Multiscale model of platelet tethering and adhesion: similarities with the leukocyte adhesion cascade

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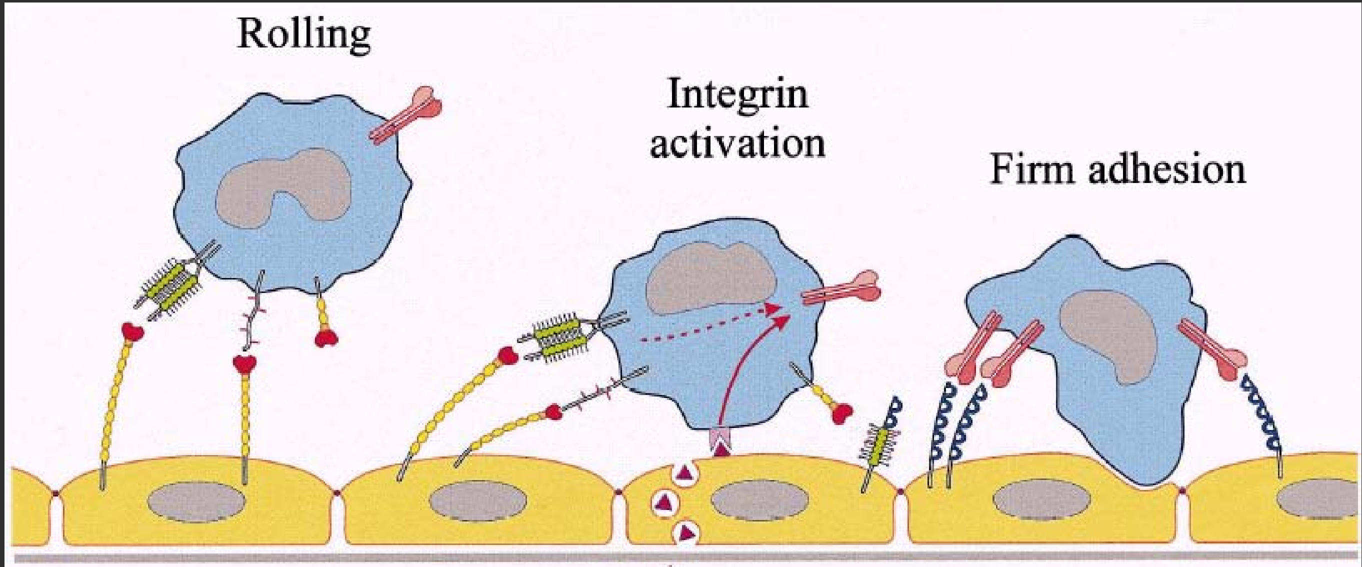
The adhesion cascade of circulating leukocytes



Ebnet and Vestweber (1999)

Mild inflammation in live mouse venule

King et al., *Microcirculation* (2003)
King et al., *Annals of BME* (2004)
King et al., *Phys. Fluids* (2005)
Lamkin-Kennard et al., *Biorheology* (2005)

