Version of December 6, 2017

Derivation of the equations for a macroscopic scale continuum model of platelet aggregation Aaron Fogelson

Platelets are a type of blood cell. They normally circulate with the blood as single cells each in an unactivated state. Under certain conditions, such as those that occur when a blood vessel is injured, platelets become activated and able to stick together in clumps or platelet aggregates to form a major part of the clot which blocks the hole in the vessel. Here we will use this context to discuss first a model with strong similarities to the continuum polymer models that were just discussed, and then to extend the discussion to multiphase mixture models in which different components move with different macroscopic velocities.

Anticiapting the extension to the multiphase mixture model in which the velocity is *not* incompressible, derivations of the key equations will be carried out without assuming that that $\mathbf{u}$ is divergence free. For the single phase model, we will then assume that $\mathbf{u}$ in the final equations is divergence free and simplify them accordingly.

The model variables are the number density of unactivated platelets and the number density of activated platelets, $\tilde{\phi}_{\mathrm{u}}$ and $\tilde{\phi}_{\mathrm{a}}$, respectively, the concentration(s) c of activating chemical(s), the fluid velocity and pressure fields $\mathbf{u}$ and p, and scalar function $\tilde{E}$ describing the distribution of links joining pairs of activated platelets, and a stress tensor $\underline{\underline{\tilde{\sigma}}}$ describing the stresses generated by these links.

The parameter ϵ that appears below is the ratio of the microscopic length scale, roughly a platelet's diameter $\approx 2\ \mu$m, to the macroscopic length scale which is the diameter of a coronary artery, roughly 1-2 mm. Hence, $\epsilon \approx 10^{-3} \ll 1$.

INSERT TWO-SCALE FIGURE

We start with a two-scale model in which we look at events on both the macroscopic scale of the vessel and on the microscopic scale of platelets, and from it we will derive a macroscale only model valid in the limit that we let $\epsilon \to 0$. Since platelets in a clot are packed about ϵ apart, the density of platelets in the clot scales like ϵ^{-3}, and this quantity blows up as we let ϵ go to 0. To obtain well behaved functions in that limit, we define scaled platelet number densities ϕ_{u} and ϕ_{a}

so that

$$\tilde{\phi}_{\rm u}(\mathbf{x},t) = \epsilon^{-3}\phi_{\rm u}(\mathbf{x},t) \tag{1}$$
$$\tilde{\phi}_{\rm a}(\mathbf{x},t) = \epsilon^{-3}\phi_{\rm a}(\mathbf{x},t). \tag{2}$$

The definitions of the variables $\tilde{\phi}_{\rm u}$, $\tilde{\phi}_{\rm a}$, c, $\mathbf{u}$, and p are standard, and each of them is a function of location $\mathbf{x}$ and time t. That of $\tilde{E}$ is not, and is given here. This function should be a function of the locations of both ends of the link. Say $\mathbf{x}$ and $\mathbf{x}+\mathbf{r}$. We will think of E as a function of $\mathbf{x}$ and of the link vector $\mathbf{r}$. The dependence on $\mathbf{r}$ is such that when $\mathbf{r}$ changes in length by an amount on the order of a platelet radius, $\tilde{E}$ should change substantially. So, $\tilde{E}$ varies rapidly with $\mathbf{r}$, but slowly as a function of $\mathbf{x}$. We define $\tilde{E}(\mathbf{x},\mathbf{r},t)$ so that $\tilde{E}(\mathbf{x},\mathbf{r},t)d\mathbf{r}$ is the concentration of elastic links between activated platelets at $\mathbf{x}$ and those in a small volume $d\mathbf{r}$ around $\mathbf{x}+\mathbf{r}$. Later we will make the change of variables $\mathbf{r}=\epsilon\mathbf{y}$, $\tilde{E}(\mathbf{x},\mathbf{r},t)=\epsilon^{-6}E(\mathbf{x},\mathbf{y},t)$, and the definitions:

$$\tilde{z}(\mathbf{x},t) = \int_{\mathbf{r}} \tilde{E}(\mathbf{x},\mathbf{r},t)d\mathbf{r} \tag{3}$$
$$z(\mathbf{x},t) = \int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)d\mathbf{y}, \tag{4}$$
$$\underline{\underline{\sigma}}(\mathbf{x},t) = \tfrac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}. \tag{5}$$

The function $\tilde{z}(\mathbf{x},t)$ is the number density of links which join activated platelets at $\mathbf{x}$ to activated platelets anywhere. The function $z(\mathbf{x},t)$ is a scaled version of this quantity. From the definitions, we see that $\tilde{z}(\mathbf{x},t)=\epsilon^{-3}z(\mathbf{x},t)$. In Eq. 5, $S(|\mathbf{y}|)$ is the (scaled) stiffness of an individual link, $\underline{\underline{\sigma}}(\mathbf{x},t)$ is the stress generated at $\mathbf{x}$ at time t due to links joining activated platelets at $\mathbf{x}$ to activated platelets elsewhere. We will see below why the factor $\frac{1}{2}$ is needed in the definition of $\underline{\underline{\sigma}}$.

PDEs for $\mathbf{u}$, p, $\tilde{\phi}_{\rm u}$, $\tilde{\phi}_{\rm a}$, and c

We assume that fluid is governed by the Navier-Stokes equations with a force density term that comes from the elastic link forces.

$$\rho(\mathbf{u}_t+\mathbf{u}\cdot\nabla\mathbf{u}) = -\nabla p + \mu\Delta\mathbf{u} + \mathbf{f}, \qquad \nabla\cdot\mathbf{u}=0. \tag{6}$$

The platelet number densities and the activating chemical satisfy the PDEs

$$(\tilde{\phi}_{\rm u})_t + \mathbf{u}\cdot\nabla\tilde{\phi}_{\rm u} = D_{\rm u}\Delta\tilde{\phi}_{\rm u} - R(c)\tilde{\phi}_{\rm u}, \tag{7}$$
$$(\tilde{\phi}_{\rm a})_t + \mathbf{u}\cdot\nabla\tilde{\phi}_{\rm a} = R(c)\tilde{\phi}_{\rm u}, \tag{8}$$
$$c_t + \mathbf{u}\cdot\nabla c = D_c\Delta c + \tilde{A}R(c)\tilde{\phi}_{\rm u}. \tag{9}$$

(10)

These equations embody the assumptions that platelets move with the local fluid velocity $\mathbf{u}$, that unactivated platelets have a diffusive motion due to the influence of red blood cells, that unactivated platelets are activated at a rate that depends on c, and that when a platelet is activated, it secretes an amount $\tilde{A}$ of activating chemical.

PDE for link distribution function:

Our first task is to derive a PDE for $\tilde{E}$ and from it a PDE for E. Let $\Omega_x(t)$ and $\Omega_\xi(t)$ be two material regions of fluid, and define $N(t)$ by

$$N(t) = \int_{\Omega_x(t)} \int_{\Omega_\xi(t)} \tilde{E}(\mathbf{x}, \boldsymbol{\xi} - \mathbf{x}, t) d\boldsymbol{\xi} d\mathbf{x}. \tag{11}$$

The quantity $N(t)$ is the number of elastic links between activated platelets in $\Omega_x(t)$ and $\Omega_\xi(t)$ Links move as the platelets to which they are attached move. We also make the modeling assumption that links can be formed and broken. Therefore,

$$\frac{dN}{dt} = \int_{\Omega_x(t)} \int_{\Omega_\xi(t)} \left\{ \tilde{\alpha}(|\boldsymbol{\xi} - \mathbf{x}|)\tilde{\phi}_{\rm a}(\mathbf{x}, t)\tilde{\phi}_{\rm a}(\boldsymbol{\xi}, t) - \tilde{\beta}(|\boldsymbol{\xi} - \mathbf{x}|)\tilde{E}(\mathbf{x}, \boldsymbol{\xi} - \mathbf{x}, t) \right\} d\mathbf{x} d\boldsymbol{\xi}. \tag{12}$$

In this equation $\tilde{\alpha}$ is the rate constant for link formation between activated platelets at locations $\mathbf{x}$ and $\boldsymbol{\xi}$ and $\tilde{\beta}$ is the breaking rate for existing links between platelets at these locations. Note that we assume that both formation and breaking of links depend only on the distance between the activated platelets and that there are also rapidly varying functions of the length of the distance between platelets and the length of the link.

Using (11), we compute $\frac{dN}{dt}$, but before doing so, we convert the integrals over $\Omega_x(t)$ and $\Omega_\xi(t)$ to ones over the preimages of these point sets, $\Omega_x(0)$ and $\Omega_\xi(0)$, respectively, under the flow map $\mathbf{x}(t) = \phi(t; \mathbf{x_0})$ and $\boldsymbol{\xi}(t) = \phi(t; \xi_{\mathbf{0}})$. This is the same trick we used in deriving the Reynolds Transport Theorem at the start of the course, but here we have two moving chunks of fluid and we map each of them back to its original location under the flow map. We introduce the Jacobian determinants $J(t; \mathbf{x_0})$ and $J(t; \xi_{\mathbf{0}})$ of the flow maps $\mathbf{x}(t) = \phi(t; \mathbf{x_0})$ and $\boldsymbol{\xi}(t) = \phi(t; \xi_{\mathbf{0}})$, respectively. Then,

$$N(t) = \int_{\Omega_x(0)} \int_{\Omega_\xi(0)} \tilde{E}(\mathbf{x}(t; \mathbf{x_0}), \boldsymbol{\xi}(t; \xi_{\mathbf{0}}) - \mathbf{x}(t, \mathbf{x_0}), t) J(t; \mathbf{x_0}) J(t; \xi_{\mathbf{0}}) d\xi_{\mathbf{0}} d\mathbf{x_0}. \tag{13}$$

We denote by $\nabla_1 \tilde{E}$ gradients of $\tilde{E}$ with respect to its first vector argument and by $\nabla_2 \tilde{E}$ gradients of $\tilde{E}$ with respect to its second vector argument. Before proceeding, recall that

$$\frac{\partial J(t; \mathbf{x_0})}{\partial t} = J(t; \mathbf{x_0}) \cdot \nabla \mathbf{u}(\mathbf{x}(t; \mathbf{x_0}), t), \tag{14}$$

$$\frac{\partial J(t; \xi_{\mathbf{0}})}{\partial t} = J(t; \xi_{\mathbf{0}}) \cdot \nabla \mathbf{u}(\xi(t; \xi_{\mathbf{0}}), t). \tag{15}$$

and

$$\frac{d\mathbf{x}}{dt}(t;\mathbf{x_0}) = \mathbf{u}(\mathbf{x}(t;\mathbf{x_0}),t), \tag{16}$$

$$\frac{d\boldsymbol{\xi}}{dt}(t;\xi_{\mathbf{0}}) = \mathbf{u}(\boldsymbol{\xi}(t;\xi_{\mathbf{0}}),t). \tag{17}$$

Now, compute the time derivative of $N(t)$ using Eq. (13).

