

Computational Modeling of Platelet Aggregation and Blood Coagulation

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Abstract

Coupled, intricate systems exist to maintain the fluidity of the blood in the vascular system while allowing for the rapid formation of a solid clot to prevent excessive blood loss subsequent to vessel injury. These systems can be invoked as part of the body's normal defense mechanism against blood loss, but these same systems are also invoked during unwanted, pathological and perhaps life threatening clot formation. Indeed, these systems can be seen as a delicate balancing act continually occurring to control clot formation and lysis in order to prevent hemorrhage without causing thrombosis. Despite more than a century of research in blood biochemistry, platelet and vascular wall biology, and fluid dynamics, the complexity of blood clotting under flow has prevented quantitative and predictive modeling. Yet quantitative modeling of blood function under flow could have numerous diagnostic and therapeutic uses.

Challenges

So, I stub my toe and start bleeding profusely but then my blood clots and saves my life, right? What's so hard about that?

If you want a detailed understanding of what is going on, plenty. There are three requirements that make things difficult:

- The blood needs to continue flowing throughout the body.
- Chemical reactions involved must occur fast enough to have the clot start forming at the site of injury instead of downstream.
- Clotting should be localized to the injury site, despite activated chemicals washing downstream.

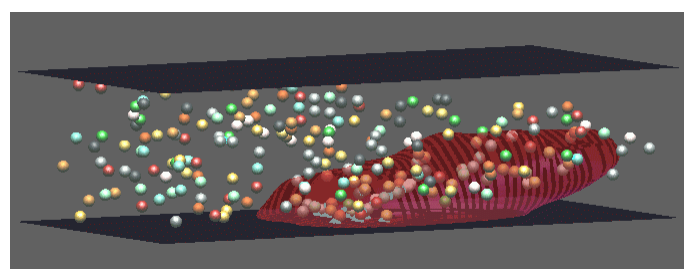
These requirements have been handled biologically by a system that involves

- Complex Flows
 - Interactions between flow and objects
 - Objects are active, moving, and deformable
 - Examples include red blood cells or platelets
- Long cascades of chemical reactions
 - Occur within the fluid and on cell surfaces
 - Have multiple feedforward and feedback loops, enabling several orders of magnitude signal amplification
 - Exhibit threshold behavior
- Chemical and cell transport
- Chemically induced phase transitions (polymerization)

These numerous challenges translate into complex models involving:

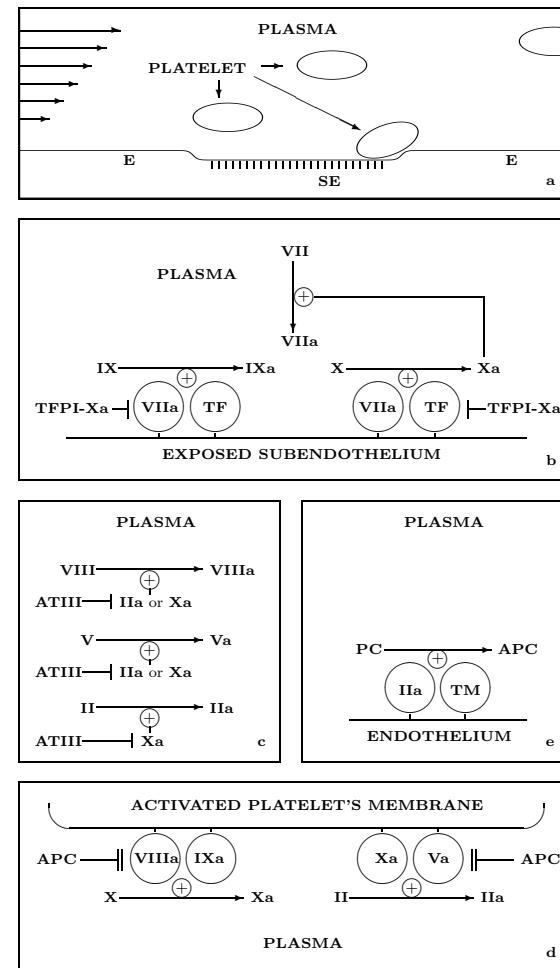
- Coupled nonlinear PDEs
- Dynamic fluid-structure interactions
- Complicated networks of kinetic equations
- Multiple spatial and temporal scales

Simulation of Aggregate Formation



Simulation of platelet aggregation by H. Yu and A. Fogelson.

Key Mechanisms of Coagulation



Coagulation reactions: (a) schematic of injured site. SE—exposed subendothelium, E—endothelium; (b) TF-VIIa system on subendothelium; (c) plasma-phase reactions; (d) VIIIa:IXa and Va:Xa complexes on activated platelet surface; (e) TM:IIa complex on endothelial surface. \oplus indicates enzymatically-promoted reaction. \dashv indicates inhibition. $\dashv\!\!|$ indicates inactivation.

