Modeling Differences Between Therapeutic Plasma Exchange Configurations

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ABSTRACT

A common error in the administration of Plasmapheresis (plasma exchange) procedures is the switching of inflow and outflow ports to the plasma exchange machine, resulting in the outflow port being upstream from the inflow port. In this paper, mathematical methods are used to determine under what conditions any significant consequences arise from such an error. We find that when full cardiac output passes into the plasma exchange circuit, the effects of the swapped configuration are insignificant.

1 Introduction

Plasmapheresis, Therapeutic Plasma Exchange (TPE), or Plasma Exchange Therapy (PET) refer to the removal and exchange of a patient's blood plasma in order to treat a variety of conditions, including many autoimmune disorders. Practitioners use three primary methods to perform the exchange: discontinuous flow centrifugation, continuous flow centrifugation, and plasma filtering. This paper is concerned with continuous flow centifugation. Patients are often connected to the TPE mechanism via an ECMO (Extracorporeal Membrane Oxygenation) Machine rather than directly to the body.

In many TPE procedures, the inflow and outflow ports to the centrifugal chamber of the plasma exchange mechanism are accidentally reversed by practitioners. This paper presents several modeling techniques used to investigate whether switching the inflow and outflow ports has significant consequences for the TPE process.

1.1 Notation

Q measures the total blood flow from the ECMO Machine in mL/sec. This flow continues into TPE circuit. Q_1 represents the flow of blood into the centrifugal chamber of the TPE Machine, where it undergoes a plasma exchange. The condition $Q_1 \leq Q$ must always be satisfied for conservation of blood volume, V.

'Plasma' refers to all the components of blood except for blood cells, and is about 55% of blood by volume, thus the parameter $[P]_0 = 0.55$ is the concentration of plasma in a given volume of blood.

The modeling approach follows the variable γ, defined as the fraction of new plasma (post-exchange) to total plasma in a given volume of blood. Due to bifurcations in the TPE system, it will have different values at different points in the system and in the body, thus γ will be sub-scripted accordingly.

It is important to note that both γ and $[P]_0$ are dimensionless variables, where $\gamma \cdot [P]_0 \cdot V$ represents the total volume of new plasma.

2 ODE Model

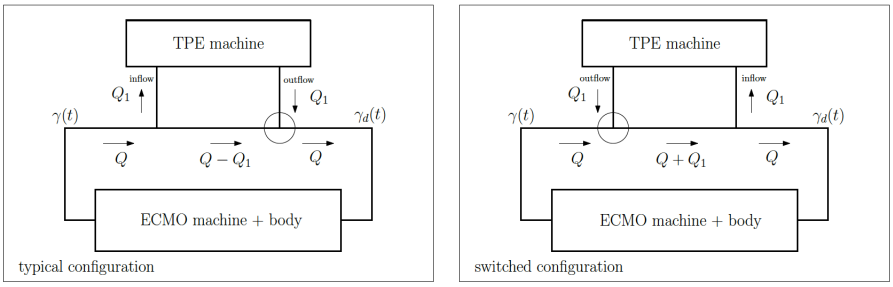

Figure 1: Schematics of the typical (left) and switched (right) configurations.

In Figure 1 we show a schematic of the TPE setup for both the typical/normal and the switched configuartions. We make two important simplifying assumptions. We assume old plasma is completely exchanged for new plasma, implying volume of plasma per unit time flowing out of the machine is $Q_1[P]_0$. We also assume old and new plasma are instantaneously mixed at the junction where outflow from the TPE machine meets the rest of the flow. This junction is circled in Figure 1. Under these assumptions, conservation of new plasma at the circled junction in the normal and switched configurations is:

$$(normal) \quad \gamma_d(t)Q[P]_0 = Q_1[P]_0 + \gamma(t)(Q - Q_1)[P]_0 \tag{1}$$

$$(switched) \quad \gamma_d(t)(Q + Q_1)[P]_0 = Q_1[P]_0 + \gamma(t)Q[P]_0. \tag{2}$$

