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(54) Title: SYSTEMS AND METHODS OF BLOOD-BASED THERAPIES HAVING A MICROFLUIDIC MEMBRANELESS EXCHANGE DEVICE

(57) Abstract: The present invention is directed to devices, systems and methods for removing undesirable materials from a sample fluid by contact with a second fluid. The sample fluid flows as a thin layer adjacent to, or between, concurrently flowing layers of the second fluid, without an intervening membrane. In various embodiments, a secondary separator is used to restrict the removal of desirable substances and effect the removal of undesirable substances from blood. The invention is useful in a variety of situations where a sample fluid is to be purified via a diffusion mechanism against an extractor fluid. Moreover, the invention may be used for the removal of components from a sample fluid that vary in size. When blood is the sample fluid, for example, this may include the removal of 'small' molecules, 'middle' molecules, macromolecules, macromolecular aggregates, and cells, from the blood sample to the extractor fluid.

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SYSTEMS AND METHODS OF BLOOD-BASED THERAPIES
HAVING A MICROFLUIDIC MEMBRANELESS EXCHANGE DEVICE

10

Cross-Reference to Related Application

This application claims the benefit of United States Provisional Patent Application No. 60/454,579, filed March 14, 2003, which is hereby incorporated by reference herein in its entirety.

15

Field of the Invention

Generally speaking, the present invention relates to the purification of a sample fluid. More particularly, the present invention relates to the purification of a sample fluid (e.g., blood fluid) by selectively removing components using a microfluidic membraneless exchange device.

Background of the Invention

Extracorporeal processing of blood is known to have many uses. Such processing may be used, for example, to provide treatment of a disease. Hemodialysis is the most 25 commonly employed form of extracorporeal processing for this purpose. Additional uses for extracorporeal processing include extracting blood components useful in either treating others or in research. Apheresis of plasma (i.e., plasmapheresis) and thrombocytes, or platelets, are the procedures most commonly employed for this purpose.

Many different extracorporeal blood processing processes have been developed, each 30 of which seeks to remove certain components from the blood, depending on the reason for processing the blood. (It will be understood that as used herein, blood, or blood fluid, refers to any fluid having blood components from which extraction of certain components, such as toxins or albumin, is desired.) The most common process utilizes an artificial membrane of substantial area, across which selected blood components are induced to flow. This flow is 35 generally induced by a transmembrane difference in either concentration or pressure, or a combination of the two. Another form of blood processing calls for the separation of certain

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5 components from blood by passing the blood over sorbent particles. In yet other forms of blood processing, not practiced as commonly, blood is directly contacted with an immiscible liquid (e.g., a fluorocarbon liquid), with the desired result being the removal of dissolved carbon dioxide and the provision of oxygen. The usefulness of blood processing techniques employing immiscible liquids is limited, however, because these immiscible liquids generally
10 have very limited capacity to accept the blood components that it is desirable to extract.

One common example of a therapeutic use for blood processing is the mitigation of the species and volume imbalances accompanying end-stage renal disease. The population of patients treated in this manner (i.e., through hemodialysis) exceeds 260,000 and continues to grow, with the cost of basic therapy exceeding \$5 billion per year excluding complications.
15 The overwhelming majority of these patients (about 90%), moreover, are treated in dialysis centers, generally in thrice-weekly sessions. While procedures have been -and continue to be- refined, the components and the geometry of hemodialysis were largely fixed in the 1970's: a bundle of several thousand, permeable hollow fibers, each about 25 cm long and about 200 μ m internal diameter, perfused externally by dialyzing solution, with the device
20 operated principally in a diffusive mode but with a transmembrane pressure applied to induce a convective outflow of water. Upward of 120 liters per week of patient blood are dialyzed against upwards of 200 liters per week of dialyzing solution, often in three weekly treatments that total as little as seven to nine hours per week. These numbers vary somewhat, and competing technologies exist, but the basic approach just described predominates.

25 Despite the benefits of therapies (e.g., hemodialysis) using the various forms of blood processing described above, the prolongation of life achieved is complicated by the progression and complexity of the disease the therapies are used to treat (few patients on dialysis are ever completely rehabilitated), and by several problems that are innate to the therapies themselves. For example, problems arise with blood processing as a result of the
30 contact of blood with extensive areas of artificial membrane (as in the case of hemodialysis), and well as the contact of blood with sorbents or immiscible fluids as described above. In particular, this contact often induces biochemical reactions in the blood being processed, including the reactions that are responsible for clotting, activation of the complement systems, and irreversible aggregation of blood proteins and cells.

35 Another problem associated with known blood processing techniques is that the contact of blood with an artificial membrane (or another medium, such as a sorbent or immiscible fluid) is likely to cause the blood-medium interface to become fouled. It is generally known that therapeutic interventions (e.g., those related to end-stage renal disease)

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5 are optimally conducted with slow delivery and in as nearly a continuous fashion as possible, in emulation of the continuous action of a natural kidney. However, fouling caused by the contact of blood with the medium limits the time that a device which contains these interfaces can be usefully employed. As a result, portable blood processing devices become impractical, and patients are generally forced to undergo the type of episodic dialysis

10 schedule described above, which creates many negative side effects such as physical exhaustion and excessive thirst. Moreover, even while daily dialysis (e.g., 1.5-2.0 hours, six days per week) or nocturnal dialysis (e.g., 8-10 hours, 6-7 nights per week) improves this situation by extending treatment times, a patient using one of these forms of treatment is still required to remain near a hospital or clinical facility that can administer the dialysis

15 procedure.

In light of the above, it would be desirable to provide techniques for processing blood in which treatment times are extended (with consequently lower rates of flow) and that do not require a patient to remain near a hospital or clinic. Moreover, it would also be desirable to provide techniques for processing blood that eliminate (or at least reduce) the inducement of 20 undesirable biochemical reactions, and where the blood-medium interfaces do not become fouled.

Summary of the Invention

The above and other deficiencies associated with existing blood processing processes 25 are overcome in accordance with the principles of the present invention which are described below. According to one aspect of the invention, a membraneless exchange device for extracting components from a sample fluid is described which includes first, second and third inlet channels, first, second and third exit channels and a microfluidic extraction channel connected to the first, second and third inlet channels and the first, second and third exit 30 channels. Moreover, laminar flows of a first extractor fluid, the sample fluid, and a second extractor fluid are established inside the extraction channel, and sheathing of the sample fluid by the first and second extractor fluids substantially limits contact between the sample fluid and the surfaces of the extraction channel.

According to another embodiment of the present invention, a system for performing 35 hemodialysis is provided which includes a membraneless exchange device including first and second dialysate inlet channels, blood inlet and exit channels, first and second dialysate exit channels and a microfluidic dialysis channel connected to the first and second dialysate inlet

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5 and outlet channels and the blood inlet and exit channels. Moreover, laminar flows of a first dialysate fluid, blood fluid, and a second dialysate fluid are established in order inside the dialysis channel, and at least some of the components of the blood fluid exits the device through the first and second dialysate exit channels. Additionally, according to the invention, a secondary processor receives the dialysate fluid and the at least some of the components of 10 the blood fluid exiting the device through the first and second dialysate exit channels.

In yet another embodiment of the present invention, a method for extracting components from a sample fluid provides which includes establishing laminar flows of a first extractor fluid, the sample fluid and a second extractor fluid inside a microfluidic extraction channel. Sheathing of the sample fluid by the first and second extractor fluids, 15 moreover, substantially limits contact between the sample fluid and the surfaces of the extraction channel. The method further includes withdrawing the first extractor fluid, the sample fluid and the second extractor fluid from the extraction channel such that at least a portion of the sample fluid is removed together with the first extractor fluid and the second extractor fluid and apart from the remainder of the sample fluid.

20 A method for performing hemodialysis is also provided which includes establishing laminar flows of a first dialysate fluid, blood fluid and a second dialysate fluid inside a microfluidic extraction channel, withdrawing the first dialysate fluid, the blood fluid and the second dialysate fluid from the extraction channel such that at least some of the components of the blood fluid are removed together with the first dialysate fluid and the second dialysate 25 fluid and apart from the remainder of the blood fluid, and providing the first and second dialysate fluids and the at least some of the components of the blood fluid to a secondary processor.

In general, however, the present invention is directed toward microfluidic membraneless exchange devices and systems, and methods of making the same, for 30 selectively removing undesirable materials from a sample fluid (e.g., blood fluid) by contact with a miscible fluid (extractor fluid or secondary fluid, e.g., dialysate). A microfluidic device, as considered in this application, has channels whose height is less than about 0.6 mm, where "height" is the dimension perpendicular to the direction of flow and also perpendicular to the interfacial area across which transport occurs. For example, flow 35 patterns and species exchanges occur when blood is flowed as a thin layer adjacent to, or between, concurrently flowing layers of a secondary fluid, without an intervening membrane. The secondary fluid, moreover, is generally miscible with blood and diffusive and convective transport of all components is expected. The following reference which refers to

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5 membraneless devices described below is hereby incorporated by reference in its entirety:
Leonard et al., Dialysis without Membranes: How and Why?, *Blood Purification* 22 (1) 2004
92-100.

Sheathing a core of blood with the miscible fluid, or assuring that the miscible fluid lies between at least a substantial portion of the blood and the enclosing boundaries of the
10 flow path, prevents or at least limits contact of the blood with these boundaries. In turn, this configuration of the two fluids prevents or at least reduces the undesirable activation of factors in the blood, thereby minimizing bioincompatibilities that have been problematic in prior techniques of blood processing.

The invention also eliminates or at least substantially reduces the fouling reactions
15 that have been known to be a major deterrent to the continuous use of an extracorporeal extraction device. In particular, as the primary transport surface in the membraneless exchange device (also referred to herein as a membraneless separator) of the invention is intrinsically non-fouling, a major deterrent to long-term or continuous operation is removed, opening the possibility to the design and construction of small, wearable devices or systems
20 with the recognized benefits of nearly continuous blood treatment. Such a device or system could be very small and worn or carried by the patient (e.g., outside of a hospital or clinic setting), and could be supplied with external buffer reservoirs (in a back-pack, briefcase, or from a reservoir located in the home, located at the place of work, etc.). Further, because fouling would be reduced, and sustained operation at low blood flows over long times would
25 be allowed, such anticoagulation as might be required is likely to have an effect confined to the extracorporeal circuit. As understood by those skilled in the art, avoiding systemic anticoagulation outside of the clinic is highly desirable.

The devices, systems and methods of the invention described herein also have the benefit of being capable of diffusing various blood components having different sizes. In
30 particular, the flow of blood and a miscible fluid with which it is in contact can be controlled for the purpose of achieving the desired separation of components (e.g., separating molecules of low molecular weight only). For example, as explained below, various flow conditions may be used that cause blood cells to move away from the blood-liquid interface, thereby making it is possible to "skim" blood in order to remove substantial amounts of plasma,
35 without cells.

