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(54) **Title**: SELECTIVE ULTRAFILTRATION MEMBERANES FOR RENAL REPLACEMENT THERAPIES

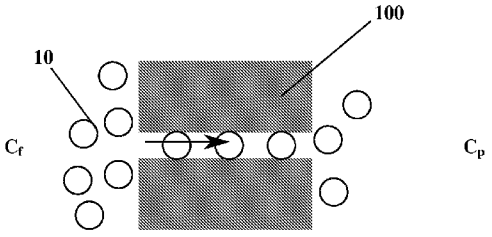

Figure 1

(Prior Art)

(57) **Abstract**: Disclosed embodiments describe both a system and method for improved ultrafiltration of charged/uncharged species. Applications of the disclosed embodiments include: devices for assisting those with compromised kidney function, as well as applications in the food, water purification and pharmaceutical industries. Disclosed embodiments incorporate application of an imposed electric field and/or surface charge patterning to a permeable membrane with or without the use of selected additive molecules in order to reduce sieving coefficients for ultrafiltration applications.

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SELECTIVE ULTRAFILTRATION MEMBRANES FOR RENAL REPLACEMENT THERAPIES

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This non-provisional patent application claims the benefit of priority to U.S. Provisional Patent Application No. 61/148,833, filed January 30, 2009, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The disclosed embodiments are in the field of ultrafiltration, and more particularly in the field of selective filtration of charged/uncharged molecules potentially in biomedical and related applications.

BACKGROUND

[0003] Ultrafiltration is a membrane based filtration process of industrial and biological significance used to separate, purify and concentrate macromolecular solutions. In human physiology, the kidney performs ultrafiltration of blood through biological membranes located in nephrons, the functional units of the kidney. A related important application of ultrafiltration (using synthetic membranes) is to replace diseased kidney function using Renal Replacement Therapy (RRT) in patients suffering from Acute Renal Failure and End-stage-Renal Disease. Synthetic membranes are used to perform ultrafiltration in the food, water purification and pharmaceutical industries to name a few applications.

[0004] The replacement of renal function in persons with renal failure by dialysis is dependent on the ability to filter out waste products while preserving metabolically costly proteins, peptides and cells. Thus, there exists a need to

maximize the retention of a large macromolecular solute of interest in the feed (supply) solution, and more specifically to improve the selectivity of current ultrafiltration systems. Examples of macromolecules of interest in this discussion are synthetic and natural proteins, carbohydrates, nucleic acids *etc.* with molecular dimensions of the order of and larger than 1 nm. Specifically, the retention of serum albumin in blood during ultrafiltration together with the clearance of middle molecules like β_2-microglobulin is not satisfactorily addressed in conventional therapies.

[0005] Diffusive transport of a molecule from one point in the fluid to another is proportional to the difference of concentrations of the molecule between the two points and is approximately inversely proportional to the molecular size, up to sizes excluded by the membrane. Thus, smaller molecules are extracted from, for example, blood more quickly than larger ones.

[0006] Conventional renal function replacement therapies often include membranes that have poor selectivity toward biologically important molecules or are too large for the possibility of patient implantation. The definition of membranes includes filtration devices utilizing well-defined pores as well as those utilizing a matrix of fibers. The former category includes membranes for industrial and therapeutic ultrafiltration and high flux dialysis; the latter category includes gels for gel permeation chromatography, the glomerular basement membrane and other extracellular matrices.

SUMMARY

[0007] This and other unmet needs of the prior art are met by devices and methods as described in more detail below.

[0008] A Renal Assist Device (RAD) employing ultrafiltration of blood (hemofiltration) can have a major impact on the cost of medical treatment of kidney failure. Dialysis is extremely expensive, time consuming, and stressful for the patient. The proposed method is superior to the prior art in hemofiltration because it significantly improves the solute retention capacity of the RAD through a nonintrusive and an inexpensive modification to the solution on the filtrate side of the membrane, rather than through costly re-design and repeated fabrication of the membrane, as required by competing nanofabrication technologies involving pore size reduction and/or surface charge modification. Disclosed method(s) may also significantly improve the capacity of ultrafiltration membranes to filter out solutes not only in implantable and extracorporeal renal replacement therapy applications, but also in food processing, pharmaceutical and waste-water-treatment applications.

[0009] The kidneys are paired organs, each similar in size to a clenched fist, that lie behind the abdominal cavity at the level of the bottom of the ribcage. In addition to their obvious role in waste excretion, the kidneys regulate multiple physiological processes essential to the health of the organism. In humans, the list of functions that kidneys accomplish include excretion of nitrogenous wastes and certain organic compounds, homeostasis of volume, osmolality, acid-base, divalent cations, phosphorus, and potassium; regulation of blood pressure and erythropoeisis, synthesis of Vitamin D, and, more controversially, antigen presentation, immunoregulation, and maintenance of redox balance. The kidney's filters ("glomeruli") are remarkable structures, in that the blood contains 40gm/L of albumin, a globular protein important for health, and the filtered fluid in Bowman's space has mere micrograms of albumin per liter. Yet, the kidney's filters are able to pass other proteins and peptides, such as hemoglobin, myoglobin, and B2-

microglobulin that are only slightly smaller than albumin (12kD-45kD, comapered to albumin's 66kD).

[0010] The numerical calculations to be described in detail below predict that the solute-pore (albumin-pore) electrostatic repulsion results in a sieving coefficient (percent transported through the membrane) of *0.1%* for a solute having a charge number characteristic of serum albumin at the physiological pH and ionic strength. It is found that higher surface charge density, smaller pore width and more complete surface coverage by charged surface-modification agent(s) leads to lower sieving coefficients. The selectivity of the membrane toward the charged solute also leads to concentration polarization.

[0011] Modification of pore wall surface charge is one strategy for improving the selectivity of a membrane toward solutes. The selectivity of a membrane to any particular solute is inversely proportional to the sieving coefficient to be defined below.

[0012] In general terms, the driving force for ultrafiltration is a pressure differential across the relevant membrane. This leads to a transfer, from the solution in the feed side (side F) toward the permeate side (side P), of solvent molecules and, of a fraction of the solute molecules on side F determined by a number of factors such as (a) the size, shape, charge of the pores/fibers, (b) the size, shape, charge, number density of the solute molecules, and (c) the filtration velocity.

[0013] A working equation that governs ultrafiltration applications with imposed electric field E_x is:

$$S = \frac{(1+s)\phi_0 K_c}{1-\left[1-(1+s)\phi_0 K_c\right]\exp\left[-\frac{(1+s)K_c}{K_d}Pe\right]}$$

where S is the sieving coefficient, ϕ_0 is the partition coefficient, K_c is the hindered convection coefficient and Pe is the Peclet number. The parameter s embodies the effect of electric field, being defined by

$$s = \frac{zDE_x FK_d}{RT\overline{u}K_c}$$

[0014] where *F* is the Faraday's constant, *R* is the universal gas constant, *T is the temperature, E_x is the imposed electric field, z* and *D* are the charge number and molecular diffusivity of the solute at the temperature of experiment, K_c and K_d are hindered convection and diffusion coefficients of the solute in the pore and $\overline{u}$ is the average velocity of the solvent within a slit-shaped pore of height *2h* due to the effect of applied pressure as well as voltages.

[0015] A small sieving coefficient is essential for the success of many ultrafiltration applications. For example, a sieving coefficient of 0.01% or lower for serum albumin is desirable for ultrafiltration-based renal replacement therapy. An example of embodiments of an ultrafiltration membrane employed as a bioartificial organ is presented in U.S. Patent No. 7,048,856 (Fissell, IV et al.) and to the extent that it is enabling is hereby incorporated by reference as though recited in its entirety.

