(54) Title: ANALYTE SENSING SYSTEM AND METHOD FOR CONTROLLING PRESENTATION OF INFORMATION

(57) Abstract: The present disclosure provides a sensor system that includes a blood access device, a flow controller, and a pressure sensor. The system is configured to draw a volume of fluid through the blood access device; receive one or more pressure signals from the pressure sensor during the draw; determine a measurement of pressure defined by the one or more pressure signals; determine whether the measurement of pressure is greater than a predetermined threshold value; and suspend presentation of the information on the monitor when the measurement of pressure is greater than the predetermined threshold value. The system prevents information from being presented to the user when the pressure sensor indicates the possibility of an occlusion.

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
ANALYTE SENSING SYSTEM AND METHOD FOR CONTROLLING PRESENTATION OF INFORMATION

TECHNICAL FIELD

[0001] This disclosure relates to intravascular analyte sensor systems and, in particular, to the use of pressure sensors in analyte sensor systems to control presentation of information.

BACKGROUND

[0002] Some analyte monitoring systems use cyclical draw and flush routines to alternately draw fluid up to a sensor assembly and then flush calibration solution over the sensor assembly. In some instances, the catheter or sensor becomes occluded and prevents an effective draw from occurring. This occlusion causes the system to fail to draw all or some of the blood that is intended for sampling. As a result, the sensor can be continuously bathed in calibration solution or the blood draw can be diluted with the calibration solution resulting in inaccurate measurements.

SUMMARY

[0003] In a first aspect, an analyte sensing system for controlling presentation of information is provided. In an embodiment, the system includes a blood access device; a pressure sensor coupled to the blood access device and configured to receive one or more pressure signals associated with the blood access device; a monitor configured to present the information; a memory; a processor; and a computing module, stored in the memory, executable by the processor, and configured to cause the processor to perform a series of functions. The functions may include drawing a volume of fluid through the blood access device; receiving one or more pressure signals from the pressure sensor during the draw; determining a measurement of pressure defined by the one or more pressure signals; determining whether the measurement of pressure is greater than a predetermined threshold value; and suspending presentation of the information on the monitor when the measurement of pressure is greater than the predetermined threshold value.

[0004] In an embodiment, the system includes a flow controller operably connected to the blood access device and configured to draw the volume of fluid through the blood access
device. The system may also include an analyte sensor configured to receive one or more signals from the fluid in the blood access device, wherein an analyte value determined from the one or more signals for the draw is the information that is not presented when the measurement of pressure is greater than the predetermined threshold. In some embodiments, the measurement of pressure is an area under the pressure curve calculated as an integral of the pressure curve over a duration of the draw, taken relative to a baseline pressure determined prior to the draw. The baseline pressure may be an average pressure determined based on one or more signals received from the pressure sensor when a flow controller is not flushing or drawing fluid through the blood access device. In one embodiment, the predetermined threshold value is based at least in part on a pressure determined during a flush and draw cycle when an occlusion is not present. In a further embodiment, the predetermined threshold value is based at least in part on a diameter of a lumen in the blood access device and/or the flow through the device.

[0005] In a further aspect, a computer program product for controlling presentation of information is provided. In an embodiment, the computer program product includes a non-transitory computer-readable medium comprising a set of codes for causing a computer to: draw a volume of fluid through the blood access device; receive one or more pressure signals from the pressure sensor during the draw; determine a measurement of pressure defined by the one or more pressure signals; determine whether the measurement of pressure is greater than a predetermined threshold value; and suspend presentation of the information on the monitor when the measurement of pressure is greater than the predetermined threshold value.

[0006] In some embodiments, the computer program product includes a set of codes for causing a flow controller to cause the volume of fluid to draw through the blood access device, wherein the flow controller is operably connected to the blood access device. The computer program product may also include a set of codes for receiving one or more analyte signals from an analyte sensor, wherein an analyte value determined from the one or more signals for the draw is the information that is not presented when the measurement of pressure is greater than the predetermined threshold. The measurement of pressure may be an area under the pressure curve calculated as an integral of the pressure curve over a duration of the draw, taken relative to a baseline pressure determined prior to the draw. In some embodiments, the baseline pressure is an average pressure determined based on one or more.
more signals received from the pressure sensor when a flow controller is not flushing or
drawing fluid through the blood access device. In some embodiments, the predetermined
value is based at least in part on a pressure determined during a flush and draw cycle when an
occlusion is not present. In still further embodiments, the predetermined value is based at
least in part on a diameter of a lumen in the blood access device.

[0007] In a further aspect, a method for controlling presentation of information is provided.
In an embodiment, the method includes providing a pressure sensor coupled to the blood
access device and configured to receive one or more pressure signals associated with a blood
access device; and providing a processor for executing computer program code stored in a
non-transitory computer-readable medium to cause the processor to: draw a volume of fluid
through the blood access device; receive one or more pressure signals from the pressure
sensor during the draw; determine a measurement of pressure defined by the one or more
pressure signals; determine whether the measurement of pressure is greater than a
predetermined threshold value; and suspend presentation of the information on the monitor
when the measurement of pressure is greater than the predetermined threshold value.

[0008] In some embodiments, the method includes causing a flow controller to cause the
volume of fluid to draw through the blood access device, wherein the flow controller is
operably connected to the blood access device. In further embodiments, the method includes
receiving one or more analyte signals from an analyte sensor, wherein an analyte value
determined from the one or more signals for the draw is the information that is not presented
when the measurement of pressure is greater than the predetermined threshold. The
measurement of pressure may be an area under the pressure curve calculated as an integral of
the pressure curve over a duration of the draw, taken relative to a baseline pressure
determined prior to the draw. In some embodiments, the baseline pressure is an average
pressure determined based on one or more signals received from the pressure sensor when a
flow controller is not flushing or drawing fluid through the blood access device. In further
embodiments, the predetermined value is based at least in part on a pressure determined
during a flush and draw cycle when an occlusion is not present.