As also discussed below, membraneless contact of a thin layer of blood with a sheathing fluid according to the present invention may be used to cause high rates of exchange per unit area of blood-sheathing fluid contact for all solutes, but with a

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5 discrimination among free (unbound) solutes that is less than the square-root of the ratio of their diffusion coefficients. Moreover, while high exchange rates (e.g., of toxic substances) are often desirable, indiscriminate transport is not. Therefore, according to the principles of the present invention, a membraneless exchange device as described herein is used in conjunction with at least one secondary processor (e.g., a membrane device or other type of 10 separator) in order to restrict the removal of desirable substances and effect the removal of undesirable substances from blood. The efficiency of such a secondary separator is greatly increased by the use of the primary separator that is capable of delivering cell-depleted (or cell-free) fractions of blood to it. Therefore, according to another aspect of this invention, transport of molecular components of blood to the sheathing fluid may be indiscriminate.

15 The sheathing fluid, carrying both those molecular components which it is, and is not, desirable to remove from blood, is provided to the secondary separator, such that the fluid entering the secondary separator is substantially cell-free. The secondary separator, meanwhile, regulates the operation of the membraneless separator through the composition of the recycle stream that it returns (directly or indirectly) to the sheath fluid inlets of the 20 membraneless separator. According to the principles of the present invention, moreover, a membrane-based secondary separator used in this manner is able to achieve much higher separation velocities because concentration polarization (i.e., the accumulation of material rejected by the secondary separator on the upstream side of the separator) is limited to proteins and does not involve cells. Moreover, because cells would be retained in the 25 primary separator (i.e., the membraneless exchange device), they would see artificial material only on its conduit surfaces, not on its liquid-liquid contact area, whence bioincompatibilities should be much reduced. As such, it should be understood that the need for anticoagulation may be greatly reduced or eliminated.

Further features of the invention, its nature and various advantages, will be more 30 apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout.

Brief Description of the Drawings

FIG. 1 shows the velocity profile of a core stream of blood sheathed on both of its 35 sides by a dialysate fluid calculated for blood with a viscosity assumed twice that of the dialysate fluid and with a centerline velocity of 5cm/sec.

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5 FIG. 2 shows a plot using Loschmidt's formula of 1870, where each fluid layer has the same thickness.

FIG. 3 shows a simplified view of a membraneless separator constructed in accordance with the principles of the present invention.

10 FIG. 4 shows membraneless separator used for the purpose of plasmapheresis in accordance with the principles of the present invention.

FIG. 5 shows the image of a portion of the membraneless separator of FIG. 5 while plasma is being skimmed from blood, as obtained by using a CCD camera.

15 FIG. 6 shows a simplified block diagram of a system including a membraneless separator and a secondary separator in accordance with the principles of the present invention.

FIG. 7 shows a more detailed view of a system including primary and secondary separators in accordance with the principles of the present invention.

FIG. 8 shows the configuration of a system subdivided into three units in accordance with the principles of the present invention.

20 FIG. 9 shows the routing of fluids between separate units in accordance with the principles of the present invention.

Detailed Description of the Invention

According to one aspect of the invention, a membraneless exchange device for extracting components from a sample fluid is described which includes first, second and third inlet channels, first, second and third exit channels and a microfluidic extraction channel connected to the first, second and third inlet channels and the first, second and third exit channels. Moreover, laminar flows of a first extractor fluid, the sample fluid, and a second extractor fluid are established inside the extraction channel, and sheathing of the sample fluid by the first and second extractor fluids substantially limits contact between the sample fluid and the surfaces of the extraction channel. In one embodiment of the device, at least 90% of the sample fluid is sheathed by the first and second extractor fluids. In other embodiments, 95% of the sample fluid is sheathed. In yet other embodiments, at least a portion of the sample fluid exits the device with the first extractor fluid through the first exit channel, and 30 advective transport of molecules within said extraction channel is substantially nonexistent. The composition of the first extractor fluid, moreover, is substantially the same as the composition of the second extractor fluid in various embodiments. In other preferred 35 embodiments, the first and second extractor fluids are different.

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5 embodiments, the sample fluid flow is between the first and second extractor fluid flows. Moreover, a first diverter is formed from a portion of the first exit channel and a portion of the second exit channel, while a second diverter is formed from a portion of the second exit channel and a portion of the third exit channel. It should also be understood that the device may include a first interface formed between the first extractor fluid flow and the sample

10 fluid flow that is aligned with at least a portion of the first diverter, and may also include a second interface formed between the second extractor fluid flow and the sample fluid flow that is aligned with at least a portion of the second diverter. In various embodiments of the invention, moreover, the sample fluid is blood fluid, in which case it is contemplated that the components extracted from the sample fluid are non-cellular components of the blood fluid.

15 Additionally, the device may use a first pump for controlling the flow of extractor fluid in the extraction channel, and may use a second pump for controlling the flow of sample fluid in the extraction channel. When a first pump is used, it may be an injection pump that controls the flow of extractor fluid into the extraction channel, and a withdrawal pump may be used that controls the flow of extractor fluid out of the extraction channel. In various embodiments,

20 additionally, a source of extractor fluid is connected to said first inlet channel and a source of sample fluid connected to said second inlet channel. It will be understood that the source of sample fluid can be, for example, a human being. In preferred embodiments, moreover, the extraction channel of the device according to the invention has a height of less than 600 μ m, and has a width-to-height ratio of at least ten. The device may also be used in a system for

25 extracting components from a sample fluid, where the system also includes a secondary processor that receives the first extractor fluid, the second extractor fluid and at least some of the components of the sample fluid upon exiting the extraction channel. It will be understood that the secondary processor may be, for example, a membrane device or a sorption device.

According to another embodiment of the present invention, a system for performing

30 hemodialysis is provided which includes a membraneless exchange device including first and second dialysate inlet channels, blood inlet and exit channels, first and second dialysate exit channels and a microfluidic dialysis channel connected to the first and second dialysate inlet and outlet channels and the blood inlet and exit channels. Moreover, laminar flows of a first dialysate fluid, blood fluid, and a second dialysate fluid are established in order inside the

35 dialysis channel, and at least some of the components of the blood fluid exits the device through the first and second dialysate exit channels. Additionally, according to the invention, a secondary processor receives the dialysate fluid and the at least some of the components of the blood fluid exiting the device through the first and second dialysate exit channels. In

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5 various embodiments, the secondary processor filters the dialysate fluid and the at least some of the components of the blood fluid exiting the device through the first and second dialysate exit channels, and returns the filtered fluid to the first and second dialysate inlet channels. In certain preferred embodiments, these components of the blood fluid are substantially non-cellular components of the blood fluid. In other embodiments, sheathing of the blood fluid

10 by the first and second dialysate fluids substantially limits contact between the blood fluid and the surfaces of the dialysis channel. Moreover, the secondary processor may be a membrane device, or may be a sorption device, for example. It will also be understood that the composition of the first dialysis fluid may be substantially the same as the composition of the second dialysis fluid. According to other aspects of the invention, meanwhile, a first

15 diverter is formed from a portion of the first dialysate exit channel and a portion of the blood exit channel, and a second diverter is formed from a portion of the blood exit channel and a portion of the second dialysate exit channel. A first pump for controlling the flow of dialysate fluid in the dialysis channel and a second pump for controlling the flow of blood fluid in the dialysis channel may also be used in accordance with the principles of the present

20 invention. According to several embodiments, the interface between the first dialysate fluid and the blood fluid is varied by adjusting the velocities of the laminar flows of the first dialysate fluid and the blood fluid. In other embodiments, the interface between the blood fluid and the second dialysate fluid is varied by adjusting the velocities of the laminar flows of the blood fluid and the second dialysate fluid. A reservoir for storing a viscosity agent

25 may also be used in the system, where the viscosity agent is mixed with the first and second dialysate fluid to alter the viscosity of the first and second dialysate fluid. Additionally, a detector for detecting a presence of an undesired blood component within the dialysate fluid upon exiting the dialysis chamber may be used. In this case, for example, the detector is a photo detector. According to another aspect of the invention, a first pump for controlling the

30 flow of dialysate fluid in the dialysis channel is adjusted based on said detected presence of an undesired blood component within said dialysate fluid. Moreover, for example, the velocities of the laminar flows of the first dialysate fluid, the blood fluid and the second dialysate fluid are adjusted based on the detected presence of an undesired blood component within the first and second dialysate fluids according to the invention. Additionally,

35 according to the invention, the first and second dialysate fluids may include at least one of the following: a hyper osmolar solution, a solution high in glucose content, or a polyelectrolyte osmotic agent.

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5 In yet another embodiment of the present invention, a method for extracting components from a sample fluid is provided which includes establishing laminar flows of a first extractor fluid, the sample fluid and a second extractor fluid inside a microfluidic extraction channel. Sheathing of the sample fluid by the first and second extractor fluids, moreover, substantially limits contact between the sample fluid and the surfaces of the
10 extraction channel. The method further includes withdrawing the first extractor fluid, the sample fluid and the second extractor fluid from the extraction channel such that at least a portion of the sample fluid is removed together with the first extractor fluid and the second extractor fluid and apart from the remainder of the sample fluid. According to the invention, moreover, establishing laminar flows includes providing first, second and third inlet channels
15 and providing first, second and third exit channels. Additionally, for example, the method includes providing the first and second extractor fluids and the at least a portion of the sample fluid to a secondary processor.

20 A method for performing hemodialysis is also provided which includes establishing laminar flows of a first dialysate fluid, blood fluid and a second dialysate fluid inside a microfluidic extraction channel, withdrawing the first dialysate fluid, the blood fluid and the second dialysate fluid from the extraction channel such that at least some of the components of the blood fluid are removed together with the first dialysate fluid and the second dialysate fluid and apart from the remainder of the blood fluid, and providing the first and second dialysate fluids and the at least some of the components of the blood fluid to a
25 secondary processor. In various embodiments, the method also includes using the secondary processor to filter the first and second dialysate fluids and the at least some of the components of the blood fluid, as well as returning the filtered fluid from the secondary processor to the extraction channel. In yet other embodiments, the method includes sheathing the blood fluid by the first and second dialysate fluids to substantially limit the contact
30 between the blood fluid and the surfaces of the dialysis channel.

35 Referring to FIG. 1, calculated for blood with a viscosity assumed twice that of the sheathing fluid and with a centerline velocity of 5 cm/sec, a flow path length of 10 cm would result in a contact time of slightly longer than 2 sec. The steady contact of two moving liquids for an exposure time determined by the length of their contact area divided by their interfacial velocity ($\tau = L/v$) is highly analogous to the sudden exposure of one volume of stagnant fluid to another for a specified time. Thus, what happens to the flowing fluids along

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5 their shared flow path is comparable to what would happen to two stagnant fluids over their exposure time to each other. The stagnant fluid problem was solved by Loschmidt in 1870.

$$E = \frac{1}{2} - \frac{4}{\pi^2} \sum_0^{\infty} \frac{1}{(2n+1)^2} \exp\left[-(2n+1)^2 \left(\frac{\pi}{2B}\right)^2 Dt\right]$$

for which the zeroth order term, $E = \frac{1}{2} - \frac{4}{\pi^2} \exp\left(-\left[\frac{\pi}{2B}\right]^2 Dt\right)$, suffices when

$$\left(\frac{\pi}{2B}\right)^2 Dt > 0.7.$$

10 This formula greatly simplifies the estimation of how much mass can be transferred between fluids in a membraneless system. In particular, this formula provides an approximation of the extraction E of a component with a diffusion coefficient D when two liquids flow side-by-side and remain in contact for an interval of time, t .

