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(54) Title: SYSTEM FOR DETERMINING AN ESTIMATED ANALYTE VALUE

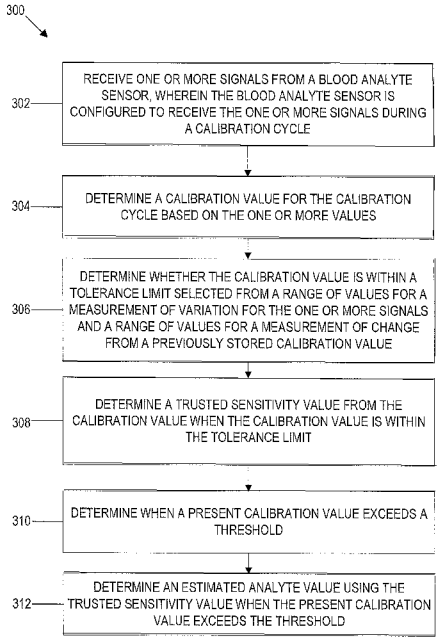


FIG. 12

(57) Abstract: The present disclosure provides a system, computer program product and method for determining an estimated analyte value. The system determines and stores a trusted sensitivity value, determines when a calibration cycle exceeds a threshold level of instability, and uses the trusted sensitivity value to determine the estimated analyte concentration. The system identifies trusted sensitivity values and calibration cycles that exceed the threshold based on evaluation of measurements of variation and measurements of change from previously determined values. In one embodiment, tolerance limits and thresholds are determined for defining a sensitivity value as a trusted value or as coming from a corrupted calibration cycle.

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SYSTEM FOR DETERMINING AN ESTIMATED ANALYTE VALUE

Technical Field

[0001] This invention relates to intravascular blood analyte sensor systems and, in particular, to a system for determining an estimated analyte value.

BACKGROUND

[0002] Analyte testing in the home is fairly common and involves the use of finger stick glucometers that return blood glucose levels on an intermittent basis throughout a day. For patients in a hospital setting, however, these intermittent tests are not frequent enough to capture a patient's (usually) more dynamically changing condition. Patients in critical care settings can experience especially high fluctuations in blood analytes such as glucose. Tracking such changes is better accomplished by more frequent sampling and reporting of analyte levels. To this end, companies have recently been developing continuous glucose monitoring systems for the hospital.

[0003] In continuous analyte monitoring the same sensor is repeatedly called upon over a series of hours or days to report sensed analyte parameters. During this time, it's advantageous to ensure that the sensor is correctly calibrated by using it to sense a calibration fluid with a known concentration of the analyte of interest, such as glucose. For example, a sensor system employed by Edwards Lifesciences, Corporation (Irvine, CA) uses a glucose-oxidase sensor mounted in a catheter tube to sense patient glucose levels continuously for up to 72 hours. This analyte sensor is cycled through sample sensing and calibration cycles in alternation to ensure high accuracy.

[0004] During the calibration cycle, calibrant fluid is flowed through tubing by a flow control device over the sensor and the sensor reading is adjusted to match the known concentration of calibrant fluid. The calibrant fluid originates from a bag filled with standard 0.9% NaCl saline, dextrose and potentially containing an anti-coagulant such as heparin. This calibrant fluid is created by taking a standard saline bag of known volume (or weight) and mixing in a known volume (or weight) of dextrose.

[0005] During sensing cycles, a vacuum pressure is generated in the catheter tube which draws blood from the patient's vasculature through the distal tip of the catheter. In the Edwards sensor system, the catheter (e.g., a JELCO 20Ga x 1.25 inch) holds the glucose sensor at its distal tip and therefore only requires approximately a small (e.g., 40-200μL) draw for enough blood to bathe the sensor and allow sensing of the glucose concentration. Typically, this catheter is inserted over a needle.

[0006] Calibration cycles may be corrupted when the patient moves or the pressure, externally or internally, changes in the system. When this occurs, blood may move up to the sensor during the calibration cycle, thus corrupting the cycle and resulting in inaccurate estimated glucose measurements.

SUMMARY

[0007] The present disclosure overcomes the problems of the prior art by providing a blood parameter sensing system that includes a sensor, a blood access system, a flow controller and a system for determining an estimated analyte value. The system is configured to identify a trusted sensitivity value based on measurements of stability and to determine an estimated analyte value using the trusted sensitivity value when the present calibration measurement exceeds a threshold and is hence determined to be corrupted.

[0008] In an aspect, the system determines an estimated analyte value using a trusted sensitivity value. The system may include a blood analyte sensor; a memory; a processor; and a computing module, stored in the memory, executable by the processor, and configured to cause the processor to: receive the one or more signals from the blood analyte sensor during the calibration cycle; determine a calibration value for the calibration cycle based on the one or more signals; determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value; determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit; determine when a present calibration value exceeds a threshold; and determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

[0009] In some embodiments, the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle. The range of values for the measurement of variation may be selected from a maximum standard deviation and a maximum coefficient of variation. The range of values for the measurement of change may be selected from a percentage change from a previously determined trusted value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored. In some embodiments, the threshold is selected from a minimum or a maximum sensitivity value determined based on the present calibration value. In further embodiments, the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value.

[0010] In a further aspect, a computer program product for determining an estimated analyte value is provided. The computer program product includes a non-transitory computer-readable medium comprising a set of codes for causing a computer to: receive one or more signals from a blood analyte sensor, wherein the blood analyte sensor is configured to receive the one or more signals during a calibration cycle; determine a calibration value for the calibration cycle based on the one or more signals; determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value; determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit; determine when a present calibration value exceeds a threshold; and determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

[0011] In an embodiment, the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle. The range of values for the measurement of variation may be selected from a maximum standard deviation and a maximum coefficient of variation. The range of values for the measurement of change may be selected from a percentage change from a previously determined trusted

value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored. In some embodiments, the threshold is selected from a minimum or a maximum sensitivity value determined based on the present calibration value. In further embodiments, the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value. In yet further embodiments, more than one tolerance limit must be met before the trusted sensitivity value is determined from the calibration value.

[0012] In a still further aspect, a method for determining an estimated analyte value is provided. The method includes providing a blood analyte sensor configured to receive one or more signals during a calibration cycle; and providing a processor for executing computer program code stored in a non-transitory computer-readable medium to cause the processor to: receive the one or more signals from the blood analyte sensor during the calibration cycle; determine a calibration value for the calibration cycle based on the one or more signals; determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value; determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit; determine when a present calibration value exceeds a threshold; and determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

[0013] In some embodiments, the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle. The range of values for the measurement of variation may be selected from a maximum standard deviation and a maximum coefficient of variation. The range of values for the measurement of change may be selected from a percentage change from a previously determined trusted value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored. In an embodiment, the threshold is selected from a minimum or a maximum sensitivity value determined based on

the present calibration value. In a further embodiment, the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value. In a still further embodiment, more than one tolerance level must be met before the trusted sensitivity value is determined from the calibration value.

[0014] These and other features and advantages of the present disclosure will become more readily apparent to those skilled in the art upon consideration of the following detailed description and accompanying drawings, which describe both the preferred and alternative embodiments of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is a perspective view of an analyte sensing system of one embodiment of the present disclosure;

[0016] FIG. 2 is a cross-sectional view of components, including a sampling line, of a flow control system of the analyte sensing system shown in FIG. 1;

[0017] FIG. 3 is an enlarged view of an adapter of the components shown in FIG. 2;

[0018] FIG. 4 is a perspective view of the components, including a sampling line, shown in FIG. 2;

[0019] FIG. 5 is a schematic of a rotary pinch valve of a flow control system of another embodiment of the present disclosure;

[0020] FIG. 6 is a perspective view of a catheter for combination with a sampling line of another embodiment of the present disclosure;

[0021] FIG. 7 is a graphical depiction of a flow profile of an embodiment of the present disclosure;

[0022] FIG. 8 is a line graph of another embodiment of the present disclosure showing sensor current over time through alternating calibration and blood sampling cycles;

[0023] FIG. 9 is an enlarged view of a portion of the line graph of FIG. 8 showing, in another embodiment, a linear regression of the calibration sensitivity;

[0024] FIG. 10 is a line graph of another embodiment of the present disclosure showing post-blood sampling calibration to compress drift error;

[0025] FIG. 11 is a flowchart of a flush-and-draw cycle according to an embodiment of the present disclosure;

[0026] FIG. 12 is a flowchart of a system for determining an estimated analyte value according to an embodiment of the present disclosure;

[0027] FIG. 13 is an exemplary set of graphs depicting experimental results comparing a coefficient of variation for signals received during a calibration cycle and an estimated glucose value calculated using a sensitivity value determined based on the signals;

[0028] FIG. 14 is an exemplary graph of error versus reference glucose indicating the number of dropped points when the estimated glucose value is determined based on sensitivity values calculated from corrupted calibration cycles;

[0029] FIG. 15 is an exemplary graph of error versus reference glucose indicating the number of dropped points when the system uses trusted sensitivity values to determine the estimated glucose values instead of sensitivity values determined from corrupted calibration cycles;

[0030] FIG. 16 is a block diagram of a blood parameter sensing computer system of another embodiment of the present disclosure; and

[0031] FIG. 17 is exemplary MATLAB code for implementing some of the functionality for determining an estimated analyte value according to an embodiment of the disclosure.

DETAILED DESCRIPTION

[0032] The present disclosure now will be described more fully hereinafter with reference to specific embodiments. Indeed, the present disclosure can be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. As used in the specification, and in the appended claims, the singular forms "a", "an", "the", include plural referents unless the context clearly dictates otherwise. The term "comprising" and variations thereof as used herein is used synonymously with the term "including" and variations thereof and are open, non-limiting terms.

[0033] Embodiments of the present disclosure include a blood analyte sensing system 10 that includes a monitor 12, a sensor assembly 14, a calibrant solution source 16 and a flow control system 18, as shown in Figure 1. Notably, the present disclosure could also be employed with other analyte or blood parameter sensing systems that require drawing of blood or fluid samples from a patient. Blood, as used herein, should be construed broadly to include any body fluid with a tendency to occlude lumens of various body-access devices during sampling. The flow control system 18 includes a flow controller 20, a monitor line 22, a sensor casing 24, an adapter 26, a sampling tube assembly 28 and at least one electrode 40, as shown in FIGs. 1, 2 4, and 5. Generally, the flow control system 18 of one embodiment of the present disclosure is configured to mediate flow of small volumes of the calibrant solution over the sensor assembly 14 and withdraw small volumes of samples of the blood from the patient for testing by the sensor assembly.

[0034] The flow control system 18 in another embodiment is able to support the flush and draw pressures and volumes, and the high number of sampling cycles over a long multi-day indwell, needed for continuous analyte (glucose) monitoring, while avoiding the formation of thrombi that occur in conventional catheters by providing a small-diameter, smooth and relatively void free surface defining a lumen extending up to the sensor assembly 14. In another embodiment, the sampling tube assembly 28 of the flow control system 18 may be employed with a range of existing catheter configurations by having the sampling tube assembly 28 sized and configured for insertion into a lumen of an existing catheter. In still other embodiments of the present disclosure, thrombus formation is inhibited by balancing the structure of various components of the flow control system 18 and operation of the flush and draw cycles by the flow controller 20.

[0035] The monitor 12 is connected in communication with the sensor assembly 14 through communication lines 36, which may be wires, and to the flow control system 18 through communication lines or wires 38, as shown in Figure 1. In a further embodiment, the monitor and the flow controller are integrated together. The communication lines 36, 38 could also represent wireless data communication such as cellular, RF, infrared or blue-tooth communication. Regardless, the monitor 12 includes some combination of hardware, software and/or firmware configured to record and display data reported by the sensor

assembly 14. For example, the monitor may include processing and electronic storage for tracking and reporting blood glucose levels. In addition, the monitor 12 may be configured for automated control of various operations of other aspects of the sensing system 10. For example, the monitor 12 may be configured to operate the flow control system 18 to flush the sensor assembly 14 with calibration solution from calibrant solution source 16 and/or to draw samples of blood for testing by the sensor assembly. Also, the monitor 12 can be configured to calibrate the sensor assembly 14 based on the flush cycle.

[0036] Referring to Figures 2 and 3, the sensor assembly 14 includes a wire electrode sensor 40 that includes, for example, a glucose-oxidase coated platinum wire covered by a membrane that selectively allows permeation of glucose. In an embodiment, the wire electrode sensor 40 resides within the sampling tube 90. The glucose-oxidase responds to the glucose by generating hydrogen peroxide which, in turn, generates an electrical signal in the platinum wire. The platinum wire is connected to a board 42, which may be puck-shaped, held in a housing 44 of the sensor assembly 14. The board 42 may include some processing component and/or just communicate the signal up through the communication lines 36 attached thereto for further processing by the monitor 12. The sensor assembly 14 may also include counter and/or reference wire electrodes bundled with the working electrode. Regardless, in the illustrated embodiment, the wire electrode sensor 40 is adapted to extend through and into the sensor casing 24 so as to be within the flow path of the blood sample, as will be described in more detail herein below. Notably, sensors for other types of blood (and biological) parameters, such as pH, pCO2, pO2, K+, Na+, Ca++, lactate and haematocrit, with drift or run-in periods may also benefit from embodiments of the present disclosure.

