Glomerular Plasmapheresis Design for an Implantable Artificial Kidney

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Abstract

This study describes the theoretical background necessary for a systematic design process of an implantable artificial kidney and provides a basic tool for further design stages. In designing an implantable artificial kidney, the natural stages of blood filtration in the kidney, including glomerular filtration (blood cell separation) and tubular separation (ion separation), are followed. The focus of this study is on pore design and the hydrodynamics of plasma, which is considered a Newtonian fluid after the pore inlet, during hemo-filtration with a varying pore longitudinal cross-section in a solid membrane. To prevent membrane clogging, two pore geometry solutions are proposed and justified in detail. One optimizes pore entrance shape and the other uses a diffuser-nozzle channel to provide backwash which removes undesired deposits on membrane pores. In the micro-filtration of fluids, pore geometry, pore size ratio, and pore edge shape affect fluid hydrodynamics in terms of pressure drop, velocity, shear stress, and flow rate. The calculation results indicate that a diffuser channel provides a smaller pressure drop than that produced by a straight channel for a variety of cross sections (rectangular, elliptical, and circular).

Keywords: Implantable artificial kidney, Blood filtration, Glomerular membrane, Diffuser, Pore design, Microfluidics

1. Introduction

Kidneys filter plasma and remove waste products from the filtrate at rates that depend on the demands of the body. Urine formation begins by filtering large amounts of blood (over 1 L/min or about 22% of the cardiac output) through the glomerular capillaries into Bowman’s capsule. The glomerular capillary membrane has three major layers: (1) the endothelium of the capillary, (2) a basement membrane, and (3) a layer of epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane [1]. The glomerular basement membrane (GBM) has been assumed to have the properties of a viscous gel in which the limiting pores cannot be directly visualized. The slit diaphragms that bridge the filtration slits are specialized cell junctions with properties of shallow adherent junctions that differentiate from typical junctional complexes during glomerular development [2].

In glomerular filtration, cells such as red blood cells (RBCs), white blood cells (WBCs), and platelets, are separated by glomerular membranes; the plasma continues its path into the tubule of nephron. Plasma is the liquid part of blood that carries the formed elements of the blood such as RBCs. These formed elements represent half of the blood volume, and they are responsible for blood’s non-Newtonian behavior. Each micro-liter of blood has $5 \times 10^6$ cells, including RBCs, platelets, and WBCs [3]. Table 1 summarizes the relative proportions of cell elements and the composition of plasma [4]. The process of separating the formed element cells of blood from the plasma is called plasmapheresis [5]. Normally, in the nephron, bio-fluid filtered by the glomerular capillaries flows into Bowman’s capsule and then into the proximal tubule, the loop of Henle, the distal tubule, the collecting tubule, and, finally, the collecting duct, before it is excreted as urine [1]. Kidney failure results in the slow accumulation of nitrogenous waste products, salts, ions, and water in the body and the disruption of normal pH balance. Diseases of the kidney are among the most prevalent causes of death and disability in many countries.

<table>
<thead>
<tr>
<th>Cell element</th>
<th>Relative proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells (erythrocytes)</td>
<td>600</td>
</tr>
<tr>
<td>White cells (leucocytes)</td>
<td>1</td>
</tr>
<tr>
<td>Platelets (thrombocytes)</td>
<td>30</td>
</tr>
<tr>
<td>Plasma</td>
<td>Weight fraction</td>
</tr>
<tr>
<td>Water</td>
<td>0.91</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.07</td>
</tr>
<tr>
<td>Inorganic solutes</td>
<td>0.01</td>
</tr>
<tr>
<td>Other organic substances</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 1. Blood constituents ($5 \times 10^6$ particles/mm$^3$) [4]

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Artificial kidneys have been invented to remove waste products from blood; the mechanical device used to clean the patient’s blood is called a dialyzer. A dialyzer provides a membrane barrier that permits the removal of metabolic waste products dissolved in water, such as urea, creatinine, uric acid, and inorganic phosphate from the blood stream. At the same time, the dialyzer prevents the loss of blood cells and important blood proteins, such as albumin and immunoglobulin.