FIG. 2, meanwhile, shows a plot using a version of Loschmidt's formula, where each 15 fluid layer has the same thickness B (i.e., B is the half-thickness of the sheathed layer of sample fluid). The situation shown in the plot of FIG. 2 can be interpreted as a blood layer, of thickness B , contacting a layer of sheathing fluid (i.e., extractor fluid). The sheathing layer is presumed to be at zero concentration and E is the fraction of material in the blood layer that is extracted in a time t , where D is the diffusion coefficient of the extracted substance. If a 20 layer of thickness twice B is bounded on both sides by fluid layers of thickness B , the formula still applies, as written. As indicated by this formula, E cannot exceed $\frac{1}{2}$ since the prescription of concurrent flow allows, at best, the two fluids to come to equilibrium.

For example, if one prescribes 90% of maximum extraction ($E = 0.45$), the ratio Dt / B^2 must be approximately 0.86. Any combination of diffusivity, layer thickness, and 25 exposure time that produces this value will produce the same extraction. Moreover, it can be shown that the necessary area ($2LW$) to achieve this extraction equals $0.86 BQ / D$, where Q is the blood (and sheath fluid) flow rate. Thus, for urea ($D = 10^{-5} \text{ cm}^2/\text{sec}$) at a blood flow rate of $0.3 \text{ cm}^3/\text{sec}$, the required area is $2.57 B 10^4 \text{ cm}^2$. If B is taken to be $100 \mu\text{m}$, the required area is 257 cm^2 . This flow corresponds to what might be needed in a wearable 30 artificial kidney. If, instead, a conventional flow of $5 \text{ cm}^3/\text{sec}$ were used, the required area would be 4300 cm^2 . Thinner films, moreover, would require less area but would result in higher shear rates and pressure gradients. In terms of extraction, any combination of length L and width W that produces the requisite area is equivalent. (If one assumes D for albumin to

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5 be $5 \times 10^{-7} \text{ cm}^2/\text{sec}$, its extraction would be 0.116, 26% of that for urea, unchangeable at this extraction level for urea).

It should be noted that use of the Loschmidt formula with flowing systems introduces an incongruity that prevents precise estimation of mass transfer rates and clearances, given that it presumes that both fluids are moving at uniform velocity. In particular, it provides an 10 excellent approximation for the sheathed fluid (blood), but ignores the nearly linear decay in velocity with distance from the interface in the sheathing fluid. Nevertheless, the Loschmidt formula is adequate for design purposes when the sheathing layer has a total thickness ($2B$) that is twice that of its half of the blood layer (as shown in FIG. 1), and thus a rate of flow nearly equal to its half of the central stream.

15 The shear-induced self-diffusion coefficient of cells, meanwhile, can be estimated by using the expression of Leighton and Acrivos (1987) for concentrated suspensions:

$D_{\text{particle}} \propto \phi^2 a^2 \dot{\gamma}^2$, where ϕ is the particle volume fraction, a is the particle radius, and $\dot{\gamma}$ is the shear rate. Then, the characteristic displacement of a cell can be expressed as $\Delta y \propto \sqrt{D_{\text{particle}} t}$. Choosing representative values for the layered flow system such that the 20 cell volume fraction $\phi \approx 0.45 / 2 = 0.225$, the average radius a of the red blood cell $\approx 2.5 \mu\text{m}$, and the average shear rate $\dot{\gamma}$ over the blood layer ≈ 3 to 28 s^{-1} (based on an average velocity range of 0.5 to 5 cm/s), we calculate that $D_{\text{particle}} \sim 10^{-8} \text{ cm}^2/\text{s}$, which is approximately three orders of magnitude smaller than the typical diffusion coefficient of small solutes. Based on this value of the shear-induced diffusion coefficient (and assuming 10 sec of contact between 25 layers), it is estimated that blood cells are displaced by a characteristic distance $\Delta y \approx 3$ to $9 \mu\text{m}$ from the central layer, depending on the choice of blood velocity and the concomitant shear rate. As explained in greater detail below, this low distance of cell migration away from the central layer facilitates the removal of cell-free portions of blood by the membraneless separators described herein.

30 It should be noted that, according to one aspect of the present invention, the removing of undesirable materials from a sample fluid occurs under conditions that prevent advective mixing of blood and the secondary fluid. In its general usage herein, advection is used to describe the transport of fluid elements from one region to another, and is used to distinguish disordered convection from diffusion unaided by convection or diffusion in the presence of 35 only ordered and unidirectional convection. The term advection is therefore used to mean a form of transport within a fluid or between two contacting miscible fluid in which clumps of

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5 fluid from two different positions are effectively interchanged. Advection, so defined, can occur in turbulent flows or in unstable laminar flows. Advective mixing, moreover, is often purposefully induced by the application of a moving agitator blade to a fluid. The prevention of advective mixing and the short contact times that lead to small areas of contact (and, in turn, to a small device that has a small size and a limited extracorporeal blood volume) is

10 greatly facilitated by the use of a microfluidic geometry. An increase in channel height raises requisite contact time and tends to reduce the stability of the sheathed flow. When total blood layer thickness is 25, 50, or 100 μm , and the blood flow is 20 ml/min (as it might be with a wearable artificial kidney), the interfacial area needed to cause a substance such as urea ($D = 10^{-5} \text{ cm}^2/\text{sec}$) to reach 90% of equilibrium is, respectively, 18, 36, and 71 cm^2 .

15 As mentioned above, the devices, systems and methods of the present invention allow the purification of blood without the use of a membrane by contact of the blood with a miscible fluid under conditions that prevent advective mixing. It will be clear from the detailed description of various embodiments of the invention provided below that the invention is useful in hemodialysis, for example. However, it should also be noted, and

20 understood by those skilled in the art, that the present invention is also useful in other situations where a sample fluid is to be purified via a diffusion mechanism against another fluid (e.g., an extractor fluid).

According to the principles of the present invention, the purification techniques described herein enable the flow of blood, completely or partially surrounded by another liquid (e.g., extractor fluid) such that the streams are contacted in a small channel and are subsequently separated at the end of the channel. The middle stream is, thus, the blood to be purified, while the surrounding stream (or streams) is the extractor fluid. This membraneless contact, or sheathing of blood with layers of a miscible fluid, according to principles of the present invention, may occur along a flow path whose cross-section is either rectangular, preferably of great breadth and limited thickness, or circular. The invention is not limited in this manner.

Persons skilled in the art will appreciate that the requisite transport areas, moreover, can be achieved by combinations of channel length, width, and number according to the principles of the present invention. In particular, $\text{Area} = 2 \times (\text{top and bottom}) \times \text{width} \times \text{length}$ $\times \text{number of channels stacked or otherwise arrayed in parallel}$. (As used herein, the term "width" refers to a dimension perpendicular to the direction of flow and parallel to the interface between the two liquids, while, as explained above, the term "height" refers to a

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5 dimension perpendicular to the direction of flow and also perpendicular to the interface between the two fluids). It is shown herein that the competing requirements of small height (to avoid excessive diffusion times and in-process volumes), short length (to avoid excessive pressure drop) and practical limitations on width of a single device, which suggests the need to array them in parallel, side-by-side or in a stack can be satisfied in practical microfluidic
10 devices.

FIG. 3 shows a simplified view of a membraneless separator 300 fabricated in flat-sheet configuration in accordance with the principles of the present invention. According to one embodiment of the present invention, three flat strips of copper foil, each three centimeters wide, four centimeters long and 100 microns thick, are soldered in their mid-sections to form extraction channel 302. The ends (one centimeter) of the outer pieces are bent 30 degrees outward to form three separate inlet channels 304, 306 and 308 and three corresponding exit channels 310, 312 and 314 as shown in FIG. 3. According to the invention, the pieces are then coated with a mold release agent, and the channel is then placed in a Petri dish. At this time, an amount of PDMS precursor/curing agent mixture (10:1 ratio),
15 sufficient to form a two centimeter-thick polymer layer after curing, is poured into the dish. After curing, the foil assembly is easily released from the PDMS replica, and the replica is sandwiched between two partially cured flat pieces of PDMS and annealed to form a well-sealed channel. Finally, slight vacuum is applied during the annealing to remove air bubbles trapped between the flow channel module and the flat pieces, and the sealed separator 300 is
20 then ready for use (preferably after the chip is rinsed with ethanol and with de-ionized water, and then dried with compressed nitrogen gas). A flat piece of PDMS which served as a cover to seal the chip by adhesion is also preferably cleaned and dried in the same manner.

It will be understood that the particular fabrication process described above is for purposes of illustration only. For example, the dimensions of membraneless separator 300
30 may be altered without departing from the scope of the present invention. Additionally, for example, it will be understood that the invention is not limited to the use of copper foil, and that other fabrication processes not described may also be employed.

FIG. 4 shows a membraneless separator 400 according to the principles of the present invention. Similar to separator 300 described above, separator 400 includes an extraction
35 channel 402, three separate inlet channels 404, 406 and 408 and three corresponding exit channels 410, 412 and 414. As also shown in FIG. 4, a first diverter 416 is formed from portions of exit channels 410 and 412, while a second diverter 418 is formed from portions of exit channels 412 and 414. It will be understood, however, that the invention is not limited

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5 by the number of exit channels (or inlet channels) that are used, nor is the invention limited by the number of diverters formed therefrom.

As illustrated in FIG. 4, membraneless separator 400 can be used as a plasmapheresis device in accordance with the principles of the present invention. For example, as shown in FIG. 4, plasma from the blood entering extraction channel 402 through inlet channel 406 is 10 skimmed and exits with sheath fluid through exit channels 410 and 414. This process of skimming is explained in greater detail below in connection with FIG. 7,

FIG. 5, meanwhile, shows an image of the right-most portion of separator 400 shown in FIG. 4, as obtained by using a CCD camera (Sensys0401E, Roper Scientific). In 15 particular, the image of FIG. 5 illustrates plasma being skimmed from blood according to the principles of the present invention. As shown in FIG. 5, a portion of the blood 501 provided through inlet channel 402 (not shown) exits through exit channel 405. Moreover, while 20 cellular components of blood 501 migrate to the center (as explained below in connection with FIG. 7), cell-depleted (or cell-free) fractions of blood 501 such as plasma 502 and 503 combine with sheath fluid 504 and 505 to exit extraction channel 400 through exit channels 404 and 406, respectively.