[0037] It should be noted that, although particularly advantageous for sensors 40 directly within the flow path of the blood sample, the particular configuration of the sensor assembly 14 that puts it within the flow of the blood and/or calibrant path may vary and still be within the scope of the present disclosure. For example, the sensor 40 could be a microfluidics sensor that is adjacent to, and routed off of, a portion of the flow control system 18 within the reach of a blood volume draw. Also, the sensor 40 could be an optical or vibrational sensor that senses blood parameters without contact with the blood sample,

such as through a vibrationally or optically transparent adjacent portion of the flow control system.

[0038] The calibrant solution source 16 is supplied, in one embodiment, from a bag 32 mounted on a pole 34. The calibrant solution supply is preferably off-the-shelf and/or not inconvenient to employ in a hospital setting and is also beneficial to the patient and includes attributes that help with function of the sensing system 10. For example, the solution in the bag may be a Plasmalyte or conventional saline with selected amounts of buffers and anti-thrombogenic compounds, such as heparin, that help with flushing the sensor assembly 14 to keep it clear of clots and thrombosis. The solution in the bag 32 may also include various nutrients to keep fluid and nutrition at appropriate levels for the patient. Although the illustrated embodiment employs a fluid bag 32, it should be noted that the calibrant solution source 16 could include several sources, including several sources at one time, and have varying compositions. For example, a pressurized canister or a reservoir may be employed.

[0039] As shown in Figure 1, the monitor line 22 of an embodiment of the flow control system 18 extends from the calibrant solution source 16 through the flow controller 20 and attaches to the rest of the flow control system 18 (sensor casing 24, adapter 26 and sampling tube assembly 28 within catheter) closer to the sensor assembly 14. Preferably, the monitoring line is a 10 foot length of PVC extension tubing with a .060 inch internal diameter.

[0040] The flow controller 20 in one embodiment of the present disclosure includes some type of hardware, software, firmware or combination thereof that electromechanically controls one or more valves, or other mechanical flow control devices, to selectively allow or stop flow through the monitor line 22. In the illustrated embodiment of Figure 5, the mechanical aspect of the flow controller 20 includes a rotary pinch valve through which extends the monitor line 22. This rotary pinch valve pinches the fluid line to stop flow and, by sliding along a short length of the fluid line, can advance or retract the calibrant solution or retract the calibrant solution supply in a column extending down to the end of the catheter. Different numbers of roller heads may be used, such as two, three, of four heads,

the latter aiding with higher draw volumes. Other configurations, such as a piston-type flow controller, could accomplish the same task.

[0041] Notably, the flow controller 20 of the illustrated embodiment employs a combination of the head (primarily, except for the short draw and infusion by pinch point advancement) generated by the elevation of the fluid bag 32 on the pole 34 and the on-off regulation of the flow induced by the head. The flow controller 20, however, could also include a combination of an actual powered pump and its programmable controller, so as to eliminate the need for the pole 34. This pump could be combined with the aforementioned calibrant solution source 16. One advantage, however, of the illustrated embodiment is that the gravity feed of the fluid bag 32 on the pole 34 is well-understood and mediated to control the amount of fluid administered to the patient. Use of active pumps should be controlled in some manner to avoid administration of excess fluid and its side-effects. Regardless, the role of the flow controller 20 can be met flexibly with various combinations of technology and the present disclosure shouldn't necessarily considered limited to any one particular configuration.

[0042] When the flow controller 20 opens its pinch valve, solution from the bag 32 is gravity fed down through the monitor line 22, the sensor casing 24, the adapter 26, the sampling tube assembly 28 and (if used) the catheter and into the patient's vasculature. Or, the flow controller 20 could advance the pinch valve in the direction of the catheter and drive the solution to flush the sensor 40 and out through the catheter. If the solution from the bag 32 includes heparin or other anti-thrombogenic agent and/or some anti-thrombogenic mechanical qualities, this flush step clears the catheter and cleans the sensor 40.

[0043] In a draw step, the pinch valve is reversed by the flow controller 20 forming a vacuum and drawing a blood sample up into the catheter from the patient's vasculature. The glucose sensor, during or after this step, can then be activated to sense the glucose concentration in the blood sample. After sufficient time has elapsed to take one or more analyte measurements, the flush cycle is then run, typically in 5 to 10 minute cycles, as described above. This process of flush-and-draw is repeated over the life of the sensing system 10, or at least the life of the glucose sensor. The description above is a more general

overview of the flush/draw process. Variations in the specifics of the flush and draw cycles and how they're adapted to work with the present system to avoid thrombosis, minimize flush and draw volumes and work with existing catheter configurations will be described in more detail below.

[0044] In an embodiment of the present disclosure, the flow profile preferably lasts for 5 to 7.5 minutes and delivers less than 500 mL of solution from the bag 32 over a 72-hour period. Also, the flow controller 20 preferably has improvements to ensure accuracy and repeatability of its control of fluid flow through the flow control system 18. For example, the above-described rollers may be accompanied by an encoder coupled with a stepper motor that provides redundant control of the roller head orientation. Also, there may be an air detection sensor distal to the roller head assembly that uses optical or ultrasonic sensing (an ultrasonic pulse) to detect gas or liquid conditions in the tube segment.

[0045] As shown in FIG. 2, in one embodiment of the present disclosure, the sensor casing 24 includes a flange 46, which may be threaded, a cylindrical body 48 defining an axial lumen 56 and a female connector 50. The sensor casing 24 preferably has a length sufficient to protect the length (approximately 2 cm in a preferred embodiment) of the wire electrode sensor 40, such as about 4 cm. If the sensor casing 24 is too short, the adapter 26 might also supply some protection.

[0046] The flange 46 is molded on the proximal end of the sensor casing 24 and extends around the cylindrical body 48 as a thin annulus with threads defined around its outer surface. The flange 46 is configured to insert into a luer connector at a distal end of the monitor line 22. Defined within the flange 46 is an annular receptacle 58 (an expansion of the axial lumen 56) configured to receive a male portion of the luer connector. Attachment of the threaded portions of the connector and flange 46 should form a fluid tight communication between the lumen of the monitor line 22 and the sensor casing 24.

[0047] The sensor casing 24 also may include an annular seal which is an elastomeric sealing member that is configured to extend between, and is compressed by attachment of, the male end of the luer connector and the flange 46. Such compression

seals off the junction between the two components and blocks wicking of blood and flush solution between the two components.

[0048] The cylindrical body 48 extends from the flange 46 to the distal end of the sensor casing 24 and ends at the female connector 50. The cylindrical body has an elongate cylindrical shape and supports on its outside surface (and may be integrally constructed with) the housing 44 containing the board 42 through which the wire electrode sensor 40 connects to the communication line 36. The housing 44 has an elliptical or cylindrical shape to fit the "puck" shape of the board 42 and includes a wire mount 54 extending off at about a 30 degree angle with respect to the axis of the sensor casing 24. The wire mount 54 helps to secure the communication lines 36 from detachment from the board 42 and its angle is tailored to having the communication line 36 extend off along and away from the patient and may allow the communication line to be taped to the patient's arm or bedside against being pulled free.

[0049] The axial lumen 56, as shown in the embodiment of FIGs. 2-4, has a cylindrical shape with a constant diameter extending down to the distal end of the cylindrical body 48. Optionally, the cylindrical body may also include a sleeve portion that extends around the axial lumen 56 and has smooth and thrombo-resistant properties that are improved with respect to the rest of the sensor casing 24. For example, the sleeve may be a portion of polyurethane or nylon tubing that is press fit into the sensor casing 24 after it is formed.

[0050] The cylindrical body 48 also defines a port 60 through which the wire electrode sensor 40 extends into the axial lumen 56 for exposure to the blood samples drawn therethrough by the flow control system 18. The port 60 is preferably sealed in some manner (such as by an elastomeric valve or being embedded in the material of the cylindrical body 48) against leakage of the calibration fluid and the blood samples and, in addition, is selected to smoothly integrate with the surrounding surface of the cylindrical body 48 that defines the axial lumen 56.

[0051] The axial lumen 56 preferably has a diameter that is selected to provide a smooth transition with the lumen of the monitor line 22 and has sufficient space to fit the diameter of the wire electrode sensor 40. Embodiments of the present disclosure with

variations of the diameter of the axial lumen 56 that achieve the objectives of providing for robust blood parameter sensing and minimized draw/flush volumes and thrombosis will be explored more below. However, for the illustrated embodiment, the diameter of the wire electrode sensor 40 is about 0.008 to .010 inch and the inside diameter of the axial lumen 56 is about .030 inch, which matches up for a smooth transition with a .030 inch lumen diameter of the monitor line 22.

[0052] The female connector 50 at the distal end of the sensor casing 24 has a cylindrical shape with an outer cylindrical wall 64 spaced from an inner cylindrical wall 66 to form an annular female receptacle. The outer cylindrical wall 64 can include threads to enable attachment to a threaded proximal end 68 of the adapter 26. The inner cylindrical wall 66 extends within the proximal end 68 of the adapter 26. The positioning of these two walls brackets the threaded proximal end 68 of the adapter 26 for a firm connection between the two. The cylindrical body 72 extends from the threaded proximal end 68 to the distal end of the adapter 26, ending at the threaded distal end 74. The cylindrical body 72 has an elongate cylindrical shape.

[0053] The threaded distal end 74 is fashioned similar to a luer connector with a pair of concentrically positioned, cylindrical outer wall 80 and inner wall 82. The cylindrical outer wall 80 has threads extending around its inside surface that is configured to mate with a threaded proximal end 84 of the sampling tube assembly 28. The cylindrical inner wall 82 projects more distal than the outer wall 80 and is configured to extend into the proximal end 84 of the sampling tube assembly 28.

[0054] The axial lumen 76 defined by the cylindrical body 72 of the adapter 26 is configured to accept a free end of the wire electrode sensor 40. The length of the axial lumen 76 is just slightly longer, such as within .05 mm to 2 mm (preferably about 1 mm) the length of the wire electrode sensor 40. In this manner, the axial lumen 76 is configured to accept and allow extension nearly to its end the remaining length of the wire electrode sensor 40. The annular seal is an annular elastomeric tube with a flange that is configured to fit within an expanded proximal end of the axial lumen 76 so as to seal against any leakage between the mating of the sensor casing 24 and the adapter 26.

[0055] Alternatively, the entire length of the axial lumen may be defined by a length of separately manufactured tubing press fit into the remainder of the adapter 26 which is formed as a molded part. This has the advantage of avoiding the difficulties of ensuring tight tolerances of the axial lumen 76 within the adapter 26, which may be molded. Ends of the tubing may extend out (e.g., .015 inch) of the surrounding opening within the cylindrical body 72 so as to enable a sealing fit at either of the proximal end 68 or the distal end 74 of the adapter 26 when connected to the sensor casing 24 and sampling tube assembly 28. Exemplary tubing may be .031 inch ID and .093 inch OD tubing with lumen clearance for .015 inch OD sensor wires.

[0056] Similar to the axial lumen 56 of the cylindrical body 48 of the sensor casing 24, the axial lumen diameter can vary within ranges depending upon several factors associated with operation of the flow control system 18. However, for the illustrated embodiment, the diameter of the axial lumen 76 is preferably about 0.30 inch which provides .020 inch clearance around the end of the wire electrode sensor 40 extending therethrough.

[0057] Referring again to Figures 2, 3 and 4, the sampling tube assembly 28 includes the threaded male proximal end 84, a locking cap 86, a sealing member 88, a sampling tube 90 and stress relief member 92. The proximal end 84 has a male shape configured to fit between the walls 80, 82 on the distal end 74 of the adapter 26. It also includes threads that fit the threads of the distal end 74 to secure it thereto in locking engagement. The locking cap 86 at the other, distal end has threads enabling it to fit the male end of a standard luer connector on standard catheters.

[0058] Also helping to secure the sampling tube 90 is the stress relief member 92, which may be a dab of elastomeric adhesive in a frustoconical shape (as shown in Figure 4) which helps to lock the sampling tube to the sealing member 88 and/or the distal end of the locking cap 86 of the sampling tube assembly 28. Or, the stress relief member 92 may be a length of tubing that has a decreasing diameter along its length to help relieve strain on the sampling tube 90.

[0059] The sampling tube 90 in one embodiment is a very small ID tube that has a relatively large OD and is constructed of a material that's mechanically thromboresistant

(and may be combined with heparin or other anti-thrombosis agents) due to its internal shape, smoothness and void-free structure. Without being wed to theory, it is believed that the smaller ID is less prone to clotting or other thrombosis since the pressure profile across the cross-section of the blood is more evenly distributed because the red blood cells and other blood components are a larger percentage of the cross section of the lumen defined therethrough. More even pressure distribution helps to ensure that the blood components do not stop against the side of the lumen walls of the sampling tube 90, cutting down on the tendency to clot. In addition, the smaller ID reduces the size of the flush and draw amounts to minimize side effects on the patient. Less blood in the draw means lower flushing volumes with the heparin in the calibration solution.

[0060] The relatively larger OD of the sampling tube 90 is advantageous in that it provides a good buckling stiffness to enable insertion of the sampling tube 90 directly into the patient (preferably in combination with a needle or other introducer) or into the lumen of an existing catheter without bending or kinking. Still, if such a combination is desired, the OD can be constrained to allow the sampling tube assembly 28 to be combined with existing catheters or introducers. In one embodiment, for example, the sampling line has an outer diameter of .030 inch configured to fit within a range of standard-sized catheter lumens, such as the three-lumen MULTI-MED central venous catheter or an ADVANCED VENOUS ACCESS (AVA) catheter (Edwards Lifesciences, Irvine, CA). Despite the aforementioned preferred configurations and sizes, a balance may be struck between a range factors, flow rates, adaptability to existing catheters, anti-thrombotic attributes and the ID/OD, length and other attributes of the sampling tube 90 to create other embodiments of the present disclosure as will be described more below.