[0016] As mentioned above, the ultrafiltration performance of a membrane with respect to retention/passage of solute is usually characterized by the sieving coefficient *S*, defined as the ratio of the permeate side (the post filtration side) concentration C_P of the solute (say in units of moles per liter) to the feed side (pre-filtration) concentration C_F of the solute.

$$S = \frac{C_P}{C_F}$$

[0017] Here, feed and permeate refer to the solution to be filtered by the membrane (feed) and that already filtered through the membrane (permeate) on its downstream side.

[0018] One embodiment of the disclosed invention involves the use of additives in the permeate solution to affect the sieving coefficient, as defined above. The principles upon which the exemplary embodiments are quantitatively based are the fundamental concepts of equilibrium partitioning and hindered transport. The term equilibrium partitioning refers to the fact that the equilibrium concentration (in moles per liter of the solution) of a solute in a porous or fibrous media constituting the membrane is different from the equilibrium concentration in a bulk solution. For membrane transport, one can define two partition coefficients (a) the feed side partition coefficient ϕ_0, and (b) the permeate partition coefficient ϕ_L.

[0019] Formally, if a coordinate *x* is used to characterize distance across the pore of length L and if *x=0* denotes the point immediately inside the membrane adjacent to the side F solution of concentration C_F and *x=L* denotes a point immediately inside the membrane adjacent to side P having concentration C_P, then, the partition coefficients are defined by

$$\phi_0 = \frac{C(x=0)}{C_F}$$

$$\phi_L = \frac{C(x=L)}{C_P}$$

[0020] Conventionally ϕ_0 is equated with ϕ_L.

[0021] The use of additives to affect the sieving of solutes, in the disclosed exemplary embodiments, utilizes the fact that the values of the partition coefficients, as defined above, may be tuned based on the concentration of dissolved solutes in the permeate side, thereby decreasing the sieving coefficient via the optimized

addition of selected additives. The effect of additives on the sieving coefficient can be demonstrated as follows. If the partitioning coefficient ϕ_0 is different from ϕ_L, then, the sieving coefficient, S is given by:

$$S = \frac{\phi_0 K_c}{1-(1-\phi_L K_c)\exp\left(-\frac{K_c Pe}{K_d}\right)}$$

where K_c is the hindered convection coefficient, K_d is the hindered diffusion coefficient and $Pe = \frac{\delta v L}{D}$ is the Peclet number which is a function of the porosity δ, filtration velocity v, diffusion coefficient D of the solute and L, the length (thickness) of the membrane.

[0022] In particular, in the small Pe limit $(Pe \to 0)$ which corresponds to purely diffusive equilibration between the permeate and feed solutions through the pore,

$$S = \frac{\phi_0}{\phi_L}$$

[0023] A physical interpretation of the last equation is that any attractive/repulsive interaction in any part of the feed-pore-permeate system biases the Brownian motion of the solute molecules to redistribute more/fewer molecules in the zone of attraction/repulsion.

[0024] With respect to the effect of additives in the disclosed exemplary embodiments, it is important to note that (a) if ϕ_L increases, then the sieving coefficient decreases, as revealed by the last two equations for S, and (b) the concentration of additives can be used to affect a change in ϕ_L. In particular, consider a permeate solution containing at least two dissolved ingredients: solute A

and an additive B. The partition coefficient ϕ_L of solute A increases with increasing concentration of additive B, under certain conditions disclosed below.

[0025] Disclosed embodiments may involve the addition of varying amounts of, for example, large soluble charged/uncharged additive molecules B in the filtrate solution at the start/during the ultrafiltration that leads to an alteration in the value of ϕ_L for solute A. An increase in ϕ_L due to the addition of the additive B will result in a lower sieving coefficient *S* for solute A or improved selectivity. This in combination with other variables such as induced electric fields and/or surface coatings serve to greatly increase the selectivity (represented by sieving coefficient) of ultrafiltration membranes. For example, if the solute of interest is a large negatively charged species, a large negatively charged additive may be an appropriate choice for addition to the permeate solution. Its presence will likely increase the repulsive effects on the solute and thus reduce the sieving coefficient and prevent migration of the solute into the permeate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] A better understanding of the exemplary embodiments will be had when reference is made to the accompanying drawings, wherein identical parts are identified with identical reference numerals, and wherein:

[0027] **FIGURE 1** is a schematic representation of an embodiment of a pore membrane.

[0028] **FIGURE 2** is a schematic representation of an embodiment of a membrane pore with an additive added into the permeate solution.

[0029] **FIGURE 3** is a schematic representation of a pore membrane incorporating an electric field.

[0030] **FIGURE 4** shows the geometry of the feed-membrane-permeate system showing Pattern A patches. There are 8 nanopores of length *1 μm* in the membrane.

[0031] **FIGURE 5** is a streamline pattern for the flow of the feed solution for Figure 4.

[0032] **FIGURE 6** shows the concentration of a charged solute at the center line of an *8 nm* wide nanopore coated with a *-46 mV* Pattern A patch.

[0033] **FIGURE 7** shows the concentration distribution of a charged solute at the center line of an *8 nm* nanopore coated with a *-100 mV* Pattern A patch.

[0034] **FIGURE 8** shows the concentration distribution of a charged solute at the centerline of 8 nm wide nanopores coated with -46 *mV* patches of both Pattern A and Pattern B and a table for the resultant sieving coefficients.

[0035] **FIGURE 9** is a plot of the calculated effect on the sieving coefficient of a pore of width 2h after applying a voltage across the edge of the pore.

[0036] **FIGURE 10** is a table of values used for the calculations displayed in Figure 9.

[0037] **FIGURE 11** shows a representation of an embodiment of a filtration system employing an additive to improve sieving coefficient.

[0038] **FIGURE 12** shows an embodiment of an implanted Renal Assist Device.

DETAILED DESCRIPTION

[0039] **Figure 1** illustrates a conventional pore membrane filtration system. The solute particles **10** are allowed to distribute on either side of the membrane **100**, their concentration difference (the difference between the concentration on the feed side and the concentration on the permeate side) only determined by size exclusion

and rate of passage across the membrane. This arrangement generally is not highly selective.

[0040] In contrast to **Figure 1**, is **Figure 2** which illustrates a pore membrane (similar to that of **Figure 1**) and the concentration differential across it. This figure illustrates the scenario where the permeate solution contains at least two dissolved ingredients: a solute A **10** and an additive B **20**. In this illustration, the partition coefficient ϕ_L of solute A increases with increasing concentration of additive B. More succinctly, an increase in ϕ_L due to the addition of additive B will result in a lower sieving coefficient for solute A or in other words, improved selectivity. The solute molecule represented on the right side of the drawing highlights the size exclusion properties relevant to disclosed embodiments. Additionally, if the additive **20** is appropriately paired with the relevant membrane **100** such that the membrane is impermeable to the additive (whether by size exclusion or other repulsive effects e.g. charge) then interaction with the solute will only occur on the permeate side of the membrane.

[0041] When a suitable additive is employed in the system the concentration differential may be decidedly altered. Figure 2 shows a stark contrast in concentration of solute **10**, when a suitable additive **20** is used. It is clear from the drawing that the additive further impedes the solute molecules from traversing the membrane pore. The additive may accomplish this through steric crowding of the pore exit alone. Additionally, the additive may have physico-chemical properties such a total molecular charge and charge distribution which cause intermolecular repulsion of the solute of interest. These properties will cause the solute to distribute more readily in the feed solution and membrane pore and significantly less in the

permeate solution. Optionally, the membrane pore and additive may be selected such that the membrane is substantially impermeable to the additive.

[0042] Specific embodiments of the additive molecule include synthetically manufactured polysaccharides and proteins, biologically extracted polysaccharides and proteins. The solute A may comprise manufactured or biologically extracted proteins or other biologically active molecules. The solvents employed in the permeate side may include water, and organic solvents. The membrane may comprise either synthetic or biological membranes, but preferably should be highly impermeable to the additive of choice. Some particular characteristics of the additive may include: high solubility in the solvent of choice; a diameter that is sufficiently large relative to the average pore diameter to hinder passage, or, if a fibrous membrane is used, then larger than the average spacing between fibers; if the solute of interest possesses a molecular charge, the additive should preferably have a charge of the same sign as the solute.