$$\begin{aligned}
\frac{dN(t)}{dt} &= \int_{\Omega_x(0)}\int_{\Omega_\xi(0)} \frac{d}{dt}\Big\{\tilde{E}\big(\mathbf{x}(t;\mathbf{x_0}),\boldsymbol{\xi}(t;\xi_{\mathbf{0}})-\mathbf{x}(t,\mathbf{x_0}),t\big)J(t;\mathbf{x_0})J(t;\xi_{\mathbf{0}})\Big\}d\xi_{\mathbf{0}}d\mathbf{x_0} \\
&= \int_{\Omega_x(0)}\int_{\Omega_\xi(0)} \Big[\ \Big\{\frac{\partial\tilde{E}}{\partial t} + \frac{d\mathbf{x}}{dt}(t;\mathbf{x_0})\cdot\nabla_1\tilde{E}\big(\mathbf{x}(t;\mathbf{x_0}),\boldsymbol{\xi}(t;\xi_{\mathbf{0}})-\mathbf{x}(t;\mathbf{x_0}),t\big) \\
&+ \Big(\frac{d\boldsymbol{\xi}}{dt}(t;\xi_{\mathbf{0}}) - \frac{d\mathbf{x}}{dt}(t;\mathbf{x_0})\Big)\cdot\nabla_2\tilde{E}\big(\mathbf{x}(t;\mathbf{x_0}),\boldsymbol{\xi}(t;\xi_{\mathbf{0}})-\mathbf{x}(t;\mathbf{x_0}),t\big)\Big\}J(t;\mathbf{x_0})J(t;\xi_{\mathbf{0}}) \\
&+ \Big\{\tilde{E}J_t(t;\mathbf{x_0})J(t;\xi_{\mathbf{0}}) + \tilde{E}J(t;\mathbf{x_0})J_t(t;\xi_{\mathbf{0}})\Big\}\ \Big]d\xi_{\mathbf{0}}d\mathbf{x_0}
\end{aligned} \tag{18}$$

Using Eqs. (15), this becomes

$$\begin{aligned}
\frac{dN(t)}{dt} &= \int_{\Omega_x(0)}\int_{\Omega_\xi(0)} \Big\{\ \frac{\partial\tilde{E}}{\partial t} + \frac{d\mathbf{x}}{dt}(t;\mathbf{x_0})\cdot\nabla_1\tilde{E}\big(\mathbf{x}(t;\mathbf{x_0}),\boldsymbol{\xi}(t;\xi_{\mathbf{0}})-\mathbf{x}(t;\mathbf{x_0}),t\big) \\
&+ \Big(\frac{d\boldsymbol{\xi}}{dt}(t;\xi_{\mathbf{0}}) - \frac{d\mathbf{x}}{dt}(t;\mathbf{x_0})\Big)\cdot\nabla_2\tilde{E}\big(\mathbf{x}(t;\mathbf{x_0}),\boldsymbol{\xi}(t;\xi_{\mathbf{0}})-\mathbf{x}(t;\mathbf{x_0}),t\big) \\
&+ \tilde{E}\ \cdot\nabla\mathbf{u}(\mathbf{x}(t;\mathbf{x_0}),t) + \tilde{E}\ \cdot\nabla\mathbf{u}(\boldsymbol{\xi}(t;\xi_{\mathbf{0}}),t)\ \Big\}J(t;\mathbf{x_0})J(t;\xi_{\mathbf{0}})d\xi_{\mathbf{0}}d\mathbf{x_0}
\end{aligned} \tag{19}$$

Now, change variables back so that the integrals are over the moving fluid regions,

$$\begin{aligned}
\frac{dN(t)}{dt} &= \int_{\Omega_x(t)}\int_{\Omega_\xi(t)} \Big[\ \Big\{\tilde{E}_t(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t) + \mathbf{u}(\mathbf{x},t)\cdot\nabla_1\tilde{E}\big(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t\big) \\
&+ \Big(\mathbf{u}(\boldsymbol{\xi},t)-\mathbf{u}(\mathbf{x},t)\Big)\cdot\nabla_2\tilde{E}\big(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t\big) + \tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t)\ \nabla\cdot\mathbf{u}(\mathbf{x},t) + \tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t)\ \nabla\cdot\mathbf{u}(\boldsymbol{\xi},t)\ \Big]d\boldsymbol{\xi}d\mathbf{x}.
\end{aligned} \tag{20}$$

Now, use this result on the left-hand side of Eq. (12), and the arbitrariness of the regions of integration, to obtain,

$$\begin{aligned}
\tilde{E}_t(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t) &+ \mathbf{u}(\mathbf{x},t)\cdot\nabla_1\tilde{E}\big(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t\big) \\
&+ \Big(\mathbf{u}(\boldsymbol{\xi},t)-\mathbf{u}(\mathbf{x},t)\Big)\cdot\nabla_2\tilde{E}\big(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t\big) \\
&+ \tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t)\ \cdot\nabla\mathbf{u}(\mathbf{x},t) + \tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t)\ \cdot\nabla\mathbf{u}(\boldsymbol{\xi},t) \\
&= \tilde{\alpha}(|\boldsymbol{\xi}-\mathbf{x}|)\tilde{\phi_{\mathrm{a}}}(\mathbf{x},t)\tilde{\phi_{\mathrm{a}}}(\boldsymbol{\xi},t) - \tilde{\beta}(|\boldsymbol{\xi}-\mathbf{x}|)\tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t).
\end{aligned} \tag{21}$$

Now let $\mathbf{r} = \boldsymbol{\xi}-\mathbf{x}$, and $\tilde{E}(\mathbf{x},\boldsymbol{\xi}-\mathbf{x},t) = \tilde{E}(\mathbf{x},\mathbf{r},t)$. Then, $\tilde{E}(\mathbf{x},\mathbf{r},t)$ satisifies the equation

$$\begin{aligned}
\tilde{E}_t(\mathbf{x},\mathbf{r},t) &+ \mathbf{u}(\mathbf{x},t)\cdot\nabla_1\tilde{E}\big(\mathbf{x},\mathbf{r},t\big) \\
&+ \Big(\mathbf{u}(\mathbf{x}+\mathbf{r},t)-\mathbf{u}(\mathbf{x},t)\Big)\cdot\nabla_2\tilde{E}\big(\mathbf{x},\mathbf{r},t\big) \\
&+ \tilde{E}(\mathbf{x},\mathbf{r},t)\ \nabla\cdot\mathbf{u}(\mathbf{x},t) + \tilde{E}(\mathbf{x},\mathbf{r},t)\ \nabla\cdot\mathbf{u}(\mathbf{x}+\mathbf{r},t) \\
&= \tilde{\alpha}(|\mathbf{r}|)\tilde{\phi_{\mathrm{a}}}(\mathbf{x},t)\tilde{\phi_{\mathrm{a}}}(\mathbf{x}+\mathbf{r},t) - \tilde{\beta}(|\mathbf{r}|)\tilde{E}(\mathbf{x},\mathbf{r},t).
\end{aligned} \tag{22}$$

Let $\mathbf{r} = \epsilon\mathbf{y}$, $\tilde{\alpha}(|\mathbf{r}|) = \alpha(|\mathbf{y}|)$, $\tilde{\beta}(|\mathbf{r}|) = \beta(|\mathbf{y}|)$, $\tilde{E}(\mathbf{x}, \mathbf{r}, t) = \epsilon^{-6}E(\mathbf{x}, \mathbf{y}, t)$, and $\tilde{\phi_{\rm a}} = \epsilon^{-3}\phi_{\rm a}$. Note that

$$\frac{\partial E}{\partial y_i} = \epsilon^6 \frac{\partial \tilde{E}}{\partial y_i} = \epsilon^6 \frac{\partial \tilde{E}}{\partial r_i}\frac{\partial r_i}{\partial y_i} = \epsilon^7 \frac{\partial \tilde{E}}{\partial r_i}, \qquad \frac{\partial E}{\partial t} = \epsilon^6 \frac{\partial \tilde{E}}{\partial t}, \qquad \frac{\partial E}{\partial x_j} = \epsilon^6 \frac{\partial \tilde{E}}{\partial x_j}$$

Thus, Eq. (22) can be written

$$\begin{aligned} E_t(\mathbf{x}, \mathbf{y}, t) \;&+\; \mathbf{u}(\mathbf{x}, t) \cdot \nabla_x E\big(\mathbf{x}, \mathbf{y}, t\big) \\ &+\; \Big(\mathbf{u}(\mathbf{x} + \epsilon\mathbf{y}, t) - \mathbf{u}(\mathbf{x}, t)\Big) \cdot \frac{1}{\epsilon}\nabla_y E\big(\mathbf{x}, \mathbf{y}, t\big) \\ &+\; E(\mathbf{x}, \mathbf{y}, t)\ \nabla\cdot\mathbf{u}(\mathbf{x}, t) + E(\mathbf{x}, \mathbf{y}, t)\ \nabla\cdot\mathbf{u}(\mathbf{x} + \epsilon\mathbf{y}, t) \\ &=\; \alpha(|\mathbf{y}|)\phi_{\rm a}(\mathbf{x}, t)\phi_{\rm a}(\mathbf{x} + \epsilon\mathbf{y}, t) - \beta(|\mathbf{y}|)E(\mathbf{x}, \mathbf{y}, t). \end{aligned} \tag{23}$$

Next, expand $\mathbf{u}(\mathbf{x} + \epsilon\mathbf{y}, t)$ and $\phi_a(\mathbf{x} + \epsilon\mathbf{y}, t)$ about $(\mathbf{x}, t)$,

$$\mathbf{u}(\mathbf{x} + \epsilon\mathbf{y}, t) = \mathbf{u}(\mathbf{x}, t) + \epsilon\mathbf{y}\cdot\nabla\mathbf{u}(\mathbf{x}, t) + O(\epsilon^2), \tag{24}$$

$$\phi_{\rm a}(\mathbf{x} + \epsilon\mathbf{y}, t) = \phi_{\rm a}(\mathbf{x}, t) + \epsilon\mathbf{y}\cdot\nabla\phi_{\rm a}(\mathbf{x}, t) + O(\epsilon^2). \tag{25}$$

Using these in Eq. (23), gives

$$\begin{aligned} E_t(\mathbf{x}, \mathbf{y}, t) \;&+\; \mathbf{u}(\mathbf{x}, t) \cdot \nabla_x E\big(\mathbf{x}, \mathbf{y}, t\big) \\ &+\; \frac{1}{\epsilon}(\epsilon\mathbf{y} \cdot \nabla\mathbf{u}(\mathbf{x}, t) \cdot \nabla_y E + O(\epsilon^2)) \\ &+\; E(\mathbf{x}, \mathbf{y}, t)\ \nabla\cdot\mathbf{u}(\mathbf{x}, t) + E(\mathbf{x}, \mathbf{y}, t)\ \nabla\cdot\mathbf{u}(\mathbf{x}, t) + \epsilon E\nabla_x \cdot (\mathbf{y}\cdot\nabla\mathbf{u}(\mathbf{x}, t)) + O(\epsilon^2) \\ &=\; \alpha(|\mathbf{y}|)\phi_{\rm a}(\mathbf{x}, t)(\phi_{\rm a}(\mathbf{x}, t) + \epsilon\mathbf{y}\cdot\nabla\phi_{\rm a}(\mathbf{x}, t) + O(\epsilon^2)) - \beta(|\mathbf{y}|)E(\mathbf{x}, \mathbf{y}, t). \end{aligned} \tag{26}$$

Now, keeping only terms of order ϵ^0 yields

$$\begin{aligned} E_t \;&+\; \mathbf{u} \cdot \nabla_x E + (\mathbf{y}\cdot\nabla\mathbf{u}(\mathbf{x}, t) \cdot \nabla_y E) + E\ \nabla\cdot\mathbf{u} + E\ \nabla\cdot\mathbf{u} \\ &=\; \alpha(|\mathbf{y}|)\phi_{\rm a}(\mathbf{x}, t)^2 - \beta(|\mathbf{y}|)E. \end{aligned} \tag{27}$$

Combining the $\mathbf{u} \cdot \nabla_x E$ term and one of the $E\ \nabla\cdot\mathbf{u}$ terms gives

$$\begin{aligned} E_t \;&+\; \nabla_x \cdot (\mathbf{u}E) + (\mathbf{y}\cdot\nabla\mathbf{u}(\mathbf{x}, t)) \cdot \nabla_y E) + E\ \nabla\cdot\mathbf{u} \\ &=\; \alpha(|\mathbf{y}|)\phi_{\rm a}(\mathbf{x}, t)^2 - \beta(|\mathbf{y}|)E. \end{aligned} \tag{28}$$

