Modeling the Bacterial Clearance in Capillary Network Using Coupled Stochastic-Differential and Navier-Stokes Equations

Presented by
Aleksandar Jeremic

Department of Electrical and Computer Engineering
McMaster University
Ontario, Canada
Motivation

- The capillary network is a complex-interconnected structure.
- A single blood cell traveling via a capillary bed passes through, on average, 40-100 capillary segments!
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Exchange process

Figure: Capillary exchange process.
Exchange mechanism

- **Diffusion**: which depends on the presence of a concentration gradient across the capillary wall.
- **Bulk flow**: which depends on pressures across the capillary wall and occurs through pores and intercellular clefts.
- **Vesicular transport**: which depends on the formation of specific transport systems in the capillary wall.
Physical model of the flow

Assumptions

- Blood is an incompressible Newtonian fluid.
- Three dimensional circular cylindrical tube.
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The equations of momentum and continuity are given by

$$\rho \left( \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u} + \mathbf{f}$$

$$\nabla \cdot \mathbf{v} = 0$$
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\]
Physical model of the flow: Starling’s law

The radial velocity $u_r$ is governed by Starling’s law which is a mathematical model for fluid movement across capillaries, given by

$$u_r = K[(p - p_i) - (\pi_c - \pi_i)]$$

where,

- $K$ is the hydraulic conductance also called the filtration constant,
- $p_i$ is the interstitial hydrostatic fluid pressure,
- $\pi_c$ is the capillary oncotic pressure (osmotic pressure of the plasma proteins), and
- $\pi_i$ is the tissue oncotic pressure (osmotic pressure of the proteins in the interstitial fluid).
The corresponding boundary conditions are

\[
\phi \frac{\partial u_z}{\partial r} + u_z = 0 \quad \text{at} \quad r = R
\]

\[
u_r = \frac{K \mu}{R} \left( \frac{p}{\rho_c - \rho_i + p_i} - 1 \right) \quad \text{at} \quad r = R
\]

\[p = p_a \quad \text{at} \quad z = 0\]

\[p = p_v \quad \text{at} \quad z = L\]
### Capillary Specifications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L$</td>
<td>1$mm$</td>
</tr>
<tr>
<td>$R$</td>
<td>1$\mu m$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>1025$kg/m^3$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>0.0015$Ns/m^2$ at 37$^\circ$</td>
</tr>
<tr>
<td>$p_{\text{arteriole end}}$</td>
<td>40$mmHg$</td>
</tr>
<tr>
<td>$p_{\text{venule end}}$</td>
<td>15$mmHg$</td>
</tr>
<tr>
<td>$p_i$</td>
<td>−6$mmHg$</td>
</tr>
<tr>
<td>$\varrho_c$</td>
<td>25$mmHg$</td>
</tr>
<tr>
<td>$\varrho_i$</td>
<td>5$mmHg$</td>
</tr>
<tr>
<td>$L_c$</td>
<td>$28.6 \times 10^{-7} cm/(s \cdot cmH_2O)$, $cmH_2O = 0.098KPa$</td>
</tr>
<tr>
<td>$\phi$</td>
<td>0 and 0.15</td>
</tr>
</tbody>
</table>

**Table:** Capillary specifications.
Physical model of the flow: Example

(a) Arteriole end.  (b) Venule end.

**Figure**: Flow velocity distribution.
Physical model of the flow: Example

**Figure:** Axial velocity profile at \( z = L/2 \) for different slip coefficients.
Physical model of the flow: Example

Figure: Axial velocity profile along the axis $r = 0$ for different slip coefficients.
Physical model of the flow: Example

Figure: Pressure profile along the axis $z = 0$ of a capillary segment.
The exchange process can be modeled with two main parameters:

- $P_A$: The probability of a particle to get absorbed into the surrounding tissues.
- $P_T$: The probability of a particle to get transmitted to the proceeding capillary network.

It can be modeled using FP equation with drift tensor coupled with the flow model.
The SDE process for the transport of particle in an open environment is given by

\[ dX_t = \mu(X_t, t)dt + \sigma(X_t, t)dW_t \]

The corresponding Fokker-Planck equation is

\[
\frac{\partial f(r, t)}{\partial t} = -\sum_{i=1}^{2} \frac{\partial}{\partial x_i} D_i^1(r, t) + \\
+ \sum_{i=1}^{2} \sum_{j=1}^{2} \frac{\partial^2}{\partial x_i \partial x_j} D_{ij}^2(r, t) f(r, t)
\]
Under the following assumptions

1. 2D Infinite medium.
2. Homogenous and isotropic diffusivity.
3. Drift free.

