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

Presented by
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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

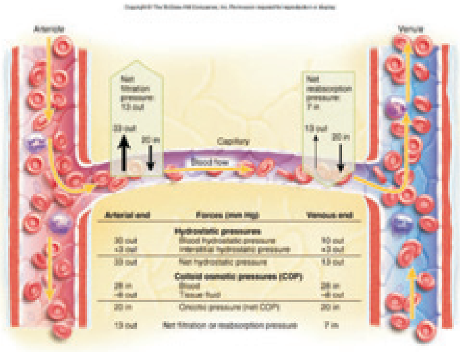
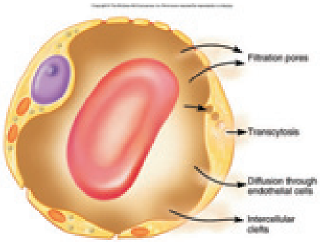


Figure: Capillary exchange process.

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

$$\overbrace{\rho\Big(\underbrace{\frac{\partial \mathbf{u}}{\partial t}}_{\substack{\text{Unsteady}\\\text{acceleration}}} + \underbrace{\mathbf{u}\cdot\nabla\mathbf{u}}_{\substack{\text{Convective}\\\text{acceleration}}}\Big)}^{\text{Inertia (per volume)}} = \overbrace{\underbrace{-\nabla p}_{\substack{\text{Pressure}\\\text{gradient}}} + \underbrace{\mu\nabla^2\mathbf{u}}_{\text{Viscosity}}}^{\text{Divergence of stress}} + \underbrace{\mathbf{f}}_{\substack{\text{Other}\\\text{body}\\\text{forces}}}$$

$$\nabla\cdot\mathbf{v} = 0$$

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$$\nabla\cdot\mathbf{v} = 0$$

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,
ϱ_c is the capillary oncotic pressure (osmotic pressure of the plasma proteins), and
ϱ_i is the tissue oncotic pressure (osmotic pressure of the proteins in the interstitial fluid).

Physical model of the flow: Boundary conditions

The corresponding boundary conditions are

$$\phi \frac{\partial u_z}{\partial r} + u_z = 0 \qquad at \;\; r = R$$

$$u_r = \frac{K\mu}{R}\left(\frac{p}{\varrho_c - \varrho_i + p_i} - 1\right) \qquad at \;\; r = R$$

$$p = p_a \qquad at \;\; z = 0$$

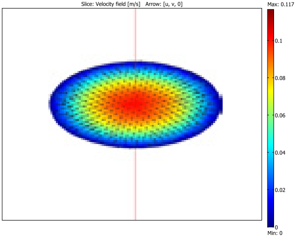
$$p = p_v \qquad at \;\; z = L$$

Capillary Specifications

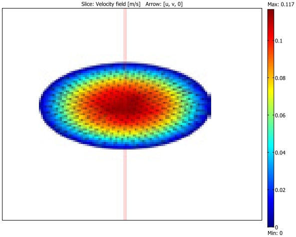
Capillary specifications	
L	$1mm$
R	$1\mu m$
ρ	$1025kg/m^3$
μ	$0.0015Ns/m^2$ at 37°
$p_{artriole\ \ end}$	$40mmHg$
$p_{vanule\ \ end}$	$15mmHg$
p_i	$-6mmHg$
ϱ_c	$25mmHg$
ϱ_i	$5mmHg$
L_c	$28.6 * 10^{-7}cm/(s \cdot cmH_2O)$, $cmH_2O = 0.098KPa$
ϕ	0 and 0.15

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

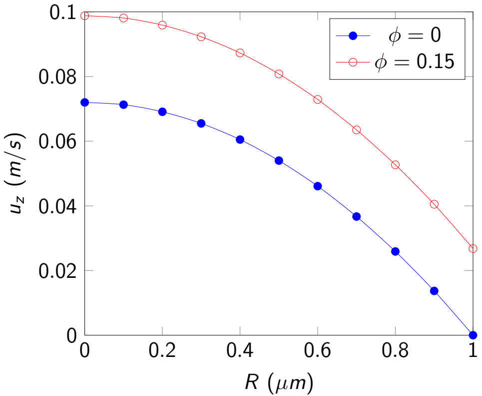


Figure: Axial velocity profile at $z = L/2$ for different slip coefficients.

