Multiscale model of platelet adhesion and thrombus formation: validation with the humanized mouse

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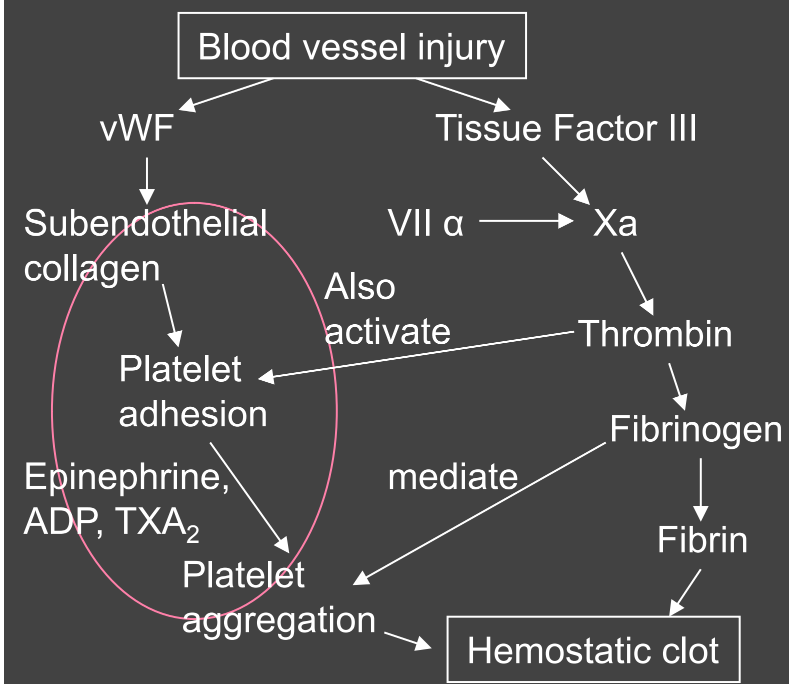
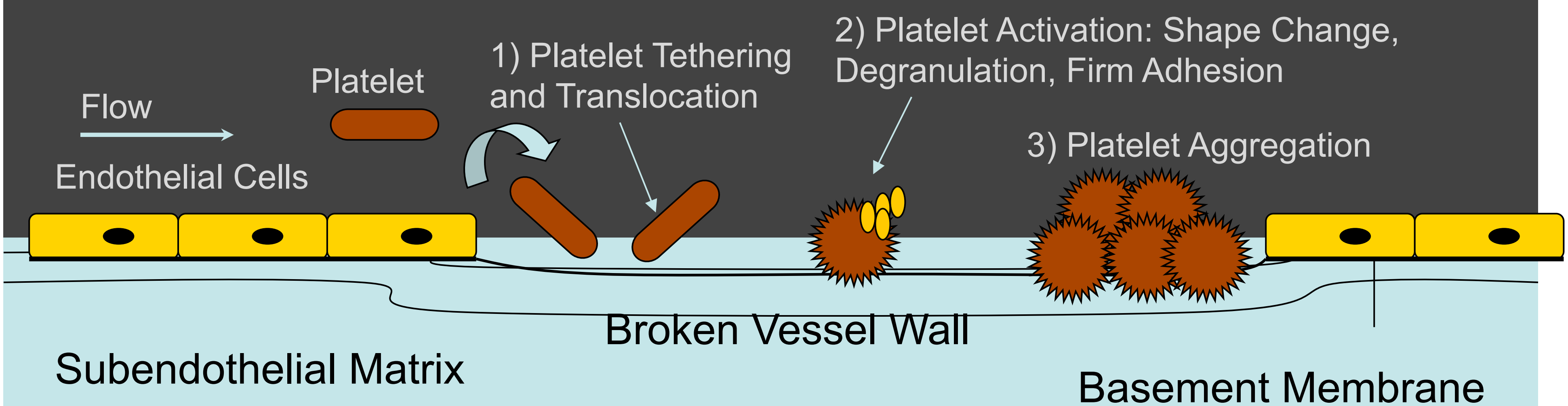
Hemostasis



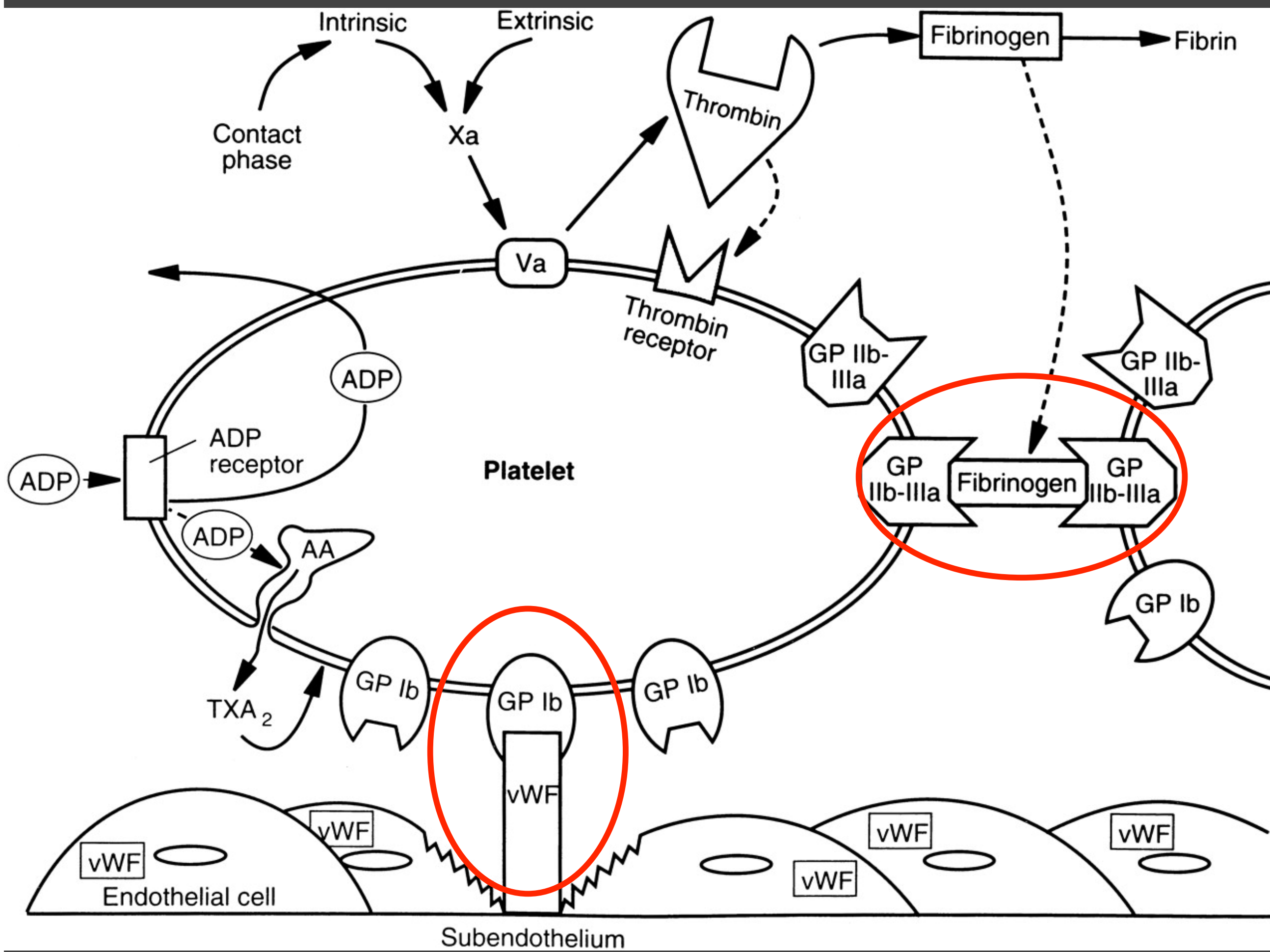
•***Hemostasis*** describes the physiological process of blood clotting at injured vessels

•***Thrombosis*** involves platelet activation and aggregation under pathological conditions

The left pathway reacts much faster than the right pathway, which makes platelet a key component in the initiation of hemostasis.



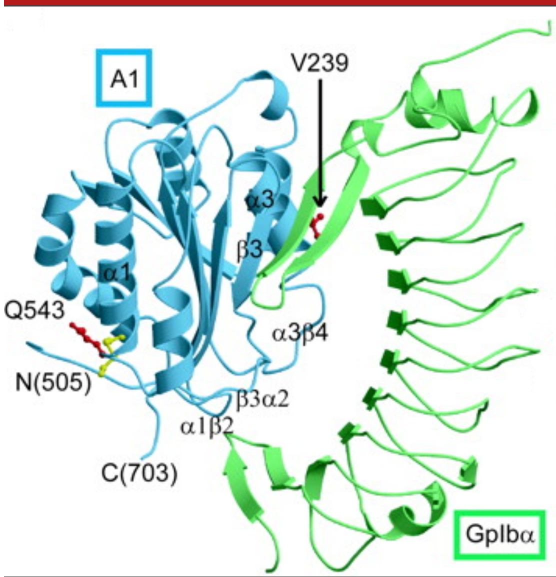
Platelets



Camacho et al. **Psychosomatic Medicine 62:326–336 (2000)**

Our research utilizes computational simulation models to study the adhesion of flowing platelets onto injured vessel surfaces, the initiation of thrombosis and the further development of micro-thrombi mediated by GPIb, integrin α2β1, GP IIb/IIIa receptors.

