Modeling Blood Cell-Substrate Interaction and Biofilm-Fluid Interaction

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Outline

1. A computational model of blood cell-fluid interaction
   a) Biological background
   b) A hybrid cell membrane sub-model
   c) Fictitious domain coupling
   d) Ligand-receptor binding/unbinding sub-model

2. Energetic variational formulation and phase-field coupling for modeling biofilm-fluid interaction

3. Concluding remarks and future plans
Autocatalytic deposition of platelets on an injured vascular wall and generation of coagulation proteases

A. Adhesion of platelet to vWF mediates capture under flow conditions, followed by platelet activation via GPVI.

B. Video microscopy of platelet aggregates forming on a surface with generation of fibrin strands.

The structural integrity of a thrombus has important medical consequences, as fragments washed away from an unstable clot in a peripheral vein can embolize to the lungs with sometimes fatal results. The stability of the thrombus is influenced by the structural heterogeneity of the thrombus as the boundaries between discreet domains with different mechanical properties are susceptible to fracture.
Membrane of blood cells

- The lipid bilayer, the “heads” are arranged to interact with the aqueous environments on the inside and the outside of a cell, while the “tails” coagulate together to form a bilayer.
- The cytoskeleton is a network of fibers extending throughout the cytoplasm. The cytoskeleton organizes the structures and activities of the cell.
Hybrid membrane model of blood cells

Property of RBC membrane
- Thickness of RBC membrane: 7.5 to 10 nm
- Density of blood in 45% of hematocrit: 1.07 g/ml
- Dilation modulus: 500 dyn/cm
- Shear modulus for RBC membrane: $4.2 \times 10^{-3}$ dyn/cm
- Bending modulus: $1.8 \times 10^{-12}$ dyn/cm.

Main idea:
1. **Cytoskeleton network** modeled by network of springs [1,2].
2. **lipid bilayer** modeled by a continuum description [3].

Total coarse-grained Helmholtz free energy of the cell

\[ V = V_E + V_{\text{in-plane}} + V_{\text{area}} + V_{\text{volume}} \]

\( V_E \): bending energy representing bending resistance of lipid bilayer \[3\];
\( V_{\text{in-plane}} \): in-plane energy of the cytoskeleton network \[2\];
\( V_{\text{area}} \): surface area conservation constraint
\( V_{\text{volume}} \): volume conservation constraint

\[ V_E = k_0 \int_{\Sigma} (H(x) - \kappa(x))^2 dS + k_1 \int_{\Sigma} K(x)^2 dS \]

Here: \( H(x) \) is the mean curvature, \( H(x) = \frac{1}{2} (\kappa_1(x) + \kappa_2(x)) \);
\( K(x) \) is the Gauss curvature, \( K(x) = \kappa_1(x) \kappa_2(x) \);
\( \kappa(x) \) is the spontaneous curvature, and is assumed to be 0;
\( \kappa_1(x) \) and \( \kappa_2(x) \) are principle curvatures at \( x \in \Sigma \).
1. A coarse-grained filament is modeled by a worm-like chain + repulsive potential for it to sustain weak compression [2].

\[ V_{\text{in-plane}} = \sum_{j=1}^{N_S} \left[ \left( \frac{K_B T l_{\text{max}} 3 x_j^2 - 2 x_j^3}{4 \rho (1 - x_j)} \right) - \left( \frac{k_p}{(m - 1) l_j^{m-1}} \right) \right] \]

Where \( l_j \) is current length of spring; \( x_j = \frac{l_j}{l_{\text{max}}} \)

2. Area conservation.

\[ V_{\text{area}} = \frac{k_s (S_{\text{total}} - S_{0,\text{total}})^2}{2S_{\text{total}}} + \sum_{j=1} k_t (S_j - S_{0,j})^2 \]


\[ V_{\text{volume}} = \frac{k_v (V_c - V_0)^2}{2V_0} \]
Nodal force calculation

1. Bending force associated with lipid bilayer

\[ F_{bend}(x) = k_b(\Delta \Sigma (H - \kappa) + 2(H - \kappa)(H^2 - K + H\kappa))n \]

2. Other nodal forces can be obtained analytically by:

\[ F_d(x) = \left. \frac{\partial (V_{\text{in-plane}} + V_{\text{area}} + V_{\text{volume}})}{\partial x} \right|_{x_i} \]

