CFD For Blood Transfusions on the Battlefield
How the Dynamics of Red Blood Cells in Flow Affects Bleeding Time

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Red Blood Cell and Platelet Margination Effect on Bleeding Time

Clinical evidence (Hardy 2006):
- Longer BT (bleeding time) for $H_t < 35\%$ (Blajchman 1994, Ouaknine-Orlando 1999)
- BT reduced by RBC transfusion (Escolar 1988, Ho 1998)
- Healthy volunteers (Valeri 2001)
  - $H_t \downarrow 15\% \rightarrow$ BT $\uparrow 60\%$
  - Platelet $\downarrow 32\% \rightarrow$ normal BT

Zhao, H., E.S.G. Shaqfeh, ¨Shear-induced platelet margination in a microchannel¨, PRE 83, 061294, (2011)
Red Blood Cell and Platelet Margination Effect on Bleeding Time

Trauma remains the leading cause of mortality for soldiers in combat, and, of trauma victims, 25% to 35% exhibit acute coagulopathy of trauma (ACOTs) characterized by an initial bleeding diathesis upon presentation to a medical facility.

Zhao, H., E.S.G. Shaqfeh, ``Shear-induced platelet margination in a microchannel”, PRE 83, 061294, (2011)
Hematocrit in Small Vessels

- System $H_t$ between 36% and 53%
- $H_t$ reduced in small vessels

PRESENT STUDY

(Lipowsky et al 1980)
Boundary Integral Simulation Details

For \( x_0 \in D \):

\[
\n_j(x_0) + \frac{1 - \lambda}{4\pi(1 + \lambda)} \int_{D} u_i(x) T_{ijk}(x, x_0) n_k(x) \, dS(x) = -\frac{1}{4\pi(1 + \lambda)\mu_1} \int_{D \cup W} \| f_i \| (x) G_{ij}(x, x_0) \, dS(x) + \frac{2}{1 + \lambda} \langle j \rangle
\]

For \( x_0 \in W \):

\[
0 = \frac{1 - \lambda}{8\pi} \int_{D} u_i(x) T_{ijk}(x, x_0) n_k(x) \, dS(x) - \frac{1}{8\pi\mu_1} \int_{D \cup W} \| f_i \| (x) G_{ij}(x, x_0) \, dS(x) + \langle j \rangle
\]

Need to solve: \( u \) on \( D \), \( \| f \| \) on \( W \)

**Strain energy (Skalak 1973)**

- Biconcave reference shape
- Principle in-plane stretch: \( \lambda_1, \lambda_2 \)

Membrane stored energy: \( W = W_S + W_D + W_B \)

- Shear\( \quad W_S = \frac{E_S}{4} [(1 - \lambda_1^2)^2 + (1 - \lambda_2^2)^2] \)
- Dilatation\( \quad W_D = \frac{E_D}{8} (\lambda_1^2\lambda_2^2 - 1)^2 \)

**Nondimensionalization:**

- \( Ca = \frac{\mu_1^2 \dot{a}}{E_S} \) where \( \dot{a} = \frac{6\langle u \rangle}{H} \Rightarrow RBC \) deformation
- Dilatation: \( \frac{\mu_1 \dot{a}}{E_D} = 10^{-2} \Rightarrow \) nearly incompressible surface (\( \Delta A/A < 0.5\% \))
- Bending: \( \frac{E_B}{E_S a^2} = 3.7 \times 10^{-3} \)
Red Blood Cell/Platelet Mixtures: Margination in a Channel

- Pressure-driven channel flow, height = 34µm
- \( Ht = 0.1 \) and 0.2
- \( Ca \) between 0.2 and 2 (max wall shear rate \( \approx 4000 \text{ s}^{-1} \))

(Zhao & Shaqfeh, Phys Rev E, 2011)
Platelet Margination: Evolution in Time

$Ca = 0.5$, $H_e = 20\%$

Time scale: 1 ms

$t = 200$

$t = 1000$

$t = 3600$
In-house experiments for margination

Dichroic mirror

![Graph showing pressure drop vs. mean velocity with different markers for different Ht values.](image-url)
In-house experiments for margination

Shaqfeh Group Lab Tour 3-4pm
Effect of Hematocrit on Platelet Margination

Is this the answer?
Effect of Hematocrit on Platelet Adsorption

Surface VWF

Cross-section of microfluidic device depicting platelet translocation on VWF

Royal College of Surgeons in Ireland

Dr. James Campbell
USAISR

48-well Plate, 20 dyne/cm²

This plate features 24 experimental channels, each with an input and output well. The higher number of experimental channels makes it ideally suited for testing larger sets of conditions, such as compound screening or genetic variants.