Notice that $\gamma_d(t)Q[P]_0$ is new plasma inflow into the ECMO machine/body compartment, while $\gamma(t)Q[P]_0$ is the new plasma outflow. The change in new plasma per unit time, equal to inflow minus outflow, can be represented by the differential equation:

$$\frac{d}{dt}(\gamma(t)[P]_0 V) = \gamma_d(t)Q[P]_0 - \gamma(t)Q[P]_0, \tag{3}$$

where V is a parameter equal to the blood volume in the ECMO machine/body compartment of the model, shown in Figure 1. Substituting (1) or (2) into (3) and dividing through by V and $[P]_0$, we obtain differential equations for the fraction of new plasma in the normal and switched configurations:

$$(normal) \quad \frac{d}{dt}\gamma(t) = \frac{Q}{V}\frac{Q_1}{Q}(1-\gamma(t)) \tag{4}$$

$$(switched) \quad \frac{d}{dt}\gamma(t) = \frac{Q}{V}\frac{Q_1}{Q+Q_1}(1-\gamma(t)). \tag{5}$$

A related model can be derived by introducing a delay s, which should be interpreted as the characteristic travel time required for a parcel of new plasma to traverse the ECMO machine/body compartment. With this assumption, $\gamma_d(t) = \gamma(t+s)$. Substituting this equality into equations 1 and 2 results in a set of algebraic delay equations for the fraction of new plasma in the normal and switched configurations:

$$(normal) \quad \gamma(t+s) = \gamma(t) + \frac{Q_1}{Q}(1-\gamma(t)) \tag{6}$$

$$(switched) \quad \gamma(t+s) = \gamma(t) + \frac{Q_1}{Q+Q_1}(1-\gamma(t)). \tag{7}$$

These delay equations can be solved numerically, but also are related to 4 and 5. The time delay s, in minutes, is small compared to the overall variation in $\gamma(t)$, which occurs over the course of hours. In this light, it reasonable to approximate the time derivative of $\gamma(t)$ with the difference quotient:

$$\frac{d}{dt}\gamma(t) \approx \frac{\gamma(t+s)-\gamma(t)}{s} \tag{8}$$

Upon rewriting 6 and 7 and substituting the difference quotient for the time derivative, we obtain:

$$(normal) \quad \frac{d}{dt}\gamma(t) = \frac{1}{s}\frac{Q_1}{Q}(1-\gamma(t)) \tag{9}$$

$$(switched) \quad \frac{d}{dt}\gamma(t) = \frac{1}{s}\frac{Q_1}{Q+Q_1}(1-\gamma(t)). \tag{10}$$

In other words, the delay equations, rewritten as differential equations under the assumption of a small delay time, are exactly those obtained in 4 and 5 with $s = \frac{V}{Q}$.

The differential equations appearing above take the general form:

$$\frac{d}{dt}\gamma(t) = \beta(1-\gamma(t)), \tag{11}$$

$$\gamma(0) = 0; \quad \beta = \{\frac{1}{s}\frac{Q_1}{Q}, \quad \frac{1}{s}\frac{Q_1}{Q+Q_1}\} \tag{12}$$

The solution is expressed analytically as

$$\gamma(t) = 1 - \exp(-\beta t) \tag{13}$$

2.1 Results of the ODE Model

Results from these models are computed with a nominal set of parameters for a typical patient. We use the relationship $s = \frac{V}{Q}$, so two of the three parameters Q, V, or s can be chosen independently. We choose to fix Q and s in our simulations. Concentration of plasma in blood is $[P]_0 = 0.55$, total flow is $Q = 83.3$ mL/sec, TPE machine flow is $Q_1 = 1.5$ mL/sec, and the time delay is $s = 60$ sec. In Figure 2, we use equations (9) and (10) to plot the new plasma concentration as functions of time for both the normal and switched configurations. In the left panel is the new plasma concentration, and on the right panel is the relative difference in new plasma concentration between the two configurations. Figure 3 contains results analogous to those in Figure 2, but for the delay equations (6) and (7). It is clear that while there exists a positive difference between the two methods, the magnitude of the difference is insignificant in a clinical setting.

