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A Multiscale Biomechanical Model of Platelets: Correlating with In-Vitro Results

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Abstract

Using dissipative particle dynamics (DPD) combined with coarse grained molecular dynamics (CGMD) approaches, we developed a multiscale deformable platelet model to accurately describe the molecular-scale intra-platelet constituents and biomechanical properties of platelets in blood flow. Our model includes the platelet bilayer membrane, cytoplasm and an elaborate elastic cytoskeleton. Correlating numerical simulations with published in-vitro experiments, we validated the biorheology of the cytoplasm, the elastic response of membrane to external stresses, and the stiffness of the cytoskeleton actin filaments, resulting in an accurate representation of the molecular-level biomechanical microstructures of platelets. This enabled us to study the mechanotransduction process of the hemodynamic stresses acting onto the platelet membrane and transmitted to these intracellular constituents. The platelets constituents continuously deform in response to the flow induced stresses. To the best of our knowledge, this is the first molecular-scale platelet model that can be used to accurately predict platelets activation mechanism leading to thrombus formation in prosthetic cardiovascular devices and in vascular disease processes. This model can be further employed to study the effects of novel therapeutic approaches of modulating platelet properties to enhance their shear resistance via mechanotransduction pathways.

Keywords

Multiscale Modeling; Platelets; Biomechanical; Mechanotransduction; Thrombosis

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We hereby declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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INTRODUCTION

Platelets play a key role in hemostasis that prompts clotting in prosthetic cardiovascular devices and arterial disease processes (Bluestein, Yin et al. 2004; Yin, Alemu et al. 2004). While platelet activation may be induced by biochemical agonists, shear stresses arising from pathological flow patterns enhance the propensity of platelets to activate and initiate coagulation cascade, causing thrombosis (O'Brien and Salmon 1990; Kroll, Hellums et al. 1996; Alemu and Bluestein 2007). The platelets undergo complex biochemical and morphological changes upon activation, aggregate and adhere to blood vessel walls to form thrombi. Several continuum-based simulations to model this complex process treat blood as continuum and solve the Navier-Stokes equations governing viscous flows (Wang and Fogelson 1999). Flow stresses acting on the platelets can be represented down to the order of microns by continuum models. However, processes such as the morphological changes in platelets upon activation happen at the molecular scales. Continuum approaches fail to capture such processes (Yamaguchi, Ishikawa et al. 2010; Bluestein, Soares et al. 2014). Mesoscopic particle-based methods were developed to model blood cells and thrombosis in flowing blood, using dissipative particle dynamics (DPD) for modeling the blood (Fedosov, Pivkin et al. 2008; Fedosov, Dao et al. 2014), blood flows in microvessel (Fedosov, Caswell et al. 2010), interactions of cells (Filipovic, Ravnic et al. 2008) and thrombosis growth (Filipovic, Kojic et al. 2008; Tosenberger, Ataullakhanov et al. 2012). However, complex processes such as platelet activation require drastically different modeling approaches in order to achieve highly-resolved microstructural mechanics and the mechanotransduction process of hemodynamic stresses that may induce platelet activation. Such approaches are needed for more accurately describing the platelets intracellular structure and the mechanotransduction processes of platelet activation by hemodynamic forces.

We have previously employed two platelet models of different coarse graining levels: one is a DPD particle-based model using 444 particles on a triangular mesh for each platelet (Soares, Gao et al. 2013) and the other is a CGMD particle-based model using 73,036 particles where the membrane stiffness was studied (Zhang, Zhang et al. 2014). The DPD model established simulations of platelets suspension through a stenosis and the CGMD model provided fine-grained mapping of hemodynamic stresses on the membrane surface. However, these two models did not include the intracellular constituents with accurate biomechanical properties needed for predicting flow-induced platelet activation. A mechanotransduction process of hemodynamic forces had to be established from the membrane to the complex intracellular constituents, particularly the cytoskeleton that may prompt spontaneous filopodia formation and growth upon flow-induced activation. Extending our previous efforts, the present work fills this gap (Soares, Gao et al. 2013; Pothapragada, Zhang et al. 2015).

Particularly, we construct a particle-based multiscale platelet model that consists of a bilayer membrane, intra-platelet cytoskeleton and gel-like cytoplasm at multiple nano-to-micro length-scales. Through coarsening the structural elements of a platelet, we designed the biomechanical-based model consisting of 140,015 particles and correlated the simulations to published in-vitro experiments for validating the target biomechanical properties for this platelet model.

