Blood flow regulates platelet-polymer aggregation

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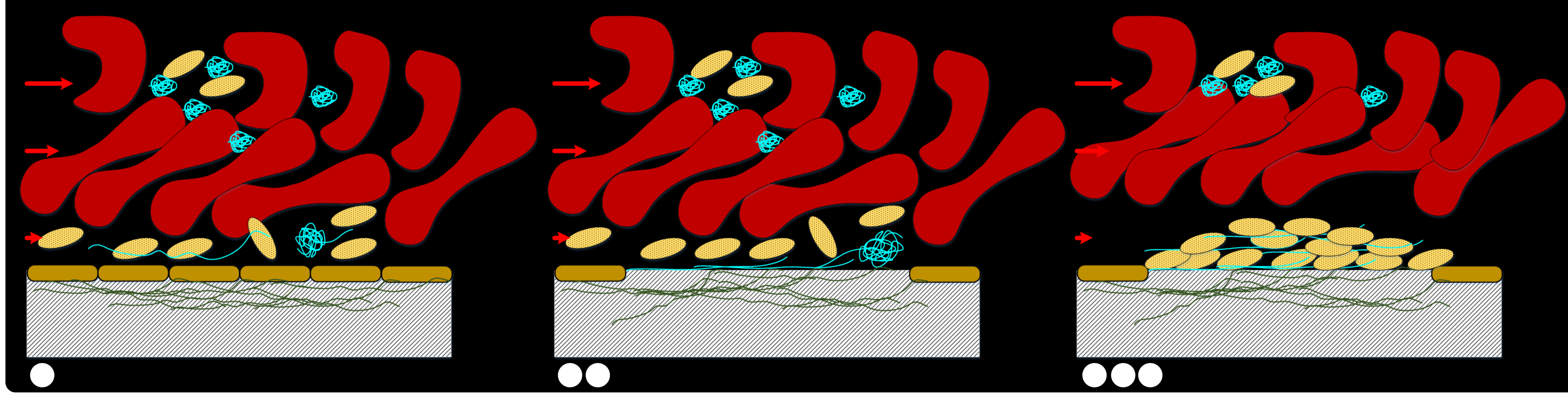
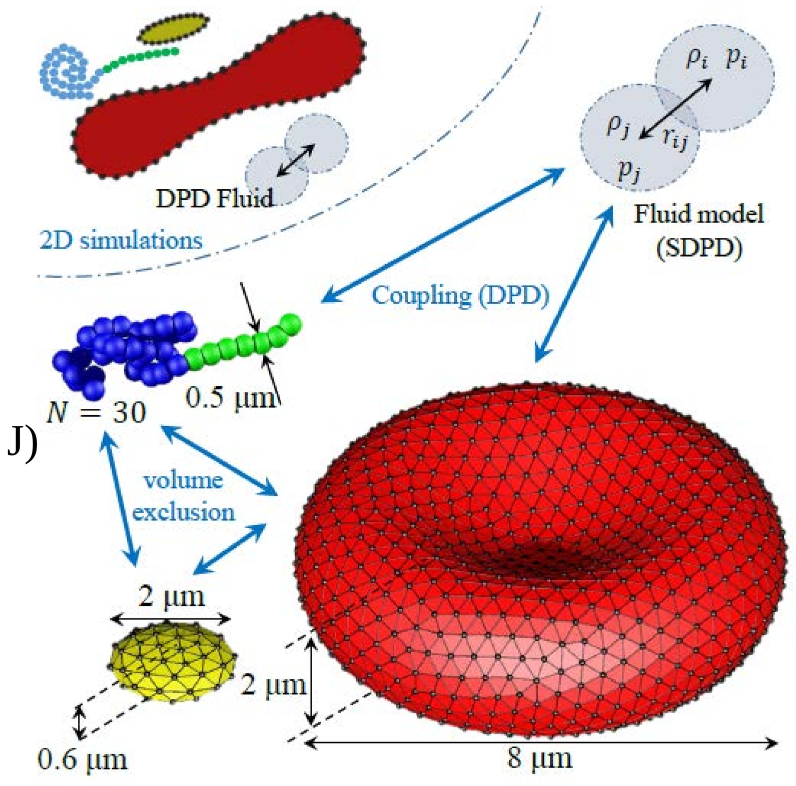
Platelets form aggregates as they adhere to the stretched von Willebrand factors (VWFs) at high shear rates. Their aggregation is critically dependent on shear rate and dissolves reversibly at low shear rates. In blood flow, red blood cells (RBCs) keep away from the vessel walls and leave a RBC free layer (RBC-FL) to which platelets and VWFs marginate. The formed aggregates in the RBC-FL gain significant hydrodynamic lift force and penetrate the RBC-core. Expectations from the experimental evidence on the shear-activated VWF-platelet interaction imply that these demarginated aggregates have to dissociate in the center of the vessel where the shear rate is low enough. Mesoscopic hydrodynamic simulations of the blood flow including RBCs, platelets, and VWFs, support this prediction. The regulation of undesired aggregates is beneficial for the vasculature, prohibiting undesired spontaneous thombosis and imminent blockage or stroke, and can be altered if the affinity of the platelets to VWFs changes, such as in von Willebrand disease type 2B.