The total force \( F \) at node \( x_i \):

\[ F = F_d(x) + F_{bend}(x) \]
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_b ) (average length of initial links)</td>
<td>( 2.4 \times 10^{-19} N \cdot m )</td>
</tr>
<tr>
<td>( l_0 ) (maximum spring extension)</td>
<td>( 75nm )</td>
</tr>
<tr>
<td>( l_{\max} ) (maximum spring extension)</td>
<td>( 3.17 \times 75nm )</td>
</tr>
<tr>
<td>( p ) (persistence length)</td>
<td>( 7.5nm )</td>
</tr>
<tr>
<td>( k_s = k_t * )</td>
<td>( 6000k_B T / l_0^2 )</td>
</tr>
<tr>
<td>( k_v * )</td>
<td>( 6000k_B T / l_0^3 )</td>
</tr>
</tbody>
</table>
Determining parameter values of cell membrane model

**RBC stretching experiments**

**Figure.** Axial and transverse diameters of the RBC versus stretching force. The optical tweezers experimental data from [1] shown with symbols. The simulation results at different levels of coarse-graining are shown with lines. Red line: \( N = 500 \), green line \( N = 1000 \), magenta: \( N = 2000 \) and cyan: \( N = 5000 \), respectively.


**Figure.** RBC shape evolution at different stretch forces (0, 90, and 180 pN) predicted by the model at \( N = 1000 \).
Coupling NS equations & solid model

Fluid domain $\Omega^f$

Fluid motion equations (Navier Stokes)
\[
\begin{aligned}
\rho_f \frac{d\vec{u}_f}{dt} &= \nabla \cdot \vec{\sigma}_f, \\
\nabla \cdot \vec{u}_f &= 0
\end{aligned}
\]
\[
\begin{aligned}
\vec{\sigma}_f &= -pI + 2\eta D \\
\vec{u}_f(t = 0) &= \vec{u}_{f0}
\end{aligned}
\]
in $\Omega \setminus \Omega_s$

Solid motion equations
\[
\begin{aligned}
\rho_s \frac{d\vec{u}_s}{dt} &= \vec{f}_s \\
\vec{u}_s(t = 0) &= \vec{u}_{s0}
\end{aligned}
\]
in $\Omega_s$

Interface conditions
\[
\begin{aligned}
\vec{u}_f &= \vec{u}_s \\
\vec{b}_i + \vec{\sigma}_f \cdot \vec{n} &= (\vec{f}_s \cdot \vec{n})\vec{n}
\end{aligned}
\]
on $\Gamma_{s1}$ and $\Gamma_{s2}$

Fictitious domain coupling

1. Add weak forms of fluid and solid motion equations

\[
\left( \rho_f \frac{d\tilde{u}_f}{dt} - \nabla \cdot \tilde{\sigma}_f, \tilde{v}_f \right) + \left( \rho_s \frac{d\tilde{u}_s}{dt} - \tilde{f}_s, \tilde{v}_s \right) = 0, \forall (\tilde{v}_f, \tilde{v}_s) \in S_v
\]

Where: \( S_u = \{(\tilde{u}_f, \tilde{u}_s)|\tilde{u}_f \in H^1(\Omega \setminus \Omega_s)^2, \tilde{u}_f = \tilde{u}_\Gamma \text{ on } \Gamma \}
\)
\( \tilde{u}_s \in H^1(\Omega_s)^2, \tilde{u}_s = \tilde{u}_f \text{ on } \Gamma_{s,i}, \quad i = 1,2 \}

\( S_v = \{(\tilde{v}_f, \tilde{v}_s)|\tilde{v}_f \in H^1(\Omega \setminus \Omega_s)^2, \tilde{v}_f = 0 \text{ on } \Gamma \}
\)
\( \tilde{v}_s \in H^1(\Omega_s)^2, \tilde{v}_s = \tilde{v}_f \text{ on } \Gamma_{s,i}, \quad i = 1,2 \}

