bandwidth infrared filters having a Gaussian transmission profile and full-width half-maximum (FWHM) bandwidth of 28 cm^{-1} corresponding to a bandwidth that varies from 0.14 μm at 7.08 μm to 0.28 μm at 10 μm . The central wavelengths of the filters are, in microns: 7.082, 7.158, 7.241, 7.331, 7.424, 7.513, 7.605, 7.704, 7.800, 7.905, 8.019, 8.150, 8.271, 8.598, 8.718, 8.834, 8.969, 9.099, 9.217, 9.346, 9.461, 9.579, 9.718, 9.862, and 9.990.

With further reference to FIG. **20**, the filtered energy beam E_f propagates to a beamsplitter **2022** disposed along the optical axis X. The beamsplitter **2022** separates the filtered energy beam E_f into a sample beam E_s and a reference beam E_r . The reference beam E_r propagates along a minor optical axis Y, which in this embodiment is substantially orthogonal to the optical axis X. The energies in the sample beam E_s and the reference beam E_r may comprise any suitable fraction of the energy in the filtered beam E_f . For example, in some embodiments, the sample beam E_s comprises about 80%, and the reference beam E_r comprises about 20%, of the filtered beam energy E_f . A reference detector **2036** is positioned along the minor optical axis Y. An optical element **2034**, such as a lens, may be used to focus or collimate the reference beam E_r onto the reference detector **2036**. The reference detector **2036** provides a reference signal, which can be used to monitor fluctuations in the intensity of the energy beam E emitted by the source **2012**. Such fluctuations may be due to drift effects, aging, wear, or other imperfections in the source **2012**. The algorithm processor **416** may utilize the reference signal to

identify changes in properties of the sample beam E_s that are attributable to changes in the emission from the source **2012** and not to the properties of the fluid sample. By so doing, the analyzer **2010** may advantageously reduce possible sources of error in the calculated properties of the fluid sample (e.g., concentration). In other embodiments of the analyzer **2010**, the beamsplitter **2022** is not used, and substantially all of the filtered energy beam E_f propagates to the fluid sample.

As illustrated in FIG. **20**, the sample beam E_s propagates along the optical axis X, and a relay lens **2024** transmits the sample beam E_s into a sample cell **2048** so that at least a fraction of the sample beam E_s is transmitted through at least a portion of the fluid sample in the sample cell **2048**. A sample detector **2030** is positioned along the optical axis X to measure the sample beam E_s that has passed through the portion of the fluid sample. An optical element **2028**, such as a lens, may be used to focus or collimate the sample beam E_s onto the sample detector **2030**. The sample detector **2030** provides a sample signal that can be used by the algorithm processor **416** as part of the sample analysis.

In the embodiment of the analyzer **2010** shown in FIG. **20**, the sample cell **2048** is located toward the outer circumference of the centrifuge wheel **2050** (which can correspond, for example, to the sample cell holder **820** described herein). The sample cell **2048** preferably comprises windows that are substantially transmissive to energy in the sample beam E_s . For example, in implementations using mid-infrared energy, the windows may comprise calcium fluoride. As described herein with reference to FIG. **5**, the sample cell **2048** is in fluid communication with an injector system that permits filling the sample cell **2048** with a fluid sample (e.g., whole blood) and flushing the sample cell **2048** (e.g., with saline or a detergent). The injector system may disconnect after filling the sample cell **2048** with the fluid sample to permit free spinning of the centrifuge wheel **2050**.

The centrifuge wheel **2050** can be spun by a centrifuge motor **2026**. In some embodiments of the analyzer **2010**, the fluid sample (e.g., a whole blood sample) is spun at a certain number of revolutions per minute (RPM) for a given length of time to separate blood plasma for spectral analysis. In some embodiments, the fluid sample is spun at about 7200 RPM. In some embodiments, the fluid sample is spun at about 5000 RPM or 4500 RPM. In some embodiments, the fluid sample is spun at more than one rate for successive time periods. The length of time can be approximately 5 minutes. In some embodiments, the length of time is approximately 2 minutes. In some embodiments, an anti-clotting agent such as heparin may be added to the fluid sample before centrifuging to reduce clotting. With reference to FIG. **20**, the centrifuge wheel **2050** is rotated to a position where the sample cell **2048** intercepts the sample beam E_s , allowing energy to pass through the sample cell **2048** to the sample detector **2030**.

The embodiment of the analyzer **2010** illustrated in FIG. **20** advantageously permits direct measurement of the concentration of analytes in the plasma sample rather than by inference of the concentration from measurements of a whole blood sample. An additional advantage is that relatively small volumes of fluid may be spectroscopically analyzed. For example, in some embodiments the fluid sample volume is between about 1 μL and 80 μL and is about 25 μL in some embodiments. In some embodiments, the sample cell **2048** is disposable and is intended for use with a single patient or for a single measurement.

In some embodiments, the reference detector **2036** and the sample detector **2030** comprise broadband pyroelectric detectors. As known in the art, some pyroelectric detectors are sensitive to vibrations. Thus, for example, the output of a

pyroelectric infrared detector is the sum of the exposure to infrared radiation and to vibrations of the detector. The sensitivity to vibrations, also known as "microphonics," can introduce a noise component to the measurement of the reference and sample energy beams E_r , E_s using some pyroelectric infrared detectors. Because it may be desirable for the analyzer **2010** to provide high signal-to-noise ratio measurements, such as, e.g., S/N in excess of 100 dB, some embodiments of the analyzer **2010** utilize one or more vibrational noise reduction apparatus or methods. For example, the analyzer **2010** may be mechanically isolated so that high S/N spectroscopic measurements can be obtained for vibrations below an acceleration of about 1.5 G.

In some embodiments of the analyzer **2010**, vibrational noise can be reduced by using a temporally modulated energy source **2012** combined with an output filter. In some embodiments, the energy source **2012** is modulated at a known source frequency, and measurements made by the detectors **2036** and **2030** are filtered using a narrowband filter centered at the source frequency. For example, in some embodiments, the energy output of the source **2012** is sinusoidally modulated at 10 Hz, and outputs of the detectors **2036** and **2030** are filtered using a narrow bandpass filter of less than about 1 Hz centered at 10 Hz. Accordingly, microphonic signals that are not at 10 Hz are significantly attenuated. In some embodiments, the modulation depth of the energy beam E may be greater than 50% such as, for example, 80%. The duty cycle of the beam may be between about 30% and 70%. The temporal modulation may be sinusoidal or any other waveform. In embodiments utilizing temporally modulated energy sources, detector output may be filtered using a synchronous demodulator and digital filter. The demodulator and filter are software components that may be digitally implemented in a processor such as the algorithm processor **416**. Synchronous demodulators, coupled with low pass filters, are often referred to as "lock in amplifiers."

The analyzer **2010** may also include a vibration sensor **2032** (e.g., one or more accelerometers) disposed near one (or both) of the detectors **2036** and **2030**. The output of the vibration sensor **2032** is monitored, and suitable actions are taken if the measured vibration exceeds a vibration threshold. For example, in some embodiments, if the vibration sensor **2032** detects above-threshold vibrations, the system discards any ongoing measurement and "holds off" on performing further measurements until the vibrations drop below the threshold. Discarded measurements may be repeated after the vibrations drop below the vibration threshold. In some embodiments, if the duration of the "hold off" is sufficiently long, the fluid in the sample cell **2030** is flushed, and a new fluid sample is delivered to the cell **2030** for measurement. The vibration threshold may be selected so that the error in analyte measurement is at an acceptable level for vibrations below the threshold. In some embodiments, the threshold corresponds to an error in glucose concentration of 5 mg/dL. The vibration threshold may be determined individually for each filter **2015**.

Certain embodiments of the analyzer **2010** include a temperature system (not shown in FIG. **20**) for monitoring and/or regulating the temperature of system components (such as the detectors **2036**, **2030**) and/or the fluid sample. Such a temperature system can include temperature sensors, thermoelectrical heat pumps (e.g., a Peltier device), and/or thermistors, as well as a control system for monitoring and/or regulating temperature. In some embodiments, the control system comprises a proportional-plus-integral-plus-derivative (PID) control. For example, in some embodiments, the

temperature system is used to regulate the temperature of the detectors **2030**, **2036** to a desired operating temperature, such as 35 degrees Celsius.

Optical Measurement

The analyzer **2010** illustrated in FIG. **20** can be used to determine optical properties of a substance in the sample cell **2048**. The substance can include whole blood, plasma, saline, water, air or other substances. In some embodiments, the optical properties include measurements of an absorbance, transmittance, and/or optical density in the wavelength passbands of some or all of the filters **2015** disposed in the filter wheel **2018**. As described above, a measurement cycle comprises disposing one or more filters **2015** in the energy beam E for a dwell time and measuring a reference signal with the reference detector **2036** and a sample signal with the sample detector **2030**. The number of filters **2015** used in the measurement cycle will be denoted by N, and each filter **2015** passes energy in a passband around a center wavelength λ_i , where i is an index ranging over the number of filters (e.g., from 1 to N). The set of optical measurements from the sample detector **2036** in the passbands of the N filters **2015** provide a wavelength-dependent spectrum of the substance in the sample cell **2048**. The spectrum will be denoted by $C_s(\lambda_i)$, where C_s may be a transmittance, absorbance, optical density, or some other measure of an optical property of the substance. In some embodiments, the spectrum is normalized with respect to one or more of the reference signals measured by the reference detector **2030** and/or with respect to spectra of a reference substance (e.g., air or saline). The measured spectra are communicated to the algorithm processor **416** for calculation of the concentration of the analyte(s) of interest in the fluid sample.

In some embodiments, the analyzer **2010** performs spectroscopic measurements on the fluid sample (known as a "wet" reading) and on one or more reference samples. For example, an "air" reading occurs when the sample detector **2036** measures the sample signal without the sample cell **2048** in place along the optical axis X. (This can occur, for example, when the opposite opening **1530** is aligned with the optical axis X). A "water" or "saline" reading occurs when the sample cell **2048** is filled with water or saline, respectively. The algorithm processor **416** may be programmed to calculate analyte concentration using a combination of these spectral measurements.

In some embodiments, a pathlength corrected spectrum is calculated using wet, air, and reference readings. For example, the transmittance at wavelength λ_i , denoted by T_i , may be calculated according to $T_i = (S_i(\text{wet})/R_i(\text{wet})) / (S_i(\text{air})/R_i(\text{air}))$, where S_i denotes the sample signal from the sample detector **2036** and R_i denotes the corresponding reference signal from the reference detector **2030**. In some embodiments, the algorithm processor **416** calculates the optical density, OD_i , as a logarithm of the transmittance, e.g., according to $OD_i = -\text{Log}(T_i)$. In one implementation, the analyzer **2010** takes a set of wet readings in each of the N filter passbands and then takes a set of air readings in each of the N filter passbands. In other embodiments, the analyzer **2010** may take an air reading before (or after) the corresponding wet reading.

The optical density OD_i is the product of the absorption coefficient at wavelength λ_i , α_i , times the pathlength L over which the sample energy beam E_s interacts with the substance in the sample cell **2048**, e.g., $OD_i = \alpha_i L$. The absorption coefficient α_i of a substance may be written as the product of an absorptivity per mole times a molar concentration of the substance. FIG. **20** schematically illustrates the pathlength L of the sample cell **2048**. The pathlength L may be determined

from spectral measurements made when the sample cell **2048** is filled with a reference substance. For example, because the absorption coefficient for water (or saline) is known, one or more water (or saline) readings can be used to determine the pathlength L from measurements of the transmittance (or optical density) through the cell **2048**. In some embodiments, several readings are taken in different wavelength passbands, and a curve-fitting procedure is used to estimate a best-fit pathlength L. The pathlength L may be estimated using other methods including, for example, measuring interference fringes of light passing through an empty sample cell **2048**.

The pathlength L may be used to determine the absorption coefficients of the fluid sample at each wavelength. Molar concentration of an analyte of interest can be determined from the absorption coefficient and the known molar absorptivity of the analyte. In some embodiments, a sample measurement cycle comprises a saline reading (at one or more wavelengths), a set of N wet readings (taken, for example, through a sample cell **2048** containing saline solution), followed by a set of N air readings (taken, for example, through the opposite opening **1530**). As discussed above, the sample measurement cycle can be performed in a given length of time that may depend, at least in part, on filter dwell times. For example, the measurement cycle may take five minutes when the filter dwell times are about five seconds. In some embodiments, the measurement cycle may take about two minutes when the filter dwell times are about two seconds. After the sample measurement cycle is completed, a detergent cleaner may be flushed through the sample cell **2048** to reduce buildup of organic matter (e.g., proteins) on the windows of the sample cell **2048**. The detergent is then flushed to a waste bladder.

In some embodiments, the system stores information related to the spectral measurements so that the information is readily available for recall by a user. The stored information can include wavelength-dependent spectral measurements (including fluid sample, air, and/or saline readings), computed analyte values, system temperatures and electrical properties (e.g., voltages and currents), and any other data related to use of the system (e.g., system alerts, vibration readings, S/N ratios, etc.). The stored information may be retained in the system for a time period such as, for example, 30 days. After this time period, the stored information may be communicated to an archival data storage system and then deleted from the system. In some embodiments, the stored information is communicated to the archival data storage system via wired or wireless methods, e.g., over a hospital information system (HIS).

Analyte Analysis

The algorithm processor **416** (FIG. **4**) (or any other suitable processor or processors) may be configured to receive from the analyzer **2010** the wavelength-dependent optical measurements $C_s(\lambda_i)$ of the fluid sample. In some embodiments, the optical measurements comprise spectra such as, for example, optical densities OD_i measured in each of the N filter passbands centered around wavelengths λ_i . The optical measurements $C_s(\lambda_i)$ are communicated to the processor **416**, which analyzes the optical measurements to detect and quantify one or more analytes in the presence of interferents. In some embodiments, one or more poor quality optical measurements $C_s(\lambda_i)$ are rejected (e.g., as having a S/N ratio that is too low), and the analysis performed on the remaining, sufficiently high-quality measurements. In another embodiment, additional optical measurements of the fluid sample are taken by the analyzer **2010** to replace one or more of the poor quality measurements.

Interferents can comprise components of a material sample being analyzed for an analyte, where the presence of the interferent affects the quantification of the analyte. Thus, for example, in the spectroscopic analysis of a sample to determine an analyte concentration, an interferent could be a compound having spectroscopic features that overlap with those of the analyte, in at least a portion of the wavelength range of the measurements. The presence of such an interferent can introduce errors in the quantification of the analyte. More specifically, the presence of one or more interferents can affect the sensitivity of a measurement technique to the concentration of analytes of interest in a material sample, especially when the system is calibrated in the absence of, or with an unknown amount of, the interferent.

Independently of or in combination with the attributes of interferents described above, interferents can be classified as being endogenous (i.e., originating within the body) or exogenous (i.e., introduced from or produced outside the body). As an example of these classes of interferents, consider the analysis of a blood sample (or a blood component sample or a blood plasma sample) for the analyte glucose. Endogenous interferents include those blood components having origins within the body that affect the quantification of glucose, and can include water, hemoglobin, blood cells, and any other component that naturally occurs in blood. Exogenous interferents include those blood components having origins outside of the body that affect the quantification of glucose, and can include items administered to a person, such as medications, drugs, foods or herbs, whether administered orally, intravenously, topically, etc.

Independently of or in combination with the attributes of interferents described above, interferents can comprise components which are possibly, but not necessarily, present in the sample type under analysis. In the example of analyzing samples of blood or blood plasma drawn from patients who are receiving medical treatment, a medicament such as acetaminophen is possibly, but not necessarily, present in this sample type. In contrast, water is necessarily present in such blood or plasma samples.

Certain disclosed analysis methods are particularly effective if each analyte and interferent has a characteristic signature in the measurement (e.g., a characteristic spectroscopic feature), and if the measurement is approximately affine (e.g., includes a linear term and an offset) with respect to the concentration of each analyte and interferent. In such methods, a calibration process is used to determine a set of one or more calibration coefficients and a set of one or more optional offset values that permit the quantitative estimation of an analyte. For example, the calibration coefficients and the offsets may be used to calculate an analyte concentration from spectroscopic measurements of a material sample (e.g., the concentration of glucose in blood plasma). In some of these methods, the concentration of the analyte is estimated by multiplying the calibration coefficient by a measurement value (e.g., an optical density) to estimate the concentration of the analyte. Both the calibration coefficient and measurement can comprise arrays of numbers. For example, in some embodiments, the measurement comprises spectra $C_s(\lambda_i)$ measured at the wavelengths λ_i , and the calibration coefficient and optional offset comprise an array of values corresponding to each wavelength λ_i . In some embodiments, as further described below, a hybrid linear analysis (HLA) technique is used to estimate analyte concentration in the presence of a set of interferents, while retaining a high degree of sensitivity to the desired analyte. The data used to accommodate the set of possible interferents can include (a) signatures of each of the members of the family of potential additional

substances and (b) a typical quantitative level at which each additional substance, if present, is likely to appear. In some embodiments, the calibration coefficient (and optional offset) are adjusted to minimize or reduce the sensitivity of the calibration to the presence of interferents that are identified as possibly being present in the fluid sample.

