Design and experimental proof of selected functions in implantable artificial kidney

by

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Abstract

Renal failure results in poisoning because metabolic by-products are not promptly removed from the body. The main remedy for this condition is hemo-dialysis, where blood bypasses the kidneys and is filtered in a “dialyzer”, stationary machine.

This research proposes and verifies novel techniques that allow an implantable device to replace a dialysis machine. This device would perform two important kidney functions: filtering solids and retaining desired electrolytes and small proteins. Three independent approaches are proposed and experimentally verified. The first approach is design optimization of the glomerular membrane as an implantable filter to separate blood cells from whole blood. We studied the parameters that minimized pressure drop per unit area in micro-channels (straight and diverging) with circular cross-sections.

The second approach, aimed at extending the filtration capability of a porous membrane, used the concept of “back-wash”. It used a natural energy source in the body, the pulsatile character of blood flow, with pressure varying between 80 and 120 mm Hg. Under similar experimental conditions, experimental results demonstrated that the permeate volumetric flow rate was higher in the backwash system compared to the no-backwash system, and this flow rate could be maintained for many more filtration cycles. The third approach, which retained body electrolytes and small proteins, used a static electric field to divert blood ions and charged proteins back to circulation. Two geometries for this electrophoretic filtration were proposed and tested: “Y” method and “cross-flow” method. The “cross-flow” method seems more promising after a preliminary comparison. A benefit of using the electrostatic deviation of charged solids before mechanical filtration is a lower density of blood solids reaching the filtration membrane, causing a lower probability of filter clogging.

Due to the importance of maintaining proper pressure drops at all renal filtration stages an implantable valveless pump was designed and fabricated for pressure drop adjustments. This pump’s novelty is that it relies entirely on blood pressure pulsations and does not require an external power supply.

None of the proposed filtration techniques requires external power supplies; all rely on energy delivered by the heart.

Keywords: Implantable Artificial kidney; Diverging pore; optimization; Backwash method; Ion protein separation; Valveless pump.
Dedication

To my wife, Mojgan and

my Son, Artin
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Glossary and symbols

**Glossary:**

a  Major axis of particle, $m$

$A_1$  Cross-section at the entrance (throat)

$A_z$  Cross-sectional area in the $z$ position, $m^2$

AC  Alternating current

ACD  Acid-citrate-dextrose

ARF  Acute renal failure

ATP  Adenosine triphosphate

b  Minor axis of particle, $m$

B  Magnetic field vector, $T$

CKD  Chronic kidney disease

CRF  Chronic renal failure

$D$  Width of the channel, $m$

$D_e$  Exit pore diameters, $m$

$D_h$  Hydraulic diameter, $m$

DC  Direct current

DEP  Dielectrophoresis

E  Electrical field, $v/m$

ESC  Extra-capillary space

ESRD  End-stage renal disease

EVAL  Ethylene vinyl alcohol

$F_d$  Drag force, $N$

$F_l$  Lift (buoyant) force, $N$
\( F_g \) Gravity force, \( N \)

\( F_m \) Magnetic force, \( N \)

GFR Glomerular filtration rate, \( ml/min \)

\( H \) Opening width of pore

HCT Hematocrit

\( J \) Flux, \( m/s \)

\( k_0, k_\infty \) Constant parameters (Hematocrit dependent)

\( K_t \) Capillary filtration coefficient

L3 Lumbar vertebrae number 3

\( P \) Pressure, \( Pa \)

\( \Delta P \) Pressure drop, \( Pa \)

\( \nabla P \) Pressure gradient

\( P_B \) Hydrostatic pressure in Bowman’s capsule

\( P_G \) Glomerular hydrostatic pressure, \( mmHg \)

PA/PES Polyamide/polyarylethersulfone

PAN Polyacrylonitrile

PDP Positive displacement pump

PES Polyethersulfone/ polyarylethersulfone

PEPA Polyethersulfone +polyarylate

PMMA Polymethylmethacrylate

PSF Polysulfone

\( Q \) Flow rate, \( m^3/sec \)

\( q \) Charge of the particle

\( q_d \) Flow rate from the output diffuse, \( m^3/sec \)

\( Q_p \) Flow rate of a diaphragm pump
Radius, \( m \)

Reynolds number

Red blood cell

Single glomerulus filtration rate, \( ml/min \)

Thoracic vertebra number 12

Time, \( s \)

Velocity, \( m/s \)

Volume stroke, \( m^3 \)

White blood cell

**Greek symbol:**

\( \alpha \) Womersley number

\( \gamma_c \) Constant parameter (Hematocrit dependent)

\( \omega \) Frequency of oscillation

\( \theta \) Angle

\( \rho \) Density, \( kg/m^3 \)

\( \mu \) Viscosity, \( cP \)

\( \eta_a \) Apparent viscosity, \( cP \)

\( \eta_o \) Newtonian suspending fluid viscosity

\( \tau \) Stress tensor, \( Pa \)

\( \gamma \) Shear rate, \( m/s \)

\( j_0 \) Bessel function

\( \pi_G \) The colloid osmotic pressure of the glomerular capillary plasma proteins, \( mmHg \)

\( \pi_B \) The colloid osmotic pressure of the proteins in Bowman’s capsule, \( mmHg \)
Scope of research

The ultimate goal of some of researchers in biomedical engineering is creating an implantable artificial kidney to perform the main functions of a real kidney. The kidney is functionally a very complex organ, and artificially replicating this organ will require years of research. This research focuses on selected functions and problems associated with an implantable artificial kidney:

- pressure drop in filtration membrane;
- decreasing volumetric flow rate due to blocking of pores in the filtration membrane;
- low pressure in the fluidic circuit due to hydraulic losses;
- ion and protein separation

The solutions for overcoming these problems are to

- optimize the design to decrease the membrane pressure drop per unit of area,
- increase the volumetric flow rate of the permeate using backwashing method,
- implement a miniature implantable valve-less pump to deliver bio-fluid in the implantable artificial kidney system,
- separate ions and proteins in pulsatile flow as a pre filter using electrophoresis method.

Similar to glomerulus filtration, for separating blood cells from whole blood, one of the most common methods is cross-flow filtration. Because of the cells’ size, the pore diameter must be in micro-metres in size, which produces a greater pressure drop for the filtration system. Blood pressure in the human cardiovascular system has limited range, and it is a challenge for implantable artificial kidney. The total pressure drop on all
the filtration stages must not exceed the difference between the systolic and diastolic levels. We analytically and numerically optimized the design of pore shape and pressure drop per unit of area for the implantable membrane to separate blood cells from whole blood in vivo condition. We simulated and numerically optimized it to demonstrate the advantage of using diverging pores instead of a regular straight channel.

The same as glomerular filtration rate (GRF) in a kidney, the volumetric flow rate of the permeate (filtrate) is an important parameter of the implantable artificial kidney. Due to deposition of cells and bio-particles on the filter’s surface, the filtrate volume will be reduced over time. This problem creates a negative effect on performance of separation. To solve this problem, we designed and used a backwash method to increase the volume of filtrate. An advantage of this system is using blood flow pulsation to generate backwash flow on membrane without any external energy. Many bio-particles have electrical charge. This characteristic of particles helps the kidney to separate bio-particles and ions. In this research, we used electrical and magnetic fields to separate ions and proteins from non-charged components. We designed, applied, and compared two methods for this purpose: Y splitter and cross-flow separation under an electrostatic field. These electrostatic separation methods can be used as a pre-filter or main filter to separate charged bio-particles and ions to return them back to blood-flow. In the appendices, we have reviewed the hemolysis issues, which is, unfortunately, present in mechanical blood treatment processes. Having a pressure drop in separation systems is unavoidable, and it reduces performance of the system, especially in systems with several stages of filtration, such as implantable artificial kidney. To solve this problem, we designed and fabricated an implantable valve-less pump to increase the flow after each filter stage. In this method, a diaphragm pump enhances the filtrate flow between consecutive stages of filtration. This pump uses varying pressure of blood pulsatile flow to activate the diaphragm. Again, the advantage of this system is that it uses the internal energy of the human body.
1. Introduction to the renal system and the artificial kidney

This chapter describes the renal system and the associated functions that an artificial kidney must perform in order to be a viable solution to current dialyses systems.

1.1. Function of the renal system

The renal system consists of two kidneys and, in humans, the kidneys are located approximately at the vertebral level T12 to L3 (Fig. 1-1). One vital duty of the kidneys is excretion of a variety of waste products produced by metabolism. Although this excretion is the major function of the kidney, the kidneys provide multiple functions [1]:

- Excretion of metabolic waste products and foreign chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Secretion, metabolism, and excretion of hormones
- Gluconeogenesis

1.2. Excretion of metabolic waste products and foreign chemicals

The waste products include urea (from the metabolism of amino acids), creatinine (from muscle creatine), uric acid (from nucleic acids), end products of hemoglobin breakdown (such as bilirubin), and metabolites of various hormones. These products have to be removed from the human body as rapidly as they are created. The kidneys also remove most toxins and other foreign chemicals that are either produced by the human body or ingested, such as drugs, and food additives.
1.3. Regulation of water and electrolyte balances

To maintain normal homeostasis, excretion of water and electrolytes and intake must be balanced. If the intake of a material exceeds its excretion, than the amount of that material in the body will increase. If intake is less than excretion, the amount of that material in the body will decrease.

Figure 1-1: Surface projection of the renal system showing kidneys at the level of T12 to L3, [Diagram by A. Ostafdar]

1.4. Renal blood flow

The blood flow in kidneys is around 22% of cardiac output or 1100 ml/min. Figure 1-2 illustrates the blood circulation in the kidneys. As the figure shows, the blood flow enters from renal artery then branches to the radial arteries (interlobar, arcuate, and
interlobular), and the afferent arterioles provide the blood for the nephron, which is the filtration unit of kidney. Each kidney in a human includes about 1 million nephrons, which are located on the cortex of the kidney. The kidney cannot produce new nephrons. Therefore, renal disease or normal aging decrease the number of nephrons [1].

Each nephron includes glomerular capillaries (the glomerulus), through which large amounts of plasma are filtered from the whole blood, and a long tubule in which the filtered plasma is converted into waste products (urine) on its way to the pelvis of the kidney (Fig 1-2)

![Diagram of kidney blood circulation](image)

Figure 1-2: The major vessels that provide blood flow to the kidney, and schematic of the blood circulation of each nephron [Diagram by A. Ostadfar]

1.4.1. Mass balance in the kidney

One of key principles in the kidney is mass balance. For any solute, such as (X), which cannot be synthesized, accumulated, or degraded by the kidney, three paths
exist: the renal artery as an entry and two paths of exit, renal vein and ureter. Figure 1-3 shows the mass balance of (X) solute in the kidney. From the mass balance theory, the input of (X) equals the output of it; therefore [2],

$$P_{X,a} \cdot RPF_a = P_{X,v} \cdot RPF_v + U_X \cdot \dot{V} \quad (1)$$

where the subscripts $a$ and $v$ are the renal artery and vein, respectively, $P_X \left( \frac{mmol}{ml} \right)$ and $RPF \left( \frac{ml}{min} \right)$ are the plasma concentration of the solute (X) and the renal plasma flow, respectively, and $U_X \left( \frac{mmol}{ml} \right)$ and $\dot{V} \left( \frac{ml}{min} \right)$ are the concentration of solute (X) in urine and urine flow, respectively.

Figure 1-3: Mass balance for solute (X) in the kidney [Diagram by A. Ostadfar].

1.5. Urine formation

The end product of the renal system is urine, and its production rate is the resultant of three renal processes, shown in Figure 1-4: (1) glomerular filtration, (2) reabsorption of useful substances from the nephron tubules into the blood capillaries, and (3) secretion of extra substances from the blood capillaries into the nephron tubules. This production rate is expressed as:
Urinary excretion rate (1.5 L/day) = Filtration rate (180 L/day) – (Reabsorption rate + Secretion rate) (178.5 L/day)  

This equation provides a conceptual framework to examine kidney functions. In this formula, the filtration rate is determined by glomerular filtration. Reabsorption and Secretion rates are the products of tubule filtration. This equation shows the base elements of the filtration procedure in the kidneys. A malfunction in any part of this procedure results in kidney disease. Each of these procedures, glomerular filtration, reabsorption, and secretion, is adjusted in relation to the needs of the body. For instance, when the body has excess sodium, the filtration rate of sodium will be increased and a little fraction of the filtered sodium will be reabsorbed, resulting in an increase of sodium in the urinary excretion.

Normal balancing in the kidney filtration procedure is vital, and any unusual state can result in changes in kidney excretion. For instance, if reabsorption remains constant, a ten percent increase in filtration rate (from 180 to 198 L/day) will raise urine volume around 13-fold (from 1.5 to 19.5 L/day) [1]. In the reabsorption and secretion procedures, substances are conveyed across the tubular membranes, and then they pass through the peritubular capillary membrane back into the blood (reabsorption) or back from blood capillaries to tubule (secretion), regarding body needs. The following sections explain these mechanisms.

1.5.1. Glomerular filtration

Urine formation begins with the filtration of a large amount of plasma through the glomerular capillaries into Bowman’s capsule (Fig. 1-4). The renal glomerulus system can filter 180 liters of whole blood per day, and the average glomerular filtration rate (GFR) is 125 ml/min. The GFR is the product of glomerular capillary filtration coefficient ($K_f$) and the net filtration pressure (Eq 3 and 4) [1].

$$\text{GFR} = K_f \times \text{Net filtration pressure}$$  \hfill (3)

The GFR can, therefore, be expressed as

$$\text{GFR} = K_f \times (P_G - P_B - \pi_G + \pi_B)$$  \hfill (4)
where \( P_g \) is glomerular hydrostatic pressure which promotes filtration, \( P_B \) is the hydrostatic pressure in Bowman’s capsule, \( \pi_G \) is the colloid osmotic pressure of the glomerular capillary plasma proteins, and \( \pi_B \) is the colloid osmotic pressure of the proteins in Bowman’s capsule.

In a normal kidney, the net filtration pressure is

\[
\text{Net filtration pressure} (10 \text{ mm Hg}) = \text{Glomerular hydrostatic pressure} (60 \text{ mm Hg}) - \text{Bowman’s capsule pressure} (18 \text{ mm Hg}) - \text{Glomerular oncotic pressure} (32 \text{ mm Hg})
\]

\( K_f \) can be calculated by dividing the GFR (125) by net filtration pressure (10), so a normal \( K_f \) is 12.5 ml/min/mmHg. This number illustrates that the glomerular capillary filtration coefficient \( (K_f) \) is 400 times greater than the \( K_f \) of most other capillary systems of the human body [1].

![Figure 1-4: Basic kidney processes that determine the composition of urine [Diagram by A. Ostadfar]](image)

The diameters of the Bowman’s capsule (Fig. 1-4.) in different species range from approximately 100 µm (mouse) to up to 300 µm (elephant); in humans, they are approximately 200 µm, in rats they are 120 µm, and in rabbits they are 150 µm [3,4,5].
Figure 1-5 shows a longitudinal section through a glomerulus and Glomerular filtration barrier. To separate plasma from whole blood, the glomerular capillary wall is made from three layers: endothelial cells, glomerular basement membrane (GBM), and podocytes.

Glomerular endothelial cells are large flat cells with fenestrated peripheral parts. These fenestrate are round or oval pores, and their diameters range from 50 nm to 100 nm. The GBM varies in width among species. In humans, the GBM thickness ranges between 240 nm and 370 nm [6,7], in rats and other investigational animals they vary between 110 nm and 190 nm [8].

Podocytes are polarized epithelial cells with a luminal and a basal cell membrane domain; the latter corresponds to the sole plates of the foot processes, which are embedded into the GBM to a depth of 40 nm to 60 nm (Fig 1-5). The border between the basal and luminal membrane is represented by the insertion of the slit diaphragm [9].

Generally, it is accepted that the charged membrane plays a significant role in preventing polyanionic macromolecules, such as albumin, from passing from side to side of the glomerular barrier [10].
Figure 1-5: Left: Schematic diagram of a cross section through a glomerulus, Right: Glomerular filtration barrier, two podocytes foot processes bridged by the slit membrane, the glomerular basement membrane (GBM) and the porous capillary endothelium are illustrated [Diagram by A. Ostafar].

1.5.2. Tubular Transport

In the nephron tubule, two mechanisms perform transportation: reabsorption and secretion; these are selective mechanisms. The tubule can select ions for reabsorption or secretion from the tubule wall, depending on body needs.

Figure 1-6 shows the reabsorption of filtered substances (water and solutes) from the tubule lumen across the tubular epithelial cells, through the renal interstitium (the space between cells in a tissue), and back into the blood capillaries which come from the glomerulus (efferent arteriols). Solutes are transported between the cells (paracellular route) by diffusion, or through the cells (transcellular route) by passive diffusion or active transport. The energy for this active transport comes from the hydrolysis of adenosine
triphosphate (ATP). Osmosis transports water through the cells and between the tubular cells. Transportation of water and solutes from the interstitial liquid into the peritubular capillaries happens by ultrafiltration (bulk flow) [1].