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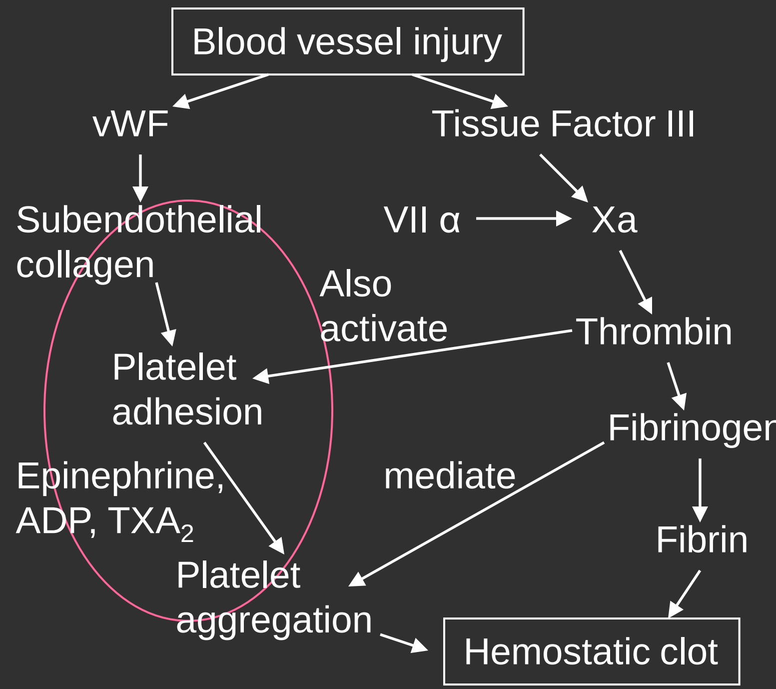
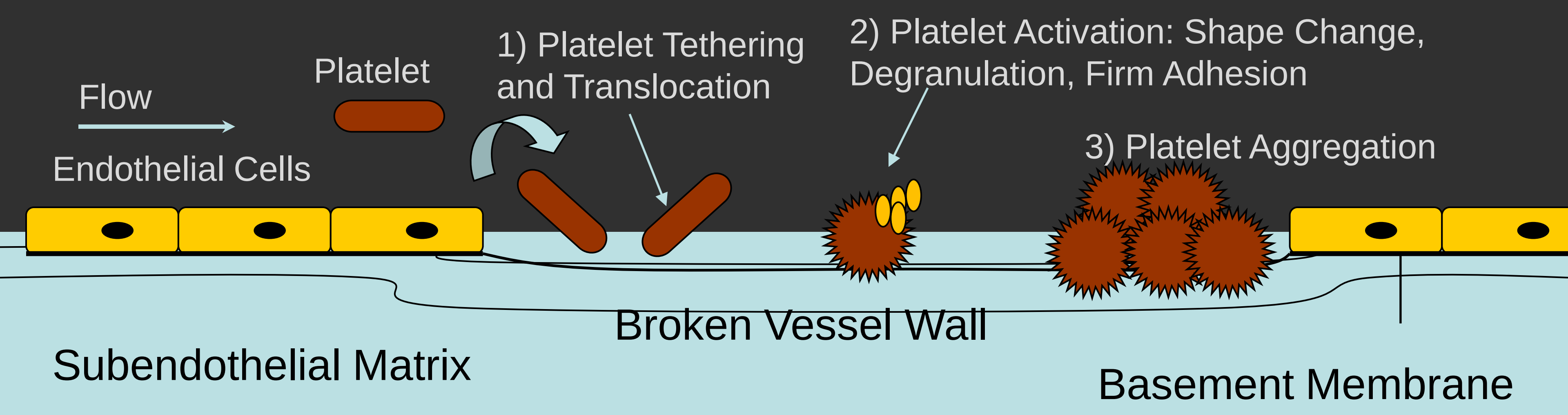
Hemostasis

•***Hemostasis :***
a self defensive mechanism in response to blood vessel injuries to prevent excessive blood loss. It describes the physiological process of blood clotting at injured vessels