Current dialyzers are large, and people with renal diseases need three to four hours of treatment (sometimes up to 5 hours for larger patients) administered three times a week in a hospital. To reduce this time, patients need alternative, preferably wearable or implantable, devices [6]. Currently, no implantable bioengineered kidneys exist. All calculations performed by manufacturers for hemo-dialysis and artificial kidneys have worked on hollow fibers and a pressure drop in the filter cartridge of a dialysis machine. After each individual dialysis, the cartridge is disposed of. In this study, the hydrodynamic features of a solid, planar membrane with embedded pores are designed and optimized for an implantable bio-separation membrane.

Many researchers have experimentally or numerically investigated the flow in diffuser-nozzle channels. Akbari [7] found that in a converging-diverging channel, the effect of the radius ratio is more significant than that of the taper angle. Sparrow and Prata [8] showed that the pressure drop for the periodic diffuser-nozzle tube is considerably greater than that for a straight tube. Wang and Vanka [9] found that for steady laminar flow, the pressure drop increases more significantly than heat transfer. Niceno and Nobile [10] and Wang and Chen [11] obtained the same results for pressure drop in a diffuser-nozzle channel. Most of these investigations were based on a fluid transportation channel, not on a filtration channel that separates bio-particles from bio-fluid with pressure limitation under in vivo conditions, such as those for an implantable filter.

Proposed pore geometries cover a wide range of cross-sectional shapes, including circles, ellipses, rectangles, rhomboids, star shapes, equilateral triangles, squares, pentagons, and hexagons [12]. For fabrication and manufacturing, the most applicable pore shapes are circular, elliptical, and rectangular. This study analyzes and compares the hydrodynamic flow parameters, namely pressure drop, velocity, and pore aspect ratio, for various pore shapes. The simplest micro-channels are straight with a linear pressure drop across the channel. This work models straight channels (pipes) and diffuser (diverging) shapes to compare their hydrodynamic differences. Diffuser shapes provide backward that removes bio-particle deposits or protein build-up from the top of a membrane surface (Fig. 1). Covering the membrane surface with non-stick biomaterials partially prevents fouling, but reliable, long-term protein deposition prevention is still a challenge for biomaterial engineers. The blockage ratio in a channel, \( \beta = \frac{D - H}{D} \) [13], where \( D \) is the width of the channel and \( H \) is opening width of pore, is explained in Fig. 2. If deposition is nucleated by bio-particle layers inside of a pore, the diffuser pore shape keeps the channel open more than a parallel channel during operation (longer life).

The diffuser shape selection is beneficial not only for the life-length but also for reduces the pressure drop.

![Figure 1](image1.png)

**Figure 1.** (Top) 2D schematic of blood filtration and deposition of bio-particles, (bottom left) fluid flow on membrane and inside of diffuser shape pores, and (bottom right) blocking of diffuser pore by bio-particle (red blood cell), removal of bio-particle from pore inlet, and returning to main line (cross flow) by backwash flow method.

![Figure 2](image2.png)

**Figure 2.** 2D schematic of bio-layer deposition inside (left) a straight pore and (right) a diffuser pore. \( D \) is the local geometry diameter and \( H \) is the effective diameter.

### 2. Pore shape design

The clogging of filter pores can be substantially reduced and the life of the filter extended by using cross-flow filtration [14]. Dialysis filters have a short life because blood components clog the pores of the membrane. In the human kidney, heparan sulfate proteoglycan (HS-PG) is the major component of anionic sites (AS) that regulate the charge selectivity of the GBM [15]. Within the GBM, HS-PG may act as an anti-clogging agent to prevent hydrogen bonding and adsorption of anionic plasma proteins. It also maintains an efficient flow of water through the membrane. A SEM image illustrates the inner view on endothelium capillary of glomerulus with a variety of oval shapes of pores. A scanning electron microscopy (SEM) image illustrates the inner view on endothelium capillary of glomerulus with a variety of oval shapes of pores [16].