2. Integration by parts

\[
\int_{\Omega \setminus \Omega_s} \rho_f \frac{d\tilde{u}_f}{dt} \cdot \tilde{v}_f \, dx + \int_{\Omega \setminus \Omega_s} \tilde{\sigma}_f \cdot \nabla \tilde{v}_f \, dx + \\
\int_{\Omega} \rho_s \frac{d\tilde{u}_s}{dt} \cdot \tilde{v}_s \, dx - \int_{\Omega} \tilde{f}_s \cdot \tilde{v}_s \, dx = -\int_{\Gamma_{s2}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f \, dx + \int_{\Gamma_{s1}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f \, dx + \int_{\Gamma_{s2}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f \, dx + \int_{\Gamma_{s1}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f \, dx
\]
Define: \( \widetilde{S}_u = \{(\tilde{u}_f, \tilde{u}_s) | \tilde{u}_f \in H^1(\Omega)^2, \tilde{u}_s \in H^1(\Omega_s)^2, \tilde{u}_f = \tilde{u}_s \text{ in } \Omega_s; \tilde{u}_f = \tilde{u}_\Gamma \text{ on } \Gamma \} \)

\( \widetilde{S}_v = \{(\tilde{v}_f, \tilde{v}_s) | \tilde{v}_f \in H^1(\Omega)^2, \tilde{v}_s \in H^1(\Omega_s)^2, \tilde{v}_f = \tilde{v}_s \text{ in } \Omega_s; \tilde{v}_f = 0 \text{ on } \Gamma \} \)

Since \( \int_{\Omega_s} \rho_s \frac{d\tilde{u}_f}{dt} \cdot (\tilde{v}_f - \tilde{v}_s)dx + \int_{\Omega_s} \tilde{\sigma}_f \cdot \nabla (\tilde{v}_f - \tilde{v}_s)dx = 0 \quad (**) \)

3. Add (*) and (**)

\[
\int_{\Omega} \rho_f \frac{d\tilde{u}_f}{dt} \cdot \tilde{v}_f dx + \int_{\Omega} \tilde{\sigma}_f \cdot \nabla \tilde{v}_f dx + \int_{\Omega_s} (\rho_s - \rho_f) \frac{d\tilde{u}_s}{dt} \cdot \tilde{v}_s dx - \int_{\Omega_s} \tilde{f}_s \cdot \tilde{v}_s dx + \int_{\Omega_s} (-\tilde{\sigma}_f) \cdot \nabla \tilde{v}_s dx =
\]

\[
- \int_{\Gamma_{s2}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f dx + \int_{\Gamma_{s1}} (\tilde{\sigma}_f \cdot \tilde{n}) \cdot \tilde{v}_f dx \quad (***)
\]

4. Eq. (***), together with \( \int_{\Omega} q \nabla \cdot \tilde{v}_f dx = 0 \) is solved by method of Lagrange multiplier.
Strong form of governing equations

\[ \frac{\partial \tilde{u}_f}{\partial t} + \tilde{u}_f \cdot \nabla \tilde{u}_f + \nabla p - \frac{1}{Re} \nabla^2 \tilde{u}_f = \lambda, \]

\[ \nabla \cdot \tilde{u}_f = 0 \]

\[(\rho_r - 1) \frac{d \tilde{u}_s}{dt} - F = -\lambda + (\nabla p - \frac{1}{Re} \nabla^2 \tilde{u}_f) \bigg|_{\Omega_s}, \]

\[ \tilde{u}_f - \tilde{u}_s = 0 \quad \text{at} \ \Omega_s \]

Where \( F = F_d(x) + F_{bend}(x) \)
Splitting Scheme

\[
\frac{\tilde{u}_f^{n+1} - \tilde{u}_f^* + \tilde{u}_f^* - \tilde{u}_f^n}{\Delta t} + \tilde{u}_f^n \cdot \nabla \tilde{u}_f^n + \nabla p^n - \frac{1}{2Re} \nabla^2 (\tilde{u}_f^* + \tilde{u}_f^n) = \lambda^{n+1} - \lambda^n + \lambda^n
\]

\[\nabla \cdot \tilde{u}_f^* = 0\]

1. Fluid sub-problem:
\[
\begin{cases}
\frac{\tilde{u}_f^n - \tilde{u}_f^*}{\Delta t} + \tilde{u}_f^n \cdot \nabla \tilde{u}_f^n + \nabla p^n - \frac{1}{2Re} \nabla^2 (\tilde{u}_f^* + \tilde{u}_f^n) = \lambda^n \\
\nabla \cdot \tilde{u}_f^* = 0
\end{cases}
\]

2. Solid sub-problem for solving \(x^{n+1}\):
\[
(\rho_r - 1) \frac{x^{n+1} + x^{n-1} - 2x^n}{\Delta t^2} - F(x^{n+1}) + (-\nabla p^n + \frac{1}{Re} \nabla^2 \tilde{u}_f^n) \bigg|_{\Omega_s} = -\lambda^n
\]

