

Integration of bioinspired artificial channels for the concept design of an artificial kidney device

A. Alayoud

Faculty of Medicine and Pharmacy; IBN ZOHR University, Agadir, Morocco.

Corresponding Author: Ahmed Alayoud , Address: Department of Nephrology, Faculty of Medicine and Pharmacy; IBN ZOHR University, Agadir, Morocco.

E-mail: a.alayoud@uiz.ac.ma

ABSTRACT:

Recently, there has been a great interest in the possible applications of synthetic transporters that mimic the structures and functions of natural ion channels for liquid separations, water purification, and biosensing. Here we propose, for the first time, the use of selective polymer membranes incorporated by synthetic artificial carriers combined with existing dialysis technologies to create a synthetic nephron. Consistent with the renal physiology, the proposed system has 3 distinct sections, replicating the glomerular filtration and tubular functions (secretion and reabsorption) and may represent a breakthrough in renal replacement therapy based on the functioning of native kidneys. Thus, this design can be used to manufacture a dialysis machine, with technical features capable of allowing dialysis treatment without ultrapure water or concentrate.

KEYWORDS: Dialysis, Synthetic transporters, Ionophores, Artificial kidney device, Selective polymer membranes

INTRODUCTION:

End-stage renal disease is significant public health problems in the world and a major source of suffering and poor quality of life for those afflicted. It is responsible for premature death and exact a high economic price for healthcare systems worldwide [1].

Until now its standard care, when kidney transplantation is not available, is lifelong hemodialysis (HD) treatments with the basic technology used has remained essentially unchanged for 50 years [2]. Indeed, existing hemodialysis and hemofiltration systems operate by withdrawing blood from a patient, treating the blood to remove waste, and re-introducing treated blood into the patient. Hemodialysis operates by bringing blood into contact with one side of a semipermeable membrane while a dialysis Solution (dialysate) is brought into contact with the other side of the membrane. Uremic toxins diffuse out of the blood, through the semipermeable membrane due to a concentration gradient across the membrane, and into the dialysate. Hemofiltration operates by passing the blood through a filter to remove elements smaller than the filter pore size and replacing with a physiologic solution free of toxins (infusate) [3].

In this sense the usual and current dialysis equipment are based on passive transport using a concentration gradient between the blood and dialysate, and requires water and drainage connections. They are so inherently water hungry since they require an approximate quantity of around 100-150 liters for the treatment of a given aqueous solution with, several tens of liters of reinfusion liquid. For this reason, artificial renal treatment is, in general, performed in equipped structures such as clinical setting and require regular and costly fluid pathway maintenance.

To limit the need of this technique on huge amounts of water several attempts have been described based essentially on the regeneration of dialysate and the ultrafiltrate using for purification either electro dialysis or reverse Osmosis or adsorption or ion exchange cartridge

[4-9]. However, these methods developed essentially for ambulatory dialysis system still keep a dependence on water use and some adjustments with concentrated solutions may be necessary, especially physiologically important electrolytes such as sodium, potassium, magnesium, and a bicarbonate generating base must be added in physiologically balanced proportions to obtain a reusable regenerated solution.

In this regard it seems that the only possibility to develop an artificial kidney completely independent of water use and which ensures a better prognosis for patients, is to imitate functions of normal nephron. Indeed physiological formation of urine is assured by two separate fundamental processes; glomerular filtration and tubular functions. To mimic the filtration process, teams have developed a small implantable artificial kidney who surgically is inserted into the patient. As in native kidneys, the cardiovascular system perfuses the kidney without the need for pumps. The implantable kidney cartridge is made of silicon with highly porous micro slits, thus generating an ultrafiltrate that drains into the patient's bladder. but its main limit is that the maintains of volume and electrolyte balance requires a mandatory contribution of oral supplementation of an electrolyte solution to replenish lost volume and minerals [10].

In fact, if current technology is able to easily imitate the filtration, it is still however unable to mime the complexity of tubular secretion and reabsorption functions. To meet this need to simulate the transport capabilities of the nephron, various groups have proposed the use of living cell-based systems to accomplish its various transport requirements [11-14]. This technique is promising but there are still several challenges to accomplish. Recently, in the same way Christa N. et al have recently proposed and created a synthetic nephron using activated wafer electrodeionization which uses ion-wafer interactions followed by ionic transport through a ion-exchange membranes and resin particles using an electric field as the driving force. They placed a porous mesh made of platinum between two ion-exchange

wafers to create a wafer that pushes ions through membranes using an electric field. The platinum meshes serve as electrodes when voltage is applied, enabling the team to select different ions and adjust their transport rates independently [15]. A major challenge with these approaches is to improve selectivity of transport and biocompatibility by avoiding the risks of releases linked to electro dialysis.