![Diagram by A. Ostadfar](image.png)

Figure 1-6: Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood [Diagram by A. Ostadfar].

The secretion mechanism is the reverse of reabsorption: in the tubule lumen, it is caused mainly by active transport. A secondary active transport method plays the main role to transport the substances in the tubule. In that method, two or more substances cooperate with a specific protein in the membrane (a carrier molecule), and they are transported together across the membrane.

Table 1-1 illustrates the renal operation of several substances that are all freely separated in the kidneys and reabsorbed at variable rates. As the table shows, tubular reabsorption is highly selective. Some materials, such as glucose and amino acids, are almost completely reabsorbed from the tubules. Many of the ions in the plasma fluid, such as sodium, chloride, and bicarbonate, are also reabsorbed, but their rates of reabsorption are changeable, depending on the needs of the body. Waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and excreted in relatively large amounts. If the concentration of these substances in the
blood or urine differs from the expected value, this denotes that the kidney function is abnormal. The rate of water reabsorption varies between ~95-99%. Most daily variation in potassium excretion is caused by changes in potassium reabsorption in the proximal tubule and secretion in distal and collecting tubules [1].

Table 1-1: Rates of Filtration, Reabsorption, and Excretion of Different Substances by the Kidneys [1]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount Filtered (mol/day)</th>
<th>Amount Reabsorbed (mol/day)</th>
<th>Amount Excreted (mol/day)</th>
<th>% of Filtered Load Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.999</td>
<td>0.999</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>4.320</td>
<td>4.318</td>
<td>0.002</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Sodium</td>
<td>25.560</td>
<td>25.410</td>
<td>0.150</td>
<td>99.4</td>
</tr>
<tr>
<td>Chloride</td>
<td>19.440</td>
<td>19.260</td>
<td>0.180</td>
<td>99.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.756</td>
<td>0.664</td>
<td>0.092</td>
<td>87.8</td>
</tr>
<tr>
<td>Urea</td>
<td>0.78</td>
<td>0.39</td>
<td>0.39</td>
<td>50</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.01591</td>
<td>0</td>
<td>0.01591</td>
<td>0</td>
</tr>
</tbody>
</table>

1.6. Kidney Diseases

Kidney diseases are among the most significant causes of death and disability in many countries throughout the world.

Severe kidney diseases can be categorized into two main groups: 1) Acute renal failure, and 2) Chronic renal failure

1.6.1. Acute renal failure

Acute renal failure (ARF) is a condition characterized by a rapid decrease of the glomerular filtration rate (GFR) and, consequently, an increase in blood nitrogen products, such as urea and creatinine. It is associated with oliguria (the low output of urine) in about two thirds of cases. Depending on the localization or the nature of the renal insult, ARF is categorized as prerenal, parenchymatous, or obstructive (postrenal).[11]
1.6.2. Chronic kidney disease

In general, chronic renal failure is similar to acute renal failure, but, in chronic kidney disease (CKD), patients lose large numbers of healthy nephrons permanently, and this situation is referred to as end-stage renal disease (ESRD).

The glomerular filtration rate (GFR) is the best measurement method to recognize level of kidney disease. Table 1-2 illustrates a classification and staging system based on the level of GFR and it guides as measurement tool for renal patients. It shows the staging system and an action plan for people with CRF [12]. Defining CKD using this staging system presents a regular standard for communication between the various health care systems and researchers. Regarding this staging (Table 1-2), five stages explain level of Chronic renal failure. In stage 1, the GFR is equal or a little more than 90 ml/min, and the patient should be under observation also control of blood pressure. In stage five of the CKD ranking, GFR is less than 15 ml/min, and this stage is the end stage of renal disease (ESRD). In this condition, the patient must be under hemodialysis machine treatment and be on a transplant waiting list.
Table 1-2: Staging system and action plan for chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR mL/min/1.73m²</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>At increased risk for CKD</td>
<td>≥ 90 with risk factors*</td>
<td>Screening CKD risk reduction</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥ 90</td>
<td>Diagnosis and treatment, Slow progression of CKD, Treat comorbidities, Cardiovascular risk reduction</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in GFR</td>
<td>60-89</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
<td>Prepare for renal replacement</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
<td>Replacement if uremic</td>
</tr>
</tbody>
</table>

*Risk factor: hypertension, dyslipidemia, diabetes mellitus, anemia, chronic analgesic ingestion
* Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests [12]

1.7. Artificial kidney

1.7.1 History of dialysis

Thomas Graham (1805-1869) first explained dialysis in 1854, and is considered the father of dialysis [13]. Graham prepared a funnel-shaped container (Fig. 1-7) where the wide open end of the funnel was covered by an ox bladder membrane. He filled the
funnel-shaped container with urine, and then he suspended it inside a larger container that was filled with distilled water. After several hours, the funnel was removed. He heated the fluid to dryness. Graham showed that the remains in the larger container consisted mainly of sodium chloride and urea, the principal components of urine. By this experiment, he proved that urea had passed through the membrane. After this test, Graham and his colleague, Dr. Richard Bright, predicted that it would take around sixty years to develop a hemodialysis machine for patients with renal disease.

![Diagram of Graham's setup](image)

Figure 1-7: Schematic of Graham's setup as the first dialysis experiment in 1854
[Diagram by A. Ostadfar]

George Haas performed the first human hemodialysis in an uremic patient in 1924 at the University of Giessen in Germany [14,15]. He used a tubular device made of collodion tube and used hirudin for anticoagulation. In 1925, he added a blood pump to his machine.

In 1943, Willem Kolff constructed the rotating-drum hemodialysis system (Fig. 1-8), originally made from a wooden core. He used cellophane membranes and an immersion bath in his design. The first recovery of an acute renal failure patient treated with hemodialysis was reported in that year [16,17]. Kolff is considered to be the Father
of Artificial Organs, and he is regarded as one of the most important physicians of the 20th century [18,19].

Figure 1-8: Schematic of Kolff's hemodialysis rotating drum (1943) [Diagram by A. Ostadfar]

In 1946, Nils Alwall introduced a new method with a vertical stationary drum kidney and circulating dialysate around the membrane [20]. He also was the inventor of the arterio venous shunt for dialysis. Dr. Alwall collaborated with Swedish businessman Holger Crafoord to establish one of the famous companies that would manufacture hemodialysis equipment in the past 50 years, Gambro. The compact lightweight AK 96 self-care machine is one of the new generations of hemodialysis machines for in-house treatment [21].

In 1960, a major breakthrough occurred with the creation of an exterior Teflon bypass by Quinton, Scribner, and Dillard [22]. This arterio-venous shunt provided for the continuous circulation of the blood when the patients were not connected to the dialysis machine. It gives ready access for long-term hemodialysis. This invention opened the new horizon to chronic renal disease therapy (Fig.1-9).
Figure 1-9: Schematic of Quinton and Scribner shunt method [Diagram by A. Ostadfar]

Figure 1-10 illustrates essential elements and blood flow diagram of a hemodialysis machine. Whole blood enters the machine from the vascular entrance via the arterial blood line; it passes through the dialyzer; and the blood is returned to the patient via the venous blood line. Dialysate is prepared and fed into the dialyzer, where water and substance exchange take place. After passing through the dialyzer, the dialysate is dumped into a drain. The blood circuit is separated from the dialysate circuit; they are only in indirect contact in the dialyzer. Figure 1-10 shows the basic components in a typical hemodialysis machine. Usually, blood flow in hemodialysis machines is at rate of 200 to 600 ml/min.
1.7.2. Hemodialysis membranes and the dialyzer

The performance of the dialyzer membrane depends on the biomaterial used, its pore size and density, thickness, biocompatibility, hydraulic permeability, and hydrophilic/hydrophobic properties [23].

To use membranes for applications such as hemodialysis, the membranes need to meet the requirements discussed below.

1.7.2.1 Membrane biocompatibility

One of the most important aspects of a hemodialysis membrane is biocompatibility; that is, the compatibility of the dialyzer membrane in contact with blood.
Three major concerns are vital in hemodialysis biocompatibility: clotting, complement activation, and adsorption of endotoxins and cytokines.

- Clotting: Clotting is usually controlled through the use of systemic heparinization, although a small percentage (<5%) of dialysis treatments are performed heparin-free due to allergic reactions to heparin [23]. Heparin-coating is an alternative method to prevent clotting, and Heparin-coated dialyzers have been introduced several years ago to protect the membrane from clotting [24].
- Complement activation: proteins of complement are so-named because they complement antibody activity to remove pathogens. Complement activation during hemodialysis was first recognized by the rapid drop in white blood cell counts (neutropenia) at the first thirty minutes of dialysis. Regenerated cellulose membranes activate complement through the alternate pathway [25]. Modified cellulose membranes approach the biocompatibility profile of synthetic materials in terms of complement activation and neutropenia (an abnormally low number of neutrophils—a type of white blood cells) [23].
- Adsorption of endotoxins and cytokines: Endotoxins are bacterial products released from gram-negative bacteria upon death. Because endotoxin fragments fall in the middle molecule range, they may be inadvertently transported from the dialysate to blood during high-flux (flow) dialysis, leading to cytokine generation that adds to the chronic inflammatory state of dialysis patients [23].

The open pore in high-flux membranes affords more adsorptive potential than do low-flux counterparts. In addition, synthetic membranes, many of which are fundamentally hydrophobic, normally are much more adsorptive than hydrophilic cellulosic membranes [26].

The adsorption features, distribution of hydrophobic and hydrophilic areas, and charge distribution on the surface and in the pores are significant factors that determine membrane biocompatibility.

1.7.2.2. Membrane Materials

Dialyzer membranes can be categorized based on their chemical compositions as either cellulosic, modified cellulosic, or synthetic [23].
Cellulosic: These membranes were exclusively used in the 1940s through the 1960s. Cellulosic membranes are polysaccharide membranes derived from cotton linters. Activating the complement cascade makes these membranes bio-incompatible [27]; however, because of their lower cost in some parts of world, medical systems still use them.

Modified cellulosic: Modified cellulosic membranes are made more bio-compatible by substituting the hydroxyl groups with other moieties or by coating the membrane with a biocompatible coating.

Non-cellulosic synthetic membranes: Currently, these membranes are very common in the dialysis field; the term “synthetic membrane” is used to denote all polymeric membranes that are not cellulose based. Figure 1-11 illustrates a synthetic membrane. The most used membranes in this category are polysulfone, polycarbonate, and polyurethane.

![Image](image.png)

Figure 1-11: Cross-section of a synthetic hemodialysis membrane, Scale bar is 10 μm [Photo by A. Ostadfar].

### 1.7.3 Hollow fibers

The first membrane materials were saponified cellulose acetate and Cuprophan [28]. The idea of the Cuprophan hollow fiber was visualized in 1969 by Heinz Ruck [29], which revolutionized dialysis technology. Currently, the hollow fiber module is a hollow fiber dialyzer which consists of semi-permeable polymeric capillaries sealed inside a tubular cartridge. Figure 1-12 shows cross-sections of a hollow fiber. The hollow fiber has three regions: lumen of the feeding line, membrane, and extra-capillary space (ESC) for permeate (filtrated) fluid.
Figure 1-12: Cross-sections of the hollow fiber. Up: radial cross-section, Down: longitudinal cross-section [Diagram by A. Ostadfar]

The schematic of a hollow fiber dialyzer is illustrated in Figure 1-14. This figure also illustrates a cut-view of a regular dialyzer which is used in hemodialysis machines.

Figure 1-13: Hollow fiber dialyzer. Up: schematic of dialyzer, Down: Cutting view of Polysulfone dialyzer module [Diagrams by A. Ostadfar]
The thickness of the membrane wall is in the range of 50-100 µm. Double-layer asymmetric hollow fibers [30] are also commercially available. Typical internal diameters for hollow fibers are from approximately 100 µm to 1.5 mm.

The ideal membrane design for hemodialysis is the hollow fiber, which has the benefit of a very high membrane area for a given volume. A large fraction of microporous membranes are still made of cellulose derivatives, but several other synthetic polymers are being used, including polysulfone, polycarbonate, polyamide, and polyacrylonitrile [31]. The mechanism of filtration in a dialyzer and hemodialysis machine is ultrafiltration to separate waste products from whole blood.

1.8. Problems encountered by renal patients in artificial kidney treatment

For less than one hundred years, the artificial kidney treatment has been the great method for treating patients with end-stage of renal disease; however this treatment method is not ideal for patients because of the following main problems encountered with hemodialysis treatment today.

- **Mortality rate**: The mortality rate for patients with end-stage renal disease is around 23% per year, and, at the moment, dialysis or transplantation are the only therapeutic options for these people [32]. This statistic shows that we have to work to find a solution to reduce this devastating rate.

- **Donation waiting list**: Chronic kidney disease (CKD) affects 26 million patients in the United States, and around 550,000 of these patients have end-stage renal disease requiring dialysis or transplantation [33], which results in a long donation waiting list for patients who applied for kidney donation.

- **Mobility and continuously**: CKD people need to be under dialysis treatment three to five times per week; each time it takes several hours. The key reason to pursue a portable artificial kidney is that it would work continuously, twenty-four hours a day, seven days a week, filtering the blood in a nonstop form very much similar to our natural kidneys. In addition, hundreds of scientific papers, including randomized controlled trials, commend the benefits of more frequent dialysis for much longer periods of times, preferably daily [34]. This time schedule shows the importance of a portable or an implantable artificial kidney.
• **Size**: Currently, dialysis machines are too large and heavy to carry and they are not wearable or portable.

• **Disposable dialyzer**: Because of blocking, clogging of the membrane, and infections, all dialyzers are disposable.

• **Vascular access**: The best solution available today for creating vascular access is the endogenous Cimino-Brescia fistula, which has the benefit of being constructed from vessels of the dialysis patients themselves. Unavoidably, because of the foreign structure of the materials and body reaction, the hazard for infection and vessel stenosis or thrombosis is much higher with this access method [35].

• **Hemodynamic instability**: One of the major peridialytic problems today is hemodynamic instability, a state where the circulatory system is not able to provide for perfusion of the tissues [36]. The risk of hemodynamic instability is raised by the requirement to sometimes remove substantial volumes of fluid if the patients are anuric and drink exaggerated amounts of fluid in between dialyses [35].

1.9. **Literature review**

Currently, no implantable artificial kidney exists because of the complicated structure and function of the kidney. Unfortunately, the academic literature of implantable artificial kidney is not rich. In this section, a selection of the related technical publications and methods is reviewed and discussed.

Topics regarding pore design, microfiltration, and ultrafiltration principles are fairly well known [37]. In the field of microfiltration, the cross-flow filtration is a well-recognized procedure for removing microparticles and microorganisms from the main fluid, and it has many industrial applications, especially in bio-separation processes [38]. Membrane blocking in filtration is prevented by the use of cross-flow on the membrane.

Microsieve filters consist of a thin membrane with uniform pores, and, in some applications, the membrane layers are strengthened by support structures. A microsieve
having a thin filtration layer with a high density of pores demonstrates superior separation performance at high flow rates[39]. The flow resistance in microsieves compared to other microfiltration membranes is small [40]. In the case of microfiltration and large particles (micro-particles), cross flow prevents (or reduces) the buildup of these particles on the surface of the microsieve. This approach was first examined in 1995 with a small module of cross-flow filtration using a microsieve with a pore diameter of 2 μm and mean particle diameter of 5 μm [39].

Since the 1990s, research has started to relate the filtration characters of the glomerulus to its real physical construction [41]. In 1999, Edwards et al. developed a theoretical model of the glomerular barrier related to the structural features of the glomerular capillary wall layers [42]. Figure 1-14 shows the schematic of their model.

Figure 1-14: Schematic structure of the glomerular wall which was developed by Edwards et al [40]; Dimensions in nm: W: 360, L: 200, X: 39, r: 30 [Diagram by A. Ostadfar

Rodewald and Karnovsky suggested that the filtration slit consists of a central fiber bonded by bridging fibers to the cell membranes on each side [43]. Figure 1-15 illustrates their suggestion.
Waugh and Addlesee outlined several engineering and medical considerations that need to be taken into account when creating such as an implantable artificial kidney [44].

In 2009, Roy et al. investigated the feasibility of an implantable bio-artificial kidney using silicon nanoporous membranes [45]. They introduced a membrane for an implantable artificial kidney using micro-electro-mechanical system (MEMS). They realized that the prototype membranes used in their experiments were not optimized for the flux requirements necessary in an implantable artificial kidney.

![Diagram of the epithelial slit](image)

Figure 1-15: Schematic diagram of the epithelial slit [Diagram by A. Ostadfar].

Kanani et al. presented that in the ultrafiltration membranes, selectivity and permeability of uniform slit pores have better performance compared to cylindrical pores [46]; their results were based on membranes with very low porosity (less than 0.0006), which was far too low for most realistic applications.

Brans et al. showed that sharp-edged pores increase drag force, and the penetration of deformable particles into the pores results in a lower drag force [47]. With regard to biomaterials, Fissell et al. demonstrated that it should be possible to create
silicon-based membranes using MEMS technology for the implantable hemofiltration [48].