In some embodiments, the analyte analysis method uses a set of training spectra each having known analyte concentration and produces a calibration that minimizes the variation in estimated analyte concentration with interferent concentration. The resulting calibration coefficient indicates sensitivity of the measurement to analyte concentration. The training spectra need not include a spectrum from the individual whose analyte concentration is to be determined. That is, the term "training" when used in reference to the disclosed methods does not require training using measurements from the individual whose analyte concentration will be estimated (e.g., by analyzing a bodily fluid sample drawn from the individual).

Several terms are used herein to describe the analyte analysis process. The term "Sample Population" is a broad term and includes, without limitation, a large number of samples having measurements that are used in the computation of calibration values (e.g., calibration coefficients and optional offsets). In some embodiments, the term Sample Population comprises measurements (such as, e.g., spectra) from individuals and may comprise one or more analyte measurements determined from those same individuals. Additional demographic information may be available for the individuals whose sample measurements are included in the Sample Population. For an embodiment involving the spectroscopic determination of glucose concentration, the Sample Population measurements may include a spectrum (measurement) and a glucose concentration (analyte measurement).

Various embodiments of Sample Populations may be used in various embodiments of the systems and methods described herein. Several examples of Sample Populations will now be described. These examples are intended to illustrate certain aspects of possible Sample Population embodiments but are not intended to limit the types of Sample Populations that may be generated. In certain embodiments, a Sample Population may include samples from one or more of the example Sample Populations described below.

In some embodiments of the systems and methods described herein, one or more Sample Populations are included in a "Population Database." The Population Database may be implemented and/or stored on a computer-readable medium. In certain embodiments, the systems and methods may access the Population Database using wired and/or wireless techniques. Certain embodiments may utilize several different Population Databases that are accessible locally and/or remotely. In some embodiments, the Population Database includes one or more of the example Sample Populations described below. In some embodiments, two or more databases can be combined into a single database, and in other embodiments, any one database can be divided into multiple databases.

An example Sample Population may comprise samples from individuals belonging to one or more demographic groups including, for example, ethnicity, nationality, gender, age, etc. Demographic groups may be established for any suitable set of one or more distinctive factors for the group including, for example, medical, cultural, behavioral, biological, geographical, religious, and genealogical traits. For example, in certain embodiments, a Sample Population includes samples from individuals from a specific ethnic group (e.g., Caucasians, Hispanics, Asians, African Ameri-

cans, etc.). In another embodiment, a Sample Population includes samples from individuals of a specific gender. In some embodiments, a Sample Population includes samples from individuals belonging to more than one demographic group (e.g., samples from Caucasian women).

Another example Sample Population can comprise samples from individuals having one or more medical conditions. For example, a Sample Population may include samples from individuals who are healthy and unmedicated (sometimes referred to as a Normal Population). In some 10 embodiments, the Sample Population includes samples from individuals having one or more health conditions (e.g., diabetes). In some embodiments, the Sample Population includes samples from individuals taking one or more medications. In certain embodiments, Sample Population includes 15 samples from individuals diagnosed to have a certain medical condition or from individuals being treated for certain medical conditions or some combination thereof. The Sample Population may include samples from individuals such as, for example, ICU patients, maternity patients, and so forth.

An example Sample Population may comprise samples that have the same interferent or the same type of interferents. In some embodiments, a Sample Population can comprise multiple samples, all lacking an interferent or a type of inter- 25 ferent. For example, a Sample Population may comprise samples that have no exogenous interferents, that have one or more exogenous interferents of either known or unknown concentration, and so forth. The number of interferents in a sample depends on the measurement and analyte(s) of interest, and may number, in general, from zero to a very large number (e.g., greater than 300). All of the interferents typi- 30 cally are not expected to be present in a particular material sample, and in many cases, a smaller number of interferents (e.g., 0, 1, 2, 5, 10, 15, 20, or 25) may be used in an analysis. In certain embodiments, the number of interferents used in the analysis is less than or equal to the number of wavelength- 35 dependent measurements N in the spectrum $Cs(\lambda_i)$.

Certain embodiments of the systems and methods described herein are capable of analyzing a material sample using one or more Sample Populations (e.g., accessed from the Population Database). Certain such embodiments may use information regarding some or all of the interferents which may or may not be present in the material sample. In some embodiments, a list of one or more possible inter- 40 ferents, referred to herein as forming a "Library of Interferents," can be compiled. Each interferent in the Library can be referred to as a "Library Interferent." The Library Interferents may include exogenous interferents and endogenous inter- 45 ferents that may be present in a material sample. For example, an interferent may be present due to a medical condition causing abnormally high concentrations of the exogenous and endog- 50 enous interferents. In some embodiments, the Library of Interferents may not include one or more interferents that are known to be present in all samples. Thus, for example, water, which is a glucose interferent for many spectroscopic mea- 55 surements, may not be included in the Library of Interferents. In certain embodiments, the systems and methods use samples in the Sample Population to train calibration meth- 60 ods.

The material sample being measured, for example a fluid sample in the sample cell 2048, may also include one or more Library Interferents which may include, but is not limited to, an exogenous interferent or an endogenous interferent. Examples of exogenous interferent can include medications, and examples of endogenous interferents can include urea in 65 persons suffering from renal failure. In addition to components naturally found in the blood, the ingestion or injection

of some medicines or illicit drugs can result in very high and rapidly changing concentrations of exogenous interferents.

In some embodiments, measurements of a material sample (e.g., a bodily fluid sample), samples in a Sample Population, and the Library Interferents comprise spectra (e.g., infrared spectra). The spectra obtained from a sample and/or an inter- 5 ferent may be temperature dependent. In some embodiments, it may be beneficial to calibrate for temperatures of the individual samples in the Sample Population or the interferents in the Library of Interferents. In some embodiments, a tempera- 10 ture calibration procedure is used to generate a temperature calibration factor that substantially accounts for the sample temperature. For example, the sample temperature can be measured, and the temperature calibration factor can be applied to the Sample Population and/or the Library Interfer- 15 ent spectral data. In some embodiments, a water or saline spectrum is subtracted from the sample spectrum to account for temperature effects of water in the sample.

In other embodiments, temperature calibration may not be used. For example, if Library Interferent spectra, Sample Population spectra, and sample spectra are obtained at approximately the same temperature, an error in a predicted analyte concentration may be within an acceptable tolerance. If the temperature at which a material sample spectrum is measured is within, or near, a temperature range (e.g., several degrees Celsius) at which the plurality of Sample Population spectra are obtained, then some analysis methods may be relatively insensitive to temperature variations. Temperature calibration may optionally be used in such analysis methods. Systems and Methods for Estimating Analyte Concentration in the Presence of Interferents

FIG. 21 is a flowchart that schematically illustrates an embodiment of a method 2100 for estimating the concentra- 20 tion of an analyte in the presence of interferents. In block 2110, a measurement of a sample is obtained, and in block 2120 data relating to the obtained measurement is analyzed to identify possible interferents to the analyte. In block 2130, a model is generated for predicting the analyte concentration in the presence of the identified possible interferents, and in block 2140 the model is used to estimate the analyte concen- 25 tration in the sample from the measurement. In certain embodiments of the method 2100, the model generated in block 2130 is selected to reduce or minimize the effect of identified interferents that are not present in a general popu- 30 lation of which the sample is a member.

An example embodiment of the method 2100 of FIG. 21 for the determination of an analyte (e.g., glucose) in a blood sample will now be described. This example embodiment is intended to illustrate various aspects of the method 2100 but is not intended as a limitation on the scope of the method 2100 or on the range of possible analytes. In this example, the sample measurement in block 2110 is an absorption spec- 35 trum, $Cs(\lambda_i)$, of a measurement sample S that has, in general, one analyte of interest, glucose, and one or more interferents.

In block 2120, a statistical comparison of the absorption spectrum of the sample S with a spectrum of the Sample Population and combinations of individual Library Interferent spectra is performed. The statistical comparison provides a list of Library Interferents that are possibly contained in sample S and can include either no Library Interferents or one or more Library Interferents. In this example, in block 2130, one or more sets of spectra are generated from spectra of the Sample Population and their respective known analyte concentrations and known spectra of the Library Interferents identified in block 2120. In block 2130, the generated spectra are used to calculate a model for predicting the analyte concentration from the obtained measurement. In some embodi- 40

ments, the model comprises one or more calibration coefficients $\kappa(\lambda_i)$ that can be used with the sample measurements $C_s(\lambda_i)$ to provide an estimate of the analyte concentration, g_{est} . In block 2140, the estimated analyte concentration is determined from the model generated in block 2130. For example, in some embodiments of HLA, the estimated analyte concentration is calculated according to a linear formula: $g_{est} = \kappa(\lambda_i) \cdot C_s(\lambda_i)$. Because the absorption measurements and calibration coefficients may represent arrays of numbers, the multiplication operation indicated in the preceding formula may comprise a sum of the products of the measurements and coefficients (e.g., an inner product or a matrix product). In some embodiments, the calibration coefficient is determined so as to have reduced or minimal sensitivity to the presence of the identified Library Interferents.

An example embodiment of block 2120 of the method 2100 will now be described with reference to FIG. 22. In this example, block 2120 includes forming a statistical Sample Population model (block 2210), assembling a library of interferent data (block 2220), assembling all subsets of size K of the library interferents (block 2225), comparing the obtained measurement and statistical Sample Population model with data for each set of interferents from an interferent library (block 2230), performing a statistical test for the presence of each interferent from the interferent library (block 2240), and identifying possible interferents that pass the statistical test (block 2250). The size K of the subsets may be an integer such as, for example, 1, 2, 3, 4, 5, 6, 10, 16, or more. The acts of block 2220 can be performed once or can be updated as necessary. In certain embodiments, the acts of blocks 2230, 2240, and 2250 are performed sequentially for all subsets of Library Interferents that pass the statistical test (block 2240). In this example, in block 2210, a Sample Population Database is formed that includes a statistically large Sample Population of individual spectra taken over the same wavelength range as the sample spectrum, $C_s(\lambda_i)$. The Database also includes an analyte concentration corresponding to each spectrum. For example, if there are P Sample Population spectra, then the spectra in the Database can be represented as $C = \{C_1, C_2, \dots, C_P\}$, and the analyte concentration corresponding to each spectrum can be represented as $g = \{g_1, g_2, \dots, g_P\}$. In some embodiments, the Sample Population does not have any of the Library Interferents present, and the material sample has interferents contained in the Sample Population and one or more of the Library Interferents.

In some embodiments of block 2210, the statistical sample model comprises a mean spectrum and a covariance matrix calculated for the Sample Population. For example, if each spectrum measured at N wavelengths λ_i is represented by an $N \times 1$ array, C, then the mean spectrum, μ , is an $N \times 1$ array having values at each wavelength averaged over the range of spectra in the Sample Population. The covariance matrix, V, is calculated as the expected value of the deviation between C and μ and can be written as $V = E((C - \mu)(C - \mu)^T)$ where $E(\cdot)$ represents the expected value and the superscript T denotes transpose. In other embodiments, additional statistical parameters may be included in the statistical model of the Sample Population spectra.

Additionally, a Library of Interferents may be assembled in block 2220. A number of possible interferents can be identified, for example, as a list of possible medications or foods that might be ingested by the population of patients at issue. Spectra of these interferents can be obtained, and a range of expected interferent concentrations in the blood, or other expected sample material, can be estimated. In certain embodiments, the Library of Interferents includes, for each of "M" interferents, the absorption spectrum normalized to unit

interferent concentration of each interferent, $IF = \{IF_1, IF_2, \dots, IF_M\}$, and a range of concentrations for each interferent from $T_{max} = \{T_{max_1}, T_{max_2}, \dots, T_{max_M}\}$ to $T_{min} = \{T_{min_1}, T_{min_2}, \dots, T_{min_M}\}$. Information in the Library may be assembled once and accessed as needed. For example, the Library and the statistical model of the Sample Population may be stored in a storage device associated with the algorithm processor 416 (see, FIG. 4).

Continuing in block 2225, the algorithm processor 416 assembles one or more subsets comprising a number K of spectra taken from the Library of Interferents. The number K may be an integer such as, for example, 1, 2, 3, 4, 5, 6, 10, 16, or more. In some embodiments, the subsets comprise all combinations of the M Library spectra taken K at a time. In these embodiments, the number of subsets having K spectra is $M!/(K!(M-K)!)$, where ! represents the factorial function.

Continuing in block 2230, the obtained measurement data (e.g., the sample spectrum) and the statistical Sample Population model (e.g., the mean spectrum and the covariance matrix) are compared with data for each subset of interferents determined in block 2225 in order to determine the presence of possible interferents in the sample (block 2240). In some embodiments, the statistical test for the presence of an interferent subset in block 2240 comprises determining the concentrations of each subset of interferences that minimize a statistical measure of "distance" between a modified spectrum of the material sample and the statistical model of the Sample Population (e.g., the mean μ and the covariance V). The term "concentration" used in this context refers to a computed value, and, in some embodiments, that computed value may not correspond to an actual concentration. The concentrations may be calculated numerically. In some embodiments, the concentrations are calculated by algebraically solving a set of linear equations. The statistical measure of distance may comprise the well-known Mahalanobis distance (or square of the Mahalanobis distance) and/or some other suitable statistical distance metric (e.g., Hotelling's T-square statistic). In certain implementations, the modified spectrum is given by $C'_s(T) = C_s - IF \cdot T$ where $T = (T_1, T_2, \dots, T_K)^T$ is a K-dimensional column vector of interferent concentrations and $IF = \{IF_1, IF_2, \dots, IF_K\}$ represents the K interferent absorption spectra of the subset. In some embodiments, concentration of the i^{th} interferent is assumed to be in a range from a minimum value, T_{min_i} , to a maximum value, T_{max_i} . The value of T_{min_i} may be zero, or may be a value between zero and T_{max_i} , such as a fraction of T_{max_i} , or may be a negative value. Negative values represent interferent concentrations that are smaller than baseline interferent values in the Sample Population.

In block 2250, a list of a number N_s of possible interferent subsets ξ may be identified as the particular subsets that pass one or more statistical tests (in block 2240) for being present in the material sample. One or more statistical tests may be used, alone or in combination, to identify the possible interferents. For example, if a statistical test indicates that an i^{th} interferent is present in a concentration outside the range T_{min_i} to T_{max_i} , then this result may be used to exclude the i^{th} interferent from the list of possible interferents. In some embodiments, only the single most probable interferent subset is included on the list, for example, the subset having the smallest statistical distance (e.g., Mahalanobis distance). In an embodiment, the list includes the subsets ξ having statistical distances smaller than a threshold value. In certain embodiments, the list includes a number N_s of subsets having the smallest statistical distances, e.g., the list comprises the "best" candidate subsets. The number N_s may be any suitable integer such as 10, 20, 50, 100, 200, or more. An advantage of

selecting the “best” N_S subsets is reduced computational burden on the algorithm processor **416**. In some embodiments, the list includes all the Library Interferents. In certain such embodiments, the list is selected to comprise combinations of the N_S subsets taken L at a time. For example, in some

embodiments, pairs of subsets are taken (e.g., $L=2$). An advantage of selecting pairs of subsets is that pairing captures the most likely combinations of interferents and the “best” candidates are included multiple times in the list of possible interferents. In embodiments in which combinations of L subsets are selected, the number of combinations of subsets in the list of possible interferent subsets is $N_S!/(L!(N_S-L)!)$.

In other embodiments, the list of possible interferent subsets ξ is determined using a combination of some or all of the above criteria. In another embodiment, the list of possible interferent subsets ξ includes each of the subsets assembled in block **2225**. Many selection criteria are possible for the list of possible interferent subsets ξ .