3. Lagrange multiplier problem for computing \(\tilde{u}_f^{n+1}\) and \(\lambda^{n+1}\):
\[
\lambda^{n+1} = \frac{\tilde{u}_f^{n+1} - \tilde{u}_f^*}{\Delta t} + \lambda^n \text{ on } \Gamma_s^{n+1}
\]
\[
\tilde{u}_f^{n+1} = \frac{x^{n+1} - x^n}{\Delta t} \text{ on } \Gamma_s^{n+1}
\]
Dealing with curvatures of surface

Computing $H, K$ and $\Delta \Sigma (H)$ for:

$$F_{bend}(x) = k_b (\Delta \Sigma (H - \kappa) + 2(H - \kappa)(H^2 - K + H\kappa))n$$

**Main idea:** Using a combination of level set method and essentially non-oscillatory (ENO) reconstruction.

- Constructing the level sets
- Computing curvatures of level sets on PDE grid points by using ENO
- Interpolate curvature to the solid interface

$$\text{dist}(A \text{ to } \Gamma_s) = \min_i \text{dist}(A \text{ to } T_i)$$

### Accuracy test using ellipsoid

#### Table 2: Accuracy of curvatures and surface laplacian

<table>
<thead>
<tr>
<th>$h$</th>
<th>Mean curvature</th>
<th>Gaussian curvature</th>
<th>Surface laplacian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$L_2$ error</td>
<td>order</td>
<td>$L_2$ error</td>
</tr>
<tr>
<td>0.2</td>
<td>2.03e-1</td>
<td></td>
<td>1.52e-1</td>
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<tr>
<td>0.1</td>
<td>1.09e-1</td>
<td>0.89</td>
<td>7.82e-2</td>
</tr>
<tr>
<td>0.05</td>
<td>5.78e-2</td>
<td>0.92</td>
<td>3.97e-2</td>
</tr>
<tr>
<td>0.025</td>
<td>3.01e-2</td>
<td>0.94</td>
<td>1.95e-2</td>
</tr>
<tr>
<td>0.0125</td>
<td>1.56e-2</td>
<td>0.95</td>
<td>1.01e-2</td>
</tr>
</tbody>
</table>
RBC tank treading movement

Go-and-stop experiments performed on the red cell. Shown are selected frames (each 16.6 μm wide) from a video recording through the rheoscope. The numbers indicate relative times. The red cell is shown tank treading in shear flow (flow direction horizontal, shear rate = 10/s). Shape. T. M. Fischer, Memory of Human Red Blood Cells, Biophysical Journal, Vol. 88, pp.3304-3313, 2004.

Platelet flipping dynamics

Figure: Comparison on the platelet flipping dynamics with Jeffery’s Orbit. $S2/S1 = 0.47$ Our numerical result shows flipping rates is close to the theoretical Jeffery’s orbit. The variation in angle to the platelet major axis is plotted against the time $t$. 
Time: 0.000125 second
Mono-flagellated Bacterium Swimming

Time: 0.01125 second
Platelet-wall interaction

Linear Shear Flow

Shear rate $\gamma$

$H$

$\alpha$

GP Ib

GP Ib

VWF

VWF

VWF

VWF
Platelet flipping experiments (from Rosen’s lab)
**Adhesion model**

**Catch bond behavior**: A increased bond life time with respect to increased force.

**Slip bond behavior**: A decrease in bond life time with respect to increase in force.

**Figure.** Schematic of bond life time for platelet glycoprotein receptor Ibα(GPIbα) and the A1 domain of von Willebrand factor (vWF-A1) bond.

**Figure.** Schematic of kinetics of two-bound state model
**Bell model:** $k_{ij}(F) = k_{ij}^0 \exp \left( \frac{Fx_{ij}}{k_BT} \right)$.

$k_{ij}(F)$: the rate of transition from state $i$ to state $j$ at force $F$.

$k_{ij}^0$: the intrinsic rate constant.

$x_{ij}$: is the distance to the transition state.

$k_B$: the Boltzmann’s constant.

$T$: absolute temperature.

