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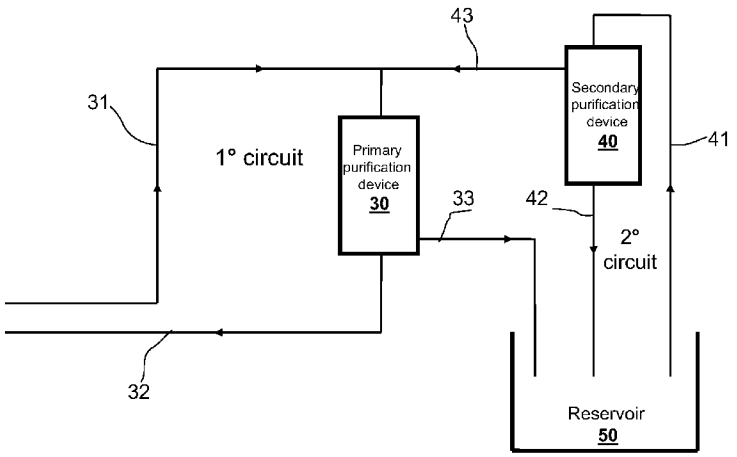
(54) **Title:** FLUID-CONSERVING CASCADE HEMOFILTRATION



(57) **Abstract:** Methods and apparatus efficiently purify blood or blood-derived fluid in a manner that reduces wasted fluid. A blood purification apparatus has a primary purification device and receives, at an input via a primary inlet line, a primary input fluid from a fluid source. The primary purification device partitions the input fluid into two output streams. The first output stream is enriched in larger components and the second output stream is enriched in smaller components. The first output stream is returnable to the source via a primary outlet line. A reservoir stores reservoir fluid and is positioned to accept the second output stream. A secondary purification device coupled to the reservoir receives reservoir fluid from the reservoir and partitions the reservoir fluid into two further streams: a third output stream enriched in larger components and a fourth output stream enriched in smaller components. The fourth output stream is coupled to merge with either the primary inlet line or to the first output stream. The third output stream is coupled to the reservoir. As a result, albumin or other intermediate weight molecules concentrates in the reservoir over time. Optionally, the apparatus may include a dialysis or adsorption module for removing low molecular weight toxins.

WO 2008/051994 A2

Fluid-Conserving Cascade Hemofiltration

Cross Reference to Related Application

This patent application claims priority to U.S. Provisional Patent Application Serial No. 60/862,508 for "Fluid-Conserving Cascade Hemofiltration" filed on October 23, 2006, hereby incorporated by reference in its entirety.

Technical Field

The present invention relates to removal of harmful components from the blood for therapeutic purposes including treatment of renal failure, liver failure, sepsis, multiple organ failure, and other diseases.

Background

Patients with diseases and other pathological conditions in which there is an accumulation of harmful components in the circulating blood may benefit from the removal of such substances via blood or plasma purification therapy. Examples of such treatments include: blood/plasma sorption therapy, hemodialysis, albumin dialysis, hemofiltration, cascade hemofiltration, plasmafiltration, fractionated plasma therapy (which may include filtration, sorption and fluid exchange), cell-based therapies, whole plasma exchange therapy, and selective blood or plasma filtration.

Blood purification techniques may have utility in the treatment of acute and chronic liver failure, hepato-renal syndrome, renal failure, trauma (the crush syndrome), congestive heart failure, rheumatoid arthritis, infection, sepsis, hyperlipidemia, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multiorgan dysfunction syndrome (MODS). Blood/plasma toxins which may contribute to these conditions may include: urea, creatinine, ammonia, bile acids, bilirubin, short-chain fatty acids, phenols, interleukins IL-6, IL-1, and IL-18; tumor necrosis factor alpha - TNFα, chemokines (IL-8), leukotrienes, platelet activating factor (PAF), thromboxane A2,

interferon gamma (INFγ), bacterial toxins, lipid A, anaphylatoxins (C3a), reactive oxygen species, vasoactive mediators such as nitric oxide (NO), certain prostaglandins, and other biologically active components.

In hemofiltration or plasmafiltration techniques, a semipermeable membrane, often a hollow-fiber filter, may be used to remove molecular weight components that, by virtue of low molecular weight and hydrodynamic radius, are small enough to permeate the membrane. Since these membranes are generally permeable to water, hemofiltration will generally remove liquid from the blood. To prevent dehydration of the patient, the removed liquid is replaced with electrolyte solution, plasma, albumin, other fluid, or a combination thereof. The fraction of blood, plasma or other body fluid that permeates the membrane is called the "ultrafiltrate". Examples of hemofiltration techniques designed to remove inflammatory mediators are described in U.S. Patents No. 6,287,516, 6,730,266; 6,736,972; 6,787,404; and U.S. Published Patent Application No. 20060129082, all of which are hereby incorporated by reference.

There is growing scientific evidence that further increasing the filtration rate in hemofiltration may be of benefit to many patients with conditions that include sepsis, SIRS, MODS, acute renal failure, and catecholamine-resistant septic shock. This type of therapy is referred to as High-Volume Hemofiltration ("HVHF"). As used herein, the rate of ultrafiltrate production is the" ultrafiltration rate," and is expressed in milliliters per minute.

Despite the potential advantages of HVHF, problems with HVHF that may limit its clinical use include:

(i) risk of fluid balance errors,

(ii) deleterious depletion of desirable blood components (e.g., nutrients, hormones, medications used in a patient, vitamins, and certain blood clotting factors);

(iii) risk of hypothermia; and

(iv) a high cost of therapy due to consumption of albumin, fresh frozen plasma and large amounts (up to 220 L/day) of sterile hemofiltration solution.

The use of cascade hemofiltration methods may reduce the amount of fluid discarded (and necessarily replaced). In cascade hemofiltration, a secondary hollow-fiber filtration cartridge removes fluid and low molecular weight components from the ultrafiltrate for return to the patient, thereby reducing the quantity of replacement fluid needed. Accordingly, the quantity of waste generated is reduced. To accomplish this, the molecular weight cutoff value for the secondary filter must be less than for primary filter. Examples of hemofiltration systems with coupled filters include those described in US Patent, 6,198,681, US Patent Application Publication No. 20040182787; Ho, et al., Gut, 2002, 50, 869-876; and Bruni, et al., Transfusion Sci. 1999, 21, 193-199, all of which are hereby incorporated herein by reference.

Despite the advantages of cascade hemofiltration in conserving fluid, if used for HVHF, the aforementioned examples still generate far more waste and necessitate administration of a correspondingly large volume of replacement fluid than is either economical, convenient or safe. For example, the method described in US Patent Application Publication No. 20040182787 might be expected to generate as much as about 70 L/day of waste under HVHF conditions. Additionally, such a treatment would cause the loss of amino acids, hormones and other beneficial molecules including medications that might be administered in a clinical setting, such as antibiotics, diuretics, cardiotropes, vasopressors, sedatives, and analgesics.

Summary of the Invention

In an illustrative embodiments of the present invention, a blood purification apparatus includes a primary purification device that receives a primary input fluid at an input via a primary inlet line. The primary purification device is adapted to partition the input fluid into a first output stream that is enriched in larger components and a second output stream that is enriched in smaller components. The first output stream is returnable to the patient via a primary outlet line. A reservoir stores reservoir fluid and is positioned to accept the second output stream. A secondary purification device is in fluid communication with the reservoir, receives reservoir fluid from the reservoir and partitions the reservoir fluid into a third output stream enriched in larger components and a fourth output stream enriched in smaller components. The fourth output stream is coupled to a position selected from the first output

stream and the primary inlet line, and the third output stream is coupled to the reservoir.

Optionally or in addition, the first and second purification devices may be a first hollow-fiber filter and a second hollow-fiber filter. The first filter may have a sieving distribution favoring larger components and the second filter may have a sieving distribution favoring smaller components, thereby retaining intermediately-sized components in the reservoir. The nominal molecular weight cutoff of the first filter may be less than about 4,000,000 daltons and the nominal molecular weight cutoff of the second filter may be less than about 2,000,000 daltons. The molecular weight cutoffs of the primary and secondary purification devices may be selected to cause retention of a toxin binding protein in the reservoir. The toxin-binding protein may be albumin. The molecular weight cutoff of the primary purification device may be selected to direct immunoglobulins and molecules larger than immunoglobulins to the first output stream. The effective or nominal molecular weight cutoffs of the primary purification device may be between 50,000 and 2,000,000 daltons.

The apparatus may also include an optional tertiary purification device adapted to remove toxins that are normally removed by the kidney or liver. For example, the tertiary purification device may be a dialysis device or an adsorption device.

Optionally or in addition, the apparatus may include a pumping system that is coupled to cause flow through the primary purification device and through the secondary purification device. The pumping system may include at least one centrifugal pump. The apparatus may be configured so that the flow rates of the second and the fourth output streams may be approximately equal. The pumping system may operate to induce a fluid flow through the primary purification device at the rate that is between 10 ml/min and 5000 ml/min. The pumping system may operate to induce a flow of the second output stream at the rate that is between 1 ml/min and 1500 ml/min. The pumping system may operate to induce a fluid flow through the second purification device at a rate that is between 10 ml/min and 5,000 ml/min. The pumping system may operate to induce a flow of the fourth output stream having a rate that is between 1 ml/min and 1500 ml/min. The pumping system may operate in a manner so as to maintain an approximately constant level of fluid in the reservoir. The reservoir may include an inlet and an outlet port. The fluid source may be a patient vasculature or a fluid source reservoir.

In accordance with another embodiment of the invention, a method for removing a component species from a source (e.g., blood or other bodily fluid in a reservoir) includes receiving a primary input fluid via an inlet line. The primary input fluid contains components of the blood. The input fluid is partitioned into a first output stream that is enriched in larger components and a second output stream that is enriched in smaller components. The first output stream is returned to the blood source and the second output stream is collected in a reservoir. Fluid is obtained from the reservoir and partitioned into a third output stream that is enriched in larger components and a fourth output stream that is enriched in smaller components. The fourth output stream is directed to merge with a fluid the input fluid stream or the first output stream. The third output stream is returned to the reservoir.

