Peritoneal Kidney Dialysis

BEE4530 Computer Aided Engineering: Applications to Biomedical Processes

By:
Arunabha Basu
Esther Lim
Sherry Zhou
Charles Zhu

Table of Contents

1. Executive Summary

Chronic kidney disease is a public health problem that afflicts over a tenth of the United States adult population. In this report, we describe the evaluation and analysis of peritoneal dialysis as a method of treatment for chronic kidney disease patients on the computational level. Using COMSOL Multiphysics and Simulation, we modeled the peritoneal cavity and surrounding blood vessels as a 2D slab using a thin-wall assumption and simulated urea mass transfer from the capillary bed through the peritoneal membrane and into the dialysate. Literature values for parameters such as urea diffusivity, bulk flow due to osmotic pressure difference, blood urea concentration, and bodily urea generation were used as modeling parameters.

Overall, our results reflected the ability of peritoneal dialysis to adequately remove waste urea from the body. With a drainage/infusion cycle every 5 hours, urea concentration can be maintained at a relatively constant level as peritoneal dialysis removes systemically generated urea. Alternatively, a greater number of shorter peritoneal dialysis sessions removed a significantly higher quantity of urea, resulting in an overall decrease in blood urea concentration.

Our sensitivity analysis reflected the significance of certain parameters in peritoneal dialysis and therefore the areas that can be emphasized in such treatment to achieve varying results. Dialysate volume, peritoneal membrane surface area, and bodily urea generation most severely affected post-dialysis urea concentration while urea diffusivity through the capillary bed, peritoneal membrane thickness, and initial urea concentration had little impact.

2. Introduction

The prevalence of chronic kidney disease in the world has been well documented: a review noted that Chronic Kidney Disease (CKD), across 26 studies, afflicted a median 7.2% of people aged 30 years and older and anywhere from 23.4 – 35.8% of people aged 64 years or older [1]. In the United States, CKD prevalence in adults age 20 and older has been estimated from 11 – 11.5% [2][3]. Regardless of the real number, CKD is generally considered to be a public health problem [4][5].

CKD is divided into 5 stages [6]. Treatment in CKD stages I – III typically involve activities that attempt to retain remaining kidney function such as improved diet, exercise, quitting smoking, or peritoneal dialysis (PD). Current treatments for Stage IV and V CKD, associated with a severe decrease in Glomerular Filtration Rate (GFR) and kidney failure, respectively, are transplantation, hemodialysis, and PD [7]. Out of these treatments, the dialyses involve complex biomedical transport processes. The key difference between them is that PD involves dialysate infusion into the peritoneal cavity and waste absorption from the abdomen whereas hemodialysis involves transfer directly from blood.

We are interested particularly in PD due to its relative novelty and significant advantage of convenience over hemodialysis. Compared to hemodialysis which requires 3 weekly clinic/hospital visits of at least a few hours, peritoneal dialysis occurs in-house, can be automated, and passively occurs during daily patient activities. Due to the significant convenience of the prodecure, patients report significantly greater satisfaction with peritoneal dialysis[8].

Our project explores urea transfer via peritoneal dialysis through computational modeling using COMSOL Multiphysics and Simulation Software. Specifically, we aim to model the change in blood urea concentration over the course of PD and the maintenance of a healthy blood urea concentration while undergoing this treatment. Our model will

include several components that affect urea transfer across the peritoneal membrane: simple diffusion from the blood to the dialysate due to a urea concentration gradient, convection of urea from the surface of the peritoneal membrane in contact with the dialysate, flow of water from the body into the dialysate due to osmotic pressure gradients, and bodily urea production.

3. Design Objectives

The objective of this project is to model peritoneal dialysis in patients by obtaining the concentration of urea remaining in the blood after a certain time period. More specifically, our goal is to determine the maximum time for which the dialysate can remain in the peritoneum before the dialysis procedure no longer has an effect. In addition to that, we would determine whether multiple, shorter sessions that replenish the dialysate before it becomes too concentrated provide any significant benefit

3.1 Problem Schematic

A diagram of the lateral and horizontal cross sections of the peritoneal cavity in the body is shown in Figure 1. In our model, we considered a small segment of the blood capillaries and peritoneal membrane as two-dimensional (2D) slabs. The transport of urea from the blood capillary layer through the peritoneal membrane into the dialysate was assumed to be uniform across the entire peritoneum. The schematic and boundary conditions used to model peritoneal dialysis are shown in Figure 2. The governing equations, boundary conditions, and initial conditions are listed in Appendix A in greater detail.
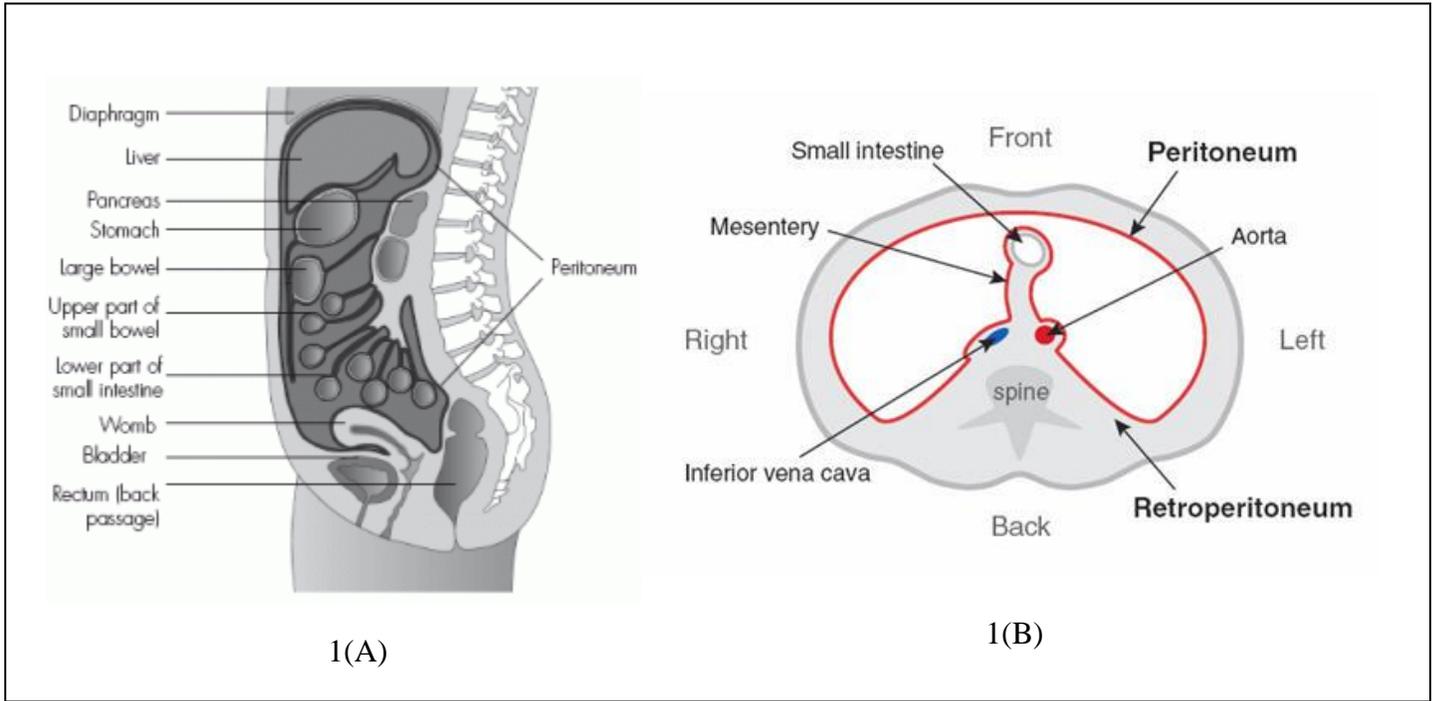
1(A)

1(B)