Returning to FIG. **21**, the method **2100** continues in block **2130** where analyte concentration is estimated in the presence of the possible interferent subsets ξ determined in block **2250**. FIG. **23** is a flowchart that schematically illustrates an example embodiment of the acts of block **2130**. In block **2310**, synthesized Sample Population measurements are generated to form an Interferent Enhanced Spectral Database (IESD). In block **2360**, the IESD and known analyte concentrations are used to generate calibration coefficients for the selected interferent subset. As indicated in block **2365**, blocks **2310** and **2360** may be repeated for each interferent subset ξ identified in the list of possible interferent subsets (e.g., in block **2250** of FIG. **22**). In this example embodiment, when all the interferent subsets ξ have been processed, the method continues in block **2370**, wherein an average calibration coefficient is applied to the measured spectra to determine a set of analyte concentrations.

In one example embodiment for block **2310**, synthesized Sample Population spectra are generated by adding random concentrations of each interferent in one of the possible interferent subsets ξ . These spectra are referred to herein as an Interferent-Enhanced Spectral Database or IESD. In one example method, the IESD is formed as follows. A plurality of Randomly-Scaled Single Interferent Spectra (RSIS) are formed for each interferent in the interferent subset ξ . Each RSIS is formed by combinations of the interferent having spectrum IF multiplied by the maximum concentration T_{max} , which is scaled by a random factor between zero and one. In certain embodiments, the scaling places the maximum concentration at the 95th percentile of a log-normal distribution in order to generate a wide range of concentrations. In some embodiments, the log-normal distribution has a standard deviation equal to half of its mean value.

In this example method, individual RSIS are then combined independently and in random combinations to form a large family of Combination Interferent Spectra (CIS), with each spectrum in the CIS comprising a random combination of RSIS, selected from the full set of identified Library Interferents. An advantage of this method of selecting the CIS is that it produces adequate variability with respect to each interferent, independently across separate interferents.

The CIS and replicates of the Sample Population spectra are combined to form the IESD. Since the interferent spectra and the Sample Population spectra may have been obtained from measurements having different optical pathlengths, the CIS may be scaled to the same pathlength as the Sample Population spectra. The Sample Population Database is then replicated R times, where R depends on factors including the size of the Database and the number of interferents. The IESD

includes R copies of each of the Sample Population spectra, where one copy is the original Sample Population Data, and the remaining $R-1$ copies each have one randomly chosen CIS spectra added. Accordingly, each of the IESD spectra has an associated analyte concentration from the Sample Population spectra used to form the particular IESD spectrum. In some embodiments, a 10-fold replication of the Sample Population Database is used for 130 Sample Population spectra obtained from 58 different individuals and 18 Library Interferents. A smaller replication factor may be used if there is greater spectral variety among the Library Interferent spectra, and a larger replication factor may be used if there is a greater number of Library Interferents.

After the IESD is generated in block **2310**, in block **2360**, the IESD spectra and the known, random concentrations of the subset interferents are used to generate a calibration coefficient for estimating the analyte concentration from a sample measurement. The calibration coefficient is calculated in some embodiments using a hybrid linear analysis (HLA) technique. In certain embodiments, the HLA technique uses a reference analyte spectrum to construct a set of spectra that are free of the desired analyte, projecting the analyte's spectrum orthogonally away from the space spanned by the analyte-free calibration spectra, and normalizing the result to produce a unit response. Further description of embodiments of HLA techniques may be found in, for example, “Measurement of Analytes in Human Serum and Whole Blood Samples by Near-Infrared Raman Spectroscopy,” Chapter 4, Andrew J. Berger, Ph. D. thesis, Massachusetts Institute of Technology, 1998, and “An Enhanced Algorithm for Linear Multivariate Calibration,” by Andrew J. Berger, et al., Analytical Chemistry, Vol. 70, No. 3, Feb. 1, 1998, pp. 623-627, the entirety of each of which is hereby incorporated by reference herein. In other embodiments, the calibration coefficients may be calculated using other techniques including, for example, regression techniques such as, for example, ordinary least squares (OLS), partial least squares (PLS), and/or principal component analysis.

In block **2365**, the processor **416** determines whether additional interferent subsets ξ remain in the list of possible interferent subsets. If another subset is present in the list, the acts in blocks **2310-2360** are repeated for the next subset of interferents using different random concentrations. In some embodiments, blocks **2310-2360** are performed for only the most probable subset on the list.

The calibration coefficient determined in block **2360** corresponds to a single interferent subset ξ from the list of possible interferent subsets and is denoted herein as a single-interferent-subset calibration coefficient $\kappa_{avg}(\xi)$. In this example method, after all subsets ξ have been processed, the method continues in block **2370**, in which the single-interferent-subset calibration coefficient is applied to the measured spectra C_s to determine an estimated, single-interferent-subset analyte concentration, $g(\xi)=\kappa_{avg}(\xi) \cdot C_s$, for the interferent subset ξ . The set of the estimated, single-interferent-subset analyte concentrations $g(\xi)$ for all subsets in the list may be assembled into an array of single-interferent-subset concentrations. As noted above, in some embodiments the blocks **2310-2370** are performed once for the most probable single-interferent-subset on the list (e.g., the array of single-interferent analyte concentrations has a single member).

Returning to block **2140** of FIG. **21**, the array of single-interferent-subset concentrations, $g(\xi)$, is combined to determine an estimated analyte concentration, g_{est} , for the material sample. In certain embodiments, a weighting function $p(\xi)$ is determined for each of the interferent subsets ξ on the list of possible interferent subsets. The weighting functions may be

normalized such that $\sum p(\xi)=1$, where the sum is over all subsets ξ that have been processed from the list of possible interferent subsets. In some embodiments, the weighting functions can be related to the minimum Mahalanobis distance or an optimal concentration. In certain embodiments, the weighting function $p(\xi)$, for each subset ξ is selected to be a constant, e.g., $1/N_s$ where N_s is the number of subsets processed from the list of possible interferent subsets. In other embodiments, other weighting functions $p(\xi)$ can be selected.

In certain embodiments, the estimated analyte concentration, g_{est} is determined (in block 2140) by combining the single-interferent-subset estimates, $g(\xi)$, and the weighting functions, $p(\xi)$, to generate an average analyte concentration. The average concentration may be computed according to $g_{est}=\sum g(\xi)p(\xi)$, where the sum is over the interferent subsets processed from the list of possible interferent subsets. In some embodiments, the weighting function $p(\xi)$ is a constant value for each subset (e.g., a standard arithmetic average is used for determining average analyte concentration). By testing the above described example method on simulated data, it has been found that the average analyte concentration advantageously has errors that may be reduced in comparison to other methods (e.g., methods using only a single most probable interferent).

Although the flowchart in FIG. 21 schematically illustrates an embodiment of the method 2100 performed with reference to the blocks 2110-2140 described herein, in other embodiments, the method 2100 can be performed differently. For example, some or all of the blocks 2110-2140 can be combined, performed in a different order than shown, and/or the functions of particular blocks may be reallocated to other blocks and/or to different blocks. Embodiments of the method 2100 may utilize different blocks than are shown in FIG. 21.

For example, in some embodiments of the method 2100, the calibration coefficient is computed without synthesizing spectra and/or partitioning the data into calibration sets and test sets. Such embodiments are referred to herein as "Parameter-Free Interferent Rejection" (PFIR) methods. In one example embodiment using PFIR, for each of the possible interferent subsets ξ , the following calculations may be performed to compute an estimate of a calibration coefficient for each subset ξ . An average concentration may be estimated according to $g_{est}=\sum g(\xi)p(\xi)$, where the sum is over the interferent subsets processed from the list of possible interferent subsets.

An example of an alternative embodiment of block 2130 includes the following steps and calculations.

Step 1: For a subset's N_{IF} interferents, form a scaled interferent spectra matrix. In certain embodiments, the scaled interferent spectra matrix is the product of an interferent spectral matrix, IF, multiplied by an interferent concentration matrix, T_{max} , and can be written as: $IF T_{max}$. In certain such embodiments, the interferent concentration matrix T_{max} is a diagonal matrix having entries given by the maximum plasma concentrations for the various interferents.

Step 2: Calculate a covariance for the interferent component. If X denotes the IESD, the covariance of X, $cov(X)$, is defined as the expectation $E((X-\text{mean}(X))(X-\text{mean}(X))^T)$ and is

$$cov(X)=X X^T/(N-1)-\text{mean}(X)\text{mean}(X)^T.$$

As described above, the IESD (e.g., X) is obtained as a combination of Sample Population Spectra, C, with Combination Interferent Spectra (CIS): $X_j=C_j+IF_j \xi_j$, therefore the covariance is:

$$cov(X)=C C^T/(N-1)+IF \Xi \Xi^T IF^T/(N-1)-\text{mean}(X)\text{mean}(X)^T,$$

which can be written as,

$$cov(X)=cov(C)+IF cov(\Xi)IF^T.$$

If the weights in the weighting matrix Ξ are independent and identically distributed, the covariance of Ξ , $cov(\Xi)$, is a diagonal matrix having along the diagonal the variance, v , of the samples in Ξ . The last equation may be written as

$$cov(X)=V_o+\Phi,$$

where V_o is the covariance of the original sample population and Φ is the covariance of the IF spectral set.

Step 3: The group's covariance may be at least partially corrected for the presence of a single replicate of the Sample Population spectra with the IESD as formed from N_{IF} replicates of the Sample Population Spectra with Combined Interferent Spectra. This partial correction may be achieved by multiplying the second term in the covariance formula given above by a correction factor ρ :

$$V=\rho V_o \square \square,$$

where ρ is a scalar weighting function that depends on the number of interferents in the group. In some embodiments, the scalar weighting function is $\rho=N_{IF}/(N_{IF}+1)$. In certain embodiments, the variance v of the weights is assumed to be the variance of a log-normal random variable having a 95th percentile at a value of 1.0, and a standard deviation equal to half of the mean value.

Step 4: The eigenvectors and the corresponding eigenvalues of the covariance matrix V are determined using any suitable linear algebraic methods. The number of eigenvectors (and eigenvalues) is equal to the number of wavelengths L in the spectral measurements. The eigenvectors may be sorted based on decreasing order of their corresponding eigenvalues.

Step 5: The matrix of eigenvectors is decomposed so as to provide an orthogonal matrix Q. For example, in some embodiments, a QR-decomposition is performed, thereby yielding the matrix Q having orthonormal columns and rows.

Step 6: The following matrix operations are performed on the orthogonal matrix Q. For $n=2$ to $L-1$, the product $P_n^||=Q(:,1:n)Q(:,1:n)^T$ is calculated, where $Q(:,1:n)$ denotes the sub-matrix comprising the first n columns of the full matrix Q. The orthogonal projection, P_n^{\perp} , away from the space spanned by $Q(:,1:n)$ is determined by subtracting $P_n^||$ from the $L \times L$ identity matrix I. The n^{th} calibration vector is then determined from $\kappa_n=P_n^{\perp} \alpha_X/\alpha_X^T P_n^{\perp} \alpha_X$, and the n^{th} error variance E_n is determined as the projection of the full covariance V onto the subspace spanned by κ_n as follows: $E_n=\kappa_n^T V \kappa_n$.

The steps 4-6 of this example are an embodiment of the HLA technique.

In some embodiments, the calibration coefficient κ is selected as the calibration vector corresponding to the minimum error variance E_n . Thus, for example, the average group calibration coefficient κ may be found by searching among all the error variances for the error variance E_n that has the minimum value. The calibration coefficient is then selected as the n^{th} calibration vector κ_n corresponding to the minimum error variance E_n . In other embodiments, the calibration coefficient is determined by averaging some or all of the calibration vectors κ_n .

EXAMPLES OF ALGORITHM RESULTS AND EFFECTS OF SAMPLE POPULATION

Embodiments of the above-described methods have been used to estimate blood plasma glucose concentrations in humans. Four example experiments will now be described.

The population of individuals from whom samples were obtained for analysis (estimation of glucose concentration) will be referred to as the "target population." Infrared spectra obtained from the target population will be referred to as the "target spectra." In the four example experiments, the target population included 41 intensive care unit (ICU) patients. Fifty-five samples were obtained from the target population.

Example Experiment 1

In this example experiment, a partial least squares (PLS) regression method was applied to the infrared target spectra of the target patients' blood plasma to obtain the glucose estimates. In example experiment 1, estimated glucose concentration was not corrected for effects of interferents. The Sample Population used for the analysis included infrared spectra and independently measured glucose concentrations for 92 individuals selected from the general population. This Sample Population will be referred to as a "Normal Population."

Example Experiment 2

In example experiment 2, an embodiment of the Parameter-Free Interferent Rejection (PFIR) method was used to estimate glucose concentration for the same target population of patients in example experiment 1. The Sample Population was the Normal Population. In this example, calibration for Library Interferents was applied to the measured target spectra. The Library of Interferents included spectra of the 59 substances listed below:

AcetylsalicylicAcid	Hetastarch	PynuvateSodium
Ampicillin-	HumanAlbumin	PyrivicAcid
Sulbactam		
Azithromycin	HydroxyButyricAcid	SalicylateSodium
Aztreonam	ImipenemCilastatin	SodiumAcetate
Bacitracin	Iohexol	SodiumBicarbonate
BenzylAlcohol	L_Arginine	SodiumChloride
CalciumChloride	LactateSodium	SodiumCitrate
CalciumGluconate	MagnesiumSulfate	SodiumThiosulfate
Cefazolin	Maltose	Sulfadiazine
Cefoparazone	Mannitol	Urea
CefotaximeSodium	Meropenem	UricAcid
Ceftazidime	OxylatePotassium	Voriconazole
Ceftriaxone	Phenytioin	Xylitol
D_Sorbitol	PhosphatesPotassium	Xylose
Dextran	Piperacillin	PC1ofSalinecovariance
Ertapenem	Piperacillin-	PC2ofSalinecovariance
	Tazobactam	
Ethanol	PlasmaLyteA	PC3ofSalinecovariance
Ethosuximide	ProcaineHCl	PC4ofSalinecovariance
Glycerol	PropyleneGlycol	ICU/
		Normaldifferencespectrum
Heparin	Pyrazinamide	

In some embodiments, the calibration data set is determined according to two criteria: the calibration method itself (e.g., HLA, PLS, OLS, PFIR) and the intended application of the method. The calibration data set may comprise spectra and corresponding analyte levels derived from a set of plasma samples from the Sample Population. In some embodiments, e.g., those where an HLA calibration method is used, the calibration data set may also include spectra of the analyte of interest.

In the example experiments 1 and 2, the Sample Population was the Normal Population. Thus, samples were drawn from a population of normal individuals who did not have identifiable medical conditions that might affect the spectra of their

plasma samples. For example, the sample plasma spectra typically did not show effects of high levels of medications or other substances (e.g., ethanol), or effects of chemicals that are indicative of kidney or liver malfunction.

In some embodiments, an analysis method may calibrate for deviations from the distribution defined by the calibration plasma spectra by identifying a "base" set of interferent spectra likely to be responsible for the deviation. The analysis method may then recalibrate with respect to an enhanced spectral data set. In some embodiments, the enhancement can be achieved by including the identified interferent spectra into the calibration plasma spectra. When it is anticipated that the target population may have been administered significant amounts of substances not present in the samples of the calibration set, or when the target population have many distinct interferents, estimation of the interferents present in the target spectrum may be subject to a large degree of uncertainty. In some cases, this may cause analyte estimation to be subject to errors.

Accordingly, in certain embodiments, the calibration data set may be enhanced beyond the base of "normal" samples to include a population of samples intended to be more representative of the target population. The enhancement of the calibration set may be generated, in some embodiments, by including samples from a sufficiently diverse range of individuals in order to represent the range of likely interferents (both in type and in concentration) and/or the normal variability in underlying plasma characteristics. The enhancement may, additionally or alternatively, be generated by synthesizing interferent spectra having a range of concentrations as described above (see, e.g., discussion of block 2310 in FIG. 23). Using the enhanced calibration set may reduce the error in estimating the analyte concentration in the target spectra.