Optionally or in addition, prior to initiating fluid flow, the reservoir may be filled with a replacement fluid. The replacement fluid may include an effective does of a therapeutic agent. Optionally or in addition, the replacement fluid may include a toxin-binding molecule. The toxin-binding molecule may be, for example, albumin. At least some of the fluid in the reservoir may be replaced with a substantially toxin-free replacement fluid.

Optionally or in addition, the flow rates in the respective streams are controlled so that no additional replacement fluid need be provided to the patient. The flow rate of the second stream and the fourth stream may be about equal so that the fluid enters the reservoir at about the same rate as fluid is removed from the reservoir.

Optionally or in addition, toxins may be removed from a fluid derived from the reservoir with a toxin-binding stationary phase. Toxin molecules in the fourth output stream may be removed by dialysis.

Optionally or in addition, the fluid source may be a patient and the input fluid drawn from the patient through the inlet line. The first output stream returns to the patient via an outlet line. The patient, inlet line, and outlet line form a circuit.

Optionally or in addition, the partitioning of the input fluid includes causing albumin to enter the second output stream and the partitioning of the reservoir fluid causes the return of albumin to the reservoir in the third output stream. Resultantly, albumin concentrates in the reservoir over time. The bodily fluid may be blood in a patient or in a reservoir or may be a non-blood fluid or blood fraction such as plasma, serum, cerebro-spinal fluid, or ascitic fluid.

Optionally or in addition, fluid may be recovered from the reservoir (e.g., after treatment). A valuable biological component may be extracted from the fluid and used for research or therapeutic uses including administering the component to a patient.

In accordance with yet another embodiment of the invention, a method for purifying a source of blood or blood-derived fluid includes creating a primary circuit coupled to the source. The primary circuit includes a primary purification device. Fluid is induced to flow from the source through the primary circuit and primary purification device to generate an output stream containing intermediate weight molecules from the blood. A reservoir collects the output stream containing intermediate weight molecules. A fluid fraction is extracted from the reservoir in a manner that leaves the intermediate weight molecules in the reservoir. As a result, the concentration of intermediate weight molecules in the reservoir will increase over time.

Optionally or in addition, the extracted fluid fraction may be returned to the source. The extracted fluid fraction may be returned to the source via the primary purification device. The extraction may be accomplished using a secondary purification device.

Optionally or in addition, a dialysis or adsorption device may be used to remove low molecular weight toxins.

In accordance with another embodiment of the invention, a method for purifying a first fluid includes removing a quantity of the first fluid from a source, selectively extracting toxin-carrying molecules from the first fluid to generate an extract fluid enriched in the toxin-carrying molecules, storing the extract fluid, recovering molecules of a lower molecular weight than the extracted toxin-carrying molecules from the extract fluid; and returning the molecules of a lower molecular weight to the source.

Optionally or in addition, the steps of removing, extracting, storing, recovering and returning are performed concurrently.

Optionally or in addition, the toxin-carrying molecule is a protein. For example, the toxin-carrying molecule may be albumin.

Brief Description of the Drawings

The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

Fig. 1 is a flow diagram showing a general method for purifying a fluid in accordance with an embodiment of the present invention;

Fig. 2 is a flow diagram of a specific embodiment in accordance with the method of Fig. 1;

Fig. 3 is a flow diagram of a further specific embodiment in accordance with the method of Fig. 1;

Fig. 4a is a block diagram showing a fluid-conserving cascade hemofiltration system, in a pre-dilution configuration, in accordance with an embodiment of the invention;

Fig. 4b is a block diagram showing a fluid-conserving cascade hemofiltration system in a post-dilution configuration, in accordance with an embodiment of the invention;

Fig. 5 is a schematic of a cascade hemofiltration system in accordance with the embodiment of Fig. 1;

Fig. 6a is a block diagram showing a fluid-conserving cascade hemofiltration system with an adsorptive column, in a pre-dilution configuration, in accordance with an embodiment of the invention;

Fig. 6b is a block diagram showing a fluid-conserving cascade hemofiltration system with an adsorptive column, in a post-dilution configuration, in accordance with an embodiment of the invention;

Fig. 7 is a schematic of a cascade hemofiltration system with an adsorptive column in accordance with the embodiment of Fig. 3;

Fig. 8 is a block diagram showing a fluid-conserving cascade hemofiltration system with a dialysis cartridge, in accordance with an embodiment of the invention; and

Fig. 9 is a schematic of a cascade hemofiltration system with a dialysis cartridge in accordance with the embodiment of Fig. 5.

Detailed Description of Specific Embodiments

Definitions. As used in this description and the accompanying claims, the following terms shall have the meanings indicated, unless the context otherwise requires:

"Toxins" means components, which due to a detrimentally high concentration in the body, may be beneficially removed from a patient. Examples of toxins include any of a variety of such molecules, which due to a detrimentally high concentration in the body, play a role in the pathophysiology of specific diseases or failure of one or more body organs. Such toxins include ammonia, urea, creatinine, free bile acids, bilirubin, phenols, inflammatory mediators ("IMs"; typically cytokines, interleukins and chemokines), and other molecules normally removed by the liver, lungs, gastrointestinal tract, kidneys, and other tissues and organs.

A "toxin-binding molecule" is a molecule, typically a macromolecule such as a protein that binds toxins. Albumin is used throughout as an exemplary toxin-binding molecule, but other proteins or non-protein macromolecules may be used as toxin-binding molecules as well.

"Components" means molecules, ions, macromolecular complexes, cells, aggregates, fragments or portions thereof, or other species that are dissolved or suspended in a fluid.

A "purification device" means a device that partitions components in an input fluid into a plurality of output streams, each containing a distribution of components that is a proper subset of the input stream components. Examples of purification devices include hemofilters, hollow-fiber hemofilters, dialysis cartridges, centrifuges and systems based on gradient centrifugation with or without use of substances such as ficoll.

An "output stream enriched in smaller components", in the context of a purification device, means a fluid stream, resulting from passage of an input fluid through the purification device, having a distribution of components that is, by a statistical measure, of lower molecular weight or hydrodynamic radius than the distribution of components in the input fluid. Examples of such statistical measures include the mean, median, mode, and range.

An "output stream enriched in larger components", in the context of a purification device, means a fluid stream, resulting from passage of an input fluid through the purification device, having a distribution of components that is, by a statistical measure, of

higher molecular weight or hydrodynamic radius than the distribution of components in the input fluid. Examples of such statistical measures include the mean, median, mode, and range.

A "nominal molecular weight cutoff" means the mean pore size of a semipermeable membrane (e.g., as stated by the manufacturer).

A "90% effective molecular weight cutoff" of a purification device means the molecular weight of components of an input fluid at which the purification device will act to direct at least 90% of those components to the output stream enriched in larger components.

A "sieving coefficient" is a measure predictive of the fractional permeation of a given blood component placed on one side of a semipermeable membrane.

A "sieving distribution" of a semipermeable membrane is the set of sieving coefficients corresponding to a plurality of components found in a fluid sample exposed to the membrane.

A "sieving distribution favoring larger components" in the context of a purification device, means that the purification device produces an output stream enriched in larger components.

A "sieving distribution favoring smaller components" in the context of a purification device, means that the purification device produces an output stream enriched in smaller components.

In illustrative embodiments of the present invention, a purification system removes toxins from a biological fluid without discarding a large portion of the fluid. As a result, large amounts of replacement fluid need not be administered to the patient. Embodiments may be used to treat acute and chronic liver failure, hepato-renal syndrome, renal failure, trauma (the crush syndrome), congestive heart failure, rheumatoid arthritis, infection, sepsis, hyperlipidemia, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multiorgan dysfunction syndrome (MODS), burns, certain congenital disorders (e.g., the Guillain-Barre syndrome, Goddpasture's syndrome, anti-GMB nephritis, Waldenstrom's macroglobulinemia, systemic lupus erythematosus) and other diseases or conditions resulting in accumulation of toxins, including mediators of inflammation and other harmful components in the blood.

Embodiments remove inflammatory mediators from bodily fluids. Other embodiments may include the use of complementary purification elements to remove toxins that are normally excreted, metabolized, or otherwise processed by the liver or kidneys. Examples of complementary purification elements include absorptive filters, adsorptive columns, dialysis cartridges, affinity columns, columns loaded with particles with specific antibodies attached to them, and cell-based artificial organs (including artificial livers). For simplicity, certain illustrative embodiments described herein relate to the purification of blood, but could also be used to purify blood plasma, blood serum, other blood fractions, or non-blood complex body fluids such as ascitic fluid and cerebro-spinal fluid. Related embodiments of the present invention provide methods and apparatus for efficiently purifying blood using ultrafiltration with a minimum of wasted fluid and minimal or no loss of beneficial molecules including hormones, electrolytes, nutrients and administered nutrients and medications (e.g., antibiotics, antivirals, diuretics, cardiotropes, vasopressors, steroids, sedatives and analgesics).

Fig. 1 shows a flow diagram of a method in accordance with an embodiment of the invention. A fluid, such as blood, blood plasma or other blood-derived fluid, is withdrawn from a source, such as a reservoir or human patient (step 100). A toxin-carrying molecule is extracted from the fluid (step 110). The toxin-carrying molecule may be, for instance, albumin. The so-formed extract fluid is stored in a reservoir (step 120). Lower molecular weight molecules (e.g., water, salts, antibiotics, nutrients, small molecule drugs, etc.) are extracted from the fluid (step 130). The lower molecular weight molecules are recycled by returning them to the source (step 140). This process (steps 100-140) may be repeated or performed continuously.

