

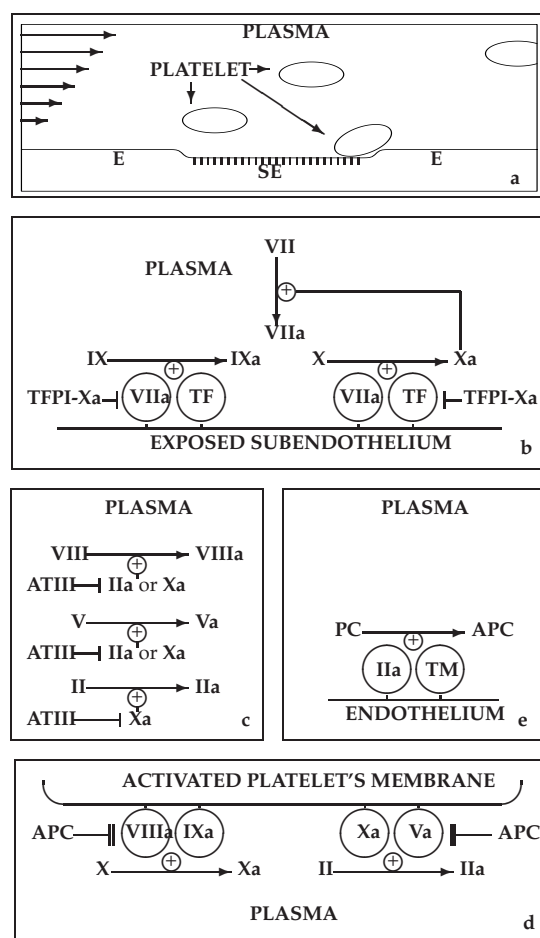
# Computational Modeling of Platelet Aggregation and Blood Coagulation

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## Abstract

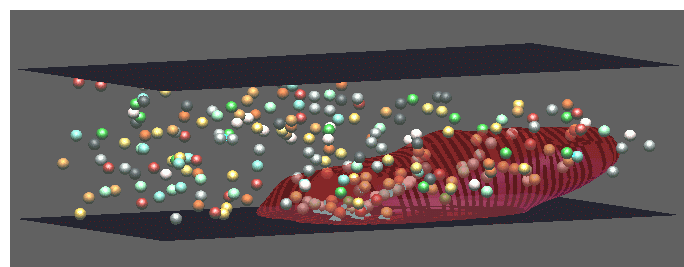
Despite more than a century of brilliant research in blood coagulation and related fields, the complexity of blood clotting under flow has prevented quantitative and predictive modeling. Yet such modeling could have numerous diagnostic and therapeutic uses. The goal of my research is to simulate these systems computationally as we seek to elucidate fundamental biological mechanisms and improve biomedical therapies and devices.

## 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. ⊕ indicates enzymatically-promoted reaction. ⊖ indicates inhibition. ⊥ indicates inactivation.

## Simulation of Aggregate Formation



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

## Challenges

Biofluid dynamics problems of this kind present numerous challenges:

- Complex Flows
  - 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
  - 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

## Immersed Boundary and Immersed Interface Methods

The Immersed Boundary (IB) and Immersed Interface (II) methods were developed for similar biofluid problems. These methods:

- Utilize a mixed Eulerian/Lagrangian description of the motion.
- Handle dynamic fluid-(deformable) structure interactions
- Do not require regriding at each time-step
- Facilitate the use of multigrid by allowing a regular grid to be used
- Have not been extended to study three-dimensional multicellular biofluid problems with chemistry

## Governing Equations

### Navier-Stokes Equations

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

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

### Fluid-Structure Interaction Equations

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

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

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

### Chemical equations

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

### Reactive boundary conditions

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

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

$u$  = Velocity

$p$  = Pressure

$f$  = Force density

$\nu$  = Viscosity

$x$  = Eulerian Coordinate

$s$  = Parametric Boundary Coordinate

$X$  = Mapping from  $s$  to  $x$

$F$  = Lagrangian force density

$T_0$  = Boundary/Interface Tension

$c_i$  = Chemical  $i$

$D_i$  = Diffusion coefficient for  $c_i$

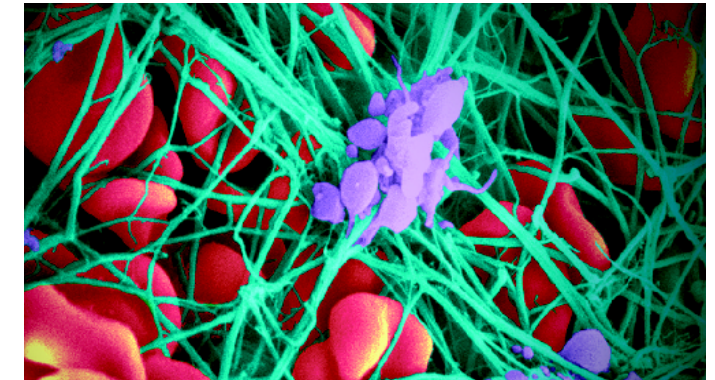
$R_i$  = Reaction terms for  $c_i$

$b_i$  = Concentration of unbound binding sites for  $c_i$

$k_i^{\text{on}}$  = Binding rate constant for  $c_i$

$k_i^{\text{off}}$  = 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).

Platelets in purple  
Fibrin in green  
Red Blood Cells in ... can't you guess?

## Future Directions

- 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
    - \* Local fluid-structure interactions
    - \* Clumping of cells and chemical reactions
- Scientific
  - Threshold mechanisms and parameters
  - Relative influence of physical and chemical processes on clot formation

## References

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