METHODS

Two particle-based methods of different coarse-grained levels were employed: coarse-graining stochastic dynamics (CGSD) and coarse-grained molecular dynamics (CGMD). The DPD CGSD method (Padding and Briels 2011) describes the top scale of the bulk transport of viscous blood plasma flow (Groot and Warren 1997). The CGMD describes the bottom scale of the platelet intracellular constituents, including the bilayer membrane (Lakes 2001; Chee, Lee et al. 2008), the cytoplasm (Kesmarky, Kenyeres et al. 2008) and a cytoskeleton composed of extensible actin filaments of the pseudopods (Kojima, Ishijima et al. 1994) at the micro to nanoscales. The interface between DPD and CGMD uses an hybrid force field (Zhang, Zhang et al. 2014). At the bottom scales, the membrane employs a reduced molecular dynamics (MD) potential that facilitates deformability in response to mechanical stimuli. The cytoplasm employs a Morse potential (Bluestein, Soares et al. 2014) and the actin filaments are described by an electrostatic-free MD potential. This platelet model embedded in the DPD fluid is used to predict mechanotransduction processes in which mechanical stimuli may activate platelets.

Platelet Model

The platelet's schematic model is depicted in Figure 1. A quiescent platelet is modeled as a discoid shaped spheroid with a 2 μm semi-major axis and 0.5 μm semi-minor axis (Frojmovic and Milton 1982; Michelson 2006). The peripheral zone (depicted by electron micrographs (Hartwig and Desisto 1991)) is modeled as a homogeneous elastic material bilayer (Lakes 2001) constructed by 2D triangulation method (Day, Snyder et al. 1992; Persson and Strang 2004). A shell of 300Å thickness represents the phospholipid bilayer membrane (100Å) and an exterior coat (150~200Å) (Michelson 2006). The membrane is allowed to deform under strain. The organelle zone, represented by the cytoplasm, is composed of homogenous nonbonded particles filling the gap between the membrane and the cytoskeleton. At the fluid-platelet interface, the membrane prevents fluid particles from penetrating while maintaining the flowing platelet flipping dynamics (Zhang, Zhang et al. 2014).

The cytoplasm rheology (Luby-Phelps 2000) and its resultant deformability under stresses (Chee, Lee et al. 2008) was modeled with a viscosity ranging from 4.1~23.9 mPa·s (Bronzino 2000; Chee, Lee et al. 2008) using a Morse potential (Liew and Mikami 2003; Bluestein, Soares et al. 2014). The cytoskeleton consists of two types of actin-based filaments: (a) a rigid filamentous core (Fox 1993) and (b) an assembly of radially spanning elastic actin filaments that mediates the contractility (Hartwig and Desisto 1991; Hartwig 1992; Fox 1993). A carbon-70 structure is used to generate the oval shaped core (Hartwig and Desisto 1991). Each actin filament is individually extensible and is tethered to the core. An α -helical structure mimics the spring-loaded molecular mechanism, with its spiral conformation continuously stretchable under external force (Idiris, Alam et al. 2000). Structural details of the actin filaments are depicted in Figure 1. Table 1 summarizes the key mechanical properties that guided our modeling approach.

We adopt CGMD potential for the elastic membrane and filamentous core, Morse potential for the cytoplasm and the molecular dynamics (MD) force fields for the actin filaments. The mathematical formulations of these forces and potentials follow.

A coarse-grained reduced MD potential (Riniker, Allison et al. 2012):

$$V_{\text{CGMD}}(r) = \sum_{\text{bonds}} k_b (r - r_0)^2 + \sum_{\text{L-J}} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r} \right)^{12} - \left(\frac{\sigma_{ij}}{r} \right)^6 \right] \quad (\text{Eq 1})$$

describes the deformability of the membrane (Lakes 2001) (the first term) and the interaction between membrane and intracellular particles (the second term).