Fig. 2 shows a flow diagram for another a method in accordance with an embodiment of the present invention. A primary circuit is created (step 200). The primary circuit includes an in-line primary purification device. Fluid is caused to flow from the source and through the primary circuit (step 210). The fluid flow may be induced by pumping, force of gravity, centrifugation, or other suitable method. The action of the primary purification device results in the generation of an output stream that contains intermediate weight molecules (step 220). The intermediate weight molecules are larger than the low molecular weight molecules of step 130 of Fig. 1, but are smaller than molecules such as antibodies or

cellular components such as red blood cells that are to be retained in the fluid source. Albumin is a specific example of an intermediate weight molecule that also happens to be a toxin-binding protein molecule. The output stream is collected in a reservoir (step 230). Fluid containing lower molecular weight molecules is extracted from the reservoir (step 240) in a manner that leaves the intermediate weight molecules in the reservoir. As a result, if the volume of fluid in the reservoir is constant or only slowly increasing, the intermediate weight molecules retained in the reservoir will increase in concentration over time. Thus, the reservoir may be thought of as a sink for intermediate-weight molecules.

Fig. 3 shows another flow diagram for yet another method in accordance with an embodiment of the invention. An input fluid is received (step 300). The input fluid is partitioned into two output streams (step 310). A first output stream is relatively enriched in larger components derived from the source fluid and a second output stream is relatively enriched in smaller components derived from the source fluid. The first stream (with the larger components) is returned to the blood source (step 320). The second stream is collected in a reservoir (step 330). Fluid collected in the reservoir is obtained and partitioned into two further streams, one containing fluid enriched in relatively larger components and the other containing fluid enriched in relatively smaller components (step 340). The stream enriched in the larger components (but also including smaller components) is returned to the reservoir and retained in it (step 360). The stream enriched in the smaller components is recycled (step 350); for example, by returning the stream to the source.

Fig. 4a shows a block-diagram for a cascade hemofiltration system in accordance with an embodiment of the present invention. Fluid (e.g., blood or plasma) is transferred from a fluid source (e.g., a patient, or reservoir of blood collected from a patient) via a primary inlet line **31** to an input of a primary purification device **30**. The primary purification device **30** partitions the blood into two streams: a first output stream ("a primary return stream") and a second output stream ("a primary ultrafiltrate stream"). Due to the action of the primary purification device, the primary return stream will contain larger components (as measured by hydrodynamic radius or mass) and the primary ultrafiltrate stream will contain smaller components including toxins and other molecular components that are to be removed, as well as components that are to be returned to the patient. The larger components (e.g., blood cells, antibodies and other large proteins) in the return stream

flow back to the fluid source through a primary return outlet line **32**. The primary purification device **30** provides the primary ultrafiltrate stream via a second outlet, which flows a through primary ultrafiltrate line **33**, into a reservoir **50**. The inlet line **31**, primary purification device **30**, and primary outlet line **32** together with the fluid source define a primary circuit when connected with a fluid source. The lines **31-33** and other lines described herein may be implemented, as is well known in the art, as standard medical-grade tubing or other suitable conduit structure.

A secondary purification device **40** accepts the toxin-containing fluid from the reservoir **50,** and creates two output streams from this fluid; a fluid having relatively smaller molecules (e.g., nutrients, medications, electrolytes, water and hormones) for return to the patient and a fluid for return to the reservoir **50** that contains relatively larger toxins (e.g., albumin-bound toxins, and mediators of inflammation such as cytokine). The returned fluid, in addition to ions, sugars, nutrients, hormones and medications may include relatively smaller toxins such as urea, creatinine and ammonia, and other small toxic components. As described below, the smaller toxins maybe removed or inactivated using various techniques, or may be returned to the patient for metabolism and excretion. By extracting fluid that contains only small toxins and other small components from the fluid held in the reservoir **50**, and returning fluid enriched with larger toxins to the reservoir **50**, the larger toxins may thereby accumulate in the reservoir **50**. At the same time, by returning fluid that contains water and small solutes to the fluid source (e.g., patient's blood circulation), only minimal or no replacement of fluid and incidental molecules is needed.

The secondary purification device **40** may operate much like the primary purification device **30**, but selects for and emits an ultrafiltrate with components smaller than those selected by the primary filtration device **30**. The secondary purification device **40** draws toxin-laden fluid from the reservoir **50** through a secondary inlet line **41** and partitions the fluid into two streams: a third stream (the first two streams are associated with the primary purification device discussed previously, and we here call the third stream a "secondary return stream") containing relatively large components, and a fourth stream (which we here call the "secondary ultrafiltrate stream") containing relatively small components. The secondary return stream flows back to the reservoir via secondary outlet line **42**, and the secondary ultrafiltrate stream flows, via secondary ultrafiltrate line **43,** back to the primary

circuit. In this embodiment, the secondary ultrafiltrate line **43** connects to the primary circuit at or upstream of an inlet of the primary purification device **30** (a "pre-dilution" configuration). Because intermediate-sized toxins will exit the primary purification device **30** in the primary ultrafiltrate stream and enter the reservoir **50,** yet will be returned to the reservoir in the secondary return stream emanating from the secondary purification device **40,** the concentration of intermediate-sized toxins, such as IMs, in the reservoir **50** will increase as a function of cumulative fluid flow through the primary purification device **30**.

Thus, as compared to prior art systems and methods that involve discarding much or all of the primary ultrafiltrate stream, the volume of replacement fluid needed is reduced or completely eliminated because the system of the present embodiment recycles water and lower molecular weight components. Like hemofiltration methods of the prior art, the system of Fig. 4a employs a toxin-sink – the reservoir **50**. However, unlike the prior art methods, in which the amount of fluid committed to the toxin-sink expands indefinitely with use, the reservoir **50** may have a limited volume because the concentration of toxins in the reservoir **50** will increase over time. By beginning a blood purification procedure on a patient with replacement fluid (e.g. 0.1L to 10L of electrolyte or albumin solution) in the reservoir **50**, it may be possible to perform the procedure with no additional source of replacement fluid. Alternately, after extended periods of use, it may be desirable or more efficacious to manually or automatically discard or replace all or some of the toxin-containing fluid in the reservoir **50**. For added convenience and therapeutic utility, the replacement fluid added to the reservoir may also contain drugs, sorbents, or other therapeutic substances.

In an alternate embodiment, the secondary ultrafiltrate stream flows, via the secondary ultrafiltrate line **43,** back to the primary circuit downstream of the primary purification device **30**, e.g., by joining with the primary outlet line **32.** Such a "post-dilution" configuration is shown in Fig. 4b. Alternately, the secondary ultrafiltrate stream may be returned directly to the fluid source.

By way of example, the primary purification device **30** may be a permselective hemofiltration cartridge with an effective molecular weight cutoff value (e.g., a 90% effective molecular cutoff) of between 5000 and 100,000 daltons and the secondary purification device **40** may be a permselective plasmafiltration cartridge with an effective

molecular weight cutoff value of between 100 and 5000 daltons. In a further example, if the primary purification device **30** has an effective cutoff value of 150,000 daltons and the secondary purification device **40** has an effective cutoff value of about 500 daltons, then molecules with a molecular weight of between about 500 and 150,000 daltons (including albumin, a 69,000 dalton protein) will tend to concentrate in the reservoir **50**, although these ranges may change depending on which components one wishes to remove from the blood and changes in the effective molecular weight cutoffs as a function of fluid flux. These changes may be a function of feed flow, ultrafiltration rate, composition and structure of the semipermeable membrane, fluid viscosity, fluid osmolarity, membrane hydrophilicity, presence or lack of an anti-fouling membrane coating, membrane polarity, and other factors. Since many inflammatory mediators fall within this range, IMs will concentrate in the reservoir **50** and be removed from the blood. Additionally toxins bound to toxin-binding molecules may accumulate in the reservoir **50**, including those bound to albumin, if present. The effective cutoff value and sieving coefficients for individual blood/plasma components and the nominal cutoff value (related to the average pore size before use) of a given permselective membrane may differ as a function of chemical and mechanical characteristics of the permselective membrane (e.g., type of polymer and porophores used, porosity wetting properties, charge, symmetry, resistance to fouling, surface exchange area, thickness),operational characteristics (feed flow rate, velocity, ultrafiltration rate, transmembrane pressure), and interactions between blood or plasma components and the filter membrane. For example, in selecting a membrane that has an effective molecular weight cutoff that allows permeation of albumin, a polysulfone membrane may require a nominal cutoff value of 400 kDa, while a polyethersulfone or cellulose acetate membrane may require a nominal cutoff value of only 100 kDa. Additionally, the effective molecular weight cutoff of the primary purification device may be selected to be low enough to retain immunoglobulins and return them to the blood source, thereby retaining the beneficial effects of these molecules. Generally, the molecular weight cutoff will be selected to be below about 1,000,000 daltons for this purpose.

The secondary inlet line **41**, secondary purification device **40**, and secondary outlet line **42** together constitute a secondary fluidic circuit. Thus, the primary ultrafiltrate line **33**, and the secondary ultrafiltrate line **43** serve to transfer ultrafiltrate fluid between the primary

and secondary circuits. In the embodiments shown in Figs. 4a and 4b, the secondary ultrafiltrate is returned to the primary fluidic circuit either upstream or downstream of the primary purification device **30**. These configurations are referred to as pre-dilution and post-dilution configurations, respectively, since they dilute the blood before it enters the primary purification device or after it exits the primary purification device and before it is directly returned to the patient. Pre-dilution may prevent adverse effects, such as protein aggregation and blood coagulation in the primary purification device **30**, that may occur due to concentration of the blood by the primary purification device. Post-dilution may enhance blood/plasma purification because in such an embodiment, the secondary output stream (primary ultrafiltrate) is not diluted.

Fig. 5 shows a specific hemofiltration system configuration in accordance with the more general embodiment of Fig 4a. The system is connected to the vasculature of a patient **10** by veno-venous attachment. A primary circuit pump **51** urges blood through the primary circuit.