Despite these advances, currently available dialysis therapies are not yet available to replace completely and independently kidney function [2]. For this reason, it seems that the alternative option to develop a physiological and independent method for dialysis is to use the membrane transport biotechnology to develop a device that will be able to filter blood in a way similar to the kidney who uses specific transport proteins to selectively transport various ions and organics out of and into the nephron.

In recent years, bioinspired artificial channels for synthetic biomolecules that mimic the structures and functions of natural ion channels have garnered much interest among molecular biology researchers [16-18]. There are three types of synthetic transporters: the mobile carrier, the single channel, and the self-assembled pore. Mobile carriers are usually molecular ionophores that are not large enough to span the membrane, they associate reversibly with ions and form ion-carrier complexes that diffuse across the membrane. A single or monomeric channel is able to span a membrane and create a tunnel through which ions may pass. Finally, a self-assembled pore is similar in function to a single channel, but it requires the self-assembly of two or more subunits to create a viable transport passage for ions or molecule (figures) [17]. Until now, many molecular designs of synthetic transporters have been developed and been extensively explored in diagnostic and therapeutic contexts. These molecules are incorporated in membranes and used in some engineering applications such as liquid separations, water purification, and biosensing [18 -24].

This paper proposes guidelines and new avenues of research for designing novel strategy based on the implementation of ionophores and biomolecules channels in synthetic membranes combined with the use of reverse osmosis to create a synthetic nephron to manufacture a dialysis machine, with technical features capable of allowing dialysis treatment without ultrapure water or concentrate, while mimicking the physiological filtration, secretion and reabsorption functioning of the native kidney.

PROPOSED MODEL AND DESIGN

Theory

Replicating kidney function is possible if the functioning of a nephron is mimicked. This complex structure consisting of an efferent arteriole bringing impure blood into it and an afferent arteriole taking filtered blood out to peritubular capillary. Impure blood first enters glomerulus where filtration takes place. The filtered plasma will be collected in Bowman's capsule and supplied to nephron tubule network for re-absorption and secretion processes. Once the lumen fluid is epured it passes back into the peritubular capillaries. Finally, the remaining liquid forms the final urine which will be expelled [25].

The theoretical model for replacing kidney function, we are proposing will therefore mimic this physiological process using current technology. It provides a blood treatment system which does not requires neither ultrapure water to generate dialysate solution and nor provision of a sterile replacement infusate formulation or concentrate.

Design

The proposed Artificial nephron is compartmentalized basically into 3 distinct sections: stage of blood ultrafiltration, stage of making up of the plasma ultrafiltrate, and stage of epuration by diffusion (Figure 1).

1. The filtration section:

Like glomerular filtration, a plasma ultrafiltrate is obtained after passing the blood through an ultrafiltration membrane. The current available technology easily provides this process, indeed modulating the transmembrane pressure at this level while using an ultrafiltration master allows obtaining a controlled ultrafiltrate flow rate whose composition is similar to that of plasma with the exception of the blood and protein elements which are returned to the blood stream. For this step we propose the use the hollow fibers of semi-permeable porous membranes with a high ultrafiltration coefficient, a sieving rate of beta microglobulin greater than 0.7 and that of albumin lower $<0,001$. It will thus allow the elimination by convection of middle molecular weight solutes (Endothelin, β 2-microglobulin...).

2. Sections of making up of the plasma ultrafiltrate ;

This section ensures a simulation of the tubular functions; Once formed, the plasma ultrafiltrate will undergo secretions and reabsorption phenomena which will eliminate toxins and maintain hydroelectrolytic homeostasis of the internal environment. In our model the biomimetism of this process can be achieved by a combination of reverse osmosis and diffusion through selective membranes . This section includes 2 steps: First the Reverse osmosis (RO) step: At this level, ultrafiltrate is delivered to RO unit in which it is purified to create pure water and the concentrate. Like the basolateral located Na-K-ATPase (sodium-potassium pump) in tubular cell, this RO is the drive for transport by the generation of a concentration gradient necessary the diffusion through selective permeability membranes (Figures 2 and 3) . The RO membrane proposed have the ability to ensure ion and molecules rejection with the passage of water. Recently the selectivity and permeability of this membrane to water can be optimized by the incorporation of artificial aquaporins [26,27]. After this first step, downstreams of RO , pure water and concentrate exits the RO and are carried to next steps to mimic tubular functions to ensure the making up of dialysate liquid. At this level there is also a recirculation conduit in fluid communication with RO via a port

,which connects the liquid after its treatment with the ultrafiltrate plasma. This recirculation circuit facilitates a high rate of fluid flow against the upstream side (feed solute) minimizing clogging and fouling.