[0061] The advantage of inserting the sampling tube 90 into an existing catheter is that a dedicated line for sampling the analyte or blood parameter is no longer needed. In addition, the sampling tube 90 can reduce the cross-sectional area through which blood is drawn to reduce clotting and sample volume. Further, the sampling tube 90 can serve as a sleeve that covers the gaps, transitions and other voids that are present in conventional catheters.

[0062] Conventional catheters 30, for example the catheter shown in Figure 6, frequently include three parts, a multi-lumen tube 94, a back form 96 and lines 98. The multi-lumen tube 94 inserts into the patient and provides lumens that exit at different points of the multi-lumen tube depending upon the function employed with each lumen. For example, one lumen may be a supply lumen 102 for administering drugs that exits at the distal end of the tube 94, another sensing lumen 104 for communicating with a pressure sensor for determining cardiac output that exits at a midpoint from the side of the tube 94 and a third sampling lumen 106 for sampling blood that exits at a proximal point 108 from the side of the tube 94.

[0063] Each of the lumens within the multi-lumen tube communicates with a dedicated channel defined in the back form. These channels diverge within the back form 96 (which typically has a triangular shape as it extends away from the patient) and each of the channels connects up with a dedicated one of the lines 98. Each time a transition between the components 94, 96, 98 occurs, there are discontinuities, gaps, rough surfaces, material variations and other voids that might promote the occurrence of clotting and other thrombosis and/or require less-desirable flow rates for the long-term, high-count sampling needed for the present disclosure.

[0064] In one embodiment of the present disclosure, the sampling line 28 connects, via the locking cap 86, to a luer lock 100 mounted on the proximal end of one of the lines 98 that communicates through the back form 96 with the sampling lumen 106 of the catheter 30. The sampling tube 90 extends through the line 98 and the back form 96 and partially through the sampling lumen 106, stopping about 1 inch short of the proximal exit point 108. Advantageously, the proximal exit point avoids draw of blood samples diluted or otherwise affected by the operations being performed in the other lumens 102, 104. Also, the sampling tube 90 provides a void-free lumen that bypasses the voids formed by the junctions between the components 94, 96, 98, and the varied internal contours of those components, so as to reduce clotting and the volume of blood draws needed to supply the sensor 40. Stopping short of the proximal exit port 108 avoids extension of the sampling tube 90 out of the exit port and making contact with the patient's vasculature.

[0065] As another alternative, the sampling tube 90 may be of sufficient length to extend out of the exit port 108. This embodiment has the advantage of extending the void-free internal diameter of the sampling tube past any irregularities at the end of the sampling lumen 106.

[0066] As shown in Figure 7, the flow profile of one embodiment of the present disclosure includes a calibration and flush phase of about 276 seconds which includes 3.2 mL/hr for calibration, a flush of 650 mL/hr and trailing rates of 1.9 mL/hr and zero flow for a short time period. In the draw and sample phase, a 3.5 mL/hr draw is used with a zero flow rest period at the end. This is followed by the beginning of the flush phase with a 24 second "clear" flush using a 5mL/hr start and then a ramped-up pre-calibration flush rate of 650 mL/hr.

[0067] In some embodiments, the system 10 may be employed over a 72 hour period and sample blood with 40 to 200 μL volumes in 5 to 10 minute cycles. With a 5 minute target blood glucose cycle and an approximate 90 second time window for draw volume, the maximum draw rate is about 200 mL/hour.

[0068] In another embodiment of the present disclosure, it has been observed by the inventors in time periods shortly (or immediately) after a sensor's calibration or initialization and shortly (or immediately) following a period of unpowered disconnect that the sensor's sensitivity may be changing rapidly. This rapid change reduces the effectiveness of the sensor's sensitivity determined during calibration. Generally, the rate of sensitivity change is proportional to an error generated by the change during the period between calibration and testing.

[0069] As shown in FIG. 8, calibration and sample pairs were taken with high sensitivity sensors using a 7.5 minute profile with a time gap between the calibration (C#) and sample (S#) phases of approximately 2.5 minutes. This data represents the time allowed for a sensor to "run-in", which means the sensor has achieved a nominal level of stability.

[0070] As shown in FIG. 9, the sensitivity change is at a substantial enough rate that the sensitivity calculated during the calibration phase is not representative of the sensitivity during the sample calibration phase. In one embodiment, the present disclosure includes the use of a statistical method to estimate the sensitivity change between the calibration and

sample. For example, a simple linear regression could be applied to the first two (or more) sensitivity calculations (vertical lines associated with C1 and C2) to estimate or interpolate the sensitivity change. Also, a logarithmic interpolation could be used. Further, leading or trailing data points could be used to model the sensitivity trends.

[0071] FIG. 9 shows that, absent such an interpolation, the sensitivity used at C1 has changed by the time the sample S1 is taken. Using the sensitivity from C1, therefore, produces an error in the estimated glucose value returned by the sensor algorithm. Conversely, such error is reduced through use of a statistical estimation of the rate of change of sensitivity as a function of time, and then use of the modified sensitivity to estimate the glucose concentration of the sample. The error reduction has been on the order of 1% to 10% using such techniques.

[0072] In another embodiment of the present disclosure, the drift in the sensor sensitivity can be reduced by shortening the time during which such drift can occur. For example, the time between C1 and S1 can be minimized to decrease the sensitivity change and allow for an improved accuracy of the calculated glucose concentration. The flow profile may be modified to minimize the time by reducing the entire profile length, such as from 7.5 minutes to 5 minutes. Further, the method may modify the order in which sample and calibration measurements are made. As shown in FIG. 10, for example, the sample value is calculated prior to the calibration value, which shortens the delay between sample and calibration to about 1.5 minutes.

[0073] Notably, the data indicated in FIG. 10 was taken with a 0 mg/dL calibration solution. Thus, the sensitivity drift is not readily apparent from the calibration phase, but is apparent from the sampling phase.

[0074] As shown in FIG. 11, other embodiments of the present disclosure may include systems, methods, processes or computer programs for calibrating a blood sensing system and/or operating a blood parameter sensor system. For example, as shown in FIG. 11, one embodiment of the present disclosure includes drawing blood 200 over a blood parameter sensor, receiving a blood signal 202 near the end of the draw, flushing the sensor with calibrant 204, receiving a calibrant signal 206 before the end of the flush and calculating a blood parameter 208 as a function of both the blood signal and the calibrant

signal. It should be understood that the sensor may be flushed with calibrant prior to the system drawing blood over the blood parameter sensor.

[0075] The inventors have also observed that continuous analyte monitoring systems employing "one size fits all" flow profiles may be unable to detect and adapt to flow problems. For example, obstructions, kinking of the blood access device or limited blood flow may create conditions where the flow profile is no longer adequate and sample dilution occurs. In some situations, subject movement causes a transient pressure spike that disrupts the calibration portion of the cycle, resulting in an inaccurate sensitivity measurement. This in turn can cause an inaccurate estimated glucose value. One way of eliminating this failure mode is to simply not display points that display such behavior during calibration. This can cause a large number of points to be dropped, however, depriving the user of estimated glucose data.

[0076] An embodiment of the present disclosure addresses this problem by providing a system and method that receives one or more signals from a blood analyte sensor, wherein the blood analye sensor is configured to receive the one or more signals during a calibration cycle; determines a calibration value for the calibration cycle based on the one or more signals; determines where the calibration cycle is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value; determines a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit; determines when a present calibration value exceeds a threshold; and determines an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold. The system is able to use the trusted sensitivity value to calculate the estimated analyte value, rather than dropping the value calculated using a sensitivity value from a calibration cycle that exceeds a threshold. This system and method results in more estimated analyte values that can be displayed to the user and allows the user to more quickly determine trends in analyte level changes.

[0077] FIG. 12 discloses a flowchart 300 of the system and method for determining an estimated analyte value. In block 302, the system receives one or more signals from a blood analyte sensor, wherein the blood analyte sensor is configured to receive the one or

more signals during a calibration cycle. In an exemplary embodiment, the blood analyte sensor is a glucose sensor. The blood analyte sensor may also be a sensor for other types of blood (and biological) parameters, such as pH, pCO2, pO2, K+, Na+, Ca++, lactate and haematocrit. In some embodiments, the one or more signals are in response to a calibration solution having a known concentration of an analyte, e.g., glucose. For example, a calibration solution may be stored in a calibrant solution source, such as a bag, and transported through the lines from the calibrant solution source and past the sensor. In one embodiment, the calibrant comprises a saline solution such that the calibrant solution can be infused into the patient. In another embodiment, the calibrant solution is moved past or over the sensor but then diverted such that the calibrant solution is reused or not infused into the patient.

[0078] In some embodiments, the blood analyte sensor receives the one or more signals during a calibration cycle. For example, calibration solution may be moved over the analyte sensor for a period of time and the analyte sensor may take multiple sensor measurements during the period of time. In an exemplary embodiment, the system alternates between a calibration cycle and a sampling cycle such that a flow controller draws blood up to analyte sensor for a patient measurement and intermittently flushes calibrant over the analyte sensor to calibrate the analyte sensor. A calibration cycle comprises a flush of calibrant solution. The calibration cycle may be only a portion of the time that the calibrant is flushed over the analyte sensor. In this manner, the calibrant solution is able to wash blood away from the analyte sensor before taking calibration measurements. In an embodiment, the calibration cycle is a predetermined period of time, such as ten seconds, wherein the analyte sensor is receiving the one or more signals as the calibrant solution is being flushed over the analyte sensor. The analyte sensor may be taking measurements and receiving signals during regular or irregular intervals during the calibration cycle, such as every millisecond.

[0079] In block 304, the system determines a calibration value for the calibration cycle based on the one or more signals. In an embodiment, the calibration value is an estimated analyte concentration for the calibration solution being flushed over the analyte

sensor during the calibration cycle. The calibration value may be a transformation or function of the one or more signals received from the analyte sensor.

[0080] Turning now to block 306, the system determines whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value. In an embodiment, the system determines whether the calibration value is within a tolerance limit indicating that the calibration value has an acceptable level of stability. Typically, calibration values for analyte sensors change slowly. If the calibration value changes very quickly, this may indicate that the calibration cycle is corrupted. For example, transient pressure spikes from the patient moving during the calibration cycle can cause instability in the calibration value. The pressure spike may push blood up to the analyte sensor during the calibration cycle, alter the measured analyte concentration, and introduce noise into the one or more signals received from the analyte sensor. Based on the altered analyte concentrations and noise in the measurements, the calibration value would be inaccurate. The inaccurate calibration value would then result in inaccurate determinations of estimated analyte concentration. The tolerance limits may be established such that the calibration value indicates an acceptable level of stability and hence the calibration value can be trusted to provide accurate determines of estimated analyte concentrations.

[0081] In one embodiment, the tolerance limit is defined as a range of values for a measurement of variation for the one or more signals received from the analyte sensor during the calibration cycle. For example, the tolerance limit may be a maximum standard deviation or a maximum coefficient of variation for the signals received during the calibration cycle.

[0082] In another embodiment, the tolerance limit may be a range of values for a measurement of change from a previously stored calibration value. For example, the tolerance limit may be a maximum percentage change from a previous sensitivity value that was within its tolerance limits. In another example, the tolerance limit may be a percentage change from a previous sensitivity value divided by the length of time since the previous sensitivity value was determined.

[0083] In some embodiments, the system determines whether multiple tolerance limits are met. For example, the calibration value may be within a tolerance limit for both the measurement of variation, e.g., a maximum standard deviation, and the measurement of change from a previously stored calibration value, e.g., a maximum percent change. As disclosed herein, the tolerance limits can change based on the most recent trusted sensitivity value.

[0084] If the calibration measurement is within the tolerance limit, then a trusted sensitivity value is determined based on the calibration value, as shown in block 308. In an embodiment, a sensitivity value for the analyte sensor is determined by dividing the measured sensor response by the known calibration solution bag concentration. The sensitivity value can then be used to adjust the analyte sensor response for blood analyte measurements in order to correct for the sensitivity level of the analyte sensor.

[0085] The system may store the trusted sensitivity value in a memory associated with the analyte sensor. In an embodiment, the trusted sensitivity value is replaced when another trusted sensitivity value is determined. In this manner, the most recent trusted sensitivity value is stored. In some embodiments, the trusted sensitivity value is stored a predetermined period of time, such as fifteen minutes or one hour. In an embodiment, the length of time varies based on the stage of the flush-draw cycle. For example, the sensitivity of the analyte sensor may be changing more quickly early in the flush-draw cycle and thus the trusted sensitivity value will be stored for a lower amount of time than when the sensitivity value is changing slowly later in the flush-draw cycle.

[0086] In block 310, the system identifies when a present calibration value exceeds a threshold. In an embodiment, the threshold is a maximum or minimum sensitivity value. Turning briefly to FIG. 17, exemplary MATLAB code for evaluating the current sensitivity value and determining if it is less than a minimum value is provided in lines 11-14. In an embodiment, when the sensitivity value is below the minimum sensitivity value, a low sensitivity error is provided to the user. FIG. 17 also provides exemplary MATLAB code for evaluating the current sensitivity value and determining if it is more than a maximum value in lines 16-19. If the sensitivity value is greater than the maximum value, the system may return a high sensitivity error. In some embodiments, if the sensitivity value is too

high or too low, then the system does not calculate an estimated analyte concentration for the blood sampling cycle associated with the calibration cycle, i.e., does not use a trusted sensitivity value to determine the estimated analyte value. In some embodiments, the system uses the trusted sensitivity value to determine the estimated analyte value for the blood sample if the calibration value exceeds the minimum or maximum threshold.