Pumping of blood through the primary circuit induces production of primary ultrafiltrate, which is urged by a primary ultrafiltrate pump **52** through the primary ultrafiltrate line **33** to the reservoir **50**. A secondary circuit pump **53** induces fluid to flow from the reservoir through the secondary circuit. A secondary ultrafiltrate pump **54** urges the secondary ultrafiltrate to the primary circuit in pre-dilution configuration. (Collectively, pumps **51**, **52**, **53**, and **54** constitute a pumping system for the embodiment.) Any of a variety of commercially available pumps may be used. For effective filtration, it may be desirable to use one or more pumps capable of generating high flow rates**.** Care should be taken, however, to chose a combination of pumps and flow rates so as to avoid hemolysis due to pumping; for example, the use of a centrifugal pump for primary circuit pump **51** may allow flow rates of as high as 0.2 to 5L/min without causing hemolysis.

As an alternative or supplement to the use of an additional replacement fluid reservoir **49** (e.g., an intravenous fluid bag separately connected to the patient), the reservoir **50** may be filled with replacement fluid prior to the start of therapy. Optionally, the replacement fluid may contain therapeutic agents for adsorption and retention of specific molecules in the reservoir **50** or for delivery to a patient such as small-molecule antibiotics, anti-coagulant and anti-inflammatory compounds. No additional replacement fluid may be needed if the

reservoir **50** is pre-filled with replacement fluid and the primary ultrafiltrate flow rate and the secondary ultrafiltrate flow rate are equal or nearly equal. Approximately equal flow may be achieved by setting the ultrafiltrate pumps **52** and **54** to similar levels of flow. However, a small degree of drift in the reservoir fluid level may be permissible depending on the size of the reservoir and the length of treatment. Alternately, by adjusting the pumps, the production of primary and/or secondary ultrafiltrate may be altered to increase or decrease the level of fluid in the reservoir **50**. Fluid may be periodically removed from the reservoir **50**, discarded, and replaced with toxin-free replacement fluid. Replacing the fluid may be especially advantageous during high-volume hemofiltration or hemofiltration lasting for more than 8 hours. For example, biochemical non-idealities may alter the binding capacity of toxin-binding molecules at high concentrations, or the secondary purification may tend to foul above a certain concentration of proteins in the secondary circuit is reached.

The range of flow rates may generally be between 10 and 5000 ml/min in the primary and secondary circuits, which will allow production of between about 1 and 1500 ml/min of primary and secondary ultrafiltrate. Since the fluid held in the reservoir **50** is excluded from the primary circuit, the fluid flow rate through the secondary purification device **40** may be chosen to be very high so as to maintain the patency of the hollow fiber lumens and to protect the permselective membrane against fouling (e.g., due to occlusion of pores by proteins, protein fragments and other components). For example, the flow rate of fluid entering the secondary purification device **40** may be about 10 times greater than then the rate at which fluid enters the primary purification device **30**.

In illustrative embodiments, the fluid flow through the primary purification device **30** may be about between 10 and 5000 ml/min. The flow rate of the second output stream (the primary ultrafiltration rate) may be about 1 to 500 or about 1 to 1500 ml/min.

Various control schemes may ensure the desired system performance. For example, flow-rate and/or reservoir level sensors may be employed along with a microcontroller to adjust the pumping rates so as to ensure a proper fluid level in the reservoir **50**. To further increase safety, efficacy, or convenience, additional sensors, such as blood-chemistry sensors, may also be incorporated into the system.

In operation, the pressure generated by pumping system in the inlet line 31 and ultrafiltrate line 43 will balance so that blood from the patient does not enter the secondary

purification device 40 via retrograde flow from the inlet line 31 to the ultrafiltrate line 43, or to the patient via flow in the reverse direction. Alternately or in addition, one or more active valve or passive valves (e.g., check-valves) may be used to prevent such unwanted flows.

The primary purification device **30** of Fig. 5 is a hollow-fiber hemofilter with a membrane having a nominal molecular weight cutoff of between 1 and 4,000,000 daltons. The secondary purification device **40** is a hollow-fiber plasmafilter having a nominal molecular weight cutoff of between 1 and 2,000,000 daltons. The primary purification device **30** has a sieving distribution favoring larger components, while the secondary purification device **40** has a sieving distribution favoring smaller components. As a result, intermediately-sized components, such as immune modulators or toxin-binding molecules, will collect in the reservoir **50.**

If the primary filter **30** has a molecular weight cutoff that is sufficiently high to allow the passage of albumin to the reservoir **50** (e.g., about 100,000 to 800,000 dalton, depending on the type of permselective filter used), and the secondary filter **40** has a molecular weight cutoff that is sufficiently low to prevent the passage of albumin (e.g., less than about 70,000 daltons), then albumin will be retained in, and concentrate within, the reservoir **50.** Removal of albumin from the blood has the benefit of removing albumin-bound toxins, but may necessitate albumin replacement.

The reservoir **50** of Fig. 5 includes an inlet port for filling the reservoir **50** with fluid, and an outlet port for draining the fluid held within the reservoir **50**. Alternately, the reservoir may be disposable. A disposable reservoir may be secured to the secondary circuit using quick-disconnects for rapidly removing or changing the reservoir fluid. Although depicted as an open basin in the schematic of Fig. 6a, the reservoir should be closed, or otherwise sealed to prevent, among other things, biohazard danger from the patient's blood and to maintain sterility of the system. Replacement fluid introduced into the reservoir may include hemofiltration fluid, a dialysate, electrolyte solution, amino acid solution, albumin solution, human serum, combinations of the foregoing, or any other solution that might be intravenously administered to a patient.

Figs 6a-9 show embodiments which utilize at least one additional, tertiary, purification devices; Figs. 6a-7 show an embodiment which includes an adsorptive device, and Figs. 8-9 show an embodiment which includes a dialysis unit. The purification devices

may operate to remove low molecular weight toxins with the result of clearing these toxins from the blood supply, thus mimicking the action of a healthy liver or kidney. These configurations may replace or supplement the liver or kidney function of a patient in septic shock or with multiorgan dysfunction syndrome. Embodiments that combine sorption and dialysis are also within the scope of the present invention.

Figs. 6a-7 show an embodiment of the present invention that includes an adsorptive device **60** positioned in the secondary ultrafiltrate line **43**. The adsorptive device **60** includes a casing defining one or more chambers, which hold adsorptive material (i.e., a toxin-binding stationary phase) to remove specific toxins. The adsorbent material may include activated charcoal, resins (e.g., uncharged, neutral, anion exchange or cation exchange resins), silica, albumin, immobilized antibodies, immobilized receptors, immobilized specific antagonists, polymers, cellulose derivatives, and immobilized antibiotics, or combinations thereof. The adsorbent material may be organized in a number of ways, e.g., as beads, rods, porous granules, a sieve, a matrix with anchored molecules, etc. The adsorptive device receives the stream of secondary ultrafiltrate and selectively or non-selectively removes components that cause or aggravate liver failure, renal failure or any other disease or pathological condition associated with accumulation in the blood circulation of toxic substances, including: ammonia, phenols, mercaptans, aromatic amino acids, urea, creatinine, oxygen reactive species, nitric oxide, and vasoactive substances. Some commercially available or preclinical systems utilizing adsorptive device technology which may be used with the embodiment of Figs. 6 and 7 include: (1) Adsorba columns (Gambro, Hechingen, Germany) which contains activated charcoal as the sorbent, (2) BioLogic-DT System (HaemoCleanse, West Lafayette, IN), which contains a mixture of charcoal, silica and exchange resins as the sorbent, (3) MARS (Molecular Adsorbent Recirculating System; Gambro GmbH, Hechingene, Germany), which uses charcoal and resin as the sorbent, and (4) Prometheus (Fresenius, Germany), which uses two types of ion exchange resins as the sorbent. Fig. 6b shows a post-dilution configuration for an embodiment that includes an adsorptive device.

In alternate embodiments, the adsorptive device may be positioned at other points in the fluidic system, e.g., the secondary filter inlet line **41** or the secondary filter outlet line **42.** The sorbent may also be included in the reservoir **50** and the reservoir **50** stirred or shaken to encourage toxin binding to the sorbent.

Figs. 8-9 show an embodiment of the present invention that includes further purification of the secondary ultrafiltrate by dialysis. This embodiment includes a dialysis cartridge **70** incorporated into the secondary ultrafiltrate line **43** and connected to a source of dialysis fluid. As with the adsorptive filter, the dialysis cartridge **70** may be incorporated at other fluidic positions within the system, e.g., positioned in the secondary filter inlet line **41** or the secondary filter outlet line **42**. Toxins in the secondary ultrafiltrate that are small enough to cross the dialysis membrane of the cartridge **70** are thus removed and prevented from re-entering the patient **10**. In further related embodiments of the present invention, any of the embodiments previously described may additionally include a cell-based device to provide specific biologic function (e.g., metabolism and/or synthesis of specific blood components). For example, a HepatAssist-2 cartridge loaded with viable liver cells (Arbios Systems, Inc.) may be included in a fluidic line of the system to provide metabolic detoxification. Additionally, various combinations of dialysis, sorption, and cell-based purification may be used.

In further related embodiments, any of the embodiments previously described may utilize a digital control system for regulating flow within parameters as described above and for maintaining acceptable operating conditions.

In a further embodiment, fluid may be recovered from the reservoir **50** and used for research (biomedical or otherwise) or for therapeutic purposes. The reservoir fluid will tend to be enriched in valuable biological components. These components may be recovered by various processing and purification procedures that are known in the art (fractionation, chromatography, etc.) and formulated and packaged for sale and use in research or for administration to patients as therapeutic agents. Example of valuable components include cytokines, chemokines, and immunomodulators.

The described embodiments of the invention are intended to be merely exemplary and numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in the appended claims. For example, the purification devices described herein may be combined with instrumentation for gas exchange (including oxygenation), pathogen sterilization, temperature control, gamma irradiation, ultraviolet light treatment, etc. The

purification devices are not limited to hollow fiber filters, but may operate on other principles, including centrifugation and gradient centrifugation.