In the case that $\nabla\cdot\mathbf{u} = 0$, then the $E\nabla\cdot\mathbf{u}$ term vanishes, and the $\nabla_x \cdot (\mathbf{u}E)$ can be written $\mathbf{u} \cdot \nabla_x E$, and the PDE becomes

$$E_t + \mathbf{u} \cdot \nabla_x E + (\mathbf{y}\cdot\nabla\mathbf{u}(\mathbf{x}, t)) \cdot \nabla_y E) = \alpha(|\mathbf{y}|)\phi_{\rm a}(\mathbf{x}, t)^2 - \beta(|\mathbf{y}|)E. \tag{29}$$

Link forces:

Now we will consider the forces that these links exert. What is the force on the activated platelets at location $\mathbf{x}$ due to links joining them to activated platelets elsewhere? It is

$$\mathbf{f}(\mathbf{x}, t) = \int_{\mathbf{r}} \tilde{E}(\mathbf{x}, \mathbf{r}, t)\tilde{\mathbf{F}}(\mathbf{r})d\mathbf{r}. \tag{30}$$

where $\tilde{\mathbf{F}}(\mathbf{r})$ is the force from a single link with link vector $\mathbf{r}$. We will consider how $\tilde{\mathbf{F}}$ should scale as ϵ becomes smaller and then derive an equation for $\mathbf{f}(\mathbf{x}, t)$ taking into account this scaling and written in terms of $E(\mathbf{x}, \mathbf{y}, t)$ instead of $\tilde{E}(\mathbf{x}, \mathbf{r}, t)$. Consider a slice through a macroscopic chunk of clot and consider the forces due to links which join activated platelets on one side of this slice to ones on the other side. The number of such links scales as ϵ^{-2}, so as ϵ is made smaller, the number of links becomes enormous. In the limit $\epsilon \to 0$, we want the total force exerted through links by platelets on one side of the slice on those on the other to be bounded (and approximately the same for all small ϵ). Hence, we assume that $\tilde{\mathbf{F}}$ scales like ϵ^2. More specifically, we assume that $\tilde{\mathbf{F}}(\mathbf{r}) = \epsilon^2 S(|\mathbf{y}|)\mathbf{y}$, where $\mathbf{r} = \epsilon\mathbf{y}$ as before. We make the change of variables from $\mathbf{r}$ to $\mathbf{y}$ in Eq. 30, and use this form of $\tilde{\mathbf{F}}$ to get that

$$\mathbf{f}(\mathbf{x}, t) = \epsilon^{-1} \int_{\mathbf{y}} E(\mathbf{x}, \mathbf{y}, t)S(|\mathbf{y}|)\mathbf{y}d\mathbf{y}. \tag{31}$$

The ϵ^{-1} looks like it will cause problems as ϵ goes to zero. But let's consider the integral in Eq. 31

$$I(\mathbf{x}, t) = \int_{\mathbf{y}} E(\mathbf{x}, \mathbf{y}, t)S(|\mathbf{y}|)\mathbf{y}d\mathbf{y}.$$

We can change variables from $\mathbf{y}$ to $-\mathbf{y}$ in the integral to obtain

$$I(\mathbf{x}, t) = \int_{\mathbf{y}} E(\mathbf{x}, -\mathbf{y}, t)S(|\mathbf{y}|)(-\mathbf{y})d\mathbf{y} = -\int_{\mathbf{y}} E(\mathbf{x}, -\mathbf{y}, t)S(|\mathbf{y}|)\mathbf{y}d\mathbf{y}.$$

The negatives in $d\mathbf{y}$ went to return the limits of integration in each component of $\mathbf{y}$ to be $-\infty$ to ∞. Now notice that

$$E(\mathbf{x}, -\mathbf{y}, t) = E(\mathbf{x} - \epsilon\mathbf{y}, \mathbf{y}, t) = E(\mathbf{x}, \mathbf{y}, t) - \epsilon\mathbf{y} \cdot \nabla_1 E(\mathbf{x}, \mathbf{y}, t) + O(\epsilon^2).$$

Using this in the last expression for $I(\mathbf{x}, t)$, we find that

$$I(\mathbf{x}, t) = -\Big(I(\mathbf{x}, t) - \epsilon \int_{\mathbf{y}} \mathbf{y} \cdot \nabla_1 E(\mathbf{x}, \mathbf{y}, t)S(|\mathbf{y}|)\mathbf{y}d\mathbf{y} + O(\epsilon^2)\Big),$$

from which we conclude that

$$I(\mathbf{x}, t) = \frac{1}{2}\epsilon \int_{\mathbf{y}} \mathbf{y} \cdot \nabla_1 E(\mathbf{x}, \mathbf{y}, t)S(|\mathbf{y}|)\mathbf{y}d\mathbf{y} + O(\epsilon^2).$$

Using this in the expression for $\mathbf{f}(\mathbf{x},t)$ in Eq. 31, we find that

$$\mathbf{f}(\mathbf{x},t) = \frac{1}{2}\int_{\mathbf{y}} \mathbf{y}\cdot\nabla_1 E(\mathbf{x},\mathbf{y},t) S(|\mathbf{y}|)\mathbf{y} d\mathbf{y} + O(\epsilon).$$

In the limit, $\epsilon \to 0$, the force density is given by

$$\mathbf{f}(\mathbf{x},t) = \frac{1}{2}\int_{\mathbf{y}} \mathbf{y}\cdot\nabla_1 E(\mathbf{x},\mathbf{y},t) S(|\mathbf{y}|)\mathbf{y} d\mathbf{y} \tag{32}$$

Having found the force density exerted on the fluid by the elastic links, we can determine the corresponding stress tensor $\underline{\underline{\sigma}}$ so that $\nabla\cdot\underline{\underline{\sigma}}(\mathbf{x},t) = \mathbf{f}(\mathbf{x},t)$. It is

$$\underline{\underline{\sigma}}(\mathbf{x},t) = \frac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t) S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}. \tag{33}$$

PDE for link stress tensor:

Recalling the definition of $\underline{\underline{\sigma}}(\mathbf{x},t)$ given in Eq. (5), we see that

$$\begin{aligned} \frac{\partial \underline{\underline{\sigma}}}{\partial t} &= \tfrac{1}{2}\int \frac{\partial E}{\partial t} S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y} \qquad (34)\\ &= \underbrace{\tfrac{1}{2}\int \alpha(|\mathbf{y}|){\phi_{\mathrm{a}}}^2 S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(A)} - \underbrace{\tfrac{1}{2}\int \beta(|\mathbf{y}|) E S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(B)} \\ &- \underbrace{\tfrac{1}{2}\int \nabla_x\cdot(E\ \mathbf{u}) S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(C)} - \underbrace{\tfrac{1}{2}\int \Big[(\mathbf{y}\cdot\nabla\mathbf{u})\cdot\nabla_y E\Big] S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(D)} \\ &- \underbrace{\tfrac{1}{2}\int E\ (\nabla_x\cdot\mathbf{u}) S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(E)} \end{aligned}$$

We work on the labeled terms one at a time

$$\begin{aligned} (A) &= {\phi_{\mathrm{a}}}^2(\mathbf{x},t)\Big(\tfrac{1}{2}\int \alpha(|\mathbf{y}|) S(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}\Big) \qquad (35)\\ &= {\phi_{\mathrm{a}}}^2(\mathbf{x},t)\Big(\tfrac{1}{6}\int \alpha(|\mathbf{y}|) S(|\mathbf{y}|)|\mathbf{y}|^2 d\mathbf{y}\Big)\underline{\underline{I}} \end{aligned}$$

$$(E) = \underline{\underline{\sigma}}(\mathbf{x},t)\nabla\cdot\mathbf{u}(\mathbf{x},t) \tag{36}$$

$$(C) = \nabla\cdot(\mathbf{u}\underline{\underline{\sigma}}) \tag{37}$$

Towards simplifying (D), we look at the ij entry of the expression defining (D).

$$\begin{aligned} (D)_{ij} &= \tfrac{1}{2}\int \Big[\sum_k \Big(\sum_l y_l \frac{\partial u_k}{\partial x_l}\frac{\partial E}{\partial y_k}\Big)\Big] S(|\mathbf{y}|) y_i y_j d\mathbf{y} \\ &= \tfrac{1}{2}\sum_k\sum_l \frac{\partial u_k}{\partial x_l}\int \Big(S(|\mathbf{y}|) y_i y_j y_l \frac{\partial E}{\partial y_k}\Big) d\mathbf{y} \\ &= -\tfrac{1}{2}\sum_k\sum_l \frac{\partial u_k}{\partial x_l}\int E\frac{\partial}{\partial y_k}\Big(S(|\mathbf{y}|) y_l y_i y_j\Big) d\mathbf{y}. \qquad (38) \end{aligned}$$

The last equality was obtained using integration by parts. Consider the integrals M_{ijkl} in this expression

$$\begin{aligned} M_{ijkl} &= \int E\frac{\partial}{\partial y_k}\Big(S(|\mathbf{y}|)y_l y_i y_j\Big)d\mathbf{y} \\ &= \int E y_l y_i y_j \frac{\partial S(|\mathbf{y}|)}{\partial y_k}d\mathbf{y} + \int ES(|\mathbf{y}|)y_i y_j \frac{\partial y_l}{\partial y_k}d\mathbf{y} \\ &+ \int ES(|\mathbf{y}|)y_l y_j \frac{\partial y_i}{\partial y_k}d\mathbf{y} + \int ES(|\mathbf{y}|)y_l y_i \frac{\partial y_j}{\partial y_k}d\mathbf{y} \\ &= \int E y_i y_j y_k y_l \frac{S'(|\mathbf{y}|)}{|\mathbf{y}|}d\mathbf{y} + \int ES(|\mathbf{y}|)y_i y_j \frac{\partial y_l}{\partial y_k}d\mathbf{y} \\ &+ \int ES(|\mathbf{y}|)y_l y_j \frac{\partial y_i}{\partial y_k}d\mathbf{y} + \int ES(|\mathbf{y}|)y_l y_i \frac{\partial y_j}{\partial y_k}d\mathbf{y} \end{aligned}$$

If we assume that $S(|\mathbf{y}|) = S_0$ is constant, then the first term vanishes, and

$$\begin{aligned} M_{ijkl} &= \int ES_0 y_i y_j \delta_{kl} d\mathbf{y} \\ &+ \int ES_0 y_l y_j \delta_{ik} d\mathbf{y} + \int ES_0 y_l y_i \delta_{jk} d\mathbf{y}. \end{aligned}$$

Substitute this expression into the final formula for D_{ij} in Eq. 38 to obtain

$$\begin{aligned} D_{ij} &= -\tfrac{1}{2}\sum_k\sum_l \frac{\partial u_k}{\partial x_l}\int ES_0 y_i y_j \delta_{kl} d\mathbf{y} \\ &- \tfrac{1}{2}\sum_k\sum_l \frac{\partial u_k}{\partial x_l}\int ES_0 y_l y_j \delta_{ik} d\mathbf{y} \\ &- \tfrac{1}{2}\sum_k\sum_l \frac{\partial u_k}{\partial x_l}\int ES_0 y_l y_i \delta_{jk} d\mathbf{y} \\ &= -\sum_k \frac{\partial u_k}{\partial x_k}\Big(\tfrac{1}{2}\int ES_0 y_i y_j d\mathbf{y}\Big) - \sum_l \frac{\partial u_i}{\partial x_l}\Big(\tfrac{1}{2}\int ES_0 y_l y_j d\mathbf{y}\Big) \\ &- \sum_l \frac{\partial u_j}{\partial x_l}\Big(\tfrac{1}{2}\int ES_0 y_l y_i d\mathbf{y}\Big) \\ &= -(\nabla\cdot\mathbf{u})\underline{\underline{\sigma}}_{ij} - (\underline{\underline{\sigma}}\nabla\mathbf{u})_{ji} - (\underline{\underline{\sigma}}\nabla\mathbf{u})_{ij} \end{aligned} \quad (39)$$

where $(\nabla\mathbf{u})_{mn} = \frac{\partial u_n}{\partial x_m}$. Hence,

$$(D) = -(\nabla\cdot\cdot\,\mathbf{u})\underline{\underline{\sigma}} - (\underline{\underline{\sigma}}\nabla\mathbf{u}) - (\underline{\underline{\sigma}}\nabla\mathbf{u})^T. \quad (40)$$