Figure 1. (A) A lateral cross section of the peritoneal cavity and the organs surrounded by the peritoneal membrane. The peritoneal cavity is the space between the parietal and visceral peritoneum. (B) A horizontal cross-section of the peritoneal cavity. The peritoneum or peritoneal membrane lines the cavity.
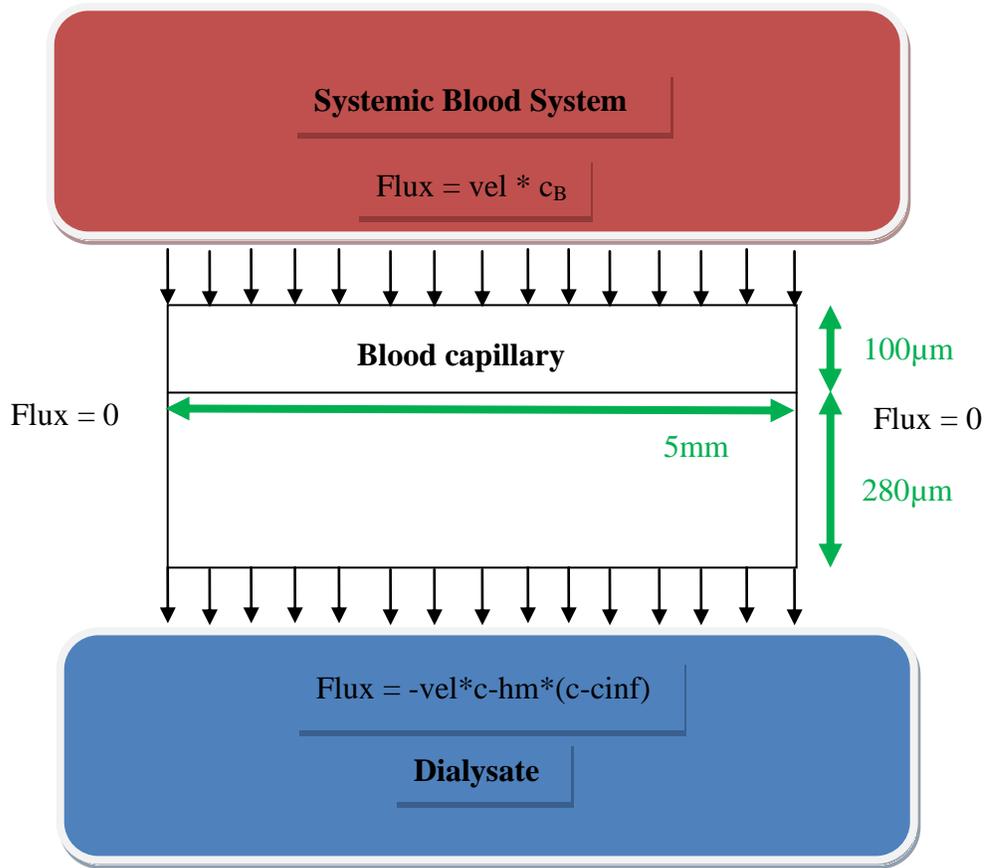
Figure 2. Schematic of COMSOL model with dimensions and boundary conditions

4. Results and Discussion

When we first developed the peritoneal dialysis model, we considered simple diffusion due to the urea concentration gradient as the sole method of mass transfer. Such a model however, utilized a systemic urea generation rate that was significantly greater than the total urea transfer rate out of the blood, which resulted in drastic increases in blood urea concentration during peritoneal dialysis. Further research led to the realization that infusing a hypertonic dialysate into the peritoneum would generate osmotic, oncotic, and hydrostatic pressure differences that would cause bulk fluid flow from the blood into the dialysate. A modified mass transfer governing equation that included bulk flow represented the inclusion of this physical mass transfer phenomenon in the dialysis model.

6

In addition to modifying the governing equations, the top boundary condition was altered to include bulk flow. The bottom boundary condition was also changed to include both bulk flow and a mass transfer coefficient term. One of the consequences of including bulk flow was the increase of dialysate volume over time, which was implemented through the addition of a global expression in COMSOL. As pressure equilibrated from solute flow over time, the velocity of the bulk flow also decreased. Experimental data from Parikova et al. served as the template for our best-fit exponential equation that modeled bulk flow over time (Figure 3)[9].
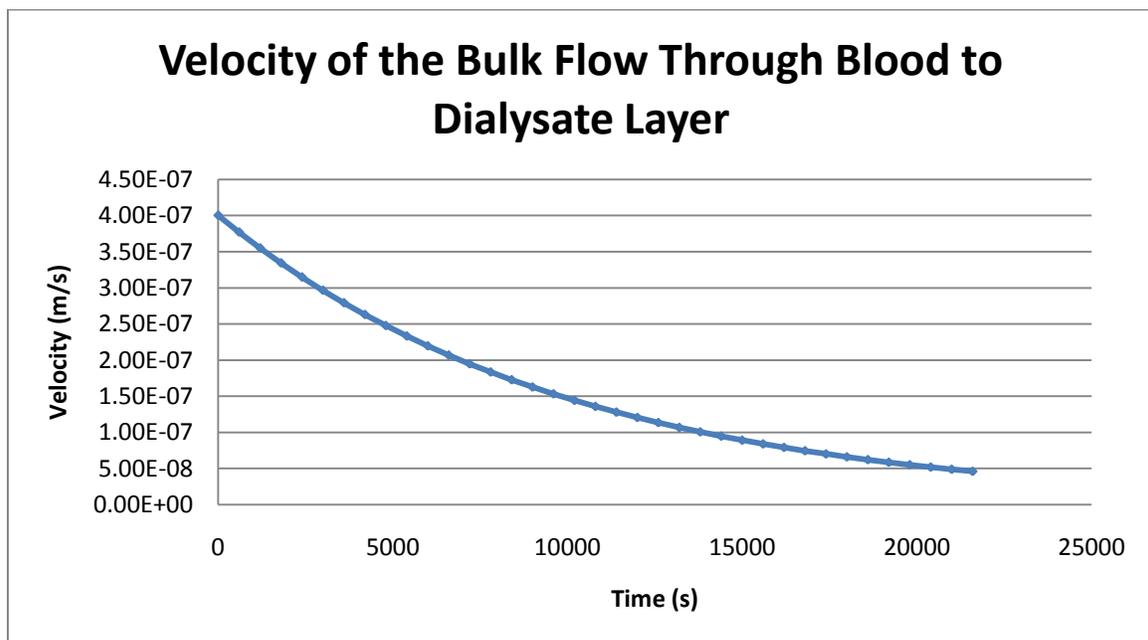

Figure 3. Velocity model of the bulk flow through the layers. These values were obtained through experimental data and fitted with an exponential equation. Velocity decreased through time as the pressure equilibrated.

The last physical phenomenon we implemented was the systemic urea generation rate. We assumed that the patient was recently diagnosed with Stage III CKD, which equates to 40% remaining kidney function [6]. Thus, the generation term we used was 60% of total rate of urea production.

After accounting for the aforementioned changes, we ran our final model in COMSOL for 6 hours. The resulting concentration profile is shown in Figure 4 below.
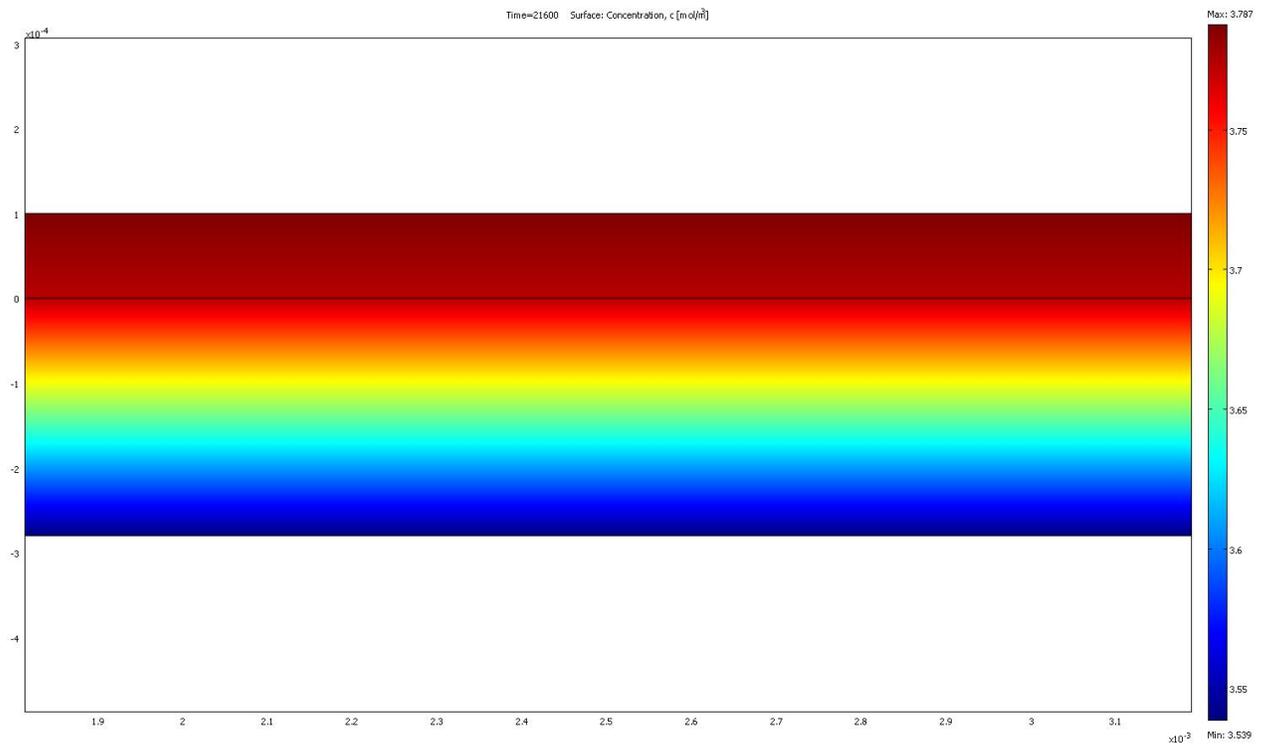
Figure 4. Enlarged and zoomed in image of surface plot of the blood layer and peritoneal membrane layer after running the dialysis for 6 hours.