What is claimed is:

1. A blood purification apparatus comprising:

a primary purification device to receive, at an input via a primary inlet line, a primary input fluid, the primary purification device adapted to partition the input fluid into a first output stream enriched in larger components and a second output stream enriched in smaller components, wherein the first output stream is returnable to the patient via a primary outlet line;

a reservoir that stores reservoir fluid, such reservoir being positioned to accept the second output stream; and

a secondary purification device, in fluid communication with the reservoir, to receive reservoir fluid from the reservoir and to partition the reservoir fluid into a third output stream enriched in larger components and a fourth output stream enriched in smaller components, wherein the fourth output stream is coupled to a position selected from the first output stream and the primary inlet line, and the third output stream is coupled to the reservoir.

2. An apparatus according to claim 1, wherein the first and second purification devices are a first hollow-fiber filter and a second hollow-fiber filter.

3. An apparatus according to claim 2, wherein the first filter has a sieving distribution favoring larger components and the second filter has a sieving distribution favoring smaller components, thereby retaining intermediately-sized components in the reservoir.

4. An apparatus according to claim 3, wherein the nominal molecular weight cutoff of the first filter is less than about 4,000,000 daltons and the nominal molecular weight cutoff of the second filter is less than about 2,000,000 daltons.

5. An apparatus according to claim 1, further including a tertiary purification device adapted to remove toxins normally removed by the kidney or liver.

6. An apparatus according to claim 6, wherein the tertiary purification device is on of a dialysis device and an adsorption device.

7. An apparatus according to claim 1, further including a pumping system coupled to cause flow through the primary purification device and through the secondary purification device.

8. An apparatus according to claim 7, wherein the pumping system includes at least one centrifugal pump.

9. An apparatus according to claim 7, wherein flow rates of the second and the fourth output streams are approximately equal.

10. An apparatus according to claim 7, wherein the pumping system operates to induce a fluid flow through the primary purification device at the rate that is between 10 ml/min and 5000 ml/min.

11. An apparatus according to claim 7, wherein the pumping system operates to induce a flow of the second output stream at the rate that is between 1 ml/min and 1500 ml/min.

12. An apparatus according to claim 7, wherein the pumping system operates to induce a fluid flow through the second purification device at a rate that is between 10 ml/min and 5,000 ml/min.

13. An apparatus according to claim 7, wherein the pumping system operates to induce a flow of the fourth output stream having a rate that is between 1 ml/min and 1500 ml/min.

14. An apparatus according to claim 7, wherein the pumping system operates in a manner so as to maintain an approximately constant level of fluid in the reservoir.

15. An apparatus according to claim 1, wherein the reservoir includes an inlet and an outlet port.

16. An apparatus according to claim 1, wherein molecular weight cutoffs of the primary and

secondary purification devices are selected so as to cause retention of a toxin binding protein in the reservoir.

17. An apparatus according to claim 16, wherein the toxin binding protein is albumin.

18. An apparatus according to any of the preceding claims, wherein the molecular weight cutoff of the primary purification device is selected to direct immunoglobulins and molecules larger than immunoglobulins to the first output stream.

19. An apparatus according to claims 16 to 18, wherein one of the effective and nominal molecular weight cutoffs of the primary purification device is between 50,000 and 2,000,000 daltons.

20. An apparatus according to any of the preceding claims, further including a fluid source selected from one of a patient vasculature and a fluid source reservoir.

21. A method for removing a component species from a fluid source, the method comprising:

receiving via an inlet line a primary input fluid containing at least components of the source fluid;

partitioning the input fluid into a first output stream enriched in larger components and a second output stream enriched in smaller components;

returning the first output stream to the fluid source;

collecting the second output stream in a reservoir;

obtaining fluid from the reservoir and partitioning the obtained fluid into a third output stream enriched in larger components and a fourth output stream enriched in smaller components;

directing the fourth output stream to merge with a fluid stream chosen from the group consisting of the input fluid or the first output stream; and

returning the third output stream to the reservoir.

22. A method according to claim 21, further comprising, prior to initiation of fluid flow,

filling the reservoir with a replacement fluid.

23. A method according to claim 22, wherein the replacement fluid includes a toxin-binding molecule

24. A method according to claim 23, wherein the toxin-binding molecule is albumin.

25. A method according to claim 22 wherein the replacement fluid includes an effective dose of a therapeutic agent.

26. A method according to claim 21, further comprising controlling flow rates in the respective streams so that no additional replacement fluid need be provided to the patient.

27. A method according to any of claims 21 to 26, wherein the flow rate of the second stream and the fourth stream are about equal so that the fluid enters the reservoir at about the same rate as fluid is removed from the reservoir.

28. A method according to claim 21, further comprising replacing at least some fluid in the reservoir fluid with substantially toxin-free replacement fluid.

29. A method according to claim 21, further comprising removing toxins in fluid derived from the reservoir with a toxin-binding stationary phase.

30. A method according to any of claims 21 to 29, wherein the fluid source is a blood source.

31. A method according to claim 21, wherein the fluid source is a reservoir.

32. A method according to claim 31, wherein the reservoir contains a patient bodily fluid.

33. A method according to claim 32, wherein the bodily fluid is selected from the group consisting of blood, plasma, serum, cerebro-spinal fluid, or ascitic fluid.

34. A method according to claim 21, further including using dialysis to remove toxin molecules from the fourth output stream.

35. A method according to claim 21, wherein the fluid source is a patient, the input fluid is drawn from the patient through the inlet line and the first output stream returns to the patient via an outlet line, wherein the patient, inlet line, and outlet line form a circuit.

36. A method according to any of claims 21 to 35, wherein the partitioning of the input fluid includes causing albumin to enter the second output stream and the partitioning of the reservoir fluid causes the return of albumin to the reservoir in the third output stream so as to cause albumin to concentrate in the reservoir over time.

37. A method according to any of claims 21 to 26, further comprising recovering the fluid from the reservoir.

38. A method according to claim 37, further comprising extracting a valuable biological component.

39. A method according to claim 38, further comprising administering the extracted valuable biological component to a patient.

40. A method according to claims 38 or 39, wherein the valuable biological includes a component is selected from the group consisting of a cytokine, a chemokine, and an immunomodulator.

41. A method according to claims 37 or 40, further comprising using the valuable biological component for research.

42. A blood purification apparatus comprising:

a primary purification means for receiving, at an input via a primary inlet line, a

primary input fluid from a source, and for partitioning the input fluid into a first output stream enriched in larger components and a second output stream enriched in smaller components, wherein the first output stream is returnable to the source via a primary outlet line;

a reservoir that stores reservoir fluid, such reservoir being positioned to accept the second output stream; and

secondary purification means, coupled to the reservoir, for receiving reservoir fluid from the reservoir and for partitioning the reservoir fluid into a third output stream enriched in larger components and a fourth output stream enriched in smaller components, wherein the fourth output stream is coupled to the input or the output of the primary purification means, and the third output stream is coupled to the reservoir.

43. A blood purification apparatus according to claim 42 comprising a tertiary purification means for adsorbing a toxin.

44. A blood purification apparatus according to claim 42 comprising a tertiary purification means for removing toxin by dialysis.

45. A method for purifying a source of blood or blood-derived fluid comprising:

creating a primary circuit coupled to the source, the primary circuit including a primary purification device;

causing fluid to flow from the source through the primary circuit and primary purification device so as to generate an output stream containing intermediate weight molecules from the blood;

collecting the output stream containing intermediate weight molecules in a reservoir;

extracting a fluid fraction from the reservoir in a manner that leaves the intermediate weight molecules in the reservoir so as to cause an increase in the concentration of intermediate weight molecules over time.

46. A method according to claim 45, wherein the extracted fluid fraction is returned to the source.

47. A method according to claim 46, wherein the extracted fluid fraction is returned to the source via the primary purification device.

48. A method according to claim 45, wherein the extraction is accomplished using a secondary purification device.

49. A method according to any of claims 45 to 48, further comprising using a dialysis or adsorption device to remove low molecular weight toxins.

50. A system for purifying a source of blood or blood-derived fluid comprising:

means for creating a primary circuit coupled to the source;

means for causing fluid to flow from the source through a primary circuit containing a primary purification device that removes an output stream containing intermediate weight molecules from the blood;

means for collecting the output stream containing intermediate weight molecules in a reservoir;

means for extracting fluid from the reservoir in a manner that leaves the intermediate weight molecules in the reservoir so as to cause an increase in the concentration of intermediate weight molecules over time.

51. A system according to claim 50, further comprising means for returning the extracted fluid to the source.

52. A system according to claim 51, further comprising means for returning the extracted fluid to the source via the primary purification device.

53. A system according to claim 50, further comprising a secondary purification means for accomplishing the extraction.

54. A system according to any of claims 50 to 53, further comprising dialysis or adsorption

means to remove low molecular weight toxins.

55. A method for purifying a first fluid, the method comprising:

removing a quantity of the first fluid from a source;

selectively extracting toxin-carrying molecules from the first fluid to generate an extract fluid enriched in the toxin-carrying molecules;

storing the extract fluid;

recovering molecules of a lower molecular weight than the extracted toxin-carrying molecules from the extract fluid; and

returning the molecules of a lower molecular weight to the source.

56. A method according to claim 55, wherein the steps of removing, extracting, storing, recovering and returning are performed concurrently.

57. A method according to any of claims 55 or 56, wherein the toxin-carrying molecule is a protein.

58. A method according to claim 57, wherein the protein is albumin.

59. A system for purifying a first fluid, the method comprising:

means for removing a quantity of the first fluid from a source;

means for selectively extracting toxin-carrying molecules from the fluid to generate an extract fluid containing the extracted protein molecules;

means for storing the extract fluid;

means for recovering molecules of a lower molecular weight than the extracted toxin-carrying molecules from the extract fluid; and

means for returning the molecules of a lower molecular weight to the fluid source.

60. A system according to claim 59, further comprising means for removing, extracting, storing, recovering and returning concurrently.