Physical model of the flow: Example

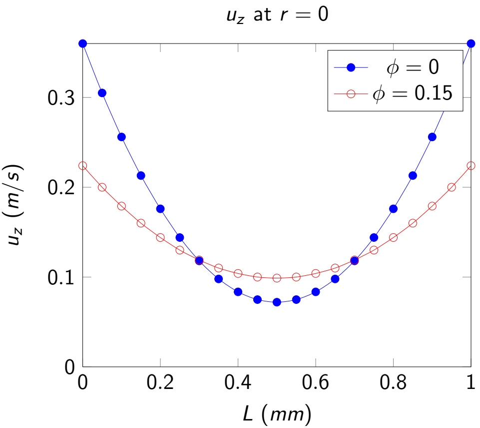


Figure: Axial velocity profile along the axis $r = 0$ for different slip coefficients.

Physical model of the flow: Example

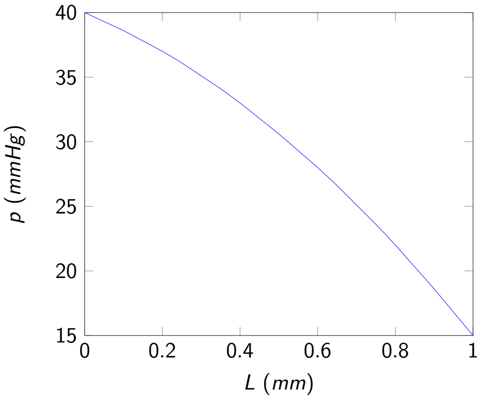


Figure: Pressure profile along the axis $z = 0$ of a capillary segment.

Physical model of the exchange process

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.

Stochastic Model

The SDE process for the transport of particle in an open environment is given by

$$\mathrm{d}\mathbf{X_t} = \boldsymbol{\mu}(\mathbf{X_t}, t)\mathrm{d}t + \boldsymbol{\sigma}(\mathbf{X_t}, t)\mathrm{d}\mathbf{W_t}$$

The corresponding Fokker-Planck equation is

$$\frac{\partial f(\mathbf{r}, t)}{\partial t} = \left[-\sum_{i=1}^{2} \frac{\partial}{\partial x_i} D_i^1(\mathbf{r}, t) + \right. \\ \left. + \sum_{i=1}^{2} \sum_{j=1}^{2} \frac{\partial^2}{\partial x_i \partial x_j} D_{ij}^2(\mathbf{r}, t) \right] f(\mathbf{r}, t)$$

Stochastic Model

Under the following assumptions

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

The solution is

$$f(\mathbf{r}, t) = \frac{1}{4\pi D(t - t_0)} e^{-\|\mathbf{r}-\mathbf{r}_0\|^2/4D(t-t_0)}$$

Anisotropic Diffusivity

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

$$\mathbf{D^2} = \mathbf{X \Lambda X}^{-1} \tag{2}$$

where $\mathbf{\Lambda} = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$. λ_1,λ_2, and λ_3 are the eigenvalues of $\mathbf{D^2}$.

In general, the contour of $f(\mathbf{r}, t)$ forms and ellipsoid with the following function

$$\frac{x^2}{{\lambda_1}^2} + \frac{y^2}{{\lambda_2}^2} + \frac{z^2}{{\lambda_3}^2} = 1 \tag{3}$$

Initial and Boundary Conditions

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

$$f(\mathbf{r}, t_0) = \delta(\mathbf{r} - \mathbf{r}_0) \qquad \text{initial consition} \tag{4}$$

$$f(\mathbf{r}, t) = 0 \qquad \text{for absorbing boundaries} \tag{5}$$

$$\hat{\mathbf{n}} \cdot \nabla f = 0 \qquad \text{for reflecting boundaries} \tag{6}$$

where $\hat{\mathbf{n}}$ 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

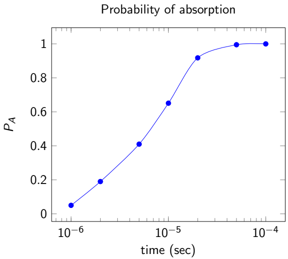
- **Capillary inner domain:** homogenous diffusivity with a convection flux corresponding to the velocity field, **u**i.e., $\boldsymbol{\mu} = \mathbf{u}$ and $\mathbf{D^2} = DI_3$
- **Capillary wall:** convection flux in the radial direction with anisotropic diffusivity with the following eigenvalues $\lambda_1 = \beta(p)cos(\theta), \quad \lambda_2 = \beta(p)sin(\theta), \quad$ and $\lambda_3 = 0$ where β is a scaling factor, function of pressure. This representation of the diffusivity tensor allows diffusion only in the radial direction.