[0087] In some embodiments, the current calibration value is determined to exceed a threshold if a measurement of variation for the one or more signals received during the calibration cycle exceeds a range of values. The measurement of variation, such as a standard deviation or coefficient of variation, can be determined for the calibration measurements. If the coefficient of variation exceeds the maximum value for the coefficient of variation, then the current calibration cycle will be determined to be corrupted. In some embodiments, if the coefficient of variation exceeds a maximum coefficient of variation (e.g., line 21 in FIG. 17), then the system attempts to use a trusted sensitivity value instead of the sensitivity value determined from the signals that exceed the threshold.

[0088] In some embodiments, the system first determines if the timespan since the trusted sensitivity value was determined exceeds a maximum time span (e.g., line 24 in FIG. 17). If the previous sensitivity value is older than the maximum time span, it may not be used to determine the estimated analyte value and the system will return an error that it is unable to determine the sensitivity (e.g., lines 26-28 in FIG. 17). If, however, the system determines that the trusted sensitivity value is within the acceptable time span for use, then the system will use the trusted sensitivity value instead of the sensitivity value from calibration cycle that exceeds the threshold to determine the estimated analyte value (e.g., lines 29-31 in FIG. 17).

[0089] In some embodiments, the current calibration cycle is determined to exceed a threshold based on a change from a previously recorded value. For example, a sensitivity shift may exceed a maximum sensitivity shift. The sensitivity shift may be a percentage change from the current value to the most recent trusted sensitivity value. In some embodiments, the change is also relative to the amount of time since the most recent trusted value was determined (e.g., line 8 in FIG. 17). In an embodiment, if the change from the

previous trusted value exceeds the maximum change then the system does not use the most recent trusted value to determine an estimated analyte value but instead returns an error that the system is unable to determine the sensitivity (e.g., lines 35-37 in FIG. 17).

[0090] If the current sensitivity value is within the thresholds for the measurements of variation and the change from the previously stored sensitivity value, then the current sensitivity value will be used to determine the estimated analyte value (e.g., lines 41-42 in FIG. 17).

[0091] In some embodiments, the threshold is set at the same level as the tolerance limit. Thus, a calibration value results in a trusted sensitivity value, e.g., is within the tolerance limit, or exceeds a threshold, e.g., is corrupted by potential dilution and therefore will not be used to determine an estimated analyte measurement. In another embodiment, the threshold may differ from the tolerance limit. For example, a sensitivity value determined during a calibration cycle may not be within tolerance limits and therefore the calibration value is not used to determine a trusted sensitivity value but the calibration value may also not exceed the threshold and hence is not discarded. In this embodiment, the calibration value and a sensitivity value determined therefrom may be used for the current analyte measurements but will not be used as a trusted value at a later date or used to determine if a later sensitivity value is a trusted value.

[0092] Turning now to block 312, the system determines an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold. In an embodiment, the system discards the sensitivity value determined when the calibration value exceeds the threshold and uses the most recent trusted sensitivity value stored by the system. By using the most recent trusted sensitivity value, the system is able to decrease the number of dropped data points that would result from using a sensitivity value determined from a corrupted calibration cycle while maintaining system accuracy.

[0093] FIG. 13 depicts an example of a traditional calibration where estimated glucose measurements (EGVs) are calculated using sensitivity values. The analog-to-digital converter (ADC) counts 402 are measurements of the values received from the glucose analyte sensor during the flush and draw cycles. Pressure values 404, coefficient of variation values (CV) 406 determined based on the signals received during the flush and

draw cycles, and glucose values 408 are determined at the same time as the ADC counts 402. The traditional calibration depicts both periods of high stability 410 and low stability 412 during the calibration cycles. Interposed between the calibration cycles are glucose measurements 414. In FIG. 13, the period of high stability 410 has a clean, noise-free calibration as indicated by the ADC count and is associated with a period of low pressure, a low coefficient of variation (CV), and an accurate estimated glucose value (EGV) as compared to a glucose value from a central line (YSI). In contrast, the period of low stability 412 has a large amount of variability as indicated by the ADC count and is associated with higher pressure, a higher coefficient of variation (CV), and an inaccurate estimated glucose value as compared to a glucose value from a central line (YSI). FIG. 13 illustrates the problems associated with using sensitivity values from calibration cycles that exceed a threshold level of instability to calculate estimated glucose values.

[0094] A comparison of FIG. 14 and FIG. 15 indicates that the system disclosed herein will address this problem by using a trusted sensitivity value to calculate estimated glucose values rather than using a sensitivity value from a calibration cycle having a sensitivity value that exceeds the threshold level of instability. The use of trusted sensitivity values will result in fewer dropped estimated glucose values. An estimated glucose value will be dropped if it is determined to be outside a certain level, such as two or three standard deviations from the mean estimated glucose value. In FIG. 14, the X-axis provides the reference glucose value (mg/dL) determined based on the central line. The Y-axis provides the error determined as the difference between the reference value and the glucose value determined from the sensor in the periphery. If the reference value and the value determined in the periphery are equal, then the error would be zero. As the glucose value determined in the periphery changes due to dilution with calibration solution, the error increases. As can be seen in reference number 416 of FIG. 14, 13.8% of all measurements are dropped because they are outliers based on their error measurements.

[0095] In contrast, as shown by reference number 418 in FIG. 15, only 1.4% of measurements are dropped when the system applies a trusted sensitivity value to calculate the estimated glucose value after determining that the calibration cycle exceeds a threshold

level of instability. In this manner, fewer measurements are dropped using the trusted sensitivity values to determine the estimated glucose values.

[0096] As will be appreciated by one skilled in the art, aspects of the present disclosure may be embodied as a system, method or computer program product. Accordingly, aspects of the present disclosure may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, etc.) or an embodiment combining software and hardware aspects that may all generally be referred to herein as a "circuit," "module" or "system." Furthermore, aspects of the present disclosure may take the form of a computer program product embodied in one or more computer readable medium(s) having computer readable program code embodied thereon.

[0097] Any combination of one or more computer readable medium(s) may be utilized. The computer readable medium may be a computer readable signal medium or a computer readable storage medium. A computer readable storage medium may be, for example, but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, or device, or any suitable combination of the foregoing. More specific examples (a non-exhaustive list) of the computer readable storage medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a hard disk, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, a portable compact disc read-only memory (CD-ROM), an optical storage device, a magnetic storage device, or any suitable combination of the foregoing. In the context of this document, a computer readable storage medium may be any tangible medium that can contain, or store a program for use by or in connection with an instruction execution system, apparatus, or device.

[0098] A computer readable signal medium may include a propagated data signal with computer readable program code embodied therein, for example, in baseband or as part of a carrier wave. Such a propagated signal may take any of a variety of forms, including, but not limited to, electro-magnetic, optical, or any suitable combination thereof. A computer readable signal medium may be any computer readable medium that is not a

computer readable storage medium and that can communicate, propagate, or transport a program for use by or in connection with an instruction execution system, apparatus, or device.

[0099] Program code embodied on a computer readable medium may be transmitted using any appropriate medium, including but not limited to wireless, wireline, optical fiber cable, RF, etc., or any suitable combination of the foregoing.

[00100] Computer program code for carrying out operations for aspects of the present disclosure may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the "C" programming language or similar programming languages. The program code may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider).

[00101] Aspects of the present disclosure are described below (and above) with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems) and computer program products according to embodiments of the present disclosure. It will be understood that each block of the flowchart illustrations and/or block diagrams, and combinations of blocks in the flowchart illustrations and/or block diagrams, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

[00102] These computer program instructions may also be stored in a computer readable medium that can direct a computer, other programmable data processing apparatus,

or other devices to function in a particular manner, such that the instructions stored in the computer readable medium produce an article of manufacture including instructions which implement the function/act specified in the flowchart and/or block diagram block or blocks.

[00103] The computer program instructions may also be loaded onto a computer, other programmable data processing apparatus, or other devices to cause a series of operational steps to be performed on the computer, other programmable apparatus or other devices to produce a computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide processes for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

[00104] In an embodiment, the computer program instructions include computer readable program code configured to have functionality to perform the steps disclosed in FIG. 11 and/or FIG. 12. The lines of code provided in FIG. 17 provide an exemplary embodiment of code for MATLAB for providing some of the functionality associated with FIG. 12. The lines of code are labeled by line number for ease of reference.

[00105] Referring now to FIG. 16, a schematic diagram of a central server 500, or similar network entity, configured to implement a blood parameter sensing system, according to one embodiment of the present disclosure, is provided. As used herein, the designation "central" merely serves to describe the common functionality the server provides for multiple clients or other computing devices and does not require or infer any centralized positioning of the server relative to other computing devices. As may be understood from FIG. 16, in this embodiment, the central server 500 may include a processor 510 that communicates with other elements within the central server 500 via a system interface or bus 545. Also included in the central server 500 may be a display device/input device 520 for receiving and displaying data. This display device/input device 520 may be, for example, a keyboard or pointing device that is used in combination with a monitor. The central server 500 may further include memory 505, which may include both read only memory (ROM) 535 and random access memory (RAM) 530. The server's ROM 535 may be used to store a basic input/output system 540 (BIOS), containing the basic routines that help to transfer information across the one or more networks.

[00106] In addition, the central server 500 (such as a combination of the monitor 12 and flow control system 18) may include at least one storage device 515, such as a hard disk drive, a floppy disk drive, a CD Rom drive, or optical disk drive, for storing information on various computer-readable media, such as a hard disk, a removable magnetic disk, or a CD-ROM disk. As will be appreciated by one of ordinary skill in the art, each of these storage devices 515 may be connected to the system bus 545 by an appropriate interface. The storage devices 515 and their associated computer-readable media may provide nonvolatile storage for a central server. It is important to note that the computer-readable media described above could be replaced by any other type of computer-readable media known in the art. Such media include, for example, magnetic cassettes, flash memory cards, digital video disks, and Bernoulli cartridges.

[00107] A number of program modules may be stored by the various storage devices. Such program modules may include an operating system 550 and a plurality of one or more (N) modules 560. The modules 560 may control certain aspects of the operation of the central server 500, with the assistance of the processor 510 and the operating system 550. For example, the modules may perform the functions described above and illustrated by the figures, such as FIGS. 11-12, and other materials disclosed herein.

[00108] The flowchart and block diagrams in the figures illustrate the architecture, functionality, and operation of possible implementations of systems, methods and computer program products according to various embodiments of the present disclosure. In this regard, each block in the flowchart or block diagrams may represent a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that, in some alternative implementations, the functions noted in the block may occur out of the order noted in the figures. For example, two blocks shown in succession may, in fact, be executed substantially concurrently, or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved. It will also be noted that each block of the block diagrams and/or flowchart illustration, and combinations of blocks in the block diagrams and/or flowchart illustration, can be implemented by special purpose hardware-based

systems that perform the specified functions or acts, or combinations of special purpose hardware and computer instructions.

[00109] As is evident from the range of modeled and experimentally verified embodiments described above, the present disclosure is not to be limited to the specific embodiments disclosed. Modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

THAT WHICH IS CLAIMED:

1. A system for determining an estimated analyte value, the system comprising:

a blood analyte sensor configured to receive one or more signals during a calibration cycle;

a memory;

a processor; and

a computing module, stored in the memory, executable by the processor, and configured to cause the processor to:

receive the one or more signals from the blood analyte sensor during the calibration cycle;

determine a calibration value for the calibration cycle based on the one or more signals;

determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value;

determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit;

determine when a present calibration value exceeds a threshold; and

determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

2. The system of claim 1, wherein the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle.

3. The system of claim 1, wherein the range of values for the measurement of variation is selected from a maximum standard deviation and a maximum coefficient of variation.

4. The system of claim 1, wherein the range of values for the measurement of change is selected from a percentage change from a previously determined trusted value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored.

5. The system of claim 1, wherein the threshold is selected from a minimum or a maximum sensitivity value determined based on the present calibration value.

6. The system of claim 1, wherein the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value.

7. A computer program product for determining an estimated analyte value, the computer program product comprising:

a non-transitory computer-readable medium comprising a set of codes for causing a computer to:

receive one or more signals from a blood analyte sensor, wherein the blood analyte sensor is configured to receive the one or more signals during a calibration cycle;

determine a calibration value for the calibration cycle based on the one or more signals;

determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value;

determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit;

determine when a present calibration value exceeds a threshold; and

determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

8. The computer program product of claim 7, wherein the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle.

9. The computer program product of claim 7, wherein the range of values for the measurement of variation is selected from a maximum standard deviation and a maximum coefficient of variation.

10. The computer program product of claim 7, wherein the range of values for the measurement of change is selected from a percentage change from a previously determined trusted value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored.

11. The computer program product of claim 7, wherein the threshold is selected from a minimum or a maximum sensitivity value determined based on the present calibration value.

12. The computer program product of claim 7, wherein the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value.

13. The computer program product of claim 7, wherein more than one tolerance limit must be met before the trusted sensitivity value is determined from the calibration value.