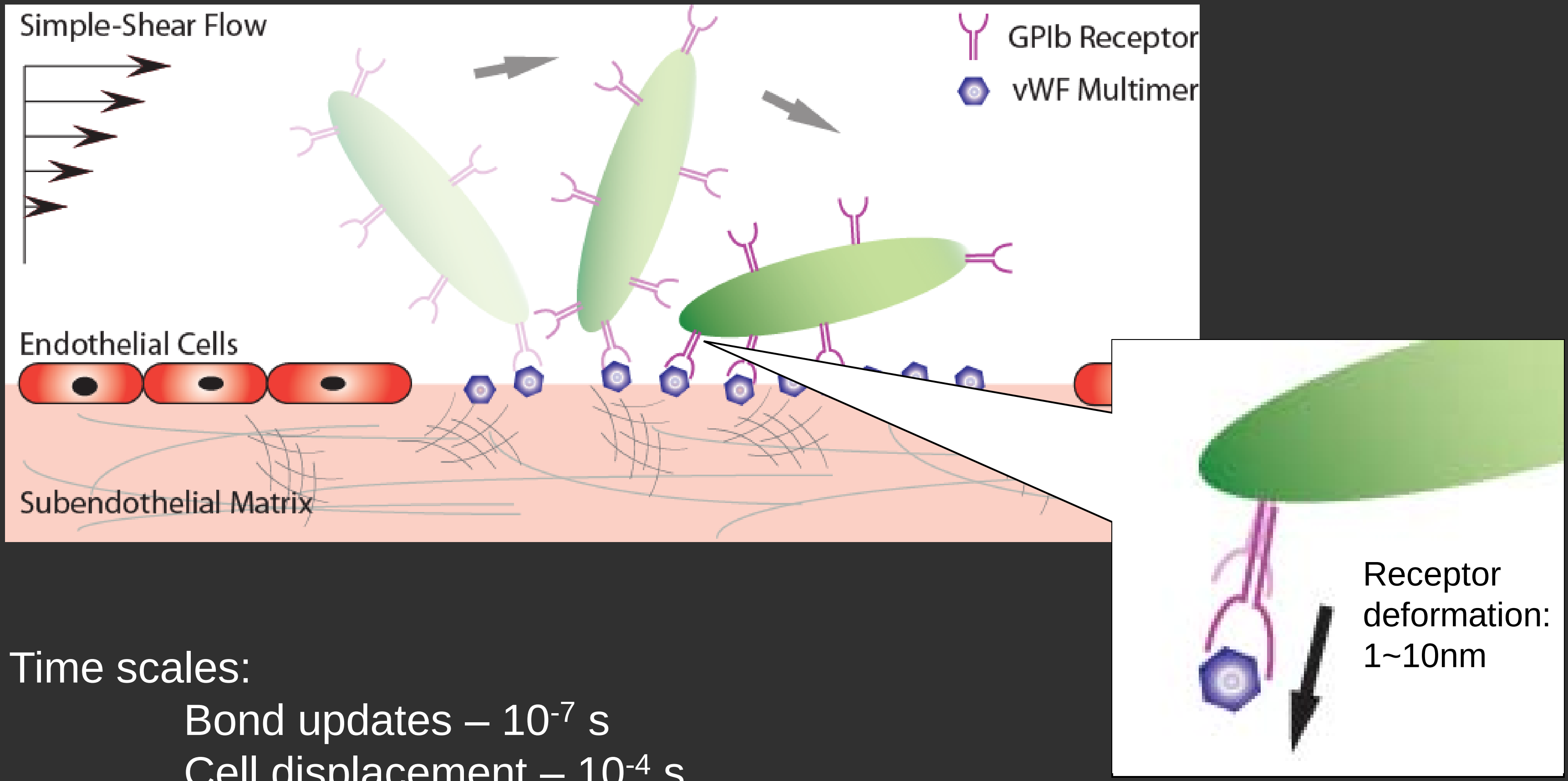




Multiscale Physics

Length Scale:

Platelet Translocation: ~1um



Time scales:

Bond updates – 10^{-7} s

Cell displacement – 10^{-4} s

Thrombus growth – 1 – 100 s

Molecular Kinetics

Here we consider the GPIb-vWF bonding which mediate initial tethering of platelets to the area of vessel injury.

Receptor-Ligand bond formation/breakage:

Using Monte Carlo method to determine each bond formation/breakage event.

$$P_f = 1 - \exp(-k_f \Delta t)$$

$$P_r = 1 - \exp(-k_r \Delta t)$$

$$k_f = k^0_{f,2-D} v_s \exp\left(\sigma \,|\, x_b - l_b \,|\, \frac{\gamma - 0.5\,|\, x_b - l_b \,|}{k_b T}\right)$$

$$k_r = k^0_r \exp\left(\frac{\gamma F_b}{k_B T}\right)$$

Bell Model

Parameter (unit)	Definition	Value	Reference
l_b (nm)	Equilibrium GPIbα-VWF bond length	128	[Singh 2006, Fox 1988]
γ (nm)	Reactive compliance	0.71	[Arya 2002]
$k^0_{f,2-D}$ (s^{-2}/μm)	Intrinsic cross-linking formation rate constant	0.05	Determined by a series of simulations
k_r (s^{-1})	Intrinsic dissociation constant	5.47	[Arya 2005]
σ (pN/nm)	Spring Constant	10	[Chtcheglova 2004]

Single Platelet: Rolling

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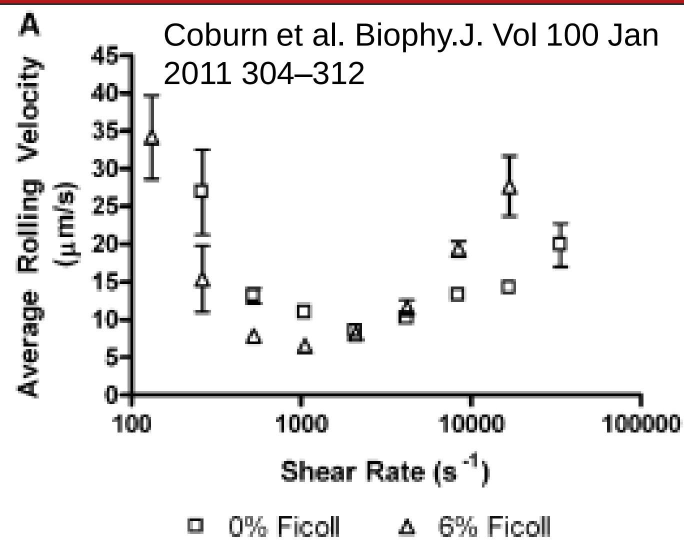
Alternative Molecular Kinetics