[0009] The features, functions, and advantages that have been discussed may be achieved
independently in various embodiments of the present invention or may be combined with yet
other embodiments, further details of which can be seen with reference to the following description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 is a perspective view of an analyte sensing system of one embodiment of the present disclosure;

[0011] 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;

[0012] FIG. 3 is an enlarged view of an adapter of the components shown in FIG. 2;

[0013] FIG. 4 is a perspective view of the components, including a sampling line, shown in FIG. 2;

[0014] FIG. 5 is a schematic of a rotary pinch valve of a flow control system of another embodiment of the present disclosure;

[0015] FIG. 6 is a graphical depiction of a flow profile of an embodiment of the present disclosure;

[0016] FIG. 7 is a flowchart of a reverse-order calibration of an embodiment of the present disclosure;

[0017] FIG. 8 is a flowchart illustrating a method for controlling presentation of information, according to an embodiment of the present disclosure;

[0018] FIG. 9 is a graphical depiction of pressure and analyte sensor output during blood draw cycles, according to an embodiment of the present disclosure;

[0019] FIG. 10 is a graphical depiction of error in glucose measurements compared to reference glucose measurements in a sheep study when information presentation is not suspended due to area under pressure curve determinations, according to an embodiment of the present disclosure;

[0020] FIG. 11 is a graphical depiction of error in glucose measurements compared to reference glucose measurements in a sheep study when information presentation is suspended due to area under pressure curve determinations, according to an embodiment of the present disclosure;
FIG. 12 is a flowchart illustrating a method for detecting an occlusion, according to an embodiment of the present disclosure;

FIG. 13 is an exemplary chart of the pressure pulsing routine, according to an embodiment of the present disclosure;

FIG. 14 is a graphical depiction of results of a pressure pulse feasibility test, according to an embodiment of the present disclosure;

FIG. 15 is a graphical depiction of results of a pressure pulse feasibility test where the area under the pressure curve is highlighted, according to an embodiment of the present disclosure;

FIG. 16 is a graphical depiction of results of a pressure pulse feasibility test when intermittent occlusions are applied, according to an embodiment of the present disclosure;

FIG. 17 is a graphical depiction of results of a pressure pulse feasibility test indicating when specific occlusions are applied, according to an embodiment of the present disclosure;

FIG. 18 is a flowchart of an analyte sensor computer system, according to an embodiment of the present disclosure.

DETAILED DESCRIPTION

The present disclosure now will be described more fully hereinafter with reference to specific embodiments of the disclosure. 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.

Embodiments of the present disclosure include a blood analyte sensor 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 FIG. 1. The system may also include other sensors, such as pressure sensors, temperature sensors, pH sensors, and the like. 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 body access devices include blood access devices such as catheters, tubes, and stents. 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 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.

[0030] 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 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.

[0031] 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 FIG. 1. In an 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 sensor 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.

[0032] Referring to FIGS. 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 hematocrit, with drift or run-in periods may also benefit from embodiments of the present disclosure.

[0033] 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.

[0034] 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.

[0035] As shown in FIG. 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. In an embodiment, the monitoring line is a 10 foot length of PVC extension tubing with a .060 inch internal diameter.

[0036] 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 FIG. 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, or four heads, the latter aiding with higher draw volumes. Other configurations, such as a piston-type flow controller, could accomplish the same task. The flow controller may be hydraulic or mechanical.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.
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.

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.

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.

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.

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.

[0046] 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.

[0047] The axial lumen 56 preferably has a diameter that is selected to provide a smooth transition with the lumen of the monitor line 22. In an embodiment, the electrode 40 resides within the sampling tube 90. 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.

[0048] 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.

[0049] 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, as shown in FIG. 3.

[0050] 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.

[0051] 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, as shown in FIG. 3.

[0052] 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.

[0053] Referring again to FIGs. 2, 3 and 4, the sampling tube assembly 28 includes the
threaded male proximal end 84, a locking cap 86, an axial lumen 94, 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.
Defined through the proximal end and locking cap 86 is the axial lumen 94. Axial lumen 94 is enlarged on the proximal end and necked down through the middle and distal portions to a smaller diameter. The sealing member 88 extends within the axial lumen 94 and is an elastomeric member that has a tightly-toleranced inner diameter configured to fit an outer diameter of the sampling tube 90, so as to secure the sampling tube to the rest of the sampling tube assembly 28. The sealing member also acts to seal the connection, through its elastic compressibility, between the adapter 26 and the sampling tube assembly 28. The face of the threaded distal end 74 of adapter 26 abuts and compacts the flanged portion of the sealing member 88 when the male proximal end 84 of the sampling line is twisted into the threads of the distal end 74. The flanged shape of the sealing member 88 secures against axial migration. Also, the sealing member 88 helps to secure the sampling tube 90 to the rest of the sampling tube assembly 28.

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 FIG. 3) 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.

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.
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.

The advantage of inserting the sampling tube 90 into an existing catheter is that the entire fluid path can be controlled. For example, the sampling line can be coated with heparin to prevent clotting, which cannot be done with a separate commercial IV catheter. 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.

As shown in FIG. 6, and for example purposes only, 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 5 mL/hr start and then a ramped-up pre-calibration flush rate of 650 mL/hr.

In some embodiments, the sensor system 10 may be employed over a 72 hour period and sample blood with 40 to 200 microliter 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 draw rate is about 200 mL/hour.
As shown in FIG. 7, 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. 7, 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.

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 may create conditions where the flow profile is no longer adequate to wash away residual calibration solution and thus blood sample dilution occurs. If the flow rate of blood over the sensor is too slow, it is possible that the calibrant solution will not be washed away when the sensor enters a blood analyte measurement phase. This, in turn, would result in an inaccurate blood analyte measurement because of the dilution of the blood with the remaining calibrant solution. The inventors have concluded that an occlusion and hence the possibility of dilution of the blood sample with calibrant solution can be detected by evaluating a pressure waveform during a blood draw cycle or during a pressure pulsing routine, as will be described in FIG. 8 and FIG. 12, respectively.