In addition to the RO this second section also includes a step of making up dialysate liquid and the infusate (The Selective transport unit): in this sense the purification process simulating the tubular functions is ensured by contacting the pure water with a side of a selective synthetic membrane while simultaneously contacting the concentrate with the opposite side of the membrane, thus allowing a net specific ionic flow across the membrane into the fluid thus creating solution which will be used as dialysate and infusate for introduction into the blood stream of a patient.

In the present work, we propose a way that has never been explored in dialysis devise, so far and that consists in confining a biological artificial channel into the artificial polymer membranes to ensure a carrier-facilitated transport. Recently progress in the field of synthetic channels has lead to a broad range of synthetic ion-selective membrane will excludes all ions except for the ion of interest [28-32]. In this regard several available selective ion membrane exist and have been developed commercially for sensing numerous ionic species including the ions of sodium, potassium, calcium, magnesium, and hydrogen, as well as, bicarbonate, nitrate, and chloride [32]. Therefore proposed membranes in our model are inspired from that used for ion selective electrodes (ISE) who are polymer inclusion membranes (PIM) containing mobile carrier or ionophore molecules . For an ISE, the PIM used contains a relatively low concentration of an ionophore whereas for separation, membrane require a higher carrier concentration. The base-polymer must be insoluble in aqueous solutions, mechanically strong and stable. For selective glucose transport we propose anthraquinone-derived receptors as a carrier [33]. A listing of synthetic transporters proposed for this module is given in Table 1. Therefore, the stacking of theses membranes allows enrichment of

dialysate liquid with reabsorption of useful substances such as glucose, Sodium, Potassium, Calcium, Magnesium, Bicarbonates, Magnesium and phosphates.

At this level, pumps controlled by the conductivity cells ensure an adjustment of the final composition of the liquid which will be used both as an infusate in postdilution and as a dialysate for the next step of diffusive epuration. The relative amounts of each liquid flow of the selective transport unit components define the final dialysate composition (Figure 4).

3. The section of diffusive epuration:

Her the design involves establishment of a flow of patient's blood first side of a semipermeable membrane in a first direction and establishment of the dialysate solution formed flowing in the opposite direction of the membrane. This dialysate is free of toxins desirably removed from blood. The hollow fibers proposed here are made of semi-permeable porous membranes with high mass transfer-area coefficient (K_oA) for urea to allow low molecular weight solute (urea, creatinine) transport by diffusion.

The dialysate enriched by waste is then passed through a second RO with training of permeate (pure water), which is returned and added to the pure water of the Selective transport unit, and the concentrate (final urine) who will be eliminated. At this level, mixing valves provide modulation of the volume and the concentration of the final removed fluid by mixing downstreams (draw solutes) of this RO.

4. Modulation and control of urine composition and volume;

On-line monitoring devices to control ultrafiltration, ion removal, density and volume of final fluid removal are incorporated into the design based on current technology used by dialysis machines; The system includes sensors for monitoring the conductivity, pressures, flow rate ,volume, optical density ,pH, and hemoconcentration of the blood to provide a biofeedback managed by a controller who controls the pumps and valves.

Biofeedback systems operates to drive dialysate conductivity, in each selective membrane of the Selective transport unit, in order to reach a predefined safety margins for each ion concentration. So, for example where Potassium concentration measure by the potassium conductivity cell at the output of the selective membrane exceeds a limit its diffusive transfer will be reduced by the drop in flow in this membrane. Dialysate composition can be further modified by changing the mixing fraction of each element.

The density of the final removed fluid, determined by the mixing ratio between pure water and concentrate of the second RO (Figure 1), will depend on the conductivity and the density of the plasma ultrafiltrate , ensuring either the concentration or dilution of the final urine evaluated by optical density monitoring. At last, the final volume of urine (diuresis) will be controlled by a blood volume monitor (BVM) which consists of an optical probe located on the arterial line of the blood circuit and measures blood volume variations through changes in hemoglobin concentration.