For pore geometry and its design aspects, the majority of the presented studies have focused on using an ultrafiltration membrane and nano-pores (regular shape), and they have focused on effects such as permeability and selectivity of bio-fluid ultrafiltration and its performance. These studies do not discuss new aspects of pore geometries or their effects on pressure drop, and they do not try to optimize the pores for volumetric flow rate in vivo conditions.

A filter (or membrane) is a barrier that separates elements and selectively transfers definite types while it limits the flow of others [49].

There are two main types of filtration: cross-flow and dead-end filtrations, see figure 1-16.

![Diagram of filtration types](image)

Figure 1-16: Schematic of dead-end filtration and cross-flow filtration [Diagram by A. Ostadfar]

Figure 1-17 shows the concentration of particles and their deposition layer (boundary layer) on the membrane in cross-flow filtration.
Hwang et al. studied the effects of particle dimensions and the filtration rate in cross-flow microfiltration [50]. They showed that an increase in filtration pressure led to a decrease in the deposited particles porosity, and it led to an increase in the mass and average filtration resistance of the cake.

Hong et al. demonstrated that the permeate flux declines faster with rising concentration of the feed particle and transmembrane pressure and with a decrease in the size of particle in suspension [51].

Figure 1-17: Schematic diagram of particle concentration and their deposition on the membrane. $C_F$, $C_B$ and $C_P$ are the concentration of particles in the feed, boundary layer, and permeate sides, respectively [Diagram by A. Ostadfar].

Filter clogging is characterized as a reduction of permeate flux through the filter and researchers in filtration industry endeavor to do everything to increase the permeate flux. Culfaz et al. investigated on micro-scale of membrane surface; they realized that the twisted shape of the hollow fiber membrane reduces the deposition rate of particles, and it increases the permeate flux [52]. Typically, possibility of maximum permeates is one of most important concerns among of separation issues. As Table 1-2 shows, the permeate (GFR) amount and increasing of that are very vital in hemofiltration and patient situation. Backwashing is known as one of the methods to clean filters, and it helps to
maximize the permeate during the filtration process, which can be used in both dead-end and cross-flow filtrations. In backwashing, an extra pump in permeate pipeline produces reverse flow in the filter.

Backwashing may also moderately eliminate or loosen blockages or clogging on the membrane surface [53]. To show the advantage of the backwashing method, Kuberkar and Davis compared the flux rate in various experiments that used and did not use backwashing [54].

Sondhi and Bhave studied the effect of backwashing on cross-flow filtration of different process flows [55]. They used a yeast solution and realized that this method minimizes membrane fouling. Other similar motivating results have been reported by Matsumoto et al. [56] in cross-flow filtration of yeast, Levesley and Hoare for the recovery of soluble proteins [57], and Cakl et al. in oil emulsion filtration [58].

Camp et al. [59] and Cleasby [60] determined that the detachment of particles in filters using the backwashing method must be mainly caused by shearing forces. This method has not been researched for hemofiltration, and research in this field presents promising novelty, especially under pulsatile flow and cardiovascular conditions.

As mentioned in section 1.5.1, the charge barrier in glomerular membranes plays a significant role in glomerular filtration. This aspect happens due to the electrical charge of glomerular membranes. The technical name of this process is electro -separation or electrophoresis. The history of electrophoresis dates back to 1909 when this phenomenon was discovered by Michaelis [61]. This technique, experimented by Tiselius in 1937, to separate biological matters resulted in incomplete separation [62]. From the 1940s onward, research focused on developing electrophoresis, and this area still holds promise for new application.

Electrical field-flow fractionation is a separation technique used to separate particles and measure parameters of suspensions. This system has been used on variety of biological objects, such as cells, viruses, proteins, lipid emulsions, liposomes, and DNA. Gale et al. used micro-electrical field-flow fractionation to show the applicability of this method to separate biological matters [63].
Lillard et al. used capillary electrophoresis method to separate hemoglobin, and they concluded that this technique can separate hemoglobin variants in a single red blood cell [64].

Pogel and Melin introduced a new electrophoresis chamber to separate bio-particles, such as proteins [65]. They designed a plane channel (two planes) for the electrophoresis device to separate particles. Experiments revealed that geometrical changes, residence time, and concentration of proteins changed the performance of the system.

Using a MEMS process, Doh and Cho offered a continuous cell separation chip using a hydrodynamic dielectrophoresis [66]. They used fixed electrodes and a sinusoidal voltage to separate viable and nonviable cells. The test voltage was $8 \, V_{p-p}$ and the electrode gap was $20 \, \mu m$, which makes a huge electrical field for separation. They believed that the separation clarities of viable and nonviable cells remain for a variety of volumetric flow rate, which is probably correct regarding the huge electrical field.

Grossman and Colburn [67], Khaledi [68], Jandic and Bonn [69], and Li [70] introduced capillary electrophoresis (CE) as a powerful technique for metal ion separation.

Vogt et al. [71] developed detection techniques for capillary electrophoresis as a practical method to analysis metal ions.

Klymenko et al. [72] explained the theory and provide a 2D simulation of ion separation in a microfluidic separation system. The key goal of their research was to examine the theoretical features of this separation technique and how such devices perform in particular when two analytes need to be focused at two different locations along the length of a straight microchannel.

Park et al. [73] showed that a “Y” junction carbon nanotube (CNT) can be used to separate $K^+$ and $Cl^-$ ions from KCl solution. The positive (6, 6) and the negative (5, 5)
CNTs are selective to Cl⁻ and K⁺ ions, respectively. These CNTs were used as the two branches of the “Y” junction carbon nanotube. Park et al. demonstrated that the ion concentration in the separation zone play main roles for the perfect separation. As a result, the concentration of ions in the zone of separation was around two times as high for the imperfect case as for the case of perfect separation.

Regarding electro-cross-flow filtration, Gordon et al. [74] used an electrically enhanced cross-flow microfiltration to treat the wastewater of oxide-chemical mechanical polishing. They realized that the filtration rate with an electrical field is more than when there is no electrical field applied. A similar work was completed by Weigert et al. [75]; they used the same method for pilot scale to separate cristobalite. Bowen and Sabuni [76] and Visvanathan and Aim [77] used electrical field to increase the permeate. Although much research has investigated the use of an electric field to increase the filtration rate, no studies have tried to understand the effects of this field on the separation of ions and proteins in the context of an implantable device.

In fluidic systems, the role of pressure is significant, and, when it drops, the performance of the system decreases. One method to boost pressure in fluid mechanics is by using a pump. Two fundamental types of pump are proposed in fluid mechanics: positive-displacement pumps (PDP) and dynamic (or momentum change) pumps [78].

The PDP powers the fluid along by volume changing. The mammalian heart is good example for a PDP. The mammalian heart is hollow muscle, which pumps blood throughout the vessels by rhythmic repeats. This muscle acts as an energized diaphragm to pump blood, and it can be considered as a natural kind of diaphragm pump. Regarding pumps classification, diaphragm pumps are categorized under reciprocating types of PDPs.

Usually after filtration, the permeate has less pressure in comparison to the feed line, and there is a need to make enough flow for the next stages. One of the best solutions to this problem given the space constraint of an implantable device is the diaphragm pump. To increase reliability, valve-less pumps have better situation in contrast to valve pump because of less parts. Several works have investigated valve-less pumps in macro and micro sizes.
Olsson et al. developed an analytical model for valve-less diffuser pumps [79]. Their model studied flows and pressures inside the valve-less pump, which was simulated by a piezoelectric disk.

Yamahata et al. [80] fabricated and characterized a polymethylmethacrylate (PMMA) valveless micropump. An external electromagnet actuator activated the micropump. They studied the effect of membrane frequency on volumetric flow rate and showed good agreement with Olsson’s theory model.

In 2003, Laser and Santiago [81] reviewed the important advancements of these devices over a period of two decades.

Their article is excellent reference to categorize pumps, especially in miniature sizes. According to their review, Figure 1-18 categorizes the types of diaphragm pumps.

![Figure 1-18: Categorization of diaphragm pumps, regarding drivers (actuators), inlet-outlet (valves), and pumping chamber [Diagram by A. Ostadfar].](image)

Chio et al. [82] simulated and experimented with a piezoelectric valve-less pump. They used a piezoelectric ceramic as an actuator to move the diaphragm. They concluded that geometric characteristics, such as the eccentricity between the piezoelectric disc and chambers and other geometric characteristics, affect the performance of the pump.

Most research on the development of miniature valve-less pumps deal with numerical analysis, simulations, or experiments based on piezoelectric models (Gerlach and Wurmus, [83], Jiankang and Lijun [84], Ullmann and Fono [85], Amos, [86], Li and Che [87], Stemme and Stemme [88], Ullmann [89]).
These miniature pumps are efficient in bio-fluids and drug delivery, especially in implantable systems. As explained before, because of the pressure drop in an implantable artificial kidney, there is a need to use a miniature pump to produce flow for the hemofiltration stages, and the valve-less pump can take on this role. However, the source of energy of these pumps is problematic as all of the introduced pumps use external (electrical) energy to pump fluids, which is not appropriate for implantable systems. An implantable valve-less pump as an assistive subsystem in an implantable artificial kidney for bio-fluid delivery (producing of fluid flow if there is a need or drug delivery such as erythropoietin hormone products) using internal body energy may prove valuable. This approach is explained in Appendix B, as an auxiliary part of the present research.

As an overview, the kidneys of adult humans normally filter 180 L/day of blood, and ~99% of this filtrate will be reabsorbed again by the kidneys as a processing method to balance blood substances. This mechanism permits removal of nitrogenous wastes products (especially urea, ammonium) at high concentrations to minimize loss of water and vital solutes (especially Na & Cl). In case of kidney malfunction, renal replacement therapy achieves this by external filtration & dialysis using dialysate liquid. Replacing this method by an implantable artificial kidney, which can filter 30-60 L/day of blood would be considered breakthrough; doing so powered by the heart (body internal energy) would be spectacular.

Fissel and Roy [90] and Tasnim et al. [91] presented some challenges and difficulties when creating an implantable artificial kidney based on recognized technologies, sciences, and measurable targets.

1.10. The road map of the present dissertation

A cautious review of the relevant literature indicates numerous requirements for new aspects of an implantable artificial kidney. The most important ideas of the current effort are to:
1. Develop analytical and numerical approaches (pores shapes, filter area, and pressure drop) for an implantable separation membrane to separate a part of the plasma from the whole blood in vivo condition.

2. Design and conduct an experimental novel idea to apply backwash method by internal cardiac energy to increase the permeate volumetric flow rate due to reducing of clogging for the first stage of blood filtration.

3. Investigate and experiment the electro (magnetic) separation effects to separate ions (Na\(^+\), K\(^+\)) and protein (Albumin) between two methods: “Y” and cross-flow separations as a pre-separation method.

4. Design and conduct an experimental novel method for a miniature pump that is activated by internal (cardiac) energy as an assistive device inside of the implantable artificial kidney.

The center of attention for the proposed research has been to develop and validate new aspects for an implantable artificial kidney and its applications. The road map diagram for this dissertation is illustrated in figure 1-19. Due to the variety of the investigated issues, one numerical-analytical and three engineered methods have been designed to perform experiments with assorted fluids, materials, and conditions regarding human blood and cardiovascular conditions.

1.1. Scholarly publications

My research activities during my Ph.D. program have resulted in the publications listed below; furthermore, some of my work is ready to submit to relevant journals, but they are not in following list. In this dissertation, I used some of these resources.

- Journal Articles:


- Refereed Conferences:


Ali Ostadfar. Andrew Rawicz , Design and Optimization of Glomerular Membrane in Implantable Artificial Kidney, CMBEC 33 Conference of the Canadian Medical and Biological Engineering Society (CMBES), June 2010, Vancouver, BC

Ali Ostadfar. Andrew Rawicz , Backwashing method to maximize membrane flux in an implantable artificial kidney, North West Biomechanics symposium, June 3-4, 2011 Vancouver, BC
Figure 1-19: Road map diagram of research presented in this dissertation
Reference


Chapter overview

This chapter describes the theoretical background necessary for optimization design of an implantable artificial kidney and provides a basic tool for further design. 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 chapter is 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. In the micro-filtration of fluids, pore geometry, size, and pore shape affect the pressure drop (Pa), fluid velocity (m/s) and flow rate (m³/s). Calculations indicate that a diffuser channel provides a smaller pressure drop than that produced by a straight channel.
2.1. Introduction

As explained in Chapter 1, kidneys filter plasma and remove waste products from the filtrate at rates that depend on the body’s demands. 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 [2].

In glomerular filtration, cells, such as red blood cells (RBCs), white blood cells (WBCs), and platelets, are separated by glomerular membranes; the filtrate continues its path into the tubule of the 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 2-1 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 2-1: Blood constituents (5x10^6 particles/mm^3) [4]

<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 2-2 summarizes the 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 (8000 Pa) due to the parameters of a properly working heart.

Medical machines 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 five 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]. In this study, the hydrodynamic features of a solid, planar membrane with embedded pores are designed 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. 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 [9]. In previous study, we compared the pressure drop in channels with circular, elliptical, and rectangular cross-sections when separating blood cells from plasma [10]. For these shapes, this study analyzed and compared the hydrodynamic flow parameters, namely pressure drop, velocity, and pore aspect ratio. The simplest micro-channels are straight with a linear pressure drop across the channel.
Our work models straight channels (pipes) and diffuser (diverging) shapes to compare their hydrodynamic differences (Fig. 2-1).

Figure 2-1. (Top) 2D schematic of blood filtration and deposition of bio-particles; (bottom left) fluid flow on membrane and inside the diffuser shape pores [Diagram by A. Ostadfar]

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. Figure 2-2 shows that if deposition is nucleated by bio-particle layers inside a pore, the diffuser (diverging) pore shape keeps the channel open more than a parallel channel during operation, resulting longer life. The shape of the diffuser is beneficial not only for the length of life but also for reducing the pressure drop by increasing the effective diameter and area of the channel.
2.2. Pore shape design

The clogging of filter pores can be substantially reduced and the life of the filter extended by using cross-flow filtration [11]. 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 [12]. 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. Images using scanning electron microscopy (SEM) illustrate the inner view of the glomerulus endothelium capillary, which has a variety of oval shaped pores [13].

In an implantable kidney, the filters must operate reliably for at least five years [14]. The diffuser, shown in Fig. 2-3, has an expanding cross-sectional area. 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, either as pulsatile or steady 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 circular. As shown in Fig 2-3, the outlet diameter of the diffuser in the length of “L” is respectively:

\[ D_e = D_i + 2L \tan(\theta) \]  

(1)

where \( D_i \) is inlet diameter of the diffuser element and \( \theta \) is the divergence angle of the diffuser.

![Diagram of circular diffuser pore in membrane](image)

Figure 2-3: 3D geometry of a circular diffuser pore in membrane. \( D_i \) and \( D_e \) are the entrance and exit pore diameters, respectively, \( L \) is pore length (or membrane thickness), and \( \theta \) is the diverging angle [Diagram by A Ostadfar].

Many parameters of fluid flow, such as the flow rate or pressure drop, can be expressed in terms of the fluid mechanics.

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. Pressure drop is the result of frictional forces on the fluid from the side walls as the fluid flows through the tube.

To compare pressure drops for similar conditions, the first assumption is a surface with a fixed area \( A \) and pores that are located in a predetermined distance from each other (Figure 2-4). The distance between pores should be determined based on the strength of material. Considering the strength of material, the thickness of the membrane (or the length of channel, named \( L \) in Figure 4) is assumed to be at least
5 \mu m. As Figure 2-5 shows, the distance between every zone is equal to 1.5 \( D_m \), where \( D_m \) is the diameter at the middle for a diffuser. This distance is dependent on the strength of the material, and it can be changed for different materials.

\[
D_m = D_i + 2 \left( \frac{L}{2} \right) \tan \theta = D_i + L \tan \theta \tag{2}
\]

where, \( D_i \), \( D_m \), \( L \) and \( \theta \) are inlet, middle diameters, pore length, and diverging angle, respectively.

To calculate the number of pores on the surface on a fixed area, \( A \), the following equation can be used:

\[
n = \frac{A}{(1.5D_m)^2} = \frac{A}{(1.5(D_i + L \tan \theta))^2} \tag{3}
\]
The number of pores on the surface is a function of inlet diameter \(D_i\), diverging angle \(\theta\), and length of channel \(L\). Changing these parameters will change the number of pores that will affect the pressure drop.