Referring now to FIG. 8, a flow diagram illustrating a method and/or process 800 for detecting an occlusion during a blood draw is provided. Occlusions may be detected by comparing a measurement of pressure to a threshold value. The process 800 may be implemented as a run-time error checking process. In one embodiment, the process 800 may be implemented as a passive monitoring routine that continuously runs. In such an embodiment, the pressure signal 902 in a blood access device, such as the monitoring line from the pinch valve to the distal end of the sampling tube, is constantly monitored to detect the occurrence of an occlusion.

As represented by event 802, in one embodiment, the system first uses a pressure sensor to detect the baseline pressure prior to starting a blood draw phase. The baseline
pressure is the pressure in the blood access device when the flow controller is not causing a flush or draw to occur through the blood access device. In an embodiment, the baseline pressure is determined based on an average of pressure values received prior to the flush or draw cycle. The pressure sensor may be used in conjunction with other components of an analyte sensor system 10. In an embodiment, the pressure sensor is fluidically coupled to the blood access device and configured to receive one or more pressure signals associated the blood access device. In one embodiment, the pressure sensor may be a sub-component of the flow control system 18. In an alternative embodiment, the pressure sensor may be an independent component of the analyte sensor system 10. Alternatively, the pressure sensor may communicate with the blood access device through a flexible membrane. In a still further embodiment, the pressure sensor could be implemented with an air coupled system. For example, an air coupled pressure transducer could be used to determine the internal pressure in the blood access device. In one embodiment, the pressure sensor may be a sub-component of the flow control system 18. In an alternative embodiment, the pressure sensor or sensors may be an independent component of the analyte sensor system 10.

[0065] Components of the analyte sensing system may include, but are not be limited to, monitors, sensor assemblies, calibration solution sources, flow control systems, processors, memory, computing modules, and/or the like. In an embodiment, a computing module is stored in the memory, executable by the processor, and configured to draw a volume of fluid through the blood access device, receive one or more pressure signals from the pressure sensor during the draw, determine a measurement of pressure defined by the one or more pressure signals, determine whether the measurement of pressure is greater than a predetermined threshold amount, and suspend presentation of information, such as an analyte measurement, on the monitor when the measurement of pressure is greater than the predetermined threshold value.

[0066] In one embodiment, the analyte sensor system 10 detects an error while gathering data related to the baseline pressure. In such an embodiment, the system may repeat the step at event 802 until a baseline pressure is accurately determined. In an alternative embodiment, the system may proceed to the next step in the occlusion detection process.

[0067] At event 804, the blood draw phase is initiated. The blood draw phase may be initiated based on a frequency defined by a blood sampling rate. In one embodiment, the
blood sampling rate may be once every 5 minutes. In such an embodiment, the blood draw phase is initiated once every 5 minutes. The blood draw phase may be initiated automatically after determining the baseline pressure or may be initiated by a user. In some embodiments, the blood draw phase draws a volume of blood up to an analyte sensor such that some analyte measurement, e.g., a glucose measurement, may be made for the volume of blood.

At event 806, the system receives data from one or more sensors during the blood draw phase. In one embodiment, received data may relate to pressure sensor output data during the blood draw phase. As shown in FIG. 9, the pressure sensor output data may be one or more pressure signals 902 that produce a pressure curve. The pressure curve may be produced by linear regression, smoothing algorithms, splicing algorithms, or any other method of creating a curve from a plurality of points. For example, e.g., the pressure curve may be determined by connecting adjacent pressure datapoints with a straight line. Data related to other blood sensing parameters may also be extracted during event 806. For example, glucose measurements from a glucose sensor may also be received.

At event 808, the system determines the measurement of pressure produced by the pressure signal 902 during the blood draw phase. In one embodiment, the measurement of pressure is determined continuously during the blood draw phase. For example, as pressure signals are received by the system during the blood draw phase, the system determines a current measurement of pressure. In another embodiment, the measurement of pressure is determined at the end of the blood draw phase. It should be understood that the measurement of pressure may be determined at any point during the blood draw cycle. That is, the measurement of pressure may be calculated with respect to a portion of the pressure signal 902 that is related to one measurement cycle.

In one embodiment, the measurement of pressure is an area under the pressure curve calculated as the integral of the pressure curve over the duration of the system blood draw phase. In such an embodiment, the integral may be calculated relative to the baseline pressure detected at event 802 prior to initiating the blood draw phase at event 804. As such, the area may be represented by:

\[ \text{Area under Pressure Curve} = \int_{x=a}^{x=b} f(x) \, dx \]

In one embodiment, the parameter x may be defined by the duration of the pressure signal. As such x=a may be a value representing the beginning of the blood draw
cycle, and \( x=b \) may be a parameter representing the end of the blood draw cycle. In one embodiment, the parameter \( f(x) \) represents the function of the pressure curve produced by the pressure signal 902 within one measurement cycle. In one embodiment, the area under the pressure curve is calculated in units \( \text{mmHg} \times \text{seconds} \). In an alternative embodiment, the area under the pressure curve is calculated in other units. In an embodiment, the baseline pressure is used to define an edge of the area under the pressure curve.

[0072] In a further embodiment, the measurement of pressure is a peak pressure. For example, the peak pressure may be the highest pressure recorded during the blood draw cycle. This peak pressure may be compared to a predetermined threshold, such as a maximum peak pressure that indicates an occlusion-free flow. One can use other methods such as mathematically calculating a peak pressure based parameter from a digitally filtered signal or accomplishing the same using analog circuitry. When the measurement of pressure, e.g., the peak pressure, exceeds the predetermined threshold, the system determines that an occlusion may be present and halts presentation of information on the display. In a still further embodiment, the measurement of pressure is a pressure signal run through a short-term filter. For example, a low pass filtered peak signal with a narrow window may be used to generate a measurement of pressure and compare the measurement of pressure to a relevant threshold indicating a potential occlusion.