[0043] An example of a suitable additive for use in improving membrane selectivity toward albumin is a dextran such as Dextran 500 (may be obtained from GE Life Sciences) or its sulfate salt. By means of example, Dextran 500 has a molecular weight close to 500,000 Da, and is readily soluble in water. The flexible polymeric structure of dextran leads to a large excluded volume; the solubility of dextran allows the use of higher concentrations to enhance repulsive interactions. Using Dextran 500 as an example of an embodiment of an additive for use in increasing the selectivity of a membrane toward a large negatively charged macromolecule of choice, Dextran has several important characteristics. The size of Dextran 500 molecules (~30 nm) will help to maintain a low probability of the additive entering an ultrafiltration membrane with sufficiently small pore sizes and fiber

spacings (*e.g.* < 10 nm) from the permeate solution, despite the flexibility of dextran. The optional use of dextran sulfate as additive B serves to electrostatically intensify the intermolecular repulsive interactions, when the solute is negatively charged (such as the protein serum albumin at physiological pH). The intermolecular repulsions between dextran (sulfate) and solute molecules in the permeate solution will lead to a higher ϕ_L (*e.g.* C_p decreases) for the solute and consequently according to the equations above, an even lower sieving coefficient.

[0044] The partition coefficients of many macromolecular solutes are increasing functions of its own concentration and the concentration of other macromolecules present in the solution. The explanation for the above-discussed increase of partition coefficients is that, as the solution concentration(s) of similar/dissimilar macromolecule(s) increases, intermolecular repulsive interactions lead to a more significant reduction in the probability of a given solute molecule being located in the solution space more significantly than the probability for the same solute molecule being located in the pore/fiber-gap space. Herein, "repulsive intermolecular interaction" should be understood to include excluded volume effects.

[0045] **Figure 3** shows a membrane pore across which an electric field has been established. According to equations above, when the electric field E_x directed as shown in **Figure 3** is increased, S decreases for negatively charged solutes. In one embodiment of the application, a voltage of several tens to thousands of millivolts may be applied using the optional electrodes. In an embodiment wherein the solute **10** comprises a negatively charged species, as the electric field is employed in the manner represented in **Figure 3**, the sieving coefficient will decrease, thus increasing the selectivity. This configuration has been demonstrated to produce sieving coefficients on the order of 0.01%.

[0046] Example calculations. The numerical simulation software COMSOL Multiphysics is used for the following calculation showing, how in one embodiment, appropriate patterning of surface charge on the pore walls can be used to enhance the selectivity to charged solutes. The geometry of the feed and permeate channels, the flow of the feed solution, and the nanopore membrane is shown in **Figure 4**. All dimensions into the plane of the paper are large enough for the problem to be treated as two dimensional. The following parameters were used for the calculations. The length of the pores is *1 μm*. The size of the feed and the permeate reservoirs is *10 μm* by *10 μm*. The feed channel flow distributes into *8* nanopores. The ionic strength of the electrolyte solution is *0.14 M*. The concentration of the charged solute in the feed is *0.6 mM.* The diffusion coefficient of the solute in the feed solution is 10^{-10} m^2/s. The solute is negatively charged and has a valence of 17. Two nanopore widths, viz. *8 nm* and *7 nm* are studied in this simulation. The dimensions of the feed and permeate channels are *10 μm by 10 μm.* On the feed side, there is forced fluid flow moving perpendicular to the nanopores. The pressure at the feed inlet is assumed to be p_o=*2 psi*. Since the pressure drop on the feed side is negligible, the pressure at the outlet of the feed side is assumed to be $0.99p_o$. On the permeate side, the upper and lower boundary are both assumed to be open boundaries with pressure equal to zero. Two surface charge patterns are used. In Pattern A (shown in Figure 4), a charged patch covers a fraction of the nanopore wall (the leftmost) and the remainder of the nanopore wall is uncharged. In Pattern B (not shown) the nanopore wall is completely covered by the charged patch or the patch length is *1 μm*. For each patch pattern, the zeta potential or the surface charge further characterizes the patch. For example, in the following text, '-46 *mV* Pattern A patch' refers to a surface modification pattern where the zeta potential is -

46 mV over the fraction covered by the patch and zero over the remainder of the pore wall. In all cases studied in this simulation, the patch length for Pattern A is *500 nm* or *50%* of the nanopore length.

[0047] The results of the calculations are as follows. The feed side solution will be forced into the nanopores due to the pressure drop across the membrane. A *-46 mV* Pattern A patch is used. The streamline pattern for the flow of the feed solution is shown in **Figure 5**. The total flow rate across the membrane is calculated to be 0.06% of the flow rate within the feed side. The concentration in the permeate channel is *0.077 mM* and the resulting sieving coefficient is *0.128*.

[0048] The concentration polarization effect is evident in **Figure 6**, as the concentration in the feed channel is higher near the membrane surface than in the bulk of the feed channel. Increasing the charge of the patch will significantly decrease the concentration of the charged species in the permeate channel. With a *–100 mV* Pattern A patch and an *8 nm* wide nanopore, the sieving coefficient is *0.0105*. The corresponding concentration distribution along the centerline of the nanopore is shown in **Figure 7**.

[0049] In **Figure 8(a)**, the concentration at the centerline of the nanopore is plotted for *8 nm* and *7 nm* wide nanopores with a *-46 mV* charged patch. For smaller channels, the sieving coefficient is even smaller. The sieving coefficients corresponding to the four *-46 mV* patches in this figure are:

- *8 nm* with **Pattern A** patch: *12.9%*
- *8 nm* with **Pattern B** patch: *8.7%*
- *7 nm* with **Pattern A** patch: *4.4%*
- *7 nm* with **Pattern B** patch: *2.9%*

[0050] The sieving coefficient calculated for *8 nm* and *7 nm* wide nanopores are listed in **Figure 8(b)** for two values *-46 mV* and *-100 mV* of the patch surface potential. Expectedly, the lowest sieving coefficient among the cases studied is obtained for the *7 nm* wide nanopore and *-100 mV* patch. The solute selectivity is less sensitive to surface coverage (Pattern A or Pattern B) for the *-100 mV* patch.

[0051] **Figure 9** using the parameters set out in **Figure 10** provides evidence of increasing the sieving coefficient by at least three orders of magnitudes for a solute of molecular size and electrical properties similar to bovine serum albumin with application of a modest voltage differential. A small sieving coefficient is essential for the success of many ultrafiltration applications. For example, a sieving coefficient of 0.01% or lower for serum albumin is desirable for ultrafiltration-based renal replacement therapy or a RAD.

[0052] In an embodiment, a first solute molecule is chosen and present in the feed solution, a suitably chosen second additive molecule is used in the permeate solution (side P); and the membrane is impermeable to the second additive molecule. In this case, the intermolecular interactions between the additive molecules and the solute molecules will take place only in the bulk solution on side P (permeate solution). In comparison to an ultrafiltration system where no such additive is added to the permeate solution, intermolecular repulsive interactions between the solute and additive will render the solute molecules less likely to locate in the bulk permeate solution, and, therefore, more likely to locate themselves inside the pore, increasing the permeate side partition coefficient ϕ_L for the solute. Moreover, the intermolecular repulsion can be made stronger by using a higher concentration of the dissolved additive.

[0053] Exemplary embodiments of the additive molecule B in the disclosed invention include but are not limited to synthetically manufactured or biologically extracted polysaccharides and proteins. Specific embodiments of the test molecule include but are not limited to synthetically manufactured or biologically extracted proteins and biological molecules. Exemplary embodiments of the solvent include but are not limited to water and organic solvents. Specific embodiments of the membrane include but are not limited to synthetic membranes and/or biological membranes either *in vitro* or *in vivo*. Specific applications for the operation of the membrane-based filter include, but are not limited to ultrafiltration, dialysis, and diafiltration.