The solution is

$$f(r, t) = \frac{1}{4\pi D(t - t_0)} e^{-\|r - r_0\|^2/4D(t - t_0)}$$
Anisotropic Diffusivity

In the case of anisotropic diffusivity, the diffusivity tensor is defined by a $3 \times 3$ matrix. We can understand the geometry of anisotropic diffusion by looking at the eigenvalue decomposition of $D$.

$$D^2 = X\Lambda X^{-1}$$  \hspace{1cm} (2)

where $\Lambda = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$. $\lambda_1, \lambda_2,$ and $\lambda_3$ are the eigenvalues of $D^2$.

In general, the contour of $f(r, t)$ forms an ellipsoid with the following function

$$\frac{x^2}{\lambda_1^2} + \frac{y^2}{\lambda_2^2} + \frac{z^2}{\lambda_3^2} = 1$$  \hspace{1cm} (3)
Initial and Boundary Conditions

For the bounded domain, Fokker Planck equation can be easily solved, numerically.

\[
f(r, t_0) = \delta(r - r_0) \quad \text{initial condition} \quad (4)
\]

\[
f(r, t) = 0 \quad \text{for absorbing boundaries} \quad (5)
\]

\[
\hat{n} \cdot \nabla f = 0 \quad \text{for reflecting boundaries} \quad (6)
\]

where \( \hat{n} \) is the normal vector to the boundary.
Boundary Conditions

The coupling between the flow model and the diffusion-convection equations is achieved by

Domain Configuration

- **Capillary inner domain**: homogenous diffusivity with a convection flux corresponding to the velocity field, i.e., $\mu = u$ and $D^2 = Dl_3$

- **Capillary wall**: convection flux in the radial direction with anisotropic diffusivity with the following eigenvalues $\lambda_1 = \beta(p) \cos(\theta)$, $\lambda_2 = \beta(p) \sin(\theta)$, and $\lambda_3 = 0$ where $\beta$ is a scaling factor, function of pressure. This representation of the diffusivity tensor allows diffusion only in the radial direction.
Boundary Conditions

**Boundary Configuration**

- **Capillary inner wall**: we use the continuity condition.
- **Capillary outer wall**: we propose an absorbing boundary condition to enforce absorption of all the particles leaving the capillary to the surrounding tissues.
- **Arteriole end**: we assume a reflecting boundary in order to prevent all particles from re-entering the arteriole.
- **Venule end**: we assume an infinite domain with continuity condition in between.
Results: COMSOL Multiphysics

(a) Probability of absorption
(b) Probability of transmission

Figure: Evolution of the probabilities of absorption and transmission.

The simulation time is 15965 seconds = 4.4 hrs!! We need a better way to simulated the capillary bed.

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Results: COMSOL Multiphysics

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Segmentation Model

Steps:

**Step 1:** discretization of the capillary into a large number of smaller sections.

**Step 2:** calculating the $P_A$ and $P_T$ of each section as a function of pressure.

**Step 3:** integrating over the capillary network.
Step 1: discretization

\[ \Delta p_i = p_{i-1} - p_i \]

Figure: Discretization of a capillary segment.

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Step 2: calculating the $P_A$ and $P_T$ of each section

$n = 20$ sections at $1.01 \mu \text{sec}$

Figure: Probability of absorption of the $i^{th}$ capillary section, for $i = 1, \ldots, n$, as a function of capillary blood pressure.
Step 2: calculating the $P_A$ and $P_T$ of each section

$n = 20$ sections at $1.01\mu\text{sec}$

![Graph showing probability of transmission vs capillary pressure](image)

**Figure**: Probability of transmission of the $i^{th}$ capillary section, for $i = 1, \cdots, n$, as a function of capillary blood pressure.
We first define the different probabilities that will be used in the example below.