Boundary Conditions

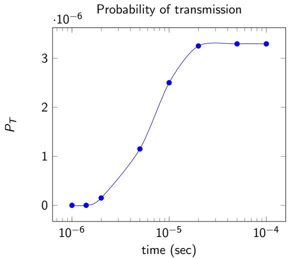
Boundary Configuration

- **Capillary inner wall:** we use the continuity condition.
- **Capillary outer wall:** we propose an absorbing boundary condition to enforce absorbtion 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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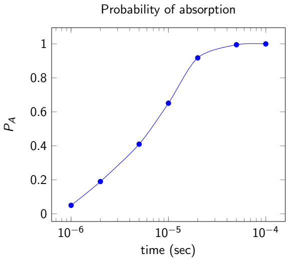

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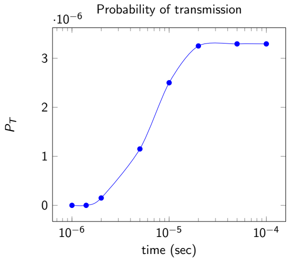

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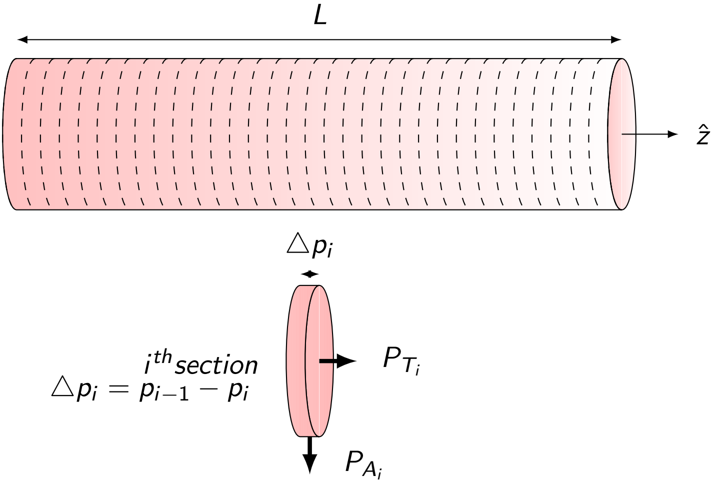
Segmentation Model

Steps:

- Step 1: discritization 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: discritization



Step 2: calculating the P_A and P_T of each section

$n = 20$ sections at 1.01μ *sec*

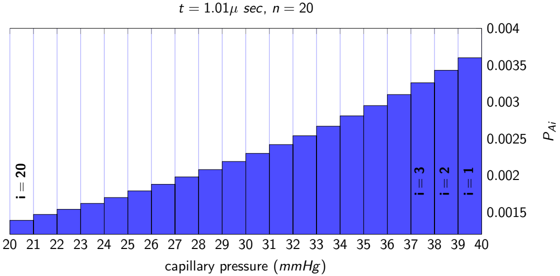


Figure: Probability of absorption of the i^{th} capillary section, for $i = 1, \cdots, n$, as a function of capillary blood pressure.

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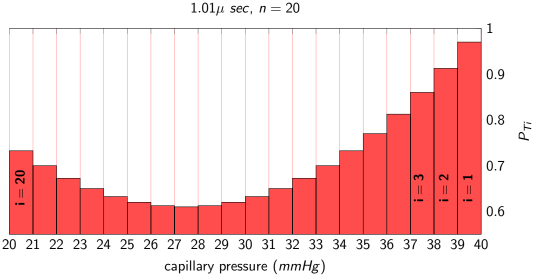

Figure: Probability of transmission of the i^{th} capillary section, for $i = 1, \cdots, n$, as a function of capillary blood pressure.