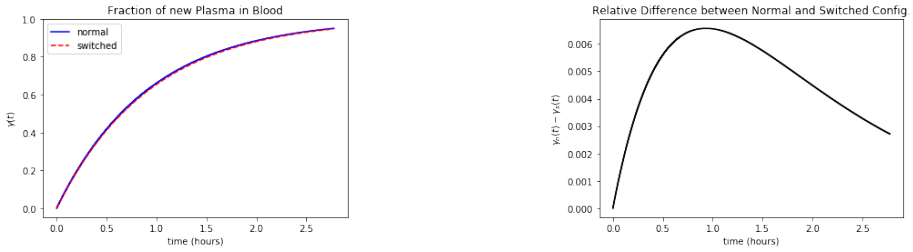

Figure 2: Comparing the normal and switched configurations using the differential equations (9) and (10). On the left is the new plasma concentration plotted as a function of time. On the right is the relative difference in new plasma concentration between the two configurations.

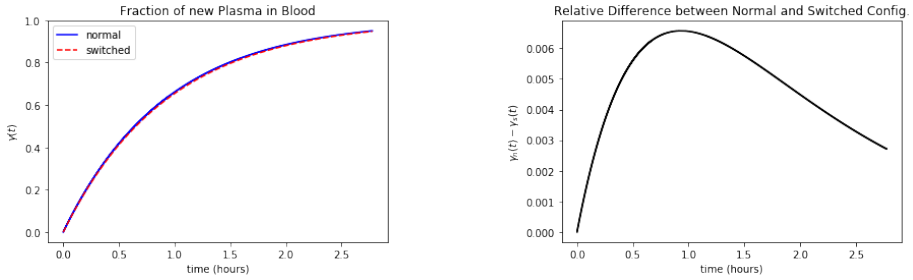

Figure 3: Comparing the normal and switched configurations using delay equations (7) and (8). On the left is the new plasma concentration plotted as a function of time. On the right is the relative difference in new plasma concentration between the two configurations.

3 Fractional Cardiac Output ADE Model

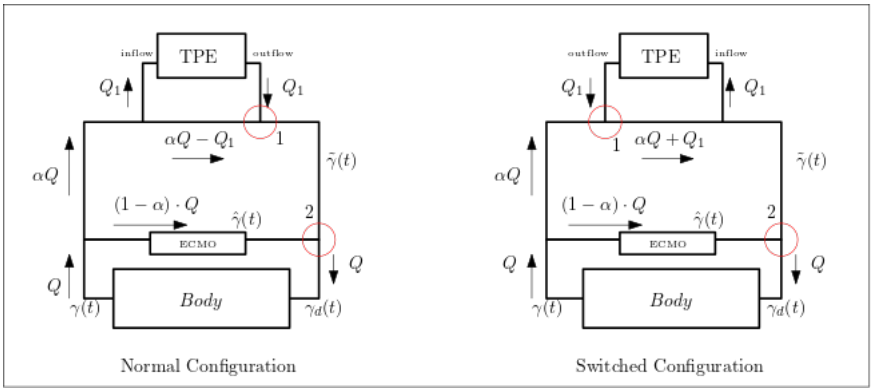

Figure 4: Schematics of the normal (left) and switched (right) configurations.

Since TPE Machines are often connected to ECMO Machines, in this section we generalize the previous model by removing the assumption that the full cardiac output Q passes through the machine (i.e. the TPE Machine is indirectly connected to the patient).