RESULTS AND DISCUSSION:

The kidney is one of the most complicated organs in the human body; therefore, it is an enormous challenge for researchers to develop a platform that can mimic its function to provide physiological support in renal failure. In this theoretical model we propose an approach of a novel technology that simulates the physiologic transport of molecules at the level of the nephron. This last is the functional and basic structural unit of the kidney, which performs its functions by using three processes to form urine: glomerular filtration, tubular reabsorption, and tubular secretion.

Glomerular filtration involves the ultrafiltration of plasma in the glomerulus. The filtrate collects in the urinary space of Bowman's capsule and then flows downstream through the tubule lumen, where tubular activity alters its composition and volume. Tubular reabsorption involves the transport of substances out of tubular urine. These substances are then returned to

the capillary blood, which surrounds the kidney tubules. Reabsorbed molecules include many important ions (such as potassium, calcium, magnesium, sodium, chloride, bicarbonate, phosphate), water, and important metabolites (amino acids, glucose). Secreted substances are taken up by the tubular epithelium from the blood surrounding the tubules and added to the tubular urine [25,34]. Compared to the nephron our system involves the same processes thus allowing several kidney functions;

1) The elimination of toxins:

The system is a renal replacement modality that combines diffusion and enhanced convection in order to remove small- and middle-molecular-weight compounds, respectively. Its clearance for a substance can be defined as the volume of plasma from which that substance is completely removed (cleared) per unit time. This clearance can easily be determined by measuring the concentrations of this substance in the final removed fluid (urine) and plasma and the urine flow rate (urine volume/time of collection).

For the convective clearance; ultrafiltration allows the removal of small and middle molecules while ensuring the retention of albumin. The quantity eliminated corresponds to the product of ultrafiltration volume and the sieving coefficient and increases with the size of a membrane pore. In order to achieve adequate clearance of middle-sized and large uremic toxins without loss of albumin, filters should be designed to have a large pore size and narrow pore distribution, with a molecular weight cut-off close to, but lower than, that of albumin (~66kDa), thus mimicking the transport properties of the kidney glomerular filtration barrier. These membranes allow the removal of an ultrafiltrate volume by increasing the transmembrane pressure (TMP), whereas the replacement solution is infused after making up at equal volume minus the desired fluid volume removal to preserve extracellular fluid balance and isovolumic state.

The more the UF increases, the more the clearance increases, however too much convective volume increases the risk of hemoconcentration, with risk of membrane coagulation. To ensure this fine balance, the filtration fraction (FF) (proportion of ultrafiltration volume obtained compared with total blood volume processed) is maintained around 25%. So at last the UF rate is adjusted to blood flow rate, thereby controlling hemoconcentration, whereas blood flow rate is adjusted to dialysis flow rate to control diffusion in the next floor.

In addition to convection, our system also allows the elimination of small molecules with molecular weight less than 500 Da by diffusion, whose the solute removal is determined by: the overall mass transfer-area coefficient of the semipermeable membrane, blood flow rate, the dialysate flow rate [35]. In our design the dialysate flow rate is amplified by the recirculation coming from the RO.

2) Hydro Electrolyte homeostasis:

The electrolyte balance of the internal environment can be maintained by controlling the amount excreted in the synthetic urine which is equal to: the filtered quantity plus the secreted quantity minus the reabsorbed quantity. This removal solute in our module is modulated by selective membranes according to blood composition. In this way, the blood osmolality, sodium, Magnesium, Calcium, Phosphates, Potassium, Glucose, Bicarbonates will be kept constant within a narrow range since it is possible to get individual transport of ions through each of the selective membrane. For that the control system of our design will be designed to use feedforward feedback controls to alter the concentration of ions that are sensed in the effluent after each selective membrane. These concentrations are used to calculate the quantity to excrete in the final urine.

The regulation of plasma osmolarity will be accomplished by varying the amount of free water excreted by the device according to density and conductivity of the plasma ultrafiltrate.

So in the case of high values, concentrated hyperosmotic urine is produced allowing dilution with a hypoosmotic infusate liquid.

3) The acid-base balance

Like the normal kidney the design offers two main ways to maintain acid-base balance by reabsorption of bicarbonate (HCO_3^-) and by elimination of acids. The reabsorption of bicarbonate can occur directly using a specific ionophore, and indirectly by combining with the proton to form and generate carbon dioxide (CO_2), which will cross selective membranes and then pass into the dialysate and reinfusion fluid. In addition to the regeneration of bicarbonate, this system can also allow the elimination of acids like ammonium (NH_4^+) by diffusion through the semipermeable membrane.