**Catch-Slip bond dynamics modeled by Bell models:**

Let $P_1(t)$ and $P_2(t)$ be probability of occupying each state.

\[
\frac{dP_1(t)}{dt} = k_{21} \times P_2(t) - (k_{10} + k_{12}) \times P_1(t)
\]

\[
\frac{dP_1(t)}{dt} = k_{12} \times P_1(t) - (k_{20} + k_{21}) \times P_2(t)
\]

**Ref:** G. I. Bell, Models for the specific adhesion of cells to cells. Science 200, 618–627 (1978).
Figure. Estimation of the $k_{off}$ values for the GPIb $\alpha$–vWF-A1 tether bond based on the duration of transient tether events. (D) Effect of shear stress on $k_{off}$ for WT and mutant substrates.

Kinetics-based adhesion model

\[ k_{on} = k_{on}^0 \exp\left(\sigma|x_b - l_b| \frac{r - 0.5|x_b - l_b|}{K_B T}\right) \]

\[ P_f = 1 - \exp(-k_{on}\Delta t) \]


Slip bond kinetics:

\[ k_{off}(F) = k_{off}^0 \exp\left(\frac{Fx_{10}}{k_B T}\right) \]

\[ P_r = 1 - \exp(-k_{off}\Delta t) \]

Figure. The number of tethering events as a function of the platelet paused time. The solid lines are the fitting lines of experimental data for shear stresses of 3.0 dyn cm\(^{-2}\) (shown in blue) and 4.0 dyn cm\(^{-2}\) (shown in red). The corresponding slopes of the fits (k\(_{off}\) values) are -4.83 and -5.18. The dashed lines are the fitting lines of simulation results (shown with circles) for shear stresses of 3.0 dyn cm\(^{-2}\) (shown in blue) and 4.0 dyn cm\(^{-2}\). The corresponding slopes of the fits (k\(_{off}\) values) are -3.31 and -3.58.

Figure. The simulated deformations of platelet structures during their adhesion to the vessel wall for platelet stiffness of 2.5 KPa (a) and 25 KPa (b). The effect of the platelet membrane stiffness on the platelet paused time (c). The paused time was 6.69 ± 0.71 s (M ± SD) for the membrane stiffness of 25 KPa, which was about twice higher than the paused time of 3.15 ± 0.69 s (M ± SD) for the membrane stiffness of 2.5 KPa.
Figure. The effect of the number of platelet receptors on the platelet-vessel wall paused time. The platelet paused time for a decreased number of GPIb functional receptors was 2.07 ± 0.41 s (M ± SD), which was significantly lower than the paused time of platelets having the normal number of receptors (3.15 ± 0.69 s, M ± SD).

Remark: decreased GPIb concentrations were found in patients with thrombocythaemia and leukemia.
Figure. a) Initial configuration of two platelets used in simulations studying the effect of mutual interaction of platelets on platelet-wall adhesion. b) Platelet-vessel wall paused time as a function of the number of interacting platelets. The platelet paused time was $1.61 \pm 0.46$ s ($M \pm SD$) for two adhesive platelets, which was significantly lower than the stopping time of platelets having the normal number of receptors ($3.15 \pm 0.69$ s, $M \pm SD$).
Microfluidic device experiments of biofilm

Figure 1. Biofilm-fluid flow interaction experiments. (a). Experimental scheme. (b). Lower effective viscosity, $\eta = 10^3 \text{ kg m}^{-1} \text{s}^{-1}$. (c). Higher effective viscosity, $\eta = 10^5 \text{ kg m}^{-1} \text{s}^{-1}$. $t = 0$ (before beginning flow), $t = 60 \text{ s}$ of flow shear, $t = 120 \text{ s}$ (30 s after stopping flow).
Model assumption:

1. Biomass growth and decay and substrate transport are neglected.
2. A biofilm is an incompressible complex fluid made of a ternary mixture of bacteria, extracellular polymeric substances (EPS) and solvent phases.
3. Bacteria behave like a Newtonian fluid.
4. EPS is viscoelastic.
Two-phase mixture of bacterium and EPS

Let $\phi_1(x, t)$ be volume fraction of EPS. $0 \leq \phi_1(x, t) \leq 1$.