We define another dimensionless variable $\alpha \in [0, 1]$ to represent the fraction of cardiac output undergoing the plasma exchange procedure. Meanwhile, $(1 - \alpha)Q$ will pass through a second compartment of the machine–following a path which takes s_1 seconds to complete, with fraction of new plasma $\hat{\gamma}(t)$. In the following equations, s_2 represents the delay associated with blood circulation in the body. Additionally, $\tilde{\gamma}(t)$ represents the fraction of new plasma after mixing point 1. As in Section 2.1, $\gamma_d(t)$ represents the fraction of new plasma in the blood downstream of the system.

3.1 Typical Configuration

We begin by considering the following conservation equations for the typical setup of the TPE Machine:

$$(Point \quad 1) \quad \tilde{\gamma}(t) \cdot \alpha Q[P]_0 = Q_1[P]_0 + \gamma(t)(\alpha Q - Q_1)[P]_0 \tag{14}$$

$$(Point \quad 2) \quad \hat{\gamma}(t)(1-\alpha)Q[P]_0 + \tilde{\gamma}(t) \cdot \alpha Q[P]_0 = \gamma_d(t)Q[P]_0 \tag{15}$$

Additionally we have the delay conditions:

$$ECMO/Body \quad delay: \quad \gamma_d(t) = \gamma(t + s_2)$$

$$Compartment \quad delay: \quad \gamma(t) = \hat{\gamma}(t + s_1)$$

Rearranging the equations we arrive at the delay equation:

$$\gamma_d(t) = (\alpha - \frac{Q_1}{Q})\gamma_d(t - s_2) + (1 - \alpha)\gamma_d(t - s_1 - s_2) + \frac{Q_1}{Q} \tag{16}$$

Which imposes the new condition $t \geq (s_1 + s_2)$. Yet if we revert to analyzing $\gamma(t) = \gamma_d(t - s_2)$, we arrive at the equation:

$$\gamma(t + s_2) = (\alpha - \frac{Q_1}{Q}) \cdot \gamma(t) + (1 - \alpha) \cdot \gamma(t - s_1) + \frac{Q_1}{Q} \tag{17}$$

which combined with the initial condition $\gamma(t \leq 0) = 0$ yields $\gamma(s_2) = \frac{Q_1}{Q}$.

3.2 Switched Configuration

Under the switched configuration we use the following equations:

$$(Point \quad 1) \quad \tilde{\gamma}(t)(\alpha Q + Q_1)[P]_0 = Q_1[P]_0 + \gamma(t)\alpha Q[P]_0 \tag{18}$$

$$(Point \quad 2) \quad \hat{\gamma}(t)(1 - \alpha)Q[P]_0 + \tilde{\gamma}(t)\alpha Q[P]_0 = \gamma_d(t)Q[P]_0 \tag{19}$$

$$ECMO/Body \quad delay: \quad \gamma_d(t) = \gamma(t + s_2)$$

$$Compartment \quad delay: \quad \gamma(t) = \hat{\gamma}(t + s_1)$$

We again solve for $\tilde{\gamma}(t)$ and γ_d:

$$\tilde{\gamma}(t)(t) = \frac{Q_1 + \gamma(t) \cdot \alpha Q}{\alpha Q + Q_1}$$

$$\gamma_d(t) = \frac{\alpha(Q_1 + \gamma(t) \cdot \alpha Q)}{\alpha Q + Q_1} + \gamma(t - s_1)(1 - \alpha)$$

Which results in the delay equation

$$\gamma(t + s_2) = \frac{\alpha^2 Q}{\alpha Q + Q_1}\gamma(t) + (1 - \alpha)\gamma(t - s_1) + \frac{\alpha Q_1}{\alpha Q + Q_1} \tag{20}$$

We can validate that the two models agree with each other by showing that equation (6) = (17) and (7) = (20) when $\alpha = 1$ and $s_2 = s$.

$$(normal) \quad \gamma(t + s) = \gamma(t) + \frac{Q_1}{Q}(1 - \gamma(t))$$

$$(switched)\gamma(t+s_2) = \gamma(t+s) = \frac{Q}{Q + Q_1}\gamma(t) + \frac{Q_1}{Q + Q_1} = \gamma(t) + \frac{Q_1}{Q + Q_1}(1 - \gamma(t))$$