The range of concentration in our domains after 6 hours was approximately 3.5 mol/m³ to 3.7 mol/m³. The highest concentration is at the top in the blood capillary layer. From this gradient seen in Figure 4, we were able to obtain a plot of the concentration of the urea in the blood shown in Figure 5 below.
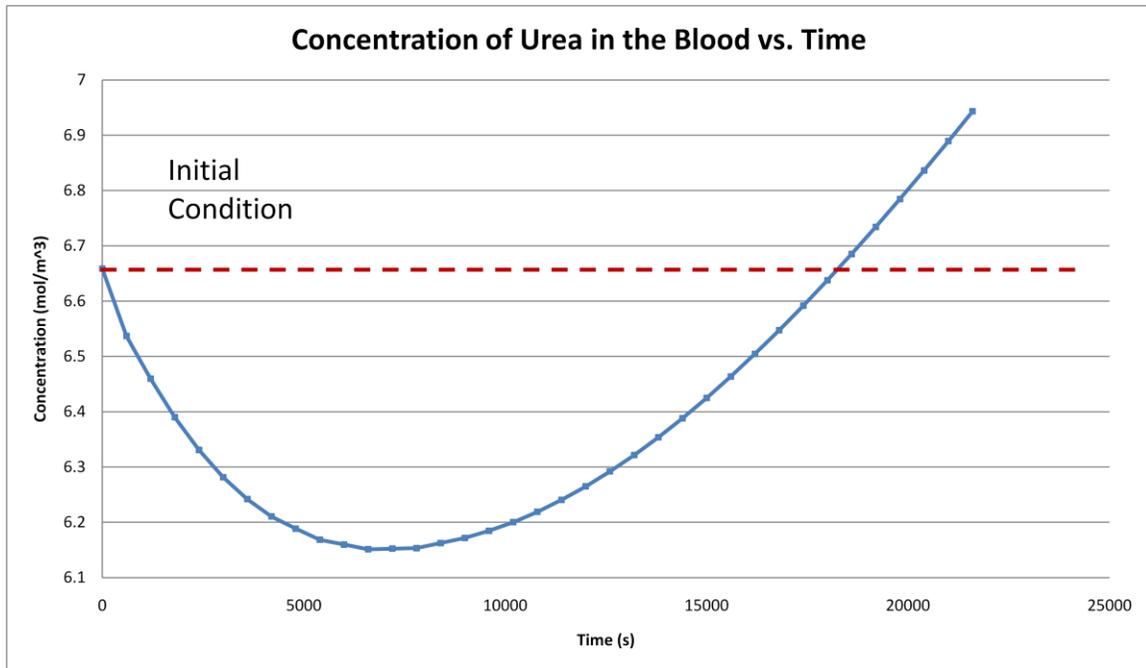
8

Figure 5. Concentration of urea in the blood for a dialysis time duration of 6 hours. At about 5 hours into the process, the urea concentration in the blood reached the initial urea concentration. After these 5 hours, the blood urea concentration surpassed the initial condition, marked by the dotted red line.

As can be seen from Figure 5, the concentration in the blood initially decreased due to the bulk flow and diffusion removing the urea into the dialysate. As the dialysate urea concentration equilibrated with that in the peritoneal membrane, the removal of urea slowed and systemic urea generation raised the levels of blood urea. Between 1-2 hours in the procedure, the concentration in the blood started to increase. After 5 hours, blood urea concentrations returned to and surpassed the initial concentration of 6.659 mol/m^3. The time duration of 5 hours before necessary dialysate drainage and re-infusion is well within standard peritoneal dialysis practices of 4-6 hours [10]. In addition to observing changes in blood urea concentration, we were also interested in analyzing the dialysate urea concentration change over time.
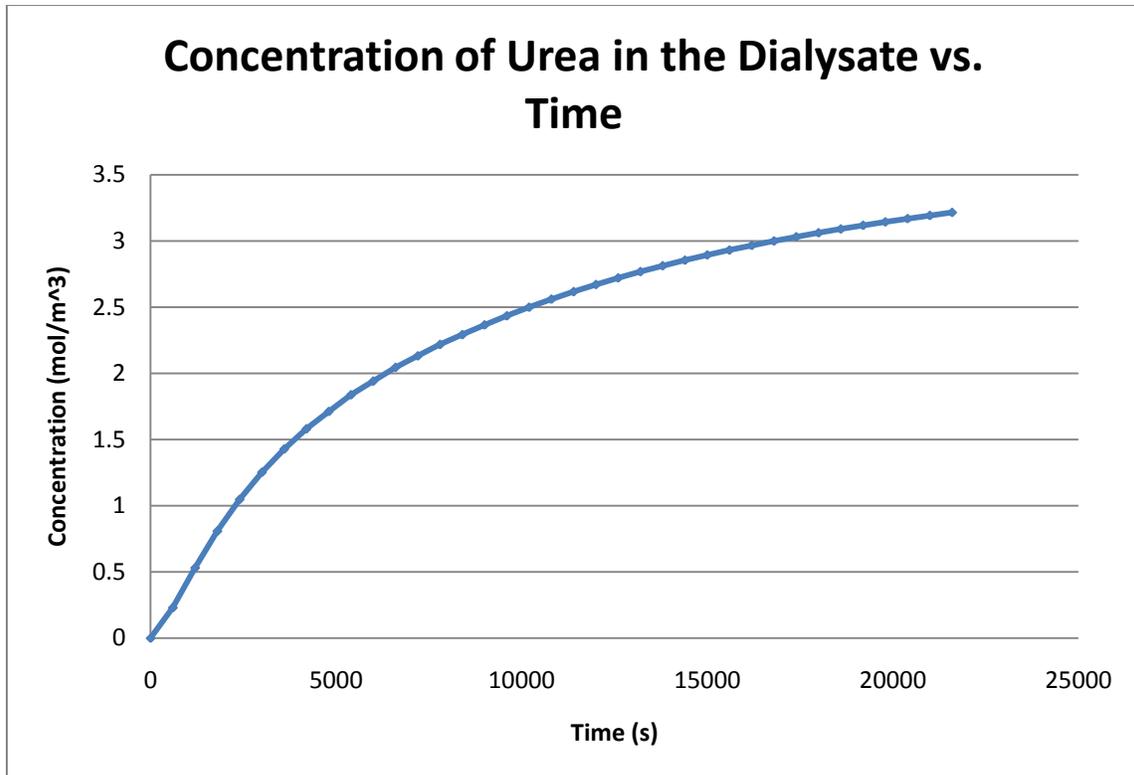
Figure 6. Concentration of urea in the dialysate during a 6-hour dialysis. The urea concentration increased and reached the final concentration of urea in the peritoneal membrane.