MD potential (Brooks, Bruccoleri et al. 1983; Allen and Tildesley 1989) without an electrostatic term for the actin-based filaments is:

$$V_{\text{MD}}(r) = \sum_{\text{bonds}} k_b (r - r_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{torsion}} k_\phi [1 + \cos(n\phi - \delta)] \quad (\text{Eq 2}) \\ + \sum_{\text{LJ}} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r} \right)^{12} - \left(\frac{\sigma_{ij}}{r} \right)^6 \right]$$

where k_b , k_θ and k_ϕ are force constants for the α -helical structure, r_0 and θ_0 are the equilibrium distance and angle, and n is the symmetry of the rotor and δ is the phase. In the last term, ϵ_{ij} is the well depth of the Lennard Jones (L-J) potential, σ_{ij} is the finite distance and r is the inter-particle distance, θ is angle and ϕ is torsional angle. In (Eq 2), a torsion term is used to induce planarity.

Morse potential (Morse 1929; Liew and Mikami 2003; Bluestein, Soares et al. 2014) is used for the cytoplasm:

$$V_{\text{Morse}}(r) = \epsilon \left[e^{\alpha \left(1 - \frac{r}{R} \right)} - 2e^{\frac{\alpha}{2} \left(1 - \frac{r}{R} \right)} \right] \quad (\text{Eq 3})$$

describing a pairwise non-bonded interactions for viscous flows at coarse-grained scales (Bluestein, Soares et al. 2014). R is the distance of minimum energy ϵ and α is a parameter that measures the curvature of the potential around R where r is the inter-particle distance.

Table 2 describes the scaling of the model and the correspondence of the model parameters to physical units. The characteristic lengths for the cytoplasm, membrane and filaments are 74.7, 33.2 and 15 nm respectively, representing the various coarse-graining levels: coarsest level for the cytoplasm, finest level for the actin-based filaments, and midlevel for the membrane and the fluid-platelet interface.

The numerical models were designed to correlate with published experimental data for the biorheology of the cytoplasm, the elasticity of the membrane, the deformability of the platelets and the stiffness of the actin filaments. Membrane elasticity was previously studied by stretching and by micropipette aspiration experiments (Lakes 2001; Pivkin and Karniadakis 2008; Fedosov, Caswell et al. 2010). We conducted an analogous numerical stretching experiment (Figure 2) in which the axial strain $\varepsilon = \Delta L/L$ was computed. Young's modulus Y_m of the membrane (Haga, Beaudoin et al. 1998) is calculated by

$$Y_m = \frac{S_{ext}}{\Delta L/L} \quad (\text{Eq 4})$$

where S_{ext} is the total stress exerted on the platelet membrane by an axial stretching force (Lu and Huang 2009). Poisson's ratio ν for membrane is:

$$\nu = -\frac{\Delta W/W}{\Delta L/L} \quad (\text{Eq 5})$$

where $\Delta W/W$ is the strain in the perpendicular direction.

A Micropipette aspiration simulation replicated an experiment (Haga, Beaudoin et al. 1998), with inner and outer radii of $r_{in} = 0.18$ and $r_{out} = 0.32 \mu\text{m}$ (Figure 3). The initial distance between the $3.77 \mu\text{m}$ micropipette and the platelet was $0.05 \mu\text{m}$. The shear elastic modulus at equilibrium conditions was calculated by:

$$\mu_s = \frac{r_{in}^2}{2.45} \left(\frac{\Delta P}{L_s} \right) \quad (\text{Eq 6})$$

where ΔP is the change in aspiration pressure, L_s is the equilibrium length of the aspired portion of the platelet pulled into the micropipette. In the simulations, we use the external forces F_{ext} exerted on the platelet pulled into the micropipette to calculate ΔP by

$$\Delta P = \frac{F_{ext}}{\pi r_i^2} \quad (\text{Eq 7})$$

Volume-stretching simulation was performed for studying the platelet deformation, and compared to experimental results (Fig. 1 in (Fedosov, Caswell et al. 2010)). Figure 2(b) depicts the simulation. Stretching forces were applied to 2% of the platelet surface (Suresh, Spatz et al. 2005; Fedosov, Caswell et al. 2010). The axial and transverse diameters of a stress-free platelet are referred to as $D_{A,0}$ and $D_{T,0}$. The applied force magnitude then varied with D_A and D_T functions of the stretching. The simulation considered the combined response of the elastic membrane, cytoplasm and the cytoskeleton.

