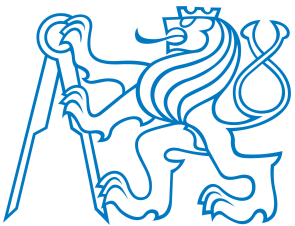
On the Mathematical Model of Delayed Activation of Platelets

Tomáš Bodnár



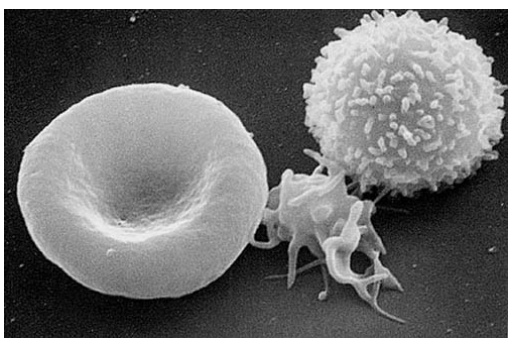
Czech Technical University

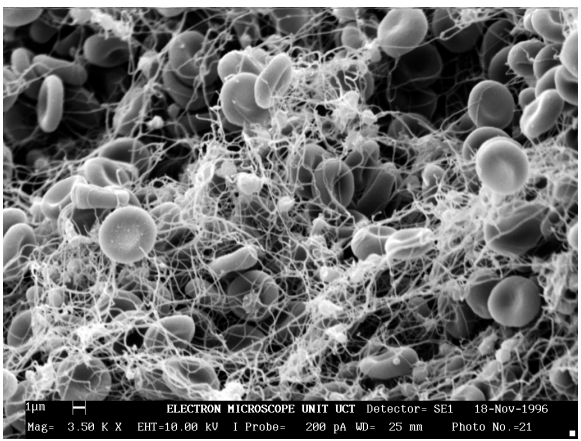
Prague - Czech Republic

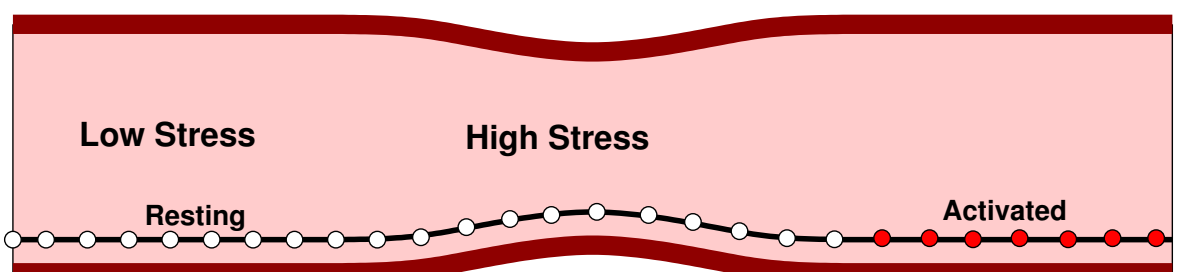
Institute of Thermomechanics

Academy of Sciences of Czech Republic

1. Platelet Activation Models







Empirical/phenomenological models

The most widely used approach defines the ***Blood Damage Index*** $\mathcal{D}$ using an empirical power law relation

$$\mathcal{D} = C\,\tau^{\alpha} t_{exp}^{\beta} \tag{1}$$

where τ is a scalar measure of *stress* and t_{exp} is the *exposure time*. The constants C, α and β have to be determined experimentally depending on type of solvent, blood cells (RBCs or platelets) and other typical flow parameters. For an overview of available model parameters see the summary in *Hund, Antaki, & Massoudi* (2010) and related references therein.

Eulerian models

An Eulerian model that can be considered as a generalization of the above approach was developed in *Yeleswarapu, Antaki, Kameneva, & Rajagopal* (1995):

$$\frac{d\mathcal{D}(t)}{dt} = \dot{\mathcal{D}}_0 + F(\mathcal{D}, \tau) + \hat{F}(\dot{\tau}) \tag{2}$$

where $\dot{\mathcal{D}}_0$ is *constant* activation/damage rate, $F(\mathcal{D}, \tau)$ is the *stress* dependent part and $\hat{F}(\dot{\tau})$ is the *stress rate* dependent contribution.