As expected, the dialysate began at an initial concentration of 0 and increased as the urea was removed from the blood (Figure 6). This amount of increase slowed as the dialysate became concentrated with urea and eventually equilibrated with the urea concentration in the peritoneal membrane.

Another change we evaluated was the inclusion of additional dialysate drainage/infusion cycles over a shorter time frame. This effectively replenishes the dialysate before the urea concentration in the blood reaches the initial concentration. COMSOL implementation involved running the model for two 3-hour sessions and re-initializing dialysate parameters between the sessions rather than performing the dialysis for 6 continuous hours (Figure 7).
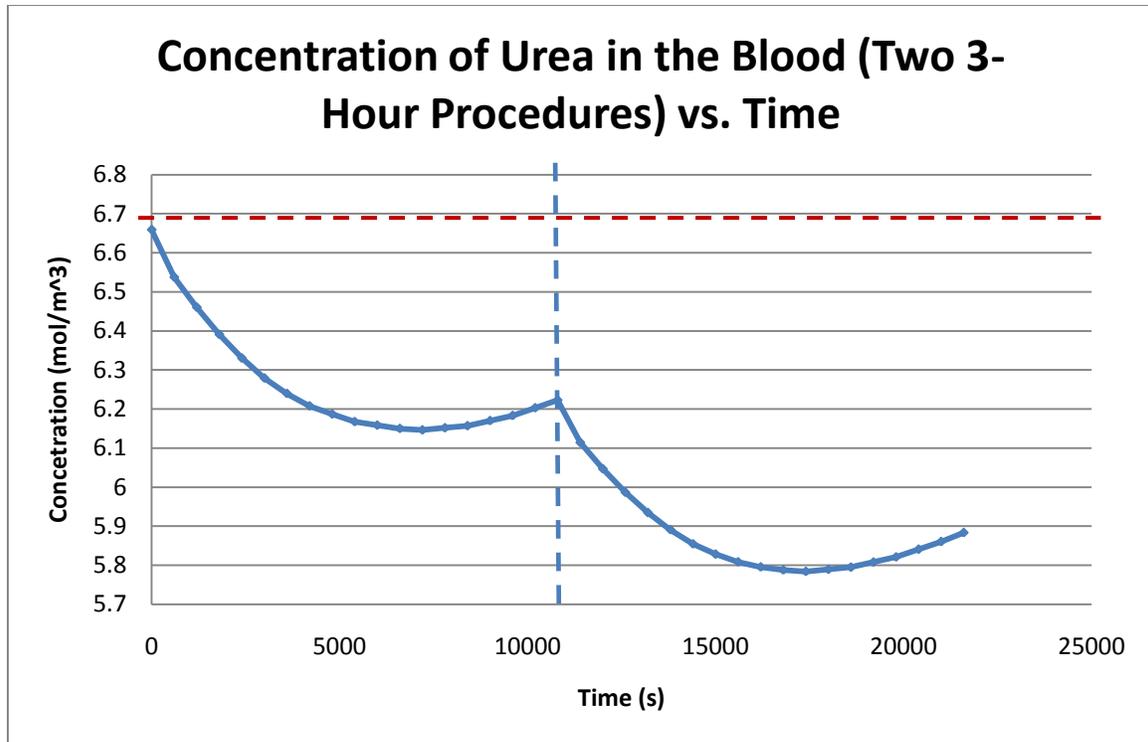
Figure 7. Concentration profile of urea in the blood after two 3-hour dialysis procedures performed back-to-back. The final urea concentration after the second dwell time did not surpass the initial condition, implying a potential benefit of multiple sessions. The initial condition is indicated by the red dotted line.

We noted that the first 3-hour dwell session resulted in a similar concentration profile as seen in Figure 5. Due to shorter time duration however, urea concentration never surpassed the initial concentration. The concentration of urea marginally increased before the dialysis bag was exchanged for a new one and the next 3-hour session began (the second dwell time). Based on these results, multiple sessions significantly reduced the urea concentration in the blood, showing the promise of being more effective than one longer session.

4.1 Sensitivity Analysis

To monitor the change in concentration of urea in the blood layer when certain parameters are altered, a sensitivity analysis was performed. The chosen parameters for this analysis were the diffusivity of urea through the peritoneal membrane, diffusivity of urea through the blood capillary, area of peritoneal membrane, generation of urea in body, mass transfer coefficient, volume of dialysate, thickness of the peritoneal membrane, and initial concentration of urea in blood.

11

Figure 8 shows that the model is most sensitive to the volume of dialysate, generation of urea in body, and area of peritoneal membrane.
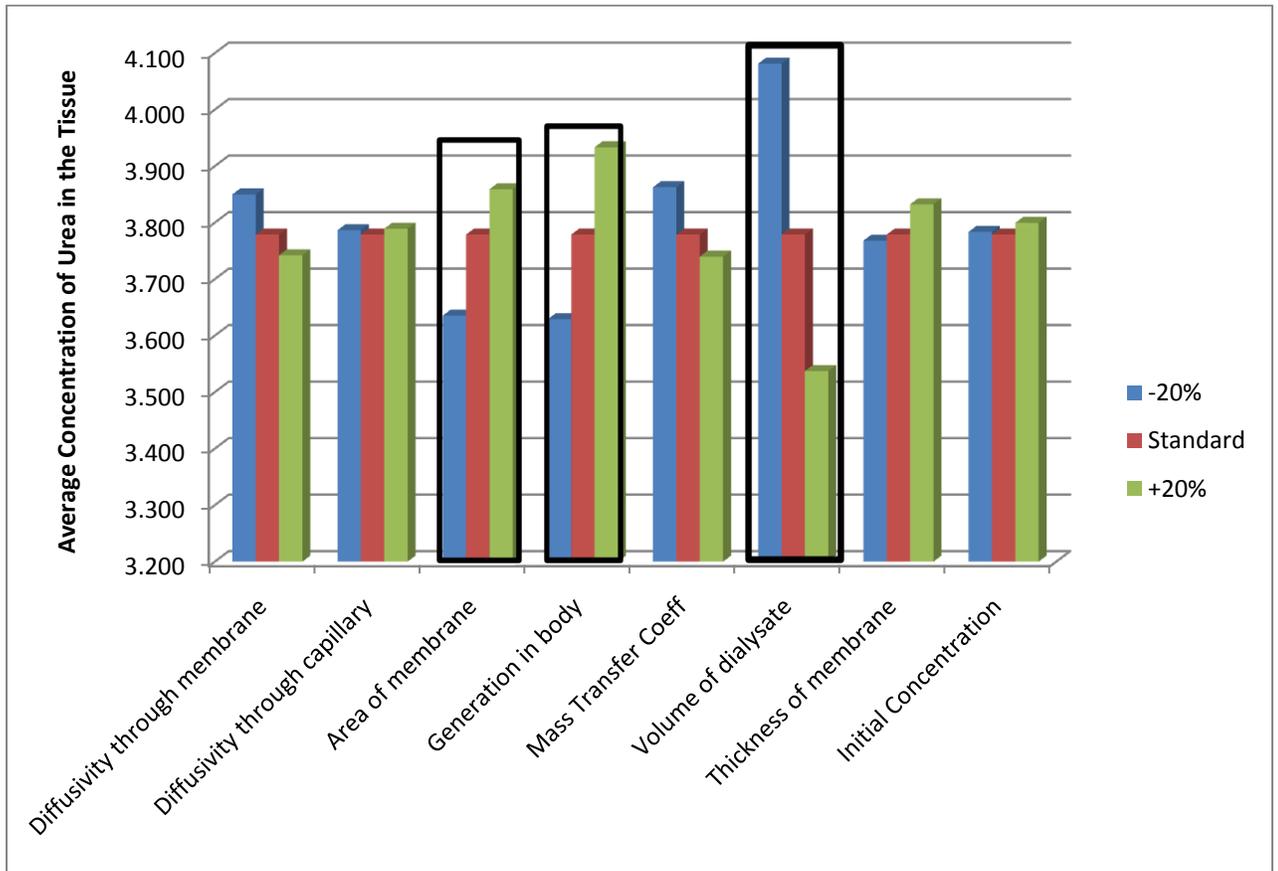

Figure 8. Sensitivity analysis of the COMSOL model when certain parameters are changed. The model is most sensitive to the boxed parameters, which are area of peritoneal membrane, generation of urea in body, and volume of dialysate.