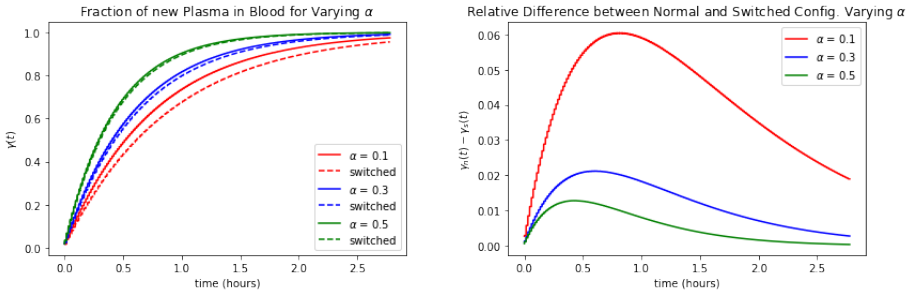

Figure 5: Comparing the normal and switched configurations while varying α (with $s_1 = 53$ sec fixed) using equations (17) and (20). On the left is the new plasma concentration plotted as a function of time. On the right is the relative difference in new plasma concentration between the two configurations.

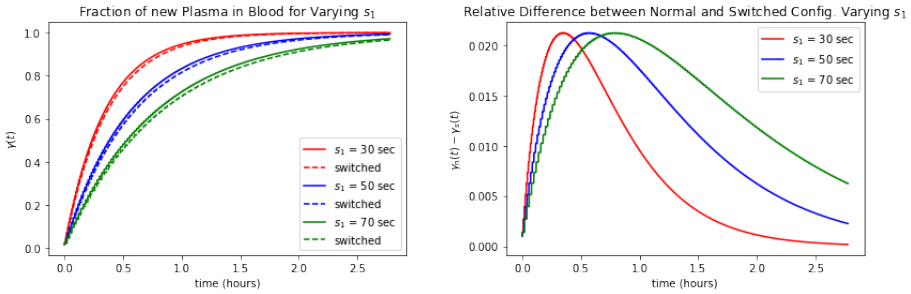

Figure 6: Comparing the normal and switched configurations while varying s_1 (with $\alpha = 0.3$ fixed) using equations (17) and (20). On the left is the new plasma concentration plotted as a function of time. On the right is the relative difference in new plasma concentration between the two configurations.

3.3 Results of the Fractional Output ADE Model

The delay equations (17) and (20) are not solvable analytically, yet we can simulate results with nominal parameters that represent the typical patient. We can no longer take advantage of the relationship $s = \frac{V}{Q}$, and must choose all parameters (discussed in section 4). In the results shown in Fig. 5 and 6, $V = 5000$ mL, $Q = 83.3$ mL/sec, $Q_1 = 1.5$ mL/sec, and $s_2 = 60$ sec.

In each case, the flow of blood with new plasma Q_1 remains fixed. However, it is clear that decreasing α leads to significant increases in the disparity between the configurations. Nevertheless, the difference remains inconsequential.

4 Modeling Circulatory Transit Time

The validity of the prior models rest on the assumption of a single transit time for blood throughout the body. In the following two sections, we attempt to remove the assumption of a scalar delay time for circulatory transit. The previously assumed circulatory delay of $s = 60$ sec represents the average delay time based on a body with 5 L of blood, and cardiac output of $83.\hat{3}$ mL/sec (average values for human beings). However, it is evident that due to the geometry of the body and the geometry of our circulatory system, that the multitude of possible paths a blood cell could travel should not be represented by a scalar variable, but rather by a distribution.

Empirical data has shown that vascular transit times can be modelled as a Gamma distribution ($s \sim \Gamma(a, b)$) [Mou+14]. We maintain that $E[s] = 60$ sec by the motivation above, choosing distribution parameters a, b such that $E[s] = \frac{a}{b} = 60$. The Gamma distribution is only defined for positive real values, which is a important qualitative feature in this context, but more importantly, it is not a symmetrical distribution (the consequences of which are discussed as they pertain to each model below).