Example Experiments 3 and 4

Example experiments 3 and 4 use the analysis methods of example experiments 1 and 2, respectively (PLS without interferent correction and PFIR with interferent correction). However, example experiments 3 and 4 use a Sample Population having blood plasma spectral characteristics different from the Normal Population used in example experiments 1 and 2. In example experiments 3 and 4, the Sample Population was modified to include spectra of both the Normal Population and spectra of an additional population of 55 ICU patients. These spectra will be referred to as the "Normal+Target Spectra." In experiments 3 and 4, the ICU patients included Surgical ICU patients, Medical ICU patients as well as victims of severe trauma, including a large proportion of patients who had suffered major blood loss. Major blood loss may necessitate replacement of the patient's total blood volume multiple times during a single day and subsequent treatment of the patient via electrolyte and/or fluid replacement therapies. Major blood loss may also require administration of plasma-expanding medications. Major blood loss may lead to significant deviations from the blood plasma spectra representative of a Normal Population. The population of 55 ICU patients (who provided the Target Spectra) has some similarities to the individuals for whom the analyses in experiments 1-4 were performed (e.g., all were ICU patients), but in these experiments, target spectra from individuals in the target population were not included in the Target Spectra.

Results of example experiments 1-4 are shown in the following table. The glucose concentrations estimated from the analysis method were compared to independently determined glucose measurements to provide an average prediction error and a standard deviation of the average prediction error. The

table demonstrates that independent of the Sample Population used (e.g., either the Normal Population or the Normal+Target Population), calibrating for interferents reduces both the average prediction error and the standard deviation (e.g., compare the results for experiment 2 to the results for experiment 1 and compare the results for experiment 4 to the results for experiment 3). The table further demonstrates that independent of the analysis method used (e.g., either PLS or PFIR), using a Sample Population with more similarity to the target population (e.g., the Normal+Target Population) reduces both the average prediction error and the standard deviation (e.g., compare the results for experiment 3 to the results for experiment 1 and compare the results for experiment 4 to the results for experiment 2).

Example Experiment No.	Interferent Calibration	Sample Population	Average Prediction Error (mg/dL)	Standard Deviation (mg/dL)
1	NO	Normal	126	164
2	YES	Normal	-6.8	23.2
3	NO	Normal + Target	8.2	16.9
4	YES	Normal + Target	1.32	12.6

Accordingly, embodiments of analysis methods that use a Sample Population that includes both normal spectra and spectra from individuals similar to those of the target population and that calibrate for possible interferents provide a good match between the estimated glucose concentration and the measured glucose concentration.

User Interface

The system 400 can include a display system 414, for example, as depicted in FIG. 4. The display system 414 may comprise an input device including, for example, a keypad or a keyboard, a mouse, a touchscreen display, and/or any other suitable device for inputting commands and/or information. The display system 414 may also include an output device including, for example, an LCD monitor, a CRT monitor, a touchscreen display, a printer, and/or any other suitable device for outputting text, graphics, images, videos, etc. In some embodiments, a touchscreen display is advantageously used for both input and output.

The display system 414 can include a user interface 2400 by which users can conveniently and efficiently interact with the system 400. The user interface 2400 may be displayed on the output device of the system 400 (e.g., the touchscreen display). In some embodiments, the user interface 2400 is implemented and/or stored as one or more code modules, which may be embodied in hardware, firmware, and/or software.

FIGS. 24 and 25 schematically illustrate the visual appearance of embodiments of the user interface 2400. The user interface 2400 may show patient identification information 2402, which can include patient name and/or a patient ID number. The user interface 2400 also can include the current date and time 2404. An operating graphic 2406 shows the operating status of the system 400. For example, as shown in FIGS. 24 and 25, the operating status is "Running," which indicates that the system 400 is fluidly connected to the patient ("Jill Doe") and performing normal system functions such as infusing fluid and/or drawing blood. The user interface 2400 can include one or more analyte concentration graphics 2408, 2412, which may show the name of the analyte and its last measured concentration. For example, the graphic

2408 in FIG. 24 shows "Glucose" concentration of 150 mg/dL, while the graphic 2412 shows "Lactate" concentration of 0.5 mmol/L. The particular analytes displayed and their measurement units (e.g., mg/dL, mmol/L, or other suitable unit) may be selected by the user. The size of the graphics 2408, 2412 may be selected to be easily readable out to a distance such as, e.g., 30 feet. The user interface 2400 may also include a next-reading graphic 2410 that indicates the time until the next analyte measurement is to be taken. In FIG. 24, the time until next reading is 3 minutes, whereas in FIG. 25, the time is 6 minutes, 13 seconds.

The user interface 2400 can include an analyte concentration status graphic 2414 that indicates status of the patient's current analyte concentration compared with a reference standard. For example, the analyte may be glucose, and the reference standard may be a hospital ICU's tight glycemic control (TGC). In FIG. 24, the status graphic 2414 displays "High Glucose," because the glucose concentration (150 mg/dL) exceeds the maximum value of the reference standard. In FIG. 25, the status graphic 2414 displays "Low Glucose," because the current glucose concentration (79 mg/dL) is below the minimum reference standard. If the analyte concentration is within bounds of the reference standard, the status graphic 2414 may indicate normal (e.g., "Normal Glucose"), or it may not be displayed at all. The status graphic 2414 may have a background color (e.g., red) when the analyte concentration exceeds the acceptable bounds of the reference standard.

The user interface 2400 can include one or more trend indicators 2416 that provide a graphic indicating the time history of the concentration of an analyte of interest. In FIGS. 24 and 25, the trend indicator 2416 comprises a graph of the glucose concentration (in mg/dL) versus elapsed time (in hours) since the measurements started. The graph includes a trend line 2418 indicating the time-dependent glucose concentration. In other embodiments, the trend line 2418 can include measurement error bars and may be displayed as a series of individual data points. In FIG. 25, the glucose trend indicator 2416 is shown as well as a trend indicator 2430 and trend line 2432 for the lactate concentration. In some embodiments, a user may select whether none, one, or both trend indicators 2416, 2418 are displayed. In some embodiments, one or both of the trend indicators 2416, 2418 may appear only when the corresponding analyte is in a range of interest such as, for example, above or below the bounds of a reference standard.

The user interface 2400 can include one or more buttons 2420-2426 that can be actuated by a user to provide additional functionality or to bring up suitable context-sensitive menus and/or screens. For example, in the embodiments shown in FIG. 24 and FIG. 25, four buttons 2420-2426 are shown, although fewer or more buttons are used in other embodiments. The button 2420 ("End Monitoring") may be pressed when one or more removable portions (see, e.g., 710 of FIG. 7) are to be removed. In many embodiments, because the removable portions 710, 712 are not reusable, a confirmation window appears when the button 2420 is pressed. If the user is certain that monitoring should stop, the user can confirm this by actuating an affirmative button in the confirmation window. If the button 2420 were pushed by mistake, the user can select a negative button in the confirmation window. If "End Monitoring" is confirmed, the system 400 performs appropriate actions to cease fluid infusion and blood draw and to permit ejection of a removable portion (e.g., the removable portion 710).

The button 2422 ("Pause") may be actuated by the user if patient monitoring is to be interrupted but is not intended to

end. For example, the “Pause” button **2422** may be actuated if the patient is to be temporarily disconnected from the system **400** (e.g., by disconnecting the tubes **306**). After the patient is reconnected, the button **2422** may be pressed again to resume monitoring. In some embodiments, after the “Pause” button **2422** has been pressed, the button **2422** displays “Resume.”

The button **2424** (“Delay 5 Minutes”) causes the system **400** to delay the next measurement by a delay time period (e.g., 5 minutes in the depicted embodiments). Actuating the delay button **2424** may be advantageous if taking a reading would be temporarily inconvenient, for example, because a health care professional is attending to other needs of the patient. The delay button **2424** may be pressed repeatedly to provide longer delays. In some embodiments, pressing the delay button **2424** is ineffective if the accumulated delay exceeds a maximum threshold. The next-reading graphic **2410** automatically increases the displayed time until the next reading for every actuation of the delay button **2424** (up to the maximum delay).

The button **2426** (“Dose History”) may be actuated to bring up a dosing history window that displays patient dosing history for an analyte or medication of interest. For example, in some embodiments, the dosing history window displays insulin dosing history of the patient and/or appropriate hospital dosing protocols. A nurse attending the patient can actuate the dosing history button **2426** to determine the time when the patient last received an insulin dose, the last dosage amount, and/or the time and amount of the next dosage. The system **400** may receive the patient dosing history via wired or wireless communications from a hospital information system.

In other embodiments, the user interface **2400** can include additional and/or different buttons, menus, screens, graphics, etc. that are used to implement additional and/or different functionalities.

Related Components

FIG. **26** schematically depicts various components and/or aspects of a patient monitoring system **2630** and how those components and/or aspects relate to each other. In some embodiments, the monitoring system **2630** can be the apparatus **100** for withdrawing and analyzing fluid samples. Some of the depicted components can be included in a kit containing a plurality of components. Some of the depicted components, including, for example, the components represented within the dashed rounded rectangle **2640** of FIG. **26**, are optional and/or can be sold separately from other components.

The patient monitoring system **2630** shown in FIG. **26** includes a monitoring apparatus **2632**. The monitoring apparatus **2632** can be the monitoring device **102**, shown in FIG. **1** and/or the system **400** of FIG. **4**. The monitoring apparatus **2632** can provide monitoring of physiological parameters of a patient. In some embodiments, the monitoring apparatus **2632** measures glucose and/or lactate concentrations in the patient’s blood. In some embodiments, the measurement of such physiological parameters is substantially continuous. The monitoring apparatus **2632** may also measure other physiological parameters of the patient. In some embodiments, the monitoring apparatus **2632** is used in an intensive care unit (ICU) environment. In some embodiments, one monitoring apparatus **2632** is allocated to each patient room in an ICU.

The patient monitoring system **2630** can include an optional interface cable **2642**. In some embodiments, the interface cable **2642** connects the monitoring apparatus **2632** to a patient monitor (not shown). The interface cable **2642** can be used to transfer data from the monitoring apparatus **2632** to the patient monitor for display. In some embodiments, the

patient monitor is a bedside cardiac monitor having a display that is located in the patient room (see, e.g., the user interface **2400** shown in FIG. **24** and FIG. **25**.) In some embodiments, the interface cable **2642** transfers data from the monitoring apparatus **2632** to a central station monitor and/or to a hospital information system (HIS). The ability to transfer data to a central station monitor and/or to a HIS may depend on the capabilities of the patient monitor system.

In the embodiment shown in FIG. **26**, an optional bar code scanner **2644** is connected to the monitoring apparatus **2632**. In some embodiments, the bar code scanner **2644** is used to enter patient identification codes, nurse identification codes, and/or other identifiers into the monitoring apparatus **2632**. In some embodiments, the bar code scanner **2644** contains no moving parts. The bar code scanner **2644** can be operated by manually sweeping the scanner **2644** across a printed bar code or by any other suitable means. In some embodiments, the bar code scanner **2644** includes an elongated housing in the shape of a wand.

The patient monitoring system **2630** includes a fluid system kit **2634** connected to the monitoring apparatus **2632**. In some embodiments, the fluid system kit **2634** includes fluidic tubes that connect a fluid source to an analytic subsystem. For example, the fluidic tubes can facilitate fluid communication between a blood source or a saline source and an assembly including a sample holder and/or a centrifuge. In some embodiments, the fluid system kit **2634** includes many of the components that enable operation of the monitoring apparatus **2632**. In some embodiments, the fluid system kit **2634** can be used with anti-clotting agents (such as heparin), saline, a saline infusion set, a patient catheter, a port sharing IV infusion pump, and/or an infusion set for an IV infusion pump, any or all of which may be made by a variety of manufacturers. In some embodiments, the fluid system kit **2634** includes a monolithic housing that is sterile and disposable. In some embodiments, at least a portion of the fluid system kit **2634** is designed for single patient use. For example, the fluid system kit **2634** can be constructed such that it can be economically discarded and replaced with a new fluid system kit **2634** for every new patient to which the patient monitoring system **2630** is connected. In addition, at least a portion of the fluid system kit **2634** can be designed to be discarded after a certain period of use, such as a day, several days, several hours, three days, a combination of hours and days such as, for example, three days and two hours, or some other period of time. Limiting the period of use of the fluid system kit **2634** may decrease the risk of malfunction, infection, or other conditions that can result from use of a medical apparatus for an extended period of time.

In some embodiments, the fluid system kit **2634** includes a connector with a luer fitting for connection to a saline source. The connector may be, for example, a three-inch pigtail connector. In some embodiments, the fluid system kit **2634** can be used with a variety of spikes and/or IV sets used to connect to a saline bag. In some embodiments, the fluid system kit **2634** also includes a three-inch pigtail connector with a luer fitting for connection to one or more IV pumps. In some embodiments, the fluid system kit **2634** can be used with one or more IV sets made by a variety of manufacturers, including IV sets obtained by a user of the fluid system kit **2634** for use with an infusion pump. In some embodiments, the fluid system kit **2634** includes a tube with a low dead volume luer connector for attachment to a patient vascular access point. For example, the tube can be approximately seven feet in length and can be configured to connect to a proximal port of a cardiovascular catheter. In some embodiments, the fluid sys-

tem kit **2634** can be used with a variety of cardiovascular catheters, which can be supplied, for example, by a user of the fluid system kit **2634**.

As shown in FIG. **26**, the monitoring apparatus **2632** is connected to a support apparatus **2636**, such as an IV pole. The support apparatus **2636** can be customized for use with the monitoring apparatus **2632**. A vendor of the monitoring apparatus **2632** may choose to bundle the monitoring apparatus **2632** with a custom support apparatus **2636**. In some embodiments, the support apparatus **2636** includes a mounting platform for the monitoring apparatus **2632**. The mounting platform can include mounts that are adapted to engage threaded inserts in the monitoring apparatus **2632**. The support apparatus **2636** can also include one or more cylindrical sections having a diameter of a standard IV pole, for example, so that other medical devices, such as IV pumps, can be mounted to the support apparatus. The support apparatus **2636** can also include a clamp adapted to secure the apparatus to a hospital bed, an ICU bed, or another variety of patient conveyance device.

In the embodiment shown in FIG. **26**, the monitoring apparatus **2632** is electrically connected to an optional computer system **2646**. The computer system **2646** can comprise one or multiple computers, and it can be used to communicate with one or more monitoring devices. In an ICU environment, the computer system **2646** can be connected to at least some of the monitoring devices in the ICU. The computer system **2646** can be used to control configurations and settings for multiple monitoring devices (for example, the system can be used to keep configurations and settings of a group of monitoring devices common). The computer system **2646** can also run optional software, such as data analysis software **2648**, HIS interface software **2650**, and insulin dosing software **2652**.

In some embodiments, the computer system **2646** runs optional data analysis software **2648** that organizes and presents information obtained from one or more monitoring devices. In some embodiments, the data analysis software **2648** collects and analyzes data from the monitoring devices in an ICU. The data analysis software **2648** can also present charts, graphs, and statistics to a user of the computer system **2646**.

In some embodiments, the computer system **2646** runs optional hospital information system (HIS) interface software **2650** that provides an interface point between one or more monitoring devices and an HIS. The HIS interface software **2650** may also be capable of communicating data between one or more monitoring devices and a laboratory information system (LIS).

In some embodiments, the computer system **2646** runs optional insulin dosing software **2652** that provides a platform for implementation of an insulin dosing regimen. In some embodiments, the hospital tight glycemic control protocol is included in the software. The protocol allows computation of proper insulin doses for a patient connected to a monitoring device **2646**. The insulin dosing software **2652** can communicate with the monitoring device **2646** to ensure that proper insulin doses are calculated.

Analyte Control and Monitoring

In some embodiments, it may be advantageous to control a level of an analyte (e.g., glucose) in a patient using an embodiment of an analyte detection system described herein. Although certain examples of glucose control are described below, embodiments of the systems and methods disclosed herein may be used to monitor and/or control other analytes (e.g., lactate).

For example, diabetic individuals control their glucose levels by administration of insulin. If a diabetic patient is admitted to a hospital or ICU, the patient may be in a condition in which he or she cannot self-administer insulin. Advantageously, embodiments of the analyte detection systems disclosed herein may be used to control the level of glucose in the patient. Additionally, it has been found that a majority of patients admitted to the ICU exhibit hyperglycemia without having diabetes. In such patients it may be beneficial to monitor and control their blood glucose level to be within a particular range of values. Further, it has been shown that tightly controlling blood glucose levels to be within a stringent range may be beneficial to patients undergoing surgical procedures.