The average concentration of urea in the blood decreased as the volume of the dialysate was increased. Although this result was expected because more urea would be able to be transported into a larger volume of dialysate over a constant time period, the large difference in the concentration of urea proved that it was a significant parameter that needs to be considered during peritoneal dialysis.

As the generation of urea was increased in the body, the average concentration of urea in the blood increased as well. With more urea in the blood initially, more urea

would be left in the blood after peritoneal dialysis. This was also a good indication that peritoneal dialysis would vary in effectiveness for different patients depending on how much kidney function was remaining. A 20% decrease in area of peritoneal membrane resulted in 3.80% decrease of average concentration of urea in blood, where as a 20% increase of peritoneal area resulted in a 2.12% increase of urea concentration. This discrepancy was unique since the change in urea concentration was relatively similar when the other parameters were increased and decreased by 20%.

Changing the diffusivity of the urea through the peritoneal membrane had the same effect on average concentration as the mass transfer area coefficient. Figure 8 shows that the model was more sensitive to changes in diffusivity of urea through the peritoneal membrane than diffusivity through the blood capillary layer. The rest of the parameters did not have a significant impact on the model.

4.2 Accuracy Check

From our results, we determined that the blood urea concentration returned to the initial concentration after approximately 5 hours. After 5 hours, the urea concentration surpassed the initial condition, rendering the process useless. The time duration of 5 hours before necessary replenishing of the dialysate is well within standard peritoneal dialysis practices of 4-6 hours [10]. The plots obtained from our COMSOL model also makes physical sense and did not produce any unexpected phenomena. For example, convective flux was greater than diffusive flux but both decreased over time as the dialysate became saturated with urea (Figures 12-15). There was also never any urea flow from the dialysate back into the body, especially since the urea concentration in the dialysate only experienced a positive trend (Figure 6). This implied that the direction of flow stayed consistent, from the blood through the membrane to the dialysate during peritoneal dialysis.

5. Conclusion

From the results, it was determined that a maximum of five hours can be allowed for the procedure before it has no further effect on an individual. After these five hours, the urea concentration in the blood increased to a level above the initial condition. These computations were performed with an initial condition that was considered to be a moderately high level of urea concentration in the blood. Since this procedure is meant for patients with moderate kidney failure, using such a concentration for the calculation can be considered as a conservative condition in which such a procedure would be used. Thus, for patients with lower concentrations of urea within the blood, a potentially longer dwell time can be performed.

Furthermore, it was shown that performing two successive 3-hour dwell times significantly reduced blood urea concentration. By draining the dialysate before it became too concentrated and infusing fresh dialysate, the new hypertonic dialysate maintained bulk flow into the peritoneal cavity via osmotic pressure and reestablished the concentration gradient to facilitate simple diffusion. As seen in Figure 14 and 15, both the convective and diffusive fluxes through the layers are shown to increase again once the dialysate is replenished after 3 hours.

5.1 Model Improvements

In order to improve the proposed model, one possible change that can be implemented is the potentially significant increase in surface area. This increase results from the increase in dialysate volume that expands the peritoneum and therefore increases the surface area of the membrane that is in contact with the dialysate. As shown in the sensitivity analysis for this model, the surface area of the membrane was shown to have some significance compared to other constants when calculating the final solution. To determine if this increase in surface area is an important aspect of this procedure, the constant value can be replaced with a function that is dependent with the changing volume of dialysate.

Another aspect of the model that can be altered to provide more physical accuracy is the implementation of the velocity model. To account for the decreasing velocity that results from osmotic pressure equilibration, experimental data was used to determine a best-fit equation as described earlier (Figure 3). An equation can instead be developed that changes the velocity as a function of osmotic, hydrostatic, and lymphatic pressures. These changes arise from use of a dialysate solution that is hypertonic to the blood and surrounding tissue. Using this type of pressure-dependent equation rather than a best-fit equation will provide a more accurate method of modeling the decrease in velocity over time and show its effects on the overall procedure.

The potential changes in concentration of urea in the dialysate from uptake into the lymphatic vessels were ignored in this model. To account for this the potential decrease in dialysate volume, another term would need to be added to the mass balance of the urea in the dialysate that accounts for the reabsorption of the urea and fluid into lymph. This change will determine the potential significance of lymphatic drainage on the effectiveness of the procedure.

The geometry of the peritoneum is very complex and thus can cause various changes in both the thickness of the peritoneal membrane at a specific section and the thickness of the tissue that is necessary for the computations. A more complex 2-D geometry or even a 3-D geometry can be used to make the model more physically accurate.

5.2 Physical Restraints

While multiple shorter sessions may be efficient and in some sense ideal, they may not be entirely realistic. Having such a short dwell time can lead to the patient changing out the dialysate up to eight times a day. Most common practices today perform an average of four dwells per day [10]. However, having such frequent changes increase the risk of infection around the area of the catheter that is surgically inserted into the body. Additionally, multiple dwells can lead to hypotension due to excessive fluid loss over a shorter period of time [11].

15

5.3 Design Recommendations

From our results, the implementation of multiple shorter sessions shows promise of decreasing the overall concentration of urea in the blood. However, as stated above, there are certain limitations to such a procedure. Clinical trials are needed in order to check for the practical significance of this procedure. Furthermore, more sanitary methods of exchanging the dialysate can be developed in order to decrease the risk of infection around the surgically implanted catheter.

Another option to improve the efficacy of this procedure is to develop a new dialysate solution. This dialysate should be formulated to increase the time required to equilibrate the osmotic and hydrostatic pressure. The velocity of the bulk flow would not decrease as quickly, allowing the dialysate to be in the peritoneum for a longer time. When preparing such a solution though, one would need to be aware of the flow of other solutes in both the blood and dialysate. For example, one way the dialysate is made hypertonic to the blood is by having high levels of glucose. However, the glucose in the dialysate can diffuse in to the blood causing high-blood sugar and leading to hyperglycemia in some patients [10].

Appendix A: Mathematical Statement of Problem

Governing Equations:

In order to model this problem, two additional equations were used in addition to the mass transfer governing equation. These two additional equations are the mass balance of urea on blood and the mass balance of urea in the dialysate.

Mass transfer governing equation
$$\frac{\partial C_{urea}}{\partial t} = D_{urea} \left(\frac{\partial^2 C_{urea}}{\partial x^2} \right) - v \frac{dC_{urea}}{dx}$$

Mass balance on blood (upper boundary on blood capillary layer)
$$\Delta \left(c_B \left[\frac{kg}{m^3} \right] \cdot V_B \ [m^3] \right) = -F \left[\frac{kg}{m^2 \ s} \right] \cdot A[m^2] \cdot \Delta t[s] + Q \left[\frac{kg}{m^3 s} \right] \cdot V_B[m^3] \cdot \Delta t[s]$$

$$\frac{d(V_B c_B)}{dt} = -F \cdot A + Q \cdot V_B$$
$$V_B \frac{dc_B}{dt} = -F \cdot A + Q \cdot V_B$$
$$V_B \frac{dc_B}{dt} = -F \cdot A + Q \cdot V_B$$

Change in concentration of urea in blood:
$$\frac{dc_B}{dt} = -\frac{F \cdot A}{V_B} + Q$$

C_B= Concentration of urea in blood in body
V_B= Volume of blood in the body
F = Diffusion flux of urea from the capillaries through the peritoneal membrane
A= Surface area of peritoneal membrane
Q = Generation of urea in blood in body
u = Velocity of water from the blood capillary through the membrane

This is implemented in COMSOL as a global equation as:
ut+((flux*area)/volume)-gen+(vel*area/volume)*u

Change in concentration of urea in dialysate
$$c_D \frac{dv}{dt} + V_D + \frac{dc_D}{dt} = h_m(c_{md} - c_D)A$$
$$u \ A \ c_D + V_D \frac{dc_D}{dt} = h_m \left(c_{boundary} - c_D \right) A$$
$$V_D \frac{dc_D}{dt} + u \ A \ c_D = h_m \left(c_{boundary} - C_D \right) A$$

This is implemented in COMSOL as a global equation as:
dialyvol*cinft+(vel*area+hm*area)*cinf-hm*area*cmd