Stiffness of the actin filaments and their extensibility play a major role in filopodial formation. (Kojima, Ishijima et al. 1994) measured the stiffness of single actin filaments by in-vitro nanomanipulation. In Figure 2(c), actin filament stretching is simulated by anchoring one end of a coil to a rigid substrate while stretching it from the other end. This stretching is very delicate in order to maintain the coil's structural equilibrium. Simulations of six filament sizes varying from 0.1 to 0.8 μm were compared with in-vitro results of actin filaments stiffness.

The flow-induced platelet activation was then simulated with wall-driven counter- Poiseuille flow generating constant shear stress of 45 dyne/cm², using DPD fluid in which embedded platelet are flowing and flipping. The formulation and parameters of the fluid-platelet interfacing follows our previous work (Zhang, Zhang et al. 2014).

RESULTS

In Table 1, we compare the model results for the rheology of cytoplasm, the elastic response of the membrane, the deformation of the platelet and the stiffness of actin filaments, and their correlation to in-vitro experimental results. Based on these verified biomechanical properties, the multiscale model depicts the mechanotransduction process where the flow-induced stresses on a flowing platelet are dynamically mapped on the membrane and propagate down the scales via the cytoplasm to the cytoskeleton.

The cytoplasmic viscosity attained for the model is 4.1 mPa-s (Table 1) - very close to experimental results (Chee, Lee et al. 2008). Elastic response of the model membrane to various stresses (Figure 4) shows that it extends transversely when stress is applied and returns to its original dimensions when removed. Elastic properties of cellular membranes intrinsically vary in health and disease (Haga, Beaudoin et al. 1998; Fedosov, Dao et al. 2014). Our membrane system possesses such certain elastic range. The impact of three different spring force constants on the elastic responses to varying stresses is depicted in Figure 4(a), showing a mostly linear elastic response to the applied stretching. The Poisson's ratio is very close to the expected range (Lakes 2001). These results illustrate that the spring-structured bilayer network could offer a parametric approach with accurate prediction of membrane elasticity analogous to the spectrin network of platelet membranes.

In Figure 5, we compare the simulation and in-vitro micropipette aspiration experiment (Haga, Beaudoin et al. 1998) where a portion of the membrane is aspirated until a new equilibrium state is reached upon re-equalization of the internal and external pressures. The shear elastic modulus of the membrane and the in-vitro data are compared in Table 1, showing a good agreement with published experimental results.

Figure 6 describes the deformability of the entire platelet structure over a range of stresses, as compared to experiments (Suresh, Spatz et al. 2005; Fedosov, Caswell et al. 2010). The platelet model at various membranous stiffness levels responds with different morphological changes in terms of the axial and transversal diameters, as expected. The deformation of platelets with spring constant of 17.1 dyne/cm is the softest one, attaining the closest agreement with in- vitro results measured in erythrocytes (Fedosov, Caswell et al. 2010).

The other two models with spring constants of 22.8 and 28.5 dyne/cm are stiffer, showing stronger resistance to the same tensile stresses. Clearly, thrombocytes are stiffer than erythrocytes. It reaffirms the capability of our model to describe platelet deformability under extracellular axial stresses.

Figure 7 shows the stiffness values of the actin filaments with varied lengths. The α -helical conformation of filaments are stretched with close to linear response and continuous (Figure 7(a)), demonstrating a typical spring-loaded mechanism. There is little impact of resting lengths on the spring mechanics, indicating the reliability of this structure. Figure 7(b) compares the simulation with in-vitro results for filaments with varied lengths under axial strains. The stiffness for 1- μ m-long actin-filaments, reported as 43.7 ± 4.6 pN/nm by an in-vitro nanomanipulation (Kojima, Ishijima et al. 1994) is in good agreement with our model (length 0.1~0.8 μ m, 56.3 ± 1.0 pN/nm)

Figure 8 shows the mapping of dynamic stresses on the membrane, cytoplasm and actin filaments of the flowing and flipping platelet under shear flow of 45 dyne/cm², similar to shear stress levels found in arterioles of ~ 60 dyne/cm² (Popel and Johnson 2005), and an histogram of percentile distribution of the stress magnitudes - its distribution is 56.63 ± 11.20 dyne/cm² (mean value $\pm$ standard deviation (SD)). Most of stress values are in the range of 45~65 dyne/cm².