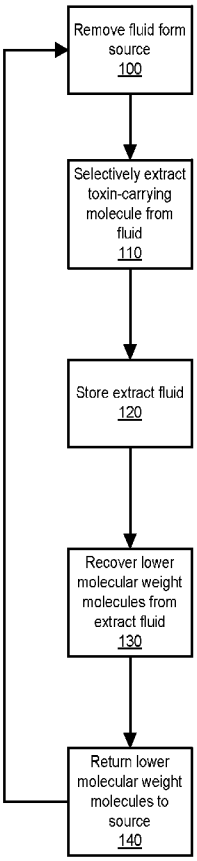

Remove fluid form source
100
Selectively extract toxin-carrying molecule from fluid
110
Store extract fluid
120
Recover lower molecular weight molecules from extract fluid
130
Return lower molecular weight molecules to source
140

Fig. 1

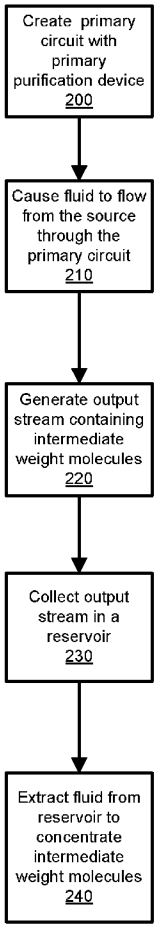

Create primary circuit with primary purification device
200
Cause fluid to flow from the source through the primary circuit
210
Generate output stream containing intermediate weight molecules
220
Collect output stream in a reservoir
230
Extract fluid from reservoir to concentrate intermediate weight molecules
240

Fig. 2

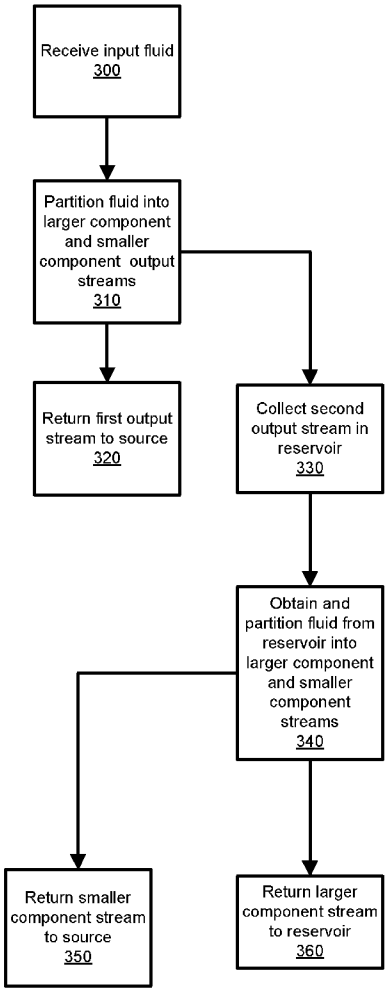

Receive input fluid
300
Partition fluid into larger component and smaller component output streams
310
Return first output stream to source
320
Collect second output stream in reservoir
330
Obtain and partition fluid from reservoir into larger component and smaller component streams
340
Return smaller component stream to source
350
Return larger component stream to reservoir
360

Fig. 3

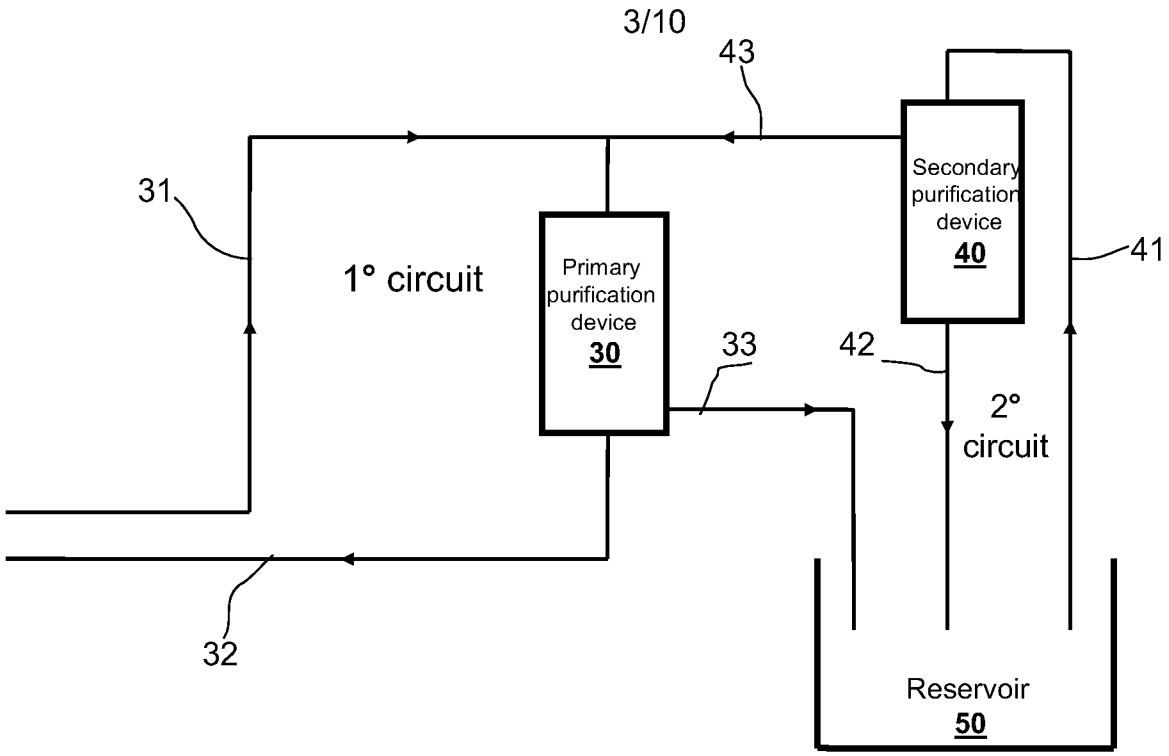

43
31
1° circuit
Primary purification device
30
Secondary purification device
40
41
33
42
2° circuit
32
Reservoir
50

Fig. 4a

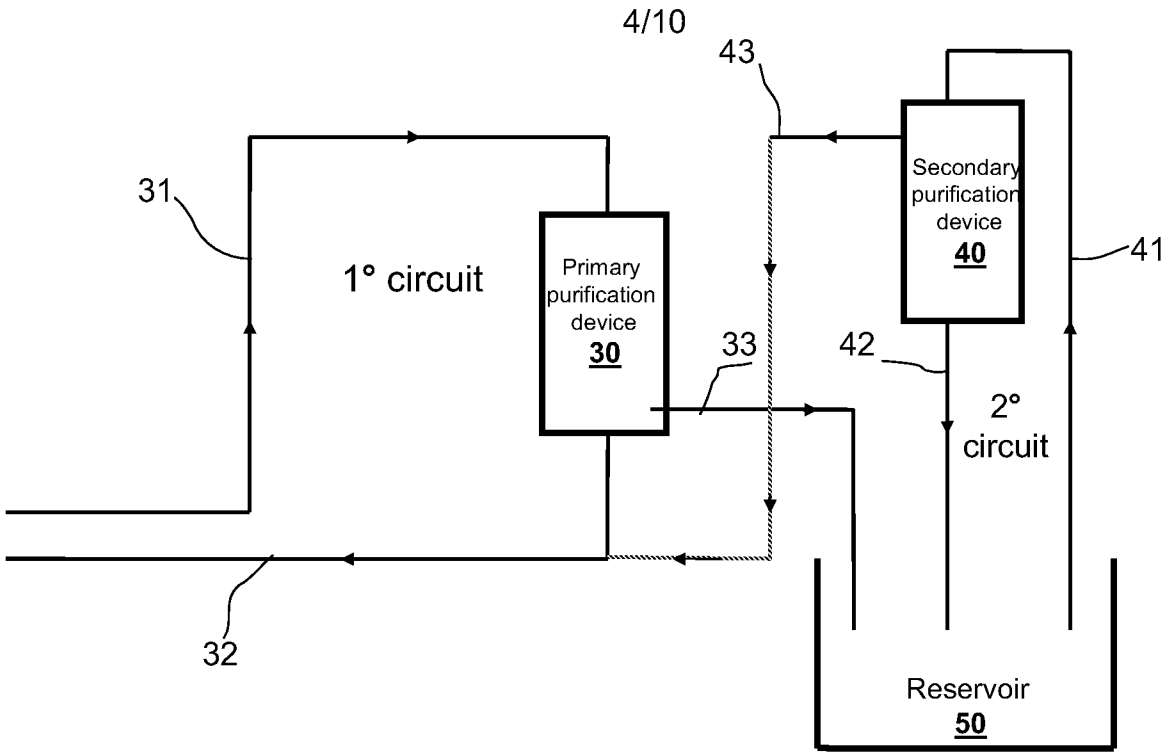

4/10
43
31
1° circuit
Primary purification device
30
Secondary purification device
40
41
33
42
2° circuit
32
Reservoir
50

