Pujos et al. (2018) — "Experimental and numerical study of platelets rolling on a von Willebrand factor-coated surface"

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1 Experimental Observations

- Experimental setup: Fixed platelets were perfused through a microfluidic channel coated with von Willebrand factor.
- Flow chamber dimensions: 400 μm wide, 4 cm long, and a height of either 14 or 63 μm (why?). The shear rate was between 1400 and 1800 s^{-1}, to facilitate unfolding of vWF.
- After 95 min of perfusion, platelets adhered at a greater concentration close to the channel entrance, and decreasing platelet concentration along the flow channel.
- Videos showed a couple of different platelet behaviors. Over the 17 minute time period illustrated in the paper, some platelets remained adhered throughout the time interval, some platelets rolled during the entire period, some platelets initially rolled and then adhered, and some platelets which were initially adhered came unstuck and began rolling.
- Note: they do not characterize the rolling at all, i.e. no rolling velocity, pause times, step size, etc are measured.

2 Model Description

- In their model, they only consider platelet dynamics on the vWF-coated surface, and a small boundary layer in the fluid above the surface, which contains platelets that are able to interact with the surface.
- Platelets in the bulk outside of this boundary layer are assumed to have some fixed concentration C_v^∞.
- To derive PDEs for the platelet concentration, consider a small volume in the boundary layer with dimensions $dx \times dy \times h$, where h is the height of the boundary layer.
- Denote the number of platelets in the boundary layer element as n_v and the number of platelets on the surface below this element as n_s.
- Platelet number can change in the volume element by transport in the flow into/out of the upstream/downstream ends, respectively, binding/unbinding to the surface, and diffusion from bulk.
- Platelet number can change on the surface element by rolling into/out of the region, and binding/unbinding.
- Then by taking limits as $dx, dy, dt \to 0$, you get an advection-reaction equation for platelets in the boundary layer and platelets on the surface:

$$\partial_t C_v + V_v \partial_x C_x = -J + \frac{D}{l_D^2}(C_v^\infty - C_v) \tag{1}$$

$$\partial_t C_s + V_s \partial_x C_s = hJ \tag{2}$$

$$J = k_{\text{on}} C_v \left(1 - \frac{C_s}{C_{s,\text{max}}}\right) - k_{\text{off}} \frac{C_s}{h}. \tag{3}$$

- Parameter definitions:

V_v	Velocity of free-flowing platelets
V_s	Velocity of rolling platelets
D	Diffusion coefficient of platelets
l_D	Characteristic length scale of diffusion
C_v^∞	Concentration of platelets in the bulk
h	Height of the boundary layer
k_{on}	On rate of platelet binding to vWF
k_{off}	Off rate of platelet binding to vWF
$C_{s,\text{max}}$	Maximum concentration of platelets on the surface

- They non-dimensionalized the above equations to get:

$$v_t + v_x = -j + d(v^\infty - v)$$
$$s_t + \epsilon s_x = j$$
$$j = v(1-s) - \alpha s.$$

- Non-dimensional parameter definitions: $v = \frac{C_v j}{C_{\text{s, max}}}$, $d = \frac{D}{l_D^2 k_{\text{on}}}$, $\epsilon = \frac{V_s}{V_v}$, and $\alpha = \frac{k_{\text{off}}}{k_{\text{on}}}$.

3 Discussion/Conclusions Overview

- Figure 9 in the paper compares experimental data on accumulation of platelets on the surface with simulations from the fitted model. The model seems to fit-ish, but it in particular underestimates platelet accumulation on the surface early in time at points close to the inflow and points near the outflow.
- Other estimated parameters seem more reasonable. $C_{s,\text{max}}$ is 1.7×10^4 mm^{-2}, compared to the theoretical maximal 2D packing concentration 12×10^4 mm^{-2}.
- k_{on} is estimated at 0.24 s^{-1}, which is consistent with estimates by Fitzgibbon et al. (2014).
- k_{off} is estimated at 6×10^{-5}, which they claim is reasonable, because the surface is densely coated with vWF.
- The height of the boundary layer is found to be 0.1 μm. This is obviously quite a bit smaller than a platelet, so they interpret the volume concentration of platelets in the boundary layer as a probability that a platelet in the bulk interacts with the wall.
- The estimated value of V_v is 0.36 mm/s. Based on a shear rate of 1500 s^{-1}, the velocity of fluid 1 platelet radius from the wall is about 1.5 mm/s. In the paper, they estimate V_v to be 0.6 based on the shear rate (somehow).
- The estimated value of V_s is effectively 0 ($\sim 10^{-10}$ to 10^{-13}). They speculate that this is due to the presence of platelets that were activated prior to fixing, and remain bound to the surface throughout the experiment.
- When they included diffusion (assumed to be shear-induced diffusion), the curve farthest from the channel entrance fit the experimental data more closely. That is, platelets accumulated more quickly when they included diffusion.
- Because their estimated value of V_s is so low, they just exclude it from the model, and their new parameter estimates remain within the same order of magnitude.
- They also eliminate the saturation term because they only see values of C_s much lower than $C_{\text{s, max}}$.
- In the supplementary data, they have a couple of figures showing model fits to data from different patients, and under different experimental conditions.

Article Evaluation

This model doesn't include any activation (platelets are fixed in the experiment) and greatly simplifies diffusion and rolling. Their data is much more suited to estimating platelet on and off rates than rolling parameters. I am dissatisfied with their interpretation of the concentration of platelets in the boundary layer as a probability of a platelet from the bulk contacting the wall. It seems to me they developed their model with the assumption that the boundary layer is large enough to contain enough platelets to reasonably be approximated as a continuum, but the estimated h based on fitting doesn't validate this assumption, so they change their interpretation of the model after the fact.

Reference

Fitzgibbon, S., Cowman, J., Ricco, A. J., Kenny, D., and Shaqfeh, E. S. G. (2014). Examining platelet adhesion via Stokes flow simulations and microfluidic experiments. *Soft matter*, 11(2):355–67.

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