GPIbα-vWF A1 Bond



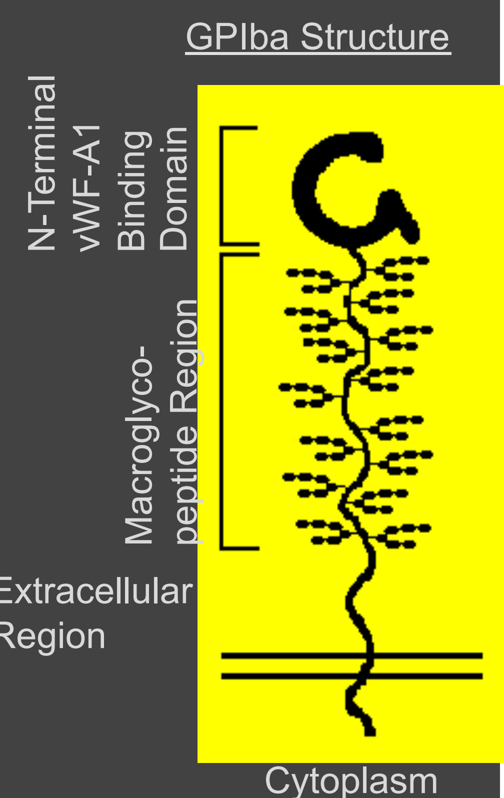
EG. Huizinga, et al. Science 16 August 2002: **Vol. 297 no. 5584** pp. 1176-1179

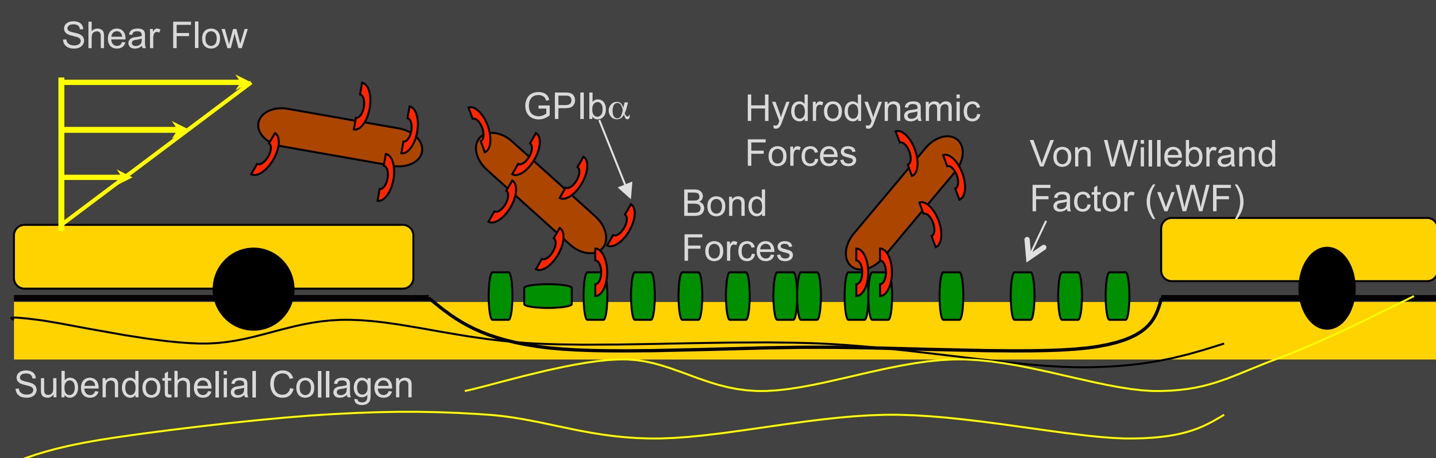
"GPIb-vWF-A1 tether bond kinetics are "selectin-like":

1) a critical level of hydrodynamic flow to initiate adhesion required
2) short-lived tethering events
3) fast intrinsic dissociation rate constant."

--TA Doggett, et al.

TA Doggett, et al. Biophysical Journal Volume 83 July 2002 194–205





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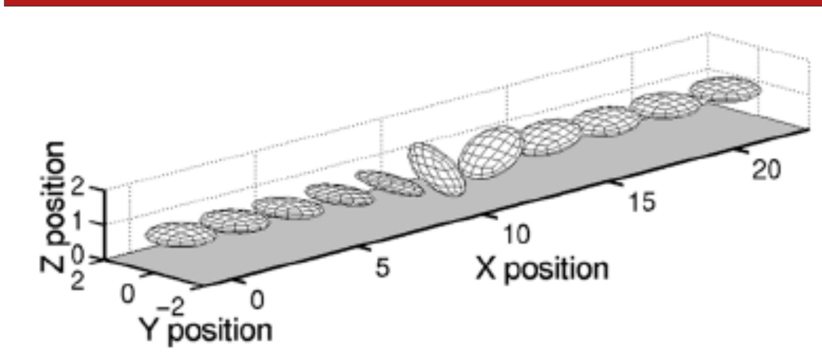
Convective Transport of a Single Platelet



Nipa Mody, et al. Phys. Fluids, 2005

One solid near-wall spheroid convects under simple shear Stoke's flow.

Governing equations:

$$\nabla p = \mu \nabla^2 u, \quad \nabla \cdot v = 0$$

$$u_\infty = \dot{\gamma} z$$

$$\mathbf{u} = \mathbf{U}^{(\mathrm{p})} + \boldsymbol{\omega}^{(\mathrm{p})} \times (\mathbf{x} - \mathbf{x}^{(\mathrm{p})}) \quad \mathbf{x} \in S^{(\mathrm{p})},$$

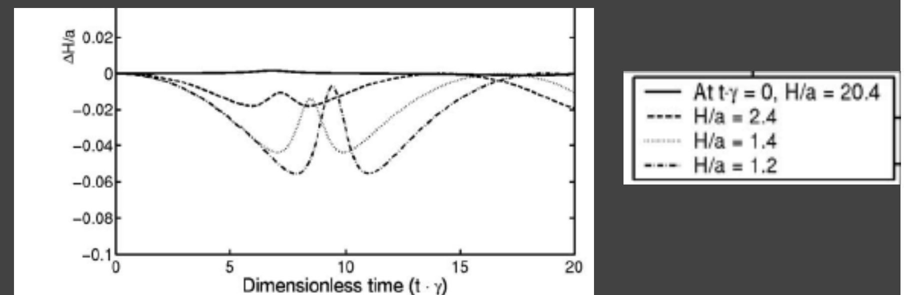
CDL-BIEM method (a boundary integral method to solve Stoke's flow):

$$v(x) - v^{\infty}(x) = v^{RC}(x) + \oint_S K(x-\xi) \cdot \phi(\xi) dS(\xi)$$

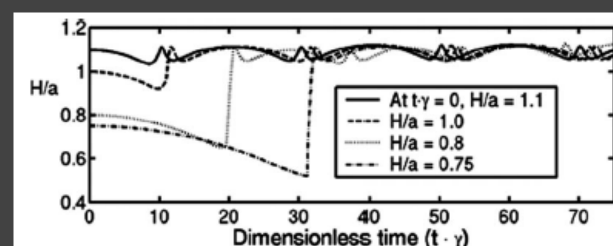
$$K(x-\xi) = -2n(\xi) \cdot \Sigma(x-\xi) \qquad \Sigma(x) = -\tfrac{3}{4\pi} xxx/|x|^5$$

$$v^{RC}(x) = \sum_{\alpha=1}^{N} [F_\alpha^e - \tfrac{1}{2}(T_\alpha^e \times \nabla)] \cdot \frac{\mathcal{G}(x - x_\alpha)}{8\pi\mu} \qquad \frac{\mathcal{G}_{ij}(x)}{8\pi\mu} = \frac{1}{|x|}\delta ij + \frac{1}{|x|^3} x_i x_j$$

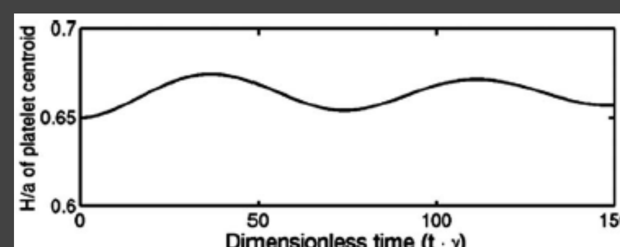
Regime 1: Modified Jeffery orbit. (H>1.2a)
H: start height, a: platelet long axis length



Regime 2: "Pole-vaulting" followed by repeated contacting. (1.1a>H>0.75a)