Boundary Conditions:
Top boundary $=$ velocity of bulk flow $*$ concentration of urea in blood $=$ u $*$ c_b

Bottom boundary $= -($velocity of flow $*$ concentration in peritoneal membrane$) -$ (mass transfer coefficient $*$
difference in urea concentration in the peritoneal membrane and dialysate$) = $ -(vel*c)-(hm*(c-cinf))

Left and right boundary: flux $= 0$

<u>Equation for velocity of convective flow</u>
The velocity of bulk flow that was implemented in COMSOL changes over time according to the exponential model.

$$vel = 4 \ X \ 10^{-7} \exp(-0.001 \ t)$$

This exponential model best fit the experimental data for the change in velocity through the membrane. This equation was obtained from experimental data of peritoneal fluid kinetics in a research paper [9].
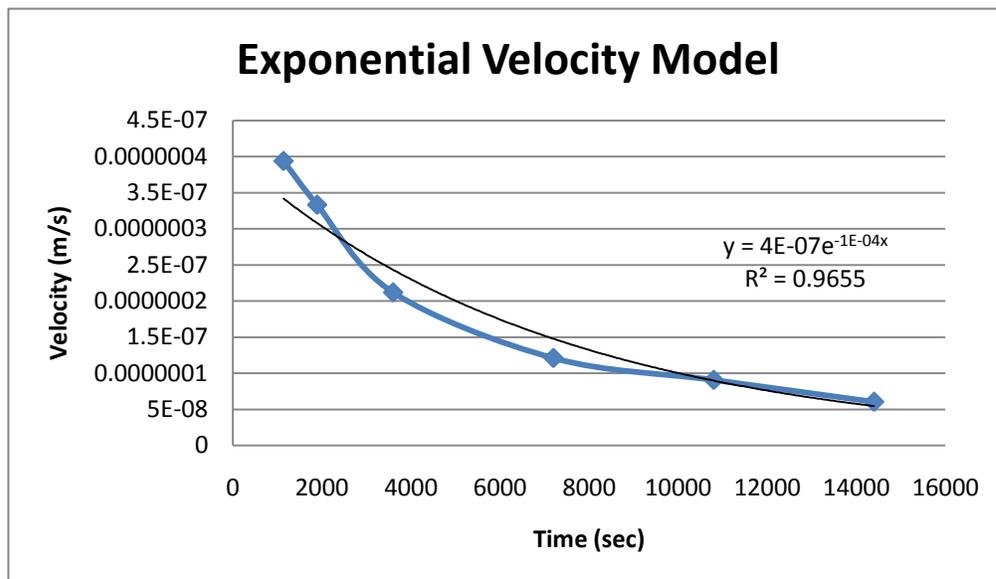

Figure 9. An exponential regression of the data points from research paper [9].

Initial conditions:

$$c_B(t = 0) = 6.6589 \frac{mol}{m^3}$$

$$c_D(t = 0) = 0$$

Input parameters:

Name	Value	Symbol (in COMSOL)	Source
Surface Area of Peritoneal	0.55 m^2	Area	Flessner, M. et al. 1984 [12]
Volume of Blood	0.005 m^3	volume	Stelin, G. et al. 1990 [13]
Urea Generation in Body	0.000316 mol/m^3(s)	gen	Khanna, R. et al. 2009 [14]
Mass Transfer Coefficient	4.848e-7 m/s	hm	Nolph, K. 1994 [15]
Volume of Dialysate	0.002 m^3	dialyvol	Stelin, G. et al. 1990 [13]
Diffusivity of urea through peritoneal membrane	1.81E-10 m^2/s	D$_1$	Flessner, M. et al. 1984 [12]
Diffusivity of urea through Tissue	1.1E-9 m^2/s	D$_2$	Conway, E. et al. 1934 [16]

Appendix B: Solution Strategy

To analyze the diffusion of urea out of the blood and into the dialysate, COMSOL Multiphysics was used, where the problem was set up as a transient diffusion problem with convection. The time interval for the calculations was from 0 to 21600 seconds (6 hours) with a time step every 600 seconds. For the calculations, a relative tolerance of 0.01 and an absolute tolerance of 0.001 were used.

The mesh for the schematic was designed as a structured mesh that consisted of 2D quadrilateral elements with four nodes. The flux at the edge of the tissue layer is used in the mass balance of the concentration of urea in the blood. Therefore the tissue layer is given a finer mesh in order to ensure that the flux used is accurate. The complete mesh of the schematic can be seen in Figure 10.
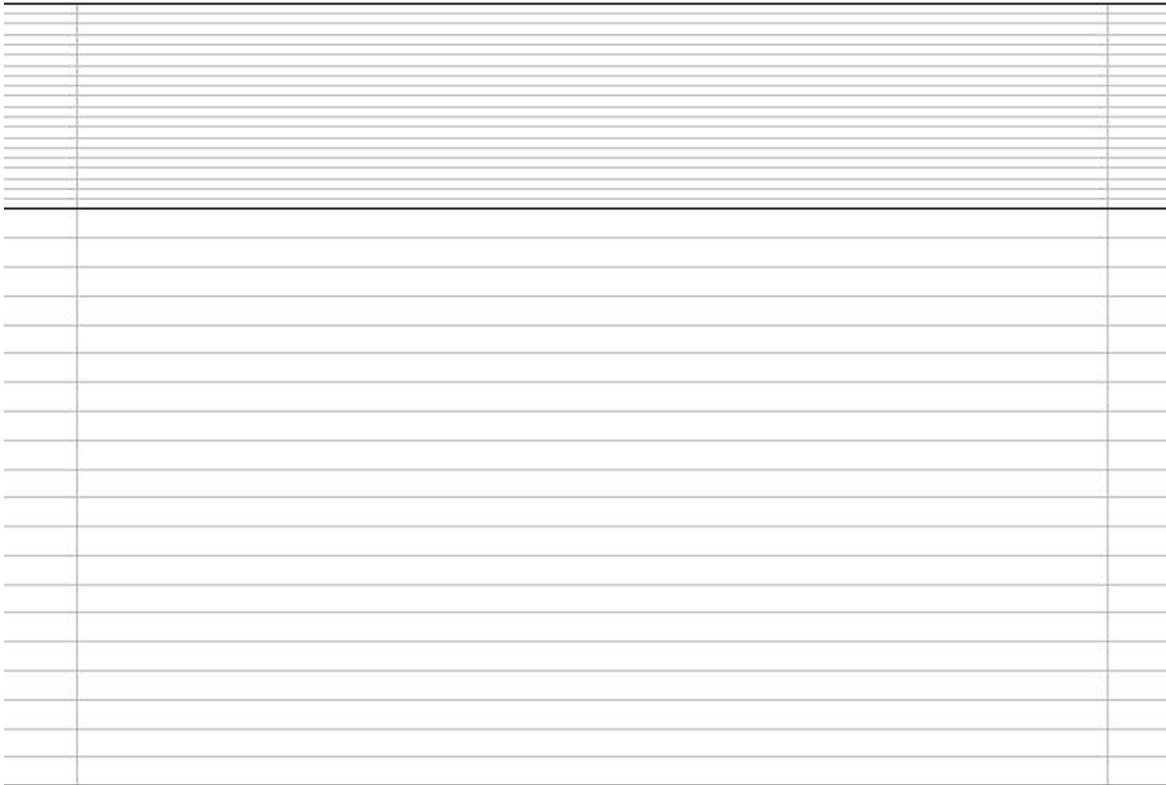

Figure 10. Enlarged version of the stuctured mesh used based on mesh convergence. There are more elements in the first layer.