4) Extracellular and blood volumes control:

In the last few years, technological advances have led to the introduction of a series of instruments and methods that allow us to evaluate the blood volume variations during the dialysis session in order to prevent hypovolemia-induced symptoms and the arterial hypotension [36]. Our system uses the same principle to control the volume by adapting the final volume of urine according to the variation in blood hemoconcentration.

The design is based on already existing dialytic technologies and who are well mastered like reverse osmosis, ultrafiltration, diffusion, and can separate ultrafiltration from tubular functions (selective secretion and reabsorption) to form the final urine and therefore ensure the kidney functions. In contrast to current dialysis techniques, it is independent of an external water or concentrate source and needs only a power source. It includes membrane dialyzers that are responsible for the removal of uremic toxins and reabsorption of necessary elements and are therefore a key element of this kidney replacement therapy. Our system is based on the current available dialysis membranes who are able to ensure high clearance of middle-sized and small water-soluble uremic toxins and which are largely used in the world. Their

design has been much improved and evolved since the introduction of Kolff 's rotating drum artificial kidney in 1945 [2].

In addition to these membranes, we propose here for the first time the use of selective polymer membranes with synthetic artificial carriers in dialysis device for the diffusive transport of ions according to a chemical concentration gradient .This kind of membrane is currently used mostly on biosensing and is based on the use of various synthetic molecules to facilitate ion and substances transport across membranes of the ion-selective electrode [17,18]. Thus for our model we propose the use of PIM incorporated by carriers which are one of the most promising materials to achieve large-scale mass separation and can be engineered to pass only the molecule of interest (Figures 4c and 4d). They have been used successfully in the sample separation and pre-concentration based on either passive or electrically driven transport [37]. They have good stability and are formed by casting solution containing a carrier (extractant), a plasticizer, and a base polymer. The base polymer provides mechanical strength to the membrane. Plasticizer is a solvent for an ionophores and improves the flexibility and transport properties of the membrane [38-40]. These membranes must be stable without releasing their content to ensure biocompatibility even though these membranes are not in contact with blood. The use of a multi-ionophore membrane containing various ionophores, selective for sodium, potassium, calcium and chloride ions as a multi-ion selective membrane is also possible [41]. Also the insertion of ion and molecule-channels in solid polymeric membranes exhibit superior mechanical stability compared to PIM [42] , this is currently possible for membranes incorporated by aquaporin [26,27] that we propose as a reverse osmosis membrane for our device to ensure energy and pressure savings required for separation. However solid-supported polymeric membranes are not yet developed for ion separation, and are steadily attracting intense research efforts, and coming years will reveal the true potential of these membranes. Thus, the most immediate challenge and need for our

device is the establishment of stable selective permeable and biocompatible membrane especially since carrier-based transport through membranes is still a “work in progress.”

This model can be compared to existing methodologies in the literature that can be divided into filtration methods and transport selective [15]. The existing methods use electrically driven techniques based on electrodeionization which remains a non-physiological approach, contrary to our design which uses the concentration gradient as a transfer driven by diffusion.

CONCLUSION:

Learning from nature is the eternal theme for the development of novel smart materials and new intelligent systems. In this sense the various intricate ion transport processes in biological membrane channels have always been a broad inspiration for editing synthetic selective membranes. Here we offer a design of dialysis device based on these membranes to mimic the functioning of the normal kidney. The potential impact of these implantable technologies of membrane in dialysis is immense, and we believe there is a need for further innovations in this type of selective membrane technology to improve outcomes for patients on renal replacement therapy. Despite the potential of this theoretical prototype, much work will require investigations on material fabrication, transport efficiency, biocompatibility analyses, and control software development before integration of this as a module for HD treatment.

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Table 1: A listing of synthetic transporters and ionophores proposed for selective transport of molecules and ions.