Governing Equations

Navier-Stokes Equations

$$\bar{u}_t + \bar{u} \cdot \nabla \bar{u} = -\nabla p + \nu \Delta \bar{u} + \bar{f}$$

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

u = Velocity
 p = Pressure
 f = Force density
 ν = Viscosity

Fluid-Structure Interaction Equations

$$\bar{f}(\bar{x}, t) = \int_S \bar{F}(s, t) \delta(\bar{x} - \bar{X}(s, t)) ds$$

$$\frac{\partial \bar{X}(s, t)}{\partial t} = \int_{\Omega} \bar{u}(\bar{x}, t) \delta(\bar{x} - \bar{X}(s, t)) d\bar{x}$$

$$\bar{F}(s, t) = T_0 \frac{\partial^2 \bar{X}(s, t)}{\partial s^2}$$

x = Eulerian Coordinate
 s = Parametric Boundary Coordinate
 X = Mapping from s to x
 F = Lagrangian force density
 T_0 = Boundary/Interface Tension

Chemical equations

$$\frac{\partial c_i}{\partial t} + \bar{u} \cdot \nabla c_i = D_i \Delta c_i + R_i(\bar{c})$$

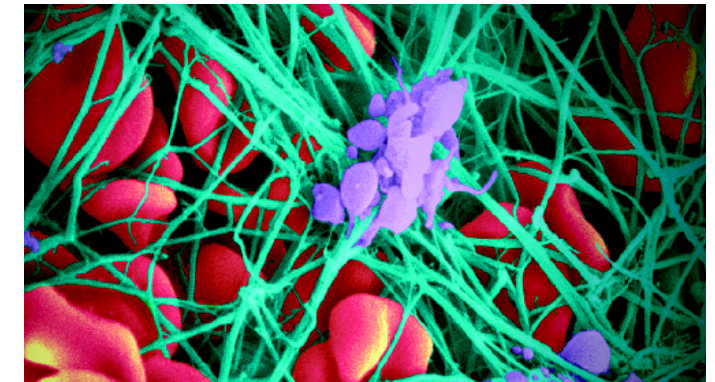
Reactive boundary conditions

$$D_i \frac{\partial c_i}{\partial n} = k_i^{\text{on}} c_i b_i - k_i^{\text{off}} c_i^m$$

$$\frac{dc_i^m}{dt} = k_i^{\text{on}} c_i b_i - k_i^{\text{off}} c_i^m + R_i(\bar{c}^m)$$

c_i = Chemical i
 D_i = Diffusion coefficient for c_i
 R_i = Reaction terms for c_i
 b_i = Concentration of unbound binding sites for c_i
 k_i^{on} = Binding rate constant for c_i
 k_i^{off} = Unbinding rate constant for c_i

Electron Micrograph of a Blood Clot



A colorized scanning electron micrograph of a blood clot formed *in vitro*. From the cover of the 4 October 2001 issue of *Nature*; image by Yuri Veklich/John W. Weisel, University of Pennsylvania. Note that this clot was formed under stationary conditions (blood from a finger prick).

Methods & Future Directions

• Methods

- Immersed Boundary (IB) and Immersed Interface (II) Methods for handling dynamic fluid-structure interactions
- Multigrid for a fast and paralyzable^Wparallelizable solver
- SAMRAI to facilitate multiprocessor communication and adaptive mesh refinement

• Algorithmic

- Extend the II method to deal with connections between different boundaries
- Extend the II method to three dimensions
- Extend the IB and II methods to incorporate chemical reactions, especially on cell surfaces

• Computational

- Scalability of Navier-Stokes, IB, and II solvers
- Adaptive Mesh Refinement and Load Balancing

• Scientific

- Threshold mechanisms and parameters
- Relative influence of physical and chemical processes on clot formation

References

- [1] Aaron L. Fogelson and Andrew L. Kuharsky. Membrane binding-site density can modulate activation thresholds in enzyme systems. *Journal of Theoretical Biology*, 193:1–18, 1998.
- [2] Long Lee and Randall Leveque. An Immersed Interface method for incompressible Navier-Stokes equations. *SIAM Journal of Scientific Computing*, 25(3):832–856, 2003.
- [3] Charles S. Peskin. Numerical analysis of blood flow in the heart. *Journal of Computational Physics*, 25(3):220–252, November 1977.
- [4] Alexandre M. Roma, Charles S. Peskin, and Marsha J. Berger. An adaptive version of the Immersed Boundary method. *Journal of Computational Physics*, 153:509–534, 1999.
- [5] Ulrich Trottenberg, Cornelis Oosterlee, and Anton Schuller. *Multigrid*. Academic Press, 2001.