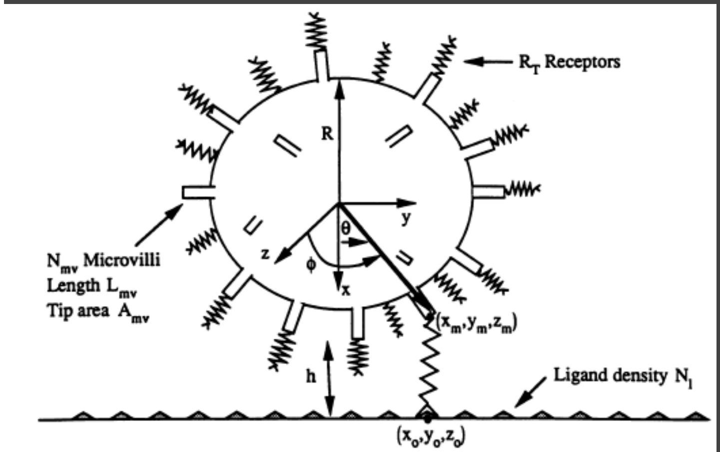
Regime 3: Wobble flow. (H<0.70a)



NA Mody, et al. PHYSICS OF FLUIDS **17**, 113302 2005

GPIbα-vWF A1 Mediated Adhesion Model

Prototype—
Selectin mediated neutrophil rolling:



DA Hammer, et al. Biophys. J. Volume 63 July 1992 35-57

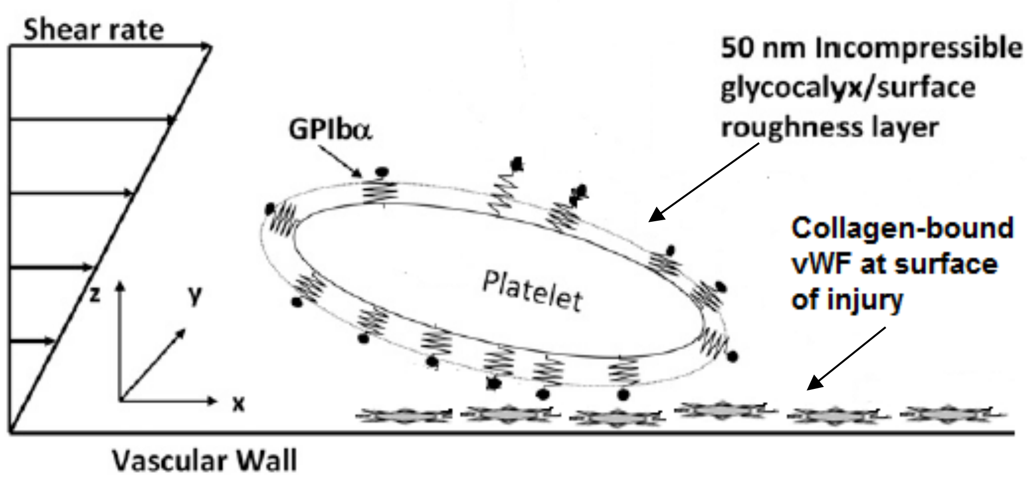
Bond kinetics, based on Bell Model:

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

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

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

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



Platelet Size: 1μm*1μm*0.25μm
Surface receptor density: ~1500/μm^2
K_r^0: 5.47S^{-1}
Other parameters see: NA Mody, et al. Biophysical Journal, Vol. 95 Sep. 2008

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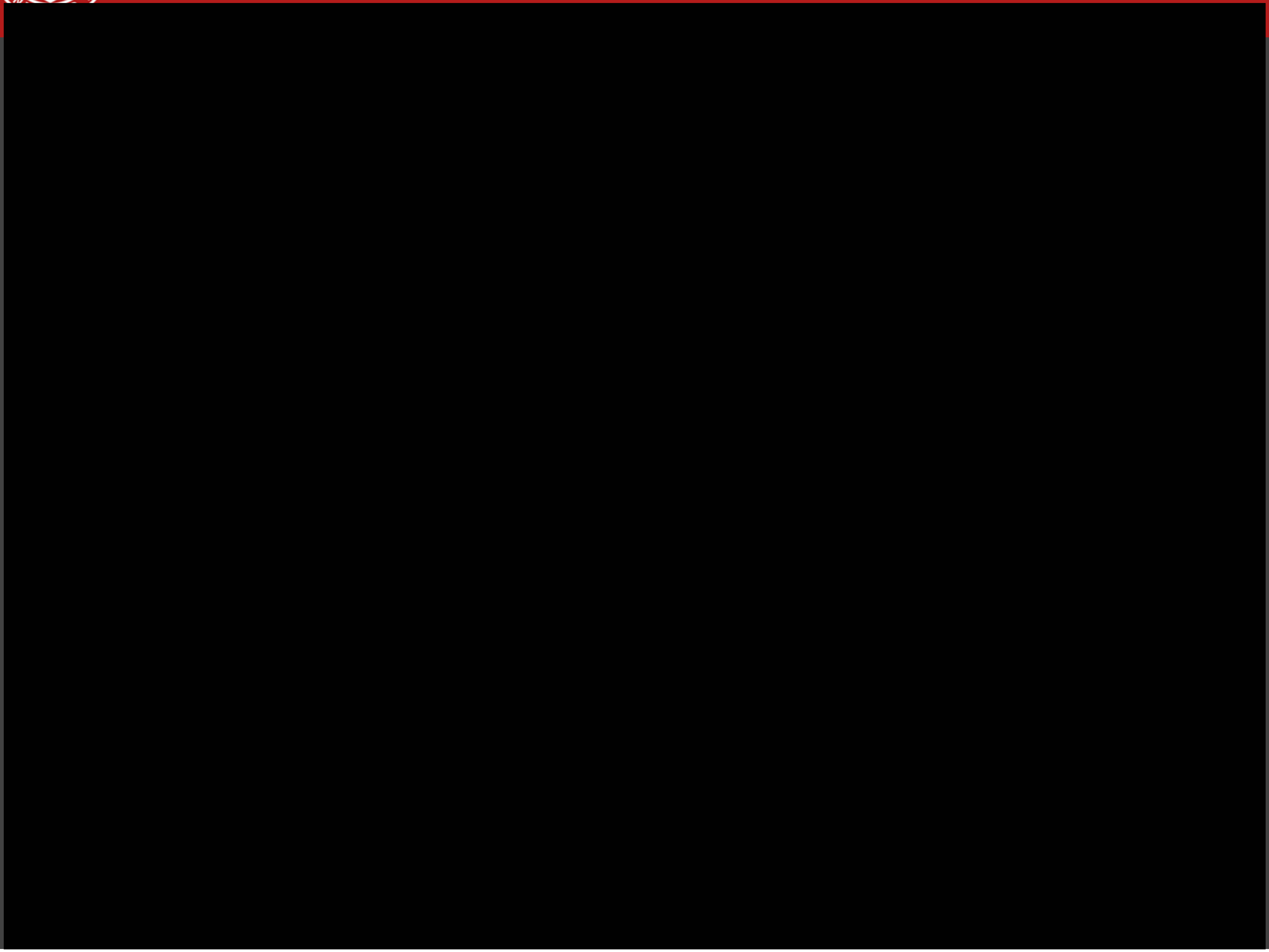
Single Platelet: Rolling



Single Platelet: Rolling

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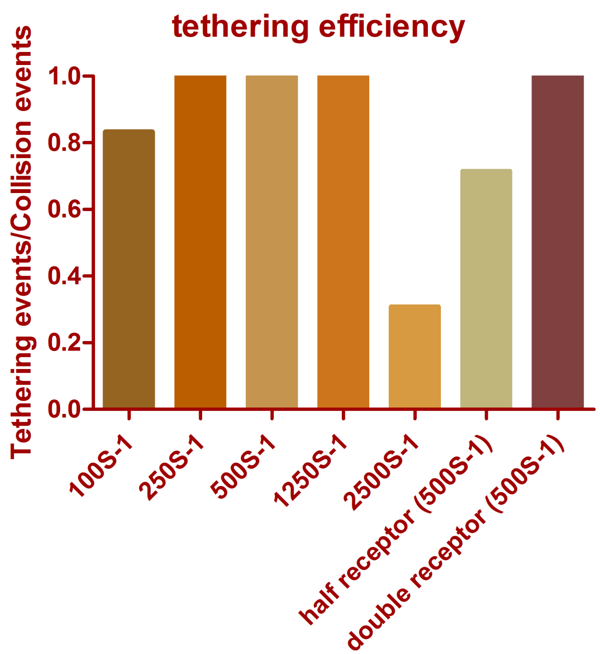