It will be understood by persons skilled in the art that a membraneless separator as described herein is not intended to, nor could it, offer sufficient discrimination between the substances it is intended to remove and those it is intended to leave behind. Accordingly, for 25 example, membraneless separators as described above will only function by themselves in the exceptional circumstance that all the components of plasma are to be removed. For example, a membraneless separator may be used alone when the removal of plasma, usually not in its entirety but without discrimination among its components, is to be removed, and the cellular components of blood are to be left behind.

In all other circumstances, according to the principles of the present invention, a 30 membraneless separator will operate in conjunction with a secondary separator that receives the sheath fluid and, optionally, a cell-depleted (or cell-free) part of the bloodstream. For example, to prevent the removal of macromolecules, the secondary separator can be used to generate a stream rich in macromolecules and free of small metabolite molecules and middle molecules that is recycled in sheath fluid to the membraneless separator. Thus, according to 35 the invention, the secondary separator regulates the operation of the membraneless separator through the composition of the recycle stream that it returns to the inlets for sheath fluid of the membraneless separator (as shown in Figure 6 and described in greater detail below). It should be understood that the secondary separator may incorporate a variety of means to

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5 remove solutes whose extraction removal from the circulation (i.e., the recycle stream) is desired, and that the invention is not limited in this manner.

One substance whose transport (i.e., removal from blood being processed) is typically undesirable is albumin. In each pass through an exchange device according to the invention, for example, albumin would be removed at more than 1/4th the rate of small solutes, and

10 albumin (which is confined to the blood space of an animal) would undergo perhaps 10 times as many passes as would urea which is distributed throughout the total body water reservoir. Thus, the fractional removal of albumin, even though its inherent diffusivity is smaller, would exceed the fractional removal of urea. According to the principles of the present invention, therefore, a secondary separator (e.g., a membrane device that permits extraction of urea and

15 water but not albumin) may be used to recycle albumin to the blood. In particular, the sheath fluid received from the recycle stream will be depleted of urea and water, but will be rich in albumin. Thus, the composition of this stream will recruit the further extraction of urea and water but will not recruit further extraction of albumin, given that the difference in albumin concentration between the blood being processed and the sheath fluid will have disappeared.

20 It will be understood that an important specification of how the membraneless separator operates is the difference between the inlet flow rate and the outlet flow rate of the sheath fluid. For example, when these flows are equal and urea and water are removed by the secondary separator, there will be, at first, an insufficient transfer of water from blood to the sheath fluid to keep up with water removal in the secondary separator. Thus the

25 concentration of proteins, including albumin, will rise in the recycle stream. When this concentration has reached a sufficiently high level, water transfer will be enhanced by a difference in protein osmotic (oncotic) pressure between the blood and the sheath fluid. Thus, the membraneless separator will balance its performance to that of the secondary separator. On the other hand, if the rate of withdrawal of sheath fluid is greater than its rate

30 of supply, sufficient water may be sent to the secondary separator to keep up with its rate of water removal, but protein concentration will rise again until a concentration difference exists in the membraneless separator between the sheath fluid and the blood, causing a diffusion of protein back into the bloodstream. Once again, the membraneless separator will balance its performance to that of the secondary separator.

35 For example, when the principal goal of the treatment is the removal of highly diffusible (in general, low molecular weight) molecules, assuming a flow of 20ml/min flow, the contact area in the membraneless separator will be in the range about 17 to 71 cm². When the principal goal of the treatment is the removal of slowly diffusible molecules (e.g.,

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5 proteins and especially immunoglobulins), the contact area in the membraneless separator will be larger, in the range of approximately 1,700 to 7,100 cm² (assuming a flow of 20ml/min), and the secondary separator will be configured to remove these molecules and to recycle smaller molecules (unless their simultaneous removal is desired).

FIG. 6 shows a simplified block diagram of a system 600 including membraneless separator 602 and secondary separator 604 in accordance with the principles of the present invention. Although not shown in detail, it will be understood that membraneless separator 602 may be similar to those separators shown in FIGS. 3 and 4 and described above, for example.

According to the principles of the present invention, blood that is to undergo processing is provided to (and removed from) membraneless separator 602. Meanwhile, sheathing fluid that is recycled by secondary separator 604 is also provided to (and removed from) membraneless separator 602. As also shown in FIG. 6, whenever secondary separator 604 transfers solutes to a second fluid (e.g., dialysate), fresh dialysate connection 606 and waste dialysate connection 608 may be used for providing fresh and waste dialysate streams, respectively. It will be understood that shunting of fresh fluid directly to the blood stream, as represented by dashed line 610, is also a possibility (but not mandatory). In general, FIG. 6 makes the role of membraneless separator 602 clear: to equilibrate solutes of interest with the sheathing fluid without transfer of cells.

It will be understood that secondary separator 604 may use any of many available separation principles known to those skilled in the art, including ultrafiltration and sorption using a wide range of sorbents targeted to particular small and large molecules, chemical reaction, and precipitation. Plasma diafiltration (a variant of hemodiafiltration), for example, may also be used according to the principles of the present invention. The following international publications which refer to hemodiafilters are incorporated by reference herein: 25 WO 02/062454 (Application No. PCT/US02/03741), WO 02/45813 (Application No. PCT/US01/47211), and WO 02/36246 (Application No. PCT/US01/45369). According to additional embodiments of the present invention, moreover, when low-molecular weight solutes are to be removed by plasma diafiltration, a stream of sterile buffer is added to the blood to allow a greater volume of fluid, with its accompanying small molecules, to pass 30 through the diafiltration membrane. In conventional diafiltration, this volume may be added before or after the diafilter. In this invention, however, it is advantageous to add it either to the bloodstream or the recycle fluid from the secondary separator 604, which is the primary 35 source of sheath fluid.

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5 A more detailed view of a system 700 which includes membraneless separator 702 and secondary separator 704 in accordance with the principles of the present invention is shown in FIG. 7. As shown in FIG. 7, separator 702 includes extraction channel 706, inlet channels 708, 710 and 712 and exit channels 714, 716 and 718.

10 According to the principles of the present invention, system 700 also includes blood supply 720, and a plurality of pumps 722, 724 and 726 (which may be either manually or automatically operated, such as by using detection and regulation techniques described below). As shown in FIG. 7, blood supply 720 provides blood to be processed to membraneless separator 702 through blood inlet channel 710. It will be understood that blood supply 720 may be a living person or other animal, for example, or may be a blood 15 reservoir. Blood withdrawal pump 722, meanwhile, is responsible for removing blood from separator 702 through blood exit channel 716.

20 As illustrated by FIG. 7, the flow of sheath fluid (or extractor fluid) into separator 702, through sheath inlet channels 708 and 712, is controlled by sheath fluid injection pump 724 (which preferably provides sheath fluid in equal parts to channels 708 and 712). The flow of sheath fluid out of separator 702, through sheath exit channels 714 and 718, meanwhile, is controlled by sheath fluid withdrawal pump 726 (which preferably draws equal amounts of sheath fluid out of channels 714 and 718). According to preferred embodiments of the present invention, pump 724 is a two-chamber pump that provides sheath fluid at equal velocities (and with substantially similar composition) to both inlet channels 708 and 712, while pump 726 is a two-chamber pump that removes sheath fluid from exit channels 714 and 718 at equal velocities. Moreover, it is also contemplated that pump 724 be replaced by two pumps (not shown) for separately providing sheath fluid to inlet channels 708 and 712, in which case the composition of the sheath fluid entering inlet channel 708 may be substantially similar to, or different from, the sheath fluid entering inlet 25 channel 712. Similarly, two pumps (not shown) can be used in place of pump 726 for the purpose of separately withdrawing sheath fluid from exit channels 714 and 718. It is also contemplated that, in other embodiments of the present invention, sheath fluid entering through inlet channel 708 and exiting through exit channel 714 flows at a different velocity than the sheath fluid entering through inlet channel 712 and exiting through exit channel 718. 30 It will be understood that the invention is not limited by the particular usage of pumps or sheath velocities described herein in connection with the description of FIG. 7.

35 As explained above, a membraneless separator according to the invention also needs one or more diverters to operate. Thus, according to the principles of the present invention, a

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5 first diverter 726 is formed from a portion of sheath exit channel 714 and a portion of blood exit channel 716. Moreover, a second diverter 728 is formed using a portion of blood exit channel 716 and a portion of sheath exit channel 718. It will be understood that, in embodiments of the present invention using more than two layers of sheath fluid, additional diverters will be used.

10 In certain preferred embodiments of the invention, the sheath fluid provided to separator 702 (from separator 704 and/or optional sheath fluid reservoir 730) by sheath fluid injection pump 724 occupies approximately 2/3 of the cross-section of extraction channel 706, with blood from blood supply 720 in the middle 1/3. In this manner, each half of the blood layer in extraction channel 706 is "serviced" by one of the sheathing layers, and 15 the sheathing layers are traveling at an average velocity that is approximately half that of the blood (even though the interfacial velocities of the blood and sheathing fluids are equal). Thus, the volume of blood and the volume of sheathing fluid that pass through the unit in a given period of time are approximately equal. Although the invention is not limited in this manner, it should be noted that, in the configurations described here, efficiency drops when 20 the volumetric flows of the two fluids (i.e., blood and sheath fluid) are very different from each other.

25 In order to cause the separation (or skimming) of all or part of the cell-depleted component of the blood being processed, according to various embodiments of the present invention, the inlet and exit flows of the sheath fluid are controlled (via pumps 724 and 726, respectively) such that more sheath fluid is withdrawn from separator 702 than is provided thereto. For example, it is possible to skim 10% of the blood flow by running sheath fluid withdrawal pump 726 at a rate that is 10% higher than the rate of sheath fluid injection pump 724. It will be appreciated that, when this is done, the blood efflux rate is determined and need not be controlled, as it should naturally have an outflow that is 90% of the inflow.

30 As explained above, when indiscriminate plasma removal is not desired, the plasma that is skimmed from the blood using membraneless separator 702 is processed by secondary separator 704, which regulates the operation of separator 702 through the composition of the recycle stream that it returns to sheath inlets channels 708 and 712 (i.e., a recycle stream is used to limit transport of blood components for which extraction is not desirable). According 35 to the principles of the present invention, a substantial benefit arises because secondary separator 704, whether membraneless or not, is able to achieve high filtration velocities due to the fact that concentration polarization is limited to proteins and does not involve cells. Moreover, because cells are retained in the membraneless separator 702, they would see

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5 artificial material only on its conduit surfaces, not on its liquid-liquid contact area, with the result being a reduction in bioincompatibilities and a reduced (or eliminated) need for anticoagulation. Additionally, because the primary transport surface in the system is intrinsically non-fouling, a major deterrent to long-term or continuous operation is removed, opening the possibility of a wearable system with the recognized benefits of prolonged, slow
10 exchange.