A little bit similar Eulerian approach to estimate blood damage $\mathcal{D}$ was developed in *Garon & Farinas* (2004). A hyperbolic transport equation

$$\frac{d\mathcal{D}_\ell}{dt} = \frac{\partial \mathcal{D}_\ell}{\partial t} + \boldsymbol{u} \cdot \nabla \mathcal{D}_\ell = \sigma \tag{3}$$

can be written for the ***linear blood damage*** $\mathcal{D}_\ell$ defined as

$$\mathcal{D}_\ell = \mathcal{D}^{1/0.785} = (3.62 \times 10^{-7})^{1/0.785} \tau^{2.416/0.785} t \tag{4}$$

The time derivative of $\mathcal{D}_\ell$ is a constant $\sigma = (3.62 \times 10^{-7})^{1/0.785} \tau^{2.416/0.785}$, which is the source term on the right hand side of transport equation (3). This model, although being formulated for blood damage, can easily be *adapted to platelet activation* modeling by switching the power-law model (1) coefficients C, α, β

Lagrangian models

As an example of Lagrangian model let's mention e.g. the one introduced for blood (erythrocyte) damage in *Grigioni, Daniele, Morbiducci, D'Avenio, Di Benedetto, & Barbaro* (2004) and *Grigioni, Morbiducci, D'Avenio, Di Benedetto, & Del Gaudio* (2005) and extended for platelets activation in *Nobili, Sheriff, Morbiducci, Redaelli, & Bluestein* (2008). It is based on ***Platelet Activation State (PAS)*** associated to kth platelet at time t:

$$\mathcal{PAS}_k(t) = \int_{t_0}^{t} Ca \left[\int_{t_0}^{\psi} \tau(\xi)^{b/a} d\xi + \frac{\mathcal{PAS}_k^{1/a}(t_0)}{C} \right]^{a-1} \tau(\psi)^{b/a} d\psi \qquad (5)$$

Here $\mathcal{PAS}_k(t_0)$ is the value of activation of the platelet at the starting time of observation t_0, $\tau = \tau(t)$ is time-dependent (local, along platelet path) scalar value of stress.

A different approach to quantify platelet exposure to excessive stress leading to its activation in complex flows was described in *Anand & Rajagopal* (2002), *Anand, Rajagopal, & Rajagopal* (2003).
Platelet activation function $\mathcal{A}$ is evaluated as an integral of the stressing history

$$\mathcal{A}(t) = \mathcal{A}(t_0) + \frac{1}{A_0}\int_{t_0}^{t} \exp\left[k\left(\frac{\tau(\xi)}{\tau_c} - 1\right)\right] H(\tau(\xi) - \tau_c)d\xi \tag{6}$$

where $\tau = \tau(t)$ is again a scalar measure of stress with τ_c being the critical value of stress above which the platelets get potentially activated.
The ***Heaviside function*** H is defined as

$$H(\tau - \tau_c) = \begin{cases} 1 \text{ for} & \tau \geq \tau_c \\ 0 \text{ for} & \tau < \tau_c \end{cases} \tag{7}$$

to assure that only supra-critical stresses are taken into consideration, i.e. contributing to platelet activation.

New Eulerian Model

The Langrangian model for activation function $\mathcal{A}(t)$ can be rewritten to more computational friendly Eulerian form for function $\mathcal{A}(\boldsymbol{x}, t)$:

$$\frac{\partial \mathcal{A}}{\partial t} + \boldsymbol{u} \cdot \nabla \mathcal{A} = C_0 \exp\left[k\left(\frac{\tau(\boldsymbol{x}, t)}{\tau_c} - 1\right)\right] H(\tau(\boldsymbol{x}, t) - \tau_c) \tag{8}$$

This transport equation has a source term on the right-hand side, that only contributes to the activation function $\mathcal{A}(\boldsymbol{x}, t)$ when $\tau(\boldsymbol{x}, t) \geq \tau_c$. Otherwise the values of $\mathcal{A}$ are only advected by flow, i.e. remembered without modification.