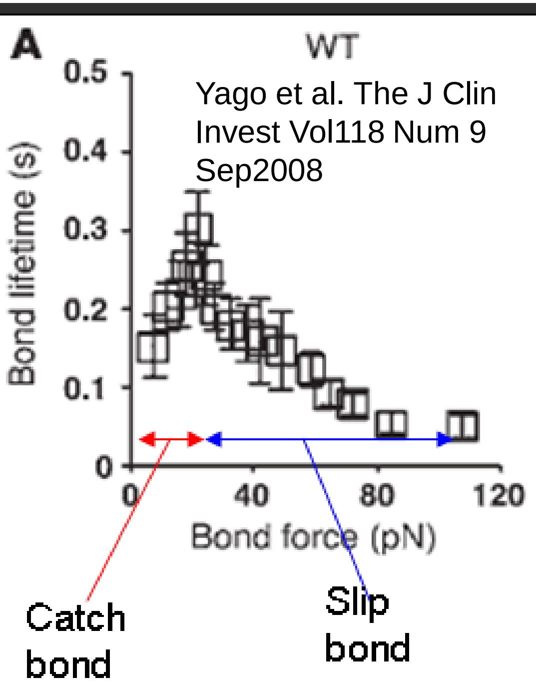
The proposed “catch bond”, “slip bond” switch for the GPIb-vWF is caused by shear/tether induced vWF conformation change. The resulted dissociation kinetics are:

Auton et al. argued that, there is a combination of NG (native, folded state) and IG (open, intermediate state) forms of vWF in the system. With the detailed description:

$$k_r = \frac{1}{1+\Phi} k_N(f) + \frac{\Phi}{1+\Phi} k_I(f), \quad \Phi = IG/NG$$

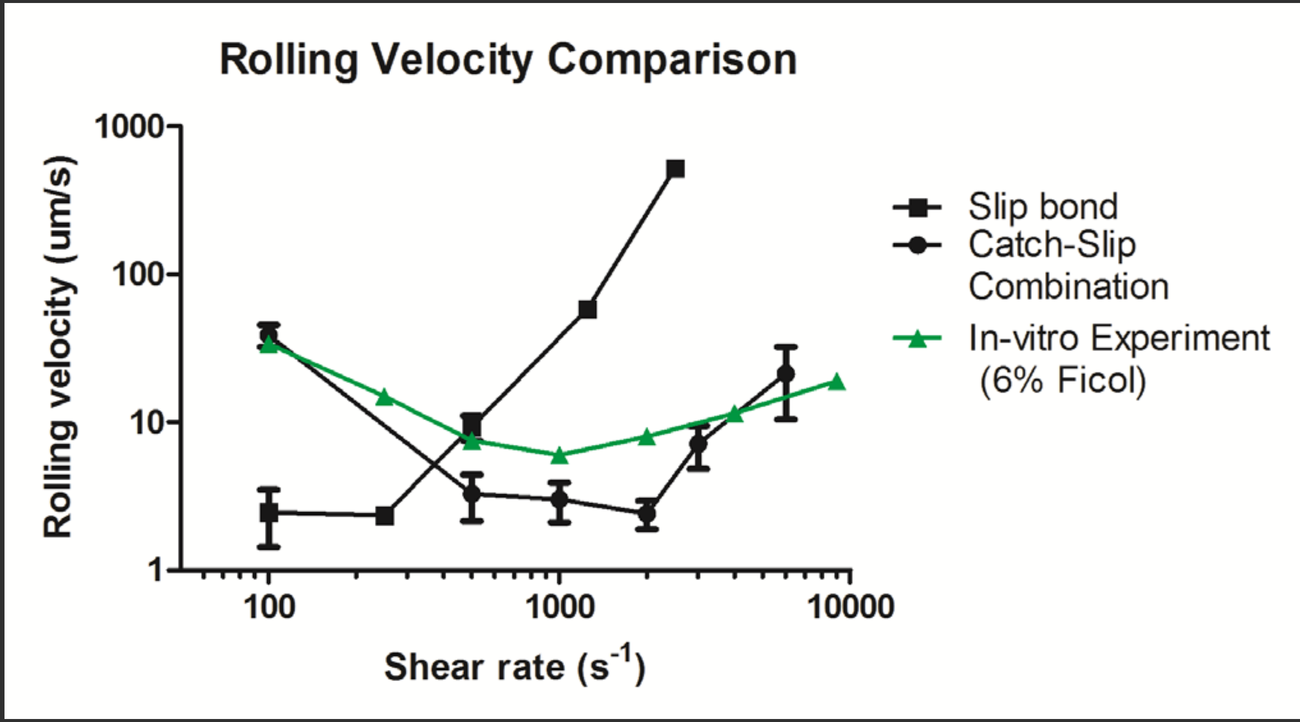
$$\Phi(f) = k^0_{NG\to IG} / k^0_{IG\to NG} * \exp(\frac{\gamma' f}{k_B T})$$

$$k_N(f) = k^0_{N,off} \exp(\frac{y_N f}{k_B T}) \qquad k_I(f) = k^0_{I,off} \exp(\frac{y_I f}{k_B T})$$