[0073] It should be understood that various measurements of pressure may be used. In some embodiments, a rapidly oscillating fluid column is used to generate a pressure signal. When an occlusion occurs, the cross-section of the lumen of the blood access device is reduced. The flow controller is continuing to flush or draw the fluid through the blood access device at a specific flow rate, and thus the reduction in the cross-section of the lumen results in an increase in driving pressure.

[0074] At event 810, the measurement of pressure, calculated at event 806, is compared to a threshold value. In one embodiment, the threshold value may be a predetermined value, for example \(-4000 \text{ mmHg} \times \text{second} \) or other large negative value indicating an occlusion, such that when the measurement of pressure exceeds this value an occlusion is determined to be present. In an embodiment, the threshold is based on the diameter of a lumen in the blood access device and/or the flow rate through the blood access device. In general, given a specific flow rate, the pressure will increase as the effective diameter decreases. In a further
embodiment, the threshold is based on the pressure applied by the flow controller. In a still further embodiment, the threshold may be determined at least in part by a baseline pressure for the blood access device, the patient, a body lumen in the patient, or other component of the dynamic fluid system comprising the flow controller, the blood access device, and the patient. It should be understood that the threshold may be determined by a user, by the manufacturer of a component of the system, or by the system itself, and that other methods of determining the threshold are possible.

[0075] In another embodiment, a measurement of pressure may be calculated and compared to a threshold value to indicate if the measurement of pressure is less than the threshold value. In some embodiments, this indicates that an occlusion is not present or that a previously-detected occlusion has cleared. In yet another embodiment, a measurement of pressure may be determined and compared to two threshold values to indicate if the determined value is greater than a first threshold value and less than a second threshold value.

[0076] As used herein, a measurement of pressure is a positive measurement. While a measurement of pressure, such as an area under a pressure curve, may have a negative sign, the sign of the area indicates the orientation of the measurement of pressure with respect to the baseline, e.g., the measurement of pressure may be positive or negative depending on whether the flow controller is flushing or drawing fluid through the blood access device. Thus, in some embodiments, when determining whether a measurement of pressure is greater than a predetermined threshold it may be necessary to take the absolute value of the measurement of pressure and the threshold. In this manner, the system is able to determine the relationship of the measurement of pressure and the predetermined threshold without regard to sign.

[0077] At event 812, if the measurement of pressure is determined to be less than the threshold value then an occlusion in not indicated based on the pressure and information determined during the blood draw cycle may be presented on the monitor.

[0078] If, however, the measurement of pressure is determined to be greater than the threshold value then an occlusion is detected at event 814. The presentation of other information, such as temperature, volume, or pH, may also be suspended when the measurement of pressure exceeds the threshold value.
[0079] Turning now to FIG. 9, an exemplary graph of pressure and analyte sensor output during blood draw cycles is provided. The analog-to-digital converter (ADC) counts 904 are measurements of the values received from the glucose analyte sensor during the flush and draw cycles. Pressure signals 902 and glucose values 906 are determined at the same time as the ADC counts 904. The pressure curve 908 is defined by a plurality of pressure signals 902. The area under the pressure curve 910 is determined relative to the baseline 912 determined just before the blood draw cycle.

[0080] The advantage of using the system to control presentation of information is provided based on a comparison between FIGs. 10 and 11. FIG. 10 provides an example chart of error in sampling line glucose measurements compared to reference glucose measurements in a sheep study. The reference glucose measurements are glucose measurements determined based on a direct-line, e.g., a line to the superior or inferior vena cava, and are assumed to be accurate measurements of blood glucose in the sheep. Sampling line glucose measurements are glucose measurements made using a catheter in a peripheral limb of the sheep. The error is the difference in the glucose measurement between the reference and the peripheral glucose measurements. If the error is large, meaning that the peripheral and central glucose measurements are not consistent, then the sample point fails a test of accuracy. As shown in FIG. 10, 27.5% of the sampling points fail based on a large measurement of error. Because this chart does not drop sampling points when the area under the pressure curve exceeds the predetermined threshold, no points are dropped.

[0081] In comparison, FIG. 11 is an example of a chart where sampling points are evaluated to determine if the area under the pressure curve exceeds a threshold. In this example, the threshold is \(-4000 \text{ mmHg} \cdot \text{sec}\). The axes are the same: i.e., a measurement of error in the glucose measurements on the y-axis as a function of the reference glucose on the x-axis, but one or more pressure signals are determined during each blood draw cycle, from which the glucose sampling points are also determined. The one or more pressure signals define a pressure curve for the blood draw cycle and the area under the pressure curve is determined. When the area under the pressure curve exceeds the predetermined threshold, the sampling point is dropped and the information related to the sampling point is not presented on the monitor. As can be seen in FIG. 11, dropping points when the area under the pressure curve exceeds the predetermined threshold results in 32.8% of the sampling
points being dropped and a much smaller percentage of the sampling points, 6.8%, failing the accuracy test. In this manner, a user is not making decisions based on substantial amounts of inaccurate data that is presented to the user. In one embodiment, detecting an occlusion may result in an error being displayed to a user. In an alternative embodiment, detecting an occlusion may result in providing the user an option to initiate a high-frequency pulsing routine, as will be discussed with respect to FIG. 12.

In one embodiment, the process 800 may be implemented in association with a computer processing device. Exemplary MATLAB code for evaluating the area under a pressure curve. In an embodiment, when the area under the pressure curve is greater than a predetermined threshold, then presentation of information on a monitor is suspended. It should be understood that the MATLAB code is merely exemplary and that the process may be implemented in various types of coding.