- $P_{A_i,t}$, the absorption probability of the $i^{th}$ section at time $t$ for a particle starting from the same section.
- $P_{t}^{A_i}$, the absorption probability of the $i^{th}$ section at time $t$ for a particle starting from the 1$^{st}$ section.
- $P_{tot,t}^{A_i}$, the total absorption probability of the sections $1, \cdots, i$ at time $t$ for a particle starting from the 1$^{st}$ section.
- $P_{T_i,t}$, the transmission probability of the $i^{th}$ section at time $t$ for a particle starting from the same section.
- $P_{tot,t}^{T_i}$, the total transmission probability from the sections $1, \cdots, i$ at time $t$ for a particle starting from the 1$^{st}$ section. Also, equal to $P_{t}^{T_i}$.
Step 3: integrating over the capillary network

For two successive sections, \( P_t^{A_1} = P_{t, t}^{A_1} = P_{A_1, t} \) and \( P_{t, t}^{T_1} = P_{T_1, t} \), since there are no preceding sections. For the second section, \( P_t^{A_2} \) is given by

\[
P_t^{A_2} = \int_{\dot{t}=0}^{t} \frac{\partial P_{t, \dot{t}}^{T_1}}{\partial \dot{t}} P_{A_2, \dot{t}} \, d\dot{t} \tag{7}
\]

we assume a steady state flow (i.e., \( \frac{dp}{dt} = 0 \))

\[
P_t^{A_2} = \int_{\dot{t}=0}^{t} P_{A_2, \dot{t}} \, dP_{t, \dot{t}}^{T_1} \tag{8}
\]

The discrete form of (8) is given by

\[
P_{t_k}^{A_2} = \sum_{j=1}^{k} \left( P_{t, j}^{T_1} - P_{t, j-1}^{T_1} \right) P_{A_2, j} \tag{9}
\]
Step 3: integrating over the capillary network

and the total absorption probability will be

\[ P_{tot,t_k}^{A_2} = P_{t_k}^{A_1} + P_{t_k}^{A_2} \]  

(10)

Similarly, the total transmission probability is

\[ P_{tot,t_k}^{T_2} = P_{t_k}^{T_2} = \sum_{j=1}^{k} (P_{tot,t_j}^{T_1} - P_{tot,t_{j-1}}^{T_1}) P_{T_2,t_j} \]  

(11)
Step 3: integrating over the capillary network

The total probabilities for $n$ sections at time $t_k$ are given by

$$P_{\text{tot},t_k}^{A_n} = \sum_{i=1}^{n} P_{t_k}^{A_i}$$

(12)

$$P_{\text{tot},t_k}^{T_i} = P_{t_k}^{T_i} = \sum_{j=1}^{k} \left( P_{\text{tot},t_j}^{T_{i-1}} - P_{\text{tot},t_{j-1}}^{T_{i-1}} \right) P_{T_i,t_j}$$

(13)

where

$$P_{t_k}^{A_i} = \sum_{j=1}^{k} \left( P_{\text{tot},t_j}^{T_{i-1}} - P_{\text{tot},t_{j-1}}^{T_{i-1}} \right) P_{A_i,t_j}$$

(14)
Results: Segmentation Model vs FEM

Figure: Comparison of the Finite Element and Segmentation Methods in calculating $P_A$ and $P_T$. 
Assumptions:

- Capillary network that has an absorbing and transmission probabilities of $P_{A,t_j} \equiv P_{A_{tot,t_j}}$ and $P_{T,t_j} \equiv P_{T_{tot,t_j}}$.
- $n$ particles entering the capillary network simultaneously.
Modeling the Capillary Exchange Process

Introduction
Capillary Blood Flow Model
Modeling the Exchange Process
Segmentation Model of the Capillary Network
Modeling the Exchange of Multiple Particles

Modeling the Capillary Bed: Modeling each segment

\[ P_j(n) = \binom{n_0}{n} P_{A,j}^n (1 - P_{A,j})^{n_0-n} \quad n = 1, \ldots, n_0 \]  
\[ P_j(m) = \binom{n_0}{m} P_{T,j}^m (1 - P_{T,j})^{n_0-m} \quad m = 1, \ldots, n_0 \]
Modeling the Capillary Exchange Process

Modeling the Exchange Process

Segmentation Model of the Capillary Network

Modeling the Exchange of Multiple Particles

Modeling the Capillary Bed: Modeling each segment

Joint probability of $n$ absorbed and $m$ transmitted particles

$$P_j(m, n) = \binom{n_0}{m} \binom{n_0 - m}{n} P_{T,j}^m P_{A,j}^n (1 - P_{A,j} - P_{T,j})^{n_0 - m - n}$$

$m + n = 1, \ldots, n_0$

(17)
Thank you