Ionophore	Transport selectivity
Hydroxymethyl-12-crown-4 with dicarboxylic chlorides and dibasic acid diethyl esters with a monocyclic crown ether	Sodium
f bis(azobenzocrown)	Sodium
Valinomycin	Potassium
Lanthanide tris(b-diketonates)	Chloride
In(III)tetraphenylporphyrin (In(III)TPPp) and tetrakis[3,5-bis(trifluoromethyl)phenyl borate(TFPB)	Chloride
The macrocyclic ligands 3,8,12,17-tetramethyl-2,18,9,11-bipyridyl-1,4,7,10,13,16- hexaazacyclooctadecanetetrahydro bromide	Chloride
Deoxy3,12-bis(TFAB)CA)	Bicarbonates
Trifluoroacetophenone derivative	Bicarbonates
1,3,5-tris[10-(1-adamantyl)-7,9-dioxo-6,10-diazaundecyl]-benzene (ETH 5506)	Magnesium
Ionomycin	Calcium
Calcium Ionophore CA 1001 (E-2026)	Calcium
9-Decyl-1,4,7-triazacyclodecane-8,10-dione	Phosphate
Gramicidin	Sodium and Potassium
Anthraquinone-derived receptors	Glucose

Figures:

Figure 1: Diagram and Schematic description of the synthetic nephron. The proposed Artificial nephron is compartmentalized into 3 distinct sections: The Ultrafiltration section (UF), Sections of making up of the plasma ultrafiltrate (Selective transport unit: with Reverse osmosis (RO) and selective synthetic membranes (SSM)), and Section of diffusive epuration (Diffusion). C: concentrate, P: permeate, CC: conductivity cell, OD: optical density sensor, BVM: blood volume monitor. MV: Mixing Valve

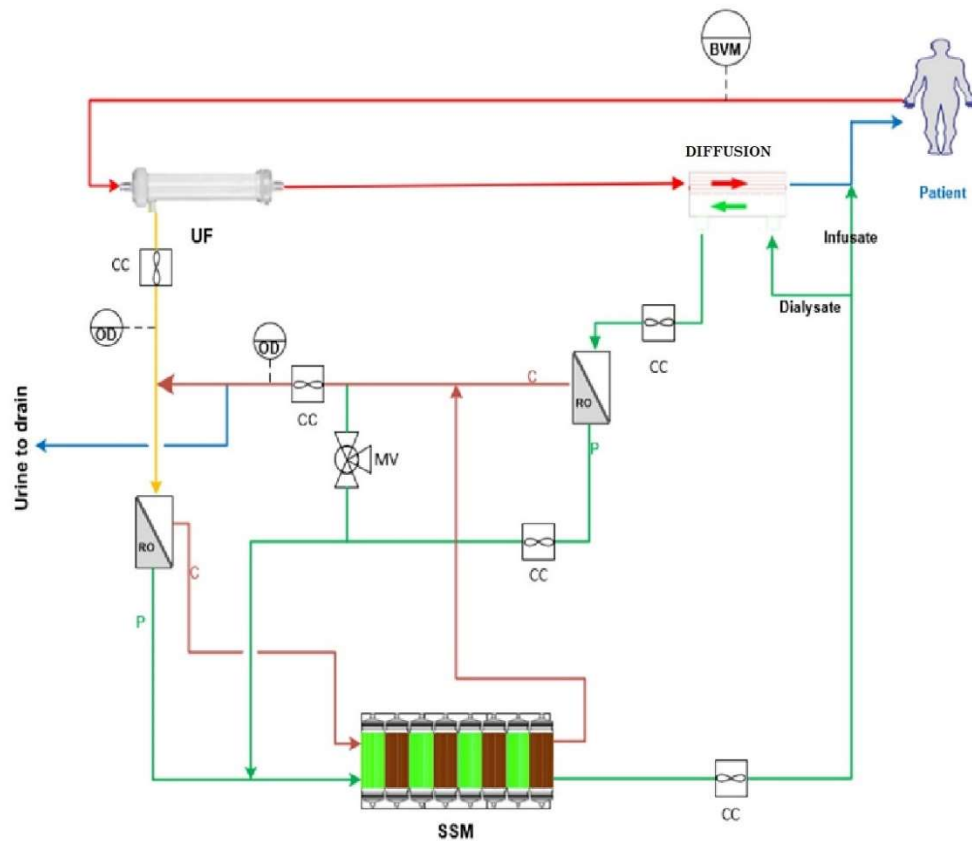
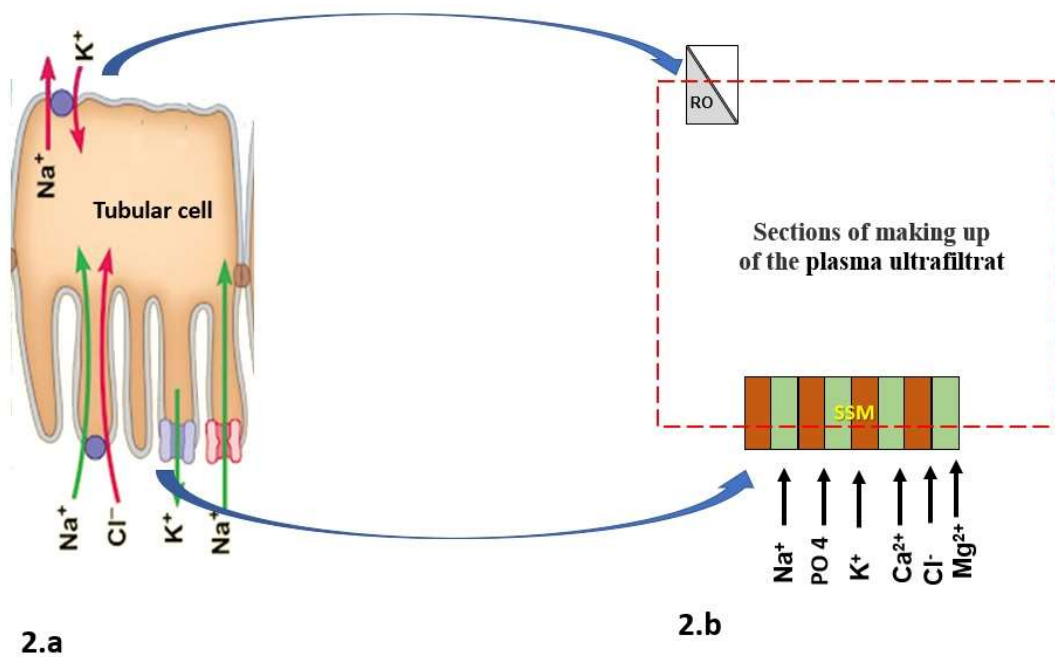