[0054] In an embodiment, an ultrafiltration membrane (optionally comprising pores) separates two solutions, one the feed solution contains a solute of interest, the other, the permeate contains a separate solution. A suitable additive B is selected and employed at a suitable concentration, but is present only in the permeate side of the membrane. In this scenario, the intermolecular interactions between the additive and the solute of interest will take place only in the solution on the permeate side of the membrane. The result being that, in contrast to a system that employs no additive, repulsive intermolecular interactions between the solute and the additive will cause the solute molecules to locate more likely in the pore than in the permeate solution. In terms of the above referenced equations, the net effect is that ϕ_L is increased, thus decreasing the sieving coefficient. Optionally, the intermolecular repulsion may be increased by employing a higher concentration of the additive.

[0055] In an embodiment, the membrane employs in silica-based synthetic nanomembranes at physiological pH, this leads to an improvement in permeability

(due to the phenomenon of electroosmosis) as well as selectivity, unlike conventional RAD technologies which involve trade-offs between permeability and selectivity. Further, no expensive surface modification step is required for the electrically enhanced RAD as compared to conventional methods and technologies that depend on repulsion between like charged walls and solutes to improve selectivity of the membrane. The membrane may be enhanced by the use of electrical fields and/or the introduction of selected additive molecules to the permeate solution prior to or during the filtration process.

[0056] **Figure 11** illustrates an embodiment of an ultrafiltration system employing a selected additive **20** to improve membrane selectivity. The system comprises a main filter chamber **200**, a membrane inside the chamber. In this embodiment, the additive **20** is delivered to the permeate side by the addition apparatus **201**, via tubing. The feed solution is delivered to the filtration chamber by tubing as well the tubing incorporating a feed line **210** and an exit opening **211**, and is shown passing through optional prefilter **212** into the filtration chamber. The permeate solution is connected to a reservoir **220**. Alternatively, the embodiment of Figure 11 may include a membrane with an induced electric field to further improve selectivity of the membrane toward the solute of interest.

[0057] In an embodiment of a device employing an additive, a first solute molecule is chosen and present in the feed solution, a suitably chosen second additive molecule is used in the permeate solution (side P); and the membrane is impermeable to the second additive molecule. In this case, the intermolecular interactions between the additive molecules and the solute molecules will take place only in the bulk solution on side P (permeate solution). In comparison to an ultrafiltration system where no such additive is added to the permeate solution,

intermolecular repulsive interactions between the solute and additive will render the solute molecules less likely to locate in the bulk permeate solution, and, therefore, more likely to locate themselves inside the pore, increasing the permeate side partition coefficient ϕ_L for the solute. Moreover, the intermolecular repulsion can be made stronger by using a higher concentration of the dissolved additive.

[0058] Specific embodiments of the additive molecule B in the disclosed invention include but are not limited to synthetically manufactured or biologically extracted polysaccharides and proteins. Specific embodiments of the test molecule include but are not limited to synthetically manufactured or biologically extracted proteins and biological molecules. Specific embodiments of the solvent include but are not limited to water and organic solvents. Specific embodiments of the membrane include but are not limited to synthetic membranes and/or biological membranes either *in vitro* or *in vivo*. Specific applications for the operation of the membrane-based filter include, but are not limited to ultrafiltration, dialysis, and diafiltration.

[0059] In an embodiment, an ultrafiltration membrane (optionally comprising pores) separates two solutions, one the feed solution contains a solute of interest, the other, the permeate contains a separate solution. A suitable additive B is selected and employed at a suitable concentration, but is present only in the permeate side of the membrane. In this scenario, the intermolecular interactions between the additive and the solute of interest will take place only in the solution on the permeate side of the membrane. The result being that, in contrast to a system that employs no additive, repulsive intermolecular interactions between the solute and the additive will cause the solute molecules to locate more likely in the pore than in the permeate solution. In terms of the above referenced equations, the net effect

is that ϕ_L is increased, thus decreasing the sieving coefficient. Optionally, the intermolecular repulsion may be increased by employing a higher concentration of the additive.

[0060] In an embodiment, the membrane employs in silica-based synthetic nanomembranes at physiological pH, which leads to an improvement in permeability (due to the phenomenon of electroosmosis) as well as selectivity, unlike conventional renal replacement therapies which involve trade-offs between permeability and selectivity. Further, no expensive surface modification step is required for the electrically enhanced RAD as compared to conventional methods and technologies that depend on repulsion between like charged walls and solutes to improve selectivity of the membrane. The membrane may be enhanced by the use of electrical fields and/or the introduction of selected additive molecules to the permeate solution prior to or during the filtration process. A diagram of an embodiment of an implanted form of a RAD is shown in **Figure 12**. The RAD may consist of a hemofiltration module and a cell bio-reactor module to replace the filtration and reabsorption tasks of a kidney, respectively. The final device may be a compact biocompatible cartridge handling afferent and efferent streams of blood and an exit stream that drains into the bladder.

[0061] Exemplary implantable embodiments comprise a main filter chamber **200** with a filter membrane, a feed line **210** for allowing a feed supply of fluid to enter the filter chamber on the feed side of the membrane, a permeate exit line **213** for reintroducing fluid into the body, and a waste exit line **214** for allowing filtered species to travel to, for example the bladder for elimination. The membrane may incorporate an electric field to increase selectivity as discussed above. Additionally, the permeate solution may contain a selected additive **20** chosen to improve the

sieving coefficient of the membrane toward a solute **10** of choice. In an embodiment, the solute of choice is a large charged macromolecule such as albumin, and the additive is a dextran such as Dextran 500.

[0062] Having shown and described an embodiment of the invention, those skilled in the art will realize that many variations and modifications may be made to affect the described invention and still be within the scope of the claimed invention. Additionally, many of the elements indicated above may be altered or replaced by different elements which will provide the same result and fall within the spirit of the claimed invention. It is the intention, therefore, to limit the invention only as indicated by the scope of the claims.

CLAIMS

Claim 1. An ultrafiltration device comprising:

a housing;

a main filtration chamber inside the housing;

an inlet port passing through the housing configured to receive a fluid;

an outlet port passing through the housing configured to return the fluid to a feed flow;

an ultrafiltration membrane contained in the filtration chamber, the membrane comprising pores capable of separating middle molecules; wherein the main filtration chamber is divided into at least two interior chambers by the filtration membrane, a feed chamber and a permeate chamber, the feed chamber containing a feed fluid and the permeate chamber containing a filtered permeate fluid, the filtered permeate fluid comprising an additive.

Claim 2. The device of claim 1 wherein the housing is made of a biocompatible material.

Claim 3. The device of claim 1 further comprising an electrode positioned in communication with the membrane such that an electric field is generated about a pore.

Claim 4. The device of claim 1 further comprising a patterned pore wall surface charge.

Claim 5. The device of claim 1 wherein the dimensions of the housing are such that the device may be implanted in vivo.

Claim 6. The device of claim 1 wherein the membrane comprises a silicon membrane.

Claim 7. The device of claim 1 wherein the membrane is substantially impermeable to the additive.

Claim 8. The device of claim 7 wherein the additive is a charged macromolecule.

Claim 9. The device of claim 8 wherein the membrane is substantially impermeable to the additive.

Claim 10. A method of selectively filtering solutes comprising:

providing a fluid;

providing an ultrafiltration system comprising:

a housing;

a membrane within the housing, the membrane separating the housing into two chambers, the membrane comprising pores;

an inlet port configured to deliver a feed fluid to a first chamber in the housing;

a first outlet port, on the first chamber configured to allow the feed fluid to leave the chamber;

a second outlet port, on a second chamber in the housing, configured to allow filtered permeate fluid to leave the chamber; and

an additive included in the second chamber volume;

delivering the fluid to the inlet port;

passing the fluid across the membrane; and

transferring the filtered fluid out of the second outlet port.

Claim 11. The method of claim 10 wherein the filtered fluid is substantially free of proteins.