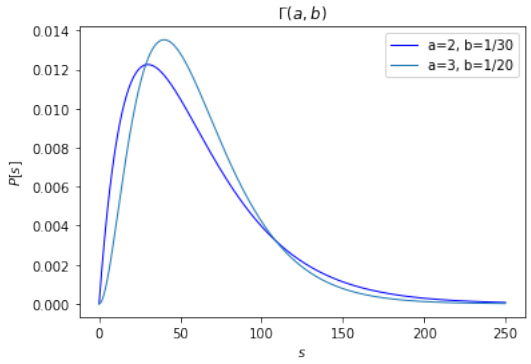

Figure 7: Gamma Distribution with $E[s] = \frac{a}{b} = 60$ sec for different a, b.

4.1 Random Travel Time Model

We return to the analytic solution of the full cardiac output ODE model (Eq. 13), written in the form:

$$\gamma(t) = 1 - \exp(\frac{1}{s}Kt), \tag{21}$$

with $K_n = \frac{-Q_1}{Q}$ in the normal configuration and $K_s = \frac{-Q_1}{Q+Q_1}$ in the switched case. The purpose of this form is to isolate the circulation time parameter s from the flow parameters.

Out first method, to incorporate the transit time distribution, is to create sample means from the analytic solution using a scalar transit time sampled from

a distribution of travel times. We expect these sample means to be normally distributed, which will allow us to analyze $E[\gamma(t)]$ and the standard error.

4.2 Results of the Random Travel Time Model

The results of the Random Travel Time Model are exhibited in Figures 8-10

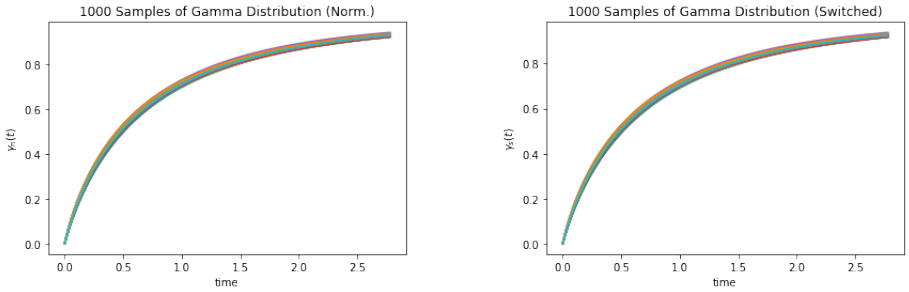

Figure 8: Plotting 1,000 sample means of the normal and switched configurations with $s \sim \Gamma(2, 1/30)$ using equation (21).

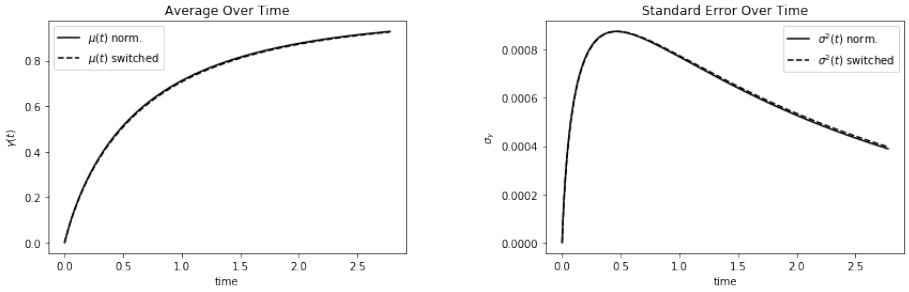

Figure 9: Comparing the mean of normal and switched configuration sample means with $s \sim \Gamma(2, 1/30)$ using equation (21). On the right is the standard error for the normal and switched configurations, where it is clear that error reaches a maximum and damps out with time.