14. A method for determining an estimated analyte value, the method comprising:

providing a blood analyte sensor configured to receive one or more signals during a calibration cycle;

providing a processor for executing computer program code stored in a non-transitory computer-readable medium to cause the processor to:

receive the one or more signals from the blood analyte sensor during the calibration cycle;

determine a calibration value for the calibration cycle based on the one or more signals;

determine whether the calibration value is within a tolerance limit selected from a range of values for a measurement of variation for the one or more signals and a range of values for a measurement of change from a previously stored calibration value;

determine a trusted sensitivity value from the calibration value when the calibration value is within the tolerance limit;

determine when a present calibration value exceeds a threshold; and

determine an estimated analyte value using the trusted sensitivity value when the present calibration value exceeds the threshold.

15. The method of claim 14, wherein the trusted sensitivity value is determined by dividing an analyte concentration determined by the analyte sensor during the calibration cycle by a known analyte concentration of a calibration solution used during the calibration cycle.

16. The method of claim 14, wherein the range of values for the measurement of variation is selected from a maximum standard deviation and a maximum coefficient of variation.

17. The method of claim 14, wherein the range of values for the measurement of change is selected from a percentage change from a previously determined trusted value and a percentage change from a previously trusted value divided by a measurement of time since the previously determined trusted value was stored.

18. The method of claim 14, wherein the threshold is selected from a minimum or a maximum sensitivity value determined based on the present calibration value.

19. The method of claim 14, wherein the threshold is determined based on at least one of a measurement of variation for the one or more signals and a measurement of change from a previously stored calibration value.

20. The method of claim 14, wherein more than one tolerance level must be met before the trusted sensitivity value is determined from the calibration value.