Fig. 4b

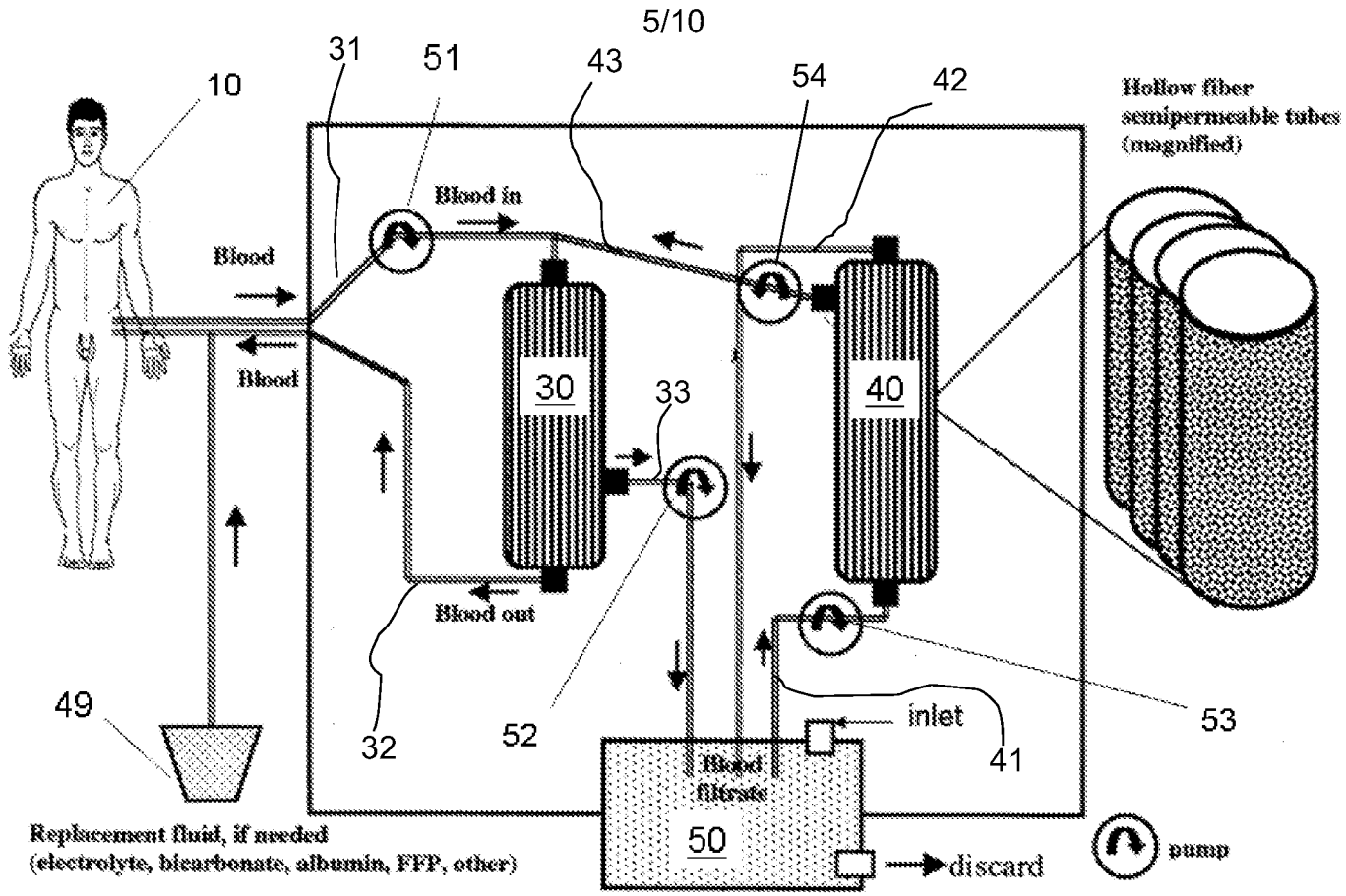

10
31
51
43
54
42
Hollow fiber
semipermeable tubes
(magnified)
Blood in
Blood
Blood
30
33
40
Blood out
49
32
52
inlet
41
53
Blood
filtrate
50
discard
pump
Replacement fluid, if needed
(electrolyte, bicarbonate, albumin, FFP, other)

Fig. 5

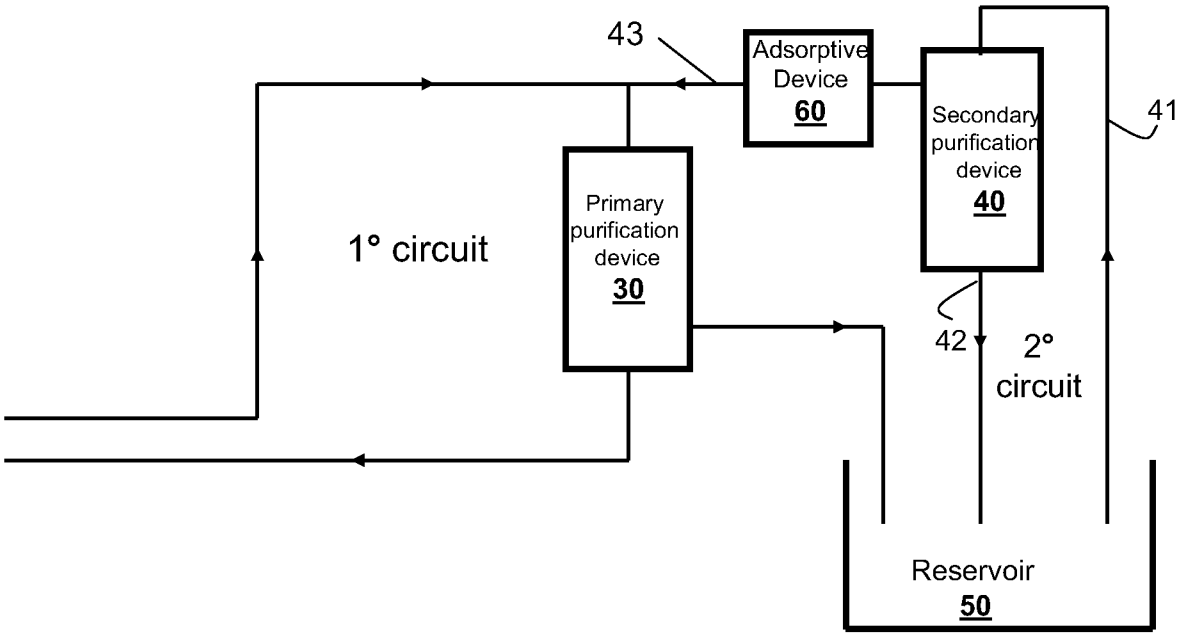

43
Adsorptive Device
60
Secondary purification device
40
41
Primary purification device
30
1° circuit
42
2° circuit
Reservoir
50

Fig. 6a

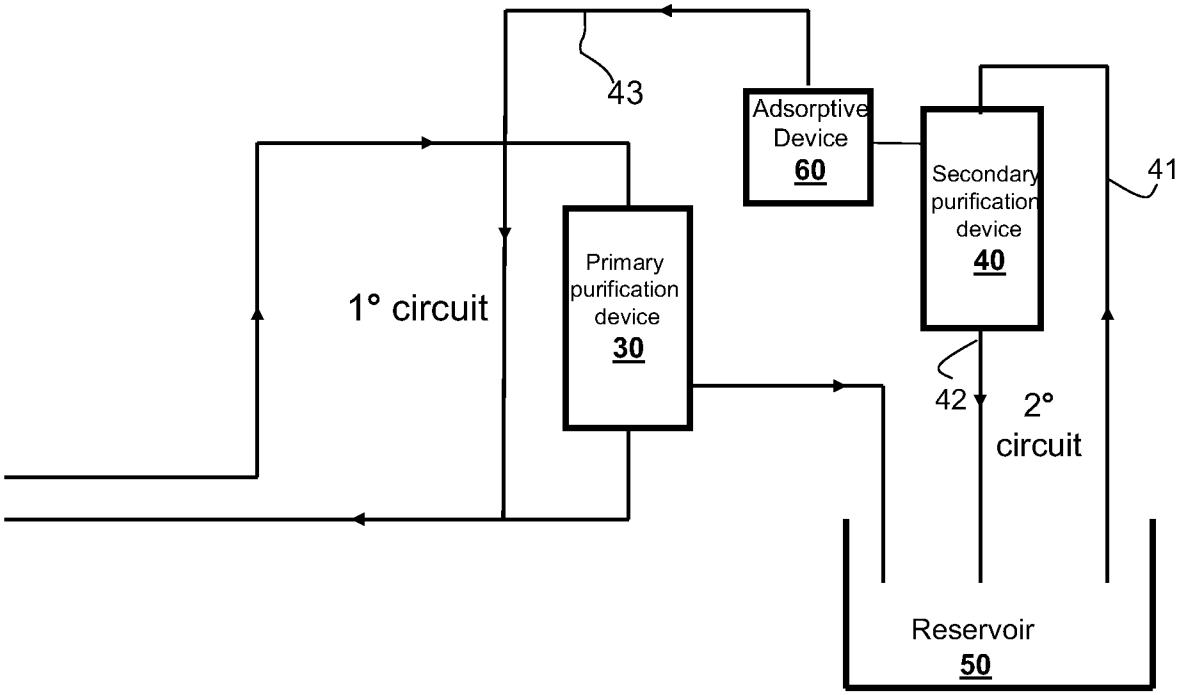

43
Adsorptive Device
60
Secondary purification device
40
41
Primary purification device
30
1° circuit
42
2° circuit
Reservoir
50