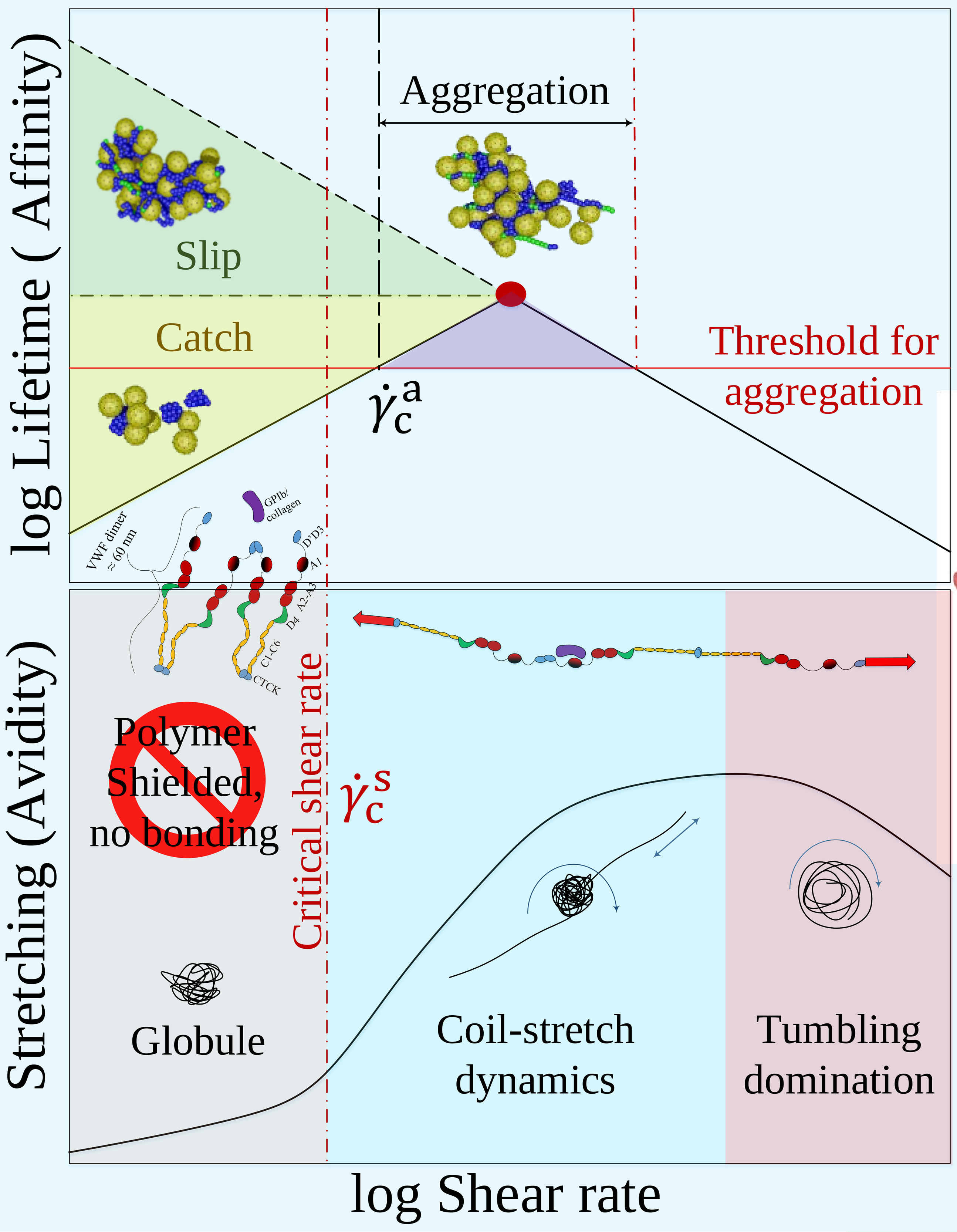
MODEL

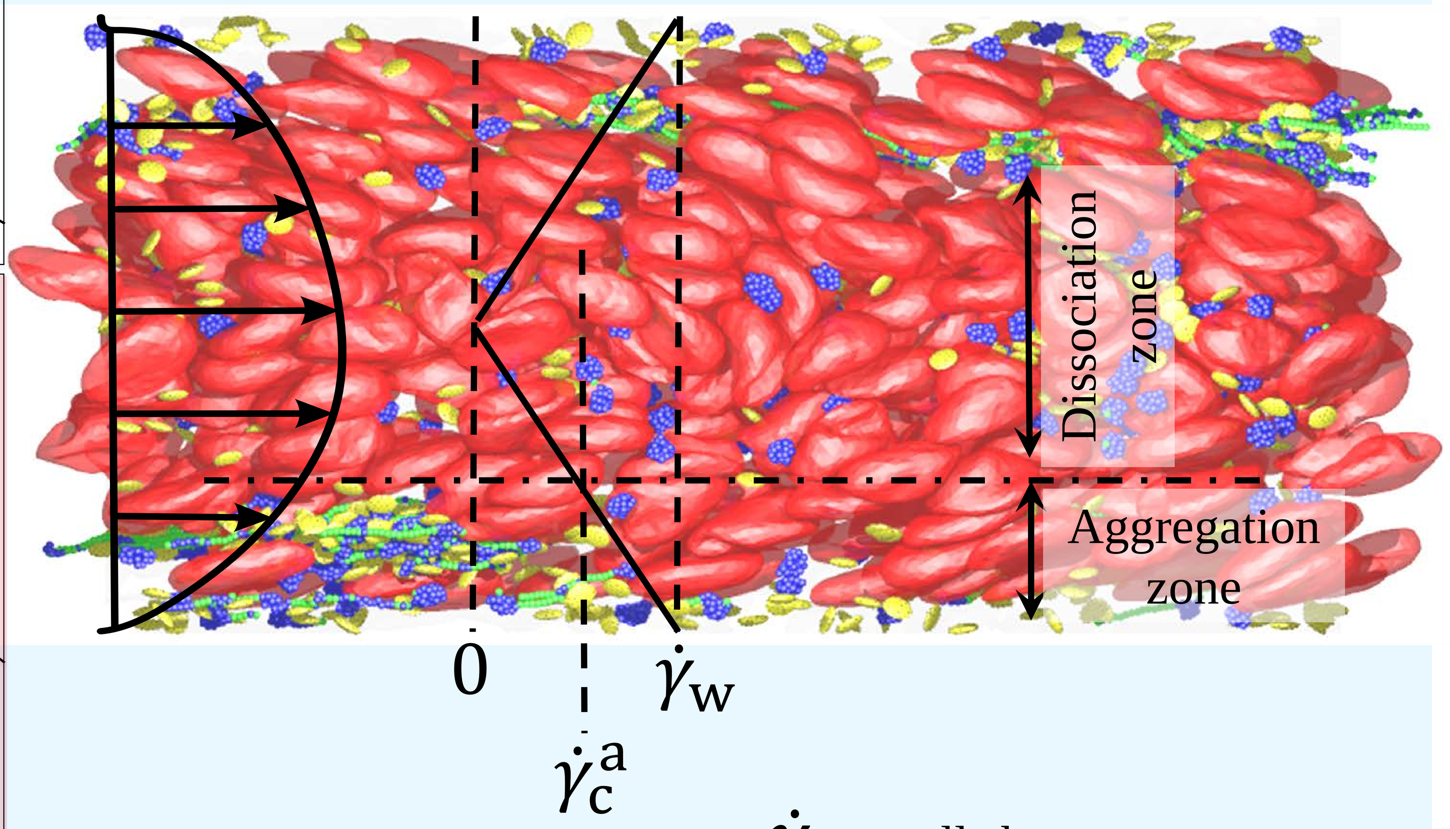
- **Hydrodynamics:** Smoothed dissipative particle dynamics (SDPD) (Espanol et al. PRE. 2003)
- **Membranes:** Triangulated mesh of springs and vertices (Fedosov et al. 2010. Biophys J)
- **VWF polymer:** Self-avoiding bead-spring model with attractive Lennard-Jones potential
- **VWF activity:** Conformation-dependent Stretched➔active, collapses➔inactive