Parameter (unit)	Definition	Value	Reference
$k^0_{NG\to IG} / k^0_{IG\to NG}$	unstressed equilibrium constant for NG – IG states	0.4	[Auton 2010]
γ’ (nm)	force compliance for two states ratio	0.45	[Auton 2010]
$k^0_{N,off}$ (s^{-1})	intrinsic dissociation constant for NG state	4.9	[Auton 2010]
$k^0_{I,off}$ (s^{-1})	intrinsic dissociation constant for IG state	1.84	[Auton 2010]
y_N (nm)	force compliance of dissociation for NG state	-0.23	[Auton 2010]
y_I (nm)	force compliance of dissociation for IG state	0.039	[Auton 2010]

Slip bond kinetics are inconsistent with experiments



Experimental data from Coburn et al. Biophy.J. Vol 100 Jan 2011 304–312, using human platelet cells. Experiments added 6% ficol to increase viscosity.

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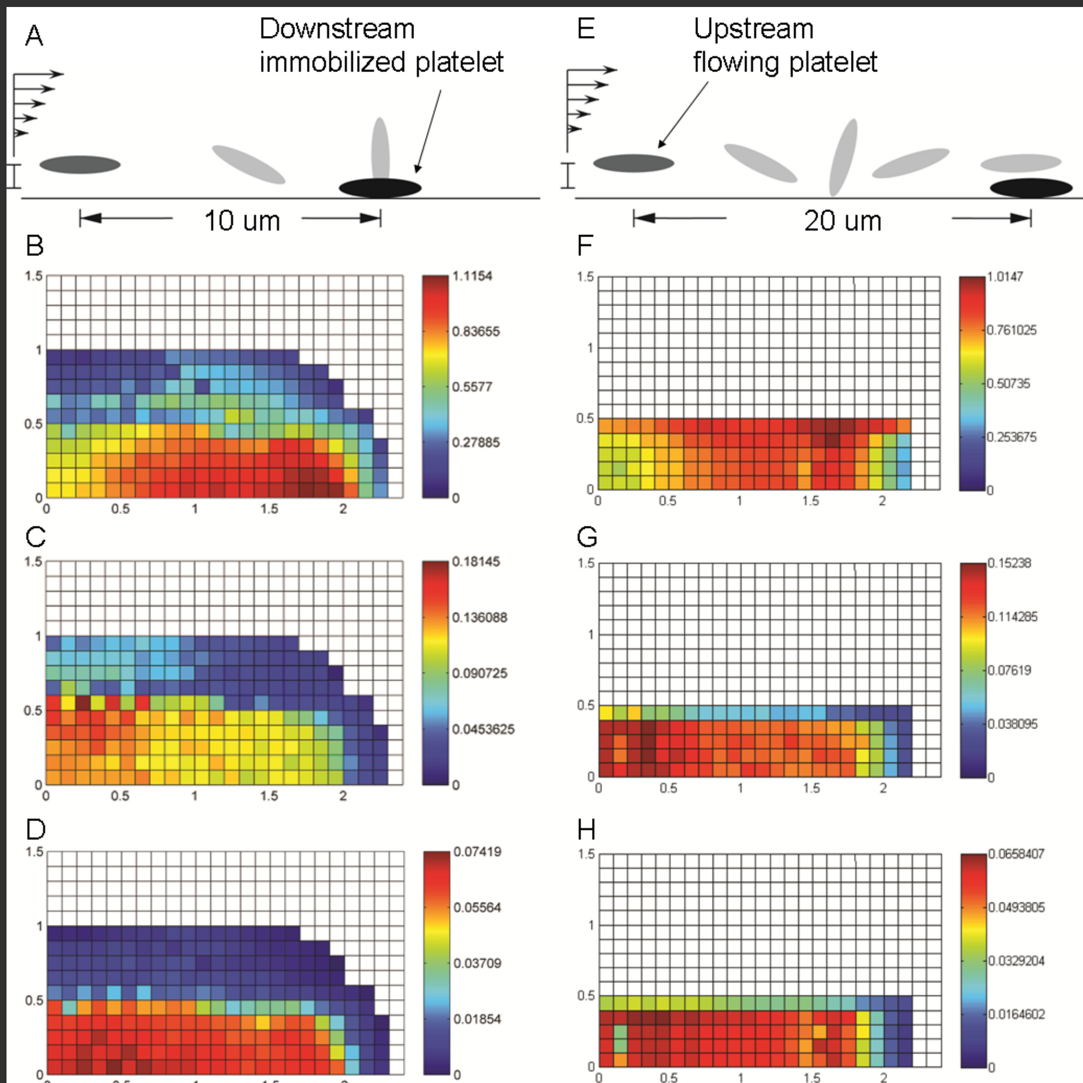
Binary collisions between two platelets

