Toward a Mathematical Model of Hemostasis

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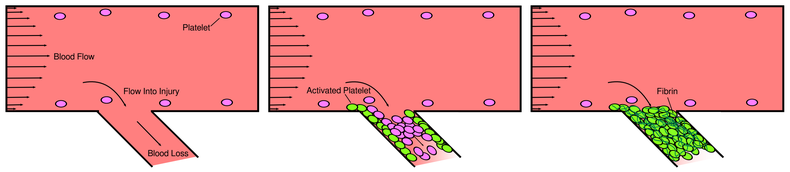
Abstract

Hemostasis is the process by which a blood clot forms to prevent bleeding. The formation time, size and structure of a clot depends on the local hemodynamics and the nature of the injury. Extravascular injuries, those which occur outside the vessel, have not been extensively modeled or understood. To understand such injuries, both experimental and computational models of hemostasis must be simultaneously developed from the ground up. Here we develop and validate a computational model against analogous experimental results for the fluid dynamics. Future steps to further communicate the experimental and computational models are also presented for modeling the platelet populations.

Clot Formation in Extravascular Injuries

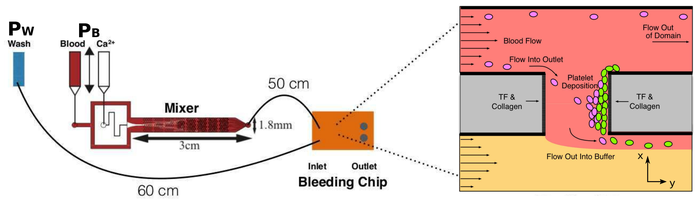


(1) An injury occurs, exposing collagen and tissue factor to blood. Collagen causes activation of platelets, while tissue factor initiates coagulation reactions.

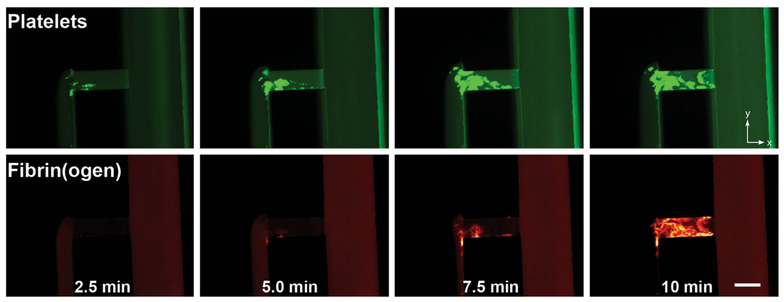
(2) Platelets begin to deposit into injury and adhere to the wall by collagen activation, forming a "platelet plug" inside the injury.

(3) Activated platelets faciliate further propagation of coagulation reactions on their surfaces. The final product of coagulation, fibrin, stops the bleeding by forming a stablizing mesh over the platelet plug.

Experimental Bleeding Chip

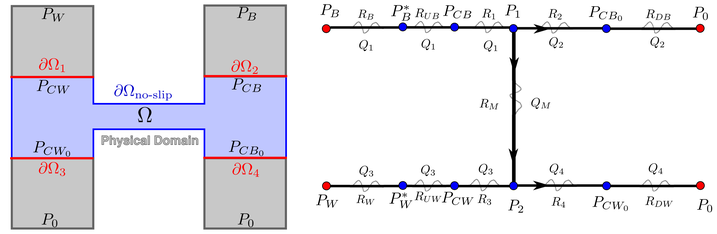


Design of extravascular injury model: Bleeding Chip.



Injury channel occlusion occurs in bleeding chip within 8 minutes [3].

Computational Fluid Dynamics of Bleeding Chip



Schematic of computational domain (left), Analogous hydraulic circuit (right).

- Fluid was modeled using the Incompressible Navier-Stokes equations:

$$\text{Conservation of Momentum:} \quad \frac{\partial u}{\partial t} + u \cdot \nabla u = \frac{1}{\mathrm{Re}} \nabla^2 u - \nabla P, \tag{1}$$

$$\text{Conservation of Mass:} \quad \nabla \cdot u = 0, \text{ in } \Omega \tag{2}$$

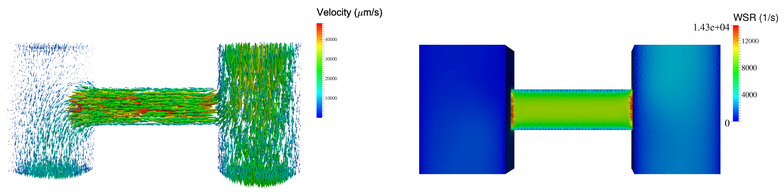
subject to the initial and boundary conditions:

$$\vec{u}\Big|_{t=0} = 0, \;\; \vec{u}\Big|_{\partial\Omega_{\text{no-slip}}} = 0, \;\; P - \frac{1}{\mathrm{Re}} \frac{\partial \vec{u}}{\partial n}\Big|_{\partial\Omega_i} = P_{C*}, \text{ for } i = 1, 2, 3, 4 \tag{3}$$

where u, P are the velocity and pressure, respectively, and the Reynolds number, Re, is the ratio of inertial to viscous forces.