Using the expressions just derived for (A), (C), (D), and (E) in Eq. (34), we obtain

$$\begin{aligned}\frac{\partial \underline{\underline{\sigma}}}{\partial t} &= \underbrace{\phi_a{}^2(\mathbf{x},t)\Big(\tfrac{1}{6}\int \alpha(|\mathbf{y}|)S_0|\mathbf{y}|^2 d\mathbf{y}\Big)\underline{\underline{I}}}_{(A)} \\ &\quad \underbrace{-\int \beta(|\mathbf{y}|)\tfrac{1}{2}ES_0\mathbf{y}\mathbf{y}^T d\mathbf{y}}_{(B)} - \underbrace{\nabla_x\cdot(\mathbf{u}\underline{\underline{\sigma}})}_{(C)} \\ &\quad + \underbrace{(\nabla\cdot\mathbf{u})\underline{\underline{\sigma}} + (\underline{\underline{\sigma}}\nabla\mathbf{u}) + (\underline{\underline{\sigma}}\nabla\mathbf{u})^T}_{(D)} - \underbrace{\underline{\underline{\sigma}}\nabla\cdot\mathbf{u}}_{(E)}.\end{aligned} \tag{41}$$

Note that the $\underline{\underline{\sigma}}\nabla\cdot\mathbf{u}$ from (E) cancels that from (D) leaving us the equation

$$\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \nabla_x\cdot(\mathbf{u}\underline{\underline{\sigma}}) = \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2\phi_a{}^2\underline{\underline{I}} - \int \beta(|\mathbf{y}|)\tfrac{1}{2}ES_0\mathbf{y}\mathbf{y}^T d\mathbf{y}. \tag{42}$$

where $\alpha_2 = \Big(\frac{1}{6}\int \alpha(|\mathbf{y}|)S_0|\mathbf{y}|^2 d\mathbf{y}\Big)$. If $S(|\mathbf{y}|) \neq S_0$ constant, we get instead the equation

$$\begin{aligned}\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \nabla_x\cdot(\mathbf{u}\underline{\underline{\sigma}}) &= \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2\phi_a{}^2\underline{\underline{I}} - \int \beta(|\mathbf{y}|)\tfrac{1}{2}ES(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y} \\ &\quad -\frac{1}{2}\sum_{k,l}\frac{\partial u_k}{\partial x_l}\int E(\mathbf{x},\mathbf{y},t)\frac{S'(|\mathbf{y}|)}{|\mathbf{y}|}y_i y_j y_k y_l d\mathbf{y}.\end{aligned} \tag{43}$$

If $\nabla\cdot\mathbf{u} = 0$, then this can be written

$$\begin{aligned}\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \mathbf{u}\cdot\nabla_x\underline{\underline{\sigma}} &= \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2\phi_a{}^2\underline{\underline{I}} - \int \beta(|\mathbf{y}|)\tfrac{1}{2}ES(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y} \\ &\quad -\frac{1}{2}\sum_{k,l}\frac{\partial u_k}{\partial x_l}\int E(\mathbf{x},\mathbf{y},t)\frac{S'(|\mathbf{y}|)}{|\mathbf{y}|}y_k y_l \mathbf{y}\mathbf{y}^T d\mathbf{y}.\end{aligned} \tag{44}$$

In the case that $S(|\mathbf{y}|) = S_0$ *and* $\beta(|\mathbf{y}|) = \beta_0$ for some constant β_0, then the last term vanishes and the next to last term is simply $\beta_0\underline{\underline{\sigma}}$ and we have a closed system without the microscale that gives *exactly* the same results as the two-scale model would.

$$\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \mathbf{u}\cdot\nabla_x\underline{\underline{\sigma}} = \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2\phi_a{}^2\underline{\underline{I}} - \beta_0\underline{\underline{\sigma}}(\mathbf{x},t) \tag{45}$$

Equation for z:

Now, we derive the PDE for z. From the definition of z (Eq. 4), and the PDE for E (Eq. 29), it follows that

$$\begin{aligned}\frac{\partial z}{\partial t} &= \int_{\mathbf{y}}\frac{\partial E}{\partial t}d\mathbf{y} \\ &= \int_{\mathbf{y}}\Big\{-\nabla_x\cdot(\mathbf{u}E) - (\mathbf{y}\cdot\nabla\mathbf{u})\cdot\nabla_y E - E\nabla\cdot\mathbf{u} + \alpha\phi_a{}^2 - \beta E\Big\}d\mathbf{y} \\ &= -\nabla_x\cdot(\mathbf{u}z) - \int_{\mathbf{y}}(\mathbf{y}\cdot\nabla\mathbf{u})\cdot\nabla_y E d\mathbf{y} - z\nabla\cdot\mathbf{u} + \phi_a{}^2\Big(\int_{\mathbf{y}}\alpha d\mathbf{y}\Big) - \int_{\mathbf{y}}\beta E d\mathbf{y}.\end{aligned} \tag{46}$$

Note that

$$
\begin{aligned}
\int_{\mathbf{y}} (\mathbf{y}\cdot\nabla\mathbf{u}) \cdot \nabla_y E d\mathbf{y} &= -\int_{\mathbf{y}} E\nabla_y \cdot (\mathbf{y}\cdot\nabla\mathbf{u}) d\mathbf{y} \\
&= -\int_{\mathbf{y}} E \sum_k \frac{\partial}{\partial y_k} (\mathbf{y}\cdot\nabla\mathbf{u})_k d\mathbf{y} \\
&= -\int_{\mathbf{y}} E \sum_k \frac{\partial}{\partial y_k} (\sum_l y_l \frac{\partial u_k}{\partial x_l}) d\mathbf{y} \\
&= -\sum_k \sum_l \int_{\mathbf{y}} E\delta_{kl} \frac{\partial u_k}{\partial x_l} d\mathbf{y} \\
&= -(\sum_k \frac{\partial u_k}{\partial x_k} \int_{\mathbf{y}} E d\mathbf{y} \\
&= -z\nabla\cdot\mathbf{u}.
\end{aligned}
$$

Using this in the equation above for z_t yields

$$
\frac{\partial z}{\partial t} = -\nabla\cdot(\mathbf{u}z) + z\nabla\cdot\mathbf{u} - z\nabla\cdot\mathbf{u} + {\phi_{\mathrm{a}}}^2 \int_{\mathbf{y}} \alpha d\mathbf{y} - \int_{\mathbf{y}} \beta E d\mathbf{y}, \tag{47}
$$

or

$$
\frac{\partial z}{\partial t} + \nabla\cdot(\mathbf{u}z) = \alpha_0 {\phi_{\mathrm{a}}}^2 - \int_{\mathbf{y}} \beta E d\mathbf{y}. \tag{48}
$$

where $\alpha_0 = \int_{\mathbf{y}} \alpha d\mathbf{y}$. If $\nabla\cdot\mathbf{u} = 0$, the second term can be written in advective form $\mathbf{u}\cdot\nabla z$, and if β is the constant β_0 the equation becomes

$$
\frac{\partial z}{\partial t} + \mathbf{u} \cdot \nabla_x z = \alpha_0 {\phi_{\mathrm{a}}}^2 - \beta_0 z. \tag{49}
$$

Special form of model:

In the special case that $S(|\mathbf{y}|) = S_0$ and $\beta(|\mathbf{y}|) = \beta_0$:

$$
\begin{aligned}
(\phi_{\mathrm{u}})_t + \mathbf{u}\cdot\nabla\phi_{\mathrm{u}} &= D_{\mathrm{u}}\Delta\phi_{\mathrm{u}} - R(c)\phi_{\mathrm{u}}, && (50)\\
(\phi_{\mathrm{a}})_t + \mathbf{u}\cdot\nabla\phi_{\mathrm{a}} &= R(c)\phi_{\mathrm{u}}, && (51)\\
c_t + \mathbf{u}\cdot\nabla c &= D_{\mathrm{c}}\Delta c - AR(c)\phi_{\mathrm{u}}, && (52)\\
\rho(\mathbf{u}_t + \mathbf{u}\cdot\nabla\mathbf{u}) &= -\nabla p + \mu\Delta\mathbf{u} + \nabla\cdot\underline{\underline{\sigma}}, \qquad \nabla\cdot\mathbf{u} = 0, && (53)\\
\underline{\underline{\sigma}}_t + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}} &= \left(\underline{\underline{\sigma}}\nabla\mathbf{u}\right) + \left(\underline{\underline{\sigma}}\nabla\mathbf{u}\right)^T + \alpha_2{\phi_{\mathrm{a}}}^2\underline{\underline{I}} - \beta_0\underline{\underline{\sigma}}(\mathbf{x}, t), && (54)\\
z_t + \mathbf{u}\cdot\nabla z &= \alpha_0{\phi_{\mathrm{a}}}^2 - \beta_0 z. && (55)
\end{aligned}
$$

where $\tilde{A} = \epsilon^{-3}A$, $\alpha_2 = \left(\frac{1}{6}\int \alpha(|\mathbf{y}|)S_0|\mathbf{y}|^2 d\mathbf{y}\right)$, and $\alpha_0 = \int \alpha(|\mathbf{y}|)d\mathbf{y}$. In this version of the model, z has no impact on the dynamics, it is used just to display results. In a later form of the model, z does affect other variables.

What kind of stresses can the model develop?

Steady state with no flow:

Assume that the system is at steady state with $\mathbf{u} \equiv 0$. The stress equation reduces to

$$0 = \alpha_2 \phi_{\rm a}(\mathbf{x}, t)^2 \underline{\underline{I}} - \beta_0 \underline{\underline{\sigma}}(\mathbf{x}, t).$$

We solve this for $\underline{\underline{\sigma}}$ to obtain

$$\underline{\underline{\sigma}}(\mathbf{x}, t) = \frac{\alpha_2 {\phi_{\rm a}}^2(\mathbf{x}, t)}{\beta_0} \underline{\underline{I}}.$$

On a surface with normal $\mathbf{n}$, the force generated is

$$\underline{\underline{\sigma}} \cdot \mathbf{n} = \frac{\alpha_2 {\phi_{\rm a}}^2(\mathbf{x}, t)}{\beta_0} \mathbf{n},$$

and these are normal forces only. In the Navier-Stokes equations, $\nabla \cdot \underline{\underline{\sigma}}(\mathbf{x}, t) = \frac{\alpha_2}{\beta_0} \nabla({\phi_{\rm a}}^2)$, which is another pressure term. Because the sign is opposite that of the pressure, we can think of this as a "suction" pressure which tries to pull the fluid into regions on high $\phi_{\rm a}$. The fluid doesn't actually move because of the incompressibility constraint.

Steady state with steady linear shear flow:

We assume that the activated platelet number density is constant $\phi_{\rm a} = \phi_0$. We look for a solution $\mathbf{u}(x, y) = (\gamma y, 0)$ which solves the Navier-Stokes equations in the absence of links. We seek $\underline{\underline{\sigma}}$ that is consistent with this flow.