It should be understood that any operation of membraneless separator 702 that allows the sheath exit flows to be larger than the corresponding inlet values will induce a convective flow from the blood stream, over and above the diffusive flow. In order to prevent such a convective flow from carrying blood cells with it (as would be the case if the distribution of
15 cells in the blood stream was uniform), it is important that cellular components of the blood have migrated to the center of the blood stream in order to permit significant plasma skimming. As should be appreciated by those skilled in the art, centripetal drift of cells occurs under a variety of flow regimes. According to the invention, therefore, various flow conditions can be used that cause blood cells to move away from the blood-liquid interface.
20 For example, when blood flows in a tube below a wall shear rate (measured as the blood-flow velocity gradient perpendicular to the tube wall) of about 100 reciprocal seconds, this shear rate causes cellular components to migrate the center and leave the sheath as cell-free, essentially pure plasma. (See Goldsmith, H.L. and Spain, S., Margination of leukocytes in blood flow through small tubes, *Microvasc. Res.* 1984 Mar; 27(2):204-22.)

25 It will be appreciated that long-term stability is necessary for satisfactory operation of the microfluidic devices described herein. For example, it is desirable to prevent inappropriate splitting of an exit stream which, uncorrected, could result either in loss of cells or unintended infusion of sheathing solution into the bloodstream. Moreover, the presence of blood cells in the sheath, or extractor fluid may also be undesirable. According to another
30 aspect of the present invention, therefore, on-board electronics and photonics (not shown), which are common features of chip-based microfluidic devices, may be used. In particular, such electronics or photonics could be used to regulate system 700 (i.e., to introduce flow changes) with an electrically activated device (e.g., a piezoelectric valve) that is mounted on the same plate, or "chip," on which separator 702 is located.

35 According to one embodiment of the invention, for example, very low concentrations of cells would be permitted and monitored (e.g., before or after the sheath fluid being provided to secondary separator 704) by using any suitable detector, such as a photo detector. An ultramicroscope (a light-scattering device that is particularly sensitive to the presence of

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5 dilute particles) is one example of a photo detector which can be used. Based on this monitoring, flow corrections that would provide the system with long-term stability can be made which include, for example, adjusting the blood-sheath fluid interface. In particular, by adjusting the flows to separator 702 to reposition the interface, desired components can be retained in the blood. For example, when an excessive number of blood cells is present, the
10 flow of blood could be decreased (or the flow of extractor fluid increased) in order to shift the blood-sheath fluid interface accordingly.

15 Additionally, according to another aspect of the invention, on-board electronics can be used to protect against the type of flow imbalances that might cause large blood losses in one direction or massive hypervolemia in the other direction, which are naturally prevented when a membrane is present but which may occur in a membraneless device. It will be
understood by those skilled in the art this type of detection and regulation may also be used with in conjunction with the other embodiments of the present invention described above.

20 As explained above, in all membraneless contact configurations, the fluids (e.g., blood and sheath fluid) must flow in the same direction. In particular, any flow in opposite directions would disrupt the blood-fluid interface and induce undesirable advection. Moreover, since the fluids must flow in the same direction, the most that can be
25 accomplished in one membraneless unit according to the invention is the equilibration of the sheath and blood streams (which, according to Loschmidt's formula provided above, means that if the sheathing fluid is flowed at the same rate as blood, the extraction E of a solute cannot exceed $\frac{1}{2}$). In other words, if the two flows are equal, at most half of any solute can be transferred. Moreover, while greater flows permit larger fractions, E , of a solute to be removed, they require higher circulation rates to the secondary separator and thus force
processing of solutes at lower concentrations, which is generally undesirable. Therefore, it is generally desirable for these flows to be nearly equal, within at least a factor of 2 or 3.

30 This limitation on extraction can be largely overcome, however, by the configurations shown in FIGS. 8 and 9 and described below which achieve the effect of opposing flows (counterflow) by the juxtapositions of modules. In particular, low extraction efficiency can be overcome by more sophisticated layouts of a microfluidic system such that flows are concurrent in each unit of the system, but the overall flow approaches countercurrent in
35 pattern and efficiency.

According to the invention, subdivision of a given, desired contact area into n units each connected to the other in a countercurrent manner, even though the flow within them is concurrent, is used to allow extraction efficiency to rise according to the formula provided

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5 above. Thus, if an area were divided into four units, for example, and each had an extraction efficiency of 50%, the composite unit would have an efficiency of 0.8 or 80%.

FIG. 8 shows the configuration of a system 800 according to the invention in which the total area of contact is partitioned into three sub-units 802, 804 and 806 (i.e., $n = 3$). In operation, blood to be processed is first provided to sub-unit 802, then passes through sub-unit 804, and finally, exits out of sub-unit 806. The sheath fluid to be used in system 800, on the other hand, is first provided to sub-unit 806 (at this point, the sheath fluid has no blood components). The sheath fluid exiting sub-unit 806 is next provided to sub-unit 804, and after exiting sub-unit 804, is provided to sub-unit 802. Thus, assuming each unit has an extraction efficiency of 50%, the overall extraction efficiency of the composite unit, E_O , is 15 equal to 0.75 or 75%. Accordingly, it becomes possible, at equal flows, to remove 75% rather than only 50% of the solute of interest. It will be understood that the extraction efficiency approaches 1.0 or 100% as the number of small units approaches infinity. Persons skilled in the art will appreciate that, although not shown, the sheath fluid exiting sub-unit 802 may be provided to a secondary separator as described above. Moreover, while 20 three sub-units 802, 804 and 806 are shown in FIG. 8, it will be understood that any number of sub-units (e.g., 2, 4, 5, etc.) may be used in system 800, all of which may be easily introduced on a master chip fabricated according to well known techniques for the general fabrication of microfluidic devices.

FIG. 9 shows another example of a system 900 using sub-units according to the 25 principles of the present invention. In particular, FIG. 9 shows two flow patterns 902 and 904 that would be superimposed on each other in a single cartridge. For example, the top could represent blood, while the bottom could represent an extractor fluid (e.g., dialysate). As shown in FIG. 9, sheath fluid flows through sub-unit 906 prior to flowing through sub-unit 908. In this manner, with sufficient contact area, the fraction of material in the blood 30 layer that is extracted will be equal to 2/3 or 67%.

Persons skilled in the art will appreciate that many different fabrication techniques can be used in accordance with the principles of the present invention. In recent years, controlled fluid movement and transport among fluids has been achieved in very small channels and at very low rates of flow largely for the purpose of assaying the contents of a 35 minute fluid sample in order to determine, for example, the catabolite concentration in the blood. These devices have been enabled by recently developed microfabrication methodologies. The Holy Grail has been the development of a "Lab on a Chip," in which several sequential analytical processes are conducted on a single chip that may be, for

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5 example, one square centimeter in area. Transport of a chemical or biochemical sample from one process to another and on and off the chip itself requires fluid handling capabilities, and thus, this enabling technology is commonly called “microfluidics.” Microfluidics is essential for nearly all on-chip applications. The synthesis of chemicals in microfluidic geometries is an application that is perhaps closer in concept to the scope of this disclosure because of the
10 need to process a relatively larger amount of fluid. Synthesis includes, perforce, the separations needed between the steps of a chemical reaction sequence. While the aims of synthesizers differ from ours, and embrace some issues that we do not now see as pertinent, all of this work, reported and emergent, is of interest. Specifically, the present invention
15 embraces some of the fabrication techniques and experimental methods developed for the fabrication and characterization of microfluidic device structures, to define upwardly scalable transport to and from blood.

According to the invention, moreover, microchannel structures for flow experiments may be formed by a rapid-prototyping technique. For example, the required structures may be realized in PDMS (silicone) resin by replica-molding from master structures created in
20 thick negative photo resist (SU-8) by optical lithography. Commercially available, standard grade mixtures of EPON SU-8 photo resist, SU-8-5 (52% solids), SU-8-25 (63% solids), SU-8 50 (69% solids) and SU-8 100 (73% solids), for example, may be spun onto Si wafer substrates at a speed of rotation that depended on the film thickness needed, yielding films that were 10 to 300 μm thick. For example, SU-8 50 spun at 1100rpm yields a 100 μm film.
25 Prior to exposure, moreover, the spun layer is preferably baked on a precisely leveled hot plate at 95°C for a time that is dictated by the film thickness (ranging from minutes to hours). These samples are then allowed to cool before further processing. Post-bake exposure, meanwhile, can be done using a direct laser writing system. The photolithographic setup consists of an Ar-ion laser (wavelength $\lambda=350\text{nm}$), focusing optics, and a computer
30 controlled sample stage. The movement of the stage along all three axes (x, y, z) is achieved by stepping motors. Desired master patterns were created by translating the samples underneath the focused laser beam to expose the outline, and then scanning across the interior so that the intended micro channel was fully exposed. Dynamical focus correction or the sample tilt with respect to the scanning laser beam was the done by on-the-fly adjustments of
35 the distance between the focusing lens and the sample stage. In a preferred embodiment, this exposure is carried out at 95°C for 15min. Development, meanwhile, can be carried out in a commercial SU8 developer, again for a time based on film thickness (with the sample being

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5 lightly stirred during development). Patterns created in SU-8, meanwhile, are used as molding masters for replication in PDMS. PDMS is prepared from a mixture of PDMS precursor and curing agent (Sylgard 184 kit, Dow Corning) in a 10:1 ratio by weight. Before curing, the mixture is placed in vacuum to evacuate bubbles formed during mixing. It is then 10 poured over the SU-8 master, which had been previously coated with a thin layer (~50nm) of chromium to improve the release of the PDMS casting, after curing. Curing is done at 70°C for approximately twelve hours. Once the SU-8 film is spun, pre-baked and cooled as described above, a Karl Zeiss MJP3P Contact Mask Aligner can be used for exposure, together with standard chromium masks or transparency masks depending on the resolution required. The films are then post-baked, and developed in the manner outlined in the 15 previous section. The same pattern transfer technique is used to produce PDMS replicas.

It is apparent to those skilled in the art that many advantages may be provided in the various embodiments of the present invention described above. For example, the devices, systems and methods according to the principles of the present invention are capable of diffusing various blood components having different sizes, including 'small' molecules, 20 'middle' molecules, macromolecules, macromolecular aggregates, and cells, from a blood sample to the extractor fluid. This ability is particularly important considering the fact that different treatments require the removal of different sized particles. For example, in dialysis, one may desire to remove molecules of low molecular weight, while in the treatment of acute liver failure, both small and intermediate-sized molecules are to be removed. In therapeutic 25 apheresis, meanwhile, one generally wishes to remove selected protein macromolecules (e.g., immunoglobulins), while in the treatments for fulminating sepsis, it is toxins of intermediate molecular weight that one generally desires to remove. On the other hand, in proposed anti-viral treatments, one wishes to remove free viral particles, while in the treatment of congestive heart failure, one simply wishes to remove water.