Figure 2: Biomimetism between the tubular cell (2.a) and the sections of making up of the plasma ultrafiltrate of de the design (2.b): Like the basolateral located Na-K-ATPase (sodium-potassium pump) in tubular cell, the Reverse osmosis (RO) is the drive for diffusion by the generation of a concentration gradient necessary to the transport of molecules and ions through artificial channels of selective synthetic membranes (SSM). PO₄:Phosphate.



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Figure 3: Mimicking the functioning of a normal nephron (3.a) by the artificial kidney device (3.b)

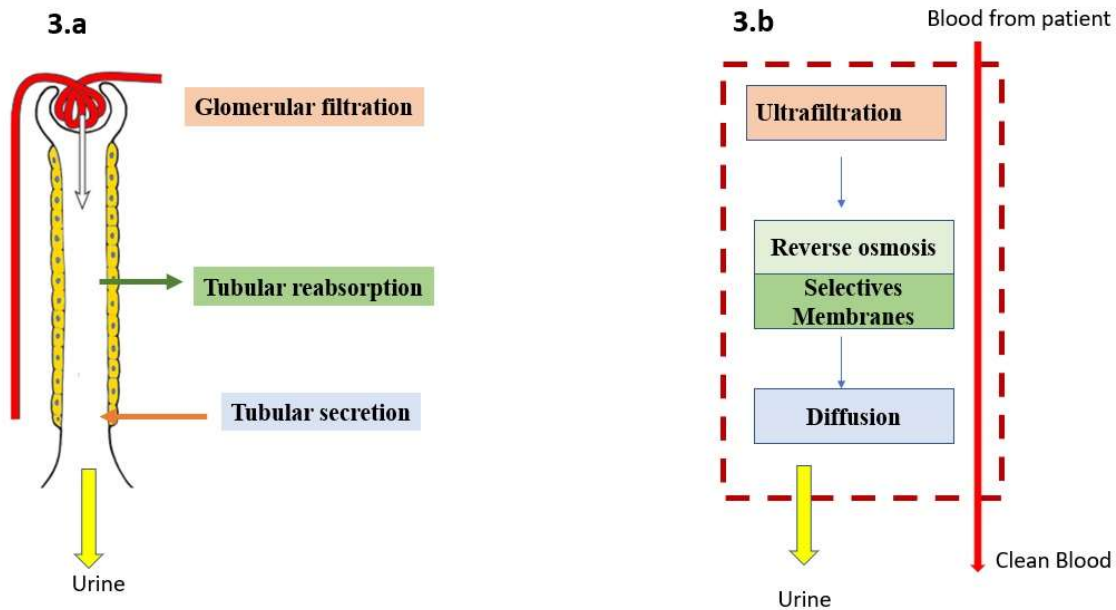
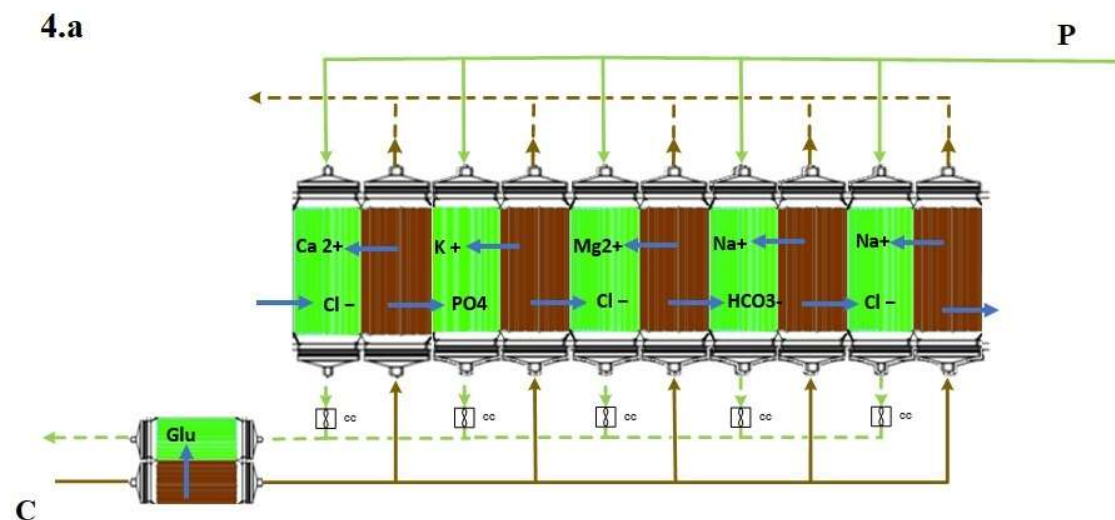


Figure 4: The Selective transport unit.

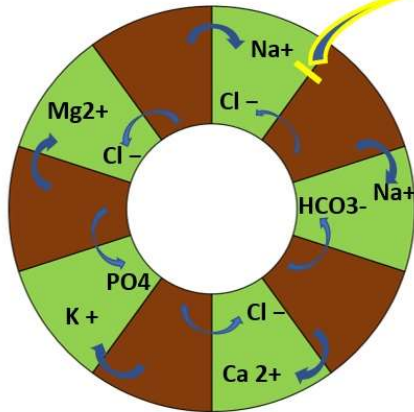