To finalize the mesh used in Figure 10 a mesh convergence was performed in order to determine the number of elements after which the calculations performed become independent of the mesh. To determine this, the average concentration of urea in the tissue was taken using a set of meshes with varying element sizes. The results from the mesh convergence are shown in Figure 11. From the mesh convergence it was determined that 600 elements would be used.
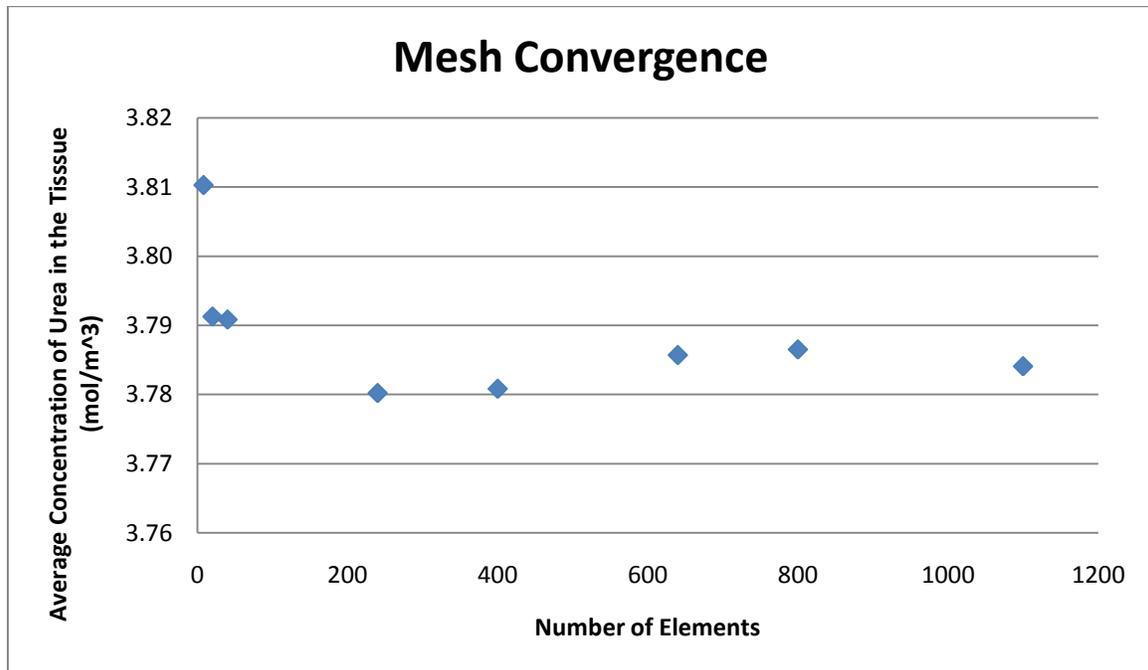

Figure 11. Mesh Convergence shown by calculating the average concentration of urea in the tissue layer for different number of elements. There are 600 elements in the final version of the Peritoneal Dialysis model.

Appendix C: Additional Visuals

The following figures show how diffusive and convective flux changes over 6 hours of peritoneal dialysis.
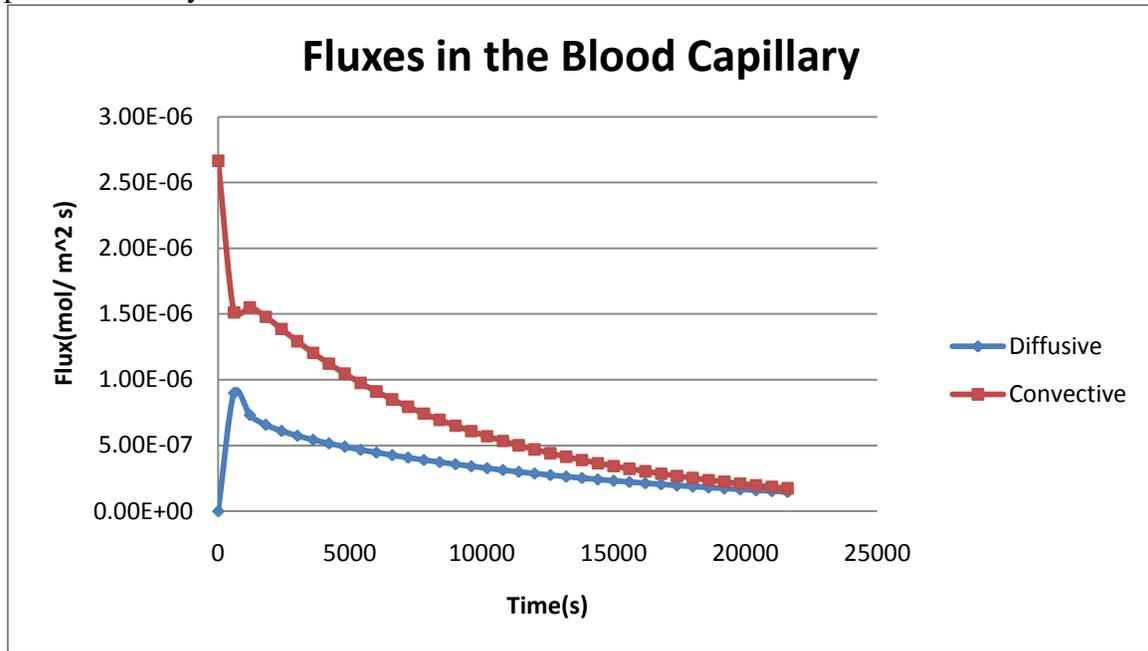

Figure 12. The diffusive and convective fluxes in the blood capillary layer during the one 6-hour peritoneal dialysis. This was taken at a point half-way through the blood capillary layer. Both of the fluxes decreased over time and the convective flux is higher than the diffusive flux.
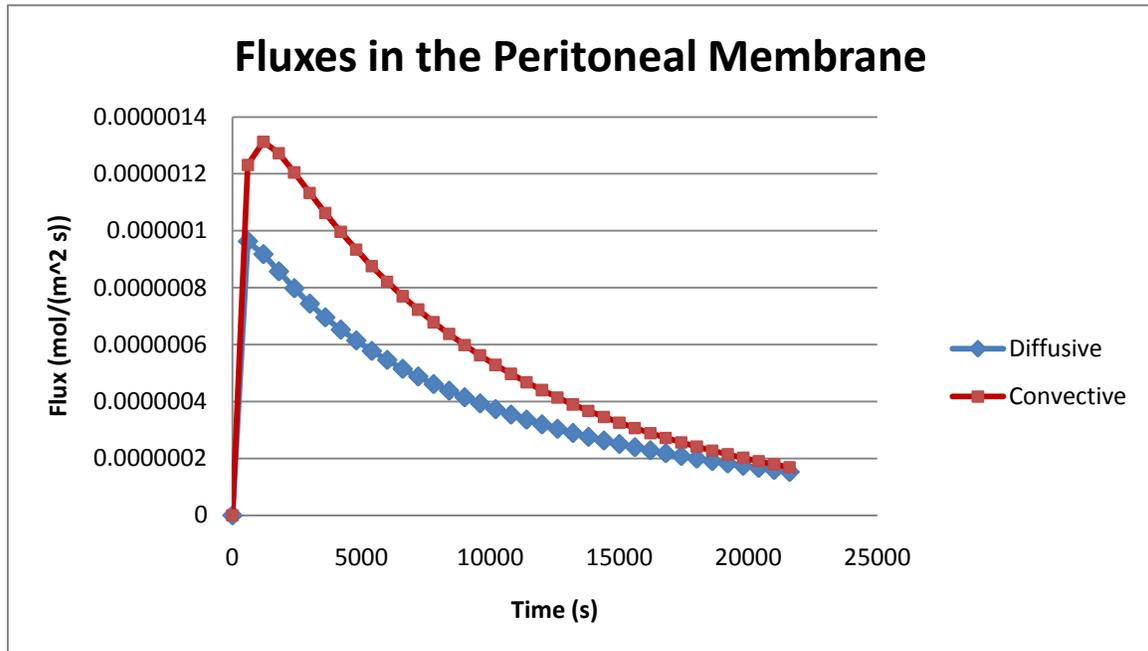