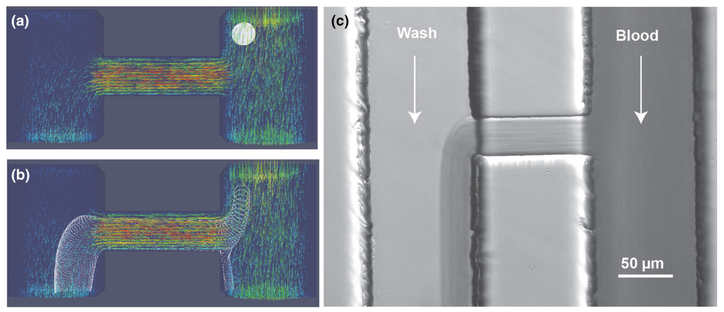
- Equations were discretized using the finite element method, evolved in time using a rotational projection method [1] and solved using the FEniCS software package [2].

Dimensions of domain represented by mesh.



Velocity (μm/s) and wall shear rate (s^{-1}) results from computational model.

Computational vs Experimental Model Validation



(a,b) A spherical source of passive tracer particles placed near inlet of injury channel at $t = 0$ (a) and after $t = 0.5$ms (b).

(c) Bright field image of whole blood in the extravascular region with same pressure data.

Incorporating a Model of Platelet Aggregation

- With the fluid model, we are incorporating a continuum model of unactivated and activated platelet populations:

$$\frac{\partial P^{m,u}}{\partial t} = \underbrace{-\nabla \cdot \left\{ W(\phi^T) \left(\mathbf{u}\, P^{m,u} - D\, \nabla P^{m,u} \right) \right\}}_{\text{Transport by advection and 'diffusion'}} + \underbrace{k_{off} P^{b,u}}_{\text{Release of } P^{b,u}}$$

$$- \underbrace{k_{adh}(\mathbf{x}) \left\{ P_{max} - P^{se,a} \right\} P^{m,u}}_{\text{Adhesion to exposed collagen}} \underbrace{A([\text{ADP}]) P^{m,u}}_{\text{Partial activation by ADP}} - k_{coh} g(\eta) P_{max} P^{m,u}$$

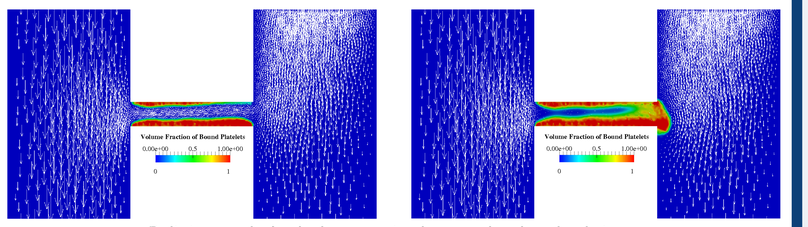
$$\frac{\partial P^{m,s}}{\partial t} = -\nabla \cdot \left\{ W(\phi^T) \left(\mathbf{u}\, P^{m,s} - D\, \nabla P^{m,s} \right) \right\} - k_{adh}(\mathbf{x}) \left\{ P_{max} - P^{se,a} \right\} P^{m,s}$$

$$+ A([\text{ADP}]) P^{m,u} - \underbrace{k_{coh}\, g(\eta)\, P_{max}\, P^{m,s}}_{\text{Cohesion to bound platelets}}$$

$$\frac{\partial P^{b,s}}{\partial t} = -k_{adh}(\mathbf{x}) \left(P_{max} - P^{se,a} \right) P^{b,s} + k_{coh} g(\eta) P_{max} P^{m,s} + A([\text{ADP}]) P^{b,u}$$

$$\frac{\partial P^{b,u}}{\partial t} = -k_{adh}(\mathbf{x}) \left(P_{max} - P^{se,a} \right) P^{b,u} + k_{coh} g(\eta) P_{max} P^{m,u} - k_{off} P^{b,u} - A([\text{ADP}]) P^{b,u}$$

$$\frac{\partial P^{se,a}}{\partial t} = \quad k_{adh}(\mathbf{x}) \left(P_{max} - P^{se,a} \right) (P^{m,u} + P^{m,s} + P^{b,s} + P^{b,u})$$



Preliminary results for platelet aggregation shows complete channel occlusion.

Conclusions & Future Work

- We developed a FEM model of the bleeding chip's fluid dynamics using pressure-driven flow boundary conditions.
- Our model showed qualitative agreement between blood flow experiments and computational passive tracer particles.
- We plan to validate the platelet model in 2D against collagen-agonist platelet experiments.

References

[1] Guermond, J. L., Peter Minev, and Jie Shen. *An overview of projection methods for incompressible flows.* Computer methods in applied mechanics and engineering 195.44 (2006): 6011-6045.

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[3] Schoeman, R. M., Rana, K., Danes, N., Lehmann, M., Di Paola, J. A., Fogelson, A. L., ... Neeves, K. B. (2016). *A Microfluidic Model of Hemostasis Sensitive to Platelet Function and Coagulation.* Cellular and Molecular Bioengineering, 1-13.

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