The general term of Hagen-Poiseuille equation is [15]

\[
\Delta P = R \cdot Q \quad (4)
\]

where \(R\) is the hydraulic resistance in the channel and \(Q\) is the flow rate. According to parallel theory in channels, when we have \(n\) channels with the same shape and size, the total resistance is equal to \(\frac{R}{n}\). Hence, the pressure drop for a surface with area \(A\) can be rewritten as

\[
\Delta P = \frac{R}{n} \cdot Q = \frac{R(1.5(D_i + L \tan \theta))^2}{A} \cdot Q \quad (5)
\]

The resistance \(R\) can be computed for a diverging pore as

\[
R = \int_0^L \frac{128 \mu \, dz}{\pi \, (D_i + 2z \tan \theta)^4} \quad (6)
\]

substituting equations (6) in (5) yields

\[
\Delta P = \frac{Q(1.5(D_i + L \tan \theta))^2}{A} \cdot \int_0^L \frac{128 \mu \, dz}{\pi \, (D_i + 2z \tan \theta)^4} \quad (7)
\]

The equation 7 was derived by author for this design. With some corrections on \(D_m\), it can be used for other design too.

### 2.3. Results and Discussion

An optimization method was used to compute the values of variables in Eq. (7) that minimize the pressure drop for a given flow rate of the filtrate. Before optimizing the function of pressure drop, we needed to determine the fixed values and existing constraints:
• We assumed that the area unit (fixed unit) of the filter is equal to 1 cm² ($A = 10^{-4} m^2$).

• The design flow rate is 60 ml/min (one kidney GFR) for $10^{-2} m^2$ (filter area). Considering $A = 10^{-4} m^2$, the flow rate ($Q$) is equal to $10^{-9} m^3/s$.

• Considering the strength of the material, the length of the channel ($L$) is more than 5 μm.

• Considering the size of particles in human blood (Table 2-3) [17], the deformability of blood cells enables them to pass through spaces as narrow as 3 μm for RBCs and 3.5 μm for WBCs [18]. Also P.J. Abatti shows that the maximum pore radius for RBC separation is 1.5 μm [19]. In order to maintain a proper safety margin to prevent RBCs, WBCs and platelets from passing through the filter, the entrance width of the micro-channel must be equal or less than 1.5 μm.

• We assumed that the diverging angle is $0 \leq \theta \leq \frac{\pi}{4}$ or 45°.

Table 2-3: Blood cell diameters in human whole blood [16]

<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>

As stated, the pressure drop is dependent on three variables: length of the channel ($L$), the inlet diameter ($D_i$), and the diverging angle ($\theta$). We considered all the above constraints and constants to minimize the pressure drop using the pattern search optimization method [20], which is available in Matlab. The minimum pressure drop was obtained for $L = 5 \, \mu m$, $D_i = 1.5 \, \mu m$, and $\theta = 13.46^\circ$. The 3D plot of the pressure drop is shown in Figures 2-6 and 2-7.
Figure 2-6: 3D view of minimization of pressure drop regarding diverging angle and inlet diameter for $L = 5 \, \mu m$. 
Figure 2-7: 3D view of minimization of pressure drop regarding diverging angle and length of pore for $D_i = 1.5 \, \mu m$

Equation 7 can confirm our achieved results as shown in Figures 6 and 7. Regarding Eq.7, clearly

$L \to 0 \quad \Rightarrow \quad \Delta P \to 0$, and $D_i \to \infty \quad \Rightarrow \quad \Delta P \to 0 \quad \quad (8)$
As we have constraints on $L \geq 5 \mu m$ and $D_i \leq 1.5 \mu m$, the optimal values for $L$ and $d$ (considering equation (8)) are $5 \mu m$ and $1.5 \mu m$, respectively. These values are compatible with the obtained result.

Then to analyze the function of pressure drop, the length of the channel was fixed to $5 \mu m$ and the number of pores versus changing values of $D_i$ and $\theta$ was plotted. Figure 2-8 illustrates that the number of pores decreases by increasing $D_i$. In addition, it decreases with increasing $\theta$. Incrementing the number of pores will cause a decrement in pressure drop and vice versa.

![Graph of Number of Pores vs. Diverging Angle](image)

Figure 2-8: Number of pores versus diverging angle ($\theta$) for a variety of inlet diameters.

Figure 2-9 shows the value of hydraulic resistance (Eq. 6) as a function of $d$ and $\theta$. Note that the resistance decreases by increasing $D_i$ and $\theta$. For minimizing the pressure drop, the number of pores should be increased and the resistance should be decreased.
Figure 2-9: Hydraulic resistance \( R (\text{Pa} \cdot \text{s} \cdot \text{m}^3) \) versus diverging angle \( \theta \) (degree) for variety of \( D_i \) (inlet diameter).

As both Figures 2-8 and 2-9 are descending, by equation 5, there must be a point at which \( n \) and \( R \) will balance each other. Figure 2-10 illustrates, the optimized (minimized) points for variety of values of diameters and \( \theta \). Also, the absolute minimum pressure drop happens at \( \theta = 13.46^\circ \) for \( D_i = 1.5 \mu m \). As the figure shows for equal pore length (\( L = 5 \mu m \)) with decreasing diameter of pore, the optimal angle decreases too.
Figure 2-10: Minimization of pressure drop versus diverging angle (θ) for variety of inlet diameters and $L=5 \, \mu m$.

The same computation was completed for a variety of channel lengths instead of inlet diameters to show minimization for different thicknesses in membrane (in case of strength of materials). The following figures show the results. Figure 2-11 and 2-12 illustrate the relationship between the number of pores and resistance, respectively, regarding the diverging angle. The figures show a logical relation between changing the length and the number of pores and resistance. Increasing theta and length of channels decreases the number of pores per unit of area (Figure 2-11) and increasing theta and the length of the channel together create very close resistances, especially after theta=15 degree (Figure 2-12).
Figure 2-11: Number of pores versus diverging angle (θ) for variety of channel lengths and inlet diameter ($D_i$) is equal 1.5 μm.

Figure 2-12: Hydraulic resistance, “$R$” ($\frac{Pa \cdot s}{m^2}$), versus diverging angle “$\theta$” (degree) for a variety of channel lengths and inlet diameter ($D$) is equal 1.5 μm.
Figure 2-13 shows the minimization of pressure drop per unit of area for a variety of lengths. The minimum happens for theta equal to 13.46 degrees and \( L \) equal to 5 \( \mu \)m. As the figure shows for same pore diameter (1.5 \( \mu \)m) with decreasing pore length, the optimal angle increases too.

![Pressure Drop Versus Diverging Angle](image)

**Figure 2-13**: Minimization of pressure drop versus diverging angle (\( \theta \)) variety of lengths and inlet diameter (\( D_i \)) is equal 1.5 \( \mu \)m.

In selecting a material for the membrane, one of the best choices is silicon nitride, which has yield strength thirty-five times higher than titanium and is biocompatible. We calculated the shear stress (parallel to surface) of a membrane with minimum thickness for the maximum human blood pressure. In this scenario, we determined that the shear stress on membrane was 160 MPa, which is smaller than the yield stress of silicon nitride (14 GPa).
2.4. Chapter conclusions

In this chapter, we studied the parameters that minimized pressure drop per unit area in micro-channels with circular cross-sections.

The length of the diverging channel, inlet diameter, and opening angle determined the number of pores, and this number plays the main role in minimizing pressure drop per unit area.

For pores with diffuser shapes, our results illustrate that the lowest pressure drop occurs for a diverging angle where $\theta = 13.46^\circ$ and inlet diameter where $D_i = 1.5 \, \mu m$. With respect to the safety factor and the size of blood cells, the parameters that should be used are inlet diameters between 0.25 $\mu m$ and 0.5 $\mu m$, membranes with a thickness of 5 $\mu m$, and the material should be silicon nitride.
References
3. Effects of pulsatile flow and back washing on plasma flow rate in an implantable plasmapheresis

Chapter overview

This chapter outlines the use of theoretical methods and experimental procedures to determine the dependence of permeate (filtrate) flux on time during cross-flow filtration combined with backwashing method in blood cell separation or plasmapheresis. For the first stage of blood filtration or cell separation, the presented method reduces filter membrane fouling in an implantable artificial kidney. The method proposed in this research uses the body’s internal energy (blood pressure pulsation) to provide enough movement for a diaphragm pump to provide a backwash flow for reducing membrane fouling. We experimentally investigated the consequence of operational parameters, such as cross-flow velocity, Womersley number, pressure difference, and filtration time, on permeate (filtrate) volumetric flow rate. The test characteristics (i.e., velocity and pressure) simulated the human cardiovascular system provided by a cardiovascular pump and a hospital monitoring system. The results demonstrate that the membrane backwashing can maintain the permeate flux at a level nearly twenty percent higher than the long-term flux. In the absence of membrane backwashing, the results show that the Womersley number and pulsatile frequency have key roles in this filtration method. It also reveals that a high Womersley number produces a constant flow rate and a high permeate flow rate.
3.1. Introduction

Tangential flow or cross-flow on a membrane is a standard filtration technique in medical and industrial applications. Cross-flow in a filtration system reduces the fouling rate of the membrane caused by undesired pore-blocking deposits. Therefore, the tangential flow allows the system to have a quasi-stationary permeate flow for a long period [1].

In cross-flow separation, several aspects play important roles, such as velocity, Reynolds number, trans-membrane pressure, membrane resistance, size of particles, particle shape, and surface conditions. A theoretical model was calculated for the geometric features of the pore in an implantable filter case [2]. The results illustrated that the geometry of the filter pores, such as channel length, angle, and cross-sectional shape, affect trans-membrane pressure.

When analyzing and designing in vivo separation or an implantable filtration system using artificial membranes, several factors should be considered: pulsatile behavior, bio-particle deposition on the filter surface, the Womersley number, and self-cleaning mechanisms.

Backpulsing and backwashing are two techniques to reduce membrane fouling. Back pulsing and differences in trans-membrane pressure are recognized as effective techniques for reducing the fouling phenomenon in the separation process. Back pulsing is a technique for membrane cleaning which periodically reverses trans-membrane pressure. During trans-membrane reversal, the filtered fluid is pushed back through the membrane to the feeding channel. Backwashing is another method for membrane cleaning used in technical literature [3]. In backwashing, the flow in the membrane is reversed to remove particles from the surface of the membrane, but with lower pressure in comparison to back pulsing.

Vigneswaran and Nakatsuka [4, 5] studied and experienced high effectiveness and performance of backwashing in water treatment, its dependence on backwashing pressure, and its frequency. Kennedy [6] reported on the cross flushing (a sudden increase in tangential flow) of a hollow fiber ultra filtration method and realized that the backwashing efficiency was highly dependent on backwashing pressure and time.

In biological systems, cross-flow microfiltration is an essential form of filtration to separate bioparticles from biofluids. Most of these bioparticles contain mostly water and they are considered as deformable objects. Some researchers approximate them as inflexible particles to simplify calculations [7].
Solomon et al. [8] demonstrated the practicability of continuous plasmapheresis flow in a micro-porous membrane. Onishi [9] et al. introduced a new type of hydrophilic membrane for blood plasma separation. Meares and Page [10] reported the relative effects of oscillatory (pulsatile) flow, such as pressure, periodic time (frequency), and flow rate, in highly porous membrane filtration.

The cross-flow filtration and pulsatile flow play key roles in the transportation of bio-fluids in the human kidney and the hemodialysis machine. In a kidney, whole blood passes through the glomerular capillaries and plasma penetrates into Bowman’s capsule through endothelium wall pores [11]. This filtration is performed by cross-flow separation in the capillaries [12], see Figure 3-1.

Figure 3-1: Schematic of filtration barrier. CL: capillary lumen; CB: cell body of a podocyte. Note the slit diaphragms bridging the floor of the filtrations slits (arrows) [Diagram by A. Ostadfar].

In the dialyzer of a hemodialysis machine, the same mechanism transfers waste and toxic products from the blood to the dialysate, Figure 3-2.

In this chapter, we present a novel method to increase permeate flow rate during cross-flow filtration to separate bio-particles using an implantable artificial membrane. To better understand the separation phenomena, we modeled and evaluated experimental results for the hydrodynamic performance of pulsatile flow and backwashing of the permeate on the membrane.
3.2. Theory and modeling

Whole blood behaves in a Newtonian or non-Newtonian manner depending upon the diameter of the vessels and the shear rate of the blood flow. Generally, it behaves as a Newtonian fluid when the shear rate is greater than $100 \text{ s}^{-1}$ [13] or as non-Newtonian fluid in human body vessels smaller than $100 \text{ µm}$ [14]. In the case of Newtonian and incompressible fluid, the flow satisfies the Navier-Stokes, linear viscosity, and continuity equations Eqs. (2-4) [15]. These equations show theory and govern condition for the fluid.

The Navier Stokes, viscosity, and continuity equations have the form:

$$\rho \left( \frac{\partial v}{\partial t} + v \cdot \nabla v \right) = \nabla \cdot \tau - \nabla P \quad (2)$$

$$\tau = \mu \cdot \gamma \quad (3)$$

$$\nabla v = 0, \quad (4)$$

where, $v$ is the three-dimensional velocity vector, $t$ is the time, $P$ is the pressure, $\rho$ is the density, $\tau$ is the stress tensor, $\mu$ is the viscosity, and $\gamma$ is the shear rate.

One of the best models for non-Newtonian fluids, such as blood, is the Quemada model. The following equation, known as the Quemada equation, accurately fits blood information over a very wide range of shear rates [16],
\[ \eta_a = \eta_o (1 - 0.5 \text{kHct})^{-2} \]  
\[ k = \frac{k_0 + k_\infty r^{0.5}}{1 + \gamma r^{0.5}} \]
\[ \gamma_r \equiv \frac{\gamma}{\gamma_c}, \]
where, \( \eta_a \) is the apparent viscosity, \( \eta_o \) is the Newtonian suspending fluid viscosity, and the three constant parameters, \( k_0, k_\infty, \) and \( \gamma_c \), are Hct (hematocrit) dependent [17].

The human heart plays the main role in the cardiovascular system. It provides the oscillatory (pulsatile) flow to transfer blood to the organs, and the flow profile depends on the frequency of oscillation, \( \omega \) (where) \( \omega = 2\pi f \), and the radius, \( r \), viscosity, \( \mu \), and density, \( \rho \), of the blood. These variables taken together form a dimensionless parameter called the Womersley's number, \( \alpha \), as shown in Eq. (6) [18] It is an expression of the pulsatile flow frequency in relation to the viscous effects. The Womersley number is an important aspect to consider in the vascular system for experimental study,

\[ \alpha = r \frac{\rho \omega}{\sqrt{\mu}} \]  

Some researchers use another dimensionless parameter in hemodynamics, the Reynolds number; It is an expression of the inertial forces to viscous forces. This number for flow in the human body, even in large diameter arteries, is generally much lower than 2000 (laminar flow<2000) [19]. We believe that the Womersley number is more important than other dimensionless numbers in the cardiovascular system because of pulsatile behavior of blood flow.

The flow waveform generated by the heart is complex, the flow profiles can be calculated in terms of Bessel functions [16].

### 3.3. Separation process

In the filtration system, the particles may foul the membrane by blocking the pores and can shape into cake layer on the surface of the membrane in further growth [20]. Several techniques can be used to remove particles or prevent them from settling on the filter. One technique to reduce membrane fouling is backwashing [21, 22].
method involves the reversing the flow of the permeate by applying pulses of higher pressure on the permeate side than on the feed side of the membrane [20].

Figures 3-3 and 3-4 show the body of the membrane and the separation system. The following sections discuss the three regions of the filtration arrangement.

Figure 3-3: Schematic of filtration and backwash; region #1 is the solution line; region 2 is the porous membrane; and region 3 is the permeate channel and backwash diaphragm. The arrows show the direction of flow [Diagram by A Ostadfar].

Figure 3-4: Schematic of experimental setup [Diagram by A Ostadfar]
3.3.1. The governing equations in the feed channel (Region-1),

Equations 2-6 describe the Newtonian and non-Newtonian behaviors of bio fluids.

3.3.2. The governing equations in the porous wall (Region-2)

Darcy’s Law comprises the description of flow through a porous medium. It is expressed by

\[ J = \frac{-K}{\mu_p} \nabla P, \quad (7) \]

where \( J \) is the flux (discharge per area, with unit of \( \text{m}^3/\text{m}^2 \text{s} \)), \( K \) is the permeability tensor, \( \mu_p \) is the plasma viscosity and \( \nabla P \) is the pressure gradient [23]. The variation of the filtration rate with trans-membrane pressure, \( P_{tm} \) (defined as the mathematical average between inlet and outlet pressure minus the permeate pressure) follows a regular pattern, increasing almost linearly with low \( P_{tm} \) before attaining a plateau for filtration flow rate. In regular cross-flow filtration, the plateau is reached at a low pressure on the order of 70-100 mmHg which increases with increasing shear rate [24, 25]. Researchers in this field have correlated the membrane separation flux \( (J) \) to the shear rate \( (\gamma) \) at the membrane surface for rigid and bio particles [26, 20]. All correlations have the common shape \([21, 26, 27, 29] \),

\[ J \propto m \gamma^n \quad (8) \]

where \( m \) and \( n \) are the regression constants or fitting parameters, depending on the system.