Comparatively, the cytoplasm experiences a slightly lower stress level of 51.46 dyne/cm², implying that the deformable membrane absorbs part of the extracellular hemodynamic forces. The spread of the stress distribution on cytoplasm has a much larger standard deviation of 34.72, than the membrane's. This is expected, as the cytoplasm is more fluidic than the membrane, thereby affecting the spread of the stress distributions. The distribution of mechanical stresses on the actin filaments is 48.15 ± 11.33 dyne/cm². Clearly, the actin-based filaments structure experiences the smallest average stress level than membrane and cytoplasm. The stress distribution on the actin filaments indicate that mostly the membrane-adjacent apical tips of the filaments that are attached to the membrane base experience higher stresses than the innermost parts.

DISCUSSION

The multiscale model of platelet in flowing blood presented herein is able to describe the mechanotransduction process of hemodynamic stresses in platelets: specifically, the dynamic flow-induced stresses acting on the membrane and propagate via the cytoplasm to the cytoskeleton. Our multiscale platelet model can accurately describe target mechanical properties of the platelet's key constituents including the membrane, cytoplasm and actin filaments. This serves to bridge the gap between the macroscales of hemodynamic stresses to the processes that occur at the molecular scales. This highly-resolved mechanotransduction model is essential for predicting flow-induced platelet activation potential at the micro to nanoscales. We also examined the modulation of the membrane stiffness. The results show a linear relationship between the membrane Young's modulus and the model parameters – covering a range of membrane stiffness. In future studies, this relationship could be efficiently employed to study new therapeutic approaches of

modulating the platelets stiffness to enhance their shear resistance via mechanotransduction pathways.

Morse potential was incorporated for the first time in a multiscale model and employed for describing the cytoplasm. The rheology of the cytoplasm is critical in a mechanotransduction process as it is the medium through which the dynamic stresses from the membrane propagate to the cytoskeleton. Other common approaches such as Lennard-Jones potential is mostly limited to atomic scales, while DPD is too coarse-grained for the precision a platelet model requires at the mesoscales. To address this challenge of the disparity in scales between the L-J and the DPD, the Morse potential was adapted and incorporated in our multiscale approach with a demonstrated ability of reproducing the gel-like intracellular cytoplasm behavior.

Cytoskeletal structure was modeled at the very finest detail in this model. Actin-based filaments were modeled as α -helical conformation whose biophysical functions are described by an electrostatic-free molecular dynamics potential. The filamentous stiffness achieved a good agreement with in-vitro measurements of single filaments. The spring mechanism of α -helical conformation enables extensibility of these filaments, potentiating a spontaneous growth of filamentous bundles upon platelet activation.

Besides its other important functions in mediating the activation process via receptors and ligands on its surface, the membrane serves as a protective barrier to the intracellular organelles and the cytoskeleton from extracellular mechanical stresses. The cytoplasm gel-like substance around the filaments further absorbs and reduces these stresses, while transducing them to the cytoskeleton. It highlights the important role that it plays in platelet response to mechanical extracellular stimuli. In this, a multiscale model that contains the internal structure of a platelet with accurate mechanics is essential for simulating the mechanotransduction process of hemodynamic stresses. Successfully describing these molecular-scale characteristics and microstructure elements in the multiscale model would contribute to bridging the gap between the macroscopic flow scales and the mesoscopic and atomic scales of complex biomolecular systems such as platelets and their activation process.

The mechanotransduction process of extracellular hemodynamic forces in platelets is integral to understanding flow induced platelet activation in platelet-mediated hemostasis and thrombosis. Quantitative mapping of these dynamic stresses on the membrane and the cytoskeleton requires an effective multiscale approach to transduce the mechanical stimuli to the internal constituents. It is evident that simplifying the process by using a completely rigid platelet model, as most such models do, would lead to erroneous estimation of the dynamic stresses acting on the platelet membrane (Zhang, Gao et al. 2014). Our multiscale platelet model continuously changes its morphology in response to the dynamic flow stresses while flowing and flipping. This, in turn, induces microstructural changes within the platelet. With such high resolution level, we observed less stress transduced to the cytoskeletal structure – affirming the damping effect of the elastic membrane combined with the gel-like cytoplasm that protects platelets from extracellular stimuli such as flow-induced stresses. The cytoplasm, which possesses the most fluidic rheology, has the largest spread in

stress levels distribution. In the single cytoskeletal filaments, the stress on the membrane-adjacent apical tips was in most of the cases higher than on the innermost parts. Hence, the mechanotransduction process indicates which parts of the intracellular constituents have the highest likelihood for spontaneous growth of filopodia bundles. This offers predictive capability of the model for describing platelet activation potentials at nanoscale.