A patient admitted to the ICU or undergoing surgery may be administered a variety of drugs and fluids such as Hetastarch, intravenous antibiotics, intravenous glucose, intravenous insulin, intravenous fluids such as saline, etc., which may act as interferents and make it difficult to determine the blood glucose level. Moreover, the presence of additional drugs and fluids in the blood stream may require different methods for measuring and controlling blood glucose level. Also, the patient may exhibit significant changes in hematocrit levels due to blood loss or internal hemorrhage, and there can be unexpected changes in the blood gas level or a rise in the level of bilirubin and ammonia levels in the event of an organ failure. Embodiments of the systems and methods disclosed herein advantageously may be used to monitor and control blood glucose (and/or other analytes) in the presence of possible interferents to estimation of glucose and for patients experiencing health problems.

In some environments, Tight Glycemic Control (TGC) can be achieved by controlling glucose within a relatively narrow range (for example between 70 mg/dL to 110 mg/dL). As will be further described, in some embodiments, TGC may be achieved by using an analyte monitoring system to make continuous and/or periodic but frequent measurements of glucose levels.

In some embodiments, the analyte detection system schematically illustrated in FIGS. **4**, **5**, and **6** may be used to regulate the concentration of one or more analytes in the sample in addition to determining and monitoring the concentration of the one or more analytes. In some implementations, the concentration of the analytes is regulated to be within a certain range. The range may be predetermined (e.g., according to a hospital protocol or a physician's recommendation), or the range may be adjusted as conditions change.

In an example of glycemic control, a system can be used to determine and monitor the concentration of glucose in the sample. If the concentration of glucose falls below a lower threshold, glucose from an external source can be supplied. If the concentration of glucose increases above an upper threshold, insulin from an external source can be supplied. In some embodiments, glucose or insulin may be infused in a patient continuously over a certain time interval or may be injected in a large quantity at once (referred to as "bolus injection").

In some embodiments, a glycemic control system may be capable of delivering glucose, dextrose, glycogen, and/or glucagon from an external source relatively quickly in the event of hypoglycemia. As discussed, embodiments of the glycemic control system may be capable of delivering insulin from an external source relatively quickly in the event of hyperglycemia.

Returning to FIGS. **5** and **6**, these figures schematically illustrate embodiments of a fluid handling system that comprise optional analyte control subsystems **2780**. The analyte control subsystem **2780** may be used for providing control of an analyte such as, e.g., glucose, and may provide delivery of

the analyte and/or related substances (e.g., dextrose solution and/or insulin in the case of glucose). The analyte control subsystem 2780 comprises a source 2782 such as, for example, the analyte (or a suitable compound related to the analyte) dissolved in water or saline. For example, if the analyte is glucose, the source 2782 may comprise a bag of dextrose solution (e.g., Dextrose or Dextrose 50%). The source 2782 can be coupled to an infusion pump (not shown). The source 2782 and the infusion pump can be provided separately from the analyte control subsystem 2780. For example, a hospital advantageously can use existing dextrose bags and infusion pumps with the subsystem 2780.

As schematically illustrated in FIGS. 5 and 6, the source 2782 is in fluid communication with the patient tube 512 via a tube 2784 and suitable connectors. A pinch valve 2786 may be disposed adjacent the tube 2784 to regulate the flow of fluid from the source 2782. A patient injection port can be located at a short distance from the proximal port of the central venous catheter or some other catheter connected to the patient.

In an example implementation for glycemic control, if the analyte detection system determines that the level of glucose has fallen below a lower threshold value (e.g., the patient is hypoglycemic), a control system (e.g., the fluid system controller 405 in some embodiments) controlling an infusion delivery system may close the pinch valves 521 and/or 542 to prevent infusion of insulin and/or saline into the patient. The control system may open the pinch valve 2786 and dextrose solution from the source 2782 can be infused (or alternatively injected as a bolus) into the patient. After a suitable amount of dextrose solution has been infused to the patient, the pinch valve 2786 can be closed, and the pinch valves 521 and/or 542 can be opened to allow flow of insulin and/or saline. In some systems, the amount of dextrose solution for infusion (or bolus injection) may be calculated based on one or more detected concentration levels of glucose. The source 2782 advantageously may be located at a short enough fluidic distance from the patient such that dextrose can be delivered to the patient within a time period of about one to about ten minutes. In other embodiments, the source 2782 can be located at the site where the patient tube 512 interfaces with the patient so that dextrose can be delivered within about one minute.

If the analyte detection system determines that the level of glucose has increased above an upper threshold value (e.g., the patient is hyperglycemic), the control system may close the pinch valves 542 and/or 2786 to prevent infusion of saline and/or dextrose into the patient. The control system may open the pinch valve 521, and insulin can be infused (or alternatively injected as a bolus) into the patient. After a suitable amount of insulin has been infused (or bolus injected) to the patient, the control system can close the pinch valve 521 and open the pinch valves 542 and/or 2786 to allow flow of saline and/or glucose. The suitable amount of insulin may be calculated based on one or more detected concentration levels of glucose in the patient. The insulin source 518 advantageously may be located at a short enough fluidic distance from the patient such that insulin can be delivered to the patient within about one to about ten minutes. In other embodiments, the insulin source 518 may be located at the site where the patient tube 512 interfaces with the patient so that insulin can be delivered to the patient within about one minute.

In some embodiments, sampling bodily fluid from a patient and providing medication to the patient may be achieved through the same lines of the fluid handling system. For example, in some embodiments, a port to a patient can be shared by alternately drawing samples and medicating

through the same line. In some embodiments, a bolus can be provided to the patient at regular intervals (in the same or different lines). For example, a bolus of insulin can be provided to a patient after meals. In another embodiment comprising a shared line, a bolus of medication can be delivered when returning part of a body fluid sample back to the patient. In some implementations, the bolus of medication is delivered midway between samples (e.g., every 7.5 minutes if samples are drawn every 15 minutes). In other embodiment, a dual lumen tube can be used, wherein one lumen is used for the sample and the other lumen to medicate. In yet another embodiment, an analyte detection system (e.g., an "OptiScanner®" monitor) may provide suitable commands to a separate insulin pump (on a shared port or different line).

Example Method for Glycemic Control

FIG. 27 is a flowchart that schematically illustrates an example embodiment of a method 2700 of providing analyte control. The example embodiment is directed toward one possible implementation for glycemic control and is intended to illustrate certain aspects of the method 2700 and is not intended to limit the scope of possible analyte control methods. In block 2705, a glucose monitoring apparatus (e.g., the monitoring apparatus 2632 of FIG. 26) draws a sample (e.g., a blood or blood plasma sample) from a sample source (e.g., a patient) and obtains a measurement from the sample (e.g., a portion of the drawn sample). The measurement may comprise an optical measurement such as, for example, an infrared spectrum of the sample. In block 2710, the measurement sample is analyzed to identify possible interferents to an estimation of the glucose concentration in the measurement sample. In block 2715, a model is generated for estimating the glucose concentration from the obtained measurement. In some embodiments, models developed from the algorithms describe above with reference to FIGS. 21-23 are used. The generated model may reduce or minimize effects of the identified interferents on the estimated glucose concentration, in certain embodiments. In block 2720, an estimated glucose concentration is determined from the model and the obtained measurement. In block 2725, the estimated glucose concentration in the sample is compared to an acceptable range of concentrations. The acceptable range may be determined according to a suitable glycemic control protocol such as, for example, a TGC protocol. For example, in certain TGC protocols the acceptable range may be a glucose concentration in a range from about 70 mg/dL to about 110 mg/dL. If the estimated glucose concentration lies within the acceptable range, the method 2700 returns to block 2705 to obtain the next sample measurement, which may be made within about one to about thirty minutes (e.g., every fifteen minutes).

In block 2725, if the estimated glucose concentration is outside the acceptable range of concentrations, then the method 2700 proceeds to block 2740 in which the estimated glucose concentration is compared with a desired glucose concentration. The desired glucose concentration may be based on, for example, the acceptable range of glucose concentrations, the parameters of the particular glycemic protocol, the patient's estimated glucose concentration, and so forth. If the estimated glucose concentration is below the desired concentration (e.g., the patient is hypoglycemic), a dose of dextrose to be delivered to the patient is calculated in block 2745. This calculation may take into account various factors including, for example, one or more estimated glucose concentrations, presence of additional drugs in the patient's system, time taken for dextrose to be assimilated by the patient, and the delivery method (e.g., continuous infusion or bolus injection). In block 2750, a fluid delivery system (e.g.,

a system such as the optional subsystem **2780** shown in FIGS. **5** and **6**) delivers the calculated dose of dextrose to the patient.

In block **2740**, if the estimated glucose concentration is greater than the desired concentration (e.g., the patient is hyperglycemic), a dose of insulin to be delivered is calculated in block **2755**. The dose of insulin may depend on various factors including, for example, one or more estimated glucose concentrations in the patient, presence of other drugs, type of insulin used, time taken for insulin to be assimilated by the patient, method of delivery (e.g., continuous infusion or bolus injection), etc. In block **2750**, a fluid delivery system (e.g., the optional subsystem **2780** shown in FIGS. **5** and **6**) delivers the calculated dose of insulin to the patient.

In block **2765**, the method **2700** returns to block **2705** to await the start of the next measurement cycle, which may be within about one to about thirty minutes (e.g., every fifteen minutes). In some embodiments, the next measurement cycle begins at a different time than normally scheduled in cases in which the estimated glucose concentration lies outside the acceptable range of concentrations under the glycemic protocol. Such embodiments advantageously allow the system to monitor response of the patient to the delivered dose of dextrose (or insulin). In some such embodiments, the time between measurement cycles is reduced so the system can more accurately monitor analyte levels in the patient.

Hemoglobin/Oxygen Monitoring

Measurement of Hemoglobin Oxygen saturation in the central venous system is a "goal directed therapy" parameter in management of patients suffering from cardiovascular diseases and sepsis. It is used routinely in ER, Trauma Center and ICU as a parameter to monitor the state of patients in critical conditions. Some systems use a fiber optic multi lumen central venous (CV) catheter to make this measurement.

Adult human blood contains four species of hemoglobin: (i) oxyhemoglobin (O₂Hb), (ii) reduced hemoglobin (RHb), (iii) methemoglobin (MetHb) and carboxyhemoglobin (COHb). MetHb and COHb are present in small concentrations except in pathologic conditions. MetHb and COHb generally do not bind to oxygen.

A parameter that characterizes hemoglobin saturation is called Functional Oxygen Saturation (FOS). FOS is defined as the hemoglobin oxygen content expressed as a percentage of the maximum oxygen binding capacity of the hemoglobin. Mathematically FOS can be represented by the following equation:

$$FOS = \frac{O_2Hb(g/dl)}{\{O_2Hb(g/dl) + RHb(g/dl)\}}$$

Because MetHb and COHb do not bind to oxygen and they exist in small concentrations, they are generally not included in the calculation of FOS.

FOS is sometimes measured by pulse oximeters and saturation catheters. FOS can also be measured by using a monitoring device such as the "OptiScanner®" available from OptiScan Biomedical Corporation of Hayward, Calif. Embodiments of such a device are described in detail above. For example, the monitoring device **102** see FIG. **1** can have FOS measurement functionality. When the monitoring device **102** is connected to the CV line of the patient for example, patient tube **512** (tube T1) in FIG. **5** for glucose measurement, simultaneous FOS measurement can be performed on the same sample. The monitoring device **102** can be provided

with an additional channel to measure FOS simultaneously with another analyte (for example, glucose).

Accurate measurement of FOS is limited among other things by variation in optical path length and variation in total hemoglobin level. For example in some embodiments, the optical path length can vary (for example, by 38%) due to manufacturing tolerance of the various parts comprising the monitoring device **102**. The total hemoglobin level can vary between individuals. Typically the total hemoglobin level can vary between approximately 7 to approximately 20 g/dl.

FIG. **28A** discloses an example embodiment **5000** of a hemoglobin sensor. The hemoglobin sensor can be included in the monitoring device **102**, for example **528** (T4) in FIG. **5**. The hemoglobin sensor can be located in the sample cell **548** in FIG. **5**. The example embodiment **5000** comprises a source module **5001**, a flow cell **5002** and a detector module **5003**. The source module **5001** and the detector module **5003** are housed in an outer casing **5004**. The outer casing **5004** can be made of metal, plastic or other composite material. In some embodiments, the outer casing **5004** may be provided with protrusions and grooves to substantially mate with the source module **5001** and the detector module **5003**. In some other embodiments, the source module **5001** and the detector module **5003** may be joined together with screws or adhesives.

The source module **5001** and the detector module **5003** define an optical path **5005**. A flow cell **5002** is disposed in the optical path **5005** between the source block **5001** and the detector block **5003**. FIG. **28B** indicates further details about the source module **5001**. FIG. **28C** indicates further details about the flow cell **5002** and FIG. **28D** indicates further details about the detector module **5003**.

The source module **5001** comprises of an optical block **5006**. In some embodiments, the optical block can include a radiation source. The radiation source may emit radiation in the ultraviolet, visible, near infrared and infrared regions. The radiation source may comprise of one or more light emitting diodes (LEDs) emitting radiation at one or more wavelengths in the radiation region described above, for example a four wavelength LED. In some embodiments the radiation source comprises laser modules emitting radiation at one or more wavelengths. An example of a laser module is a solid state laser. In some other embodiments, the radiation source is semiconductor based. In some other embodiments, the radiation source comprises heating elements. Other radiation sources may be used as well.

In addition to the radiation source, the optical block may comprise filter arrays. The filter arrays may be configured to allow radiation at one or more wavelengths. The filter arrays may comprise of low pass, band pass, high pass and notch filters. The filter arrays may be mechanical or electrically tunable. The optical block can include other passive and active optical components, including diffusers, isolators, pinholes, beam expanders and switches, for example.

The source block may further comprise lens assemblies to focus or collimate the radiation. The lens assembly can include microscope objective and other optical lenses. The lens assembly may be formed by injection molding or other optical manufacturing techniques. The lens assembly may be formed as a single module. In some embodiments, the lens assembly can include micro-optical components or fiber-optic components. The lens assembly may be designed to focus radiation in a small spot on the flow cell **5002**. The focused spot size may be between 50 microns and 1 millimeter. In some embodiments, it may be advantageous to focus the radiation in spot sizes less than 50 microns or more than 1 mm. The source components of the source module may be

designed to deliver an amount of radiation power. The amount of radiation power may vary with intended application.

An example embodiment of a flow cell is illustrated in FIG. 28C. The flow cell 5002 is a container that can hold the sample for analysis, for example 548 in FIG. 5. In some embodiments, the flow cell 5002 includes windows that are made of a material that is substantially transparent to electromagnetic radiation for analysis. The flow cell 5002 may be a part of the larger fluidics network. In some embodiments the flow cell 5002 can include some components of a centrifuging system. The sample may enter the flow cell by flowing. The flow cell 5002 may be configured such that the tube may be pinched between the two supports.

As shown in FIG. 28C, the flow cell 5002 may comprise of a tube 5007, for example, the tube that runs through the receiving 1204 in FIG. 12, placed between two supports 5008, for example, the pinch platen 1202 in FIG. 12. The tube 5007 may be formed of rubber or plastic. Other material that is compatible with the application may also be used. The tube 5007 may be a part of a larger fluidic network. The cross-sectional geometry of the tube may be elliptical, rectangular, square or circular. In the example illustrated in FIG. 28C, the thickness of the tube wall may vary from approximately 0.013 inches to approximately 0.017 inches. The lumen of the tube may vary from approximately 0.0125 inches to approximately 0.0135 inches. Other sizes and dimensions for the tube different from those mentioned above are possible. The tube is placed between two supports. A window 5009 transparent to the emitted radiation is included in the two supports. The window 5009 is configured to be in the optical path 5005. In some embodiments the window 5009 is designed to let the radiation of interest through and substantially reject stray or scattered radiation.

The details of an example detector module 5003 are illustrated in FIG. 28D. The detector module 5003 may comprise a collection lens assembly. The collection lens assembly may comprise high numerical aperture lenses such as microscope objectives. The collection lens assembly may also include spatial filters and other types of filters to reduce scatter. The lens assembly may be formed by injection molding or other optical manufacturing techniques. The lens assembly may be formed as a single embodiment. In some embodiments, the lens assembly can include micro-optical components or fiber-optic components.

In addition to the collection lens assemblies, the detector module 5003 can include optical filters configured to allow radiation of interest while discarding scatter or stray radiation. The radiation from the collection assembly is directed towards a detector configured to detect radiation in the ultraviolet, visible, near infrared and infrared regions. The detector may be a solid state detector coupled to a photo-multiplier tube or an avalanche diode. In some embodiments, the detector may be a charge coupled device. The detector may interface with an electronic device such as a computer or microchips. The electronic device may be used to record and analyze the information detected.