MATLAB code for determining the area under a pressure curve:

```matlab
function[BloodDrawPressureAUC] = Calculate_BloodDrawPressureAUC(RawPressure,BeginBloodDrawTicks,FinishBloodDrawTicks,parameters)

%Calculate blood draw pressure area under curve
%
%Get baseline pressure just before blood draw
BeginIdx = find(RawPressure.Ticks >= (BeginBloodDrawTicks - Parameters.PressureTimeOfset - Parameters.PressureBaselineTimeLength), 1,'first');
FinishIdx = find(RawPressure.Ticks <= (BeginBloodDrawTicks - Parameters.PressureTimeOfset), 1,'last');
PressureBaselineValues = RawPressure.Value(BeginIdx:FinishIdx);
PressureBaseline = mean(PressureBaselineValues);
%
%Extract data during blood draw phase
TicksStart = (BeginBloodDrawTicks + Parameters.PressureTimeOfset);
TicksFinish = (FinishBloodDrawTicks - Parameters.PressureTimeOfset);
BeginIdx = find(RawPressure.Ticks >= TicksStart, 1,'first');
FinishIdx = find(RawPressure.Ticks <= TicksFinish, 1,'last');
DrawPressure.Ticks = RawPressure.Ticks(BeginIdx:FinishIdx);
DrawPressure.Value = RawPressure.Value(BeginIdx:FinishIdx);
%
%Integrate area under curve
BloodDrawPressureAUC = 0;
for i = 1:length(DrawPressure.Ticks)-1)
```

31996-1 CCHDM-6614 PCT
BloodDrawPressureAUC = BloodDrawPressureAUC + (((DrawPressure.Value(i)+DrawPressure.Value(i+1))/2)-PressureBaseline)* (double((DrawPressure.Ticks(i+1)-DrawPressure.Ticks(i))/Parameters.TicksPerSecond));

end

[0084] Now referring to FIG. 12, a flow diagram illustrating another method and/or process 1200 for detecting an occlusion is provided. In some embodiments, the method may also detect when an occlusion is cleared. The method 1200 detects the presence of an occlusion or the clearing of an occlusion based on the comparison of a measurement of pressure to a predetermined threshold value. In some embodiments, the measurement of pressure is determined during a pressure pulsing routine. The pressure pulsing routine is a predetermined period of time when the system alternatively draws and flushes a small volume of fluid through a blood access device. An advantage of the pressure pulsing routine is that it quickly and accurately detects an occlusion without requiring that the user wait until the end of an analyte detection cycle, which may require waiting five minutes or more.

[0085] Turning briefly to FIG. 13, an exemplary chart of the pressure pulsing routine is provided. In this example, alternating flush (or positive pulse) 1302 and draw (or negative pulse) 1304 cycles are depicted. As can be seen, the flush and draw cycles occur quickly and with a short period of time between the flush and draw. In this example, the flush and draw cycle are approximately 0.75 seconds long and there is approximately 1.5 seconds between them. During the cycle, the flow controller draws or flushes a small volume of fluid, e.g., approximately 15 µL, through the blood access device. As can be seen, the rate of flow through the blood access device reaches a maximum of, in this example, approximately 40 µL/sec. Thus, the pressure pulsing routine completes a full flush and draw in less than four seconds and may be able to detect an occlusion in this time, rather than forcing the user to wait until the end of a analyte detection cycle, which can last five minutes or more.

[0086] Returning to FIG. 12, in some embodiments, the system receives an input to initiate the pressure pulsing routine, as shown in event 1202. The user may suspect that an occlusion is present in the blood access device and desire confirmation. For example, the user may visually determine that liquid is not passing through the blood access device as it should. Alternatively, the user may suspect an occlusion in the blood access device based on a measurement taken during an analyte detection cycle. For example, and as disclosed in FIG.
8, the system may evaluate the pressure signals received during the blood draw portion of the analyte testing and detect a possible occlusion based on the measurement of pressure being greater than a predetermined threshold. The system may receive input from the user, such as the user selecting a button or running a routine on a computing device, to initiate the pressure pulsing routine. In an alternative embodiment, the pressure pulsing routine is automatically initiated based on occurrence of predefined criteria, e.g., the measurement of pressure determined during the blood draw cycle of an analyte testing being greater than the predetermined threshold. In a further embodiment, the process 1200 is implemented as an active debugging mechanism. In such an embodiment, a user receives active and/or interventional feedback about the current state of the occlusion as they readjust the catheter or otherwise attempt to resolve the occlusion.

[0087] In some embodiments, as shown at event 1204, the blood draw phase is halted when the pressure pulsing routine is initiated. In this embodiment, the user is able to interrupt a blood draw phase at any point during the blood draw phase to initiate the pressure pulsing routine. For example, the user may be monitoring a patient’s blood glucose level and suspect that an occlusion is present in the blood access device. For example, blood draw may have slowed to an unacceptable rate. When this occurs, the user desires to determine whether an occlusion is present quickly without having to wait until the end of the blood draw phase. The user initiates the pressure pulsing routine and the system halts the blood draw phase so that the pressure pulsing routine can be implemented instead.

[0088] At event 1206, the system alternatively draws and flushes a small volume of fluid over the course of a predetermined time period. In one embodiment, the predetermined time period may be a few seconds. For example, the predetermined time period may be between 2 and 5 seconds, 1 and 10 seconds, 0.5 and 30 seconds, or any combination thereof. The volume of fluid may vary based on the diameter of the blood access device and other characteristics of the flow machinery, i.e., the flow controller, etc. For example, the system may flush and draw approximately 15 μL of fluid through the blood access device. In one embodiment, the system may alternate flushing a solution in and drawing a small amount of blood back repeatedly for a few seconds. The system may draw a small amount of blood and determine the measurement of pressure prior to flushing a small volume of solution.
At event 1208, the system receives one or more pressure signals during the flush and/or draw. The pressure sensor output data may be one or more pressure signals that produce a pressure curve. The pressure curve may be produced by linear regression, smoothing algorithms, splicing algorithms, or any other method of creating a curve from a plurality of points. For example, e.g., the pressure curve may be determined by connecting adjacent pressure datapoints with a straight line.