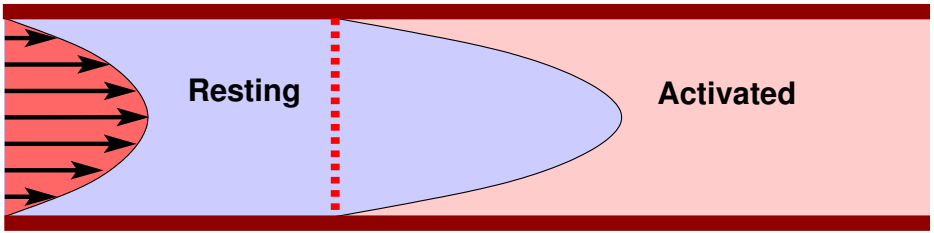
Problem of Delayed Activation

For the delayed activation suggested for Lagrangian formulation suggested in *Anand et al.* (2003) it is assumed that specific platelet does not gets activated immediately (after accumulating sufficient amount of stress), but after a certain time t_{act}. It means that the values of $\mathcal{A}(t - t_{act})$ have to be considered when deciding whether the platelet gets activated.

IF $\mathcal{A}(t - t_{act}) > \mathcal{A}_c$ THEN Activate the Platelet

Immediate Activation

Delayed Activation



Sequential Multistage Activation Algorithm

Step A

Stress accumulation – The general concept of this stage follows the strategy described in model (8). The function $A(\boldsymbol{x}, t)$ is introduced to describe the local (in space and time) amount of excessive stress accumulated by platelet. The values of this function A are governed by a transport equation (9).

$$\frac{\partial A}{\partial t} + \boldsymbol{u} \cdot \nabla A = Q(\tau) H(\tau(\boldsymbol{x}, t) - \tau_c) \tag{9}$$

On the right-hand side of (9) appears a stress dependent source term $Q(\tau)$. It is multiplied by the Heaviside function $H(\tau - \tau_c)$ which ensures that only supra-critical stresses are contributing to platelet activation. Lower, physiologically standard values are not taken under consideration for damage accumulation and have no effect on platelet activation.

Step B

Aging (delaying) – The values of platelet accumulated excessive stress $A(\boldsymbol{x}, t)$ are compared to the threshold value A_c to decide which platelets (fluid parcels) are supposed to start the "aging" process, directly leading to activation. This process can be simulated by the equation (10) for quantity $B(\boldsymbol{x}, t)$, having (in this specific case) the physical meaning of time count (or age) since the platelet accumulated damage has reached its threshold value.

$$\frac{\partial B}{\partial t} + \boldsymbol{u} \cdot \nabla B = H(A(\boldsymbol{x}, t) - A_c) \tag{10}$$

It is easy to see that only where the accumulated stress exceeds its threshold, i.e. for $A \geq A_c$, the platelet delay count starts and $B(\boldsymbol{x}, t)$ grows. Here the growth rate is equal to 1, so the meaning of B is the time since the moment the platelet accumulated stress $A \geq A_c$. Evidently this is easy to generalize, by assuming other than constant (unit) growth rate.

Step C

Activation – The activation process itself is defined here just as a binary switch between activated and resting states of the platelet, that takes a place when (and where) $B \geq B_c$. Thus the activation state function $C(\boldsymbol{x}, t)$, can easily be described by

$$C = H(B(\boldsymbol{x}, t) - B_c) \tag{11}$$

In the case, we are just interested in simple delayed activation and B has really the physical meaning of time as described above, the threshold value B_c represents the activation (delay) time t_{act}. Again, this stage can easily be generalized, e.g. by assuming smooth rather than sudden transition of activation state as well as considering other activation factors (than time count).

Algorithm summary

The model can be summarized as a set (sequence) of coupled equations

$$\frac{\mathrm{D}A}{\mathrm{D}t} = Q(\tau)H(\tau - \tau_c) \qquad \textbf{Accumulation}$$

$$\frac{\mathrm{D}B}{\mathrm{D}t} = H(A - A_c) \qquad \textbf{Aging}$$

$$C = H(B - B_c) \qquad \textbf{Activation}$$

The local activation state $C(\boldsymbol{x}, t)$ is the final product of a sequence of activation indicators based on stressing and delay time count in this case.