In an implantable kidney, the filters must operate reliably for at least five years [17]. This may be accomplished using low-adhesion surfaces, adhesion-unfriendly geometry, and self-cleaning mechanisms. For the membrane with micro-channels shown in Fig. 3, backwash is one of the methods used to remove particles which block the entrance. After a comparative analysis of differently shaped micro-channels, this study found that the best backwash is obtained with a nozzle working as a diffuser. The diffuser, shown in Fig. 4, has an expanding cross-sectional area [18]. By changing the direction of flow, the diffuser’s function changes to a nozzle, and the fluid jet detaches blocking bio-particles.
The flow inside a micro-channel is assumed to be three-dimensional and fully developed, steady or pulsatile laminar flow. The blood is assumed to be an incompressible liquid, which, after the pore entrance, is pure plasma. The shear stress-shear rate relationship of plasma is normally considered to be linear, and hence plasma is treated as a Newtonian fluid [6]. For each channel, the cross-sectional geometry was considered to be either rectangular, elliptical, or circular. As shown in Fig. 5, the effective width and height of the diffuser element at its entrance, respectively, and θ is diverging angle:

\[
X(z) = X_i + 2z \tan(\theta) \\
Y(z) = Y_i + 2z \tan(\theta)
\]  

(1)

where \(X_i\) and \(Y_i\) are the width and height of the diffuser element at its entrance, respectively, and \(\theta\) is the divergence angle of the diffuser.

The diameter plays main role in circular channel calculations. For non-circular cross sections, such as rectangular or elliptical, designers use the hydraulic diameter formula which reduces any cross-sectional shape to behave like a round tube [19]. The hydraulic diameter at the \(z\) axis is:

\[
D_h(z) = \frac{4A_z}{P_z}
\]  

(2)

where \(A_z\) and \(P_z\) are the cross-sectional area and the circumference, respectively (Table 2), in the \(z\) position (Eq. (1)). Many parameters of fluid flow, such as the flow rate or pressure drop, can be expressed in terms of the flow velocity. The average velocity at location \(z\) can be defined from the continuity equation as:

\[
V(z) = \frac{\dot{m}}{\rho A_z} = \frac{A_v}{A_z}
\]  

(3)

where \(\dot{m}\) is the mass flow rate and \(A_v\) and \(v\) are the cross section and velocity at the entrance (throat), respectively. The pressure drop is a fluidic term used to describe a decrease in a pressure field from one point in a channel or tube to another point downstream. The pressure drop is the result of frictional forces on the fluid from the side walls as the fluid flows through the tube. The pressure drop per length for flow can be described by the Hagen-Poiseuille equation [20]:

\[
\frac{dP}{dz} = \frac{128\mu Q}{\pi D_h(z)^4}
\]  

(4)

\[
\Delta P = \int \frac{128\mu Q}{\pi D_h(z)^4} dZ
\]

The shear stress on the wall is defined as:

\[
\tau_s = \frac{\Delta P D_h}{4l}
\]  

(5)

where \(\mu\) is viscosity, \(Q\) is the flow rate in the pore, \(l\) is the length of the channel, and \(D_h\) is the hydraulic diameter for non-circular pipes.

Numerical and analytical results are often presented in terms of dimensionless factors, such as the Fanning friction factor \(f\), which is a dimensionless number used in fluid flow calculations [21]. Another important dimensionless number in fluid mechanics is the Reynolds number, \(Re\), which represents the ratio of inertial forces to viscous forces; it indicates whether the fluid exhibits laminar or turbulent flow. The Fanning friction factor \(f\) for rectangular channel can be calculated with respect to the Reynolds number as [22]:

\[
f Re = \frac{4\pi^2(1+\varepsilon)}{3\varepsilon(1+\varepsilon)}
\]  

(6)

where \(\varepsilon\) is the aspect ratio (the aspect ratio of a shape is the ratio of its shortest dimension to its longest dimension, (see Table 2). \(f Re\) or the friction factor multiplied by the Reynolds number, is required in the model to predict hydrodynamic characteristics such as the pressure drop [23]. The Fanning factor for an elliptical shape is defined as:

\[
f Re = \frac{4(x^2 + y^4)A_e}{xy(\frac{1}{2}x^2 + y^2)}
\]  

(7)

where \(Re\) the Reynolds number, can be calculated as [15]:

\[
Re = \frac{\rho Q}{\mu \sqrt{A_z}}
\]  

(8)
Table 2. Geometrical characteristics of various cross sections, regarding diverging shape of microchannel (pores), x and y are function of z axis.