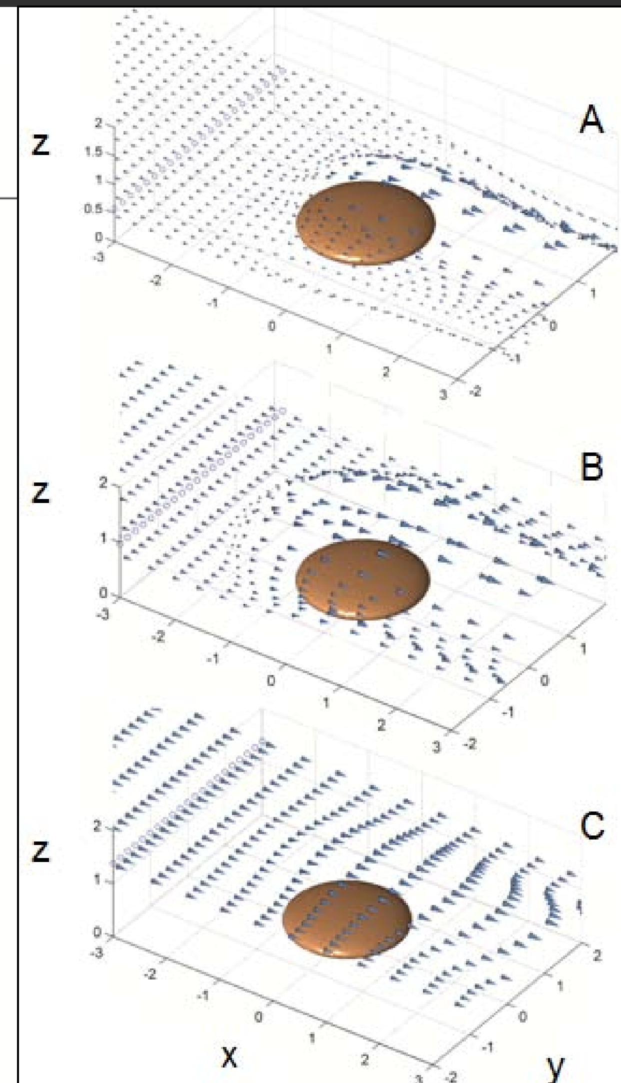
Two Platelets: One adherent to the injury site and one freely flowing