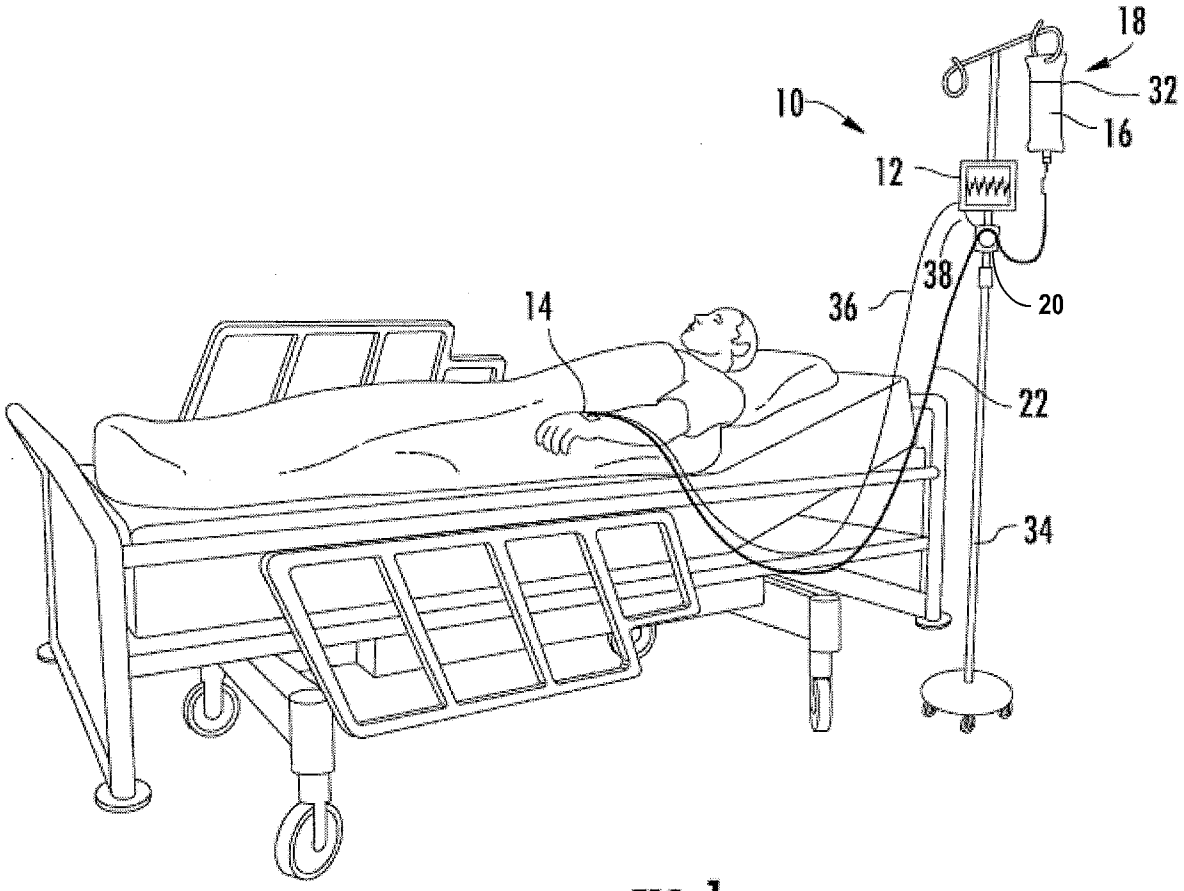


FIG. 1

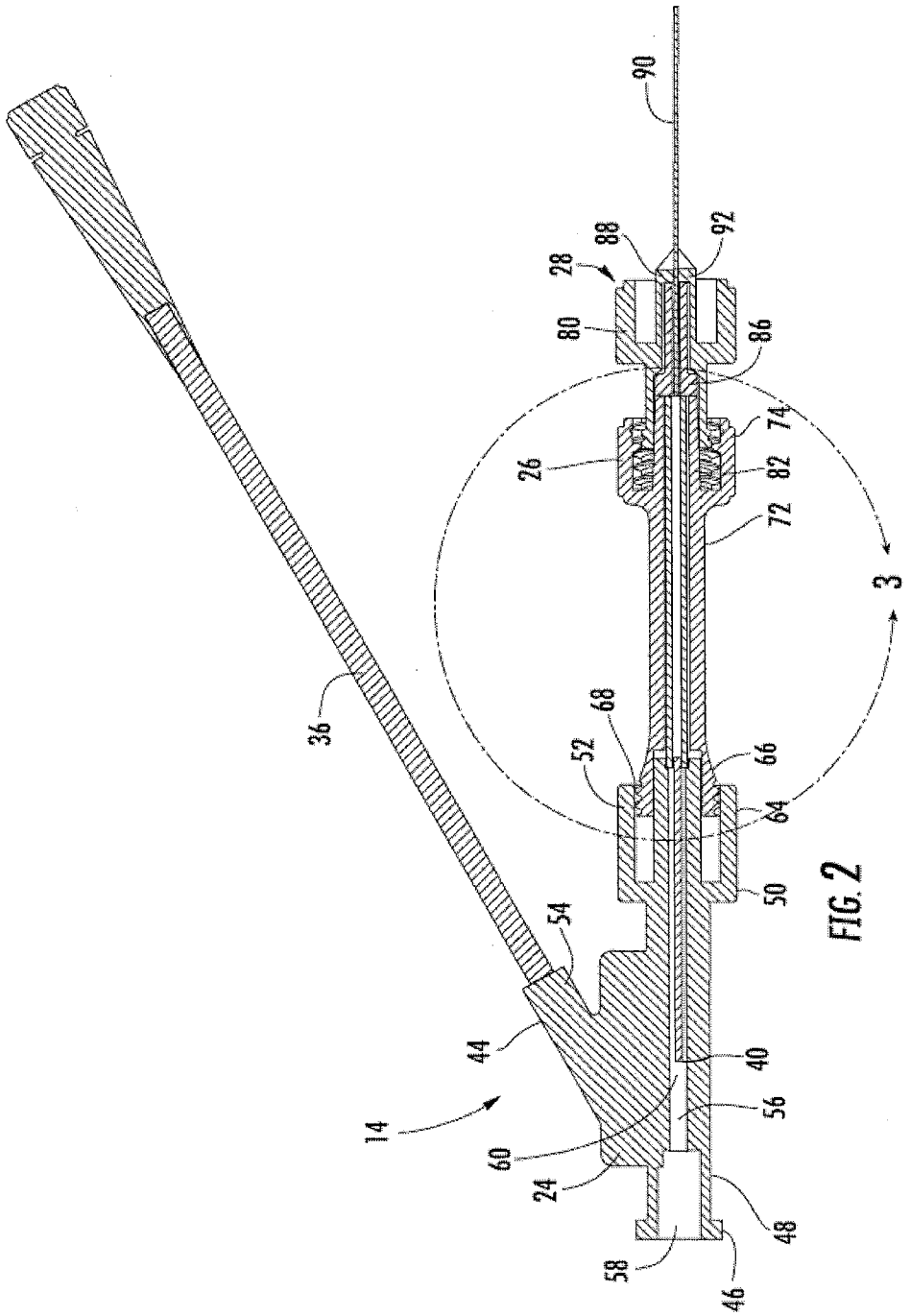

90
88
92
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FIG. 2

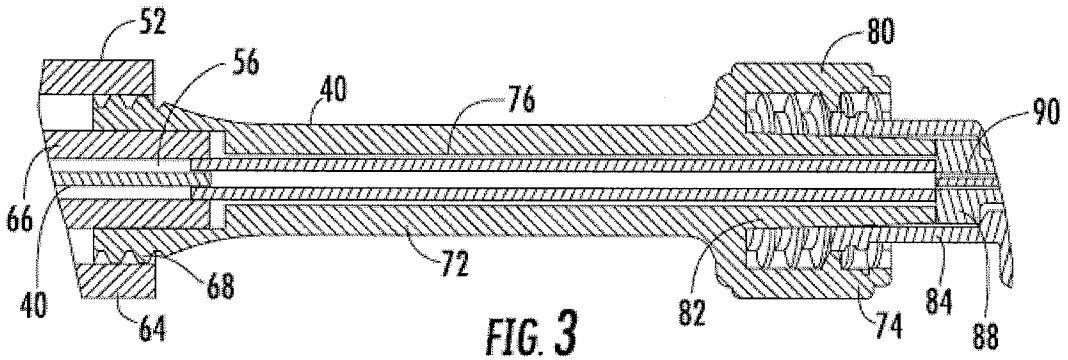


FIG. 3

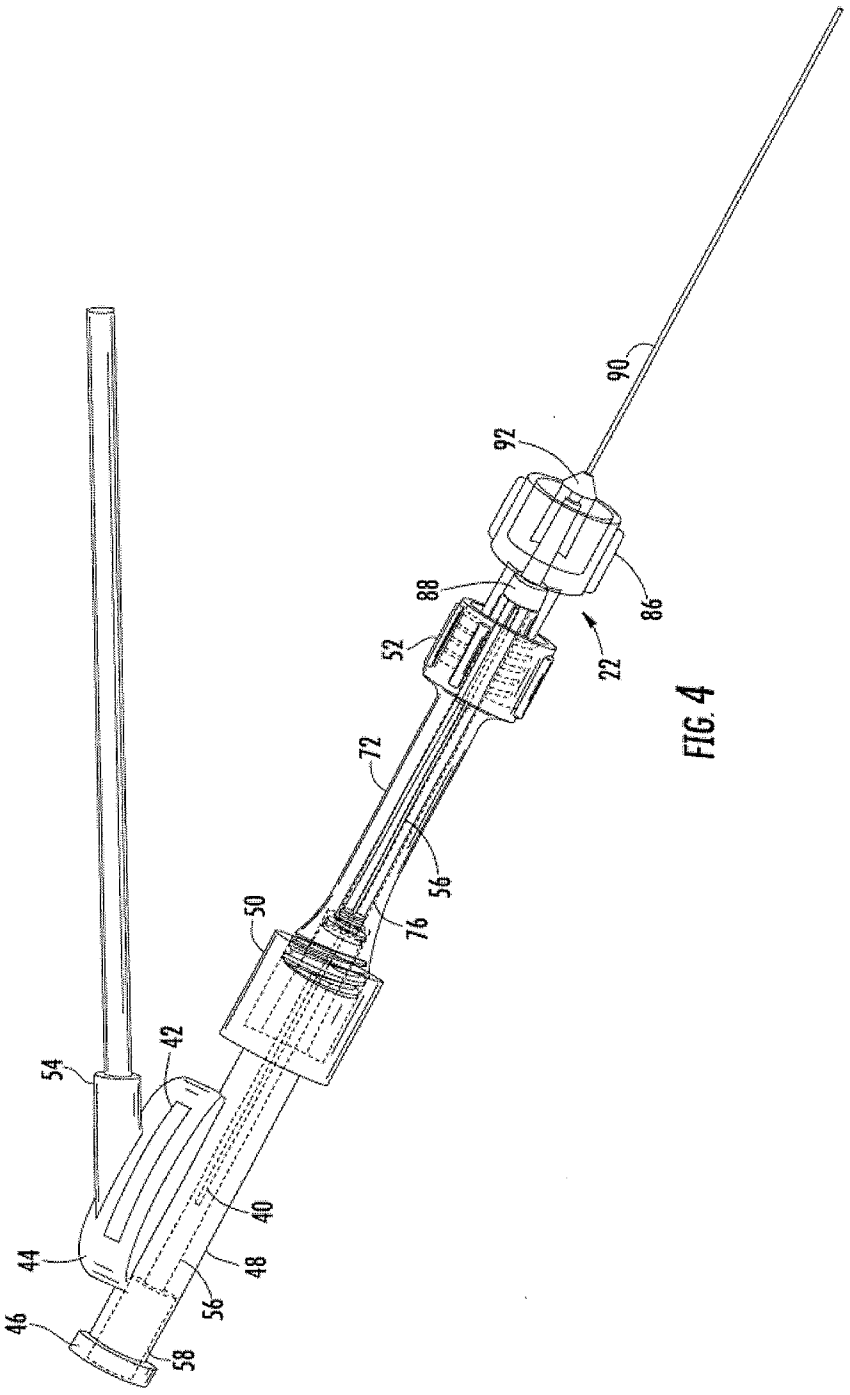


FIG. 4

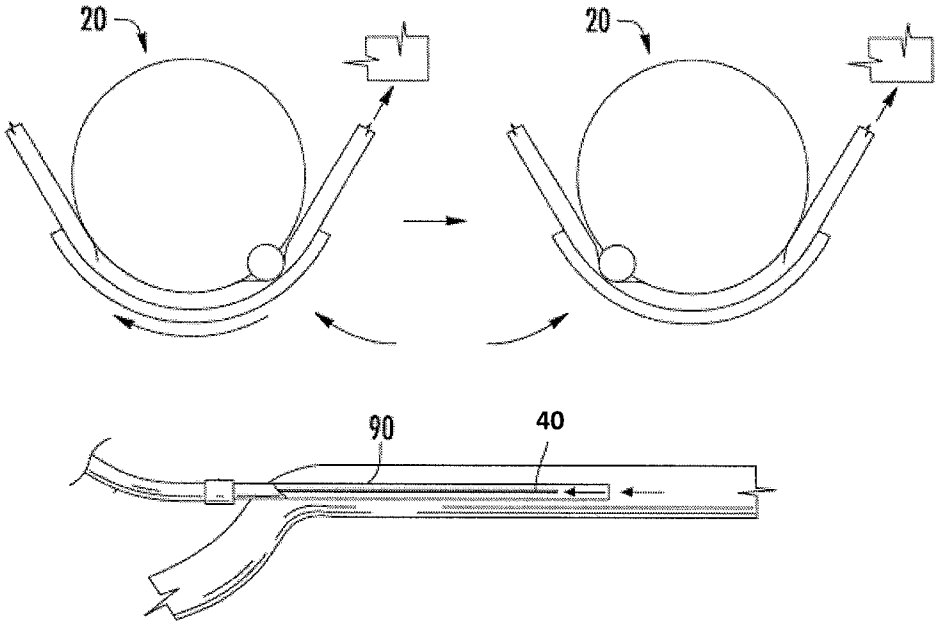


FIG. 5

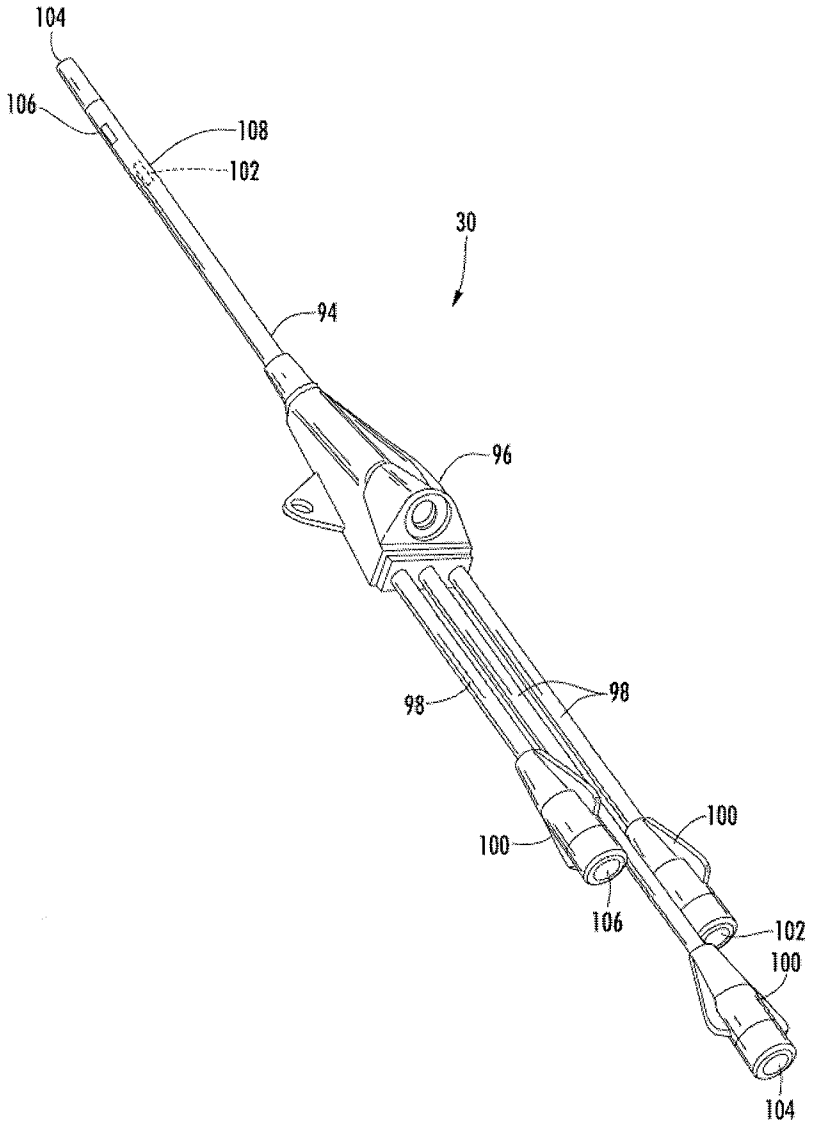


FIG. 6

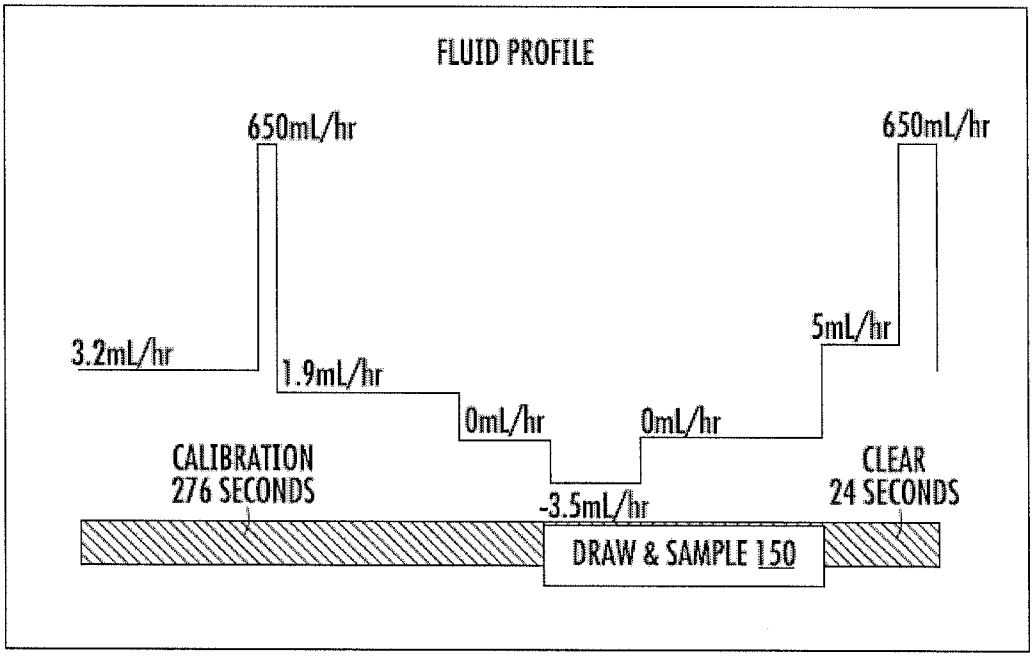

FLUID PROFILE
650mL/hr
650mL/hr
3.2mL/hr
1.9mL/hr
0mL/hr
0mL/hr
5mL/hr
CALIBRATION
276 SECONDS
-3.5mL/hr
CLEAR
24 SECONDS
DRAW & SAMPLE 150

FIG. 7

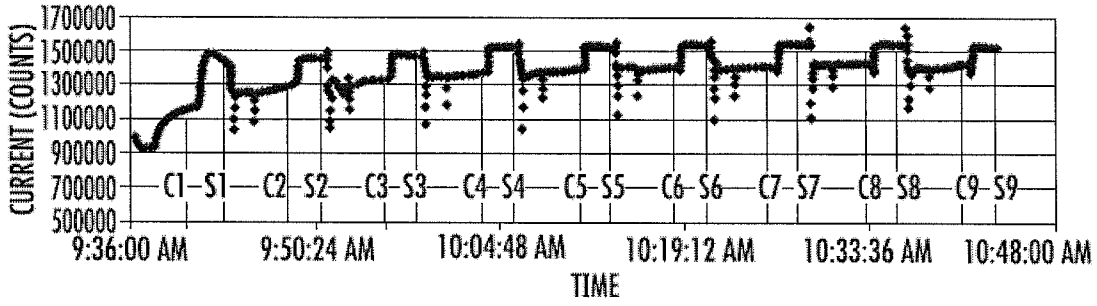


FIG. 8

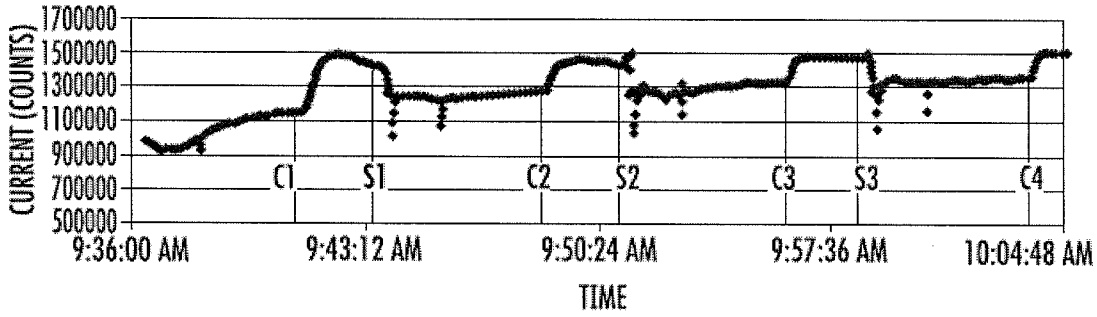


FIG. 9

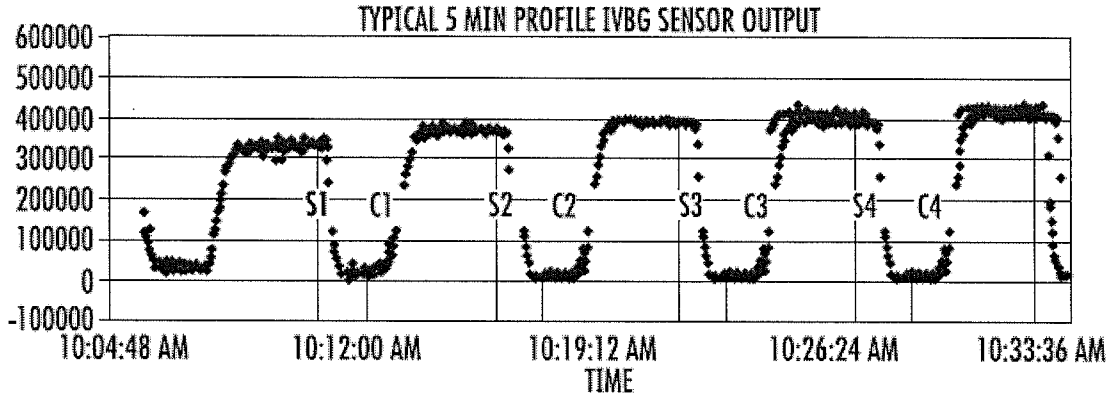


FIG. 10

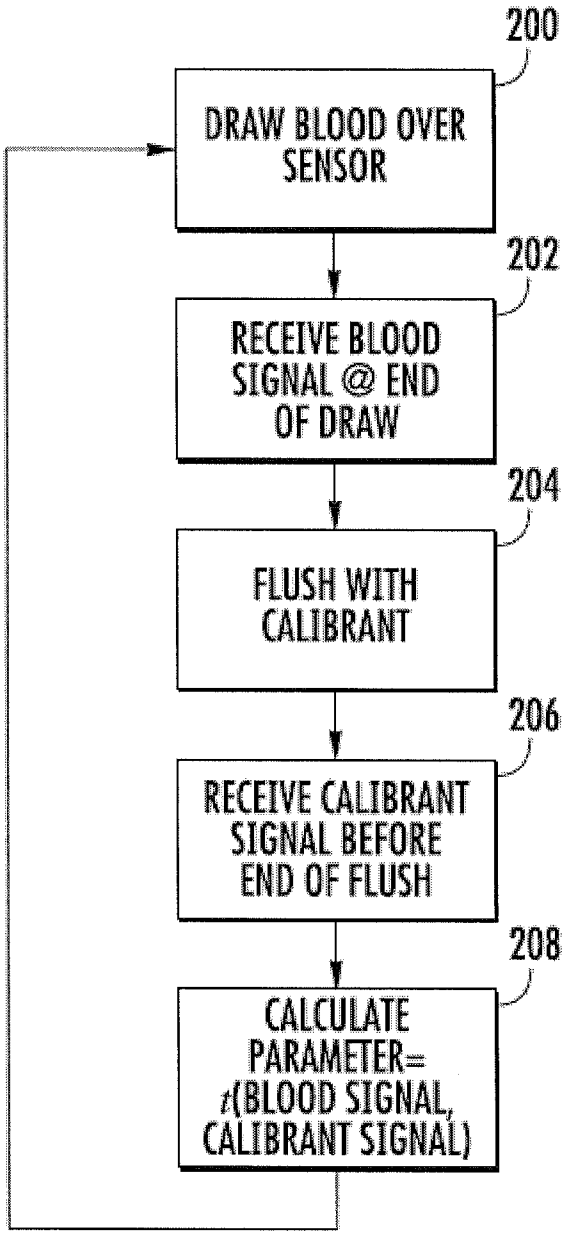

200
DRAW BLOOD OVER SENSOR
202
RECEIVE BLOOD SIGNAL @ END OF DRAW
204
FLUSH WITH CALIBRANT
206
RECEIVE CALIBRANT SIGNAL BEFORE END OF FLUSH
208
CALCULATE PARAMETER= f(BLOOD SIGNAL, CALIBRANT SIGNAL)