4.a: Schematic description of the Selective transport unit. P: pure water (Permeate of the RO), C: Concentrate. CC: conductivity cells. The stacking of selective polymer inclusion membranes (PIMs) allows enrichment of dialysate liquid with reabsorption of useful substances such as glucose (Glu), Sodium (Na^+), Potassium (K^+), Calcium (Ca^{2+}), Magnesium (Mg^{2+}), Bicarbonates (HCO_3^-), Chloride (Cl^-)



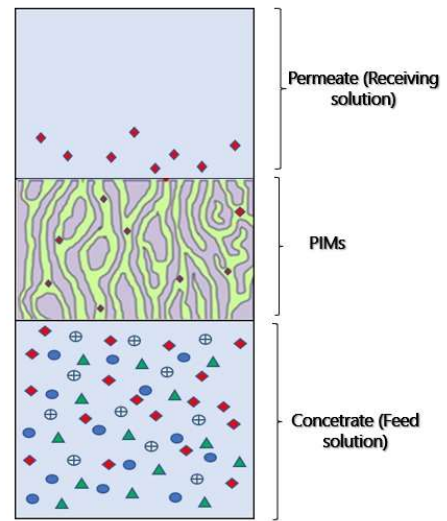
4.b: Circular arrangement and stacking of selective polymer inclusion membranes (PIMs)

4.c: Description of selective transport through PIMs

4.b



4.c



4.d: Solute–solute selectivity is induced by use of ionophor. Ionophor can transfer ions from the concentrate solution, into a hydrophobic medium of the PIMs, where the ions typically would not be soluble. They can do this by binding to particular ions and acting as a mobile carrier, escorting them through the PIM to the receiving solution (Permeate)

4.d