At event 1210, the system determines the measurement of pressure produced by the pressure signal during the pressure pulsing routine. The measurement of pressure may be determined with respect to one flush or draw cycle. In one embodiment, the measurement of pressure is an area under the pressure curve calculated as the integral of the pressure curve for a single flush or draw cycle. In such an embodiment, the integral may be calculated relative to the baseline pressure. The baseline pressure is the pressure in the blood access device when the flow controller is not causing a flush or draw to occur through the blood access device. In an embodiment, the baseline pressure is determined based an average of pressure values received prior to the flush or draw cycle. As such, the area under the pressure curve may be represented by:

\[
\text{Area under Pressure Curve } = \int_{x=a}^{x=b} f(x) \, dx
\]

In one embodiment, the parameter \( x \) may be defined by the duration of the pressure signal. As such \( x=a \) may be a value representing the beginning of the pressure pulsing routine for one flush or draw cycle, and \( x=b \) may be a parameter representing the end of the pressure pulsing routine for one flush or draw cycle. In one embodiment, the parameter \( f(x) \) may represent the function of the pressure curve produced by the pressure signal within one flush or draw cycle. In one embodiment, the measurement of pressure is calculated in units mmHg*seconds. In alternative embodiments, the measurement of pressure may be calculated in other units.

In a further embodiment, the measurement of pressure is a peak pressure. For example, the peak pressure may be the highest pressure recorded during the blood draw cycle. This peak pressure may be compared to a predetermined threshold, such as a maximum peak pressure that indicates an occlusion-free flow. One can use other methods such as mathematically calculating a peak pressure based parameter from a digitally filtered signal or accomplishing the same using analog circuitry. When the measurement of pressure,
e.g., the peak pressure, exceeds the predetermined threshold, the system determines that an occlusion may be present. If the measurement of pressure is less than a predetermined threshold, the system may determine that the occlusion has cleared or that no occlusion is present. In a still further embodiment, the measurement of pressure is a pressure signal run through a short-term filter. For example, a low pass filtered peak signal with a narrow window may be used to generate a measurement of pressure and compare the measurement of pressure to a relevant threshold indicating a potential occlusion.

[0093] It should be understood that various measurements of pressure may be used. In some embodiments, a rapidly oscillating fluid column is used to generate a pressure signal. When an occlusion occurs, the cross-section of the lumen of the blood access device is reduced. The flow controller is continuing to flush or draw the fluid through the blood access device at a specific flow rate, and thus the reduction in the cross-section of the lumen results in an increase in driving pressure.

[0094] At event 1212, the measurement of pressure, determined at event 1212, is compared to a threshold value. In one embodiment, the threshold value may be a predetermined value, for example -4000 mmHg*second or other large negative value indicating an occlusion, such that when the measurement of pressure exceeds this value an occlusion is determined to be present. In an embodiment, the threshold is partially based on the diameter of a lumen in the blood access device. In a further embodiment, the threshold is based on the pressure applied by the flow controller. In a still further embodiment, the threshold may be determined at least in part by a baseline pressure for the blood access device, the patient, a body lumen in the patient, or other component of the dynamic fluid system comprising the flow controller, the blood access device, and the patient. It should be understood that the threshold may be determined by a user, by the manufacturer of a component of the system, or by the system itself, and that other methods of determining the threshold are possible.

[0095] In one embodiment shown at event 1214, if the measurement of pressure is determined to be greater than the threshold value then the user is notified of the detection of an occlusion. The user may be notified by an alert, e.g., a visible and/or audible alert, produced by the system. A graphical display can be presented to the user such that a trend can show when the excessive occlusion pressures have returned to within a normal range.
This provides continuous real-time feedback to the user when the occlusion has been resolved.

[0096] In some embodiments, the pressure pulsing routine continues while the user attempts to clear the occlusion. In an embodiment, the alternative flush and draw cycles of the pressure pulsing routine are effective in clearing the occlusion. In further embodiments, the user attempts to clear the occlusion by adjusting the blood access device or adjusting the patient. Further methods of clearing the occlusion may also be used, such as flushing calibrant solution through the blood access device, administering medicine, or repositioning the blood access device.

[0097] In an embodiment, the pressure pulsing routine continues to monitor the measurement of pressure determined during the flush or draw cycle to determine if the occlusion has cleared. For example, a measurement of pressure may be determined and compared to a threshold value to indicate if the area is less than the threshold value. In some embodiments, this indicates that an occlusion is not present or that a previously-detected occlusion has cleared. In yet another embodiment, a measurement of pressure may be determined and compared to two threshold values to indicate if the determined value is greater than a first threshold value and less than a second threshold value.

[0098] At event 1216, in some embodiments if the measurement of pressure is determined to be less than the threshold value then the pressure pulsing routine is halted. In this embodiment, when the measurement of pressure is less than the threshold value, the system determines that an occlusion is not present, e.g., the occlusion has been cleared, and the system is ready to return to analyte sensing and display of information.

[0099] Turning now to FIGs. 14 and 15, results are provided of a pressure pulse feasibility test. In the pressure pulse feasibility test, flush 1402 and draw 1404 cycles are quickly alternated and the pressure 1406 in the blood access device is monitored. A pressure curve is derived from the pressure signals received during the flush and draw cycles. The area under the pressure curve (mmHg*sec) 1408 is determined by integrating the area under the pressure curve relative to the baseline 1410. Flush and draw cycles may also be described as positive and negative pulses, respectively. In this example, the area under the pressure curve is determined at the completion of the flush or draw cycle, but it should be understood that the area under the pressure curve may be determined at any point during the flush or draw cycle.
FIG. 15 depicts the areas 1502 which are used to determine the area under the pressure curve during the flush and draw cycles, and indicates the corresponding value in the area under the pressure curve 1408 chart.