FIG. 11

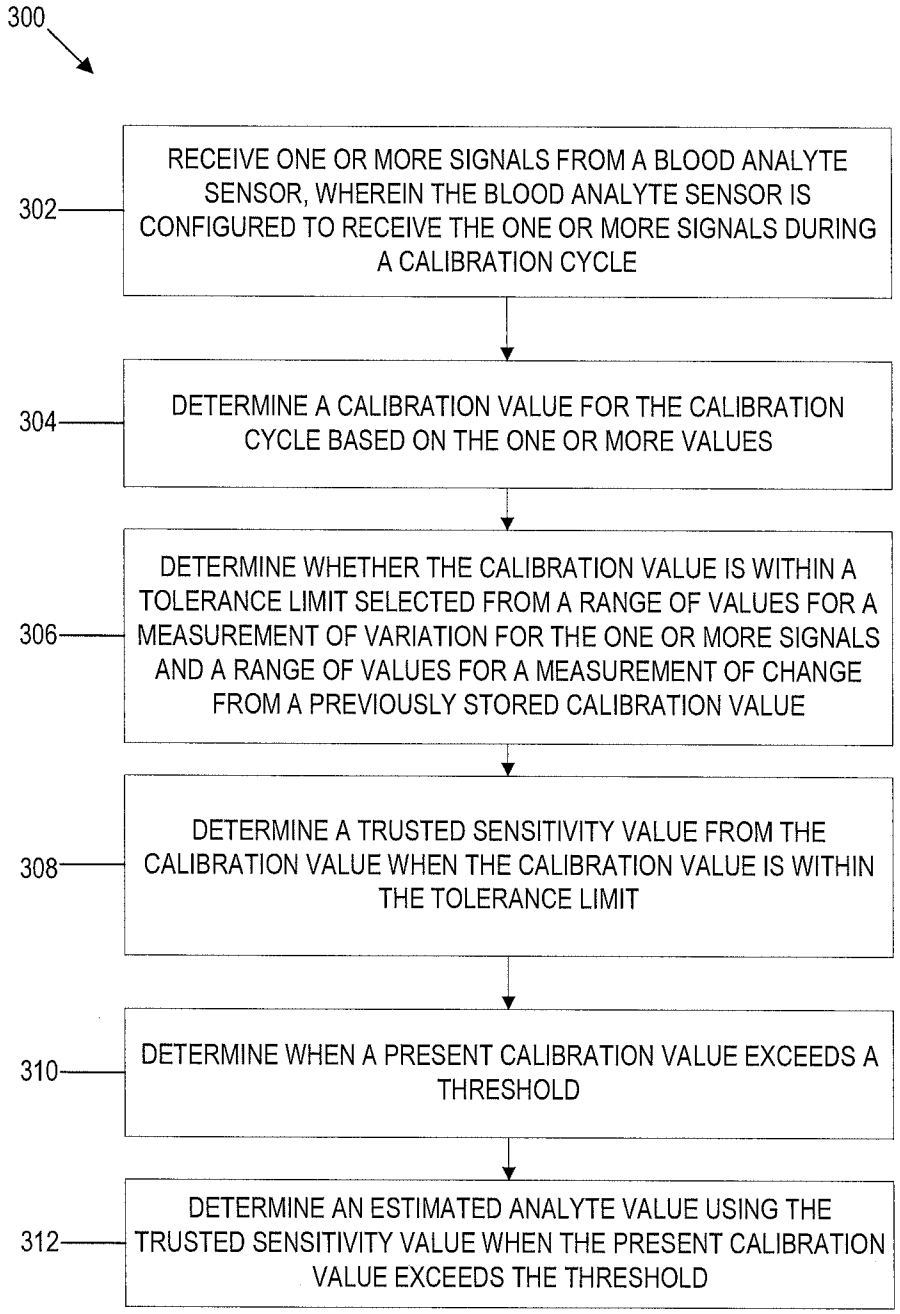

300
302
RECEIVE ONE OR MORE SIGNALS FROM A BLOOD ANALYTE SENSOR, WHEREIN THE BLOOD ANALYTE SENSOR IS CONFIGURED TO RECEIVE THE ONE OR MORE SIGNALS DURING A CALIBRATION CYCLE
304
DETERMINE A CALIBRATION VALUE FOR THE CALIBRATION CYCLE BASED ON THE ONE OR MORE VALUES
306
DETERMINE WHETHER THE CALIBRATION VALUE IS WITHIN A TOLERANCE LIMIT SELECTED FROM A RANGE OF VALUES FOR A MEASUREMENT OF VARIATION FOR THE ONE OR MORE SIGNALS AND A RANGE OF VALUES FOR A MEASUREMENT OF CHANGE FROM A PREVIOUSLY STORED CALIBRATION VALUE
308
DETERMINE A TRUSTED SENSITIVITY VALUE FROM THE CALIBRATION VALUE WHEN THE CALIBRATION VALUE IS WITHIN THE TOLERANCE LIMIT
310
DETERMINE WHEN A PRESENT CALIBRATION VALUE EXCEEDS A THRESHOLD
312
DETERMINE AN ESTIMATED ANALYTE VALUE USING THE TRUSTED SENSITIVITY VALUE WHEN THE PRESENT CALIBRATION VALUE EXCEEDS THE THRESHOLD

FIG. 12

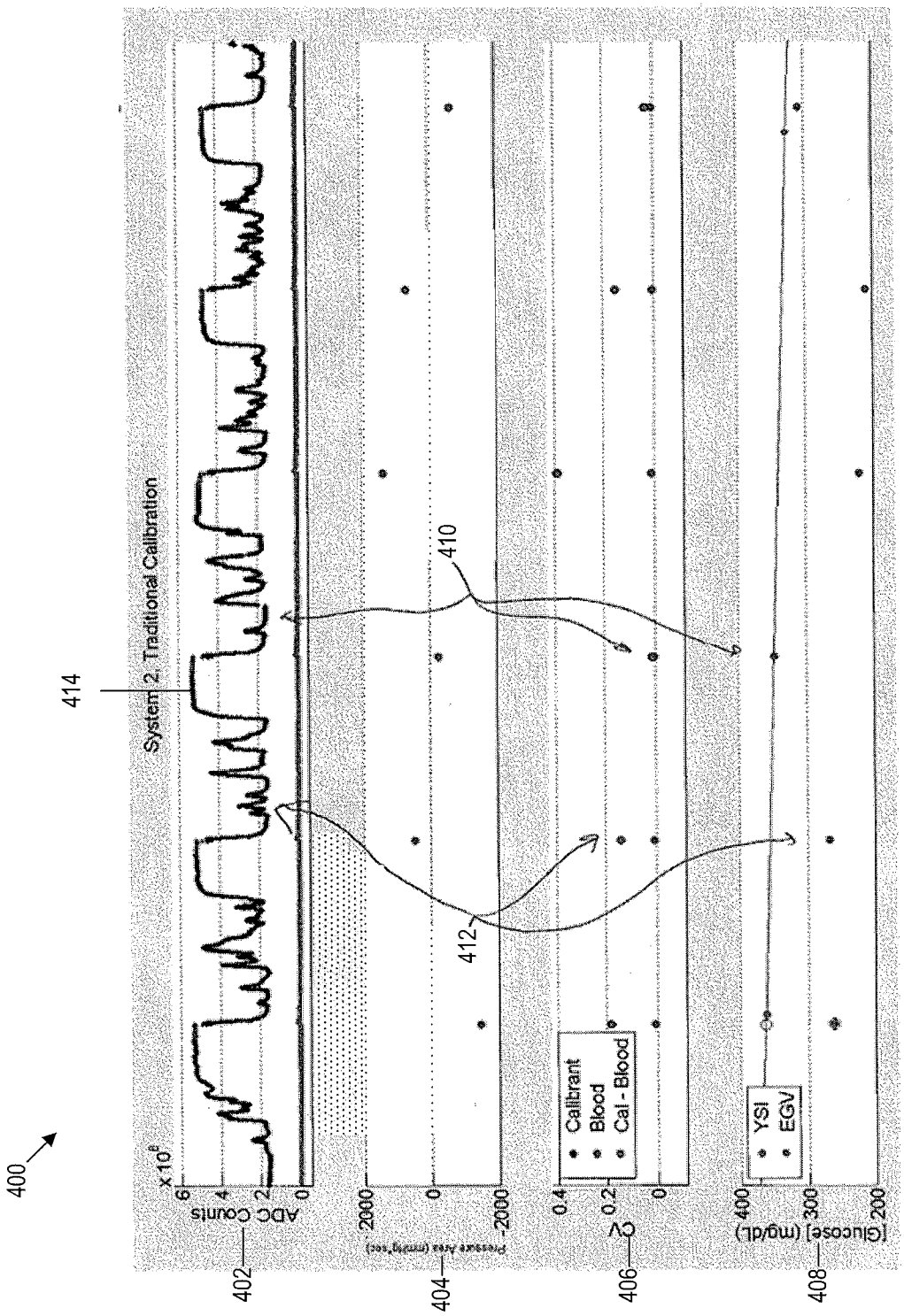

400
414
System 2: Traditional Calibration
ADC Counts
x10^6
6
4
2
0
402
Pressure Area (mmHg*sec)
2000
0
-2000
404
410
412
Calibrant
Blood
Cal - Blood
0.4
0.2
0
406
YSI
EGV
[Glucose] (mg/dL)
400
300
200
408

FIG. 13

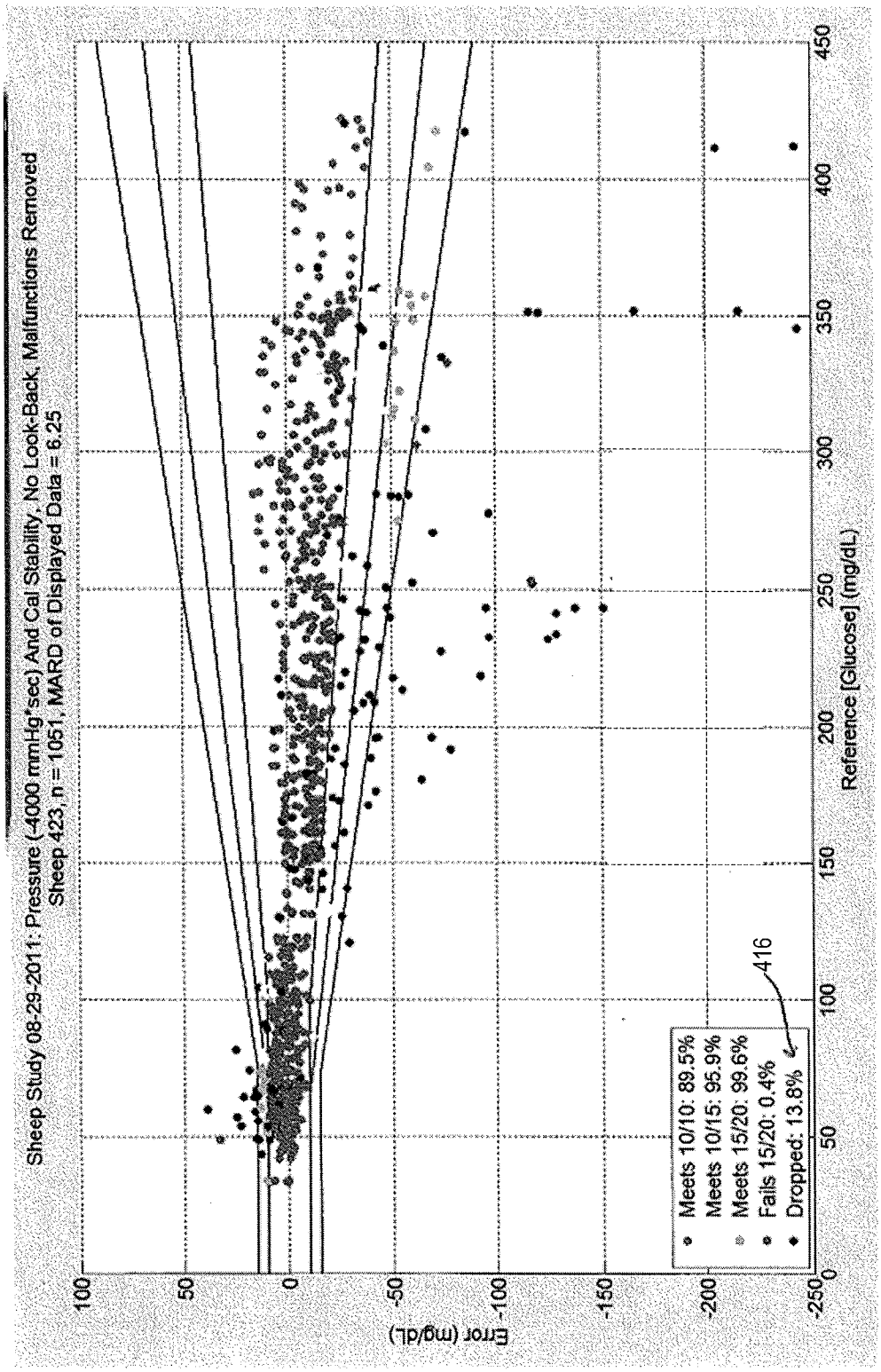

Sheep Study 08-29-2011: Pressure (-4000 mmHg*sec) And Cal Stability, No Look-Back, Malfunctions Removed
Sheep 423, n = 1051, MARD of Displayed Data = 6.25
Error (mg/dL)
Reference [Glucose] (mg/dL)
Meets 10/10: 89.5%
Meets 10/15: 95.9%
Meets 15/20: 99.6%
Fails 15/20: 0.4%
Dropped: 13.8%
416