One way to measure FOS is by performing absorption spectroscopy on the sample containing the analyte either in-vivo or in-vitro. In absorption spectroscopy, the sample containing the analyte is illuminated with radiation of wavelength that is absorbed by the analyte. At any given wavelength the measured absorbance is proportional to the concentration of the analyte and the thickness of the sample (or path length) through which the radiation passes. To accurately determine the concentration of the analyte, it is advantageous to eliminate the dependency on path length. To eliminate path length dependency, a ratio of the absorption spectra

at two or more wavelengths can be taken. Knowing the absorption coefficients of the analyte at the wavelengths of interest and the intensity of the radiation transmitted through the sample, concentration of the analyte can be determined. For further details on this method, see, e.g., U.S. Pat. No. 5,127,406, which is incorporated herein by reference in its entirety and made part of the specification thereof.

In some embodiments, it is advantageous to compare the ratio of the absorption spectra at two wavelengths with a reference curve. The reference curve can be obtained previously by any number of methods. For example in one method, the ratio of the absorption spectra at two wavelengths can be obtained for several known concentrations of the analyte. Comparison of the ratio of the absorption spectra at two wavelengths with a reference curve may reduce computational time and resources. For more details on this method, see, e.g., U.S. Pat. No. 5,204,532, which is incorporated herein by reference in its entirety and made part of the specification thereof.

In some embodiments, it may be advantageous to take ratios of first, second, third or fourth derivatives of the absorption spectra instead of the absorption spectra, for example, as described in U.S. Pat. No. 5,377,674, which is incorporated herein by reference in its entirety and made part of the specification thereof. Ratiometric derivative spectroscopy may improve spectral resolution and may allow accurate measurement of concentration in presence of other interferents.

A method to determine FOS can comprise obtaining the transmission spectra of the sample containing one or more analytes at one or more wavelengths and taking the ratio of the transmission spectra themselves or the first or the second derivative of the transmission spectra. The wavelengths at which the transmission spectra are obtained are selected from the wavelength region where the absorption by hemoglobin varies substantially with saturation. The method can further include obtaining the transmission spectra at two or more reference wavelengths that are chosen from the wavelength region where the absorption by hemoglobin does not change substantially with saturation. Obtaining the ratio of the transmission spectrum at the reference wavelengths may allow quantification and correction for scattering errors. This method can be generalized to measure the concentration of one or more analytes. The analytes can include glucose, cholesterol, urea etc and other analytes mentioned above. Additionally, this method can be used to determine FOS.

For example FIG. 29 illustrates a graph of transmission through hemoglobin versus wavelength. The graph is obtained by using a model that simulates absorption by hemoglobin but does not account for scattering effects. Curve 5101 indicates the modeled transmission of radiation from 600 nanometer (nm) to 1000 nm through a sample containing 100% saturated hemoglobin. Similarly, curves 5102, 5103, 5104, 5105, 5106, 5107 and 5108 indicate the modeled transmission of radiation from 600 nm to 1000 nm through a sample containing 90%-30% saturated hemoglobin.

As observed from FIG. 29, the transmission of radiation from approximately 610 nanometers to approximately 725 nm varies substantially with saturation. However the transmission of radiation from approximately 830 nm to 940 nm does not change substantially with saturation. FOS can be obtained by taking the ratio of the transmission spectra at two or more wavelengths selected between approximately 610 nm and approximately 725 nm. For example, FOS can be determined by taking the ratio of the transmission spectra at 635 nm and 700 nm. To quantify and correct for errors due to scattering in determination of concentration, the ratio of transmission spectra at two or more reference wavelengths

selected between approximately 830 nm and approximately 940 nm can be obtained. For example 860 nm and 940 nm can be chosen as reference wavelengths. Wavelengths other than those specified here can also be chosen. The wavelength range indicated here is only an example and wavelengths outside these ranges may be selected. Some example wavelength ranges are 500-1100 nm, 1100-4600 nm and 4600-10,000 nm.

FIG. 30 illustrates an example apparatus 5200 that can be used to determine FOS using various embodiments of the methods indicated above. The apparatus comprises a flow cell 5201. The flow cell may be an OptiScan ScvO₂ flow cell. Other embodiments of a flow cell may be used as well for example, 548 in FIG. 5. The flow cell has an inlet tube 5202 and an outlet tube 5203. The inlet tube 5202 is connected to the outlet port of a pediatric ECMO oxygenator 5204. Other kinds of oxygenators may be used as well. The outlet tube 5203 is connected to a reservoir (not shown). The reservoir may be connected to the inlet port of 5204. The sample, which can be heparinized human blood, for example circulates through the fluidic network. Embodiments of a method to mix Heparin with blood are outlined in U.S. patent application Ser. No. 12/123,404, filed May 19, 2008, entitled "Fluid Mixing Systems and Methods," which is incorporated herein by reference in its entirety and made part of the specification hereof. The oxygenator can adjust the saturation of the heparinized human blood.

The illustrated flow cell 5201 further includes a radiation input cable 5205 and a radiation output cable 5206. The radiation output cable 5206 may be connected to a spectrophotometer 5207 such as Ocean Optics Fiber Optic Spectrophotometer (available from Ocean Optics, Inc., Dunedin, Fla.). Other types of detectors besides a spectrophotometer may be used as well. The radiation input cable 5205 may be connected to a radiation emitter that emits radiation at multiple wavelengths. The radiation emitter may be designed to emit continuously from 500 nm to 1000 nm. Alternate emission ranges may be used as well.

A procedure that can be used to measure FOS with this apparatus is described below. Prior to beginning measurements, the spectrophotometer is adjusted to full scale, for example 4000 counts, by obtaining a first transmission spectrum through saline. Heparinized human blood containing 100.3% saturated hemoglobin from the oxygenator 5204 is introduced in the flow cell 5201 through the inlet tube 5202. The sample in the flow cell is illuminated by radiation from 500 nm to 1000 nm via the radiation input cable 5205. The transmission spectrum through the sample is recorded by the spectrophotometer 5207. The sample from the flow cell is then allowed to flow in to the reservoir. The flow cell is flushed with saline to remove traces of the sample from the flow cell. A second transmission spectrum through saline is obtained. The oxygenator 5204 is adjusted to change the saturation of hemoglobin in the heparinized human blood to 93.8%. Following the procedure described above, the transmission spectrum through heparinized human blood containing 93.8% saturated hemoglobin is recorded. This procedure is followed to obtain transmission spectra through sample containing 79%, 69.6%, 66.9% and 67.4% saturated hemoglobin. The flow cell is flushed with saline before introducing new sample with different saturation percentage. The transmission spectrum through saline is obtained before and after the introduction of sample. The samples used can have the percentage of saturation of hemoglobin different from the percentage of saturation indicated in this example.

FIG. 31 indicates a graph illustrating the transmission spectra through saline and sample containing hemoglobin

with different saturation values. Curve 5300 is the transmission spectra through the apparatus when the source is turned off. The group of curves 5301 is the transmission spectra of radiation from 500 nm to 1000 nm through saline. As described above, the transmission spectra through saline is obtained before and after obtaining the transmission spectra through the sample. From FIG. 31, it is observed that the individual curves in the group of saline curves as approximately similar and overlap each other substantially. Curve 5302 represents the transmission spectra through a sample containing 100% saturated hemoglobin. Curve 5303 indicates the transmission spectra through a sample containing 93.8% saturated hemoglobin. Curve 5304 indicates the transmission spectra through a sample containing 79% saturated hemoglobin. Curve 5306 indicates the transmission spectra through a sample containing 67.4% saturated hemoglobin. FOS is measured by forming a ratio of the transmission at 635 nm to the transmission at 700 nm. FOS is also calculated by using a hemoglobin measuring system such as the IL 682 CO-Oximeter from Instrumentation Laboratory, Lexington, Mass. The FOS measurement determined using the standard instrument is used as a reference.

FIG. 32 indicates a comparison between the reference FOS measurement and the FOS measurement obtained by the new method. Curve 5401 is the reference FOS measurement obtained by using a standard instrument and samples containing hemoglobin with different percentages of saturation. The points 5402 are the FOS measurements obtained by the new method on the same samples. It is observed from the Figure that the points approximately lie on Curve 5401. A regression analysis of the curve 5401 and points 5402 indicates an R-square value of approximately 0.976. The FOS calculated by the new method thus has a standard error of about 2.2% with respect to the standard instrument.

The signal-to-noise (S/N) ratio of the apparatus is measured by taking the ratio of the noise generated when the source is switched off to the signal generated during a saline measurement. FIG. 33 shows a graph of the S/N of the apparatus versus wavelength. This particular prototype has a peak S/N of approximately 85 dB. In general, the S/N may vary from 65 dB-95 dB. The S/N ratio may be a possible factor in the standard error between the measurement obtained by the apparatus using the new method and the FOS obtained by a standard instrument. In some embodiments, S/N of about 95 dB may result in a standard error of approximately 1% or less between the FOS measured by the new method and the FOS obtained by a standard instrument.

In some embodiments, the new method of measuring FOS can be affected by variation of the path length and variation in the total hemoglobin (THb) content. FIG. 34 shows a graph of the FOS obtained by the new method as compared to the FOS measured by a standard instrument for samples with different levels of THb and contained in a flow cell with different optical path length. For example, in FIG. 34, curve 5601 is the comparison between the FOS obtained by an embodiment of the new method and the FOS obtained by a standard instrument. The THb content in the samples for this measurement is 13.6 g/dL and the apparatus is configured to have an optical path of 0.013". To obtain curve 5602, the THb content in the samples is reduced to 12.2 g/dL while maintaining the optical path through the apparatus at 0.013". To obtain curve 5603, the THb content is maintained at 13.6 g/dL similar to the first measurement while the optical path length is decreased to 0.007". Both changes produced slightly greater percentage error in the FOS measurement obtained by the new method as compared to the FOS measurement obtained by a standard measurement.

In some embodiments, a scattering correction may be made to the FOS measurements obtained by the new method. The scattering correction may be determined by taking a second ratio of the transmission spectra at two wavelengths selected from a region in which the transmission spectra is approximately the same for all saturation levels of hemoglobin. For example, referring to FIG. 31, scattering correction may be determined by taking the ratio of the transmission spectra at 860 nm and 940 nm.

The effect of incorporating scattering correction in the original method to measure FOS is shown in FIG. 35. The curves shown in FIG. 35 are obtained by applying the scattering correction to the curves shown in FIG. 34. Employing scattering correction may improve the correlation between the FOS measurement obtained by the new method and the FOS measurement obtained by a standard instrument for different level of THb content and different values of the optical path. In FIG. 35, curve 5701 is obtained by applying the scattering correction to curve 5601 of FIG. 34. Similarly curves 5702 and 5703 are obtained by applying the scattering correction to curves 5602 and 5603, respectively. From FIG. 35 it can be observed that the scattering correction has improved the correlation between the FOS measured by the new method and the FOS measured by the standard instrument as compared to the FIG. 34.

To reduce the effect of variation in the THb content on the FOS measurement, one approach is to incorporate a diffuser in the apparatus. The diffuser scatters the radiation significantly before the radiation is scattered by the sample. In some embodiments, the diffuser may be replaced by a scattering element. The diffuser may be disposed in the optical path between the radiation source and the sample. In one embodiment the diffuser may be joined to the sample. In an alternate embodiment, the diffuser may comprise TEFLON® tape. For example, referring to FIG. 30, a TEFLON® tape approximately 0.001 inches-approximately 0.005 inches may be wrapped around the flow cell containing the sample.

FIG. 36 is a graph illustrating the transmission spectra through sample containing hemoglobin with different levels of saturation when a diffuser is disposed in the optical path between the source and the sample. The procedure used to obtain the transmission spectra is similar to the procedure used to obtain the transmission spectra shown in FIG. 31. Curve 5801 is the transmission spectra through the apparatus when the source is turned off. The group of curves 5802 is the transmission spectra of radiation from 500 nm to 1000 nm through saline. From FIG. 36, it is observed that the individual curves in the group of saline curves as approximately similar and overlap each other substantially. Curve 5803 represents the transmission spectra through a sample containing 100% saturated hemoglobin. Curve 5804 indicates the transmission spectra through a sample containing 99.9% saturated hemoglobin. Curve 5805 indicates the transmission spectra through a sample containing 84.4% saturated hemoglobin. Curve 5806 indicates the transmission spectra through a sample containing 56.3% saturated hemoglobin. In certain embodiments comprising a diffuser, significant increase in the intensity of the source radiation may be required. In certain embodiments, the transmission of the radiation through blood may be significantly higher relative to water because the effect of whole blood scattering is minor in comparison to the scattering by the diffuser. This effect can be verified by observing that the blood counts obtained for the various wavelengths is significantly higher in FIG. 35 as compared to FIG. 36.

FIG. 37 indicates the S/N of the apparatus comprising a diffuser versus wavelength. In some embodiments, the spec-

trometer acquisition time may be increased to achieve a full scale signal with saline. In a particular prototype, the peak S/N value was found to be about 67 dB. In general the S/N value may vary from 65 dB-95 dB.

FIG. 38 shows a graph of the FOS obtained by the apparatus comprising a diffuser as compared to the FOS measured by a standard instrument for samples with different levels of THb. For example, in FIG. 38, curve 6001 is the comparison between the FOS obtained by an embodiment of the new method and the FOS obtained by a standard instrument. The THb content in the samples for this measurement is 13.6 g/dL and the apparatus is configured to have an optical path of 0.013". Curve 6002 is the comparison between the FOS obtained by an embodiment of the new method and the FOS obtained by a standard instrument. The THb content in the samples for this measurement is 12.2 g/dL and the apparatus is configured to have an optical path of 0.013".

FIG. 39 shows a graph of the FOS obtained by employing the scattering correction to the curves shown in FIG. 38. Comparison of FIG. 39 with FIG. 35 indicates that incorporating a diffuser and scattering correction may reduce the scattering effect and improve the correlation between the FOS measured by the new method and the FOS measured by a standard instrument.

In alternate embodiments, to improve the correlation between the FOS measured by the new method and the FOS measured by a standard instrument a modulated LED and a Lock-In-Amplifier as described, for example, in U.S. patent application Ser. No. 11/734,261, filed Apr. 11, 2007, entitled "Noise Reduction for Analyte Detection Systems," which is hereby incorporated by reference herein in its entirety, can be used to reduce noise. Lower noise detectors may also be used to reduce noise and improve S/N ratio.

Measurement of Physiological Parameters

In certain applications, an analyte detection system may be used to estimate concentration of one or more analytes in a sample such as, e.g., a body fluid sample from a patient. The analyte detection system may be in fluid communication with the patient and may have the capability to draw fluid samples from the patient at various intervals (e.g., about every fifteen minutes). The analyte detection system may analyze a portion of the drawn sample to determine analyte values for one or more analytes in the sample. For example, embodiments of such systems may be used to determine glucose concentration, hemoglobin concentration, etc. in a blood sample or blood plasma sample.

In certain embodiments, measurements made by an analyte detection system may be combined with measurements by one or more devices to provide information relating to one or more physiological parameters. In certain such embodiments, the devices may be external to the analyte detection system and measurements by the device may be communicated (via wired and/or wireless techniques) to the analyte detection system for processing. Various non-limiting, illustrative examples of such embodiments will now be described.

FIG. 40 is a block diagram that schematically illustrates an embodiment of a system 62100 for determining cardiac output Q and oxygen extraction ratio O₂ER in a patient. The system 62100 comprises an analyte detection system 62104 and a pulse oximeter 62108. For example, embodiments of the apparatus 100 (including the monitoring device 102) described with reference to FIGS. 1-3 above may be suitable for use with embodiments of the system 62100 shown in FIG. 40. Other analyte detection systems may be used including, but not limited to, embodiments of the system 400 (FIG. 4), the fluid system 510 (FIGS. 5-6), and the patient monitoring system 2630 (FIG. 26) shown and described above. In yet

other embodiments, commercially available analyte detection systems may be used including, for example, an OptiScanner® monitoring system available from OptiScan Biomedical Corporation, Hayward, Calif.

