Modeling platelet function in the scope of ISTC project #3744

September 17, 2011

Platelets may be activated in two different ways: by chemicals and by shear rate [7–9]. In the scope of current project attention will be concentrated on activation of platelets by chemicals in the conditions of low-shear flows. These conditions are as a rule typical for small and moderate vessels, where the blood coagulation cascade and platelets are activated nearly simultaneously [4]. The constructed model is aimed to describe the processes of blood coagulation to be compared with [1,4].

The mathematical models developed in [2,3,5,6] are proposed as a prototype for platelets modeling approach. A resulting model will be mainly based on [6]. In [2,3] there are no actual parameters of numerical calculations. The model developed in [5] is generalized in [6].

The mechanistic model of platelet aggregation developed in [10] is also generalized in [6].

There are four types of platelet species in the model: mobile unactivated, mobile activated, platelet-bound activated and subendothelium-bound activated; their concentrations are denoted as: $P^{m,u}$, $P^{m,a}$, $P^{b,a}$, $P^{se,a}$. Although platelets are described in the model in terms of number densities (number/volume), the size of a platelet enters into the model: maximum number density for platelets is $P_{max} = 6.67 \cdot 10^7$ *platelets per* mm^3 based on the assumption that 20 platelets fit tightly into 300 μm^3. The total platelet fraction ϕ^T is the ratio of the sum of the four platelet number densities to this maximum density:

$$\phi^T = \frac{P^{m,u} + P^{m,a} + P^{b,a} + P^{se,a}}{P_{max}} \tag{1}$$

The bound platelet fraction ϕ^B is similarly the ratio of the sum of bound activated and subendothelium-bound activated platelet number densities to the maximum density:

$$\phi^B = \frac{P^{b,a} + P^{se,a}}{P_{max}} \tag{2}$$

The bound platelet fraction ϕ^B determines the resistance to flow in the corresponding portion of a thrombus.

The velocity $\vec{V}(\vec{x},t)$ and pressure $p(\vec{x},t)$ fields are described by Navier-Stokes equations with some additional terms:

$$\frac{\partial \vec{V}}{\partial t} + \left(\vec{V}\nabla\right)\vec{V} = -\frac{1}{\rho}\nabla p + \nu\left(\frac{M_2}{M_1}\right)\Delta\vec{V} - \nu\left(\frac{M_2}{M_1}\right)\alpha(\phi^B)\vec{V} \tag{3}$$

$$\nabla\vec{V} = 0 \tag{4}$$

Here $\nu\left(\frac{M_2}{M_1}\right)$ is the blood viscosity[1]. The term $-\nu\alpha(\phi^B)\vec{V}$, called the Brinkman term, represents frictional resistance to the fluid motion due to bound platelets and relates to the inverse permeability

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[1] the dependence of the blood viscosity on fibrin moments is described in ISTC project #3744 reports

of the growing platelet mass. In this term the frictional resistance is assumed to increase with ϕ^B according to the function $\alpha(\phi^B)$:

$$\alpha(\phi^B) = \frac{\alpha_{max}(\phi^B)^2}{(\phi^B_0)^2 + (\phi^B)^2} \tag{5}$$

ϕ^B_0 is set to 0.5 and the α_{max} is set to be sufficiently large that there is little flow through a thrombus with $\phi^B \approx 1$.

The kinetics of platelet concentrations is described by the following system of equations:

$$\begin{aligned}
\frac{\partial P^{m,u}}{\partial t} =& -\nabla \cdot \Big(W(\phi^T)(\vec{V} P^{m,u} - D\nabla P^{m,u})\Big) - k_{adh}(x)(P_{max} - P^{se,a})P^{m,u} - \dots \\
& \cdots - \left(A_1(\theta) + A_2([ADP])\right) P^{m,u} \qquad (6) \\
\frac{\partial P^{m,a}}{\partial t} =& -\nabla \cdot \Big(W(\phi^T)(\vec{V} P^{m,a} - D\nabla P^{m,a})\Big) - k_{adh}(x)(P_{max} - P^{se,a})P^{m,a} + \dots \\
& \cdots + \left(A_1(\theta) + A_2([ADP])\right) P^{m,u} - k_{coh} g(\eta) P_{max} P^{m,a} \qquad (7) \\
\frac{\partial P^{b,a}}{\partial t} =& -k_{adh}(x)(P_{max} - P^{se,a})P^{b,a} + k_{coh} g(\eta) P_{max} P^{m,a} \qquad (8) \\
\frac{\partial P^{se,a}}{\partial t} =& k_{adh}(x)(P_{max} - P^{se,a})\left(P^{m,a} + P^{m,u} + P^{b,a}\right) \qquad (9)
\end{aligned}$$

According with [6], for the mobile unactivated and activated platelets, the term $J^m = \vec{V} P^m - D\nabla P^m$ is the flux of these platelets due to advection with the fluid and diffusion. In reality, platelets have non-zero size and may not move as readily as fluid through a region which is already occupied in part by thrombus-bound platelets. To take this into account, the specific function $W(\phi^T)$ is introduced. $W(\phi^T)$ monotonically decreases from $W(0) = 1$ to $W(1) = 0$. According to [6] (see fig. 1):

$$W(\phi^T) = tanh(\pi(1 - \phi^T)) \tag{10}$$

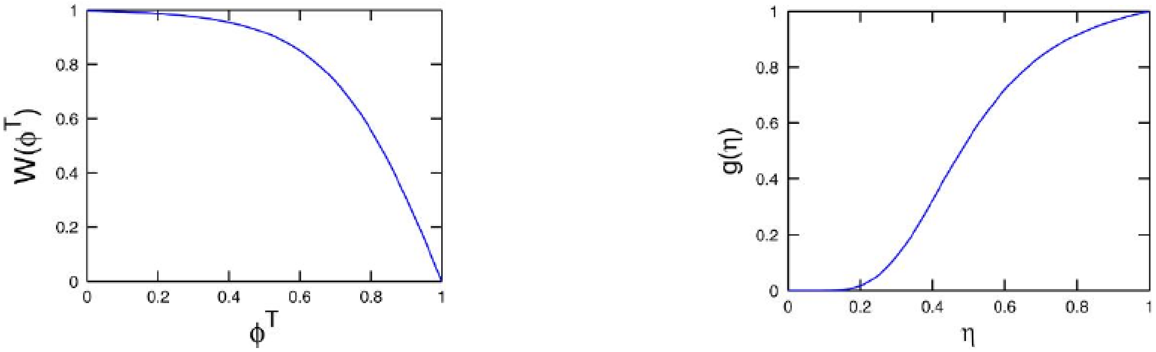

Figure 1: Left: Platelet density-dependent mobility limitation function. Right: Binding affinity function.

The second term in each of equations (6) and (7) describes platelet adhesion to the exposed subendothelial material. The parameter $k_{adh}(x)$ is assumed to be a positive constant for points within one platelet diameter's distance of the subendothelium and zero elsewhere. Since P_{max} is the maximum number density of platelets, $P_{max} - P^{se,a}$ indicates the portion of the space just over the injury available for platelets to bind to the subendothelium. The rate of binding is assumed to be proportional to this value and to the local density of platelets that are sufficiently close to the subendothelium to be able to bind to it.

References

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