- **VWF Avidity:** VWF polymers shield their adhesive sites from platelet receptors when they are collapsed. At high shear rates ($\dot{\gamma} > \dot{\gamma}_c^s$), they stretch critically and expose their adhesive sites for binding platelets. (Schneider et al. 2007. PNAS, Fu et al. 2017. Nat Comm)
- **VWF Affinity:** The adhesive bonds between VWFs and platelets have two states induced by shear stress (force). (Kim et al. 2010. Nature)
- **Reversible Aggregation:** It is known that at high shear rates ($\dot{\gamma} > \dot{\gamma}_c^s$), the VWF polymers stretch and form aggregates with platelets. If their affinity drops at low shear rates ($\dot{\gamma} > \dot{\gamma}_c^a$), they dissociate reversibly (catch scenario); otherwise, they remain stable (slip scenario)

In Blood Vessel:
Unaggregated platelets and polymers marginate toward the walls.
Local shear rate in blood vessel decreases from the maximum shear rate $\dot{\gamma}_w$, at the wall to zero at the center.





$\dot{\gamma}_w$: wall shear rate

$\dot{\gamma}_c^a$: critical shear rate for stable aggregation; depends on the platelet-VWF affinity.

$\dot{\gamma}_c^s$: critical shear rate for VWF polymer stretching; depends on the self-association of polymer