[00100] FIGs. 16 and 17 provide results of a pressure pulse feasibility test when occlusions are purposely applied to the blood access device, and the resulting change in the area under the pressure curve. As can be seen, the pressure pulsing routine applies alternating flush and draw cycles, resulting in positive and negative areas under the pressure curve. When the intermittent occlusions are applied to the blood access device, the area under the pressure curves increases. If the user determined that 200 mmHg*sec is a threshold value, then the system would indicate occlusions when the area under the pressure curve exceeds the 200 mmHg*sec. As mentioned, in some instances the absolute value of the area and the threshold are used so that the area determined during draws, i.e., negative pulses, is a positive value.

FIG. 17 depicts when during the pressure pulsing routine occlusions are applied. The resulting area under the pressure curve values depicted in FIG. 17 increase from approximately 50 mmHg*sec to approximately 200 mmHg*sec. In this case, the system is able to notify the user that an occlusion has been detected.

[00101] Referring now to FIG. 18, a schematic diagram of a central server 500, or similar network entity, configured to implement a pressure sensor system, according to one embodiment of the 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. 18, 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.
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.

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 FIG. 8 and FIG. 12, and other materials disclosed herein.

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. In a still further embodiment, analog circuits may be used instead of or in addition to digital circuits.

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.

[00106] 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.

[00107] 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.

[00108] 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).
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 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.

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

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

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.

[00113] As is evident from the range of modeled and experimentally verified embodiments described above, the disclosure is not to be limited to the specific embodiments disclosed and that 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.
WHAT IS CLAIMED IS:

1. An analyte sensing system for controlling presentation of information, the system comprising:
   a blood access device;
   a pressure sensor coupled to the blood access device and configured to receive one or more pressure signals associated the blood access device;
   a monitor configured to present the information;
   a memory;
   a processor; and
   a computing module, stored in the memory, executable by the processor, and configured to cause the processor to:
   draw a volume of fluid through the blood access device;
   receive one or more pressure signals from the pressure sensor during the draw;
   determine a measurement of pressure defined by the one or more pressure signals;
   determine whether the measurement of pressure is greater than a predetermined threshold value; and
   suspend presentation of the information on the monitor when the measurement of pressure is greater than the predetermined threshold value.

2. The system of claim 1, further comprising a flow controller operably connected to the blood access device and configured to draw the volume of fluid through the blood access device.

3. The system of claim 1, further comprising an analyte sensor configured to receive one or more analyte signals for calculating an analyte value, wherein the suspended presentation of the information is the analyte value.
4. The system of claim 1, wherein the measurement of pressure is an area under the pressure curve calculated as an integral of the pressure curve over a duration of the draw, taken relative to a baseline pressure determined prior to the draw.

5. The system of claim 4, wherein the baseline pressure is an average pressure determined based on one or more signals received from the pressure sensor when a flow controller is not flushing or drawing fluid through the blood access device.

6. The system of claim 1, wherein the predetermined threshold value is based at least in part on a pressure determined during a flush and draw cycle when an occlusion is not present.

7. The system of claim 1, wherein the predetermined threshold value is based at least in part on a diameter of a lumen in the blood access device.

8. A computer program product for controlling presentation of information, the computer program product comprising:
   a non-transitory computer-readable medium comprising a set of codes for causing a computer to:
   - draw a volume of fluid through a blood access device;
   - receive one or more pressure signals from a pressure sensor during the draw;
   - determine a measurement of pressure defined by the one or more pressure signals;
   - determine whether the measurement of pressure is greater than a predetermined threshold value; and
   - suspend presentation of the information on a monitor when the measurement of pressure is greater than the predetermined threshold value.

9. The computer program product of claim 8, further comprising a set of codes for causing a flow controller to cause the volume of fluid to draw through the blood access device, wherein the flow controller is operably connected to the blood access device.
10. The computer program product of claim 8, further comprising a set of codes for receiving one or more analyte signals from an analyte sensor, wherein an analyte value determined from the one or more signals for the draw is the information that is not presented when the measurement of pressure is greater than the predetermined threshold value.

11. The computer program product of claim 8, wherein the measurement of pressure is an area under the pressure curve calculated as an integral of the pressure curve over a duration of the draw, taken relative to a baseline pressure determined prior to the draw.

12. The computer program product of claim 11, wherein the baseline pressure is an average pressure determined based on one or more signals received from the pressure sensor when a flow controller is not flushing or drawing fluid through the blood access device.

13. The computer program product of claim 8, wherein the predetermined value is based at least in part on a pressure determined during a flush and draw cycle when an occlusion is not present.

14. The computer program product of claim 8, wherein the predetermined value is based at least in part on a diameter of a lumen in the blood access device.

15. A method for controlling presentation of information, the method comprising:

   providing a pressure sensor coupled to the blood access device and configured to receive one or more pressure signals associated with a blood access device; and

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

   draw a volume of fluid through the blood access device;

   receive one or more pressure signals from the pressure sensor during the draw;
determine a measurement of pressure defined by the one or more pressure signals;
determine whether the measurement of pressure is greater than a predetermined threshold value; and
suspend presentation of the information on a monitor when the measurement of pressure is greater than the predetermined threshold value.

16. The method of claim 15, further comprising causing a flow controller to cause the volume of fluid to draw through the blood access device, wherein the flow controller is operably connected to the blood access device.

17. The method of claim 15, further comprising receiving one or more analyte signals from an analyte sensor, wherein an analyte value determined from the one or more signals for the draw is the information that is not presented when the measurement of pressure is greater than the predetermined threshold value.

18. The method of claim 15, wherein the measurement of pressure is an area under the pressure curve calculated as an integral of the pressure curve over a duration of the draw, taken relative to a baseline pressure determined prior to the draw.

19. The method of claim 18, wherein the baseline pressure is an average pressure determined based on one or more signals received from the pressure sensor when a flow controller is not flushing or drawing fluid through the blood access device.