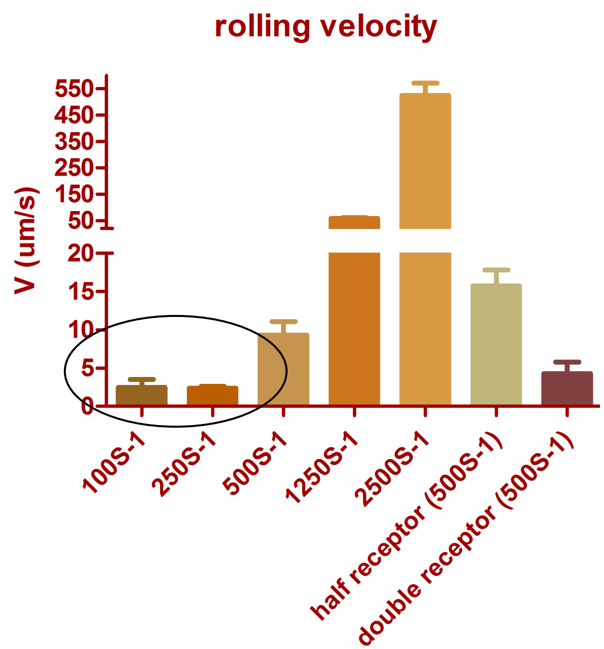

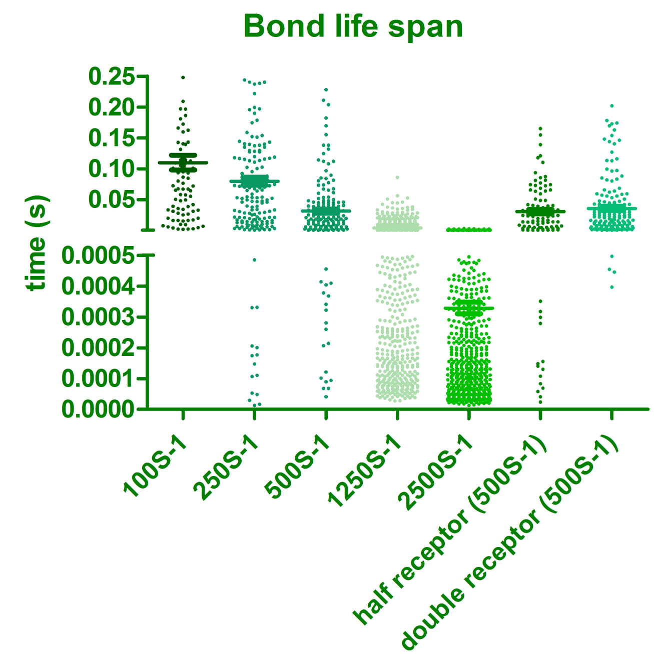

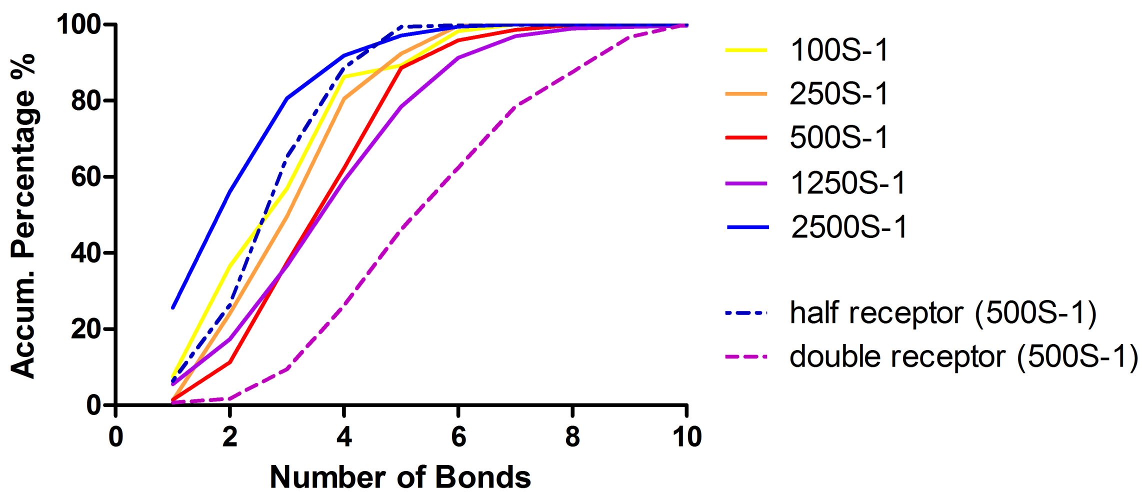

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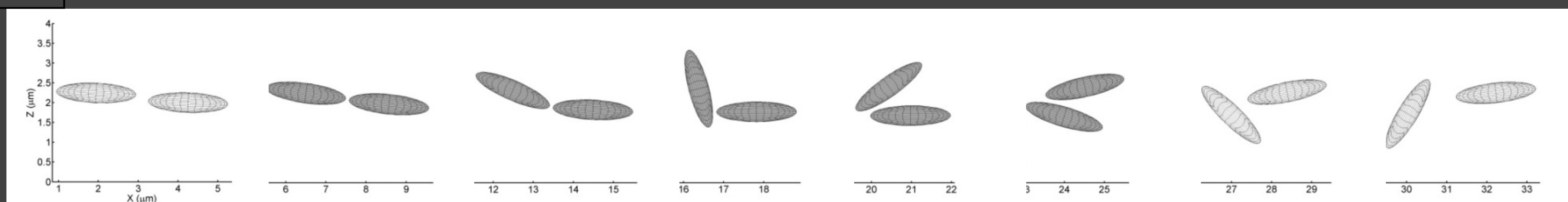
Two Platelets: Collision in Flow

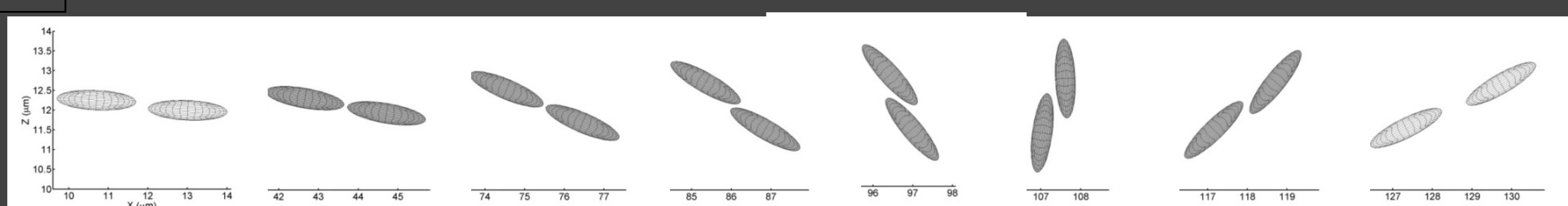
Both near-wall and far-wall platelet collision events have identical initial configurations: DX = 2.5 mm; DZ = 0.25 mm between centroids.