Bioflux 1000
Example Experimental Data
Platelet Adhesion Model

$k_{on} \sim 30 / \mu m^2 s$ (weak)
$k_{off} \sim 5 / s$

$L \sim 200 nm$

$k_{on}^2 \sim 0.05 / \mu m^2 s$ (strong)
$k_{off}^2 \sim 0$

$k \sim 200 pN / \mu m$

$GPIb + vWF \xleftrightarrow{k_{on}} GPIbvWF$

$GPIIb/IIIa + vWF \xleftrightarrow{k_{on}} GPIIb/IIIavWF$

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Translocation Paths and Distance

\[ \gamma = 1500 \text{s}^{-1} \]
Combining Multi-body Calculations and Adhesive Dynamics
Adhesion rate: slope of bonds per time over first 48 non-dimensional time (roughly 100ms real time)

Comparison of Simulations and Experiments

Adhered platelet area versus time, Ht 30%, Donor 2 run 1

Area occupied by platelets on slide, snapshots taken every 30 seconds

Relative adhesion rate, normalized to Ht 30%

Simulation and best-fit line: Ht 30%

Extremely encouraging!
Simulations with a suspension of red blood cells and platelets including all hydrodynamic and interactions have been developed.

We have examined the concentration distributions and rheology at finite concentrations including wall interactions. We show that the balance between wall lift and collisions produces the clarified Fahraeus-Lindquist layer near the walls.

Simulations of red blood cell and platelet mixtures have demonstrated platelet margination into the associated FL layer. Recently we have added adsorption to these simulations. We believe this is the key to understanding bleeding time dilation at reduced hematocrit.

We have used our simulations to choose parameters for margination experiments conducted at Stanford.

We have compared our simulations to experiments conducted by collaborators at USAISR and found platelet adhesion activity to fall similarly as hematocrit is decreased.

Ongoing work is underway to improve the performance of the simulations to allow for higher hematocrit, larger geometries, and bifurcations.
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• Stanford HIVE Visualization Center
Platelet Adhesion Sequence

Collagen Fibrils
Smooth Muscle Cells

Aspirin

2-MeSAMP

VWF

Fibrinogen

GPVI

Ca Mobilization

PLCy

TXA2

ADP

α2BI

GPIb/V/IX

αIIβ3

Platelet Adhesion Sequence
A Balance Between Lift and Collisional Forces

Narsimhan, V., H. Zhao, E.S.G. Shaqfeh, "Coarse-grained theory to predict the concentration distribution of red blood cells in wall-bound Couette flow at zero Reynolds number", Phys. Fluids 25, 061901 (2013)

Large scale DNS

Collisional

Theory

Lift Velocity**


Model Basics: Lift velocity

\[ \frac{\partial n}{\partial t} + \frac{\partial}{\partial z} \left( u_{\text{lift}} n \right) = f^{\text{coll}} \]

Lift Velocity (\( \nu = 0.95 \) vesicle)

Calculate \( u_{\text{lift}} \) from existing Boundary integral

Comparison with Experiments**


**Model Basics: Lift velocity**

\[ \frac{\partial n}{\partial t} + \frac{\partial}{\partial z} \left( n u_{\text{lift}} \right) = f^{\text{coll}} \]

Lift

Calculate \( u_{\text{lift}} \) from existing Boundary integral

\[ u = \gamma z \]

Comparison with Experiments**

\[ u_{\text{lift}} h^2 \]


Model Basics: Collisional Forces

\[
PDE: \quad \frac{\partial n}{\partial t} + \frac{\partial}{\partial z} \left( u_{\text{lift}} n \right) = f^{\text{coll}}
\]

\[
f^{\text{coll}}(z) = \gamma \iint_{\text{channel}} \left[ n(z - \delta)n(z - \delta - k) - n(z)n(z - k) \right] |k| \, dk \, dy
\]

\[\delta(k, y) = \text{displacement/collision}\]

Cutoff radius \( R \): Hydrodynamic Screening

Simulation Geometry

Collisional Displacement**


Kumar, A. and Graham, M.D. *PRL.*, 109, (2012), 108102

Comparison with DNS (RBCs)

Theory captures cell-free layer and concentration at core of channel.

Underpredicts layering phenomenon
Comparison with in-vitro experiments

**CFL vs Hematocrit**

- H = 14.3, Ca ~ 0.4-1.6, Bugliarello et al (1963):

  - Theory: H = 14, Ca = 1, R = 2.25-2.75

**Scaling Arguments**


- CFL ~ HCT^{-1/2} 

**Bugliarello et al (1963):**

- H = 14.3, Ca ~ 0.4-1.6,

- Theory: 
  
  - H = 14, Ca = 1, R = 2.25-2.75

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