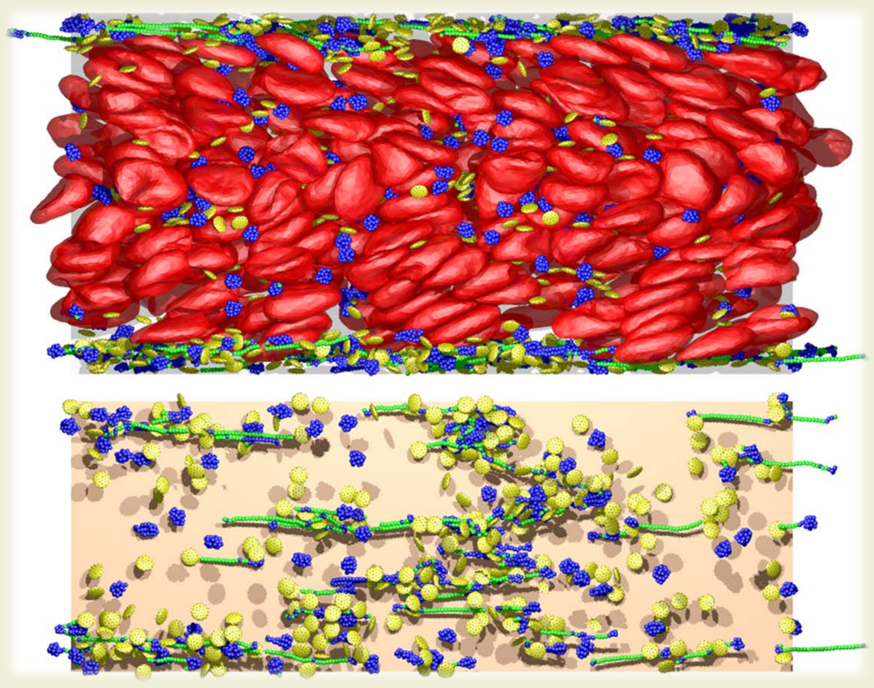
Catch Scenario

Aggregation & Demargination:
Similar to slip scenario

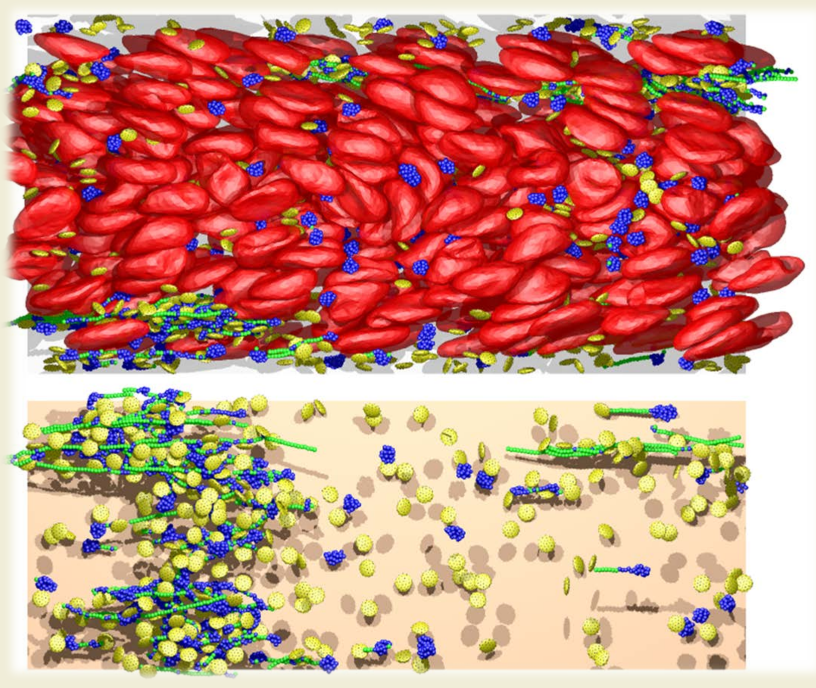
Dissociation:
Once the aggregates pass the layer of critical shear rate for stable aggregation ($\dot{\gamma} > \dot{\gamma}_c^a$), they dissociate

Remargination:
Dissociated polymersw and platelets remarginate back to the vessel wall.

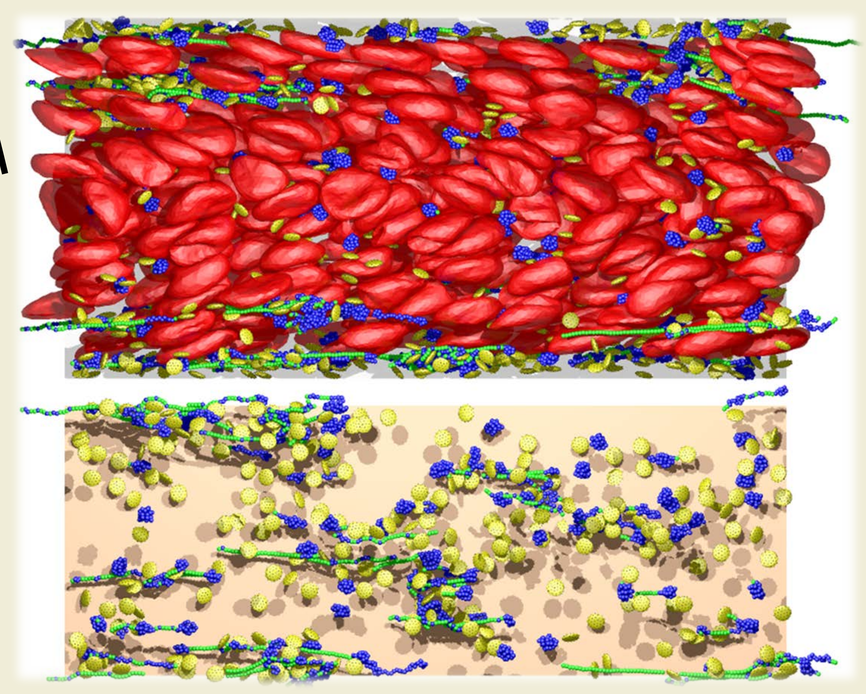
Steady-state:
The system reaches a steady-state while aggregation, penetration, dissociation, and remargination occur successively.