In Region-2 with a periodic backwash flow, two flow directions should be considered: the regular filtration flow and the backwash. The backwashing mechanism for cross-flow separation is a periodic operation in which a cycle of forward separation of duration \( t_F \) is followed by a cycle of backwashing of duration \( t_R \). During backwashing, back flow eliminates the biolayer from membrane surface. The net permeate flux, \( J_{NET} \), during one cycle obeys both the filtration as well as the backwashing mechanism, an it can be described by [20]

\[ J_{NET} = \frac{\int_0^{t_F} J_F dt - \int_0^{t_F + t_R} J_R dt}{t_F + t_R}, \quad (9) \]
Eqs. 7 and 8 can be used to calculate $J_F$ and $J_R$ to explain filtration process with the back-washing feature.

3.3.3. The governing equations in permeate channel (Region-3)

In Region-3, as shown in Fig. 3-3, Eqs. (10, 11) define the rules for diaphragm pump and the diffuser/nozzle shape for the outlet which introduces the concept of a valve-less pump. The diffuser, a flow channel with a gradually expanding cross section, is the key element in the valve-less pump (Fig, 3-3). The nozzle works in the opposite direction with a converging cross section [28]. During supply and pump modes, the nozzle and diffuser change their duties, see Figure 3-5.

![Diagram of Nozzle and Diffuser](Diagram by A Ostadfar)

This pressure is produced by oscillatory (pulsatile) movements of the diaphragm to push back the permeate flow as a backwashing flow on the membrane. Additionally, the diaphragm movements push forward the liquid in the permeate channel after the diffuser/nozzle element for the next process.

The flow rate of a diaphragm pump during its pump phase is equal to the product of the stroke $\Delta V$ and the operating frequency ($f$) [30]

$$Q_P = f \cdot \Delta V \ , \tag{10}$$
where $\Delta V$ is equal to the backwashing flux ($J_R$) through the membrane plus the flow rate from the output nozzle $q_n$.

$$\Delta V = J_R + q_n,$$  \hspace{1cm} (11)

The vital aspect in this process is a phase shift between regions 1 and 2 (the diaphragm). To produce this shift, we can put a throat in inlet of one of these regions to make the phase shift between two sides. Of course an optimization will be required for this aspect.

3.4. Material and Methods

The Polyethersulfone (PES) membrane is a hydrophilic membrane constructed of pure polyethersulfone polymer. PES membrane filters are designed to remove particles during general filtration. Their low protein and drug-binding characteristics are suited for use in life science applications. The optimum range of pore diameter prefers to be between 0.25 – 0.5 $\mu$m. The mean pore size of the test membrane (PES) was 0.45 $\mu$m, see Figure.3-6, and area was $35 \times 10^{-4} m^2$. The membrane module (cartridge) was produced from an ACRYLITE FF acrylic sheet and its design provided cross-flow and back-washing on the membrane.

Because bovine blood is more readily available and more cost-effective to use, it was used rather than human blood for testing and experimenting. The average diameter of bovine red blood cells is around 6$\mu$m, and it simulates similar test conditions compared to human red blood cells with a 7$\mu$m diameter. Freshly collected blood was anticoagulated with acid-citrate-dextrose (ACD, USP) formula.
A COBE Century Perfusion Pump (COBE Cardiovascular Inc.) was used to provide the pulsatile flow in circulation. This pump is intended for use in cardiopulmonary surgical procedures or as an arterial pump in operating rooms. The test circuit was equipped with blood pressure transducers, PX272 (Edwards life sciences LLC), to measure the fluid pressure. The HP component monitoring system, 54S model (Hewlett Packard Company), was used to monitor and record test outcomes.

After the membrane had been placed in the membrane module, the blood was circulated in the test circuit by the COBE pump. Under pulsatile flow conditions, the pump’s rotational speed and average flow rate were varied from 30 RPM to 110 RPM and 0.22 LPM to 0.81 LPM, respectively. The flow pressure was measured and recorded by pressure transducers and a HP monitoring system. The flow rate of permeate was measured by collecting a volume of permeate during a specific time period.

Two types of flux measurements were performed: the cross-flow filtration using bio-fluid (bovine blood) without backwashing, and cross-flow filtration with backwashing. Flow parameters, such as pressure, permeate flow, and the Womersley number, were determined for a range of RPMs (pulse-rate).

3.5. Results and discussion

3.5.1. Measurement errors

Several kinds of errors influence the accuracy of the results obtained in this research, such as environmental errors (temperature fluctuations), device errors (pressure sensor and pump) and human errors (reading and calculating). According to the COBE pump manual, the flow rate readout accuracy is ±10% or ±0.01 LPM, whichever is greater [31]. The error in the Pressure Transducers is ±1.5% of reading or ±1 mm Hg, whichever is greater [32]. In the volumetric measuring tool, the error is ±0.5% at 20°C.

With regards to the evaporation error, Bansal et al. suggested a correlation based on the saturated pressure and the velocity of air [33]. For ambient conditions, the calculated evaporation rate (error) of the permeate during the test time was less than $0.5 \cdot 10^{-6}$ L or 0.012% of the permeate volume.

3.5.2. Flow and flux analysis
The relationship between the Womersley number (Eq. (6)), hydraulic diameter of the channel, and the range of heartbeats (pump frequencies) for blood, plasma, and water are shown in Figure 3-7. The thick lines designated with letters are blood (B), plasma (P) and water (W) for a heartbeat of 100 beats per minute; the dashed lines show similar fluids for a heartbeat of 80 beats per minute. As the figure indicates, for these fluids, the dimensionless pulsation character (Womersley number) for plasma fluid is between blood and water, with a slight tendency to water fluid.

When $\alpha$ is small, the pulsatile effects on the flow profile are slight, and the flow is quasi-steady. At larger $\alpha$ values, the velocity profiles are blunted in the interior of the tube, and the fluid velocity has large differences in amplitude near the wall (Figure 3-8). Figure 3-9 presents the experimental results of flow rate versus time during microfiltration with and without backwashing.

![Figure 3-7: Effect of radius on the Womersley number in whole blood, blood plasma and water for a variety of heartbeats (Hz)](image-url)
Figure 3-8: Velocity profiles for Womersley numbers, 3, 6 and 12, simulated by MATLAB software
(The ordinate is vessel diameter and the abscissa is longitudinal cross section)

Figure 3-10 shows a comparison between filtration methods and the permeate volume. The permeate flow rate, with and without backwashing, depends on RPM. In other words, increasing the RPM in vitro or the heartbeat in vivo will result in an increase of the volumetric flow rate of permeate that is proportional to blood flow pressure. More variations in the pulsatile pressure has a positive effect on the filtration of the permeate. Under the same conditions, the volume of the permeate in the backwash method is around twenty percent more than without the backwash filter. This percentage is vital for people who have renal problems.
Figure 3-9: A permeates flow rate evaluation between backwash (dash line) versus without backwash (solid line) methods, regarding time for blood separation and oscillatory flow in RPM 90.

In staging a system and action plan for chronic kidney disease, five stages are used to describe kidney conditions. In this system, for Glomerular filtration rates less than 90 ml/min, the patient has a renal problem; with a filtration rate less than 15 ml/min, the patient needs to be under treatment by a dialysis machine [34]. This staging system verifies the importance of the twenty percent increase of the permeate volume which the backwash produces. The effect of the pressure increase in the blood channel (feeding line) on permeate flow rate is shown in Figure 3-11. As depicted in the figure, an increase in the inlet pulsatile pressure results in increase of the flow rate of the permeate. The figure reveals that, during similar test conditions, increasing the gradient of the permeate flow rate in the backwash method is more than without backwash.
Figure 3-10: A comparison between filtration methods and the permeate volume regarding RPM. The volume of the permeate using the backwash method is twenty percent higher than without the backwash filter under the same conditions.

Figure 3-11: Effects of pressure on volumetric flow rate. Regarding mean arterial pressure (MAP), increasing the MAP will cause the flow of the permeate in backwash method to rise 1.1 to 1.3 times more than without backwash.

Considering $J \propto m^n$ from Section 3.3.2 and the type of procedure, researchers have correlated a variety of numbers for $m$ and $n$. 
Figure 3-12 shows the experimental outcomes of microfiltration flux for the present work compared with formerly reported assessments. The following correlation was acquired for the relationship between the flux amount and the shear rate for cross-flow filtration for frequencies less than 2 Hz, which correlates to a heartbeat that is less than 120 beats per minute):

\[ J = 1.01 \times 10^{-5} \gamma^{0.43} \quad (12) \]

where \( J(\text{m}^3/\text{m}^2\text{s}) \) is the plasma flux and \( \gamma \) is the shear rate on the membrane surface.

![Graph showing comparison of effect of shear rate on filtration flux](image)

Figure 3-12: Comparison of the effect of shear rate on filtration flux obtained for three different research works (present work, Cakl [21], Gomma [26]). Increasing the shear rate will cause the filtration flux to rise.

### 3.6. Chapter conclusion

This research was performed in order to study the cross-flow microfiltration of whole blood. It introduced a new method of using the internal energy of blood circulation as a self-cleaning mechanism for an implantable cell separation system to increase permeate flow rate.
We used a cardiovascular pump to generate pulsatile flow on a 0.45 µm Polyethersulfone (PES) membrane. For similar experimental conditions, the results illustrated that the permeate flow rate and its volume were higher in a system using backwash compared to a system without backwash. The increase in the permeate flow rate was 20% by the end of experiment for the backwash method.

The effect of the oscillatory parameter on the permeate flow rate was studied. Increasing the RPM and pulsatile character in the fluidic setup resulted in an increase of permeate rate. This research found a new correlation between filtration flux and shear rate in oscillatory flow for low frequencies (a heartbeat of 120 beats per minute or \( f < 2 \) Hz).

The efficiency of the filtration process is multi-facetted, and optimization of this process has not been performed yet. However, from the obtained results, we can expect that the process optimization would largely improve the life of the filter membrane. In addition, fluidic resistance of system (implantable artificial kidney) must be minimized to assure enough blood flow for separation especially in case of low blood pressure reaction in main arteries such as the mechanism for dilating main arteries when arterioles blood flow increases the endothelium-derived relaxing factor (EDRF).
References


4. Ion and protein separation

Chapter overview

This chapter outlines the design and testing procedures for electromagnetic separation of electrolytes and proteins in bio-fluids such as blood. It shows the use of experimental procedures to determine separation dependence on voltage (electro-separation) in a Y splitter and cross-flow electro separation. We investigated experimentally the effect of operational parameters, such as voltage and filtration methods, on bio-fluids, such as sodium and potassium electrolytes and Albumin proteins. The experiment simulated the human cardiovascular system using a cardiovascular pump and two filtration modules (Y and cross-flow) for electro filtration. Electrodes and a metallic mesh were used as an electrical field operator to separate charged particles. Several electrical fields from 0.83 Kv/m to 10 Kv/m were produced by a power supply. The results demonstrate that with an increase of voltage on the electrodes and electrical field, the rate of separation increases for both ions and protein. The results illustrate that the performance of cross-flow electro-separation is better than the Y splitter method. The outcomes show that, in implantable electro-separation, the direction of fluid flow on electrodes or the metallic mesh and the electrical field play the main role in electro-separation.
4.1. Introduction

Electrophoresis is the motion of charged particles relative to a fluid under the influence of an Electric field. Ferdinand Frederic Reuss observed the electrokinetic phenomenon for the first time in 1807 [1]. He realized that the application of an electric field caused clay particles suspended in water to move. This phenomenon occurs because of the presence of a charged interface between the surface of the particles and water.

Michaelis discovered and used the term electrophoresis in 1909 [2]. Other scientists, such as Tiselius [3] and Hjertén [4], continued their research on electrophoresis in biological matters. The electrical field is worth considering, is given various current applications: optical tweezers [5], sorting of magnetic activated cells, [6,7] centrifugation [8], filtration,[9] and electrical field-based manipulations and separations [10,11,12], which are commonly used in research laboratories for manipulation, and separation of bio-particles and macromolecules, the electrical field is worth considering [13].

According to the nature of bio-particles, several types of electric fields can be applied to manipulate them:

(1) A DC field for electrophoresis (EP) of charged bio-particles [11];
(2) A non-uniform AC field for dielectrophoresis (DEP) of polarized (charged or neutral) bio-particles [12,14,15 and16];
(3) Combined AC and DC fields for manipulating charged and neutral bio-particles [17].

Figure 4-1 illustrates the electro-filtration principle (electrophoresis) and particle manipulation by Electric field. The figure shows the particle's electrical charge and location of the electrodes. The particle will move towards the oppositely-charged electrode. In this chapter, we investigate the use of a DC electric field for manipulating ions and protein in a fluidic circuit to separate them as an assistive or pre-filter method in blood filtration systems, such as an implantable artificial kidney.
Electro-separation (Electrophoretic separations) is based upon the fact that the electrical force \( F \) on a charged particle in an electrical field \( E \) is proportional to the charge of the particle \( q \), or
\[
F = qE \quad (1)
\]

In addition to this force, the charged particle is affected by several forces: drag \( F_d \), lift (buoyant) \( F_l \), and gravity \( F_g \). Balancing of these forces define trajectory of particle and performance of separation. Figure 4-2 shows these forces on the particle in a moving fluid.

\[ F_d \text{ and } F \text{ play the main role in this free body diagram and create more of an effect on particle trajectory compared to other forces.} \]
If magnets are used to separate particles, the method is known as magnetophoresis. For this method, equation (1) will become
\[ F_m = q (v \times B) \quad (2) \]
where \( v \) is particle’s velocity, \( \times \) is the cross or vector product, and \( B \) is the magnetic field vector.

Regarding the right-hand rule, pointing the thumb in the direction of the moving positive charge (\( v \)) or positive current and the fingers in the direction of the magnetic field (\( B \)), the resulting force (\( F \)) on the charge points outwards from the palm. The force for negatively charged particles is in the opposite direction.

The heart produces a pulsatile flow to transport blood and bio-fluids to the body’s organs. A single dimensionless parameter called the Womersley number [18], is an expression of the pulsatile flow frequency in relation to the viscous effects. The Womersley number is a significant fluidic factor to consider in the vascular system for experimental study.

Reynolds number is another dimensionless number in fluidic systems, which is very popular among engineers. This number helps to predict the transition between laminar and turbulent flows. Generally, this number in the human body is less than 2000 (laminar flow<2000).

4.2. **Method and material**

Pulsatile pump, monitoring system, and power supply:

The COBE Century Perfusion Pump (COBE Cardiovascular Inc.) was used to provide the pulsatile flow in circulation. This pump is intended for use in cardiopulmonary surgical procedures or as an arterial pump in operating rooms. The test circuit was equipped with blood pressure transducers, PX272, (Edwards Lifesciences LLC) to measure flow pressure. To provide a variety of voltages, a DC power supply (Heath, 2718 tri power supply) was used. A flame photometer (FLM3 flame photometer) was used to measure the concentration of ions (Figure 4-3). FLM3 is designed for fast and accurate quantitative determination of Na and K in serum/plasma and urine. It burns samples in its chimney to produce light, and it measures the type and concentration of ions by several photocells which detect wavelength and intensity of light. To measure
protein levels, the Qubit 2.0 Fluorometer was used (Figure 4-4). The Qubit 2.0 employs specifically designed fluorometric technology, using Molecular Probes dyes, that bond to target molecules to measure their concentration.

Figure 4-3: Flame photometer [Photo by A. Ostadfar]

Figure 4-4: The Qubit Fluorometric Quantitation System [Photo by A. Ostadfar]
4.2.1 Operation Solution:

For test solution, we simulated the human levels of sodium and potassium electrolytes using NaCl and KCl. The average concentration (Na 140 mmol/L and K 5 mmol/L) was very close to normal human conditions. Also, for the separation tests, we provided Bovine serum albumin (BSA) to create a viscous fluid with Albumin protein. The average concentration of the BSA in the solution was 4 g/100 ml.

4.2.2 Separation modules:

As previously mentioned, in this work, two methods were used for separation: the Y splitter method and the cross-flow separation method. In the Y splitter, the solution flow passes through the splitter and two electrodes, which are installed on the splitter wall, produce electrical field to change trajectory of particles, (Fig. 4-5). The electrodes are isolated by Teflon, and they are connected to a DC power supply to provide an electrical field. Two neodymium magnets (NdFeB, Grade N52) were also used to provide a magnetic field for "Y" magneto-separation. These magnets are very powerful, and their $Br_{max}$ (Residual Induction) is around 14800 Gauss or 1.48 Tesla. Static magnetic fields less than 2 Tesla produces no substantial harmful bio-effects on human tissues [19].

Figure 4-5: Schematic of a Y splitter used to separate particles using an electrical field
[Diagram by A Ostadfar]

In cross-flow electro-separation, the flow passes over a charged metallic filter (mesh), and this electrical charge repels the like-charged particles from the mesh. The
result is a different concentration of charged particles in the permeate channel in comparison to the inlet solution. Figure 4-6 illustrates electro-separation using the cross-flow method. As the figure shows, because of the electrical charge (negative) on metallic filter, the concentration of similarly charged particles after the mesh is less than in the main solution. This method is very similar to kidney glomerulus filtration in a Bowman capsule, which filters whole blood from plasma by electromechanical separation as well it is similar to nephron tubule to transport charged substances by electrochemical transportation. The cross flow fluids are electrolyte and protein solutions. Figure 4-7 shows the metallic mesh and its wire diameter.