The pulse oximeter **62108** may comprise any type of device suitable for estimating oxygen saturation in a patient. For example, any type of commercially available pulse oximeter or photoplethysmograph may be used. For example, in some embodiments, the pulse oximeter **62108** may comprise a component that can be attached to the patient's finger or earlobe and used to measure arterial oxygen saturation, SaO₂, of the patient's blood using optical techniques. Many widely available pulse oximeters also determine the patient's pulse rate. For example, certain embodiments of the pulse oximeter **62108** may utilize photoemitters (e.g., light emitting diodes) that emit red light and infrared light and photo-detectors that detect the light after passage through the patient's body (e.g., through the finger or earlobe). Comparison of the amounts of detected light and the amounts of emitted light at the red and infrared wavelengths provides an estimate of the arterial blood saturation SaO₂ (sometimes called SpO₂). In the embodiment illustrated in FIG. **40**, the pulse oximeter **62108** and the analyte detection system **62104** are separate instruments. In other embodiments, the pulse oximeter **62108** is integrated with the analyte detection system **62104**, thereby advantageously providing a unitary device for measuring a range of analyte and physiological parameters of the patient.

In some embodiments of the pulse oximeter **62108**, the measurements are made as a function of time (e.g., to remove baseline optical absorption not due to arterial oxygen saturation), and such embodiments typically also determine the pulse rate (PR) of the patient. Embodiments of the pulse oximeter **62108** may provide measurements of arterial oxygen saturation SaO₂ (and pulse rate PR) that are separated in time by, for example, a fraction of a second to several seconds. In comparison, some embodiments of the analyte detection system **62104** may provide measurements separated in time by longer intervals such as, for example, minutes to fractions of an hour (e.g., 15 minutes) to hours. Certain embodiments of the system **62100** shown in FIG. **40** may account for the different measurement rates of the devices in the system **62100**.

In the illustrated embodiment, the analyte detection system **62104** comprises a user interface **62112** for inputting data to the system **62100**, a fluid handling system **62116** for receiving a fluid sample for analysis, a processor **62120** for coordinating operation of the system **62104** and for performing analysis of the fluid sample, and an output device **62124** (e.g., a display) for outputting analysis results. The user interface **62112** and the output device **62124** may comprise a touch-screen display.

In some embodiments, the fluid handling system **62116** receives the fluid sample and transports portions of the sample in the analyte detection system **62104**. For example, in certain embodiments, the fluid handling system **62116** may transport a portion of the sample to a fluid component separator (e.g., a filter and/or a centrifuge) where the sample is separated into components (e.g., blood plasma may be separated from a whole blood sample). One (or more) components may be transported to an analysis system for determination of analyte values. For example, in some embodiments, the analysis system may analyze a blood sample to determine hemoglobin concentration, Hb, and oxygen saturation. In some implementations, the blood sample is drawn from a patient's vein, and the analysis system determines a patient's venous oxygen saturation SvO₂.

In certain embodiments, the fluid handling system **62116** is configured to be in fluid communication with a patient, for example, via a catheter inserted into a patient's vein, such as, for example, a central venous catheter (routinely used in emergency rooms, trauma centers, and ICUs to monitor critical care patients). Embodiments of the fluid handling system **62116** may be configured to draw fluid samples (e.g., venous blood samples) from the patient from time-to-time, e.g., every fifteen minutes. Examples of such fluid handling systems **62116** are described above including, but not limited to, the fluid handling system **510** shown and described with reference to FIGS. **5** and **6**.

The processor **62120** may comprise a general purpose computer and/or a special purpose computer configured with software code modules to implement methods described herein. The software code modules may be implemented as software, firmware, and/or hardware in various embodiments. The processor **62120** may include on-board memory (e.g., random access memory RAM). In some embodiments, the system **62100** comprises additional data storage devices including any type of volatile and/or nonvolatile memory such as, e.g., RAM, read-only memory ROM, flash memory, a hard disk drive, an optical drive, and so forth. The data storage devices can be used to store executable instructions, data (e.g., measurements by the analyte detection system **62104** and/or the pulse oximeter **62108**), analysis results, etc. The processor **62120** may be configured to receive, store, and/or process information entered via the user interface **62112**, information relating to measurements by other devices (e.g., the pulse oximeter **62108**), and/or information relating to measurements by the analyte detection system **62104**. The processor **62120** may be local to the analyte detection system **62104** or remote from the system **62104**. In some embodiments, multiple processors are used, some or all of which may be remote from the system **62100**.

The components of the system **62100** may communicate via wired and/or wireless techniques. In some embodiments, information from one component (such as the pulse oximeter **62108**) is communicated to another component (e.g., the analyte detection system **62104**) via a network (such as, e.g., a hospital information system). The system **62100** may be configured to receive information (e.g., patient data including patient age, height, weight, gender, medical conditions, etc.) from the network. It should be apparent that the system **62100** may be configured in many different ways to meet the needs of a particular implementation (such as in an ICU, doctor's office, home, etc.).

FIG. **41** is a flowchart schematically illustrating an embodiment of a method **63200** for determining a physiological parameter using a measured analyte value. In this embodiment of the method **63200**, in block **63210** a first device is used to obtain a first measurement of a first parameter for a patient. For example, the first device may comprise the pulse oximeter **62108**, and the first parameter may be oxygen saturation in the patient's arterial blood (SaO₂). In certain embodiments, measurements of additional parameters may be obtained. The first measurement may represent a single estimation of the first parameter or it may represent a sequence of estimations. For example, many embodiments of pulse oximeters provide near continuous output at a measurement rate that may exceed about 1 Hz. The first measurement may represent a measurement at a particular time. In some embodiments, the first measurement may represent a time series of measurements over a time interval. The time series may comprise regularly spaced or irregularly spaced measurements.

In block **63220**, an analyte detection system is used to obtain a second measurement of a second parameter in a fluid sample from the patient. For example, the analyte detection system may comprise the analyte detection system **62104** shown in FIG. **40**. The fluid sample may comprise a blood sample from the patient. The second parameter may be the same or different from the first parameter. In some embodiments, measurements of additional parameters may be obtained. For example, in certain embodiments, the analyte detection system measures a second parameter that is hemoglobin concentration and a third parameter that is venous oxygen saturation (SvO₂). As with the first measurement, the second (and/or other) measurements may comprise a single measurement at a particular time or a time series of measurements over a time interval.

In block **63230**, a third parameter is determined based at least in part on the first measurement of the first parameter and the second measurement of the second parameter. The third parameter may comprise a physiological parameter of a patient. For example, as will be further described below, in some embodiments arterial oxygen saturation (SaO₂) measured by a pulse oximeter is combined with venous oxygen saturation measurements (SvO₂) and hemoglobin measurements by an analyte detection system to determine cardiac output (Q) of the patient. In block **63230**, the determination may be made by a suitable processor or computer (such as, e.g., the processor **62120** shown in FIG. **40**). The determination may use a variety of mathematical and/or statistical methods. For example, in some embodiments, a time series of measurements may be averaged, filtered, correlated, transformed, etc.

In some embodiments, rates of measurement by the first device and the analyte detection system may be different. For example, a pulse oximeter may provide measurements at a rate of about 1 Hz, and an analyte detection system may provide measurements at a rate of about 1 mHz (e.g., about every 15 minutes). Therefore, in some embodiments the measurements by the first device and/or the analyte detection system are stored (e.g., in a data storage device) and some or all of the measurements are combined (e.g., by the processor **62120**). For example, in one embodiment, an analyte measurement by the analyte detection system may be made a time Δt after a fluid sample (e.g., a blood sample) is drawn from the patient at time t. Thus, an analyte measurement at time t may represent conditions in the patient at time t-Δt. Accordingly, some embodiments of the method **63200** determine the third parameter based at least in part on the second measurement determined at time t, and a first measurement (e.g., by the pulse oximeter) at the earlier time t-Δt. In such embodiments, the determination of the third parameter advantageously may more accurately reflect the value of the third parameter in the patient at the time the fluid sample was drawn. In some such embodiments, the value of the first measurement at t-Δt is stored for later combination with measurements made at time t. In other embodiments, a time series of measurements from the first device is stored, and one or more values based on the time series are used in the determination of the third parameters. For example, a measurement close in time to t-Δt may be used, an interpolated (or extrapolated) measurement may be used, and so forth. It will be appreciated that many data analysis and signal processing methods may be used in various embodiments for determining the third parameter.

In block **63240**, embodiments of the method **63200** may display (e.g., on the display **62124**) and/or store (e.g., in a data storage device) information relating to the third parameter determined in block **63230**. For example, in some embodiments, the display **62124** may output an estimated value of the

cardiac output (Q), oxygen extraction ration (O₂ER), etc. Trend graphics (e.g., graphs, charts, etc.) showing a trend in the estimate of the third parameter as a function of time may be output by the display. Many variations are possible. In some embodiments, the determined third parameter may be communicated to other devices, components, systems, networks, etc. For example, the system **62100** may communicate a value of the cardiac output Q to a hospital information system for storage in a patient's electronic file.

10 Example Embodiments for Determination of Cardiac Physiological Parameters

In the following, a non-limiting example of an embodiment for determining physiological parameters related to cardiac function will be described. This example is intended to illustrate features of the systems and methods described herein and is not intended to be limiting.

Returning to FIG. **40**, the embodiment of the system **62100** may be used to determine cardiac output Q, oxygen extraction ratio O₂ER, among other useful physiological parameters of the patient.

Cardiac output Q may be measured as the volume of blood ejected from the left side of the patient's heart per minute. Cardiac output may be measured in liters per minute (L/min). Cardiac output is equal to the stroke volume (SV) of the heart (the volume of blood pumped per heart beat) multiplied by the pulse rate (PR): $Q=SV*PR$.

Certain embodiments of the systems and methods described herein use the Fick principle for determination of cardiac output. The Fick principle has historically been used as an indirect measurement of Q based on assumptions about heart operation. Under the Fick principle, the rate at which oxygen is consumed in the body is a function of the rate of blood flow and the rate of oxygen pick up by the red blood cells in the lungs. The Fick principle involves calculating the oxygen consumed over a given period of time from measurement of the oxygen concentration of venous blood and arterial blood. The cardiac output Q may be calculated from the Fick equation:

$$VO_2=Q*(CaO_2-CvO_2),$$

where VO₂ is the consumption rate of oxygen (measured, for example, in liters of oxygen per minute), Q is the cardiac output (measured, for example, in liters per minute), and CaO₂ and CvO₂, respectively, are the arterial ("a") and venous ("v") oxygen contents. The Fick equation may be interpreted as providing oxygen consumption rate (VO₂) in terms of the difference between the volumetric flow of arterial blood (Q*CaO₂) and the volumetric flow of venous blood (Q*CvO₂).

Oxygen in blood is carried as oxygen bound to hemoglobin (Hb) and as dissolved oxygen. Not only is the amount of dissolved oxygen typically much smaller than the amount of oxygen bound to hemoglobin, but only the difference between arterial and venous dissolved oxygen appears in the Fick equation. Accordingly, in certain embodiments, the amount of dissolved oxygen is neglected. The amount of oxygen carried by hemoglobin may be calculated as follows. Each gram of hemoglobin can carry about 1.34 ml of oxygen (the Hufner number). The concentration of Hb-bound oxygen (in arterial or venous blood) is the product of the Hufner number, the concentration of hemoglobin, and the oxygen saturation (the ratio of oxygenated Hb to total Hb):

$$CaO_2=1.34*Hb*SaO_2$$

$$CvO_2=1.34*Hb*SvO_2$$

where SaO₂ and SvO₂ are the arterial and venous oxygen saturations, respectively. Substituting these equations into the Fick equation provides an estimate for cardiac output as:

$$Q = VO_2 / (1.34 * Hb * (SaO_2 - SvO_2)).$$

Accordingly, certain embodiments of the system **100** shown in FIG. **40** use this equation to determine cardiac output Q by measuring (or estimating) VO₂, measuring hemoglobin concentration Hb and venous oxygen saturation SvO₂ in a venous blood sample from the patient (e.g., via the analyte detection system **62104**), and measuring arterial oxygen saturation SaO₂ (e.g., via the pulse oximeter **62108**).

In some embodiments, the oxygen consumption rate VO₂ may be estimated with a spirometer (with the patient rebreathing air) and a carbon dioxide absorber, and the measurement of VO₂ may be provided to the system **62100**.

In other embodiments (e.g., in an ICU), it may be undesirable (or inadvisable) to measure a patient's VO₂ directly, and in such embodiments, VO₂ may be estimated from patient data including, for example, height (H), weight (W), age (A), gender, etc. In various embodiments, mathematical formulas and/or look-up tables may be used to estimate VO₂. For example, in some embodiments, the following empirical formulas may be used for VO₂ (measured in ml/min):

$$VO_2(\text{males}) = 12.04 + 0.687 * H(\text{cm}) + 1.929 * W(\text{kg}) - 0.802 * A(\text{yr})$$

$$VO_2(\text{females}) = 63.23 + 0.457 * H(\text{cm}) + 1.318 * W(\text{kg}) - 0.621 * A(\text{yr})$$

The above formulas are taken from A. M. Roza, et al., "The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass," The American Journal of Clinical Nutrition, vol. 40, pp. 168-182, July 1984, which is hereby incorporated by reference herein in its entirety. In other embodiments, other formulas for VO₂ may be used including, for example, formulas described in Table 1 in G. Neto, et al., "Non-exercise models for prediction of aerobic fitness and applicability on epidemiological studies: descriptive review and analysis of the studies," Rev. Bras. Med. Esporte, vol. 9, No. 5, September/October 2003, which is hereby incorporated by reference herein in its entirety. In the embodiment of the system **62100** shown in FIG. **40**, the user interface **62112** may be used to input patient data (e.g., H, W, A, gender, etc.), and the processor **62120** may calculate VO₂ from the patient data. In other embodiments, the system **62100** may receive patient data over a network such as a hospital information system.

As described above, certain embodiments use the formula $Q = VO_2 / (1.34 * Hb * (SaO_2 - SvO_2))$, to determine cardiac output Q. Under the assumption that a patient's VO₂ is relatively constant within a time interval, ratios of the cardiac output at different times (in the time interval) are (at least approximately) independent of the value of VO₂ for the patient. Accordingly, certain embodiments determine relative changes in cardiac output Q of a patient without needing to determine (or estimate) VO₂. In certain such embodiments, patient data (e.g., H, W, A, gender) may not be needed for the determination of relative change in cardiac output. For example, in one embodiment, the relative change in cardiac output between times t₁ and t₂ is determined from $(Q(t_2) - Q(t_1)) / Q(t_1)$, which is independent of the value of VO₂ (and the Hufner number). As will be appreciated, relative changes in other physiological parameters may be determined in other embodiments.

As schematically illustrated in the embodiment shown in FIG. **40**, in block **62130** the analyte detection system **62104** determines the hemoglobin concentration (Hb) in a venous

blood sample drawn from the patient. For example, with reference to FIGS. **5** and **6** above, hemoglobin concentration may be measured by the hemoglobin sensor **526** (Hb**12**) in certain embodiments. As blood starts to arrive at the hemoglobin sensor **526** (Hb**12**), the hemoglobin level rises. A hemoglobin level can be selected, and the system can be pre-set to determine when that level is reached. A controller such as the fluid system controller **405** of FIG. **4** above can be used to set and react to the pre-set value, for example. In some embodiments, when the sensed hemoglobin level reaches the pre-set value, substantially undiluted sample is present at the first connector **524** (C1). The preset value can depend, in part, on the length and diameter of any tubes and/or passages traversed by the sample. In some embodiments, the pre-set value can be reached after approximately 2 mL of fluid (e.g., blood) has been drawn from a fluid source. A nondiluted sample can be, for example, a blood sample that is not diluted with saline solution, but instead has the characteristics of the rest of the blood flowing through a patient's body (preferably a vein in the patient's body). A loop of tubing **530** (e.g., a 1-mL loop) can be advantageously positioned as illustrated in FIG. **5** to help insure that undiluted fluid (e.g., undiluted blood) is present at the first connector **524** (C1) when the hemoglobin sensor **526** registers that the preset Hb threshold is crossed. The loop of tubing **530** provides additional length to the Hb sensor tube **528** (T4) to make it less likely that the portion of the fluid column in the tubing at the first connector **524** (C1) has advanced all the way past the mixture of saline and sample fluid, and the nondiluted blood portion of that fluid has reached the first connector **524** (C1).