Aggregation



Demargination



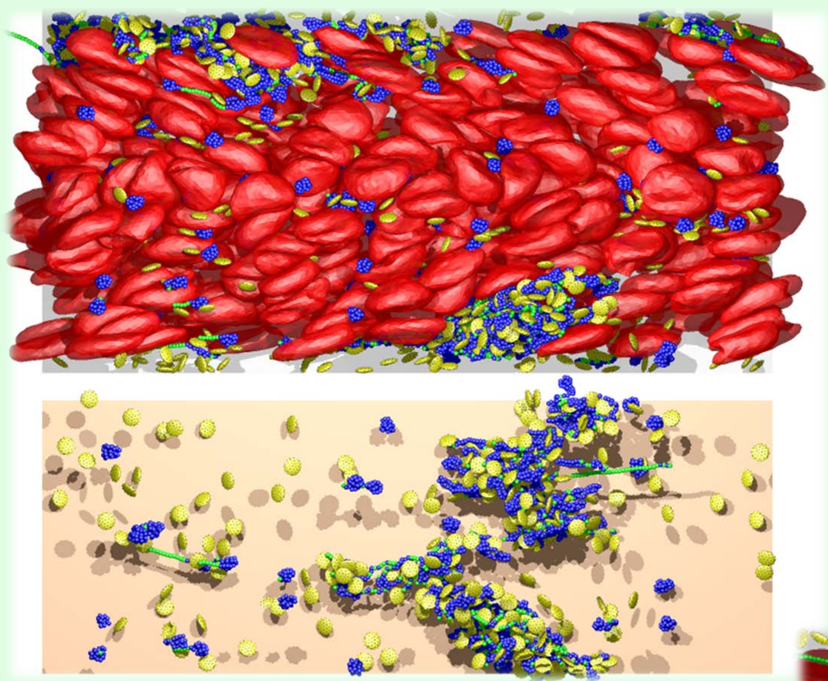
Dissociation

Slip Scenario

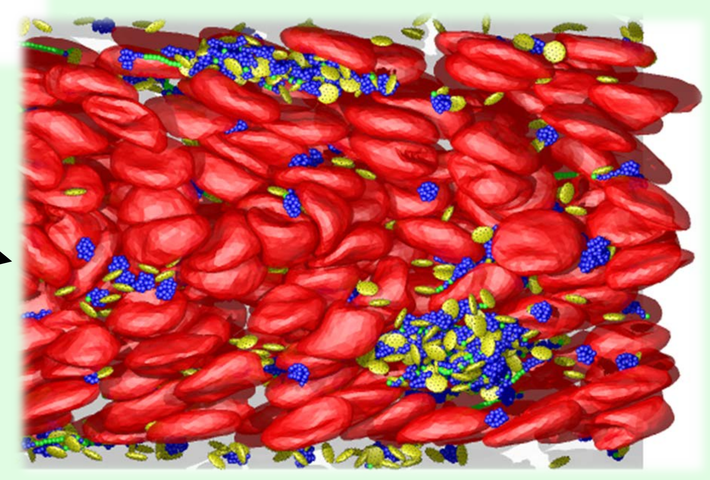
Aggregation:
The aggregates form and grow at the high shear rate region close to the vessel walls.

Demargination:
The formed aggregates obtain hydrodynamic lift forces strong enough to let them penetrate the central blood flow.

Migration toward the center:
The aggregates remain stable and migrate toward the center of the vessel.



Aggregation and demargination



Migration toward the center

Mitglied der Helmholtz-Gemeinschaft