30 It should also be apparent that a device or system according to the invention may be used to process the blood of a single individual for the purpose of treating any of a large number of disease states. For example, therapies according to the invention may be used in the treatment of acute renal failure, acute liver failure, high antibody levels in myasthenia gravis and other autoimmune diseases. Additional uses include, for example, the removal by 35 either precipitation or sorption of LDL in homozygous hyperlipidemia, in addition to the removal of malignant sepsis or fluid in cases of congestive heart failure, for example. The invention may also be used to aid in the reduction of viral burdens in AIDS patients, as well

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5 as for treatment of patients requiring other types of blood purification. Patients with diabetes, patients that have suffered a drug overdose, patients that have ingested a poison, patients suffering from renal failure, patients suffering from acute or chronic liver failure, or patients that have Myasthenia gravis, lupus erythematosus, or another autoimmune disease may also benefit from the devices and systems of the present invention. For example, while an
10 exchange device according to the invention is not a cure for diabetes, it can be useful in the amelioration one or more symptoms of diabetes. Moreover, the device or system of the invention could be useful in clearing the blood of IgG molecules or other molecules, which are causative of an autoimmunity disorder. Additionally, the device or system of the invention can be used in acute dialysis or for extended dialysis. One skilled in the art will
15 also appreciate that patients (or animals, in the case of veterinary use of the present invention) suffering from disorders, diseases and syndromes not listed herein may nonetheless be included in the patient pool intended for the device and system according to the invention.

Additionally, because the membraneless devices and systems described above have a small need for supporting machinery, and may be expected to be much smaller, to avoid high
20 cell concentrations and membrane contact, and to operate throughout at low rates of shear, they are especially compatible with cognate processes. In one embodiment, a wearable (or at least portable) system according to the invention can run between 20 and 24 hours per day at a flow rate of about 20 cc/min, for example. The patient could then have, for example, 4-5 hours each day without the device in place which could be used for personal hygiene (e.g.,
25 showers or baths), sports activities, or other activities not amenable to the small system being worn or used. The invention thus addresses a problem recognized by the dialysis community (i.e., the negative side effects such as physical exhaustion, thirst, etc. associated with an episodic dialysis schedule), for which daily or nocturnal hemodialysis is not always a sufficient alternative. In particular, the invention described herein allows the patient to move
30 about in a normal manner (e.g., go to work, school, home, etc.) while being subject to ongoing dialysis.

In addition to the treatment of various disease states, a device or system according to the invention may also be used for extracting blood components that are useful in treating others, as well as for purposes of studying the processes by which molecules and cells
35 segregate and diffuse in blood. For example, it is known to those skilled in the art that diffusion of individual molecular species in blood may not occur independently and may not depend on size in the simple manner dictated by the Stokes-Einstein equation. Moreover, many solutes may partition into multiple forms: free, in complexes, bound to plasma protein,

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5 bound to cell-surface moieties, or as intracellular solutes. Relative to the rate of diffusion of the solute, its different forms may or may not be in local equilibrium. These phenomena are likely obscured when a membrane is present because it slows and controls overall transfer rates. Therefore, a membraneless device or system according to the invention can be a useful scientific tool to study these phenomena and a system in which rates are raised enough that

10 partitioning may set limits on how much and how quickly a solute can be removed. A particular example is bilirubin bound to albumin. Another example is inorganic phosphorous which exists as partially ionized salts, as two anionic forms in plasma and in several intracellular forms.

Persons skilled in the art will also appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration and not of limitation, and that the present invention is limited only by the claims that follow.

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What Is Claimed Is:

1. A membraneless exchange device for extracting components from a sample fluid, comprising:
 - first, second and third inlet channels;
 - first, second and third exit channels; and
 - a microfluidic extraction channel connected to the first, second and third inlet channels and the first, second and third exit channels, wherein laminar flows of a first extractor fluid, the sample fluid, and a second extractor fluid are established inside the extraction channel and wherein sheathing of the sample fluid by the first and second extractor fluids substantially limits contact between the sample fluid and the surfaces of the extraction channel.
2. The device of claim 1, wherein at least 90% of the sample fluid is sheathed by the first and second extractor fluids.
3. The device of claim 2, wherein at least 95% of the sample fluid is sheathed by the first and second extractor fluids.
4. The device of claim 1, wherein at least a portion of the sample fluid exits the device with the first extractor fluid through the first exit channel.
5. The device of claim 1, wherein advective transport of molecules within said extraction channel is substantially nonexistent.
6. The device of claim 1, wherein the composition of the first extractor fluid is substantially the same as the composition of the second extractor fluid.
7. The device of claim 1, wherein the sample fluid flow is between the first and second extractor fluid flows.
8. The device of claim 1, further comprising:
 - a first diverter formed from a portion of the first exit channel and a portion of the second exit channel; and

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a second diverter formed from a portion of the second exit channel and a portion of the third exit channel.

9. The device of claim 8, wherein a first interface that is formed between the first extractor fluid flow and the sample fluid flow is aligned with at least a portion of the first diverter, and wherein a second interface that is formed between the second extractor fluid flow and the sample fluid flow is aligned with at least a portion of the second diverter.
10. The device of claim 1, wherein the sample fluid is blood fluid.
11. The device of claim 10, wherein the components extracted from the sample fluid are non-cellular components of the blood fluid.
12. The device of claim 1, wherein a first pump is used for controlling the flow of extractor fluid in the extraction channel and wherein a second pump is used for controlling the flow of sample fluid in the extraction channel.
13. The device of claim 12, wherein the first pump is an injection pump that controls the flow of extractor fluid into the extraction channel and wherein the device further comprises a withdrawal pump that controls the flow of extractor fluid out of the extraction channel.
14. The device of claim 1, wherein a source of extractor fluid is connected to said first inlet channel and wherein a source of sample fluid connected to said second inlet channel.
15. The device of claim 14, wherein the sample fluid is blood fluid and the source of sample fluid is a human being.
16. The device of claim 1, wherein the extraction channel has a height of less than 600 μm .

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17. The device of claim 1, wherein the extraction channel has a width-to-height ratio of at least ten.
18. A system for extracting components from a sample fluid, comprising:
 - a device as defined by claim 1; and
 - a secondary processor that receives the first extractor fluid, the second extractor fluid and at least some of the components of the sample fluid upon exiting the extraction channel.
19. The system of claim 18, wherein said secondary processor is a membrane device.
20. The system of claim 18, wherein said secondary processor is a sorption device.
21. A system for performing hemodialysis, comprising:
 - a membraneless exchange device comprised of:
 - first and second dialysate inlet channels;
 - blood inlet and exit channels;
 - first and second dialysate exit channels; and
 - a microfluidic dialysis channel connected to the first and second dialysate inlet and outlet channels and the blood inlet and exit channels, wherein laminar flows of a first dialysate fluid, blood fluid, and a second dialysate fluid are established in order inside the dialysis channel, and wherein at least some of the components of the blood fluid exits the device through the first and second dialysate exit channels; and
 - a secondary processor that receives the dialysate fluid and the at least some of the components of the blood fluid exiting the device through the first and second dialysate exit channels.
22. The system of claim 21, wherein the secondary processor filters the dialysate fluid and the at least some of the components of the blood fluid exiting the device through the first and second dialysate exit channels and returns the filtered fluid to the first and second dialysate inlet channels.

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23. The system of claim 21, wherein the at least some of the components of the blood fluid are substantially non-cellular components of the blood fluid.
24. The system of claim 21, wherein sheathing of the blood fluid by the first and second dialysate fluids substantially limits contact between the blood fluid and the surfaces of the dialysis channel.
25. The system of claim 21, wherein the secondary processor is a membrane device.
26. The system of claim 21, wherein the secondary processor is a sorption device.
27. The system of claim 21, wherein the composition of the first dialysis fluid is substantially the same as the composition of the second dialysis fluid.
28. The system of claim 21, further comprising:
 - a first diverter formed from a portion of the first dialysate exit channel and a portion of the blood exit channel; and
 - a second diverter formed from a portion of the blood exit channel and a portion of the second dialysate exit channel.
29. The system of claim 21, further comprising:
 - a first pump for controlling the flow of dialysate fluid in the dialysis channel; and
 - a second pump for controlling the flow of blood fluid in the dialysis channel.
30. The system of claim 21, wherein the interface between the first dialysate fluid and the blood fluid is varied by adjusting the velocities of the laminar flows of the first dialysate fluid and the blood fluid.
31. The system of claim 21, wherein the interface between the blood fluid and the second dialysate fluid is varied by adjusting the velocities of the laminar flows of the blood fluid and the second dialysate fluid.

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32. The system of claim 21, further comprising a reservoir for storing a viscosity agent, wherein the viscosity agent is be mixed with the first and second dialysate fluid to alter the viscosity of the first and second dialysate fluid.
33. The system of claim 21, further comprising a detector for detecting a presence of an undesired blood component within the dialysate fluid upon exiting the dialysis chamber.
34. The system of claim 33, wherein the detector is comprised of a photo detector.
35. The system of claim 33, wherein a first pump for controlling the flow of dialysate fluid in the dialysis channel is adjusted based on said detected presence of an undesired blood component within said dialysate fluid.
36. The system of claim 21, wherein the velocities of the laminar flows of the first dialysate fluid, the blood fluid and the second dialysate fluid are adjusted based on the detected presence of an undesired blood component within the first and second dialysate fluids.
37. The system of claim 21, wherein the first and second dialysate fluids are comprised of at least one of the following: a hyper osmolar solution, a solution high in glucose content, or a polyelectrolyte osmotic agent.
38. A method for extracting components from a sample fluid, comprising:
 - establishing laminar flows of a first extractor fluid, the sample fluid and a second extractor fluid inside a microfluidic extraction channel, wherein sheathing of the sample fluid by the first and second extractor fluids substantially limits contact between the sample fluid and the surfaces of the extraction channel; and
 - withdrawing the first extractor fluid, the sample fluid and the second extractor fluid from the extraction channel such that at least a portion of the sample fluid is removed together with the first extractor fluid and the second extractor fluid and apart from the remainder of the sample fluid.
39. The method of claim 38, wherein the establishing laminar flows comprises:

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providing first, second and third inlet channels; and
providing first, second and third exit channels.

40. The method of claim 38, further comprising:

providing the first and second extractor fluids and the at least a portion of the sample fluid to a secondary processor.

41. A method for performing hemodialysis, comprising:

establishing laminar flows of a first dialysate fluid, blood fluid and a second dialysate fluid inside a microfluidic extraction channel;
withdrawing the first dialysate fluid, the blood fluid and the second dialysate fluid from the extraction channel such that at least some of the components of the blood fluid are removed together with the first dialysate fluid and the second dialysate fluid and apart from the remainder of the blood fluid; and

providing the first and second dialysate fluids and the at least some of the components of the blood fluid to a secondary processor.

42. The method of claim 41, further comprising:

using the secondary processor to filter the first and second dialysate fluids and the at least some of the components of the blood fluid; and
returning the filtered fluid from the secondary processor to the extraction channel.