Claim 12. The method of claim 10 wherein the membrane comprises pores.

Claim 13. The method of claim 10 wherein the ultrafiltration system further comprises an electrode positioned such that an electric field is generated about a pore.

Claim 14. The method of claim 10 wherein the fluid is a biological fluid.

Claim 15. The method of claim 10 wherein the ultrafiltration system is configured to be implanted in vivo.

Claim 16. The method of claim 10 wherein the system further comprises an apparatus for delivering additional additive to the second chamber volume.

Claim 17. An implantable renal assist device comprising:

a housing, the housing including a first chamber and a second chamber,

the first chamber housing a feed fluid flow and the second chamber including filtered permeate fluid;

a membrane separating the first chamber and the second chamber, the membrane comprising nanopores;

an inlet port passing through the housing into a first chamber configured to receive a fluid;

a first outlet port passing through the housing and out of the first chamber configured to return the fluid to a source flow;

a second outlet port passing through the housing and out of the second chamber configured to deliver filtered fluid to an elimination source;

an electrode positioned in communication with the membrane such that an electric field is generated about at least one pore;

the filtered permeate fluid further comprises an additive; and

the membrane is substantially impermeable to the additive.

Claim 18. The device of claim 17 wherein the additive comprises a large macromolecule.

Claim 19. The device of claim 18, wherein the additive molecule is charged.

Claim 20. The device of claim 1, 11 or 18 wherein the system is capable of separations in vitro.

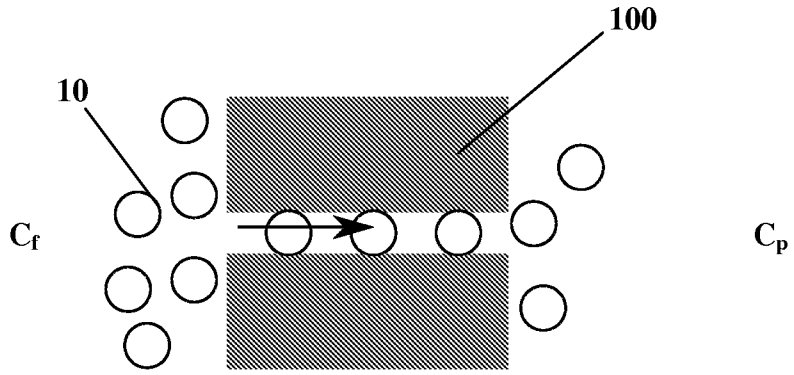

Figure 1

(Prior Art)

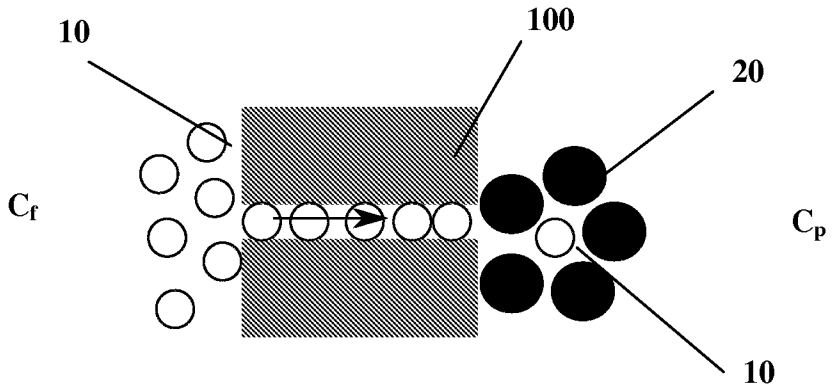

Figure 2

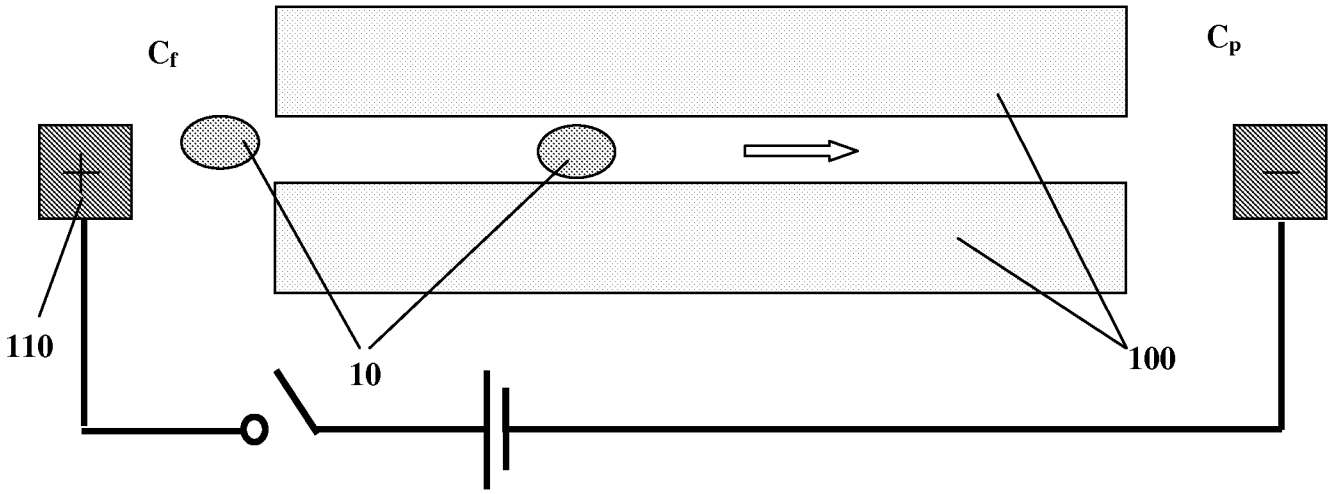

Figure 3

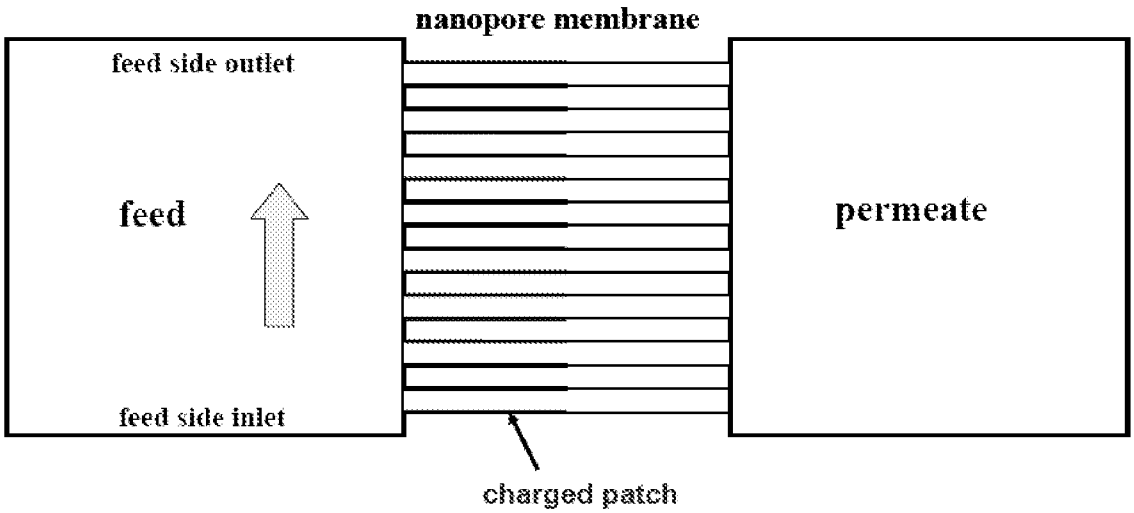
nanopore membrane
feed side outlet
feed
feed side inlet
permeate
charged patch