FIG. 14

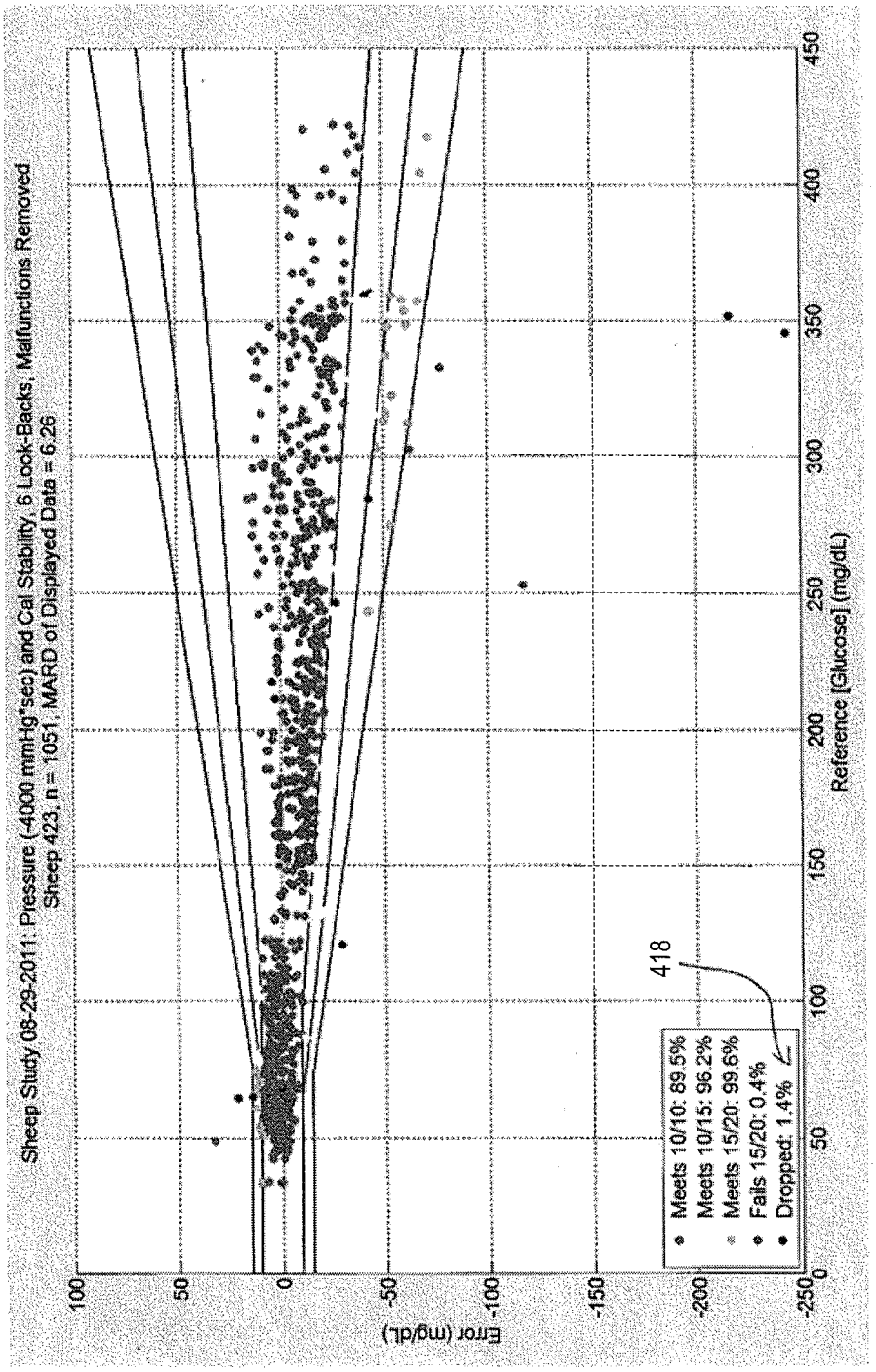

Sheep Study 08-29-2011: Pressure (-4000 mmHg*sec) and Cal Stability, 6 Look-Backs, Malfunctions Removed
Sheep 423, n = 1051, MARD of Displayed Data = 6.26
Error (mg/dL)
Reference [Glucose] (mg/dL)
Meets 10/10: 89.5%
Meets 10/15: 96.2%
Meets 15/20: 99.6%
Fails 15/20: 0.4%
Dropped: 1.4%
418

FIG. 15

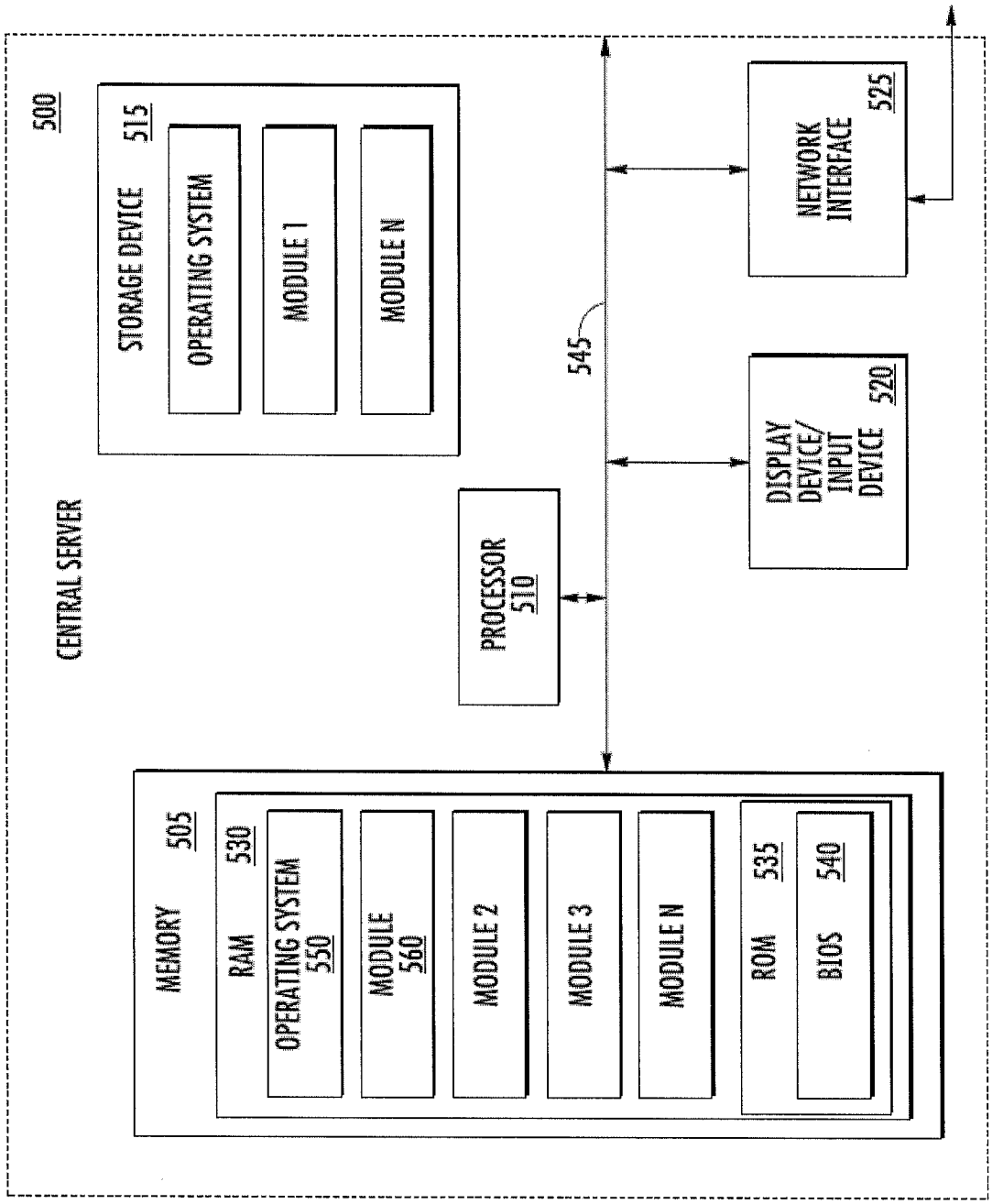

500
CENTRAL SERVER
STORAGE DEVICE 515
OPERATING SYSTEM
MODULE 1
MODULE N
545
NETWORK INTERFACE 525
DISPLAY DEVICE/ INPUT DEVICE 520
PROCESSOR 510
MEMORY 505
RAM 530
OPERATING SYSTEM 550
MODULE 560
MODULE 2
MODULE 3
MODULE N
ROM 535
BIOS 540

FIG. 16

```
function[Sensitivity] =
Update_Sensitivity(RawSensitivity,CalibrantCV,PastSensitivity,FinishCalibrationTicks,Parameters)

%Update sensitivity

%Calculate sensitivity timespan, sensitivity shift, etc.
TimeSpan = double(FinishCalibrationTicks-PastSensitivity.Ticks)/(Parameters.TicksPerSecond*60);
SensitivityShift = abs((RawSensitivity-PastSensitivity.Value)/PastSensitivity.Value)/TimeSpan;

%Sensitivity update logic
if RawSensitivity < Parameters.MinSensitivity

   %Low sensitivity error
   Sensitivity = struct('Ticks',PastSensitivity.Ticks,'Value',PastSensitivity.Value,'Valid',0,'Flag','SensitivityLow');

elseif RawSensitivity > Parameters.MaxSensitivity

   %High sensitivity error
   Sensitivity = struct('Ticks',PastSensitivity.Ticks,'Value',PastSensitivity.Value,'Valid',0,'Flag','SensitivityHigh');

elseif (CalibrantCV > Parameters.MaxCalibrantCV)

   %Attempt to use old sensitivity
   if TimeSpan > Parameters.MaxSensitivityTimeSpan

      %Unable to determine sensitivity
      Sensitivity =
struct('Ticks',PastSensitivity.Ticks,'Value',PastSensitivity.Value,'Valid',0,'Flag','SensitivityUnableToDetermine');
   Else
 Sensitivity = struct('Ticks',PastSensitivity.Ticks,'Value',PastSensitivity.Value,'Valid',1,'Flag','');
   end

elseif (SensitivityShift > Parameters.MaxSensitivityShift)

   %Keep old sensitivity, but do not use for calculations
   Sensitivity =
struct('Ticks',PastSensitivity.Ticks,'Value',PastSensitivity.Value,'Valid',0,'Flag','SensitivityUnableToDetermine');

else

   %Use new sensitivity
   Sensitivity = struct('Ticks',FinishCalibrationTicks,'Value',RawSensitivity,'Valid',1,'Flag','');
end
```

FIG. 17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/072293

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/00(2006.01)i, A61B 5/145(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B 5/00; A61M 31/00; G06F 17/18; G01N 33/66; A61B 5/1468; G06F 17/40; A61B 5/145

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: blood, sensor, calibration, sensitivity, measurement

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012-0191362 A1 (NIKOLAUS SCHMITT et al.) 26 July 2012 See abstract, paragraphs [0086]-[0135], claims 1-20 and figures 1A-5.	1-20
A	US 8257300 B2 (ERWIN S. BUDIMAN et al.) 04 September 2012 See abstract, column 6, line 30 - column 18, line 42, claims 1-5 and figures 1-4.	1-20
A	US 2012-0209098 A1 (PAUL V. GOODE, JR. et al.) 16 August 2012 See abstract, paragraphs [0312]-[0366], claims 1-19 and figures 6-12B.	1-20
A	US 8306766 B2 (JOHN C. MUELLER, JR. et al.) 06 November 2012 See abstract, column 11, line 45 - column 33, line 48, claims 1-5 and figures 8-27.	1-20
A	US 2009-0177062 A1 (JAMES SAY et al.) 09 July 2009 See abstract, paragraphs [0225]-[0278], claim 52 and figures 18A-22.	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2014 (26.03.2014)	**26 March 2014 (26.03.2014)**

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Facsimile No. +82-42-472-7140

Authorized officer
YANG, Jeong Rok
Telephone No. +82-42-481-5709

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PCT/US2013/072293

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