Figure 13. The diffusive and onvective fluxes in the peritoneal membrane during the one 6-hour peritoneal dialysis session. This was taken at a point half-way through the peritoneal membrane. Both fluxes decrease over time and the convective flux is consistently higher than the diffusive flux.
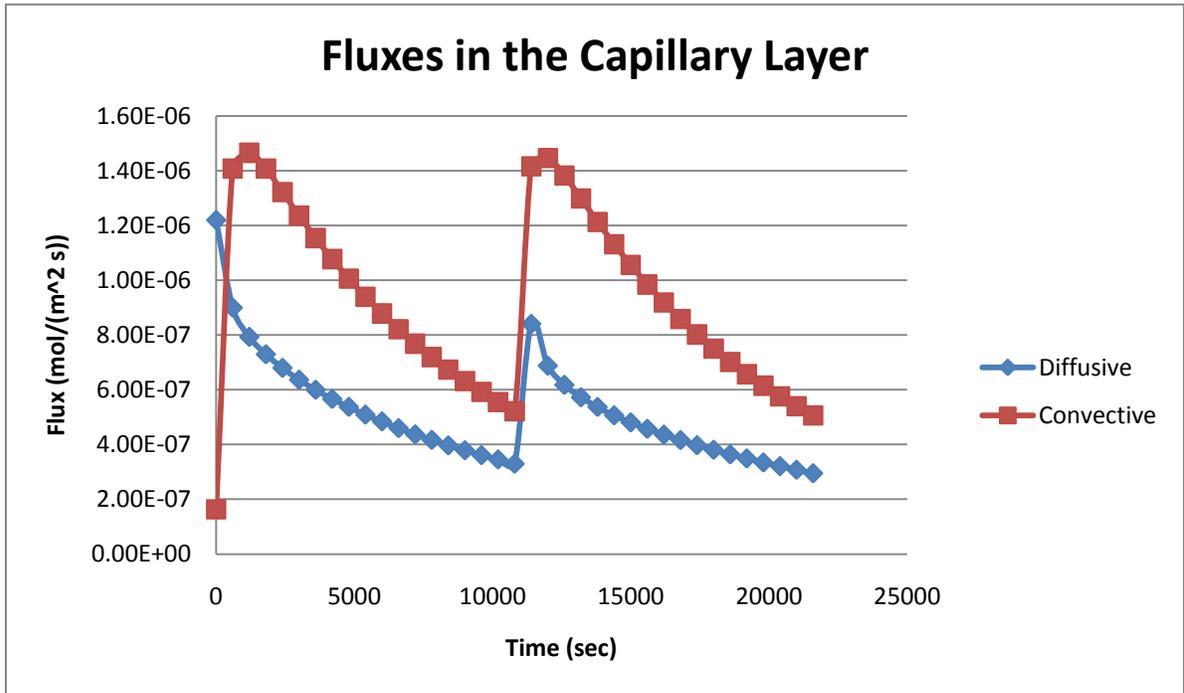
22

Figure 14. The diffusive and convective fluxes in the blood capillary layer during the two successive 3-hour peritoneal dialysis sessions. This was taken at a point half-way through the blood capillary layer. When the new dialysate is added into the peritoneal cavity, both the fluxes increase before decreasing towards the end.
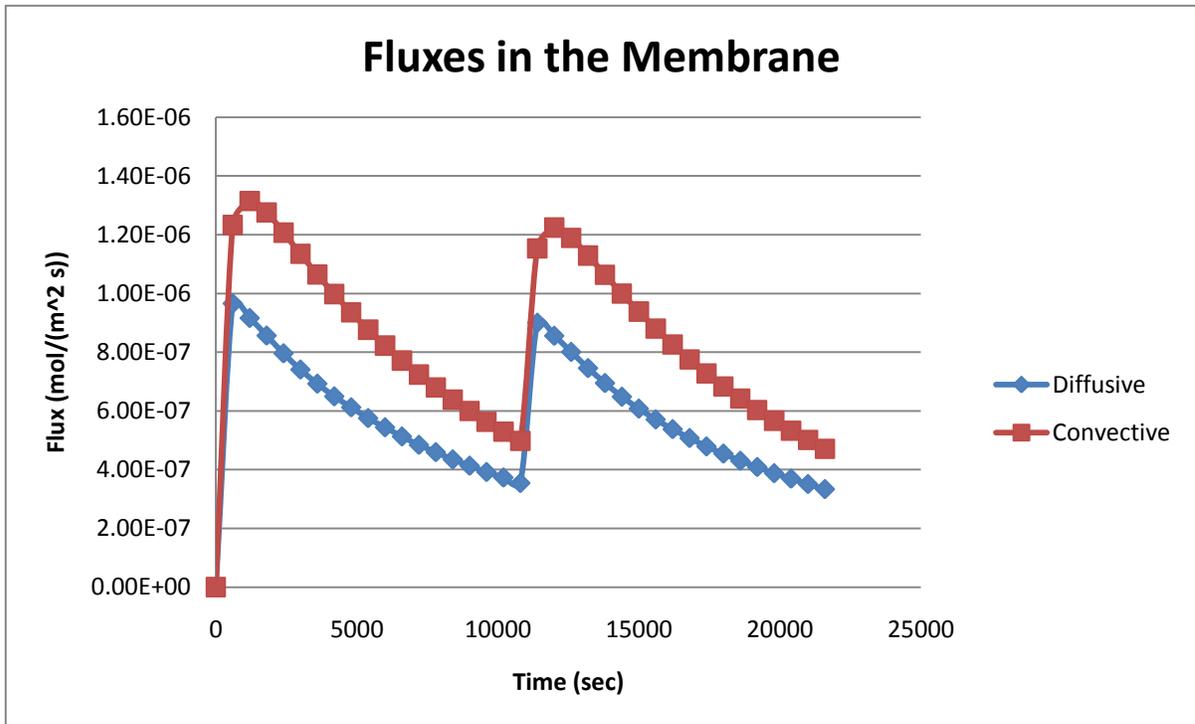

Figure 15. The diffusive and convective fluxes in the peritoneal membrane during the two successive 3-hour peritoneal dialysis sessions. This was taken at a point half-way through the peritoneal membrane. When the new dialysate is added into the peritoneal cavity, both the fluxes increases before decreasing towards the end. The convective flux remains higher than the diffusive flux throughout the process.

Appendix D: References

[1] Zhang QL, Rothenbacher D. (2008). Prevalence of chronic kidney disease in population-based studies: Systematic review. *BMC Public Health* 8,117.

[2] Levey AS, et al.(2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine* 150, 604-612.

[3] Coresh J, et al. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *American J Kidney Disease* 41(1),1-12.

[4] Schieppati A, Remuzzi G. (2005). Chronic renal diseases as a public health problem: Epidemiology, social, and economic implications. *Kidney International* 68, S7-S10.

[5] Levey AS, et al. (2007). Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. *International Society of Nephrology* 72, 247-259.

[6] Levey AS, et al.(2003). National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Annals of Internal Medicine* 139(2),137-147.

[7] Trevino-Becerra A, et al. (2009). Substitute treatment and replacement in chronic kidney disease: peritoneal dialysis, hemodialysis and transplant. *Cirugia Y Cirujanos* 77(5), 383-387.

[8] Rubin HR, et al. (2004). Patient Ratings of Dialysis Care With Peritoneal Dialysis vs Hemodialysis. *JAMA* 291, 697-703.

[9] Parikova, A., Smit, W., Strujik, D., Zweers, M., Krediet, R. (2005). The contribution of free water transport and small pore transport to the total fluid removal in peritoneal dialysis. *Kidney International* 68**,** 1849-1856.

[10] Strauss, G., Holmes, D., Dennis, R., Nortman, D. Short-Dwell Peritoneal Dialysis: Increased use and impact on clinical outcome.
http://www.advancesinpd.com/adv93/11short93.html

[11] Ehrman, J., Gordon, P., Visich, P., Keteyian S. (2008) Clinical Exercise Physiology, Second edition. Champaign, IL: Human Kinetics.

[12]Flessner, M., Dedrick, R., Schultz, J. (1984). A distributed model of peritoneal-plasma transport: theoretical considerations. *The American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 246, 597-607.

[13] Stelin, G., Rippe, B. (1990). A phenomenological interpretation of the variation in dialysate volume with dwell time in CAPD. *Kidney International* 38, 465-572.

[14] Khanna, R., Krediet, R. (2009) Nolph and Gokal's Textbook of Peritoneal Dialysis, third edition. Springer, US.

[15] Nolph, K. (1994). Clinical implication of membrane transport characteristics on the adequacy of fluid and solute removal. *Peritoneal Dialysis International* 14(3), S78-S81.

[16] Conway, E., Kane, F. (1934). Diffusion rates of anions and urea through tissue. *Biochemistry Journal* XXVIII , 1769-1783.

Images in Figure 1 were taken from:
1. www.buzzle.com/.../peritoneal-cavity.jpg
2. www.theodora.com/anatomy/images/image1038.gif

Note: Copyright for images was not obtained.