43. The method of claim 42, wherein sheathing of the blood fluid by the first and second dialysate fluids substantially limits contact between the blood fluid and the surfaces of the dialysis channel.

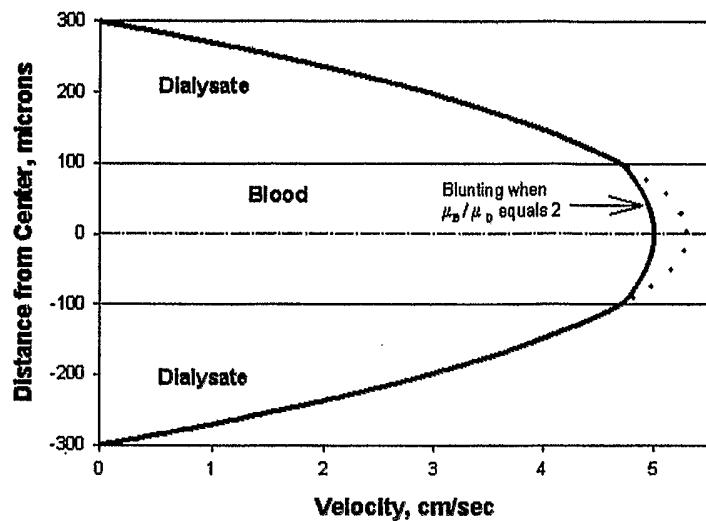


FIG. 1

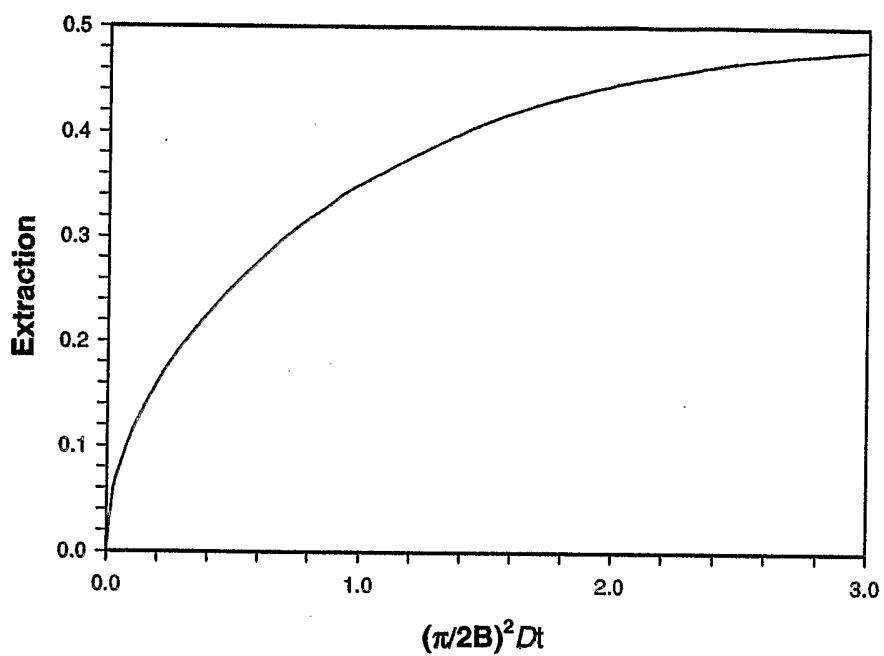


FIG. 2

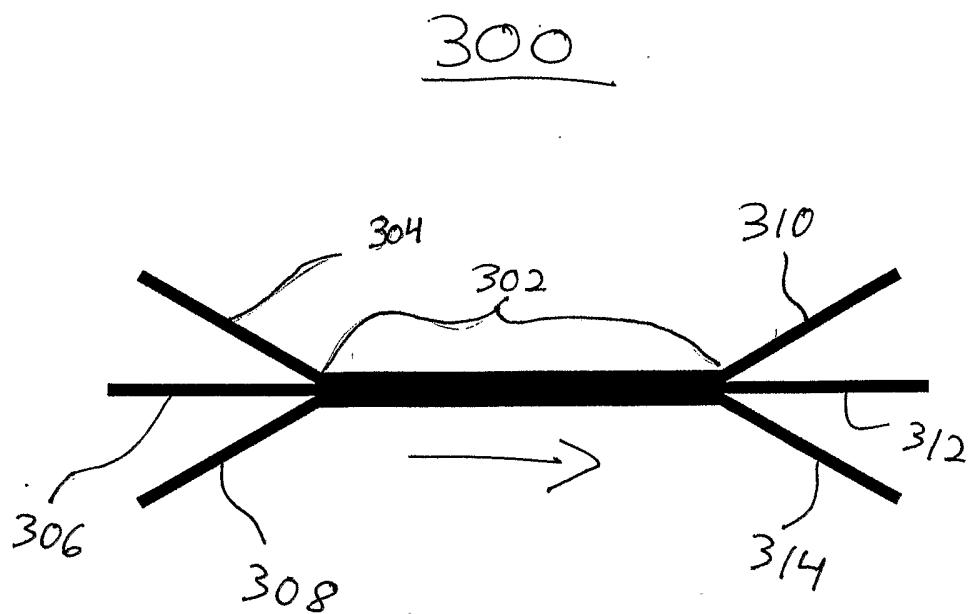
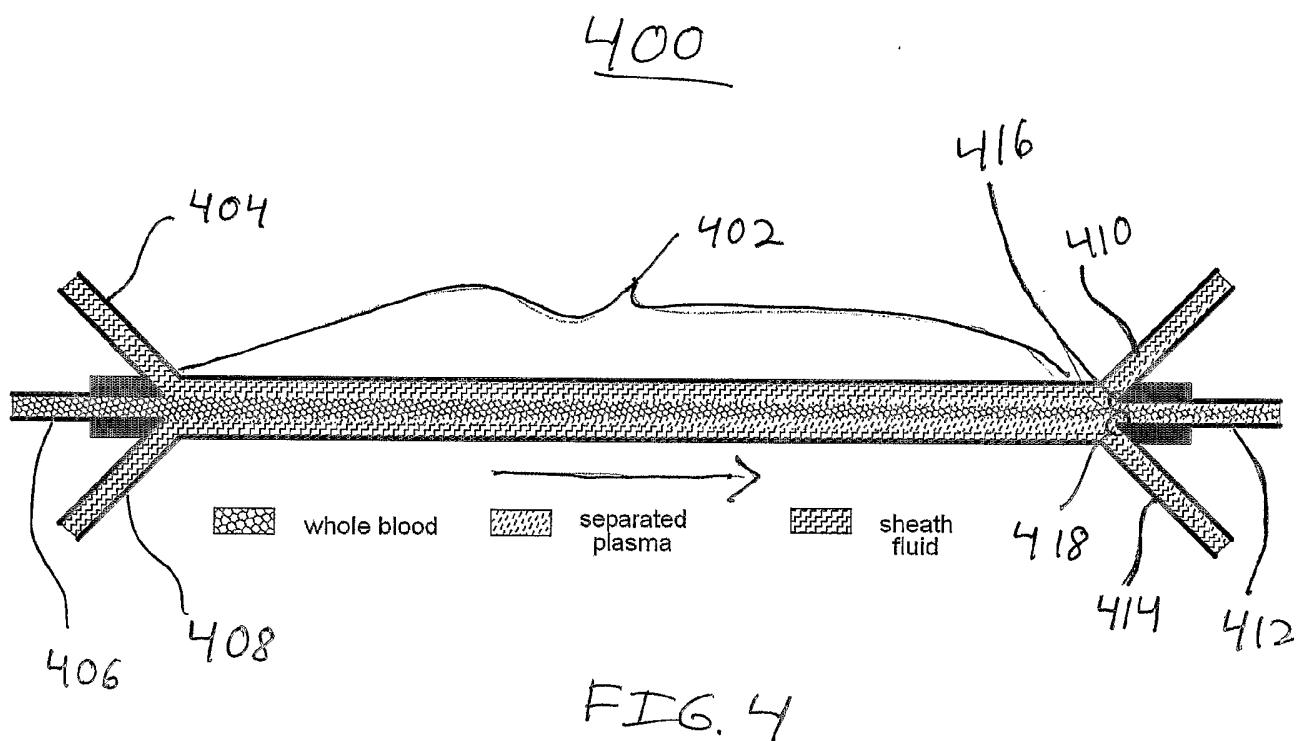