The PDE for $\underline{\underline{\sigma}}$ reduces to

$$\mathbf{u} \cdot \nabla \underline{\underline{\sigma}} = \underline{\underline{\sigma}} \nabla \mathbf{u} + (\underline{\underline{\sigma}} \nabla \mathbf{u})^T + \alpha_2 \phi_0^2 \underline{\underline{I}} - \beta_0 \underline{\underline{\sigma}}. \tag{56}$$

For this situation,

$$\nabla \mathbf{u} = \begin{bmatrix} 0 & 0 \\ \gamma & 0 \end{bmatrix}$$

where I am using the convention that $(\nabla \mathbf{u})_{ij} = \frac{\partial u_j}{\partial x_i}$. It follows that

$$(\mathbf{u} \cdot \underline{\underline{\sigma}})_{ij} = \gamma y \frac{\partial}{\partial x} \sigma_{ij}$$

and

$$\underline{\underline{\sigma}} \nabla \mathbf{u} + (\underline{\underline{\sigma}} \nabla \mathbf{u})^T = \begin{bmatrix} 2\gamma\sigma_{12} & \gamma\sigma_{22} \\ \gamma\sigma_{22} & 0 \end{bmatrix}.$$

Using these relations in Eq. 56, we find that σ_{11}, σ_{12}, and σ_{22} satisfy the equations

$$\gamma y \frac{\partial}{\partial x}\sigma_{11} = 2\gamma\sigma_{12} + \alpha_2\phi_0^2 - \beta_0\sigma_{11} \quad (57)$$

$$\gamma y \frac{\partial}{\partial x}\sigma_{12} = \gamma\sigma_{22} - \beta_0\sigma_{12} \quad (58)$$

$$\gamma y \frac{\partial}{\partial x}\sigma_{22} = \alpha_2\phi_0^2 - \beta_0\sigma_{22}. \quad (59)$$

We assume that the stresses are uniform is x. Then $\sigma_{22} = \frac{\alpha_2\phi_0^2}{\beta_0}$ and $\sigma_{12} = \frac{\gamma}{\beta_0}\sigma_{22} = \gamma\frac{\alpha_2\phi_0^2}{\beta_0^2}$. The links generate a shear stress σ_{12} that is proportional to the shear rate γ. For a *simple* fluid with viscosity μ, the shear stress in a linear shear flow is $\sigma_{12} = \mu\gamma$. Here the stresses due to the links are like an additional viscosity term with viscosity $\frac{\alpha_2\phi_0^2}{\beta_0^2}$. So the total shear stress in the case of the links is

$$\sigma_{12} = \big(\mu + \frac{\alpha_2}{\beta_0^2}\phi_0^2\big)\gamma.$$

Note that $\alpha_2\phi_0^2$ has dimensions of "stress/time" and $\frac{\gamma}{\beta_0^2}$ has dimensions "time", so that the new term has the correct dimensions. In steady state there is continued turnover of links due to formation and breaking. There is no memory or elastic force. The dynamic links generate viscous stresses.

We can also solve for σ_{11} to find that

$$\sigma_{11} = \frac{\alpha_2\phi_0^2}{\beta_0}\big(1 + 2\frac{\gamma^2}{\beta_0^2}\big).$$

Note that $\sigma_{11} > \sigma_{22}$ for any nonzero value of γ. This is an example of a "normal stress difference", something that cannot happen in a simple fluid. If the shear-rate is much lower than the link breaking rate, the normal stress difference is tiny.

Flow between parallel platelets where the top plate is moved at specified velocity for a specified time:

In this example, we illustrate that links can generate elastic stresses if they do not break or almost elastic forces on time scales much shorter than β_0^{-1}. Consider flow between two parallel plates at $y = 0$ and $y = L$. The bottom plate remains stationary, but the top plate is moved at speed U for the time period $0 < t < T$ and is stationary otherwise. We assume that $\mathbf{u}(\mathbf{x}, 0) = 0$ and that at $t = 0$, there is an isotropic link stress $\underline{\underline{\sigma}}(\mathbf{x}, 0) = \frac{\alpha_2\phi_0^2}{\beta_0}\underline{\underline{I}}$. We look for a unidirectional flow solution $\mathbf{u} = (u(y,t), 0, 0)$ and assume that none of the variables depends on x or z. After a little work similar to that in the previous example, we see that $u(y,t)$ and $\sigma(y,t) \equiv \sigma_{12}(y,t)$ satisfy the PDEs

$$u_t = \mu u_{yy} + \sigma_y, \tag{60}$$

$$\sigma_t = \chi u_y, \tag{61}$$

where $\chi \equiv \frac{\alpha_2 \phi_0^2}{\beta_0}$. They satisfy the initial conditions $u(y,0) = 0$ and $\sigma(y,0) = \chi$, and u satisfies the boundary conditions $u(0,t) = 0$ and $u(L,t) = U$ for $0 < t < T$ and $u(L,t) = 0$ otherwise.

We use a finite-difference method to solve these equations numerically. Introduce a grid $y_j = jh$ for $j = 0, ..., N+1$ where $(N+1)h = L$, and define discrete values u_j at these nodes. Define discrete values $\sigma_{j-1/2}$ at the cell centers $y_{j-1/2} = (j - \frac{1}{2})h$ for $j = 1, ..., N+1$. Since, u is known at $j = 0$ and $j = N+1$, the discrete problem's unknowns are u_j for $j = 1, ..., N$ and $\sigma_{j-1/2}$ for $j = 1, ..., N+1$. Use the approximate spatial derivatives

$$u_{yy}(y_j) \approx \frac{u_{j-1} - 2u_j + u_{j+1}}{h^2}, \tag{62}$$

$$u_y(y_{j-1/2}) \approx \frac{u_j - u_{j-1}}{h}, \tag{63}$$

$$\sigma_y(y_j) \approx \frac{\sigma_{j+1/2} - \sigma_{j-1/2}}{h}, \tag{64}$$

in a semi-discrete (method of lines) discretization of the PDEs for u and σ to get the system of ODEs

$$\frac{d}{dt} u_j = \mu \frac{u_{j-1} - 2u_j + u_{j+1}}{h^2} + \frac{\sigma_{j+1/2} - \sigma_{j-1/2}}{h}, \quad \text{for } j = 1, ..., N, \tag{65}$$

$$\frac{d}{dt} \sigma_{j-1/2} = \chi \frac{u_j - u_{j-1}}{h}, \quad \text{for } j = 1, ..., N+1. \tag{66}$$

To track the displacement of the material, also include ODEs for $x_j(t)$,

$$\frac{d}{dt} x_j = u_j(t). \tag{67}$$

Solve the system of ODEs (65), (66), (67) using an ODE solver such as MATLAB's ode23s. There are five parameters in the problem L, T, U, μ, and χ. We set $L = 1$, $T = 1$, and $U = 1$. Some example solutions are shown in Fig. **??**. Note that just after the top wall starts to move, the link forces actually accelerate the motion of the fluid to the right near the top wall.

INSERT FIGURES

Preformed platelet aggregate in a four-mill flow:

Here we again consider the model subsystem

$$\mathbf{u}_t + \mathbf{u}\cdot\nabla\mathbf{u} = -\nabla p + \mu\Delta\mathbf{u} + \nabla\cdot\underline{\underline{\sigma}} + \mathbf{f}_{bg}, \tag{68}$$

$$\nabla\cdot\mathbf{u} = 0, \tag{69}$$

$$\underline{\underline{\sigma}}_t + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}} = \underline{\underline{\sigma}}\nabla\mathbf{u} + (\underline{\underline{\sigma}}\nabla\mathbf{u})^T \tag{70}$$

where $\mathbf{f}_{bg}$ is a prescribed body force designed to drive a (spatially-periodic) four-mill flow in the absence of link forces $u_{fm}(x, y) = u_0 \sin(2\pi x)\cos(2\pi y)$ and $v_{fm}(x, y) = -u_0 \cos(2\pi x)\sin(2\pi y)$ on $[-1/2, 1/2] \times [-1/2, 1/2]$. It is easy to determine the necessary $\mathbf{f}_{bg}$ by inserting this velocity field into the steady-state version of Eq. 68 with $p = 0$ and $\underline{\underline{\sigma}} = 0$. We imagine that at time $t = 0$, activated platelets are distributed radially-symmetrically in a circle around the origin according to the function $\phi_{\mathrm{a}}(\mathbf{x}, 0) = \phi_0(\mathbf{x})$, we define $\underline{\underline{\sigma}}(\mathbf{x}, 0) = \frac{\alpha_2\phi_0(\mathbf{x})^2}{\beta_0}\underline{\underline{I}}$ and $z(\mathbf{x}, 0) = \frac{\alpha_0\phi_0(\mathbf{x})^2}{\beta_0}$. So contours of $\phi_{\mathrm{a}}(\mathbf{x}, 0)$, $\sigma_{ij}(\mathbf{x}, 0)$, and $z(\mathbf{x}, t)$ are circles around the origin. We also assume that $\mathbf{u}(\mathbf{x}, 0) = (u_{fm}(\mathbf{x}), v_{fm}(\mathbf{x}))$.

We consider two experiments with this setup. In one, the link stiffness coefficient $S_0 = 0$, so it is as if there were no links. In the other S_0 is set to a positive value. The results are shown in Figs. **??**-**??**. The panels in the column A column show the velocity field $\mathbf{u}(\mathbf{x}, t)$ and a contour of the link concentration $z(\mathbf{x}, t)$ at several times. The column B panels show a set of contours of z. The panels in column C show two sets of fluid marker points (i.e., points that move passively at velocity $\mathbf{u}$), one starting a liitle inside the outermost contour of z shown and the other outside of the region where $z > 0$. If Fig. **??**, the links exist but exert no forces on the fluid because $S_0 = 0$. The fluid motion extends the z distribution and the fluid marker distribution in the $\pm x$-directions and compresses it near the middle of the domain in the y-direction. When the flow carries links or markers close enough toward the left and right edges of the domain, the flow carries them up and down along those edges. In Fig. **??**, the effect of the links becomes evident by the second row of panels. The z contours are less extended in the x-direction, the inner set of fluid markers is also less extended forming an approximate ellipse, while the outer set of fluid markers looks much like those in the case $S_0 = 0$. Also the velocity vectors in the region of nonzero z are much shorter than at those locations initially. Moving forward in time (down in rows), we see little change in the z-contours or the locations of the innter set of fluid markers while the outer set of markers continues to move as before. The links further reduce the fluid velocity in the region with nonzero z and along the x-axis "downstream" of that region. The main conclusion is that the initially isotropic stress can evolve into a stress that resists further deformations of the region in which there are links.

See Figures 4 and 5 in [1]

Formation and behavior of platelet aggregate in a four-mill flow:

Let's return to the complete version of the special form of the model ($S(|\mathbf{y}|) = S_0 = 0$ and $\beta(|\mathbf{y}|) = \beta_0$) given by Eqs. (50-55). For this experiment, we again prescribe a force to drive a four-mill flow in the absence of link forces. We also begin with $\phi_{\mathrm{u}}(\mathbf{x}, 0) = \phi_0$, $\phi_{\mathrm{a}}(\mathbf{x}, t) = 0$, $\underline{\underline{\sigma}}(\mathbf{x}, t) = 0$, and $z(\mathbf{x}, 0) = 0$, that is, we begin with no activated platelets or interplatelet links, and with a uniform distribution of unactivated platelets. We assume that the platelet activation rate function $R(c)$ has the form $R(c) = R_0 H(c - 1)$ where H is the Heaviside function and R_0 is a specified constant. Thus platelets become activated at a constant rate R_0 whenever they encounter activating chemical above a threshold concentration, which we normalize to 1. We specifiy $c(\mathbf{x}, 0)$ so that $c(\mathbf{x}, 0) > 1$ in a circle around the stagnation point at the origin. Fig. **??** shows the evolution of the velocity field, the distribution of links, and the region in which $c(\mathbf{x}, t) > 1$ at time t.