Contact time

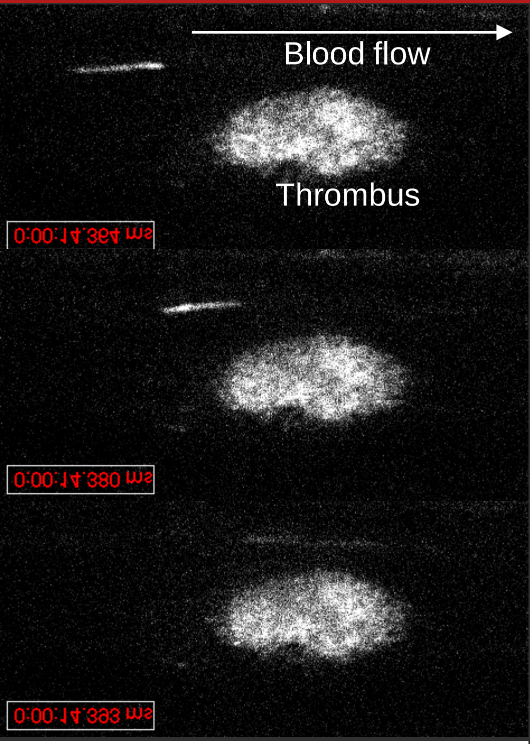
Max contact area

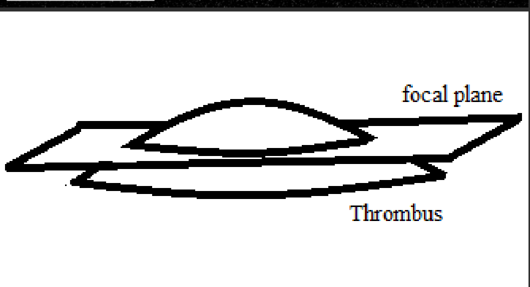
Contact area time integral



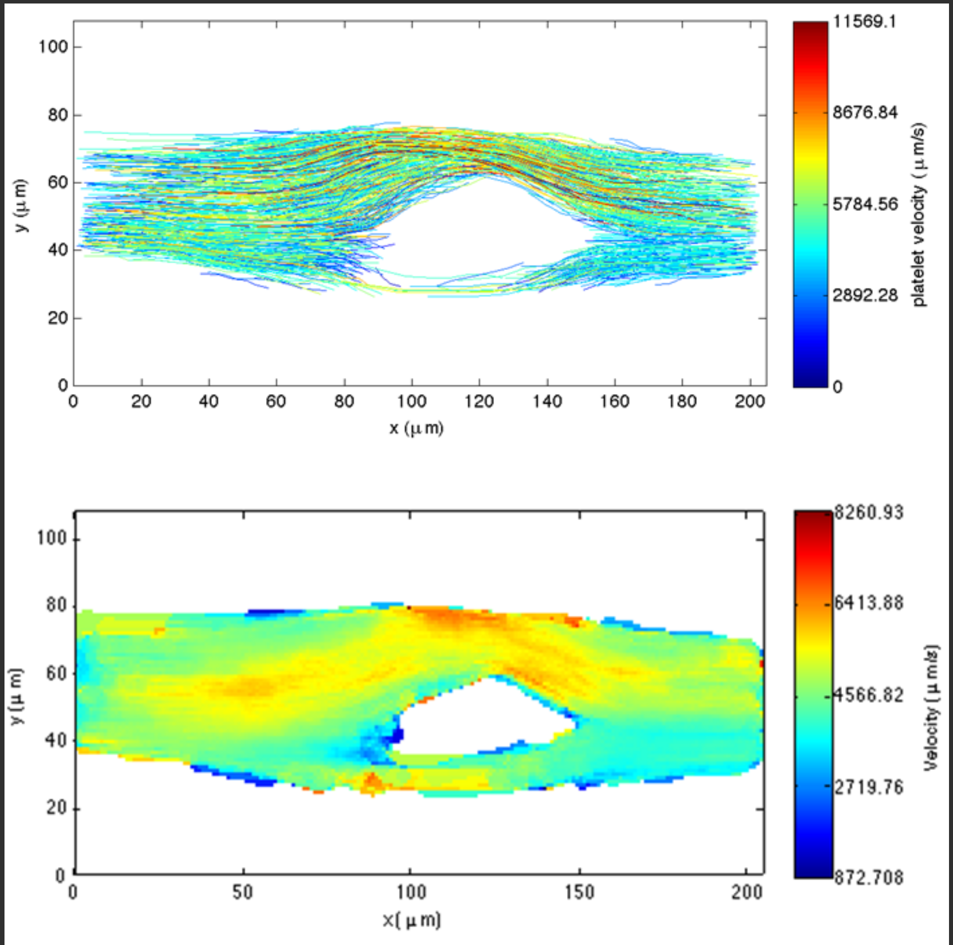


In-vivo flow visualization





Digital analysis of platelet flow around a platelet-rich thrombus *in vivo*. (~3600 frames, 54 s real time)
Up: cell trajectories color coded by velocity magnitude.
Down: 2-D color map of velocity magnitude.



Deformable Red Cells

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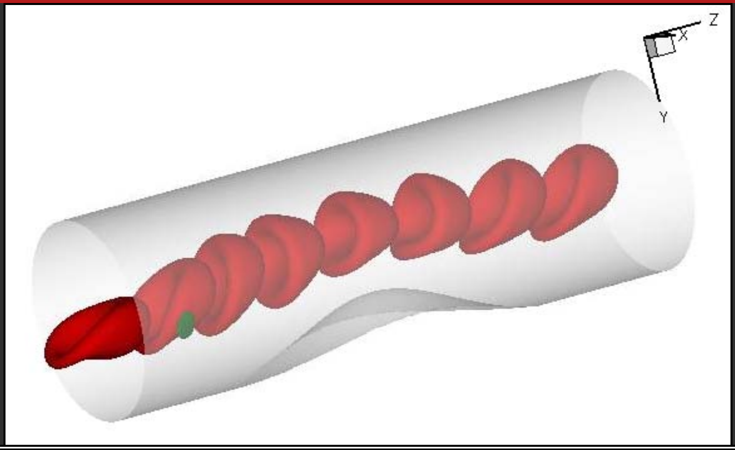