Figure 4-6: Schematic of cross flow electro separation to separate electrolytes (ions) and protein solutions [Diagram by A Ostadfar].

Figure 4-7: Metallic mesh as electrode for electro-separation. The unit bar is 100 micrometer [Photo by A Ostadfar].
Figure 4-8 shows the schematic of the test setup and the arrangement of the system. The Cobe pump produces a pulsatile flow for the system, and the DC power supply generates the voltage for the electrodes and the meshes that separate ions and proteins. The Y splitter and cross-flow separator are located in the separation module. For consistency between tests, the pump speed was always one RPM, resulting in a flow rate of 2 ml/min.

Figure 4-8: Schematic showing the setup for the separation experiment [Diagram by A Ostadfar]

Figure 4-9 and 4-10 show the separation modules, the Y splitter, and the cross-flow electro- filtration, respectively, used in the experiment.
4.3. **Results and discussion**

Measurement error:

Calibration is one of the most important methods for measurement devices, especially in chemical facilities, to reduce the degree of error. In this research, devices, such as the flame photometer, were calibrated before testing using reference solutions to obtain level of errors. The devices were then calibrated according to these errors. This calibration allows for reliable results while minimizing error. The measurement errors for
the flame photometer and the Fluorometer devices were + 0.3% and +0.1%, respectively.

The measured error for the power supply was ± 1%. With regard to using microfuge tubes to collect samples, no evaporation error occurs during the tests.

Ion separation:

Several types of voltage measurements were performed to produce the electrical field needed for electro-separation. Figures 4-11 through 4-19 illustrate the experimental results using the methods described above for separating ions. Figure 4-11 and 4-12 show the results for the Y splitter. As the figure shows, compared to the main solution (feeding line), increasing the voltage and electrical field results in a concentration of Na and K ions at the outlet N (negative electrode side) that is greater than the concentration P (positive electrode side). In these figures, C denotes the control fluid. For zero voltage (v=0), we used only the magnets (M) to produce a magnetic field for the separation. This condition is shown as v=0, M in the figures. As Figures 4-11 and 4-12 show, the amount of separation caused by a magnetic field is less than the electrical separation method. This result, when compared to the electrical separation, proves that the magnetic method is not appropriate for separating charged particles.

Figure 4-11: Sodium concentration in Y splitter electro-separation

Figure 4-11: Sodium concentration in Y splitter electro-separation
Figure 4-12: Potassium concentration in Y splitter electro-separation

Figure 4-13 and 4-14 illustrate the results of cross-flow for ion electro separation. For both sodium and potassium, the figures show that the separation rate is increased by increasing the voltage or electrical field between the two electrodes. The results demonstrate that the trajectory force on charged particles has a linear relationship to electrical field. The open area in of the mesh filter was considered to be close to the cross-sectional area of the Y splitter channel to perform similar test conditions. The data in the figures demonstrate that the performance of cross-flow electro-separation is better than the Y splitter method.
Protein separation: Several types of voltages and electrical fields were tested for protein separation using both the Y splitter and cross-flow methods. In the Y method, which was used for the ions experiments, the concentration of the protein increase at
one outlet and decreases at the other outlet. Figure 4-15 shows the results for the Y separation method.

In the experiment using the cross-flow method, the metallic meshes were charged by negative voltages (from the filter side) and positive voltages (from the wall side). Figure 4-16 shows that, by increasing the voltage and electrical field between the meshes, the rate of albumin filtration decreased in the permeate side (the permeate mesh was negatively charged). This result means that the proteins were repelled from the mesh surface with a negative charge, and they preferred to continue their way by tangential flow on the mesh in the direction of the outlet. The results follow the trend for these separations. Figure 4-15 and Figure 4-16 illustrate the performance of the separations for a Y splitter and cross-flow electro-filtration, respectively.

![Figure 4-15: Albumin concentration in Y splitter electro separation](image)
Technically, the performance of the cross-flow filtration is better than the dead-end filtration techniques, and our experiment confirms that the cross-flow electro-separation has better performance in comparison to the Y separation method.

Figures 4-17, 44-18, and 4-19 show a comparison between cross-flow electro-separation and Y splitter methods. As Figure 4-17 and 4-18 illustrate, the Y separation method needs a greater electrical field (~3 fold more) to have the same range of ion separation. For instance, in Figure 4-17, to have ion separation in the range of 146.5 mmol/L and 147 mmol/L, the cross flow method and the Y method need 3.3 Kv/m and 10 Kv/m, respectively. In the other word, the cross-flow electro-separation has better performance for ion separation compared to the Y separation method.
Figure 4-17: Graph comparing cross-flow and Y electro-separations for sodium

Figure 4-18: Graph comparing cross-flow and Y electro-separations for potassium

Figure 4-19 shows an evaluation between cross-flow and Y separation for albumin. Like the previous figures (Figure 4-17 and Figure 4-18), this figure emphasizes the better performance of cross-flow separation versus Y separation. In this experiment, the metallic mesh was charged by negative (filter side) and positive charges. By increasing the voltage and electrical field on the filter side of the mesh, the rate of albumin filtration decreased. This decrease means that the proteins were repelled from
the mesh with a negative charge and they preferred to continue their way by tangential flow.

Figure 4-19: Comparison graph between cross flow and Y electro separations for Albumin

4.4. Chapter conclusion:

This research was performed to study the separation of electrolyte (ions) and bio-fluid (proteins) solutions using electromagnetic fields. We used a cardiovascular pump to generate pulsatile flow in a fluidic system in order to simulate pulsatile behaviour of bio-fluids in the human body. The results show that the performance of electro-separation is superior in comparison to magnetic separation. We introduced and tested two methods, Y splitter and cross-flow separation, to use electrical energy for pre-separation or separation in an implantable separation under pulsatile flow.

The resulting performances of both methods were compared to each other to identify the superior technique.

The results illustrate that both methods can be used to filter (or pre-filter) ions and proteins. Regarding the graphs and results, the performance of cross-flow separation is more than the Y splitter method due to the smaller electrical filed that is needed to separate charged particles. As the results show, one cycle of separation separates a few percent of charged particles. For better performance, designers can replicate these methods to produce several stages. This research and the experimental
results are useful to researchers and designers as it allows them to have a better understanding of this type of separation techniques. Future researchers and designers can select the best structure for an implantable separator as an implantable artificial kidney.
References


5. Conclusions and future works

This research studied the design and provided experimental proof for selected functions of an implantable artificial kidney. The foci of this dissertation were on studying several functions of implantable blood filtration, such as pore and membrane design, backwash method, ion and protein separation, valve-less implantable pump (appendix) with the aim of helping researchers and designers to create a durable and reliable implantable artificial kidney in the future.

5.1. Conclusions and contributions

The key contributions of the present dissertation can be summarized as follows:

1. Analytical and numerical approaches for pore shape, filter area, and pressure drop were developed for an implantable separation membrane to separate blood cells from whole blood in vivo condition. When designing pores, to reduce pressure drop in the system, the best method is to use diverging pores. Implantable devices have size limitations, and we realize that the diverging angle ($\theta$), length of the channel, $L$ (or membrane thickness), and the inlet diameter ($d$) have effects on the membrane area. Thus, a greater diverging angle results in larger membrane and a bigger device. Considering pressure drop per unit of area as an objective function and the constraints of $L \geq 5 \mu m$ and $d \leq 1.5 \mu m$, the minimum pressure drop happens when $\theta = 13.46^\circ$ and the membrane thickness equals to $5 \mu m$. Considering the normal range of blood pressure for a person and the shear stress the membrane can withstand, one of the best materials for membrane in this work is silicon nitride.

2. A novel method was designed and experimentally evaluated by applying internal cardiac energy to increase the permeate volumetric flow rate for the first stage of blood filtration. This study investigated the cross-flow filtration of blood. As explained in chapter three, we introduced a new technique to use the
internal energy of blood circulation as a self-cleaning mechanism to enhance the permeate flow for an implantable cell separation system. We used a cardiovascular pump to generate pulsatile flow on a separation membrane. During similar experimental conditions, the results demonstrated that the permeate flow was higher (around 20%) in the backwash system compared to a system without backwash.

3. A methodical experimental approach was developed to investigate the electro (magnetic) separation effects for pre-separating ions (Na⁺, K⁺) and protein (Albumin) using two methods: Y and cross-flow separations. These experiments led to the development of using electrical energy for pre-separation or separation in an implantable device under pulsatile flow. In this method, we used a cardiovascular pump to generate pulsatile flow in a fluidic system to simulate the pulsatile behaviour of bio-fluids in the human body. The results demonstrated that both techniques can be used as a filter (or pre filter) to separate ions and proteins; however, the performance of cross-flow separation is better than the Y splitter. To provide full separation, designers can use a cascade (replication) technique to create several stages for enhanced separation.

4. We designed a novel miniature valveless implantable pump that is activated by internal (cardiac) energy. This device is to be used inside of an implantable artificial kidney (see appendix B). Due to the pressure drop that occurs during separation, also delivery of biofluid or drug in vivo, this pump was desiged and tested to produce enough flow for the fluids. Experiments studied the technical characteristics of an implantable valveless pump to transport bio-fluids or drugs in vivo, and it used pulsatile circulation energy as an internal energy source to power the pump. Numerical modeling and experimental tests were compared against each other. The results illustrate that the roles of a small diameter and angle in the nozzle/diffuser element are significant for the embedded pumping system’s efficiency of circulation. In the case of blood delivery, reducing the amount of mechanical parts, such as valves, in the design procedure decreases the shear stress on the blood cells membrane; thus the probability of hemolysis is largely reduced in the pumping process. As
a parallel work with the implantable artificial kidney, this novel idea is suitable for practical applications in vivo, such as a drug delivery pump or as a part of implantable devices for other purposes.

The location of an implantable artificial kidney is essential because the original kidneys are not regularly removed unless they are causing severe trouble, such as frequent infections, inordinately high blood pressure, or they are significantly enlarged. If the original kidneys are not removed, the implantable artificial kidney is located in a different place than the existing kidneys. Up to this point, no complete implantable artificial kidney exists; therefore, the size and pressure drop inside of the system has no empirical data to base a suggested location of such a device.

However, theoretically, there are two possible locations for such a device. For the case of two original kidneys plus an implantable kidney, one of the best locations is in the iliac fossa, where the artery and the vein of the iliac can supply blood for the device. This location is provides enough space for the device, and it also provides enough blood pressure (around 100 mmHg mean arterial pressure) for the device. A tube can connect to the device to carry urine to the bladder. As a suggestion, the volume (size) of this device for an adult should be approximately 200 ml (kidney shape) to be placed in that location.

If, because of medical troubles, the original kidneys must be removed, the device could be located in same location of the removed kidney, where it can use the original renal artery, vein, and ureter.

Given the fact that an ultimate device has not been developed yet, estimation of total pressure drop in an implantable artificial kidney is not feasible. Therefore, as a reasonable solution, we can consider approximate pressures and vascular resistances in normal kidney (table 2-2) to predict pressure drop in the implantable device. Consequently, total pressure drop in implantable kidney must not exceed ~96 mmHg (~12768 Pa) in an individual with normal blood pressure.

In this dissertation, a variety of numerical models and experimental techniques were applied and developed to study the functions of implantable artificial kidney. The
combination of these developed tools will help designers and researchers create and modify a realistic device in the field of implantable artificial kidneys. The ultimate goal is to help the millions of renal patients around the world.

5.2. Future works

The following guidelines should be considered as extensions of this dissertation:

1. The efficiency of the separation system is multi-faceted, and optimization has not been performed yet. However, from the obtained results, it can be concluded that the procedure for optimizing this system would largely develop the operation time of filter membrane.

2. The effects of hemolysis as a vital parameter must be studied to reduce the risk of blood cell damage in implantable artificial devices. The roughness of the surface, filter pores, and other components introduce shear stress in the implantable artificial kidney. This shear stress is a well known factor that causes hemolysis. Therefore, methodical investigation about this stress will be useful to reduce hemolysis.

3. A reliable manufacturing method needs to be created to produce the diverging pores. This method needs to accurately control the angle of the diverging pores in micro or nano sizes. As mentioned, pore design pays a vital role pressure drop theories.

4. Separation of electrolytes, proteins, nitrogen, and nitrogenous products (as a second stage of separation need to occur in real time in the human body as most vital aspect in implantable artificial kidney. This issue can lead to several types of research in the field.
Appendices

Appendix A

Womersley Number and Matlab code for calculating Womersley numbers and velocities

The Womersley number can be written as

\[ \alpha = r \sqrt{\frac{\rho \omega}{\mu}} \]

where \( \omega \) is the frequency of oscillation (\( \omega = 2\pi f \)), \( r \) is radius, \( \mu \) is viscosity, and \( \rho \) is the density of the blood.

The following MATLAB code was developed by David Wootton at Drexel University [1].
(The code is reproduces here with permission from David Wootton):

WomersleyQWave.m

```
% Calculates Womersley solution for fully developed, periodic laminar flow in a straight tube
% Calculates velocity profiles, and pressure, wall shear stress, and centerline velocity waveforms
% Also produces an animation of the flow profile.
% Developed for Biofluid Mechanics, Mechanical Engineering and Mechanics, Drexel University,
% Philadelphia PA, 19104.
% Copyright David Wootton, March, 2003
%
T = 1; % period, in seconds
a = 0.25; % radius, in cm
% KQ is from workspace, as is KQ0 (DC component of flow)
u = 0.04; % kinematic viscosity, in cm2/s
rho = 1.0; % density, g/ml
ny = 41; % # points in profile (over diameter)
nt = 100; % # time points to calculate over period
nf = size(KQ); nf = nf(1); % # of nonzero frequencies
temp2 = ones(nt); temp2 = temp2(1,:);
```
\[
y = [-1: 2/(ny-1): 1]';
\]
\[
t = [0: T/nt : T]; t = t(1:nt); \]
\[
w0 = 2*pi/T; \quad \% \text{fundamental radian frequency}
\]
\[
alpha0 = a*sqrt(w0/nu); \quad \% \text{Womersley parameter, fundamental frequency}
\]
\[
w = w0*[1:nf]; \quad \% \text{array of radian frequencies}
\]
\[
alpha = a*sqrt(w/nu); \quad \% \text{array of Womersley parameters}
\]
\[
K = 0*KQ; \quad \% \text{initialize pressure gradient array}
\]
\[
Q = KQ0*temp2; \quad \% \text{initialize flow rate array with DC flow component}
\]
\[
Pp = -8*nu*Q/(pi*a^4); \quad \% \text{initialize pressure gradient array with DC component}
\]
\[
\text{Tau\_steady} = a*Pp/2; \quad \% \text{initialize wall shear stress array with DC component}
\]
\[
\text{Tau} = \text{Tau\_steady};
\]
\[
j = sqrt(-1);
\]
\[
j32 = j^1.5;
\]
\[
u = (2*KQ0/(pi*a^2))*((1 - y.*y)*temp2);
\]
\[
\text{for } n = 1:nf \quad \% \text{Sum over all frequencies}
\]
\[
K(n) = KQ(n)*j*w(n)*rho/(pi*a^2*(1 - 2*besselj(1,j32*alpha(n))/(j32*alpha(n)*besselj(0,j32*alpha(n))))));
\]
\[
Ktau(n) = rho*K(n)*a*besselj(1,j32*alpha(n))/(j32*alpha(n)*besselj(0,j32*alpha(n))));
\]
\[
\text{for } k = 1:nt \quad \% \text{Calculate for each point in time}
\]
\[
Q(k) = Q(k) + real(KQ(n)*exp(j*w(n)*t(k)));
\]
\[
Pp(k) = Pp(k) + real(K(n)*exp(j*w(n)*t(k)));
\]
\[
\text{Tau}(k) = \text{Tau}(k) + real(Ktau(n)*exp(j*w(n)*t(k)));
\]
\[
\text{for } m = 1:ny \quad \% \text{Calculate for each spatial location y}
\]
\[
u(m,k) = u(m,k) + real((K(n)*a^2/(nu*alpha(n)^2*i))*(1 - besselj(0,j32*alpha(n)*y(m))/besselj(0,j32*alpha(n)))*exp(i*w(n)*t(k)));
\]
\end{verbatim}
\begin{verbatim}
    end% y loop
    end% t loop
    end% f loop
\end{verbatim}
\begin{verbatim}
u\_min = min(min(u)); \quad \text{umax} = max(max(u));
\end{verbatim}
\begin{verbatim}
\% Make an animated velocity profile plot
\text{clearM;}
\text{for } n = 1:nt
\text{plot(u(:,n),y); axis([1.1*u\_min 1.1*umax -1 1]);}
\text{xlabel('U(y,t)'); ylabel('y'); title('Velocity Profiles');}
\text{M(n) = getframe;}
\text{end}
\text{moviereps = 10; \% number of repetions of the movie}
\text{speedratio = 0.5; \% ratio of movie speed to actual speed}
\text{movie(M,moviereps,speedratio*nt/T);}
\text{figure; \% Plot selected velocity profiles on a static plot}
plot(u(:,1),y,u(:,11),y,u(:,21),y,u(:,31),y,u(:,41),y,u(:,51),y,u(:,61)
,y,u(:,71),y,u(:,81),y,u(:,91),y);
legend('0%','10%','20%','30%','40%','50%','60%','70%','80%','90%');
title('Velocity Profiles'); xlabel('U(y;percent of period)');
ylabel('y');

figure;