At $t = 0$, $c > 1$ only in a prescribed circle and there are no activated platelets or links. In the second panel, the region in which $c > 1$ has expanded in the $\pm x$-directions and inside of this region there $z > 0$, but small. The velocity field has not been noticeably affected by the links, which is not surprising since links form isotropically and must be reoriented and stretched to resist the fluid motion. By the third panel, the above-threshold region has grown a little and higher values of z have developed (as indicated by the second z contour). The velocity within the inner z contour has been reduced compared to that is this region initially. The spread of the region $c > 1$ is due both to advection and diffusion and the release of more chemical as platelets become activated. As we proceed through the remaining panels, we see that the region in which $c > 1$ and $z > 0$ increases in area, but slowly, that higher link densities develop, and that the velocity becomes very small (below a threshold for plotting vectors) in much of the region where links exist. There is an interesting change in the shape at the left and right ends of the aggregate where the lesser $\pm x$-extent for $y = 0$ than for y somewhat above and below the x-axis is due to the reduced x-component of the velocity near the x-axis.

See Figures 3 in [2]

Interpretting what has occured, we can say that the addition of a bolus of actiating chemical in part of a fluid unactivated platelet mixture can cause platelet activation and link formation sufficient to form a solid aggregate in which the velocity is essentially 0. Another way of saying this is that the addition of the activating chemical initiated a process leading to a phase transition in part of gtthe mixture from viscous fluid to elastic solid which we regard as formation of a solid platelet aggregate.

Embolization and approximate closure model:

Real platelet thrombi can also break apart when subject to sufficiently high stresses from the fluid. A thrombus is said to embolize when a piece breaks off of it. Our next experiment looks at whether the model we have been examining can capture this behavior as well. The experiments begin as did the last ones, but after the aggregate has developed for a time, we apply extra forces to the fluid in the attempt to pull the aggregate apart. We first did this while aactivation and link formation (and breaking) were allowed to continue, but the aggregate remained intact. We then applied the extra force and, starting at the same time, allowed no further platelet activation land link formation. Again the aggregate remained intact although there was some thinning ('necking off') of the aggregates spatial extent in the $\pm y$-direction near $x = 0$. Why did the aggregate not come apart in these "grab and pull" experiments? We speculated that perhaps a relatively few very long links generated the force that held it together. Recall that in the form of the model we are considering here, links break at a constant rate β_0 indepdentent of how long they have become.

To examine this hypothesis, we solved the equations of the two-scale form of the model in which Eqs. (29) and (5) are used to calculate the stress in place of Eqs. (54). We assumed for these calculations that $\beta(|\mathbf{y}|) = \beta_0$ so that both forms of the model should produce the same resulting fluid and platelet motions. The simulation with the two-scale model confirmed our hypothesis. Furthermore, if the two-scale model is run with a breaking rate function $\beta(|\mathbf{y}|)$ that increases sufficiently rapidly with $|\mathbf{y}|$, then the aggregate could be pulled apart in these experiments. So our inability to break apart the platelet aggregate in the special form of the model was due to the assumption that $\beta(|\mathbf{y}|)$ is constant which led to the nonphysical behavior of there being very long links that generate large forces. The limitation is not present in the two-scale version of the model where the link breaking rate can be made strain dependent.

Let's recall the result of our attempt to derive a general equation for the link stress tensor from the two-scale model. Still assuming that the link stiffness $S(|\mathbf{y}|) = S_0$ is constant, but allowing $|\mathbf{y}|$-dependent link breaking, we obtained the equation

$$\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}} = \left(\underline{\underline{\sigma}}\nabla\mathbf{u}\right) + \left(\underline{\underline{\sigma}}\nabla\mathbf{u}\right)^T + \alpha_2{\phi_{\mathrm{a}}}^2\underline{\underline{I}} - \int \beta(|\mathbf{y}|)\tfrac{1}{2}E(\mathbf{x},\mathbf{y},t)S_0\mathbf{y}\mathbf{y}^T d\mathbf{y}. \qquad (71)$$

It was only when we assumed that $\beta(|\mathbf{y}|)$ is constant that we could reduce the last term to one in which the microscale variable $\mathbf{y}$ did not appear. The question we now face is whether we can allow strain-dependent link breaking in a useful way without having to solve the equations of the two-scale model? Towards answering that, note that if β were a function of $\mathbf{x}$ and t, but not of $|\mathbf{y}|$, then it could be pulled out of the integral to give us an equation for $\underline{\underline{\sigma}}$ with no reference to the microscale variable $\mathbf{y}$. For example, if we assumed that β is a function of

$$< |\mathbf{y}| > (\mathbf{x}, t) = \frac{\int_y E(\mathbf{x}, \mathbf{y}, t)|\mathbf{y}|d\mathbf{y}}{\int_y E(\mathbf{x}, \mathbf{y}, t)d\mathbf{y}}, \tag{72}$$

that is, a function of the mean length of all links emanating from activated platelets at $\mathbf{x}$ at time t, then we would obtain

$$\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}} = \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2{\phi_{\mathrm{a}}}^2\underline{\underline{I}} - \beta(< |\mathbf{y}| > (\mathbf{x}, t))\underline{\underline{\sigma}}(\mathbf{x}, t). \tag{73}$$

Note that in the definition of $< |\mathbf{y}| > (\mathbf{x}, t)$, we divide by $\int_y E(\mathbf{x}, \mathbf{y}, t)d\mathbf{y}$ because E itself is not a probability density. Note that this integral equals $z(\mathbf{x}, t)$, so provided we solve the PDE for z, this is a quantity available from the macroscale model. It is not obvious how to obtain the numerator from macroscale quantities, but recall the definition of $\underline{\underline{\sigma}}$ itself

$$\underline{\underline{\sigma}}(\mathbf{x}, t) = \frac{1}{2}S_0\int_y E(\mathbf{x}, \mathbf{y}, t)\mathbf{y}\mathbf{y}^T d\mathbf{y}.$$

From this, it is easy to see that the trace of $\underline{\underline{\sigma}}$ is given by

$$\mathrm{Tr}(\underline{\underline{\sigma}}(\mathbf{x}, \mathrm{t})) = \frac{1}{2}\mathrm{S}_0\int_{\mathrm{y}} \mathrm{E}(\mathbf{x}, \mathbf{y}, \mathrm{t})|\mathbf{y}|^2 \mathrm{d}\mathbf{y} = \frac{\mathrm{S}_0}{2} < |\mathbf{y}|^2 > (\mathbf{x}, \mathrm{t}). \tag{74}$$

So, $< |\mathbf{y}|^2 > (\mathbf{x}, t) = \frac{2}{S_0}\mathrm{Tr}(\underline{\underline{\sigma}}(\mathbf{x}, \mathrm{t}))$, and a plausible surrogate for $< |\mathbf{y}| > (\mathbf{x}, t)$ is therefore

$$< |\mathbf{y}| > (\mathbf{x}, t) \approx \sqrt{\Big(\frac{2}{S_0}\frac{\mathrm{Tr}(\underline{\underline{\sigma}}(\mathbf{x}, \mathrm{t}))}{z(\mathbf{x}, t)}\Big)}. \tag{75}$$

We therefore define the link breaking rate, not as a function of $|\mathbf{y}|$, but instead

$$\beta = \beta\Big(\frac{2}{S_0}\frac{\mathrm{Tr}(\underline{\underline{\sigma}}(\mathbf{x}, \mathrm{t}))}{z(\mathbf{x}, t)}\Big). \tag{76}$$

For future convenience, define $\mathcal{E}(\mathbf{x}, t) = \Big(\frac{\mathrm{Tr}(\underline{\underline{\sigma}}(\mathbf{x}, \mathrm{t}))}{z(\mathbf{x}, t)}\Big)$ Using this in the derivation of the equation for $\underline{\underline{\sigma}}(\mathbf{x}, t)$ (and similarly in the derivation of the equation for z), we obtain the PDEs

$$(\underline{\underline{\sigma}})_t + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}} = \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2{\phi_{\mathrm{a}}}^2\underline{\underline{I}} - \beta(\mathcal{E}(\mathbf{x}, t))\underline{\underline{\sigma}}(\mathbf{x}, t). \tag{77}$$

and

$$z_t + \mathbf{u}\cdot\nabla z = \alpha_0{\phi_{\mathrm{a}}}^2 - \beta(\mathcal{E}(\mathbf{x}, t))z(\mathbf{x}, t). \tag{78}$$

We call the version of the model, using Eqs. (77-78) as the “approximate closure” form of the model. The reason for the notation $\mathcal{E}$ is that this quantity has the interpretation of being the average elastic strain energy per link for links emanating from platelets at $\mathbf{x}$. If one has a two-scale model with a specific choice of $\beta(|\mathbf{y}|)$, it is not obvious how to choose a different function $\beta(\mathcal{E})$ for the approximate closure model so that the closure model well approximates the behavior of the two-scale model. Bob Guy did some analysis of this question is his thesis (see also his paper XXXX), but we do not discuss that here. In Fig. **??**, we show some results from a "grab and pull" experiment with the two-scale model and with the approximate closure form of the model.

See figures in [3]

Since our goal in having a macroscale model of platelet aggregation is not to match the behavior of the two-scale model, but to understand platelet aggregation, we can take the "approximate closure" model as our macroscale model of platelet aggregation. We note that an approximate closure similar to the one we use appears in the polymer literature. In the context of "transient network" models of polymers in which links can break but are then immediately reformed at a reference length, Phan-Thien and Tanner proposed a breaking rate that is a function of $\mathrm{Tr}(\underline{\underline{\sigma}})$. In their context, the number density of links remained constant, so division by z could be ignored. In that context the closure is call the "PTT-closure."

Interactions with the Vessel Wall:

The model as described so far does not involve blood vessel walls or platelet interactions with the injured portion of the wall. Based on the derivation so far, it is relatively straightforward to add these. We prescribe the locations of the top and bottom vessel wall. The velocity is assumed to satisfy the no-slip condition on these walls, and the diffusing species ϕ_{u} and c are assumed to satisfy no-flux boundary conditions all along the walls. No boundary conditions are needed for the non-diffusing quantities at these walls since the fluid velocity is zero there. At the upstream inlet to the domain we specify a nonzero concentration of unactivated platelets and zero concentrations for activated platelets and activating chemical. We use "outflow" boundary conditions at the downstream outlet of the domain.