Step 3: integrating over the capillary network

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, $P_t^{A_1} = P_{tot,t}^{A_1} = P_{A_1,t}$ and $P_{tot,t}^{T_1} = P_{T_1,t}$, since there are no preceding sections. For the second section, $P_t^{A_2}$ is given by

$$P_t^{A_2} = \int_{\acute{t}=0}^{t} \frac{\partial P_{tot,\acute{t}}^{T_1}}{\partial \acute{t}} P_{A_2,\acute{t}} d\acute{t} \qquad (7)$$

we assume a steady state flow (i.e., $\frac{dp}{d\acute{t}} = 0$)

$$P_t^{A_2} = \int_{\acute{t}=0}^{t} P_{A_2,\acute{t}} dP_{tot,\acute{t}}^{T_1} \qquad (8)$$

The discrete form of (8) is given by

$$P_{t_k}^{A_2} = \sum_{j=1}^{k} (P_{tot,t_j}^{T_1} - P_{tot,t_{j-1}}^{T_1}) P_{A_2,t_j} \qquad (9)$$

Step 3: integrating over the capillary network

and the total absorption probability will be

$$P^{A_2}_{tot,t_k} = P^{A_1}_{t_k} + P^{A_2}_{t_k} \tag{10}$$

Similarly, the total transmission probability is

$$P^{T_2}_{tot,t_k} = P^{T_2}_{t_k} = \sum_{j=1}^{k} (P^{T_1}_{tot,t_j} - P^{T_1}_{tot,t_{j-1}}) P_{T_2,t_j} \tag{11}$$

Step 3: integrating over the capillary network

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

$$P^{A_n}_{tot,t_k} = \sum_{i=1}^{n} P^{A_i}_{t_k} \tag{12}$$

$$P^{T_i}_{tot,t_k} = P^{T_i}_{t_k} = \sum_{j=1}^{k} (P^{T_{i-1}}_{tot,t_j} - P^{T_{i-1}}_{tot,t_{j-1}}) P_{T_i,t_j} \tag{13}$$

where

$$P^{A_i}_{t_k} = \sum_{j=1}^{k} (P^{T_{i-1}}_{tot,t_j} - P^{T_{i-1}}_{tot,t_{j-1}}) P_{A_i,t_j} \tag{14}$$

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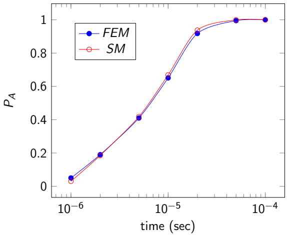
Results: Segmentation Model vs FEM



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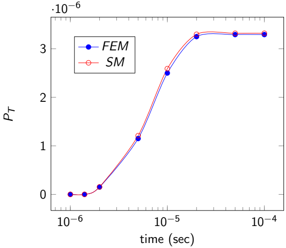

(b) Probability of transmission

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

Modeling the Capillary Bed: Modeling each segment

Assumptions:

- capillary network that has an absorbing and transmission probabilities of $P_{A,t_j} \equiv P^{A_n}_{tot,t_j}$ and $P_{T,t_j} \equiv P^{T_n}_{tot,t_j}$.
- n particles entering the capillary network simultaneously.

Modeling the Capillary Bed: Modeling each segment

probability that there are *n* absorbed transmitted particles

$$\mathrm{P}_j(n) = \binom{n_0}{n} P_{A,t_j}^{n} (1 - P_{A,t_j})^{n_0 - n} \quad n = 1, \dots, n_0 \qquad (15)$$

probability that there are *m* transmitted particles

$$\mathrm{P}_j(m) = \binom{n_0}{m} P_{T,t_j}^{m} (1 - P_{T,t_j})^{n_0 - m} \quad m = 1, \dots, n_0 \qquad (16)$$

Modeling the Capillary Bed: Modeling each segment

joint probability of n absorbed and m transmitted particles

$$\mathrm{P}_j(m,n) = \binom{n_0}{m}\binom{n_0-m}{n} P^m_{T,t_j} P^n_{A,t_j} (1 - P_{A,t_j} - P_{T,t_j})^{n_0-m-n} \quad m+n = 1,\ldots,n_0 \qquad (17)$$

Thank you