Let the mixing energy between bacteria and EPS be [1]

$$E_{coh}(\phi_1) := \lambda_1 \int_\Omega \left( \gamma_1 G_1(\phi_1) + \frac{1}{2} |\nabla \phi_1|^2 \right) dx.$$  

Let the elastic energy of EPS be [2]:

$$E_{ela}(\Phi, \phi_1) := \int_\Omega \left( \phi_1 \frac{\lambda_\Phi}{2} |\nabla \Phi|^2 \right) dx.$$  

Let $F$ be the deformation-gradient tensor (strain) and assume $\nabla \cdot F_0 = 0$. Then $F = \nabla \times \Phi$.

Let the kinetic energy of the mixture transport be:

$$E_{kin}(u) := \int_\Omega \left( \frac{1}{2} \rho |u|^2 \right) dx$$

Let $E_{tot1} = E_{coh}(\phi_1) + E_{ela}(\Phi, \phi_1) + E_{kin}(\mathbf{u})$

$$
\mathbf{u}_t + \mathbf{u} \cdot \nabla \mathbf{u} + \nabla p = \nabla \cdot (\sigma_{vis} + \sigma_{coh} + \sigma_{ela})
$$

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

$$
\Phi_t + \mathbf{u} \cdot \nabla \Phi = 0
$$

$$
(\phi_1)_t + \nabla \cdot (\phi_1 \mathbf{u}) = \nabla \cdot \left[ \tau_1 \nabla \frac{\delta E_{tot1}}{\delta \phi_1} \right]
$$

Here $\sigma_{coh} := -\lambda_1 \nabla \phi_1 \otimes \nabla \phi_1$, $\sigma_{ela} := -\lambda_\Phi \phi_1 (\nabla \Phi)^t \nabla \Phi$, $\sigma_{vis} = \frac{1}{2} \eta(\phi_1)(\nabla \mathbf{u} + (\nabla \mathbf{u})^t)$.

$$
\frac{\delta E_{tot1}}{\delta \phi_1} = (-\lambda_1 \Delta \phi_1 + \lambda_1 \gamma_1 G'_1(\phi_1)) + \frac{\lambda_\Phi}{2} |\nabla \Phi|^2 =: \mu_1.
$$

Theorem. $\frac{dE_{tot1}}{dt} + \int_\Omega (\tau_1 |\mu_1|^2 + \eta |\nabla \mathbf{u}|^2) \, dx = 0$
Let $\phi_2$ be the volume fraction of the binary mixture. $0 \leq \phi_2 \leq 1$.

$$E_{tot2}(\mathbf{u}, \Phi, \phi_1, \phi_2)$$
$$:= E_{kin}(\mathbf{u}) + E_{ela}(\Phi, \phi_1) + E_{coh1}(\phi_1, \phi_2) + E_{coh2}(\phi_2)$$

Here

$$E_{coh1}(\phi_1, \phi_2) := \int_{\Omega} \lambda_1 \phi_2 \left( \gamma_1 G_1(\phi_1) + \frac{1}{2} |\nabla \phi_1|^2 \right) dx$$

$$E_{coh2}(\phi_2) := \int_{\Omega} \lambda_2 \left( \gamma_2 G_2(\phi_2) + \frac{1}{2} |\nabla \phi_2|^2 \right) dx$$

Theorem. $$\frac{dE_{tot2}}{dt} + \int_{\Omega} (\tau_1 |\mu_1|^2 + \tau_1 |\mu_2|^2 + \eta(\phi_1, \phi_2) |\nabla \mathbf{u}|^2) dx = 0.$$
Governing equations of biofilm model

\[ u_t + u \cdot \nabla u + \nabla p = \nabla \cdot (\eta(\phi_1, \phi_2) \nabla u + w \Phi + \mu_1 \nabla \phi_1 + \mu_2 \nabla \phi_2) \]

\[ \nabla \cdot u = 0 \]

\[ \Phi_t + u \cdot \nabla \Phi = 0 \]

\[ (\phi_1)_t + \nabla \cdot (\phi_1 u) = \tau_1 \Delta \mu_1 \]

\[ (\phi_2)_t + \nabla \cdot (\phi_2 u) = \tau_2 \Delta \mu_2 \]

Here \( w = -\lambda \Phi \nabla \cdot (\phi_1 \nabla \Phi) \);

\[ \mu_1 = -\lambda_1 \nabla (\phi_2 \nabla \phi_1) + \lambda_1 \gamma_1 \phi_2 G_1'(\phi_1) + \frac{\lambda \Phi}{2} |\nabla \Phi|^2; \]

\[ \mu_2 = -\lambda_2 \Delta \phi_2 + \lambda_2 \gamma_2 G_2'(\phi_2) + \gamma_1 G_1(\phi_1) + \frac{1}{2} |\nabla \phi_1|^2. \]
Unconditional stable splitting scheme