<table>
<thead>
<tr>
<th>Cross section of pore</th>
<th>Area (A)</th>
<th>Perimeter (P)</th>
<th>Aspect ratio (ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circle</td>
<td>$\pi d^2/4$</td>
<td>$\pi d$</td>
<td>1</td>
</tr>
<tr>
<td>Rectangle</td>
<td>$x y$</td>
<td>$2(x+y)$</td>
<td>$y/x$</td>
</tr>
<tr>
<td>Ellipse</td>
<td>$\pi xy/4$</td>
<td>$2\pi \sqrt{\frac{1}{8}(x^2+y^2)}$</td>
<td>$y/x$</td>
</tr>
</tbody>
</table>

3. Results and discussion

Considering the size of particles in human blood (Table 3) [24], the deformability of blood cells enables them to pass through spaces as narrow as 3 µm for RBCs and 3.5 µm for WBCs [25]. In order to maintain a proper safety margin to prevent RBCs and WBCs from passing through the filter, the entrance width of the micro-channel is set to 1.5 µm. The aspect ratio (Table 2) varies in the range $0 < \varepsilon \leq 1$ and the diffuser opening angle, $\theta$, is equal to 0, 5, and 10 degrees, respectively (Fig. 4). The single glomerulus filtration rate (SNGFR) is considered to be around 62 nL/min [1]. Although temperature has a significant effect on blood separation [26], because the implant inside a human body is at a temperature of 37°C, the temperature dependence is neglected in the model. A combination of analytical and numerical methods is used to demonstrate the effect of pore shape on flow characteristics with Maple software (version12 by Waterloo Maple Inc).

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>7-8</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>7-20</td>
</tr>
<tr>
<td>Platelets</td>
<td>2-4</td>
</tr>
</tbody>
</table>

3.1 Effects of aspect ratio and divergence angle on pressure

The pressure drop during filtration indicates the performance of a process during fluid circulation. A higher pressure drop in a pore indicates lower performance of filtration due to pore blocking or particle build-up. In order to reduce or eliminate this undesired behavior, this study focuses on filter self-cleaning methods, pore shape modification, and material properties.

Table 4 summarizes approximate pressures and vascular resistances in the circulation of a normal kidney [1]. The maximum pressure at the entrance of a glomerular capillary is limited to around 60 mmHg due to the parameters of a properly working heart. There is a maximum afferent blood pressure in a glomerular capillary delivered by the blood circulation system, so the maximum pressure drop on a glomerule should not exceed 8000 Pa. The proposed model is based on this maximum pressure drop. Figures 6 and 7 illustrate the pressure drop as a function of pore geometry, such as the aspect ratio $(0.1 \leq \varepsilon \leq 1)$, diameter, and maximum entrance length (1.5 µm) obtained from Eq. (4), for rectangular, elliptical, and circular pores for divergence angles of $\theta = 0^\circ$, $5^\circ$, and $10^\circ$ for a straight channel.

Figure 6. Pressure difference ($\Delta P$) as a function of angle $(\theta)$ and aspect ratio $(\varepsilon)$ for pores with rectangular and elliptical cross sections.

Figure 7. Pressure difference ($\Delta P$) as a function of angle $(\theta)$ and diameter D (µm) for pore with circular cross section.

![Image](image1.png)

![Image](image2.png)
or a 250-fold lower pressure drop (see Fig. 6). Figure 7 shows similar results for a straight circular shape.

3.2 Effects of aspect ratio on wall shear stress

The relationship between the wall shear stress and the aspect ratio is plotted in Figs. 8 and 9, obtained from Eq. (5), for diffuser angles of $\theta = 0^\circ$, $5^\circ$ and $10^\circ$ for a straight channel for circular, elliptical, and rectangular pore shapes.

The maximum wall shear stresses for $\theta = 0^\circ$ with circular, rectangular, and elliptical cross sections were 42000, 2025, and 4536 Pa, respectively. For $\theta = 10^\circ$, the wall shear stress for a given aspect ratio decreased to one sixth of the initial wall shear stress.

![Figure 8. Wall shear stress ($\tau$) as a function of angle ($\theta$) and aspect ratio ($\epsilon$) for pores with rectangular and elliptical cross sections.](image)

![Figure 9. Wall shear stress ($\tau$) as a function of angle ($\theta$) and diameter (D) (\(\mu m\)) for pore with circular cross section.](image)

3.3 Effects of aspect ratio on friction factor and Reynolds number

In fluids dynamics, the flow rate depends on the velocity and cross-sectional area of the channel and the friction factor has a direct effect on fluid velocity. From Eq.(7) and Eq.(8), the Fanning friction factor and Reynolds number are dependent on the aspect ratio. As shown in Eq.(6) and Eq.(7), the product of the friction factor and the Reynolds number is a function of only the aspect ratio, which is a geometrical parameter. This dependence is plotted in Fig. 10, which compares rectangular and elliptical shapes under equalized cross-sectional area conditions. If only the wall shear stress and pressure drops are considered, the calculation results and Fig. 6-10 indicate that the performance of micro-channels with elliptical shapes, for a given cross-sectional area, is 10-13% (Fig. 10) better than those obtained using other cross-sectional shape.