Fig. 6b

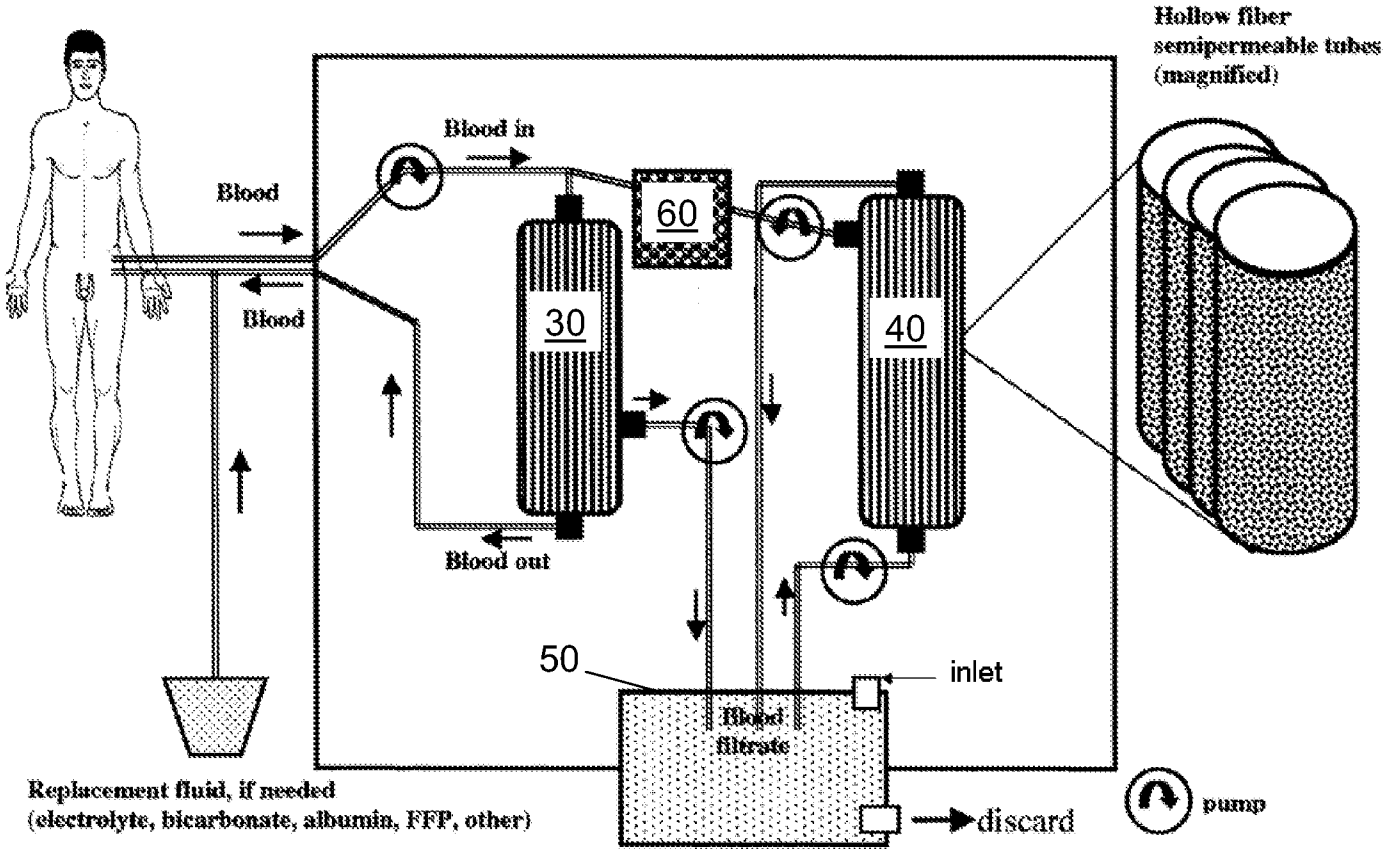

Hollow fiber
semipermeable tubes
(magnified)
Blood in
Blood
Blood
60
30
40
Blood out
50
inlet
Blood
filtrate
Replacement fluid, if needed
(electrolyte, bicarbonate, albumin, FFP, other)
discard
pump

Fig. 7

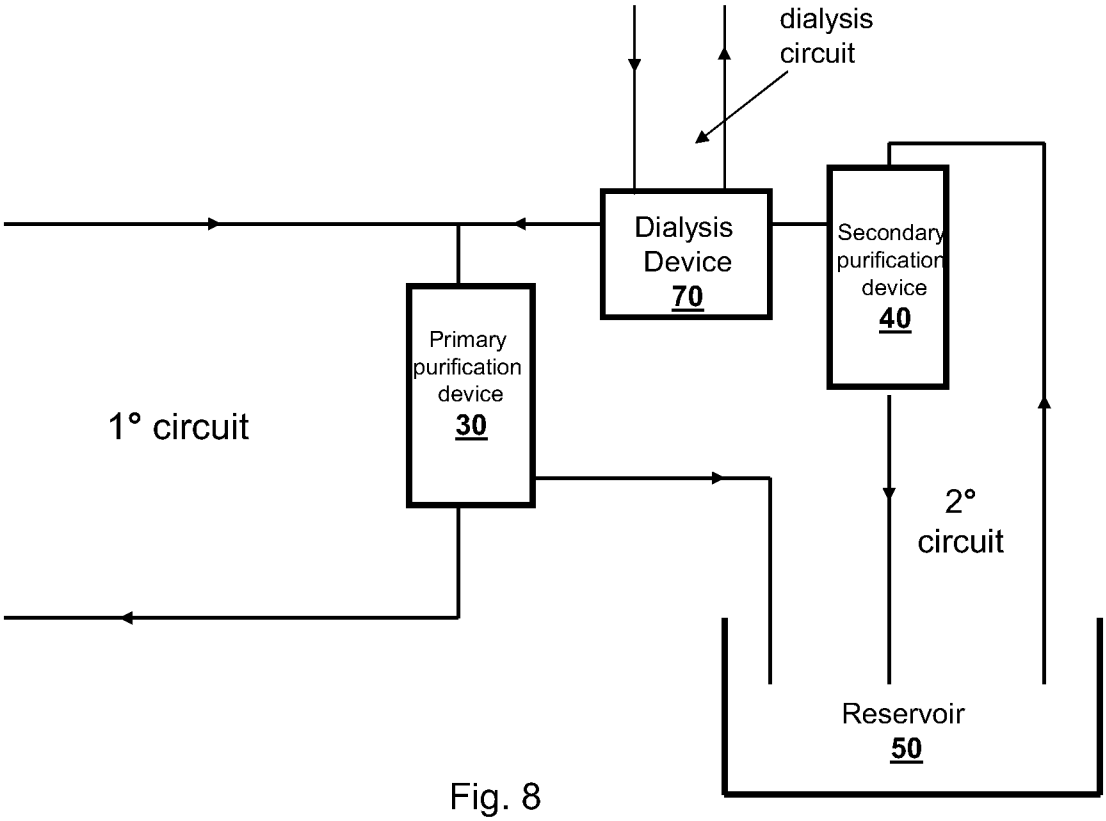

dialysis
circuit
Dialysis
Device
70
Secondary
purification
device
40
Primary
purification
device
30
1° circuit
2°
circuit
Reservoir
50

Fig. 8

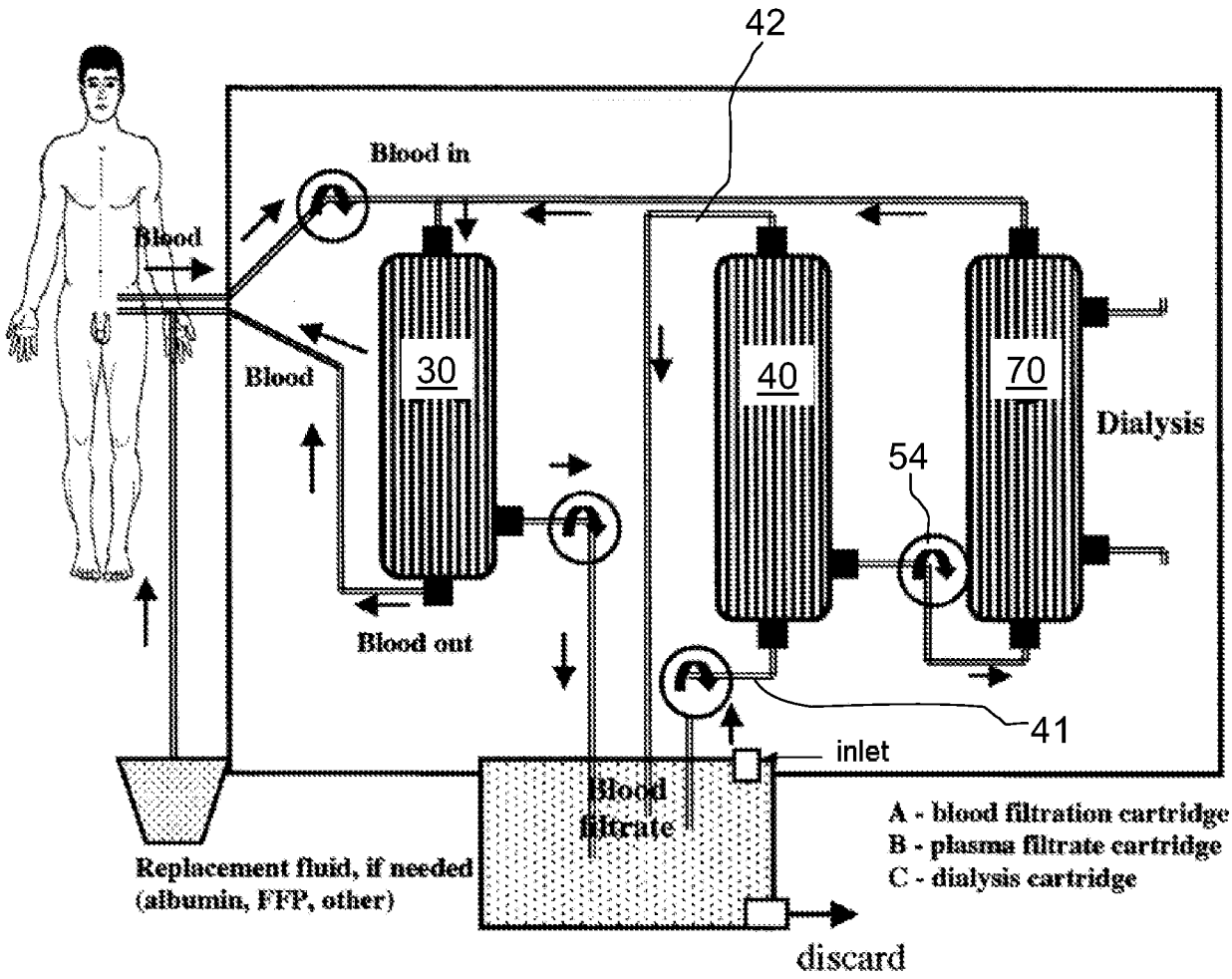

42
Blood in
Blood
Blood
30
40
70
Dialysis
54
Blood out
41
inlet
Blood filtrate
A - blood filtration cartridge
B - plasma filtrate cartridge
C - dialysis cartridge
Replacement fluid, if needed (albumin, FFP, other)
discard

Fig. 9