4.3 Convolution Integral Model

We introduce a new perspective of modeling $\gamma(t)$ called the convolution integral [Zie00; Krz19]. The schematic of the model is shown in Fig. 10. We claim that a sample of homogeneously mixed blood, where circulatory transit time is Gamma distributed, will contain "blood particles" whose transit times are

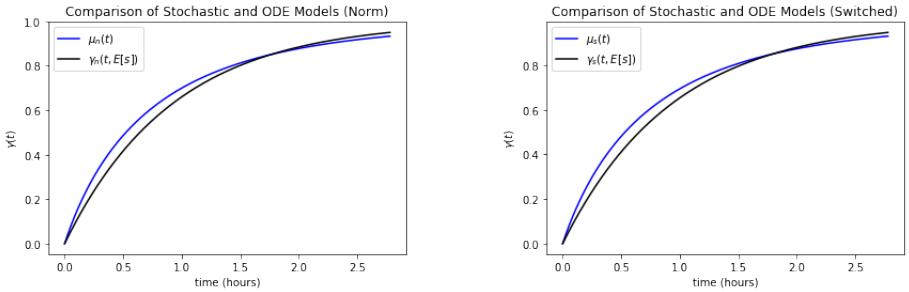

Figure 10: Comparison of the SDE Model (blue) and the analytic solution to the ODE Model (black) in the normal and switched configurations using the results above. The asymmetry of the Gamma distribution creates the case that $E[\gamma(t;s)]$ need not equal $\gamma(t, E[s])$. The stochastic curve begins increasing faster than the single transit time model, yet eventually gets overtaken.

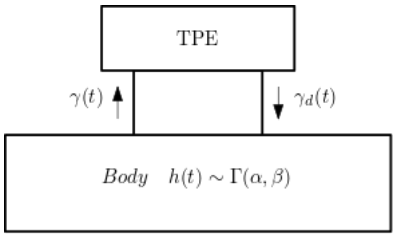

Figure 11: Schematics of the convolution integral system.

Gamma distributed. Thus, given $\gamma_d(t)$ a function of $\gamma(t)$, and the transit time probability density function $h(\tau) \sim \Gamma(a, b)$ we can write

$$\gamma(t) = \int_0^t \gamma_d(t-\tau) \cdot h(\tau; a, b) d\tau \tag{22}$$

Where $\gamma(t)$ represents the fraction of new plasma to total plasma in the blood entering the TPE/ECMO machine.

In this case we return to the system described in Section 2.1. We use the conservation equations to solve for $\gamma_d(t)$ in terms of $\gamma(t)$ in the normal and switched configurations:

$$(normal) \quad \gamma_d(t) = \frac{Q_1}{Q} + \gamma(t)\frac{Q - Q_1}{Q} \tag{23}$$

$$(switched) \quad \gamma_d(t) = \frac{Q_1}{Q + Q_1} + \gamma(t)\frac{Q}{Q + Q_1} \tag{24}$$

This assumes the TPE process is instantaneous. If we would like to take into account a delay (s) for the plasma exchange, the equations become:

$$(normal) \quad \gamma_d(t) = \frac{Q_1}{Q} + \gamma(t-s)\frac{Q-Q_1}{Q} \tag{25}$$

$$(switched) \quad \gamma_d(t) = \frac{Q_1}{Q+Q_1} + \gamma(t-s)\frac{Q}{Q+Q_1} \tag{26}$$

While we can't solve these equations analytically, we can simulate their results using nominal parameters that represent a typical patient. In the following results $a = 2$, $b = 0.033$, $V = 5$ L, $Q = 83.3$ mL/sec, and $Q_1 = 1.5$ mL/sec. Note that when creating a numerical scheme for simulation, the convolution is insensitive to direction of convolution.