FIG. 3



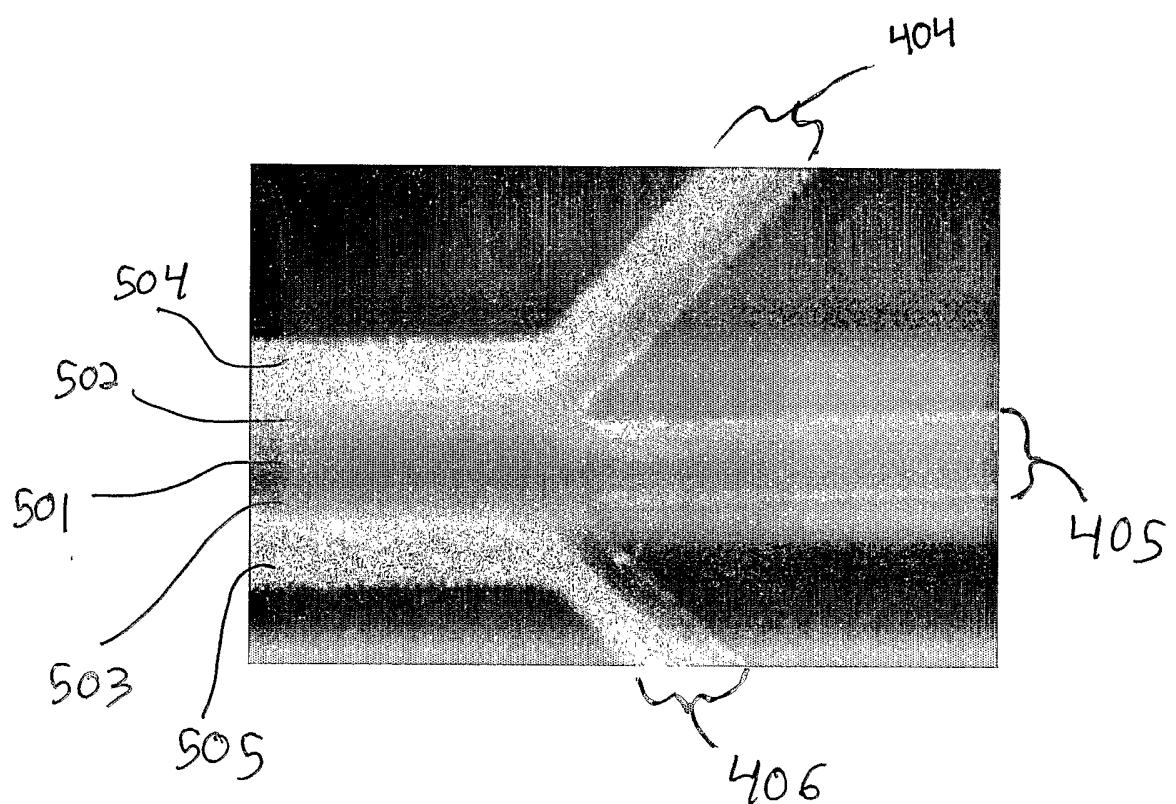


FIG. 5

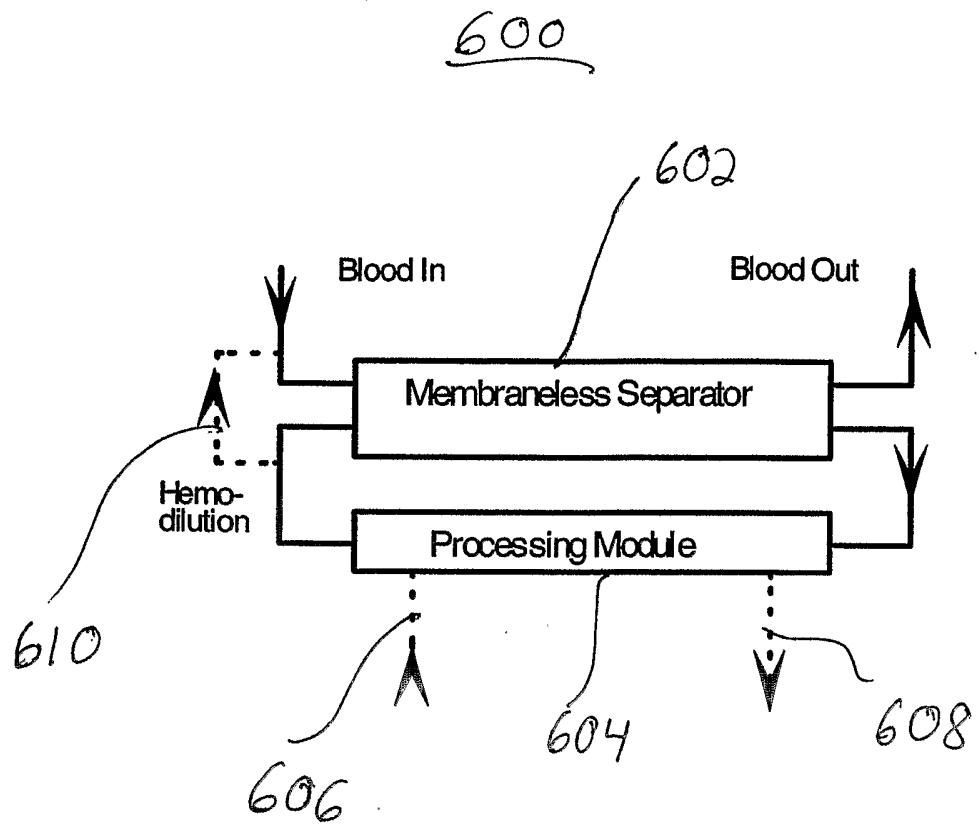


FIG. 6

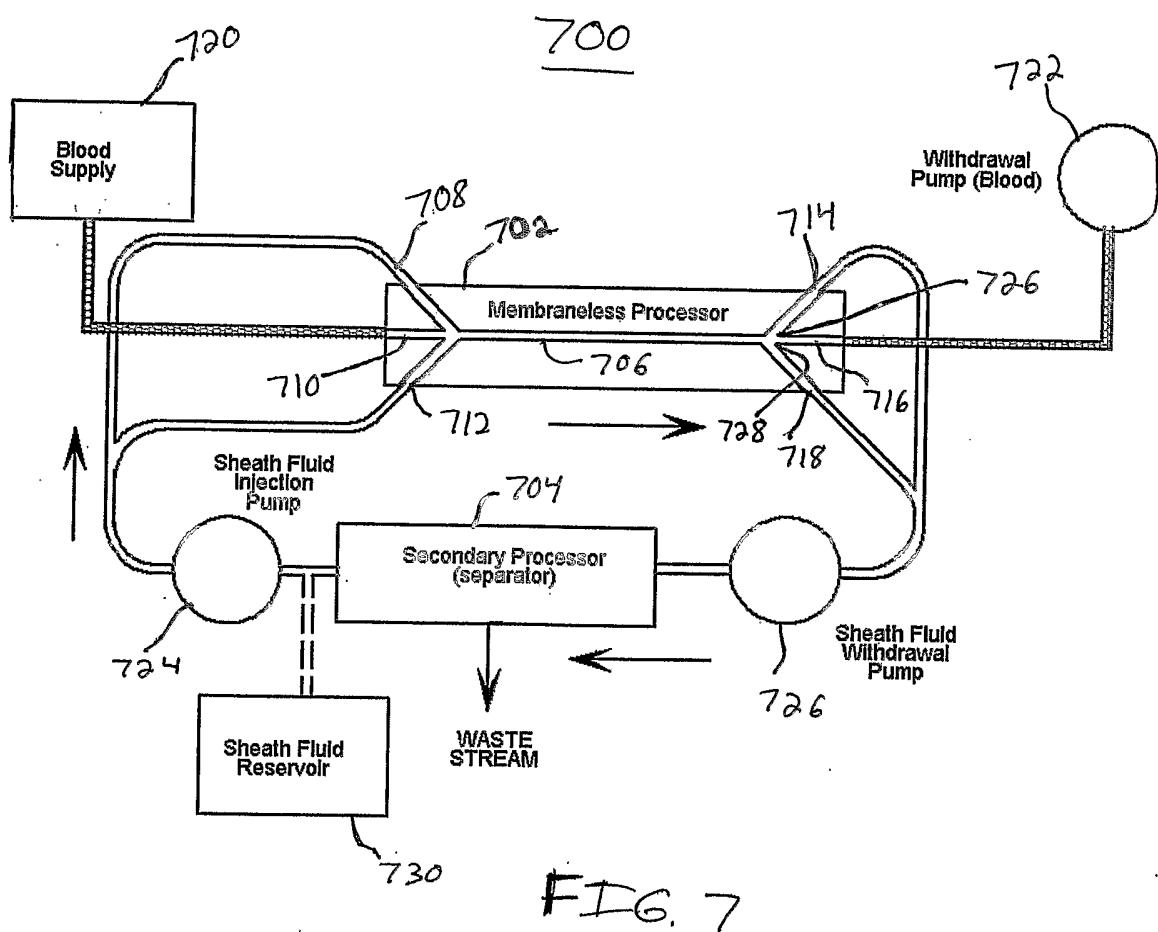


FIG. 7

800

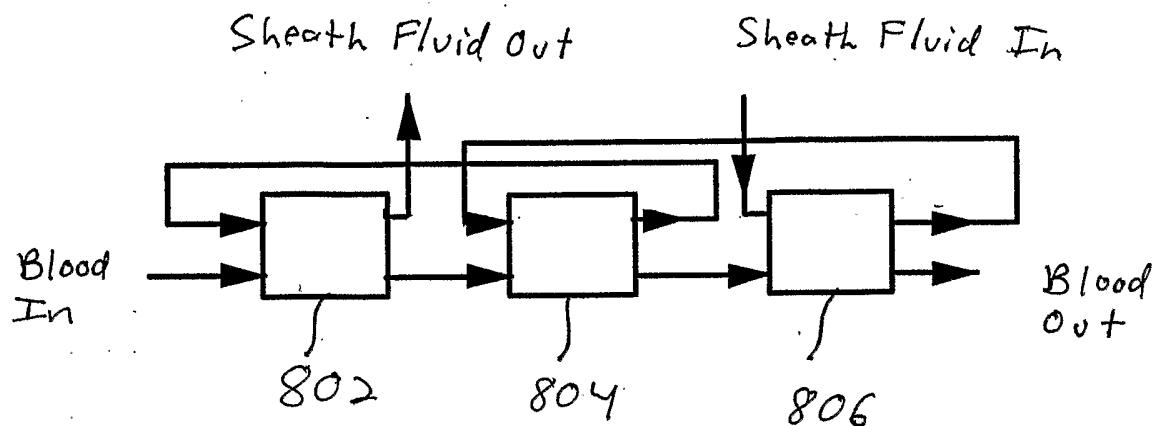


FIG. 8

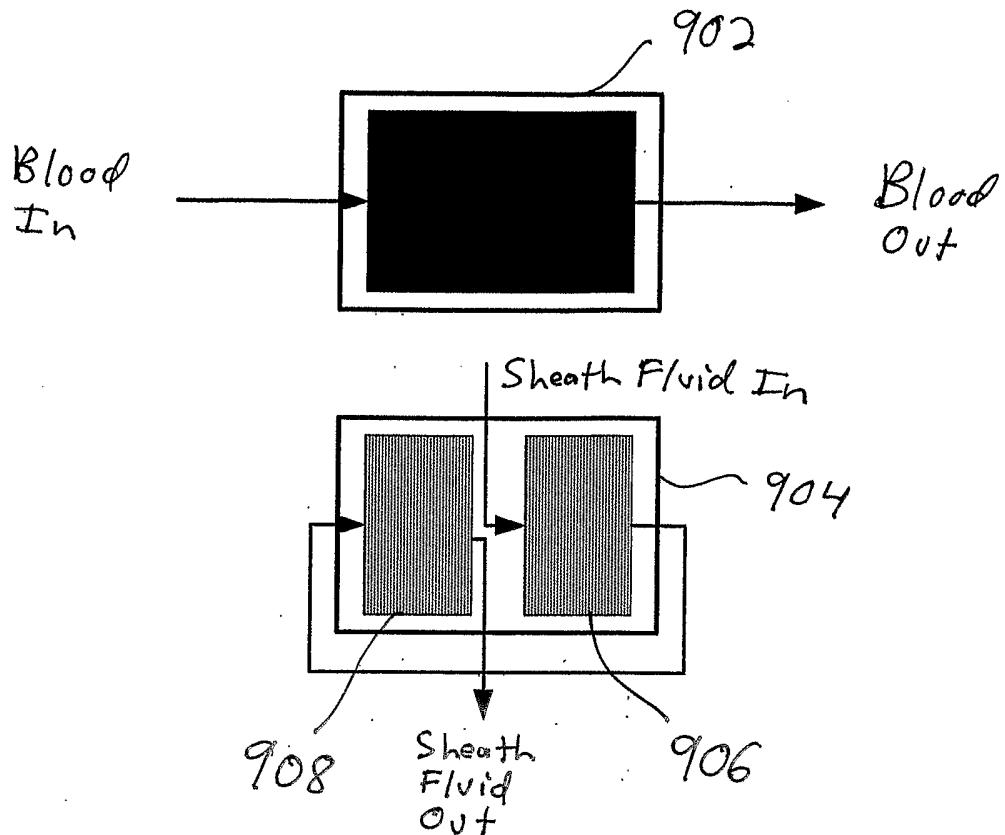
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FIG. 9