To model the injury, we prescribe the number density $w(\mathbf{x}, t)$ of "wall reactive" sites in a thin region along the injuried portion of the wall. There are two types of platelet interactions with the injured wall. Platelets can be activated and they can adhere to the wall. Both of these interactions can be described using w. For the activation, we assume that platelets are activated by contact with the wall at a rate $R^{\mathrm{w}}(w(\mathbf{x}, t))\phi_{\mathrm{u}}(\mathbf{x}, t)$. This term appears in the equation for ϕ_{u} (with a minus sign), in the equation for ϕ_{a} and in the equation for c multiplied by the factor A to give modified versions of those equations

$$(\phi_{\rm u})_t + \mathbf{u}\cdot\nabla\phi_{\rm u} = D_{\rm u}\Delta\phi_{\rm u} - (R(c)\phi_{\rm u} + R^{\rm w}(w)\phi_{\rm u}) \tag{79}$$

$$(\phi_{\rm a})_t + \mathbf{u}\cdot\nabla\phi_{\rm a} = +(R(c)\phi_{\rm u} + R^{\rm w}(w)\phi_{\rm u}) \tag{80}$$

$$c_t + \mathbf{u}\cdot\nabla c = D_{\rm c}\Delta c + A(R(c)\phi_{\rm u} + R^{\rm w}(w)\phi_{\rm u}) \tag{81}$$

To model adhesion of activated platelets to the wall, we imagine a set of "adhesive links" like the platelet-platelet ones, but this time joining activated platelets to reactive wall sites. Through a derivation much like that for the platelet-platelet link distribution E, we derive a PDE for the distribution functions $E^{\rm w}$ of the adhesive links. We can define the corresponding stress tensor $\underline{\underline{\sigma}}^{\rm w}(\mathbf{x},t)$ and number density of adhesive links $z^{\rm w}(\mathbf{x},t)$ from $E^{\rm w}$ in a similar way, and derive macroscale PDEs for them under a similar closure approximation to get

$$(\underline{\underline{\sigma}}^{\rm w})_t + \mathbf{u}\cdot\nabla\underline{\underline{\sigma}}^{\rm w} = \underline{\underline{\sigma}}^{\rm w}\nabla\mathbf{u} + (\underline{\underline{\sigma}}^{\rm w}\nabla\mathbf{u})^T + \alpha_2^{\rm w} w\phi_{\rm a} - \beta^{\rm w}\underline{\underline{\sigma}}^{\rm w} \tag{82}$$

$$(z^{\rm w})_t + \mathbf{u}\cdot\nabla z^{\rm w} = \alpha_0^{\rm w} w\phi_{\rm a} - \beta^{\rm w} z^{\rm w} \tag{83}$$

where the breaking rate $\beta^{\rm w}$ is here a function of

$$\mathcal{E}^{\rm w} = \frac{2}{S_0^{\rm w}}\frac{\mathrm{Tr}(\underline{\underline{\sigma}}^{\rm w})}{z^{\rm w}}. \tag{84}$$

The final change to the model is to include $\nabla\cdot\underline{\underline{\sigma}}^{\rm w}$ in the Navier-Stokes equations to get:

$$\rho(\mathbf{u}_t + \mathbf{u}\cdot\nabla\mathbf{u}) = -\nabla p + \mu\Delta u + \nabla\cdot\underline{\underline{\sigma}} + \nabla\cdot\underline{\underline{\sigma}}^{\rm w} \qquad \nabla\cdot\mathbf{u} = 0. \tag{85}$$

The most common occurence of platelet aggregation in response to wall injury in arteries is when an atherosclerotic plaque on the wall of an artery ruptures and exposes clot-promoting material to the blood. Here are several simulations of such an event. We specify where on the plaque the rupture occurs by defining a distribution of wall reactive sites w there. In these experiments, some of the rates (activation, link formation, link breaking) differed in some simulations. The first example involves a plaque rupture that leads to eventual vessel occlusion and flow cessation. The second and third examples are based on ruptures at symmetric locations on the upstream and downstream shoulders of the plaque and the very different aggregation behavior that results in the two cases. The reason for the difference is the much higher shear rates and shear stresses at the upstream shoulder where the vessel lumen is narrowing than at near the downstream shoulder where the lumen is widening. For the upstream rupture, platelet aggregates grow but portions of them are broken off because of the shear stress (and strain-dependent link breaking rate) so that by the end there seems to be no platelets remaining over the injury. In Fig. **??** we plot $\mathcal{E} + \mathcal{E}^{\rm w}$ in the two cases and see that this quantity is much higher in the high shear stress region.

Model limitations:

So this model can capture growth of an aggregate up to the point where the vessel is occluded and can capture growth and embolization of an aggregate when the shear stresses lead to link breaking that outpaces link formation. These are significant accomplishments of the model. But the model has serious limitations. The easier one to describe is that the number density of platelets in the aggregates the model produces are at most only a slight amount higher than the background number density of unactivated platelets in the blood. In real aggregates, the number density of platelets is up to 100$\times$ that in the bulk blood. The second limitation is that for a wall-bound aggregate to form in this model, the rates of platelet activation and link formation must be much greater than in reality so that an aggregate forms very quickly. For a persistent aggregate to form on the wall it must bring the fluid velocity there to zero quickly, or else the platelets will be carried away by the flow. Thus, platelets must be activated and links form rapidly. The speed at which aggregates have to form in this model is much greater than in reality. Both of these limitations are due to the model's assumption that all platelets including the ones in aggregates move at the fluid's velocity, that is, the model does not allow for relative motion between platelets in an aggregate and the fluid.

Two Phase Models:

To overcome these limiations, we built a model in which platelets in an aggregate have their own velocity field that is generally different from that of the fluid. We did this in the context of two-phase mixture models which we now briefly consider.

Suppose we have two materials which for simplicity I will call "fluid" and "network". The fluid is a Newtonian fluid and the network can be a suspension of polyner strands or groups of bound platelets. The mixture models are continuum models and take a macroscopic perspective. From that perspective, it is reasonable to allow that both fluid and network may exist simulataneously at a location in space. Together the two materials fill the volume of space at that location, so letting $\theta_{\rm f}(\mathbf{x},t)$ and $\theta_{\rm n}(\mathbf{x},t)$ denote the fraction of the volume occupied by fluid and network, respectively, at location $\mathbf{x}$ at time t, we conclude that $\theta_{\rm f}(\mathbf{x},t)+\theta_{\rm n}(\mathbf{x},t)=1$. We assume that each material has its own velocity field, $\mathbf{u}_{\rm f}$ for the fluid and $\mathbf{u}_{\rm n}$ for the network. It follows from conservation of mass (and the assumption that the mass densities of the two materials are the same), that the volume fractions satisfy the PDEs

$$(\theta_{\rm f})_t + \nabla\cdot(\mathbf{u}_{\rm f}\theta_{\rm f}) = g \qquad (86)$$

$$(\theta_{\rm n})_t + \nabla\cdot(\mathbf{u}_{\rm n}\theta_{\rm n}) = -g \qquad (87)$$

where g describes the rate of conversion of network into fluid (if positive) or vice versa. The function g could be the result of chemical processes involving say, degradation, of the network into small pieces that individually have no effect on the motion. Note that by adding Eqs. (86) and (87) and recalling that $\theta_{\rm f} + \theta_{\rm n} = 1$, that

$$\nabla\cdot(\theta_{\rm f}\mathbf{u}_{\rm f} + \theta_{\rm n}\mathbf{u}_{\rm n}) = 0. \tag{88}$$

This is an incompressibility-like constraint on the volume-fraction-weighted average velocity of the mixture at each location. In regions in which both fluid and network are present the individual velocity fields $\mathbf{u}_{\rm f}$ and $\mathbf{u}_{\rm n}$ need not be incompressible! One material can move into the region while the other material moves out so that Eq. (88) holds.

The velocity fields are assumed to satisfy two sets of momentum equations the exact form of which depends on what we assume about the mechanical properties of each material. Let's assume that the fluid is a Newtonian fluid and that the network is a viscoelastic material with a stress obtained from an Oldroyd-B type model. Then,

$$(\theta_{\rm f}\mathbf{u}_{\rm f})_t + \nabla\cdot(\theta_{\rm f}\mathbf{u}_{\rm f}\mathbf{u}_{\rm f}) = -\theta_{\rm f}\nabla p + \nabla\cdot(\theta_{\rm f}\underline{\underline{\sigma}}^{\rm fv}) + \xi\theta_{\rm f}\theta_{\rm n}(\mathbf{u}_{\rm n} - \mathbf{u}_{\rm f}) + \theta_{\rm f}\nabla\mu_f, \tag{89}$$

and

$$(\theta_{\rm n}\mathbf{u}_{\rm n})_t + \nabla\cdot(\theta_{\rm n}\mathbf{u}_{\rm n}\mathbf{u}_{\rm n}) = -\theta_{\rm n}\nabla p + \nabla\cdot(\theta_{\rm n}\underline{\underline{\sigma}}^{\rm nv}) + \nabla\cdot(\theta_{\rm n}\underline{\underline{\sigma}}^{\rm n}) + \xi\theta_{\rm f}\theta_{\rm n}(\mathbf{u}_{\rm f} - \mathbf{u}_{\rm n}) + \theta_{\rm n}\nabla\mu_n. \tag{90}$$

Here,

$$\underline{\underline{\sigma}}^{\rm fv} = \eta_f(\nabla\mathbf{u}_{\rm f} + (\nabla\mathbf{u}_{\rm f})^T) + \lambda_f\nabla\cdot(\mathbf{u}_{\rm f})\underline{\underline{I}} \tag{91}$$

and

$$\underline{\underline{\sigma}}^{\rm nv} = \eta_n(\nabla\mathbf{u}_{\rm n} + (\nabla\mathbf{u}_{\rm n})^T) + \lambda_n\nabla\cdot(\mathbf{u}_{\rm n})\underline{\underline{I}}. \tag{92}$$

are viscous stress tensors for the fluid and network, respectively, including terms that would vanish if the individual velocity fields were incompressible. The constants η_f and η_n and the shear viscosities and λ_f and λ_n are the bulk viscosities of the materials. The tensor $\underline{\underline{\sigma}}^{\rm n}$ represents the extra stresses generated by elastic connections within the network. It evolves according to the PDE

$$(\underline{\underline{\sigma}}^{\rm n})_t + \nabla\cdot(\mathbf{u}_{\rm n}\underline{\underline{\sigma}}^{\rm n}) = \underline{\underline{\sigma}}^{\rm n}\nabla\mathbf{u}_{\rm n} + (\underline{\underline{\sigma}}^{\rm n}\nabla\mathbf{u}_{\rm n})^T + \alpha\underline{\underline{I}} - \beta_{\rm n}\underline{\underline{\sigma}}^{\rm n}. \tag{93}$$

Eqs. (89-90) contain the term $\pm\xi\theta_{\rm f}\theta_{\rm n}(\mathbf{u}_{\rm f} - \mathbf{u}_{\rm n})$ which is a force (per unit volume) due to drag between the two materials when they move at different velocities. The terms μ_f and μ_n are chemical potentials which can be used to model other physical processes such as osmosis, electrostatics if the network is charged, and so on. In Eq. (93), the term $\alpha\underline{\underline{I}}$ describes some process of generating isotropic stress, whether from Brownian motion or link creation of something else. Finally, the term p, the "pressure", is a Lagrange multiplier that enforces the constraint given in Eq. (88). Eqs. (86 - 93) comprise a generic mixture model in which the functions g and α remain to be specified. The left hand sides of Eqs. (89 and (90) are equivalent to the expressions $\theta_{\mathrm{f}}\frac{D}{Dt}\mathbf{u}_{\mathrm{f}}$ and $\theta_{\mathrm{n}}\frac{D}{Dt}\mathbf{u}_{\mathrm{n}}$, respectively.

Note that Eqs. (89-90) have similarities to the Navier-Stokes equations, but notice that they are variable-coefficent PDEs because the volume fractions θ_{f} and θ_{n} can vary in space and time. Notice also the locations of the factors θ_{f} and θ_{n} in these equations and that they are different for the term with p and the other stress terms. That these are correct can be shown explicitly from a variational derivation of the momentum equations using the "Principle of Virtual Power", which is also called the "Principle of Maximum Dissipation Rate". The main reason for the difference is that p enforces a condition on a quantity that involves both components of the mixture, i.e, Eq. (88).