Figure 4

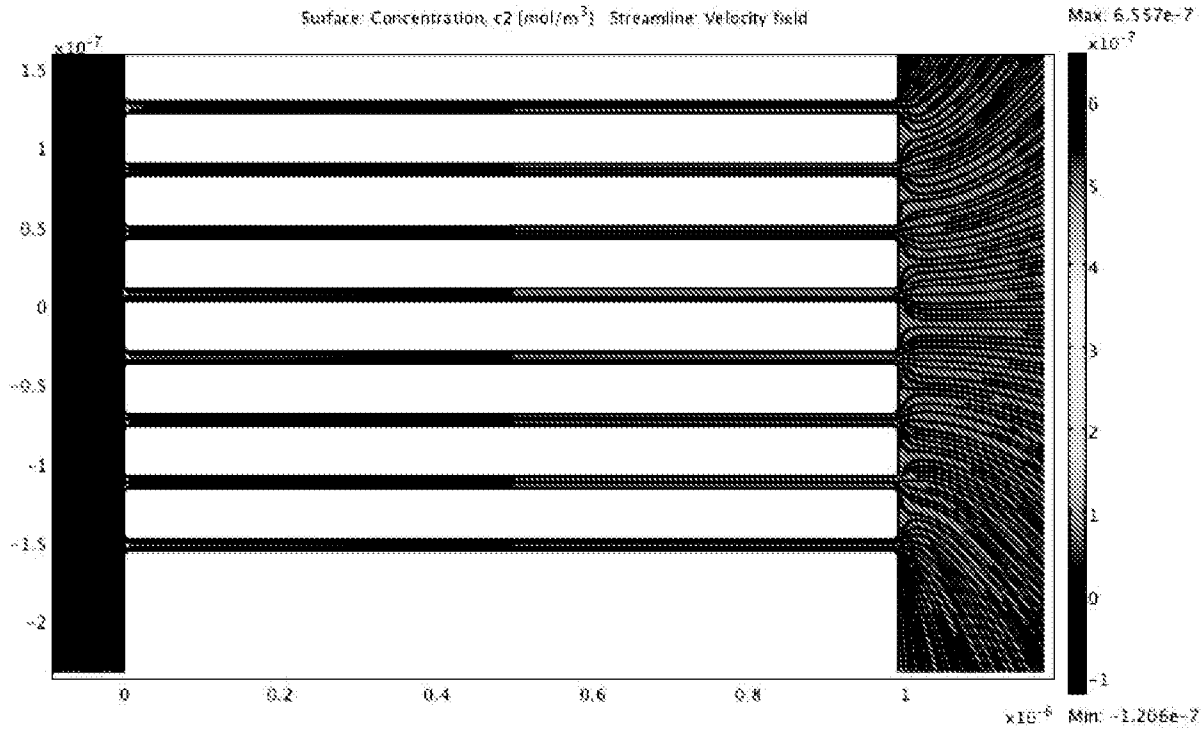
Surface: Concentration, c2 (mol/m^3) Streamline: Velocity field
Max: 6.557e-7
x10^-7
x10^-7
1.5
1
0.5
0
-0.5
-1
-1.5
-2
0
0.2
0.4
0.6
0.8
1
x10^-6
Min: -1.266e-7

Figure 5

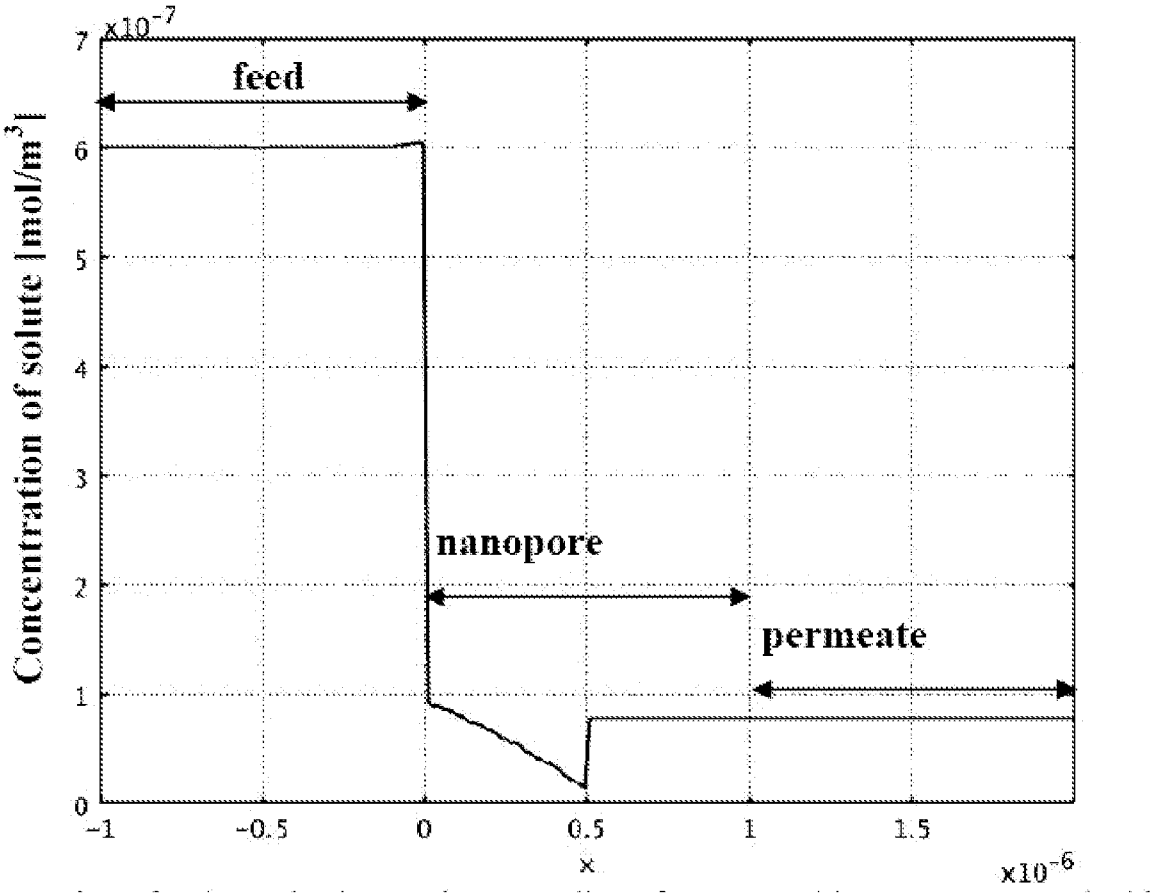
x10^-7
7
6
5
4
3
2
1
0
feed
nanopore
permeate
Concentration of solute [mol/m^3]
-1
-0.5
0
0.5
1
1.5
x
x10^-6