With respect to blood pressure in a kidney (Table 4) and blood cell dimensions, the best pore aspect ratio is $0.2 \leq \epsilon \leq 0.4$ for rectangular and elliptical (diffuser) shapes and $0.4 \leq \epsilon \leq 0.7$ for a circular (diffuser) shape. Although Fig. 6-9 illustrate that the minimum pressure drop and wall shear stress occur at $\theta = 10^\circ$ for all pore shapes, the minimum loss and pore density per area are obtained with $\theta \leq 5$.

![Figure 10. Comparison of fRe values as a function of aspect ratio ($\epsilon$) in rectangular (square) and elliptical (diamond) micro-channels with equal cross-sectional areas.](image)

Table 4. Approximate pressures and vascular resistances in circulation of a normal kidney [1].

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Pressure in vessel (mmHg)</th>
<th>% of total renal vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal artery</td>
<td>100</td>
<td>End 100</td>
</tr>
<tr>
<td>Interlobar, arcuate, and interlobular arteries</td>
<td>-100</td>
<td>85</td>
</tr>
<tr>
<td>Afferent arteriole</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Glomerular capillaries</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Efferent arteriole</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>Peritubular capillaries</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Interlobar, interlobular, and arcuate veins</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Renal vein</td>
<td>4</td>
<td>-4</td>
</tr>
</tbody>
</table>

Manufacturing membranes with rectangular-shaped diverging pores with micrometer sizes is impractical, and thus only elliptic and circular diffuser shapes of pores are selected for the membrane filter elements.

3.4 Simulation of pore models by finite element analysis

To simulate the differences among the pores models, this paper employed COMSOL Multiphysics finite element analysis software and its fluid module. The models developed are two-dimensional (2D). As expected, the pressure drop conditions in diffuser pores are better than those in a straight pore for the given inlet conditions, as shown in Fig. 11.

The maximum pressure in the straight channel is higher than those in diffuser channels. The pressure was reduced with a low gradient in the straight channel. This low gradient creates resistance inside the fluidic system, and thus the fluid requires more pressure to flow. Because of the blood pressure range inside of the human body, the maximum produced pressure in the system has a limit, which affects filter design.
The 2D results of COMSOL software validate the selection of the diverging shape pores.

![Figure 11. 2D pressure drop simulation by COMSOL for three pore shapes. (Left) Straight, (middle) \( \theta = 5^\circ \) diverser, and (right) \( \theta = 10^\circ \) diverser.](image)

4. Conclusion

The pressure drop, wall shear stress, and friction factor in micro-channels with rectangular, elliptical, and circular cross sections were studied. The highlights of this study are as follows:

1. The elliptical diffuser shape is the best with respect to filtration pressure drop in membranes and practicality for fabrication.
2. Results illustrate that the optimum pressure drop and wall shear stress occur for \( \theta = 10^\circ \) diverser divergence for all pore diverser shapes. However, with respect to pressure recovery, minimum loss, and pore density per filter surface area, the best angle is \( \theta \leq 5^\circ \).
3. The length of the channel, as reflected in the thickness of the membrane, increases the pressure drop; however, an excessively thin membrane may not provide sufficient mechanical self-support and reliability due to fatigue mechanisms caused by the pulsating blood pressure.

The design rules for glomerular filtration are limited to the mechanical stage of separation of solid blood components from liquids (plasma). If only this stage is used, because of the electrical charge of bio-particles, proteins will deposit on the filtering membrane surface (pore clogging), leading to a loss of electrolytes and proteins. To avoid these detrimental effects, another filtration stage should be added.

Filtration membranes with a permanent negative charge prevent the loss of bio-particles with negatively charged ions. They also reduce or prevent clogging and thrombosis of blood particles on the membrane. Pulsatile flow in blood vessels and an artificial membrane will be used in membrane back-wash self-cleaning process. A future study will describe how these effects extend the usability of the filtration membrane and thus an artificial implantable kidney.

References