Necessarily, not all platelet intracellular structures and mechanisms were incorporated into our multiscale model. That would make the computationally intensive simulations (performed on some of the world's largest high-performance computing clusters (Zhang, Zhang et al. 2015; Zhang, Zhang et al. 2016)) too prohibitive. Among few other intracellular constituents, the microtubular system which serves as the cytoskeletal support system within the cytoplasm and is involved in platelet shape change upon activation was excluded. However, this exclusion is circumvented by the combined interaction of the membrane, cytoplasm and cytoskeleton that are included in the model, which successfully replicates the expected mechanical properties of a platelet.

While the accuracy of our numerical simulations was investigated by studying the emerging mechanical properties of our multiscale model and comparing it with published in- vitro results, there is still scarcity of such experimental information even in the most recent literature on platelets. At extreme conditions such as high shear stresses in cardiovascular devices and in pathological flows fields, highly-resolved experiments were hardly performed. Our group is actively conducting such flow experiments where platelet properties are studied under the relevant flow conditions (Zhang, Zhang et al. 2014; Pothapragada, Zhang et al. 2015), as well as developing non-invasive methods to test the mechanical properties of platelets (Leung, Lu et al. 2015). Additionally, platelet sensitivity to flow stresses and subsequent flow-induced activation greatly increases the difficulty for directly measuring platelets under extreme flow patterns.

In summary, we have developed an accurate multiscale particle-based platelet model. The model integrates MD for describing filamentous extensibility and CGMD for the cytoplasmic viscosity and membranous viscoelasticity at the nano to micro scales with DPD at the micro to macroscales of viscous shear blood flows. The mechanics of the model were investigated by correlating the various model constituents with in-vitro experimental results. The results of our simulations were consistent with the intra-platelet rheology and the target biomechanical properties of platelets. Our multiscale platelet model can be used for simulating complex flow induced platelet activation. It will be further utilized for simulating platelet aggregation, deposition and attachment onto vascular walls and devices for simulating thrombus formation. It can also be employed to study new therapeutic approaches of modulating the platelets stiffness to enhance their shear resistance via mechanotransduction pathways.

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Figure 1:
A schematic of the structure: an intercellular-constituents model of human platelets

(a) Schematic 2-D membrane stretching experiment:

(b) Schematic deformation experiment for testing platelet deformation in response to the axial strain

(c) Single actin filament-stretching experiment. This demonstrated helical structure has 1619 atoms, 1618 bonds, 3033 angles, 4342 dihedrals, 201 improers and 198 cross-terms. Its resting length is 808.76 nm.

Figure 2:

Stretching experiments for (a) the bilayer membrane, (b) a single platelet and (c) an actin filament.

Figure 3:
Schematic of micropipette aspiration experiment simulation to test the shear elastic modulus of the platelet membrane

(a) membrane-stretching response: stress ($\mu\text{N}/\text{m}$) vs. strain ($\Delta L/L$)

(b) Young's modulus of the membrane ($\mu\text{N}/\text{m}$) vs. the spring force constants (dyne/cm)

Figure 4:

Results of membrane-stretching experiment: (a) the elastic response of the membrane for a range of spring force constants and (b) the linear relationship between the membranous Young's modulus vs. the spring force constants

(a) Shear elastic modulus μ_s (dyne/cm) vs. external force F (pN)

(b) Shear elastic modulus normalized by membrane thickness μ_{sn} (dyne/cm²) vs. external force F (pN)

Figure 5:

The responses of the platelet in the micropipette aspiration experiments. The “mean” and “SD” (standard deviation) values of the shear elastic modules for platelets are from Table 1 (Haga, Beaudoin et al. 1998).

Figure 6:

The elastic deformation of the platelet model, in comparison with the in-vitro results (Suresh, Spatz et al. 2005; Fedosov, Caswell et al. 2010). D_A is axial diameter and D_T is the transverse diameter. The platelet-deforming response is presented as the diameter change ratios (y-axis) vs. stretching force in pN (x-axis).