Figure 6

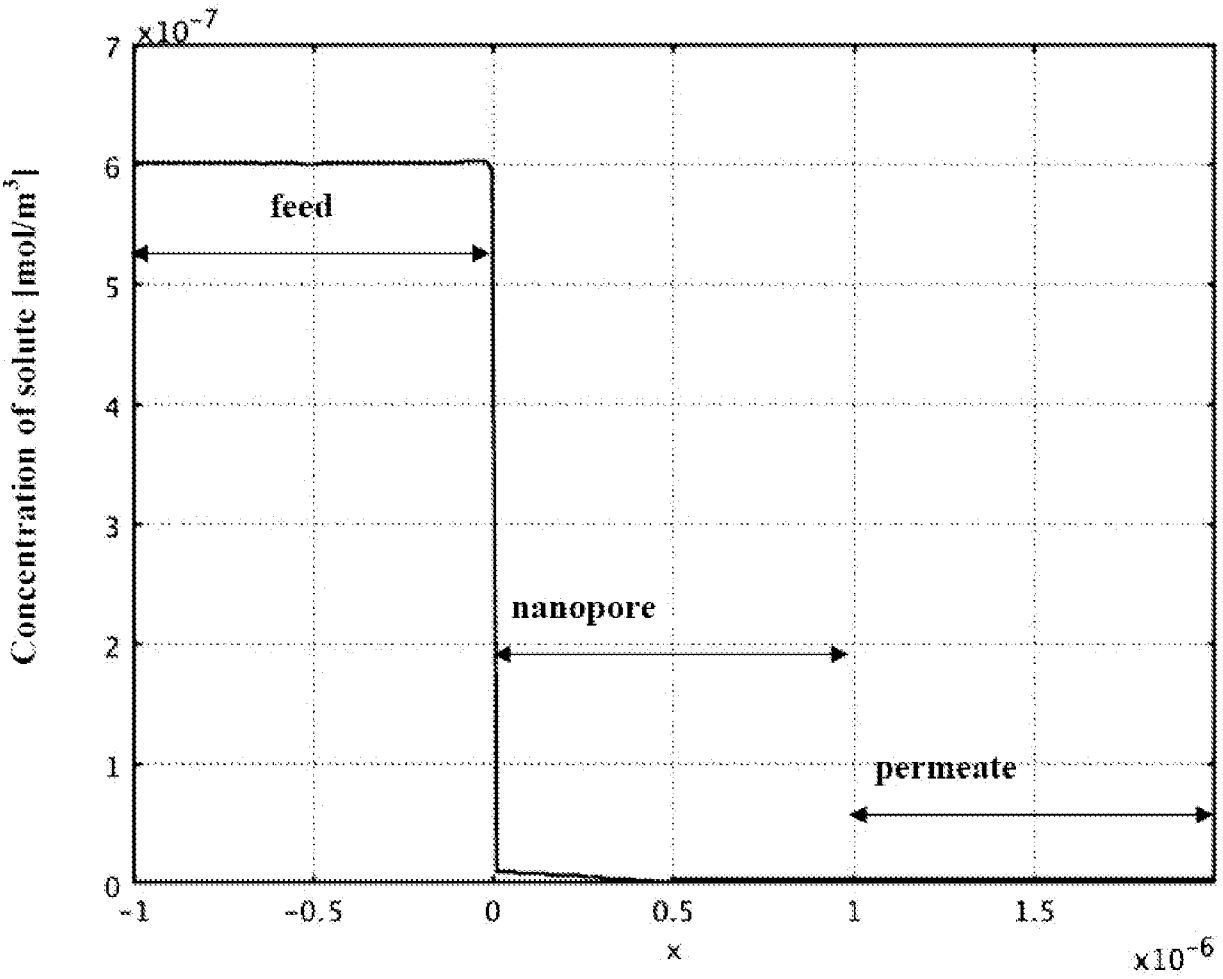
x10^-7
7
6
5
4
3
2
1
0
Concentration of solute [mol/m^3]
feed
nanopore
permeate
-1
-0.5
0
0.5
1
1.5
x
x10^-6

Figure 7

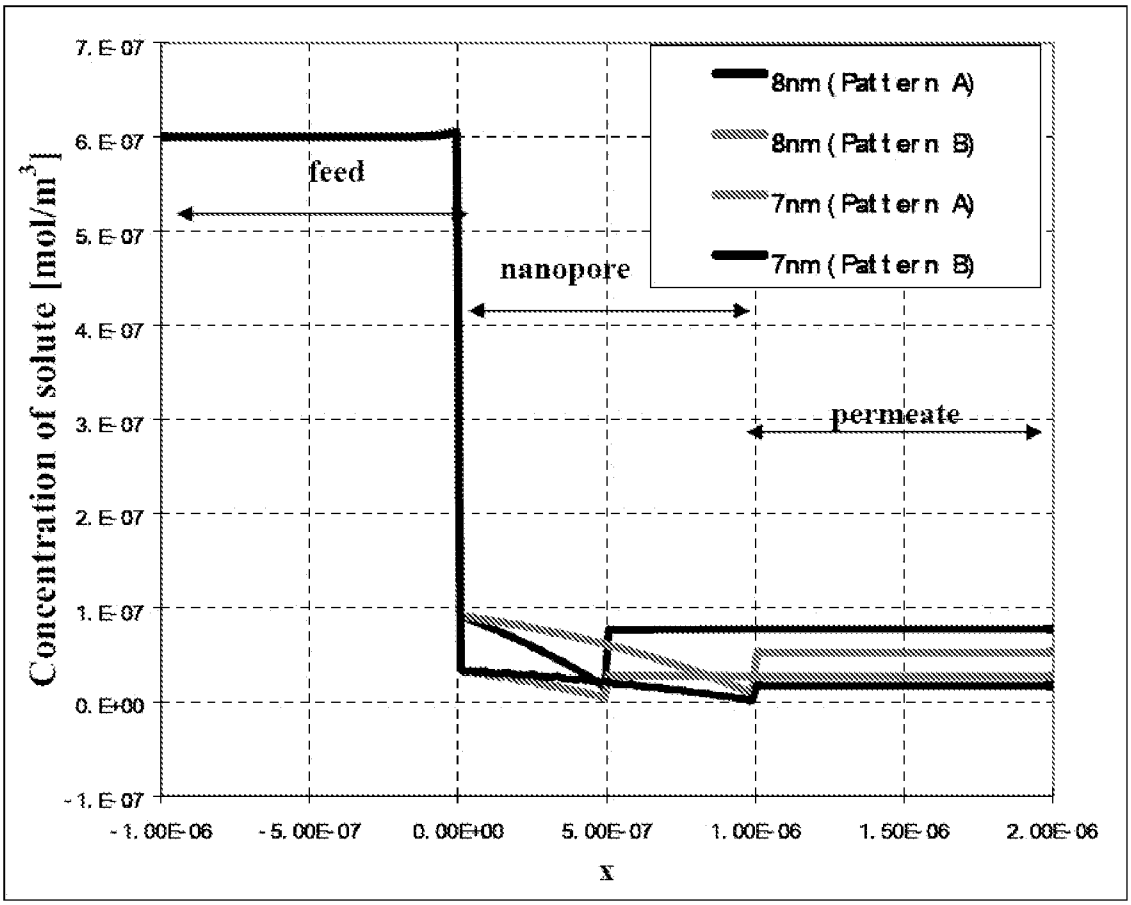

Figure 8(a)

8 nm nanopore			*7 nm* nanopore	
	Surface pattern		Surface pattern	
Zeta potential (*mV*)	**Pattern A**	**Pattern B**	**Pattern A**	**Pattern B**
-46	*0.129*	*0.087*	*0.044*	*0.029*
-100	*0.0105*	*0.01*	*0.001*	*0.001*

Figure 8(b)

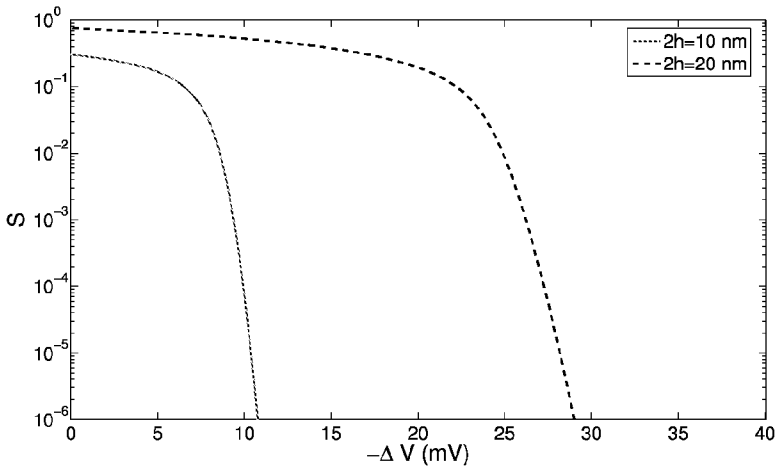

Figure 9

Quantity	Value
Temperature (T)	300 K
Viscosity of water at $T = 300K$	$0.00089\,\mathrm{kg \cdot m^{-1} \cdot s^{-1}}$
Charge number of BSA in PBS at pH 7.4	−15
Stokes-Einstein Radius of Bovine Serum Albumin	36 Å
Length of a membrane pore	$4\,\mu$m
Dielectric constant of water at $T = 300K$	78
Transmembrane Pressure	2 psi
Surface charge density on pore wall	$-0.01\,\mathrm{C \cdot m^{-2}}$