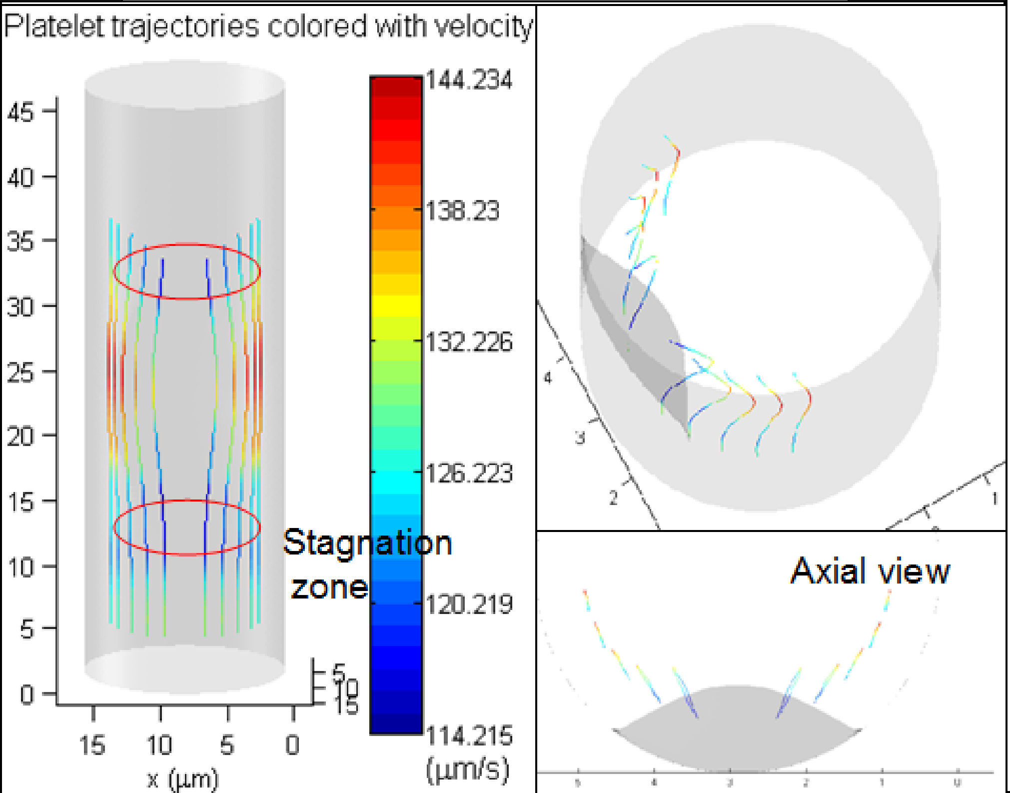

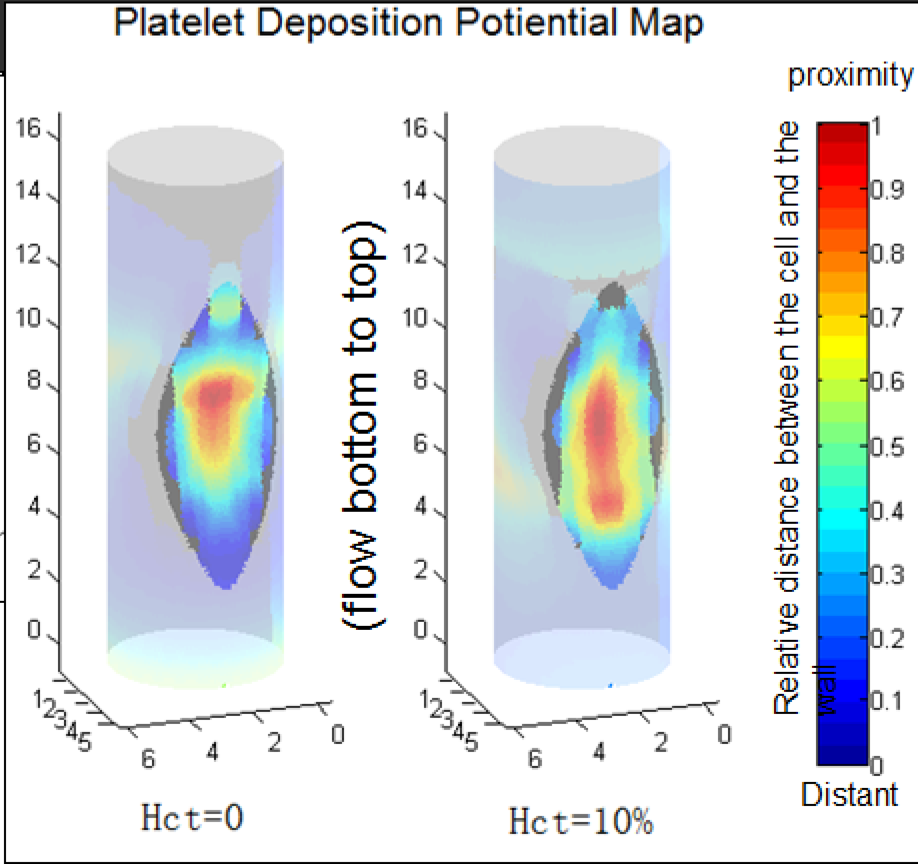

Conclusions

Platelet Adhesive Dynamics
(multiscale hydrodynamics + molecular kinetics):
–Flow characteristics of platelet shaped cells
–Characterizing particle-particle collision phenomena
–Model can differentiate between two different kinetic models

Vessel scale hydrodynamic calculations
–Platelet velocity drops upstream and downstream the thrombus
–RBCs enhance platelet deposition onto the thrombus surface.

Thrombus self-stabilizing dynamics in vivo:
–Thrombus shifts towards low shear stress region
–Characterizing the flow pattern around a human-like thrombus in vivo

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