Claim: Convolution is not sensitive to direction

$$\gamma(t) = \int_0^t \gamma_d(t-\tau) \cdot h(\tau; a, b) d\tau$$

with dummy variable $\tau' = t - \tau, d\tau' = -d\tau$ we rewrite Equation (22) as:

$$\gamma(t) = -\int_t^0 \gamma_d(\tau') \cdot h(t-\tau'; a, b) d\tau = \int_0^t \gamma_d(\tau') \cdot h(t-\tau'; a, b) d\tau'$$

4.4 Results of the Convolution Integral Model

The results for the Convolution Integral Model are shown in Fig. 12 - 14.

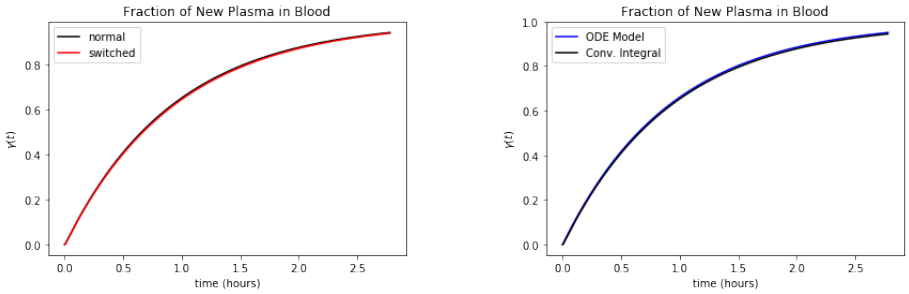

Figure 12: On the left: A comparison of the normal and switched configurations using equations 23, 24. On the right: a comparison of the Convolution Integral using equation 23 (black) and the ODE Model using equation 13 (blue). The results regarding switching the configuration of the TPE machine remains the same, and our solution agrees with the ODE Model.

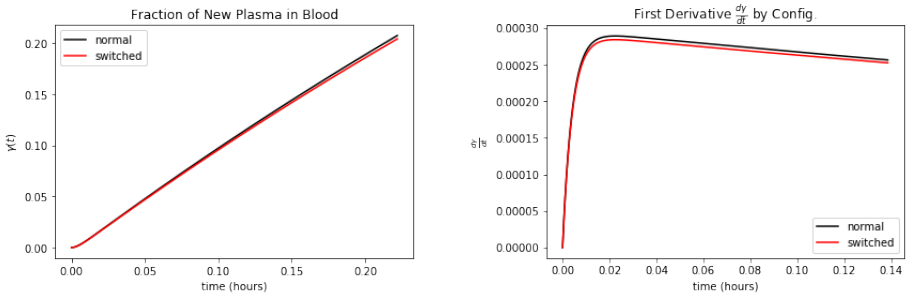

Figure 13: The convolution integral model is qualitatively different than the ODE model–namely, its second derivative is positive at the start of the treatment. The second derivative of the solution is positive a the beginning of treatment, with a corresponding point of inflection at the maximum of the first derivative.

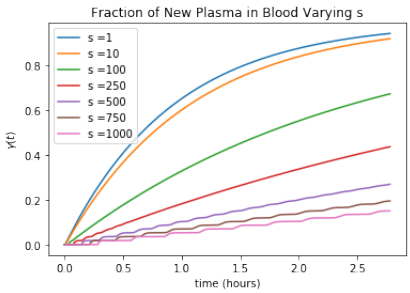

Figure 14: Fraction of new plasma in blood while varying delay parameter s seconds. The convolution integral model has a different and far more severe sensitivity to a TPE machine delay than previously observed. A machine associated delay causes rapid jumps in $\gamma(t)$ which damp out in time, yet it drastically slows the process.

5 Conclusion

Under various modeling schemes with varying degrees of granularity, we find that the switched configuration is only significantly slower in the case where a very small fraction of cardiac output enters the centrifugation chamber. However, even though in this case the length-scale of the procedure is increased, it is not compromised.

We are currently implementing Immersed Boundary CFD simulations to understand how mixing depends on the machine geometry to test the assumption of perfect, instantaneous mixing. Early simulations lead us to believe that geometry can optimized to validate the assumption.

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