% Plot time waveforms of flow, pressure gradient, wall shear stress,
% and centerline velocity
subplot(2,2,1); plot(t,Q); xlabel('time (s)'); ylabel('Flow Rate (ml/s)');
subplot(2,2,2); plot(t,Tau,t,Tau_steady); xlabel('time (s)'); ylabel('Wall Shear Stress (dyn/cm^2)');
subplot(2,2,3); plot(t,Pp); xlabel('time (s)'); ylabel('Pressure Gradient (dyn/cm^2)');
subplot(2,2,4); plot(t,u((ny+1)/2,:)); xlabel('time (s)'); ylabel('Centerline Velocity (cm/s)');

Reference:
Appendix B

Internal miniature pump used in an implantable artificial kidney to deliver bio-fluids

Chapter overview

This appendix describes the design and testing procedure for an innovative implantable pump for medical applications. In contrast to traditional drug delivery methods, this implantable pump delivers drugs or bio-fluids (blood, plasma, etc.) with better performance. The valve-less feature of the pump reduces the probability of damaged blood cells during pumping, which may be caused by shearing forces on the cell membrane. High accuracy of drug (or bio-fluid) administration in an implantable pump is beneficial when treating patients. In addition, the pump does not require an external power source because it relies entirely on the body’s own energy from the pulsating character of blood circulation. A theoretical model of the pump elements was built based on the nozzle-diffuser elements. This exercise shows that the efficiency ratio decreases when there is an increase in diameter of the nozzle-diffuser element. The efficiency ratio is also affected by the angle and the length of the channel. The maximum flow rate for the designed pump is around 1 ml/min based on a frequency of 1.16 Hz in the pulsatile flow regime. The total dimensions (nozzle-diffuser elements and pumping chambers) of our pump are 45 mm × 6 mm × 15 mm. However, the dimensions can vary (from micro to macro) sizes depending on the application.
1. **Introduction**

The fluid pump is one of the oldest fluid-energy-transfer devices known. Ancient civilizations designed several types of pumps; e.g., the undershot-bucket waterwheels, or norias, used in Asia and Africa (1000 B.C.), and Archimedes’ screw pump (250 B.C.). Diffusers may have evolved from these water system when it was discovered that, if the outlet section of the pipe was flared, the flow rate increased without any extra effort [1].

Valves are often the least reliable component in pump design. To overcome this problem, a valve-less pump is proposed. Valve-less micro-pumps using two different types of fixed channels have been presented in literature: (i) nozzle-diffuser elements and (ii) valvular conduits [2-4]. Diffuser/nozzle systems applied as a flow diode in a microstructure pump were first presented by Stemme [5]. A valve-less micro-pump based on piezoelectric actuators and diffuser/nozzle elements [6,7] was one of the earliest types of micro-pumps proposed in micro-electro-mechanical systems (MEMS). These pumps can generate a flow rate ranging from picoliters to milliliters per minute.

Visghal *et al.* [8] presented the effect of a low Reynolds number on flow through nozzle/diffuser elements in a valve-less micro-pump. Figure 1 illustrates the operating principle of a valve-less micro-pump. A number of medical devices and systems, such as blood pressure sensors, micro-needles, glucose sensors, DNA analyzing system, etc., are designed and fabricated by MEMS specialists [9, 10]. The micro-pump, which plays a major part in the delivery system, transfers the fluid from the reservoir to the human body and its organs with a high efficiency, accuracy, and reliability.

The small dimensions and high precision of micro-pumps have made them useful for chemotherapy, insulin delivery for diabetic patients, and drug administration for cancer patients [11]. The piezoelectric actuator in a valve-less micro-pump makes fluid flow by electromechanical conversion [12]. A comparative analysis of micro-actuators, such as the electromagnetic actuator [13], the electrostatic actuator [14], and the thermo pneumatic actuator [15], shows that the piezoelectric actuator can provide better
reliability and moderate pressure at a low power consumption [16]. In contrast to traditional drug delivery methods, such as oral pills, ointments or injections using a syringe, an implantable pump drug delivery system offers a more efficient and effective drug therapy that allows a more accurate drug dosage. In addition to drug delivery applications, the implantable pump can provide enough flow pressure (bio-fluid delivery) for implantable filters, which usually have high pressure drop problems [17].

Figure 1: Schematic of nozzle/diffuser (valve-less) pump. (a) Pump action in supply phase, (b) pump action in pump phase. The $Q$ is the flow rate and the $+$ and $-$ signs and arrows show the amount of flow rate in the nozzle and diffuser elements [Diagram by A Ostadfar]

One requirement for an implantable device is low power consumption, especially if this power is provided by internal sources of the human body. In this section, the theory and principle of the pumping and actuation method for drug (or bio-fluid) delivery in an implantable valve-less pump is discussed. Our design and its experimental results are also presented, which show a unique structure in drug (or bio-fluid) delivery by using the body’s internal energy, blood pressure fluctuations.

2. **Methods**

2.1. **Theoretical model**

2.1.2. **Flow characters in nozzle/diffuser design**
In this section, a nozzle/diffuser design is introduced. Figure 2 illustrates a schematic diagram of the pump with the nozzle/diffuser elements. As shown in Figure 2, the diaphragm moves upward during the pump phase, and it moves downward in the supply phase. In the pump phase, the solid arrows represent flow through the nozzle/diffuser section whereas the dotted arrows illustrate the flow through the nozzle/diffuser in supply mode. The size of the arrows represents the power of the flows. Figure 3 shows the nozzle/diffuser channels, where $D_i$ and $D_o$ are diameter, $v$ is the fluid velocity, $\theta$ is the angle, $L$ is the length, $Re$ is Reynolds number, $\rho$ is the fluid density, and $\mu$ is the viscosity. The subscripts (i), (o), indicate the small and large diameters, $n$ and $d$ represent the nozzle and diffuser parts, respectively.

![Figure 2: Schematic of pump. The solid and dashed lines show the flow rates (vector) and amount of diaphragm deflection in maximum (systolic) and minimum (diastolic) pressure; the dotted line shows the neutral position (no pressure) of the diaphragm [Diagram by A Ostadfar]](image)

Figure 3: Nozzle and diffuser elements. Left: nozzle element; Right: diffuser element. The arrows show flow direction [Diagram by A Ostadfar]

For a low Reynolds numbers ( $1 < Re < 50$) and $\theta < 40^o$, the flow resistance coefficient for the diffuser shape can be written as [18,19]:

- $Re_n = \frac{\rho v_i D_i}{\mu}$
- $Re_d = \frac{\rho v_o D_i}{\mu}$
\[
\xi_d = \frac{A_d}{Re_d}, \quad A_d = 20 \left( \frac{D_i^2}{D_o^2} \right)^{0.33} (\tan \theta)^{0.75}
\]

\[
\xi_n = \frac{A_n}{Re_n}, \quad A_n = \frac{19}{\left( \frac{D_o^2}{D_i^2} \right)^{0.5}} (\tan \theta)^{0.75}
\]

where \(A_d\) and \(A_n\) are functions of the angle and the inlet and outlet diameters.

From Eqs. 1 and 2, the efficiency ratio (\(\eta\)) for nozzle/diffuser elements is written as:

\[\eta = \frac{\xi_n}{\xi_d} = \frac{A_n Re_d}{A_d Re_n}\] (3)

Sangki Lee and Kwang kim [18] re-wrote efficiency ratio as:

\[\eta = \frac{\xi_n}{\xi_d} = \left( \frac{A_n}{A_d} \right)^2\] (4)

From Eqs. 1, 2 and 4, for a low Reynolds number, the efficiency ratio (\(\eta\)) is determined only by the geometry of the nozzle/diffuser elements.

2.1.2. The diaphragm deflection

The blood pressure deforms the diaphragm during systolic and diastolic periods. Figure 4 illustrates the deflection of the diaphragm caused by blood pressure.

The governing equation for plate deflection under a uniform pressure loading, \(P\) is [20]

\[
\frac{\partial^4 w}{\partial x^4} + 2 \frac{\partial^4 w}{\partial x^2 \partial y^2} + \frac{\partial^4 w}{\partial xy^4} = \frac{P}{D},
\]

where \(w\) is the normal deflection of a point of the diaphragm at a location \((x, y)\). The term \(D\) denotes the rigidity of the membrane, and it is expressed as [20]

\[D = \frac{E t^3}{12(1-\nu^2)}\] (6)

where \(E\) is Young’s modulus, \(\nu\) is Poisson’s ratio, and \(t\) is the thickness of the diaphragm.

Using Navier’s method (double trigonometric series solution), the deflection of a rectangular diaphragm (Eq. 5) can be written as [20]
where \( a \) and \( b \) are the sides of a rectangular diaphragm (see Figure 4).

\[
w(x, y) = \frac{16P}{D \pi^6} \sum_{m=1,3,\ldots}^{\infty} \sum_{n=1,3,\ldots}^{\infty} \frac{\sin \frac{m \pi x}{a} \sin \frac{n \pi y}{b}}{mn\left[\left(\frac{m}{a}\right)^2 + \left(\frac{n}{b}\right)^2\right]^2},
\]

Figure 4: Top: Top view of a rectangular diaphragm; \( a \) and \( b \) are the diaphragm dimensions. Below: Schematic of diaphragm deflection during systolic pressure (solid line) and diastolic pressure (dashed line). \( W_S \) and \( W_D \) are the deflections for systolic and diastolic pressure, respectively. [Diagram by A Ostadfar]

2.1.3. Flow rate and pressure (pump head)

Reciprocating displacement of diaphragm in pumping chamber increases fluid pressure in pump and its outlet. The flow rate and pressure produced by reciprocating displacement pumps, such as the being discussed pump, depend on five factors: (i) the stroke volume, \( \Delta V \); (ii) the dead volume of the pump, \( V_o \), or the minimum fluid volume contained between the inlet and outlet nozzle/diffuser element at any point during the pump cycle; (iii) the pump frequency, \( f \); (iv) the properties of the nozzle/diffuser valves; and (v) the properties of the operating fluid [21].

In general form, the stroke volume of a diaphragm can be written as [22]

\[
\Delta V = \int_0^a \int_0^b w(x, y) \, dx \, dy \tag{8}
\]

where \( w(x, y) \) is the diaphragm deflection (Eq. 7) and \( a \) and \( b \) are the dimensions of the diaphragm sides.
Because of the minimum permanent pressure (diastolic pressure) in the cardiovascular system, the diaphragm is always under pressure; therefore, the net stroke volume for the implantable diaphragm is the stroke volume under systolic pressure minus the stroke volume under diastolic pressure. We can rewrite Eq. (8) as

\[ \Delta V = \int_{0}^{b} \int_{0}^{b} w_s(x, y) \, dx \, dy - \int_{0}^{a} \int_{0}^{b} w_d(x, y) \, dx \, dy \]  

(9)

where \( w_s(x, y) \) and \( w_d(x, y) \) are the diaphragm deflection for systolic and diastolic pressures, respectively.

The mean outlet flow rate, \( Q \), during period \( T \), is \([19, 23]\)

\[ Q = \frac{2 \Delta V \sqrt{\eta} - 1}{T \sqrt{\eta} + 1} \]  

(10)

where \( \Delta V \) is the stroke volume, and \( \eta \) is the efficiency ratio (Eq. 3-4).

The pump-head is one of the mechanical characteristics to introduce pressure in the pump. The total pump-head can be measured by installing pressure gauges at the suction and discharge tubes. The total pump-head may also be determined by the energy difference between two points in the pumping system.

The total pump-head can be determined by \([24]\):

\[ Total \ head \ = \ (H_2 - H_1) + \sum h_{f(1-2)} \]  

(11)

where \( H \) is the head height (in meters) or static pressure, subscripts 1 and 2 denote the upstream and downstream of the pumping system, respectively, and \( h_f \) is the piping losses or the friction head (m) between two points. Figure 5 illustrates a schematic diagram for the pump-head as presented in this work.
3. Materials and devices

3.1. Valve-less Pump module

The diaphragm is made from 100% natural latex for medical applications with a thickness of 0.18 mm ± 0.02 mm. The Poisson’s ratio, ν, and Young’s modulus, E, are 0.49 and 6 MPa, respectively.

The pump module was made from an ACRYLITE FF acrylic sheet, and it was designed and fabricated following the valve-less pump specifications (nozzle/diffuser shape). The angle of the nozzle/diffuser valve, theta (θ), is 10°. Figure 6 shows the valve-less pump that was fabricated and used in this experimental work.

3.2. Pulsatile pump and monitoring system

A COBE century perfusion pump (COBE cardiovascular Inc.) was used to provide pulsatile flow in circulation. This pump is intended for use in cardiopulmonary surgical procedures or as an arterial pump in operating rooms. The test circuit was equipped with blood pressure transducers, PX272, (Edwards Life Sciences, LLC) to
measure the flow pressure. An HP component monitoring system, 54S model (Hewlett Packard Company), was used to monitor and record test outcomes as shown in Figure 7. Water at a temperature of $22^\circ C \pm 2^\circ C$ was used as the operational fluid.

![Figure 7: Hewlett Packard (HP) patient monitor (left) and COBE perfusion (Cardiovascular) pump (right) [A Ostadfar]

3.3. **Procedure**

After the valve-less pump was placed in the fluidic system, the fluid (water) was circulated in the test circuit with a COBE pump for a variety of rotational speeds (RPM) to make pulsatile flow. The pulsatile flow pressures of COBE pump were monitored by pressure transducers and a HP monitoring system. The flow rate of the valve-less pump was determined by measuring the liquid volume and timing the collection period. The pump pressure head had a direct relation to the COBE pump pressure (as a main feeder), and the pressure head was measured regarding the COBE pump RPMs (pulse-rate).
4. Results and discussion

4.1. Measurement errors

Several types of errors affect the accuracy of the results, such as environmental errors (temperature and humidity changes), device errors (pressure sensor, pump) and human errors (reading and calculation). According to the COBE pump manual, the flow rate readout accuracy is \( \pm 10\% \) or \( \pm 0.01 \) LPM, whichever is greater [25].

The error in the Edwards Pressure Transducers is \( \pm 1.5\% \) of the reading or \( \pm 1 \) mmHg, whichever is greater [26], and in the flow rate measuring tool, the error is \( \pm 0.5\% \) at 20°C. For the evaporation error, Bansal et al. suggested a correlation based on saturated pressure and velocity of air [27]. For ambient conditions, the calculated evaporation rate (error) of water after pumping was \( 7.8 \cdot 10^{-9} \) l per minute.

4.2. Effect of nozzle/diffuser geometry on the efficiency ratio (\( \eta \))

The efficiency ratio of the nozzle/diffuser channel and its relation to channel geometry was calculated using Eqs. 1-4 and modeled with Maple software (commercial computer algebra system). Figures 8 through 10 illustrate the results.

Figure 8 shows 3D results for the efficiency ratio with respect to small and large diameters for the designed and tested pump. The figure shows that by increasing the inlet and outlet diameters in the nozzle/diffuser channel, the efficiency ratio will be reduced. The opening angle \( \theta \) for this design was 10°. In Figure 9, the small diameter and the length of the channel are subject to fluctuation, the figure shows that, with an increasing small diameter, the efficiency ratio is reduced rapidly (sharp gradient), and the gradient increase for the length of channel is minimal.

Figure 10 shows a comparison between the small diameter and the opening angle \( (0 < \theta < 45^\circ) \) on the efficiency ratio, such as Figure 9 with an increasing small diameter, the efficiency ratio curve is decreased rapidly and this curve, for theta \( (\theta) \), has an increasing gradient which is sharper than the length \( L \) gradient in Figure 9.
Figure 8: 3D result for the efficiency ratio ($\eta$) versus the small ($d$) and large ($D_o$) diameters (m) for the pump, $d$, and $D_o$.

Figure 9: 3D result between efficiency ratio ($\eta$), ($d$) small diameter and ($L$)channel length (m) for present pump.
4.3. **Effect of fluid pressure on diaphragm deflection (w)**

As discussed in Section 2.2, Eqs. 5-7 are the governing equations for diaphragm deflection under variable pressure. The experimental results show two deflections on the diaphragm (see Figure 11). These deflections are produced by the systolic and diastolic pressures (pulsatile pressures) of the COBE pump. With Eq. 7 and Maple software, numerical calculations were performed, and the results were compared with our experimental results (see Figure 12 and Figure 13).