A **CLOSE TO WALL**

Mody and King, Part I, Biophys. J. 2008



B **FAR FROM WALL**



A **CLOSE TO WALL**

- Contact Time T_c = **22.84 ms**
- Max (Instantaneous Contact Area A_c) =

Platelet 1: 1.27 μm^2; Platelet 2: 1.26 μm^2

$$\int_0^{T_c} A_c^{\text{platelet}}\,dt$$

= **9.7** μm^2-ms Platelet 1

= **10.0** μm^2-ms Platelet 2

B **FAR FROM WALL**

- Contact Time T_c = **17.39 ms**
- Max (Instantaneous Contact Area A_c) =

Platelet 1: 0.8 μm^2; Platelet 2: 0.85 μm^2

$$\int_0^{T_c} A_c^{\text{platelet}}\,dt$$

= **6.0** μm^2-ms Platelet 1

= **6.1** μm^2-ms Platelet 2

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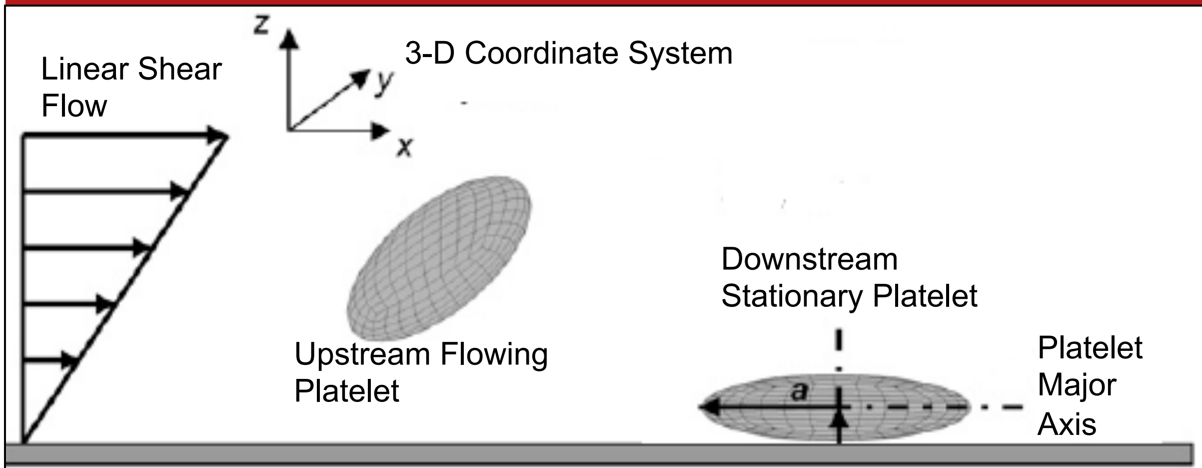
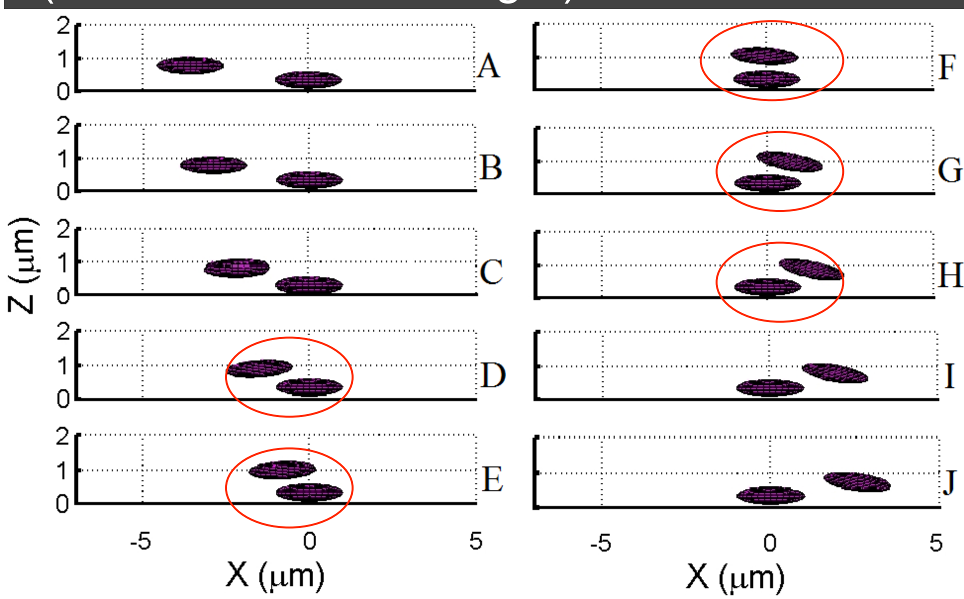
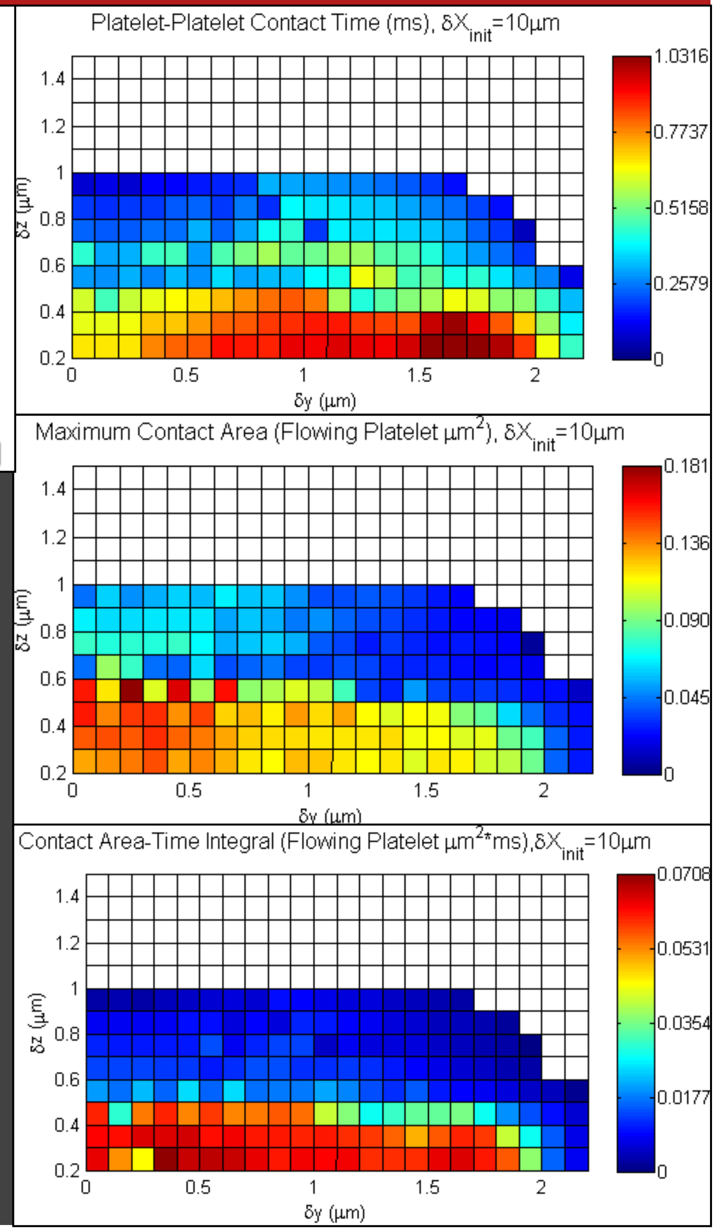
Two Platelets: the beginnings of aggregation



Contact: when closest distance < 0.128um (trimolecular bond length)





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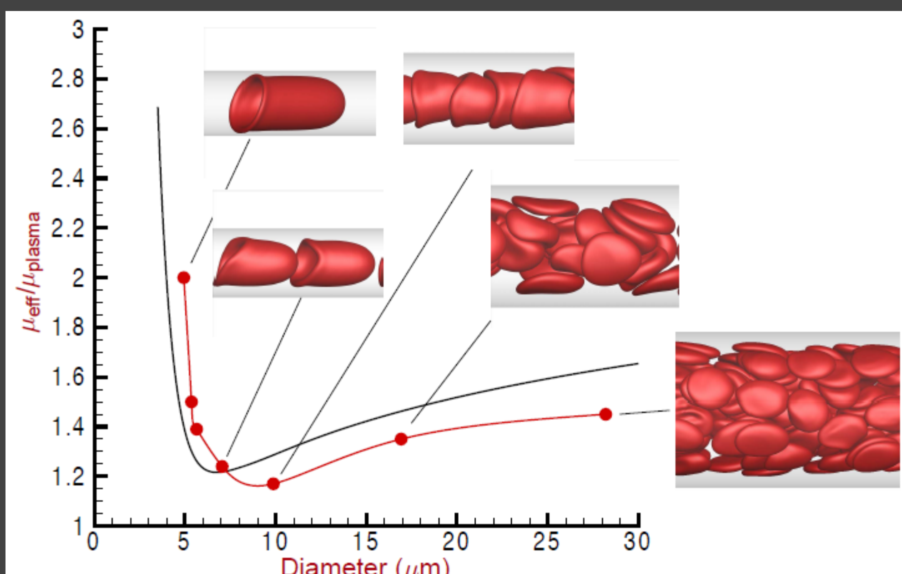
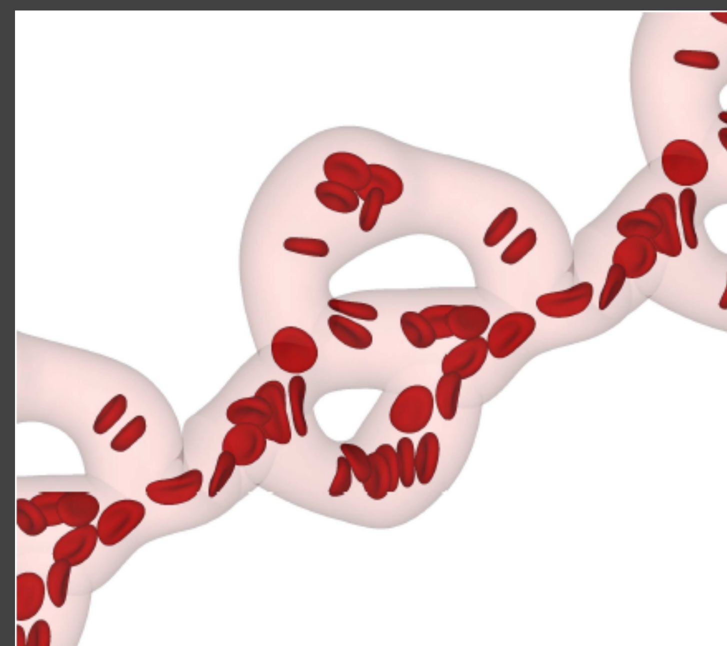
More blood cells— An Alternative Approach

A spectral surface integral methods developed for solving the viscous flow, and the motion of the massless membrane:
-Fast: an O(N logN) particle-mesh Ewald (PME) approach
-handle deformable RBCs
-deals with a large number of cells
-deal with complicated vessel geometry



Effective viscosity at Hct=30%


Blood flow through complex network

Jonathan B. Freund, et al. Chap.3, Computational Hydrodynamics of Capsules and Cells