Figure 10

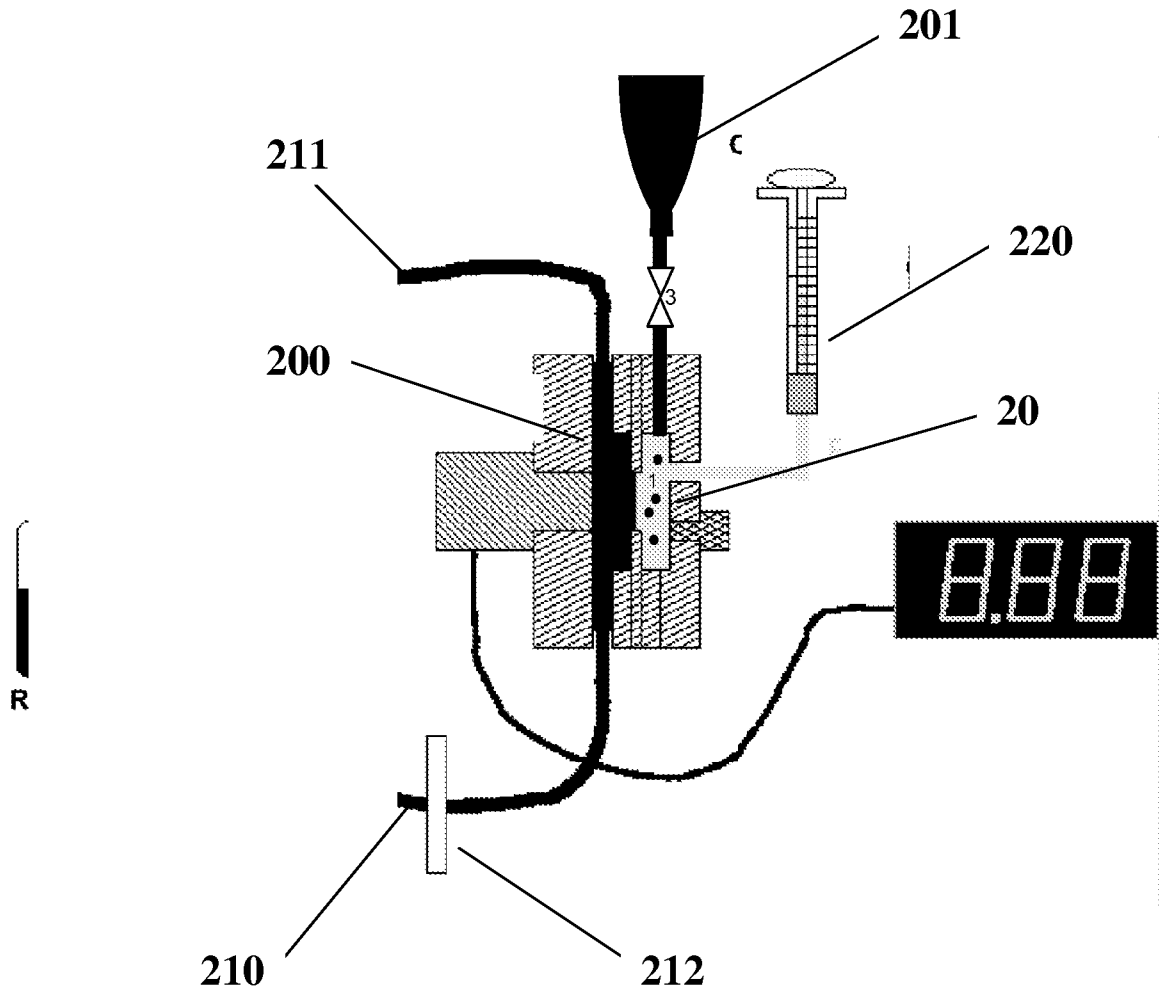

Figure 11

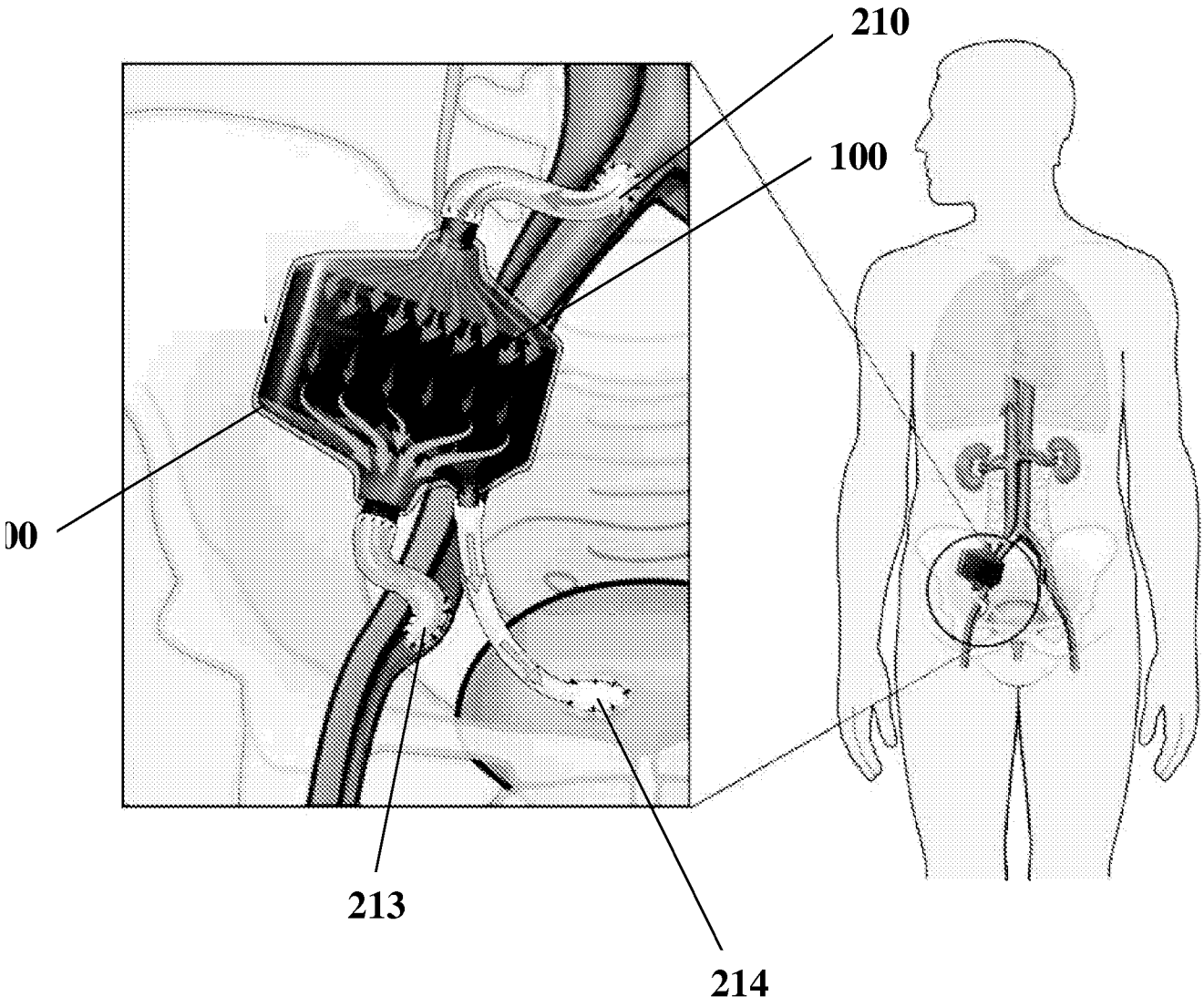

Figure 12