Figure 12 illustrates the diaphragm deflection under systolic pressure, while Figure 13 demonstrates the deflection under diastolic pressure. Figure 14 shows the numerical 3D deflection simulated in Maple of the diaphragm in Cartesian coordinates; the colors show the degree of deflection. The figures are consistent with the design and fabrication criteria. As expected, the maximum deflection is located in the middle of the diaphragm (see location C in Figure 4).
Figure 11: Diaphragm deflection for systolic pressure (solid line) and diastolic pressure (dashed line). The lines illustrate a polynomial trend line. (1 mm Hg = 133.3 Pa)
Figure 12: A comparison between experimental and numerical results for the diaphragm deflection during systolic pressure. The lines illustrate a polynomial trend line. (1 mm Hg = 133.3 Pa)

Figure 13: A comparison between experimental and numerical results for diaphragm deflection during diastolic pressure. The lines illustrate a polynomial trend line. (1 mm Hg = 133.3 Pa)
4.4. **Effect of the pump flow rate and pressure (pump head)**

The measured flow rate of the pump at different RPMs is shown in Figure 15. The flow rate increased as a function of the frequency (RPM), and the maximum flow rate was measured at 70 RPM. The flow rate was approximately 1.03 ml per minute, but, above 70 RPM, the flow rate starts to decrease because of the maximum diaphragm deflection, which allows a smaller net stroke volume (Eq. 9) in the pumping chamber. The average heartbeat for an adult is around 70 beats per minute, and the same test condition (70 RPM) by the COBE pump provides a similar frequency for the designed pump.
The relationship between frequency and pump head was also characterized for the pump at various frequencies (RPM). As expected, the frequency of the pulsatile flow and the pressure on the diaphragm determined the maximum pressure head. As shown in Figure 16, increasing the flow rate increases the observed frequency. Considering static pressure ($H_{2-1}$) and piping losses ($\sum h = 0.1$ mm) in the system, the maximum pump head is 20.6 mm, which means that the investigated valve-less pump can pump fluid (water) up to 20.6 mm.

Figure 15: Variation of nozzle/diffuser pump flow rate versus pulsatile flow frequency (COBE RPM)
5. **Chapter conclusions**

Experiments were conducted to study the mechanical characteristics of an implantable valve-less pump (micro-pump) to transport bio-fluids or drugs to the human body. In case of drug delivery, the inlet of pump should be connected to a drug reservoir to provide enough fluid for the pump. These experiments also introduced a new method to use blood circulation energy as an internal energy source to energize the implantable pump.

Numerical modeling was performed on the nozzle/diffuser elements in the design of the implantable valve-less pump. Pulsatile blood circulation was generated with a hospital COBE pump.

The results show that small diameters and the angle of the nozzle/diffuser element are important in determining the efficiency of circulation of the embedded pumping system. Our results confirm that the deflection of the pump diaphragm depends directly on the pressure of the fluid used (blood pressure), and this deflection creates a differential volume to produce pressure (pumping) for moving the fluid. In addition, the results show that the pulsatile flow frequency (heartbeat) increases the pump flow rate.

The valve-less nature of this design reduces the possibility of damage. The lack of mechanical closing of valves lowers the shear stress on blood cells, and thus the probability of hemolysis is reduced in the pumping process.
Because of the benefits of an implantable valve-less pump, such as the simplicity of design, the use of an internal energy source, and biological compatibility, it is suitable for practical applications in the human body, which include drug delivery, or as a part of implantable devices, such as an artificial kidney.
References:


Appendix C

Review of Red Blood cell Hemolysis

Chapter overview

Implantable assistive devices give hope of a permanent clinical solution to people with chronic failure, such as heart or kidney failures. While long-term use of continuous-blood flow is being researched, the eliminating the extreme level of blood damage in these devices is an important design challenge. Blood damage or hemolysis depends on exposure time and shear stress, and device designers have usually preferred design estimations and calculations rather than experimental studies to make a decision in their design. In this chapter, the hemolysis aspects and numerical and experimental methods are reviewed to explain the risk of blood cell damage in implantable artificial devices.
Introduction

Recently, various types of implantable assistive devices have been developed and used for treating patients with chronic diseases. In an implantable artificial kidney, the roughness of the surfaces, filter pores, and other components introduce shear stress in the system. This shear stress is well known as a factor causing hemolysis [1]. The estimation of hemolysis within an implantable artificial kidney is important for the development of a blood-compatible implantable artificial kidney. Hemolysis is the damage of the red blood cells’ membrane, and it is assessed by the amount of hemoglobin released from inside the red blood cells to the plasma. Hemolysis or damage of the red blood cells has been modeled with shear stress and exposure time (or accumulated number of events) in previous studies [2-4]. Predicting or estimating hemolysis is one of the best methods to analyze the problem without using physical experiments, and this method is a very valuable tool for some devices, such as the implantable artificial kidney.

An important factor in the development of an implantable artificial device is the decrease of hemolysis and thrombus creation so that durable use of these devices is feasible. Many studies have investigated hemolysis in an implantable pump, and, while shear stress [5-7], solid friction[8], and heat generation [9-10] have been listed as the main causes of hemolysis, it has also been suggested that roughness of surface has an influence [11-13]. Umezu et al. reported an increase in the hemolysis level with a raise in the arithmetic mean level of roughness (Ra), and they evaluated the detailed flow in the vicinity of the roughened surfaces [13].

Analysis and methods

Blood cells are exposed to positive pressures up to 200 kPa (~2atm, ~ 500 mmHg) and negative pressures down to -70 kPa (~-0.7 atm, -500 mmHg). Outside the body, when RBCs are exposed to pressures up to 150 atmospheres, neither hemolysis nor a measurable change of osmotic fragility result [14]. Recently, the hemolysis threshold was recognized at 130 MPa (~1300 atmospheres) [15,16]. Negative pressure also does not cause hemolysis [17]. Only the dynamic element is related to blood damage caused by shear. No general pressure limits for the dynamic pressure can be prescribed for avoiding blood damage because, first, pressure drop is not directly related
to shear and, second, blood damage is a nonlinear function of shear and exposure time [18]. Shear originates in the difference of fluid velocity between the blood layers in the channel; this difference creates a force which is called shear. The velocity difference between the two flow layers divided by the distance between the two flow layers is defined as the shear rate, measured in units of s\(^{-1}\). The wall shear rate and shear stress for cylindrical channels can be calculated by Equations 1 and 2, which show shear rate for general fluids and Newtonian fluids, respectively.

\[ \gamma = \frac{v}{d} \quad (1) \]
\[ \gamma = \frac{32Q}{d^3\pi} \quad (2) \]
\[ \tau = \gamma \cdot \mu \quad (3) \]

where \( \gamma \) is the wall shear rate, \( v \) is fluid velocity, \( Q \) is the volumetric flow, \( d \) is the channel diameter, \( \tau \) is the wall shear stress in a cylindrical channel, and \( \mu \) is the viscosity.

Equation 4 defines the pressure drop in a cylindrical channel, and Equation 5 describes wall shear stress in a similar channel as a function of the pressure gradient:

\[ \Delta P = \frac{128\mu Q}{d^4\pi} \quad (4) \]
\[ \gamma = \frac{\Delta P d}{4\pi l} \quad (5) \]

As explained before, hemolysis is a nonlinear function of shear and exposure time \((t)\), and, regarding these relations, most researchers [1–6] based their hemolysis prediction upon the following power-law equation [19-24]:

\[ \frac{\Delta H_b}{H_b} = C \cdot t^a \cdot \tau^b \quad (6) \]

where \( \Delta H_b \) is the increase of the plasma free (released) hemoglobin concentration and \( H_b \) is hemoglobin concentration, \( \tau \) (N/m\(^2\)) is the shear stress, and \( t(s) \) is the exposure time.

Two sets of numbers are defined for the constants \( a, b \) and \( C \). The first equation (Eq.7) was introduced by Giersiepen et al. [25]:
\[
\frac{\Delta H_b}{H_b} = 3.62 \cdot 10^{-7} \cdot t^{0.785} \cdot \tau^{2.416} \quad (7)
\]

The second equation (Eq.8) was proposed by Heuser et al. [26]:

\[
\frac{\Delta H_b}{H_b} = 1.8 \cdot 10^{-6} \cdot t^{0.765} \cdot \tau^{1.991} \quad (8)
\]

The threshold of shear stress for exposure times above 100 seconds is around 150 Pa, which approaches the shear rate of \(~45000\text{s}^{-1}\) for a blood viscosity of \(~3.3\) mPa.second. For specify short times that approach the residence time inside the cannulas, the threshold was about 400 Pa – 500 Pa [27]. Allowing for relaxation after shear stress reduces hemolysis remarkably [28].

The Normalized Index of Hemolysis (NIH) is a standard clinical (experimental) indicator used to describe hemolysis in flow loop tests. The NIH is proportional to the increase of plasma free hemoglobin concentration, the volume of circulated blood, the volumetric flow rate of blood flow, and the hematocrit and time of the circulations [29].

\[
N.I.H\left(\frac{g}{100L}\right) = \Delta H_b \cdot V \cdot \frac{(100 - Hct)}{100} \cdot \frac{100}{Q \cdot t} \quad (9)
\]

where \(\Delta H_b\) is the increase of plasma free hemoglobin concentration(mg/L), \(V\) is the volume of circulated blood \((L)\), \(Hct\) is the blood hematocrit, \(Q\) is volumetric flow rate of the blood flow \((L/min)\), and \(t\) is the time of the test \((\text{min})\).

Surface roughness and the chemistry of the surface have major roles in hemolysis, and they may even govern capillary flow, especially at shear stress below the critical limit of \(~150\text{Pa}\) [30]. The influence of surface roughness on hemolysis has been investigated for medical devices, especially for centrifugal and impeller pumps used for heart assistive systems or heart–lung machines. Roughnesses exceeding 0.1 µm appear to increase hemolysis rates significantly [31-33].

Siliconizing (silicon coating) the internal surface of stainless steel tubing decreases hemolysis [34]. Currently, this method is used for blood access cannulas in
hemodialysis systems. Decreasing the rate of hemolysis is possibly a combination effect of reduced roughness and modified chemical interface.

Table 1 [35, 36] summarizes research regarding hemolysis and the condition under which it was studied. This table shows all the results together which makes it simple to observe why there have been many disagreements among various researchers as to the mechanism and levels of threshold for red blood cell damage.

Table 1: Summary of the effect of shear stress on hemolysis

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Order of magnitude of exposure time (sec)</th>
<th>Threshold level of damage (Pa)</th>
<th>References and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turbulent jet</td>
<td>$10^{-5}$</td>
<td>4000</td>
<td>Forstrom and Blackshear</td>
</tr>
<tr>
<td>Oscillating wire</td>
<td>$10^{-4}$</td>
<td>560</td>
<td>William Stal. (human, canine)</td>
</tr>
<tr>
<td>Oscillating bubble</td>
<td>$10^{-3}$</td>
<td>450</td>
<td>Rooney (human, canine)</td>
</tr>
<tr>
<td>Capillary flow</td>
<td>$10^{-2}$</td>
<td>500</td>
<td>Bacher and Williams (bovine blood)</td>
</tr>
<tr>
<td>Capillary flow</td>
<td>$10^{-2}$</td>
<td>450-700</td>
<td>Keshaviah and Blackshear (canine blood)</td>
</tr>
<tr>
<td>Concentric cylinder maximum stress, 60Pa</td>
<td>$10^2 - 10^3$</td>
<td>Relatively little hemolysis per unit time</td>
<td>Shapiro and Williams (surface effects dominate)</td>
</tr>
<tr>
<td>Concentric cylinder maximum stress, 25 Pa</td>
<td>$10^3$</td>
<td>Relatively little hemolysis per unit time</td>
<td>Knapp and Yarborough (surface effects dominate)</td>
</tr>
<tr>
<td>Concentric cylinder maximum stress, 60Pa</td>
<td>$10^3$</td>
<td>Relatively little hemolysis per unit time</td>
<td>Steinbach and Blackshear (surface effects dominate)</td>
</tr>
</tbody>
</table>
The cross-flow filtration method used to minimize cell deposition on the membrane surface also affects the hemolysis rate. The trans-membrane pressure drop, wall shear rate, and pore size are major factors that result in hemolysis in filtration membranes. These factors produce shear stress and membrane tension on red blood cell membranes which cause lysis.

Rand modeled the deformation of the cell in a micropipette (Figure 1). Regarding the figure and Laplace’s law for wall tension, two equations were derived:

\[ P_3 - P_1 = \frac{2\sigma}{R_p} \]  \hspace{1cm} (10)
\[ P_3 - P_2 = \frac{2\sigma}{R_c} \]  \hspace{1cm} (11)

where \( P \) is pressure, \( \sigma \) is membrane tension, and \( R_p \) and \( R_c \) are the pore and cell radii, respectively.

Figure 1: Deformation of a red blood cell in a micro-pore [Diagram by A Ostadfar]

Blachshear et al. introduced two equations (Eqs.12 and 13) for membrane tension as a function of time [37]:

\[ \sigma_t = \frac{33}{1+0.2t} \text{, for } t \leq 4 \text{ sec} \]  \hspace{1cm} (12)
\[ \sigma_t = 2 + \frac{60}{t} \text{, for } t > 4 \text{ sec} \]  \hspace{1cm} (13)
where $\sigma_t$ is lysis membrane tension (dyne/cm) and $t$ is time (sec).

**Results and discussion**

Three hemolysis experiments conducted by researcher that all had similar tension for lysis: Blachshear and Anderson (33 dyne/cm), Rand (28.6 dyne/cm) and Zydney (25.6 dyne/cm) [38].

Considering Table 1, the recorded stress range for hemolysis is between 150 Pa and 4000 Pa. Obviously, the stress will be affected by the pore edge, the shape of the pore inlet, and the flow regime of the fluid in bio-fluid separation.

Figure 2 is a 3D plot of Equation 7. Designers can use this figure as an assistive tool for predicting when hemolysis will occur. In this graph, the exposure time was considered between 0 seconds and 1 second with a shear stress between 0 Pa and 250 Pa. As the figure shows, increasing the time and stress will cause the blood damage, $\frac{\Delta H_b}{H_b}$, or $D$ to increases to around 0.22.

![Figure 2: Hemolysis prediction](imageverb.png)

Figure 2: Hemolysis prediction $\frac{\Delta H_b}{H_b}$, (or $D$) using equation 7, regarding $\tau$ (Pa) and $t$ (sec)
Similar to Figure 2, Figure 3 illustrates a 3D plot for equation 8. The range of time and stress were similar to equation 7. As the figure shows, increasing the time and stress will cause the blood damage, $\frac{\Delta H_b}{H_b}$, or D to increase to around 0.1.

Figure 3: Cell damage (Hemolysis) prediction, $\frac{\Delta H_b}{H_b}$ (or D) using equation 8, regarding $\tau$ (Pa) and t (sec)

As the figures show, these two models differ even in a similar situation. This difference is probably caused because of an unknown mechanical characteristic of blood cell hemolysis. Most researchers prefer to use equation 7 in their research and manuscripts as the main equation in hemolysis field, but, for this purpose, they need to have fully functional product and then they can measure hemolysis rate of the product such as figure 4. Figure 4 illustrates an example for NIH during hemolysis test for a pediatric centrifugal pump [29].
Most foci on hemolysis were on external assistive devices; recently, focus has turned to implantable heart pumps because these machines are operational in medical equipment, and researchers can make experiments using these machines. For some cases, such as an implantable artificial kidney, we have to use numerical or simulation methods to understand hemolysis aspects in these systems. During device design, the predicting when hemolysis will occur can be calculated using equation 7 to evaluate or predict cell damage in the system. The designers can change their design and compare shear stress and other design parameters to the threshold of damage. This re-design and comparison is a useful tool in engineering design. Some software are very helpful for engineering design purposes. Finite element analysis methods and its software are a very useful method to understand the mechanical damage in blood cell membranes [39, 40, 41], and it helps to reduce the problem of hemolysis on artificial surfaces or the inlets of filter pores in an implantable artificial kidney.
References


Appendix D

Yield stress calculation for membrane

\[ \tau = \frac{F}{A_{cm}} \]

\[ \tau = \frac{P_{\text{blood}} \cdot A_{1cm}^2}{\left(10^{-2} \cdot l \cdot 10^{-6} - \sqrt{n} \cdot A_{cp}\right)} \]

\[ \tau = \frac{P_{\text{blood}} \cdot A_{1cm}^2}{\left(10^{-2} \cdot l \cdot 10^{-6} - \sqrt{n} \cdot A_{cp}\right)} \]

\[ A_{cp} = d \cdot l, \ d = \text{Pore diameter} , l = \text{Pore length (membrane thickness)} \ n = \]

Pore numbers per unit of area

For \(l = 5 \mu m, \sqrt{n} \sim 26660, A_{cp} = 0.25 \times 5 \times 10^{-12}, P_{\text{blood}} = 26 kPa \)

\[ \tau = 100 \text{ MPa} \]

Titanium yield stress: \( \tau = 400 \text{ MPa} \)

Silicon nitride yield stress: \( \tau = 14 \text{ GPa} \)

![Diagram of membrane unit area and cross section](image)

Figure 1: Schematic of membrane unit area (down) and cross section of membrane (up)