Two phase platelet aggregation model:

We next use the framework of multiphase mixture models to formulate a two-phase platelet aggregation model. We will limit ourselves to describing the model ignoring interations with the vessel wall. The first difference between this model and the single phase model is that it includes three populations of platelets, unactivated, activated but unbound, and bound to other platelets in an aggregate with number densities ϕ_{u}, ϕ_{a}, and ϕ_{b}, respectively. The platelets that are not bound to anything are assumed to move with the fluid at its velocity $\mathbf{u}_{\mathrm{f}}$ while the bound platelets move at a different "bound-platelet" velocity which we denote $\mathbf{u}_{\mathrm{b}}$. Again, we assume there is one activating chemical with concentration c. The PDEs for the platelet number densities and the activating chemical concentration are

$$(\phi_{\mathrm{u}})_t + \nabla\cdot(\phi_{\mathrm{u}}\mathbf{u}_{\mathrm{f}}) = D_{\mathrm{u}}\Delta\phi_{\mathrm{u}} - f_{ua} \tag{94}$$

$$(\phi_{\mathrm{a}})_t + \nabla\cdot(\phi_{\mathrm{a}}\mathbf{u}_{\mathrm{f}}) = D_{\mathrm{u}}\Delta\phi_{\mathrm{a}} + f_{ua} - f_{ab} \tag{95}$$

$$(\phi_{\mathrm{b}})_t + \nabla\cdot(\phi_{\mathrm{b}}\mathbf{u}_{\mathrm{b}}) = f_{ab} - f_{ba} \tag{96}$$

$$c_t + \nabla\cdot(c\mathbf{u}_{\mathrm{f}}) = D_{\mathrm{c}}\Delta c + Af_{ua} \tag{97}$$

Letting v_p denote the volume of a single platelet, we have that the volume fraction of bound platelets is

$$\theta_{\mathrm{b}}(\mathbf{x}, t) = v_p\phi_{\mathrm{b}}(\mathbf{x}, t) \tag{98}$$

and the volume fraction of "fluid" including the individual unactivated and activated platelets is $\theta_{\mathrm{f}} = 1 - \theta_{\mathrm{b}}$. We do not need a PDE for θ_{b}, but if we multiply Eq. 96 by v_p we would find that

$$(\theta_{\mathrm{b}})_t + \nabla\cdot(\theta_{\mathrm{b}}\mathbf{u}_{\mathrm{b}}) = v_p(f_{ab} - f_{ba}).$$

The volume fraction conversion function g from the generic multiphase model is here given by $v_p(f_{ba} - f_{ab})$. The two velocity fields satisfy the equations

$$(\theta_{\rm f}\mathbf{u}_{\rm f})_t + \nabla\cdot(\theta_{\rm f}\mathbf{u}_{\rm f}\mathbf{u}_{\rm f}) = -\theta_{\rm f}\nabla p + \nabla\cdot(\theta_{\rm f}\underline{\underline{\sigma}}^{\rm fv}) + \xi\theta_{\rm f}\theta_{\rm b}(\mathbf{u}_{\rm b} - \mathbf{u}_{\rm f}), \tag{99}$$

and

$$(\theta_{\rm b}\mathbf{u}_{\rm b})_t + \nabla\cdot(\theta_{\rm b}\mathbf{u}_{\rm b}\mathbf{u}_{\rm b}) = -\theta_{\rm b}\nabla p + \nabla\cdot(\theta_{\rm b}\underline{\underline{\sigma}}^{\rm bv}) + \nabla\cdot(\theta_{\rm b}\underline{\underline{\sigma}}^{\rm b}) + \xi\theta_{\rm f}\theta_{\rm b}(\mathbf{u}_{\rm f} - \mathbf{u}_{\rm b}). \tag{100}$$

and are subject to the constraint

$$\nabla\cdot(\theta_{\rm f}\mathbf{u}_{\rm f} + \theta_{\rm b}\mathbf{u}_{\rm b}) = 0. \tag{101}$$

For several reasons, the description of platelet-platelet links and of the platelet-platelet link stress tensor are more complicated than in the single-phase model. One reason is that links can form between pairs of activated platelets, an activated platelet and a bound platelet, and between pairs of bound platelets, hence link formation occurs at a rate of the form

$$C(\phi_{\rm a}, \phi_{\rm b}) = \alpha_0^{aa}{\phi_{\rm a}}^2 + \alpha_0^{ab}\phi_{\rm a}\phi_{\rm b} + \alpha_0^{bb}{\phi_{\rm b}}^2 \tag{102}$$

The actual link formation function in the model is somewhat more complicated then this, but the differences are not important for our present discussion. The density of platelet-platelet links $z_{\rm b}(\mathbf{x}, t)$ evolves according to the PDE

$$(z_{\rm b})_t + \nabla\cdot(\mathbf{u}_{\rm b}z_{\rm b}) = \alpha_0^{aa}{\phi_{\rm a}}^2 + \alpha_0^{ab}\phi_{\rm a}\phi_{\rm b} + \alpha_0^{bb}{\phi_{\rm b}}^2 - \beta^{\rm b}z_{\rm b}. \tag{103}$$

If each link were treated as a linear spring with $S(|\mathbf{y}|) = S_0\mathbf{y}$, as in the single-phase model, then the link stress tensor $\underline{\underline{\sigma}}^{\rm b}$ would satisfy a PDE similar to the one we have seen before. For reasons that are made clear below, let's call the stress tensor with links with constant stiffness and zero rest length $\underline{\underline{\sigma}}_0^{\rm b}$. It would satisfy the equation

$$(\underline{\underline{\sigma}}_0^{\rm b})_t + \nabla\cdot(\mathbf{u}_{\rm b}\underline{\underline{\sigma}}_0^{\rm b}) = \underline{\underline{\sigma}}_0^{\rm b}\nabla\mathbf{u}_{\rm b} + (\underline{\underline{\sigma}}_0^{\rm b}\nabla\mathbf{u}_{\rm b})^T + (\alpha_2^{aa}{\phi_{\rm a}}^2 + \alpha_2^{ab}\phi_{\rm a}\phi_{\rm b} + \alpha_2^{bb}{\phi_{\rm b}}^2)\underline{\underline{I}} - \beta^{\rm b}\underline{\underline{\sigma}}_0^{\rm b}. \tag{104}$$

The parameter S_0 would be part of the parameters α_2^{aa}, α_2^{ab}, and α_2^{bb} in this equation. Suppose this equation held and we had a steady-state with no flow, similar to the first case we considered with the single-phase model. Then, we see that

$$\underline{\underline{\sigma}}_0^{\rm b} = \frac{(\alpha_2^{aa}{\phi_{\rm a}}^2 + \alpha_2^{ab}\phi_{\rm a}\phi_{\rm b} + \alpha_2^{bb}{\phi_{\rm b}}^2)}{\beta^{\rm b}}\underline{\underline{I}}$$

which is a suction pressure. In the single phase model, the pressure p adjusts to balance this suction pressure and preserve the incompressibility of the fluid velocity field. Here, $\mathbf{u}_{\rm b}$ is not incompressible, and the suction pressure induces a bound platelet velocity that collapses the aggregate to a point!

(Another way to see the problem is to note that the term $-\theta_{\rm b}\nabla p$ in general is not a gradient field cannot balance the gradient field given by the divergence of the above suction pressure stress.) The origin of the problem is that the "rest configuration" for each link is one of zero length.

To include link springs with non-zero resting length, R, we would set $S(|\mathbf{y}|) = S_0\Big(1 - \frac{R}{|\mathbf{y}|}\Big)$. But then $S'(|\mathbf{y}|) \neq 0$. Recall our derivation of the equation for the link stress tensor from the two-scale model. In general, we showed that the stress tensor $\underline{\underline{\sigma}}$ satisfies

$$\begin{aligned}\frac{\partial \underline{\underline{\sigma}}}{\partial t} + \nabla\cdot(\mathbf{u}\underline{\underline{\sigma}}) &= \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big) + \big(\underline{\underline{\sigma}}\nabla\mathbf{u}\big)^T + \alpha_2{\phi_{\rm a}}^2\underline{\underline{I}} - \int \beta(|\mathbf{y}|)\tfrac{1}{2}ES(|\mathbf{y}|)\mathbf{y}\mathbf{y}^T d\mathbf{y}\\ &\quad -\frac{1}{2}\sum_{k,l}\frac{\partial u_k}{\partial x_l}\int E(\mathbf{x},\mathbf{y},t)\frac{S'(|\mathbf{y}|)}{|\mathbf{y}|}y_iy_jy_ky_l d\mathbf{y}.\end{aligned}$$

We would obtain a similar expression here with the $\alpha_2{\phi_{\rm a}}^2\underline{\underline{I}}$ term modified because links can form in multiple ways in the new model. Using the above expression for $S(|\mathbf{y}|)$ in the last term in this equation produces a horrendous mess! This leads to the question: Can we get the effect of a nonzero link rest length without dealing with this term? Consider the expression for the stress tensor with $S(|\mathbf{y}|)$ as given above.

$$\underline{\underline{\sigma}}^{\rm b}(\mathbf{x},t) = \frac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S_0\Big(1 - \frac{R}{|\mathbf{y}|}\Big)\mathbf{y}\mathbf{y}^T d\mathbf{y}. \tag{105}$$

Note that this can be written

$$\underline{\underline{\sigma}}^{\rm b}(\mathbf{x},t) = \frac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S_0\mathbf{y}\mathbf{y}^T d\mathbf{y} - R\frac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S_0\frac{1}{|\mathbf{y}|}\mathbf{y}\mathbf{y}^T d\mathbf{y}.$$

The first term is the stress tensor $\underline{\underline{\sigma}}_0^{\rm b}$ we get from E for the case of zero resting length links. This stress tensor satisfies Eq. 104. Consider the second term and suppose we approximate $\frac{1}{|\mathbf{y}|}$ by $\frac{1}{<|\mathbf{y}|>}$. If we do this, then that fraction can be pulled out of the integral to give the approximation

$$R\frac{1}{2}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S_0\frac{1}{|\mathbf{y}|}\mathbf{y}\mathbf{y}^T d\mathbf{y} \approx \frac{R}{<|\mathbf{y}|>}\int_{\mathbf{y}} E(\mathbf{x},\mathbf{y},t)S_0\mathbf{y}\mathbf{y}^T d\mathbf{y} = \frac{R}{<|\mathbf{y}|>}\underline{\underline{\sigma}}_0^{\rm b}.$$

Recall also that an approximation to $<|\mathbf{y}|>(\mathbf{x},t)$ is given by

$$<|\mathbf{y}|>(\mathbf{x},t) \approx \sqrt{\frac{2}{S_0}\frac{\mathrm{Tr}(\underline{\underline{\sigma}}_0^{\rm b}(\mathbf{x},\mathrm{t}))}{z_{\rm b}(\mathbf{x},t)}}.$$

These two observations motivate us to modify our definition of $\underline{\underline{\sigma}}^{\rm b}$ from that given in Eq. 105 and to instead *define* $\underline{\underline{\sigma}}^{\rm b}$ as

$$\underline{\underline{\sigma}}^{\rm b}(\mathbf{x},t) = \underline{\underline{\sigma}}_0^{\rm b}(\mathbf{x},t)\Big(1 - R\frac{S_0 z_{\rm b}(\mathbf{x},t)}{2\mathrm{Tr}(\underline{\underline{\sigma}}_0^{\rm b}(\mathbf{x},\mathrm{t}))}\Big) \tag{106}$$

where $\underline{\underline{\sigma}}_0^{\rm b}$ is obtained by solving Eq. 104. Then, $\nabla\cdot(\theta_{\rm b}\underline{\underline{\sigma}}^{\rm b})$ appears in the momentum equation for $\mathbf{u}_{\rm b}$.

To complete the description of the two-phase model it remains to specify the platelet state transition rates f_{ua}, f_{ab}, and f_{ba}, the form of the drag coefficient $\xi = \xi(\theta_{\mathrm{b}})$, and the form of the link breaking rate β^{b}. These specifications are not important to our current discussion of two-phase models, so we omit them.

For results see [4].

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