20. The method of claim 15, wherein the predetermined value is based at least in part on a pressure determined during a flush and draw cycle when an occlusion is not present.
FIG. 6
FIG. 7

1. Draw blood over sensor
2. Receive blood signal @ end of draw
3. Flush with calibrant
4. Receive calibrant signal before end of flush
5. Calculate parameter = t(Blood signal, Calibrant signal)
FIG. 8

1. **Determine Baseline Pressure**
2. **Initiate Blood Draw Cycle**
3. **Receive Data During Blood Draw Cycle**
4. **Determine a Measurement of Pressure**
   - **Is the Measurement of Pressure > Threshold Value?**
     - **Yes**: **Occlusion Detected**
     - **No**: **Display Information for the Blood Draw Cycle**
Take "Area Under Curve" here
RECEIVE INPUT TO INITIATE PRESSURE PULSING ROUTINE

STOP BLOOD DRAW PHASE

ALTERNATELY DRAW / FLUSH A SMALL VOLUME OF SOLUTION

RECEIVE ONE OR MORE PRESSURE SIGNALS DURING THE DRAW / FLUSH

DETERMINE A MEASUREMENT OF PRESSURE DEFINED BY THE ONE OR MORE SIGNALS

IS THE MEASUREMENT OF PRESSURE > THRESHOLD VALUE

YES

NOTIFY USER OF OCCLUSION

NO

STOP PRESSURE PULSE ROUTINE

FIG. 12
INTERNATIONAL SEARCH REPORT

International application No. PCT/US2013/073293

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/02(2006.01)i, A61B 5/021(2006.01)i, A61B 5/027(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 5/02; A61M 37/00; A61B 5/157; A61B 5/0215; A61B 5/028; A61M 1/16; A61B 5/021; A61B 5/027

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, pressure, sensor, flush, draw, occlusion, presentation, monitor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2005-0004502 Al (JOHN J. D MAHONY et al.) 06 January 2005</td>
<td>1-20</td>
</tr>
<tr>
<td>Y</td>
<td>US 2007-0244382 Al (MARK RIES ROBINSON et al.) 18 October 2007</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td>See abst ract, paragraphs [0062]- [0085] and figures 3-12.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>US 2012-0220883 Al (DALE R. MANSTROM et al.) 30 August 2012</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td>See abst ract, paragraphs [0037]- [0074] and figures 1-8.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>US 6299583 Bl (PHILIP E. EGERS et al.) 09 Oct ober 2001</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td>See abst ract, column 23, line 16 - column 29, line 25 and figures 2-33.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>30 2012-085644 Al (GAMBOO LUNDIA AB) 28 June 2012</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td>See abst ract, paragraphs [0025]- [0045] and figures 1-3.</td>
<td></td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "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

10 April 2014 (10.04.2014)

Date of mailing of the international search report

11 April 2014 (11.04.2014)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AU 2003-237776 A8</td>
<td>13/10/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1480713 A2</td>
<td>01/12/2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1480713 A4</td>
<td>02/12/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1480713 Bl</td>
<td>20/11/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003-0152482 Al</td>
<td>14/08/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 7540851 B2</td>
<td>02/06/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 03-082144 A2</td>
<td>09/10/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 03-082144 A3</td>
<td>19/02/2004</td>
</tr>
<tr>
<td>US 2007-0244382 Al</td>
<td>18/10/2007</td>
<td>CA 2630094 Al</td>
<td>24/05/2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1954190 A2</td>
<td>13/08/2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1954190 A4</td>
<td>13/10/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2009-0043240 Al</td>
<td>12/02/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2007-059476 A2</td>
<td>24/05/2007</td>
</tr>
<tr>
<td>US 2012-0220883 Al</td>
<td>30/08/2012</td>
<td>AU 2009-291623 Al</td>
<td>18/03/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2734698 Al</td>
<td>18/03/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2734698 C</td>
<td>01/05/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2762123 Al</td>
<td>18/03/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2762123 C</td>
<td>11/06/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2803747 Al</td>
<td>18/03/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102202562 A</td>
<td>28/09/2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2334227 Al</td>
<td>22/06/2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 211659 A</td>
<td>30/05/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 211659 do</td>
<td>31/05/2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 225761 do</td>
<td>27/06/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2012-501807 A</td>
<td>26/01/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 10-2011-0063667 A</td>
<td>13/06/2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2011113976 A</td>
<td>20/10/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2478338 C2</td>
<td>10/04/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2010-0234698 Al</td>
<td>16/09/2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012-0136244 Al</td>
<td>31/05/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013-0324864 Al</td>
<td>05/12/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013-0331714 Al</td>
<td>12/12/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 8298156 B2</td>
<td>30/10/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 8485985 B2</td>
<td>16/07/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2010-030882 Al</td>
<td>18/03/2010</td>
</tr>
<tr>
<td>US 6299583 Bl</td>
<td>09/10/2001</td>
<td>AU 1999-20332 Al</td>
<td>30/09/1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1999-20332 B2</td>
<td>06/03/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2000-63766 Al</td>
<td>13/02/2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 6376600 A</td>
<td>13/02/2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2256915 Al</td>
<td>17/09/1999</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (July 2009)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 2256915 C</td>
<td>11/03/2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP 0943289 Al</td>
<td>22/09/1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JP 11-318834 A</td>
<td>24/11/1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US 5788647 A</td>
<td>04/08/1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US 5928155 A</td>
<td>27/07/1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wo 01-06920 Al</td>
<td>01/02/2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wo 98-32373 Al</td>
<td>30/07/1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wo 2012-085644 Al</td>
<td>28/06/2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au 2011-346745 Al</td>
<td>02/05/2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca 2822015 Al</td>
<td>28/06/2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cn 103282062 A</td>
<td>04/09/2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ep 2468324 Al</td>
<td>27/06/2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kr 10-2013-0118354 A</td>
<td>29/10/2013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>