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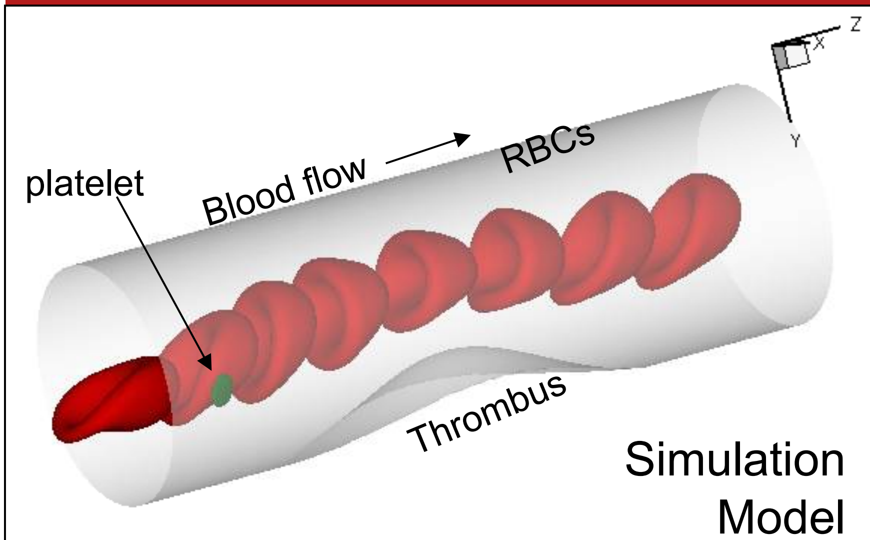
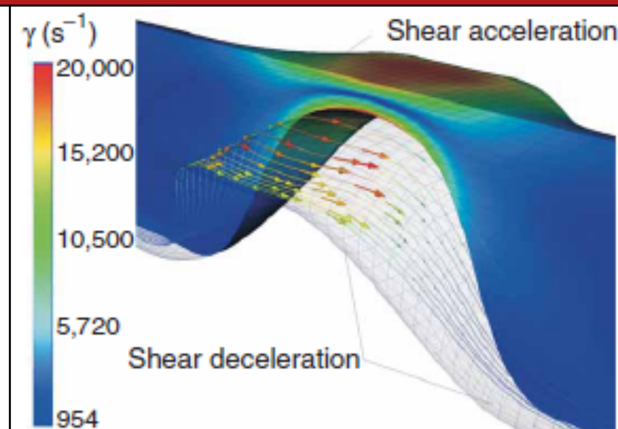
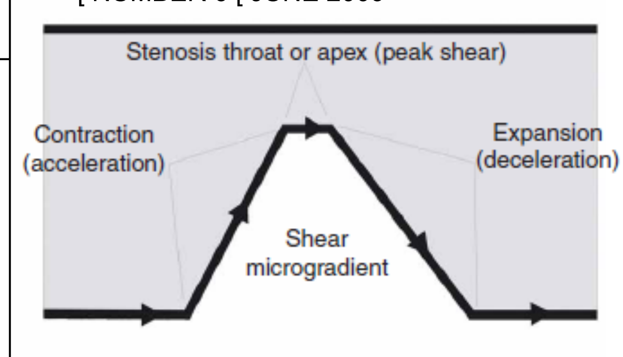
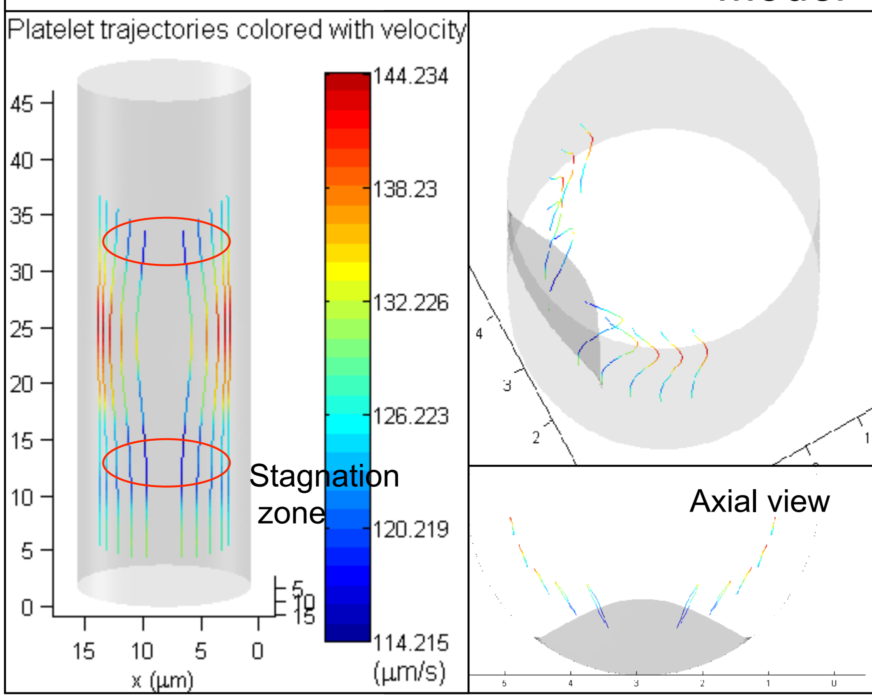
Clumps of Platelets: Micro Thrombi



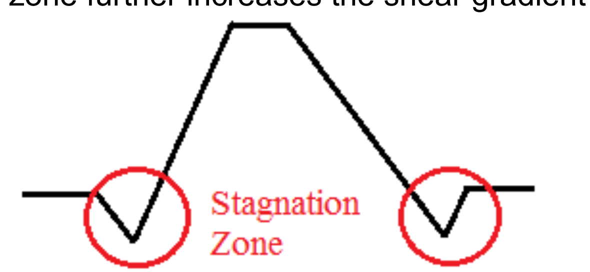


WS Nesbitt, et al. NAT MED. VOLUME 15 [NUMBER 6 [JUNE 2009





We propose: the existence of stagnation zone further increases the shear gradient



"A shear gradient–dependent platelet aggregation mechanism drives thrombus formation"— WS Nesbitt, et al. NATURE MEDICINE. VOLUME 15 NUMBER 6 JUNE 2009

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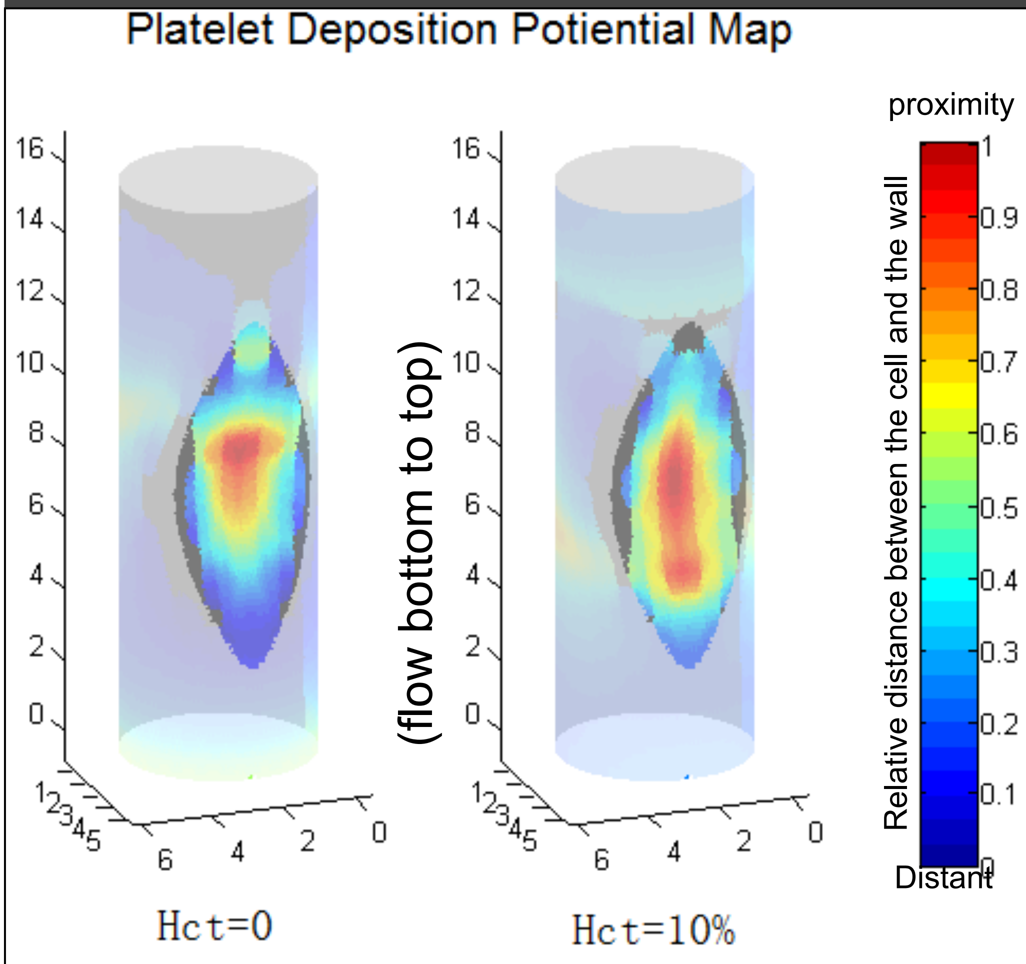
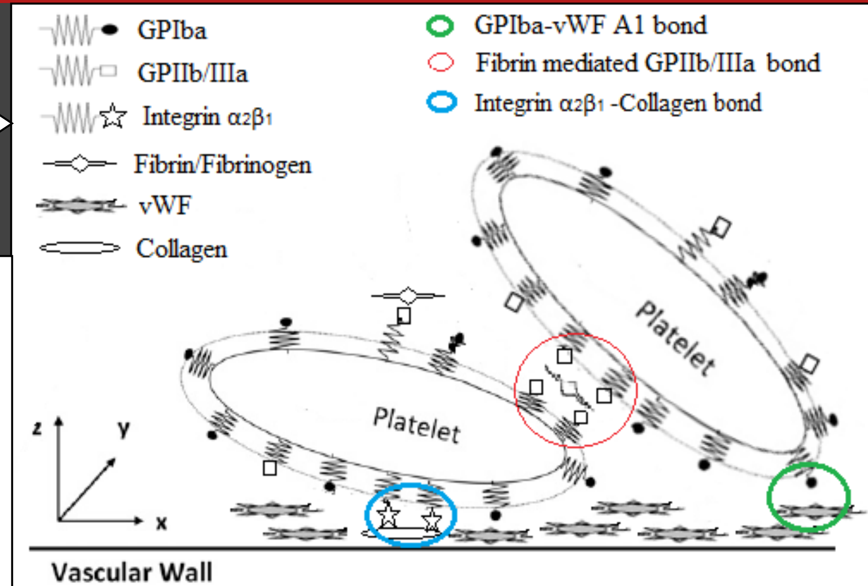
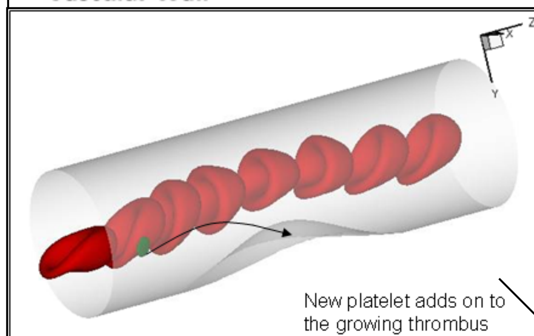
Modeling Thrombus Growth