Step 1. Find \((\Phi^{n+1}, \phi_1^{n+1}, \phi_2^{n+1}, \mu_1^{n+1}, \mu_2^{n+1})\) such that:

\[
\frac{\Phi^{n+1} - \Phi^n}{\Delta t} + \nabla \cdot (u^* \cdot \Phi^n) = 0
\]

\[
w^{n+1} + \lambda \Phi \nabla \cdot (\phi_1^{n+1} \nabla \Phi^{n+1}) = 0
\]

\[
\frac{\phi_1^{n+1} - \phi_1^n}{\Delta t} + \nabla \cdot (u^* \cdot \phi_1^n) = \tau_1 \Delta \mu_1^{n+1}
\]

\[
\mu_1^{n+1} = -\lambda_1 \nabla (\phi_2^{n+1} \nabla \phi_1^{n+1}) + \lambda_1 \gamma_1 \phi_2^{n+1} G_1'(\phi_1^n) + \frac{\lambda \Phi}{2} |\nabla \Phi^{n+1}|^2
\]

\[
\frac{\phi_2^{n+1} - \phi_2^n}{\Delta t} + \nabla \cdot (u^* \cdot \phi_2^n) = \tau_2 \Delta \mu_2^{n+1}
\]

\[
\mu_2^{n+1} = -\lambda_2 \Delta \phi_2^{n+1} + \lambda_2 \gamma_1 G_2'(\phi_2^{n+1}, \phi_2^n) + \frac{\lambda \Phi}{2} |\nabla \phi_1^{n+1}|^2 + \gamma_1 G_1(\phi_1^{n+1})
\]

\[
u^* = u^n - \Delta t (\phi_2^n \nabla \mu_2^{n+1} + \phi_1^n \nabla \mu_1^{n+1} + \Phi^n \nabla w^{n+1})
\]

Step 2. Find \((u^{n+1}, p^{n+1})\) such that:

\[
\frac{u^{n+1} - u^*}{\Delta t} + c(u^{n+1}, u^n) + \nabla p^{n+1} - \nabla \cdot (\eta(\phi^1, \phi^2) \nabla u^{n+1}) = 0
\]

\[
\nabla \cdot u^{n+1} = 0
\]

Where \(c(u^{n+1}, u^n) = u^{n+1} \cdot \nabla u^n + \frac{1}{2} u^n \cdot \nabla u^{n+1}\)

**Theorem.** The numerical scheme is unconditionally energy-stable.

### Viscosity affecting biofilm-fluid interaction

<table>
<thead>
<tr>
<th>Case 1</th>
<th>$\eta_{EPS}$</th>
<th>$\eta_b$</th>
<th>$\eta_s$</th>
<th>$\lambda_\phi$ (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>$10^{-2}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>Case 2</td>
<td>10.0</td>
<td>$10^{-1}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>Case 3</td>
<td>100</td>
<td>$10^{-1}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
</tr>
</tbody>
</table>

*Figure 5.* Effect of biofilm viscosity on biofilm-flow interaction at $u_{max} = 0.001 \text{ m s}^{-1}$. Velocity profile and biofilm volumetric fraction $\phi_\alpha$ over time. (a) Case 1. (b) Case 2. (c) Case 3.
<table>
<thead>
<tr>
<th></th>
<th>$\eta_{EPS}$</th>
<th>$\eta_b = \eta_s$</th>
<th>$\lambda_{\Phi} (S)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 4</td>
<td>1.0</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
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<tr>
<td>Case 5</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
<td>1</td>
</tr>
<tr>
<td>Case 6</td>
<td>$10^{-5}$</td>
<td>$10^{-3}$</td>
<td>$10^2$</td>
</tr>
</tbody>
</table>

Figure 6. Effect of elastic relaxation on biofilm-flow interaction at $u_{max} = 0.001 \, m \, s^{-1}$. EPS volumetric fraction $\phi_n$ at $t = 1.0 \, s$.  
Future Plan

1. Model for studying blood cell dynamics.
   a) New consistent surface finite element coupled with NS solver for simulating fluid/cell interactions.

   a) Heterogeneity of EPS network on visco-elasticity.
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