In block **62134** shown in FIG. **40**, the analyte detection system **62104** measures venous oxygen saturation SvO₂. For example, in certain embodiments, the analyte detection system **104** may calculate SvO₂ as Functional Oxygen Saturation (FOS), which is defined as the hemoglobin oxygen content as a percentage of the maximum oxygen binding capacity of the hemoglobin. Mathematically FOS can be represented by the following equation:

$$FOS = \frac{O_2Hb(\text{g/dl})}{O_2Hb(\text{g/dl}) + RHb(\text{g/dl})}$$

where O₂Hb represents oxyhemoglobin and RHb represents reduced hemoglobin. In embodiments of the analyte detection system **62104** described in more detail above, FOS can be measured with use of, for example, the hemoglobin sensor **5000** shown and described with reference to FIGS. **28A-28D**.

An embodiment of a method to determine SvO₂ (e.g., FOS) can comprise obtaining transmission spectra of the blood sample at one or more wavelengths and taking the ratio of the transmission spectra themselves or the first or the second derivative of the transmission spectra. The wavelengths at which the transmission spectra are obtained are selected from the wavelength region where the absorption by hemoglobin varies substantially with saturation. The method can further include obtaining the transmission spectra at two or more reference wavelengths that are chosen from the wavelength region where the absorption by hemoglobin does not change substantially with saturation. Obtaining the ratio of the transmission spectrum at the reference wavelengths may allow quantification and correction for scattering errors. Further details for measuring FOS are provided above.

In block **62138** shown in FIG. **40**, the pulse oximeter **62108** measures arterial blood saturation SaO₂ (e.g., via optical techniques). Embodiments of the pulse oximeter **62108** may also measure pulse rate PR.

In blocks **62142** and **62146** of the embodiment shown in FIG. **40**, the analyte detection system **104** determines cardiac output Q according to the above-described equation $Q=VO_2/(1.34 \cdot Hb \cdot (SaO_2 - SvO_2))$. For example, the patient data may be used in block **62142** to estimate VO_2 , and as described, the pulse oximeter **62108** is used to determine SaO_2 and the analyte detection system **62104** is used to determine Hb and SvO_2 . In certain embodiments, the processor **62120** may select measurements taken at appropriate times to make the determination of Q (e.g., measurements corresponding to the same clock time). In other embodiments, the calculation of Q (or other physiological parameters) may be made by other processors or computers in communication with the system **62100**.

Embodiments of the system **62100** may be used to determine other physiological parameters. For example, the fraction of blood utilized in the body is called the oxygen extraction ratio, O_2ER , and is determined from the following equation:

$$\begin{aligned} O_2ER &= (Q \cdot CaO_2 - Q \cdot CvO_2) / (Q \cdot CaO_2) \\ &= 1 - CvO_2/CaO_2 \\ &= 1 - SvO_2/SaO_2 \end{aligned}$$

Therefore, in block **62150** of FIG. **40**, embodiments of the system **62100** may utilize SaO_2 from the pulse oximeter **62108** and SvO_2 from the analyte detection system **62104** to determine O_2ER .

Yet other physiological parameters may be determined. For example, stroke volume SV of the heart may be determined from cardiac output Q (e.g., determined as described above) and pulse rate PR (e.g., determined from the pulse oximeter): $SV=Q/PR$. Cardiac Index (CI) is defined as cardiac output Q divided by the patient's body surface area (BSA): $CI=Q/BSA$. In some embodiments, BSA is determined from patient data according to a formula from the above-incorporated article by Roza, et al.:

$$BSA \text{ (cm}^2\text{)} = 71.84 \cdot W(\text{kg})^{0.425} \cdot H(\text{cm})^{0.725}$$

Hospital Intensive Care Units (ICUs) monitor many aspects of patients' physiology and biological systems. Nurses who care for ICU patients are especially interested in tracking levels of certain chemical parameters in the patients' blood. One parameter is glucose level, and health of an ICU patient can be monitored and improved with "tight glycemic control" or "TGC." TGC can include: 1) continuous monitoring (which can include periodic monitoring, at relatively frequent intervals of every 15, 30, 45, and/or 60 minutes, for example) of glucose levels; 2) calculation of substances that tend to increase glucose levels (e.g., sugars such as dextrose) and/or decrease glucose levels (e.g., insulin); and/or 3) responsive delivery of those substances, if appropriate under the controlling TGC protocol.

Another parameter that can be monitored in ICUs is level of Hemoglobin (Hb). If the Hb level of a patient goes down without an apparent external reason, the patient could be suffering from internal bleeding. Indeed, many ICU patients (some estimate as many as 10%) suffer from what appears to be spontaneous internal bleeding that may not be otherwise detectable until the consequences are too drastic to easily overcome. Level of Hb can be measured indirectly because its relationship to oxygen in the veins and arteries (at different points in the vasculature with respect to the heart and lungs) is understood. In some embodiments, level of Hb can be

measured using the apparatus, systems, and methods taught in the section above entitled "HEMOGLOBIN/OXYGEN MONITORING."

Another parameter that can be monitored in ICUs is lactate level, which can be related to sepsis or toxic shock. Indeed, high levels and/or rapid rise in lactate levels can be correlated to organ failure and oxygenation problems in the blood and organs. However, other direct measures of the biological effects related to lactate level problems can be difficult to measure, only becoming measurable with a delay (e.g., 2-6 hours later). Thus, measurement of lactate level can help provide a valuable early warning of other medical problems. Indeed, if a problem with lactate levels is detected, a nurse or doctor may be able to prevent the correlated problems by providing more fluids.

Another parameter that can be monitored in ICUs is central venous oxygen saturation ($ScvO_2$). It can be advantageous to try to maintain an $ScvO_2$ of 65-70% or greater in ICU patients (to help avoid sepsis, for example). In some embodiments, level of $ScvO_2$ can be measured using the apparatus, systems, and methods taught in the section above entitled "HEMOGLOBIN/OXYGEN MONITORING."

Levels of lactate and $ScvO_2$ in a patient can be used together to provide information and/or warnings to a health care provider, which can be especially useful in an ICU setting. For example, if lactate is high and $ScvO_2$ are both high, a warning can be provided (e.g., automatically using an alarm). If lactate is high, but $ScvO_2$ is low, a patient may benefit from additional fluids. If $ScvO_2$ is high, but lactate is low, a cardiac problem may be indicated. Thus, a system that provides information about both lactate and $ScvO_2$ can be very beneficial in the ICU environment.

Although the systems and methods disclosed herein have been described in terms of examples for determining physiological parameters relating to a patient's cardiovascular system, the examples are intended to be illustrative and not to limit the scope of the disclosure. In other embodiments, the systems and methods may be used to determine physiological parameters relating to, for example, a patient's respiratory, urinary, nervous, gastrointestinal, and/or endocrine systems. Additionally, although the example embodiments have been described in terms of an analyte detection system and a pulse oximeter, in other embodiments, measurements from different instruments, monitors, devices, and so forth may be combined according to the inventive principles described herein.

Reference throughout this specification to "some embodiments" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least some embodiments. Thus, appearances of the phrases "in some embodiments" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment and may refer to one or more of the same or different embodiments. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to one of ordinary skill in the art from this disclosure, in one or more embodiments.

As used in this application, the terms "comprising," "including," "having," and the like are synonymous and are used inclusively, in an open-ended fashion, and do not exclude additional elements, features, acts, operations, and so forth. Also, the term "or" is used in its inclusive sense (and not in its exclusive sense) so that when used, for example, to connect a list of elements, the term "or" means one, some, or all of the elements in the list.

Similarly, it should be appreciated that in the above description of embodiments, various features are sometimes

grouped together in a single embodiment, figure, or description thereof for the purpose of streamlining the disclosure and aiding in the understanding of one or more of the various inventive aspects. This method of disclosure, however, is not to be interpreted as reflecting an intention that any claim require more features than are expressly recited in that claim. Rather, inventive aspects lie in a combination of fewer than all features of any single foregoing disclosed embodiment.

Embodiments of the disclosed systems and methods may be used and/or implemented with local and/or remote devices, components, and/or modules. The term "remote" may include devices, components, and/or modules not stored locally, for example, not accessible via a local bus. Thus, a remote device may include a device which is physically located in the same room and connected via a device such as a switch or a local area network. In other situations, a remote device may also be located in a separate geographic area, such as, for example, in a different location, building, city, country, and so forth.

Methods and processes described herein may be embodied in, and partially or fully automated via, software code modules executed by one or more general and/or special purpose computers. The word "module" refers to logic embodied in hardware and/or firmware, or to a collection of software instructions, possibly having entry and exit points, written in a programming language, such as, for example, C or C++. A software module may be compiled and linked into an executable program, installed in a dynamically linked library, or may be written in an interpreted programming language such as, for example, BASIC, Perl, or Python. It will be appreciated that software modules may be callable from other modules or from themselves, and/or may be invoked in response to detected events or interrupts. Software instructions may be embedded in firmware, such as an erasable programmable read-only memory (EPROM). It will be further appreciated that hardware modules may be comprised of connected logic units, such as gates and flip-flops, and/or may be comprised of programmable units, such as programmable gate arrays, application specific integrated circuits, and/or processors. The modules described herein are preferably implemented as software modules, but may be represented in hardware and/or firmware. Moreover, although in some embodiments a module may be separately compiled, in other embodiments a module may represent a subset of instructions of a separately compiled program, and may not have an interface available to other logical program units.

In certain embodiments, code modules may be implemented and/or stored in any type of computer-readable medium or other computer storage device. In some systems, data (and/or metadata) input to the system, data generated by the system, and/or data used by the system can be stored in any type of computer data repository, such as a relational database and/or flat file system. Any of the systems, methods, and processes described herein may include an interface configured to permit interaction with patients, health care practitioners, administrators, other systems, components, programs, and so forth.

A number of applications, publications, and external documents may be incorporated by reference herein. Any conflict or contradiction between a statement in the body text of this specification and a statement in any of the incorporated documents is to be resolved in favor of the statement in the body text.

Although described in the illustrative context of certain preferred embodiments and examples, it will be understood by those skilled in the art that the disclosure extends beyond the specifically described embodiments to other alternative

embodiments and/or uses and obvious modifications and equivalents. Thus, it is intended that the scope of the disclosure should not be limited by the particular embodiments described above.

What is claimed is:

1. A system for determining a physiological parameter in a patient, the system comprising:

an analyte detection system configured to measure first analyte data in a fluid sample received from a patient by irradiating the fluid sample with electromagnetic radiation having a wavelength in the range between approximately 600 nm and 12 μ m, the analyte detection system further configured to irradiate in the lower near-infrared portion of the range and irradiate separately in the higher, mid-infrared portion of the range;

a medical sensor configured to measure second analyte data in the patient; and

a processor configured to receive the first analyte data and the second analyte data and to determine a physiological parameter based at least in part on the first analyte data and the second analyte data.

2. The system of claim 1, wherein the analyte detection system further comprises a fluid handling system configured to draw the fluid sample from the patient.

3. The system of claim 2, wherein the fluid sample comprises blood.

4. The system of claim 1 wherein the medical sensor comprises a pulse oximeter.

5. The system of claim 1 further comprising a user interface configured to allow input of patient data.

6. The system of claim 5 wherein the patient data includes one or more of a patient's height, weight, age, and gender.

7. The system of claim 1 further comprising a data storage device configured to store at least one of the first analyte data and the second analyte data.

8. The system of claim 7, wherein the processor is configured to determine the physiological parameter based at least in part on information determined from the stored analyte data.

9. The system of claim 8, wherein the processor is configured to use the stored analyte data to provide an estimated analyte value, where the estimation comprises at least one of interpolation, extrapolation, averaging, filtering, and correlation.

10. The system of claim 1 wherein the medical sensor is physically remote from the analyte detection system.

11. The system of claim 1 wherein the processor is configured to receive at least one of the first analyte value and the second analyte value via wireless techniques.

12. The system of claim 1 wherein the processor is configured to receive at least one of the first analyte value and the second analyte value via a network.

13. The system of claim 12, wherein the network comprises a hospital information system.

14. The system of claim 1 wherein the first analyte data comprise a value for venous oxygen saturation and a value for venous hemoglobin concentration, the second analyte data comprise a value for arterial oxygen saturation, and the physiological parameter comprises a cardiovascular parameter.

15. The system of claim 14, wherein the cardiovascular parameter comprises cardiac output.

16. The system of claim 15, wherein the processor is configured to determine the cardiac output based at least in part on the formula:

$$Q=VO_2/(K*Hb*(SaO_2-SvO_2)),$$

where

Q is the cardiac output;

VO2 is a consumption rate of oxygen determined at least in part on patient data received by the processor;

K is a Hufner number relating amount of oxygen carried by saturated hemoglobin;

Hb is the venous hemoglobin concentration;

SvO2 is the venous oxygen saturation; and

SaO2 is the arterial oxygen saturation.

17. The system of claim 1, wherein the medical sensor is configured to measure second analyte data in the patient by irradiating the sample with near-infrared radiation.

18. The system of claim 17, wherein the analyte detection system includes the medical sensor, and the system is configured to measure the first analyte in the mid-infrared range and the medical sensor is configured to measure the second analyte in the near-infrared range.

19. The system of claim 1, wherein one of the near-infrared portion or the mid-infrared portion is used for calibration of the analyte detection system and the other of the near-infrared portion or the mid-infrared portion is used to measure the first analyte data.

20. The system of claim 1, wherein one of the near-infrared portion or the mid-infrared portion is used to detect the arrival of the sample in the analyte detection system.

21. The system of claim 1, wherein one of the near-infrared portion or the mid-infrared portion is used to determine interferences present in the sample.

22. A system for determining a physiological parameter in a patient, the system comprising:

- an analyte detection system configured to measure first analyte data in a fluid sample received from a patient by irradiating the fluid sample by an electromagnetic radiation having wavelength in the range between approximately 600 nm and 12 μm;
- a medical sensor configured to measure second analyte data in the patient; and
- a processor configured to receive the first analyte data and the second analyte data and to determine a physiological

parameter based at least in part on the first analyte data and the second analyte data.

23. A system for determining a physiological parameter in a patient, the system comprising:

- an analyte detection system configured to measure a first analyte in a fluid sample received from a patient by irradiating the fluid sample by an electromagnetic radiation having wavelength in the mid-infrared range and a second analyte by irradiating the fluid sample with electromagnetic radiation having wavelength in the near-infrared range; and
- a processor configured to receive the first analyte data and the second analyte data and to determine a physiological parameter based at least in part on the first analyte data and the second analyte data.

24. The system of claim 23, wherein the analyte detection system comprises a medical sensor configured to measure the second analyte, the medical sensor located remotely from the analyte detection system.

25. The system of claim 23, wherein the analyte detection system further comprises a fluid handling system configured to draw the fluid sample from the patient.

26. The system of claim 25, wherein the fluid handling system comprises:

- a fluid passageway adapted to be connected to the patient; at least one pump configured to withdraw body fluid from the patient; and
- at least one fluid control element configured to isolate the fluid sample from the withdrawn body fluid and direct the sample portion to a sample analysis chamber.

27. The system of claim 25, wherein the fluid handling system is configured to return a portion of the withdrawn body fluid that is not directed toward the sample analysis chamber to the patient.

28. The system of claim 23, wherein the fluid sample includes whole blood or plasma.

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专利名称(译)	使用测量的分析物值确定生理参数的系统和方法		
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摘要(译)

提供了用于确定患者的生理参数的系统和方法。在某些实施例中，系统可包括：分析物检测系统，被配置为测量从患者接收的流体样本中的第一分析物数据；医学传感器，被配置为测量患者中的第二分析物数据；以及处理器，被配置为接收第一分析物数据。第二分析物数据和至少部分地基于第一分析物数据和第二分析物数据确定生理参数。在某些这样的实施例中，医学传感器可以是脉搏血氧计，并且生理参数可以包括心血管参数，包括例如心输出量。

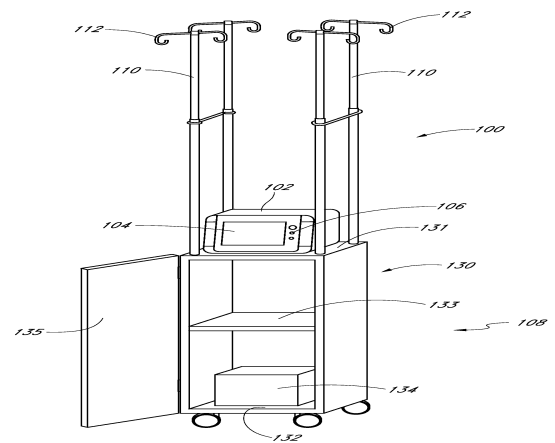


FIG. 1