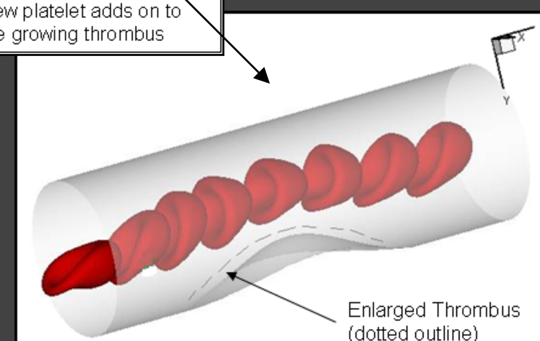
RBCs enhance platelets deposition.

Thrombus Growth Model









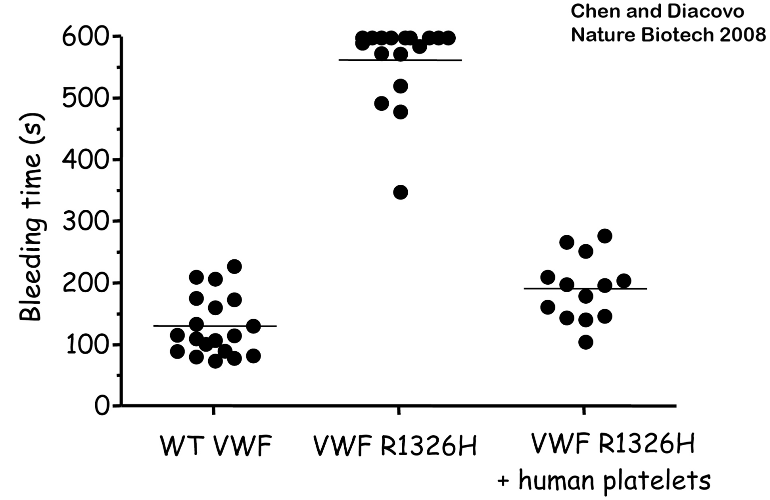
Humanized Mouse Model

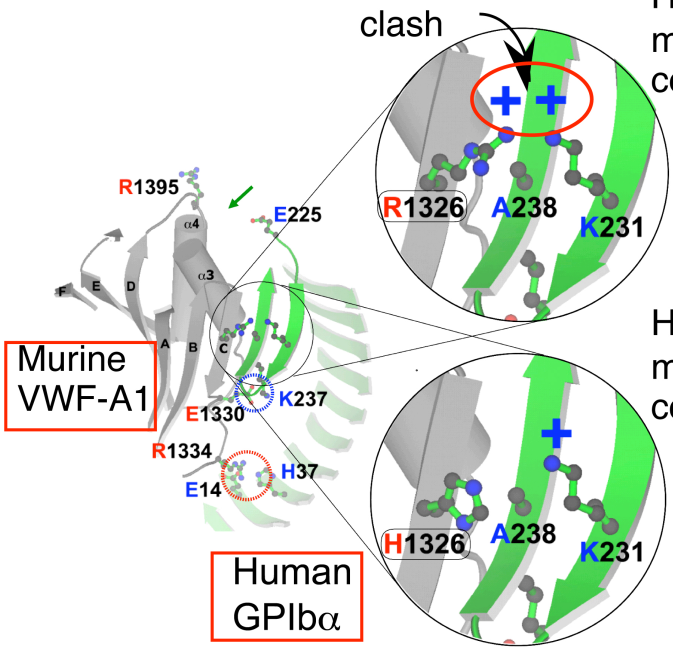
VWF $R^{1326}H$ mice

pulsed nitrogen dye laser

Test thrombus formation

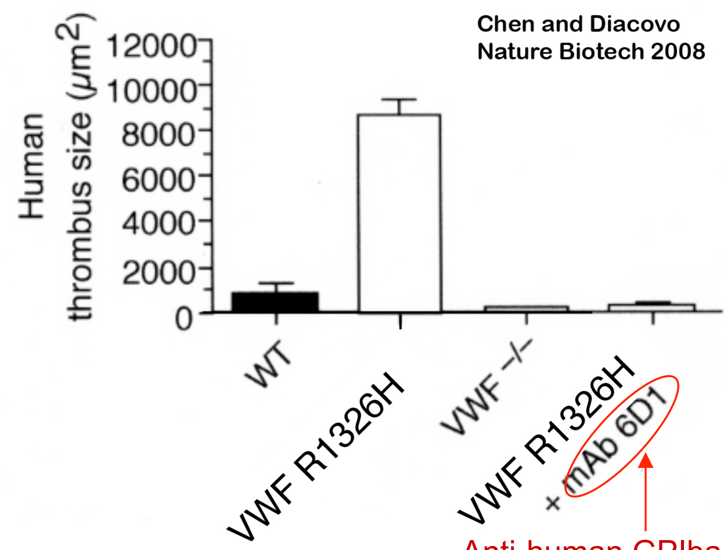
Inject fluorescent human platelets





Chen and Diacovo
Nature Biotech 2008

Human platelets in mice



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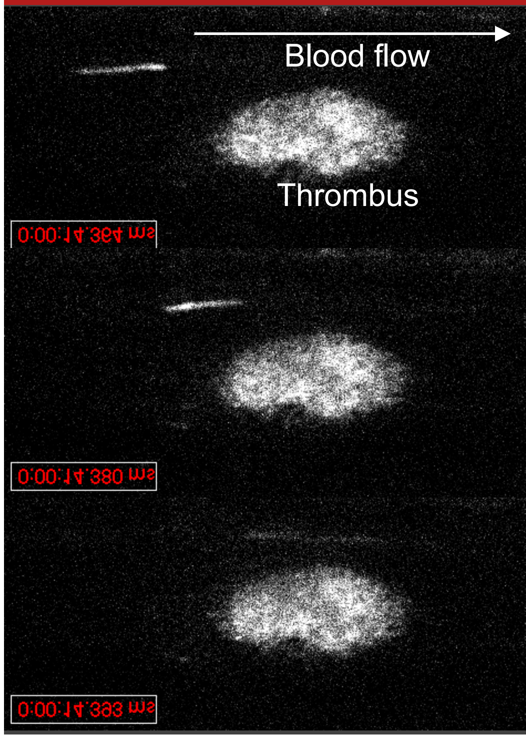
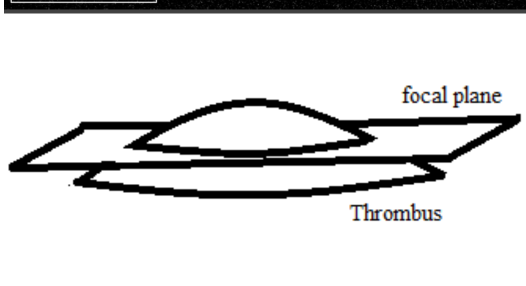
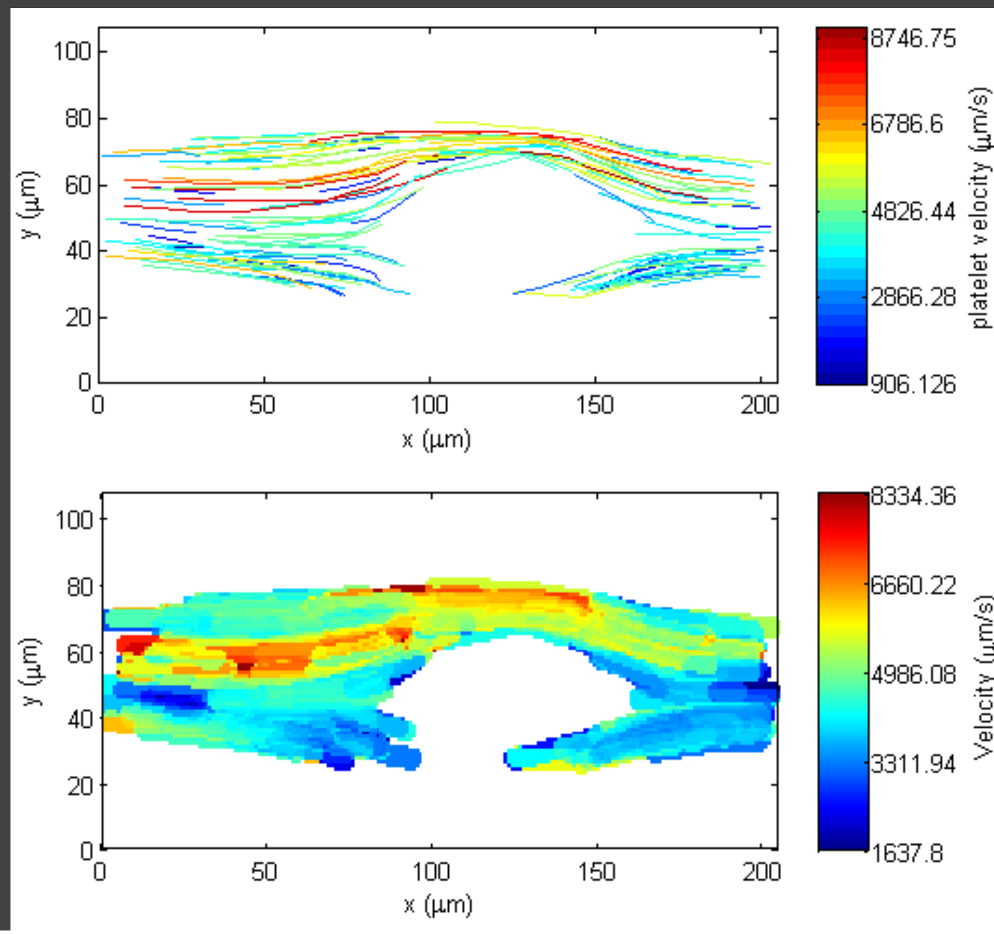
Platelet Flow past a growing Thrombus