Figure 7:

Actin filament-stretching experiments: (a) the response of individual actin filaments for a range of resting lengths: between 0.1 and 0.8 μm (The legend values indicate the resting lengths of actin filaments in nm). (b) Comparison between the stiffness of actin filaments in our model and the stiffness for 1- μm -long actin filament (reported as 43.7 ± 4.6 pN/nm in this work (Picas, Rico et al. 2012)).

Figure 8:
The flow-induced mechanotransduction process: the dynamic stress distributions on the membrane, cytoplasm and cytoskeletal architecture (actin filaments).

Table 1:

Properties of the intra-platelet constituents and blood plasma system

Properties	Simulation results	Experiment results	Units	References
Platelet conformation				
<i>Diameter</i>	4	2 ~ 5	μm	(Michelson 2006)
<i>Aspect ratio</i>	0.25	0.25		(Frojmovic and Milton 1982)
<i>Thickness</i>	300	250 ~ 300	A	(Michelson 2006)
Plasma				
<i>Mass density</i>	1.060	1.060	g/cm ³	(Chee, Lee et al. 2008)
<i>Viscosity</i>	1.12	1.10 ~ 1.30	mPa·s	(Kesmarky, Kenyeres et al. 2008)
<i>Reynolds' number</i>	0.97	~1.0 ^a		(Ku 1997)
Cytoplasm				
<i>Viscosity</i>	4.1	4.1 ~ 23.9	mPa·s	(Bronzino 2000; Chee, Lee et al. 2008)
<i>Mass Density</i>	1.060	1.060	g/cm ³	(Chee, Lee et al. 2008)
Membrane				
<i>Young's modulus</i>	31.2	18.9 ^b	μN/m	(Fedosov, Caswell et al. 2010)
<i>Poisson's ratio</i>	0.37	0.25 ~ 0.35		(Lakes 2001)
<i>Shear elastic modulus</i>	(3.3 ± 0.9)×10 ⁻²	(2.9 ± 1.4)×10 ⁻²	dyne/cm	(Haga, Beaudoin et al. 1998)
Actin Filaments				
<i>Stiffness</i>	56.3 ± 1.0	43.7 ± 4.6 ^c	pN/nm	(Kojima, Ishijima et al. 1994)

Notes:

^a(Ku 1997) reported that typical Reynolds number in small arterioles is 1.0.^b(Fedosov, Caswell et al. 2010) presented Young's modulus of a red blood cell at 18.9 μN/m. Platelets deformability is less than that of red blood cells.^c(Kojima, Ishijima et al. 1994) measured the stiffness for 1-μm-long actin filaments without tropomyosin.

Table 2:

Reference units used in the simulations; model parameters and translation of various input and output data from dimensionless to real units

Quantity	Symbols	Model values	SI values	SI units
Length	σ_r	1	177.78	nm
Mass	m_r	1	1.99×10^{-18}	kg
Time	t_r	1	4.17	μs
Velocity	$v_r = \sigma_r/t_r$	1	4.27	cm/s
Energy	$\varepsilon_r = m_r \cdot v_r^2$	1	3.61×10^{-21}	$\text{kg m}^2/\text{s}^2$
Force	$f_r = m_r \cdot v_r/t_r = \varepsilon_r/\sigma_r$	1	2.03×10^{-2}	pN
Mean flowrate of the fluid	$v_u = v_u^* v_r$	0.75	3.2	cm/s
Diameter of the platelet	$D_p = D_p^* \cdot \sigma_r$	22.5	4	μm
Shear rate	$\dot{\gamma} = \dot{\gamma}^* \cdot v_r/\sigma_r$	0.017	4000	s^{-1}
Shear stress	$\tau = \tau^* \cdot \varepsilon_r/\sigma_r^3$	6.959	44.76	dyne/cm^2
Viscosity of the plasma ^b	$\mu = \mu^* \cdot \varepsilon_r/(v_r \sigma_r^2)$	417.54	1.119	$\text{mPa}\cdot\text{s}$
Reynolds number ^c	$Re = \rho_f^* v_u^* D_f^* / \mu_f^* = \rho_f v_u D_f / \mu_f$		0.970	

Notes:

(a) k_B is the Boltzmann's constant.

(b) The normal value of plasma viscosity is 1.10~1.30 mPa·s (Kesmarky, Kenyeres et al. 2008).

(c) Typical Reynolds number range of blood flow in the body varies from 1 in small arterioles to approximately 4000 in the largest artery, the aorta (Ku 1997).