Digital analysis of platelet flow around a platelet-rich thrombus in vivo. (~400 frames, 6s real time)
Up: cell trajectories color coded for velocity magnitude.
Down: 2-D color map of velocity magnitude.



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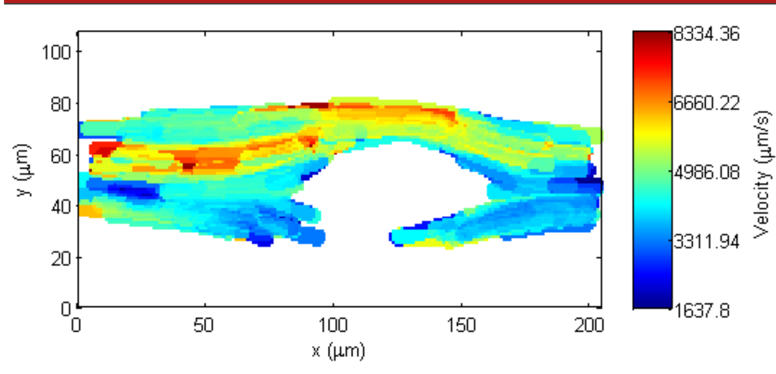
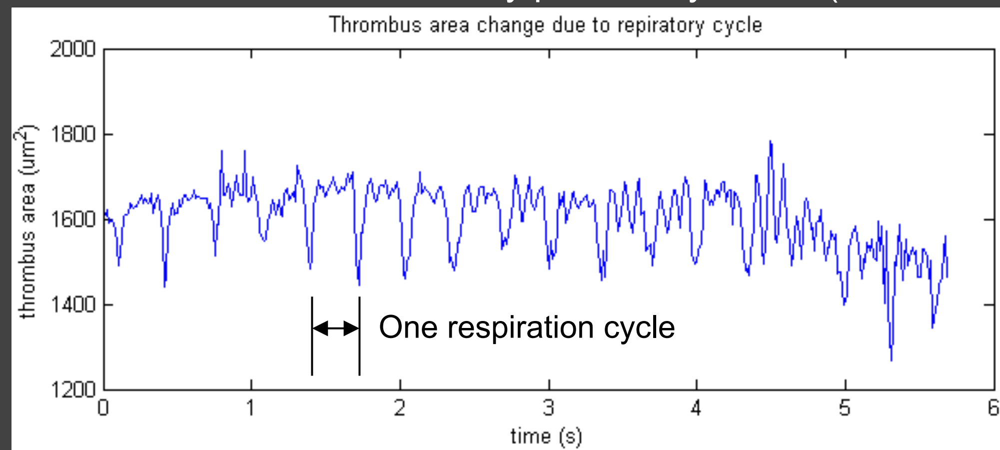
Detecting Thrombus Shape Change



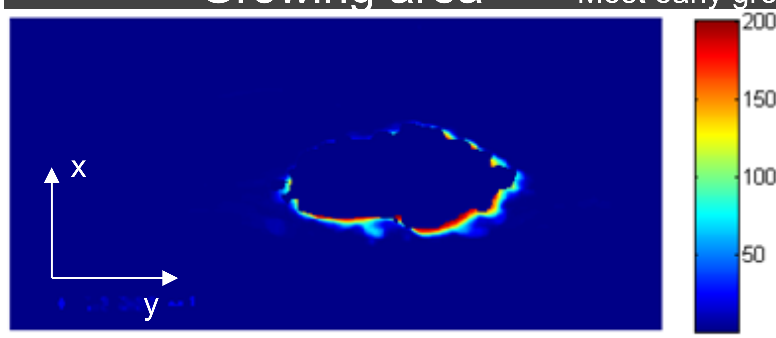
Thrombus tend to shrink at surface with high shear stress and extend at surface with low shear stress where platelet is more easy to tether.

Thombus shift is not caused by pulmonary effect. (400



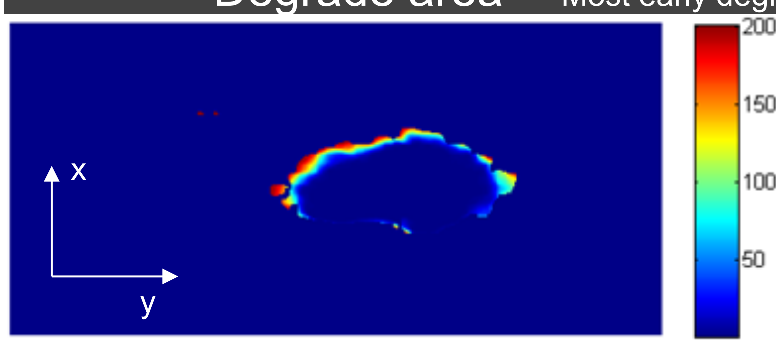
Growing area

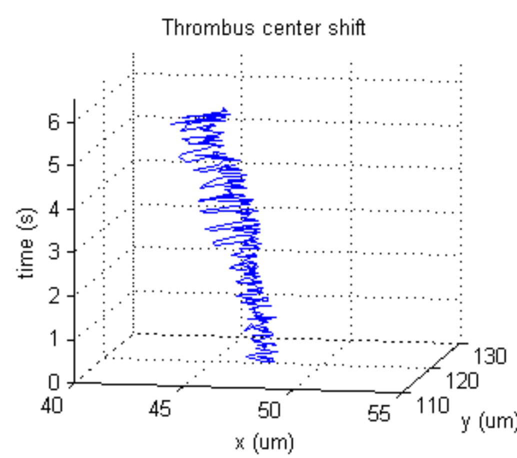
Most early growth

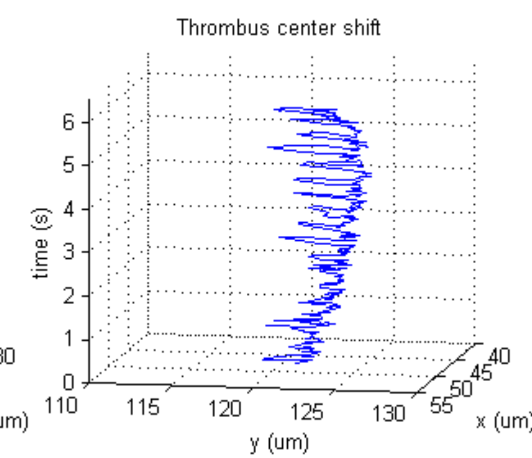


Degrade area

Most early degraded







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Conclusions

Platelet Adhesive Dynamics:
–Flow characteristics of platelet shaped cells
–Characterizing particle-particle collision phenomena
–Dynamics of GPIba-A1 mediated platelet-vessel tethering/rolling, initiation of thrombosis.

The **existence of "stagnation zones"** both upstream and downstream the thrombus enhances the shear-gradient dependent thrombus formation

RBCs enhance platelet deposition, which leads to enhancement of thrombus growth.

Characterizing the flow pattern around a human thrombus in vivo.

Explore the thrombus shifts towards low shear stress region.

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