Numerical Tests

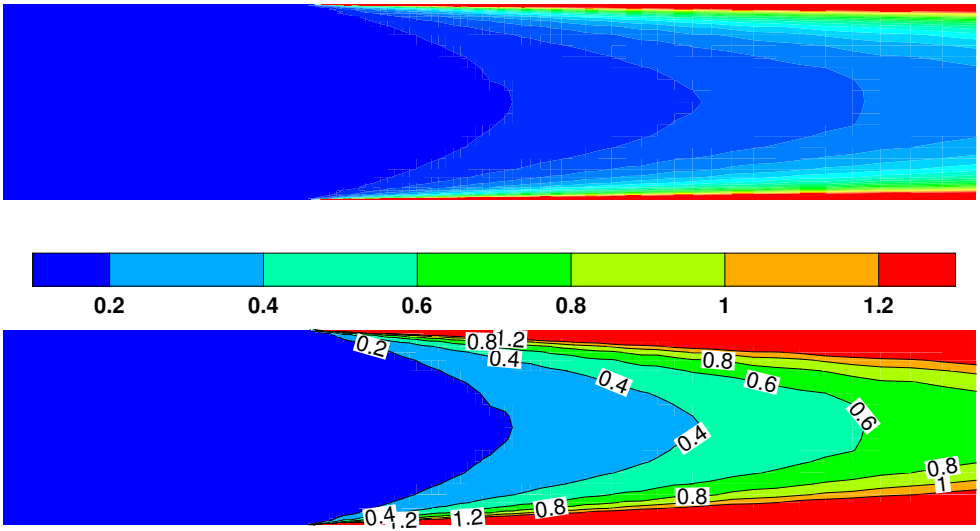
Delay demonstration

Poisseuille flow in a segment of straight blood vessel is considered. The accumulated excessive stress function $A(\boldsymbol{x}, t)$ is not computed, but prescribed as a step-wise function of axial distance. It means $A = 0$ starting from the inlet, while it jumps suddenly to $A = 1$ for $x \geq L$.

Prescribed accumulated excessive stress $A(\boldsymbol{x}, t)$

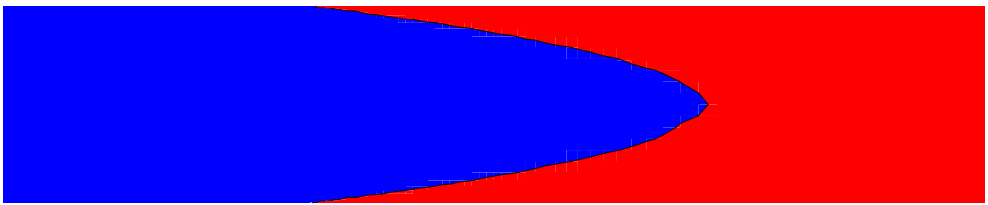
The platelet aging (time count till activation) starts once the distance $x = L$ is crossed. Because of the non-uniform (parabolic) velocity profile, platelet needs to travel certain distance to reach the "activation time" threshold.

This leads to parabolic contour lines of $B(\boldsymbol{x}, t)$.



Computed delay time $B(\boldsymbol{x}, t)$

If, for example the platelet activation delay is set to $t_{act} = 0.4s$, the contours of platelet activation state $C(\boldsymbol{x}, t)$ will have the shape shown in the following figure. The blue color corresponds to resting platelets, while red color is used to mark the region occupied by activated platelets.

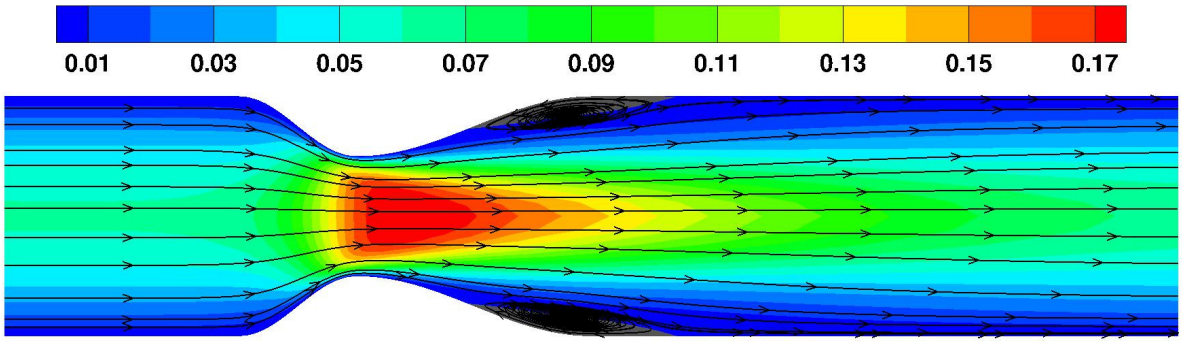


Platelet activation state $C(\boldsymbol{x}, t)$.

Evidently, the immediate activation will result in a straight line interface contour at $x = L$.

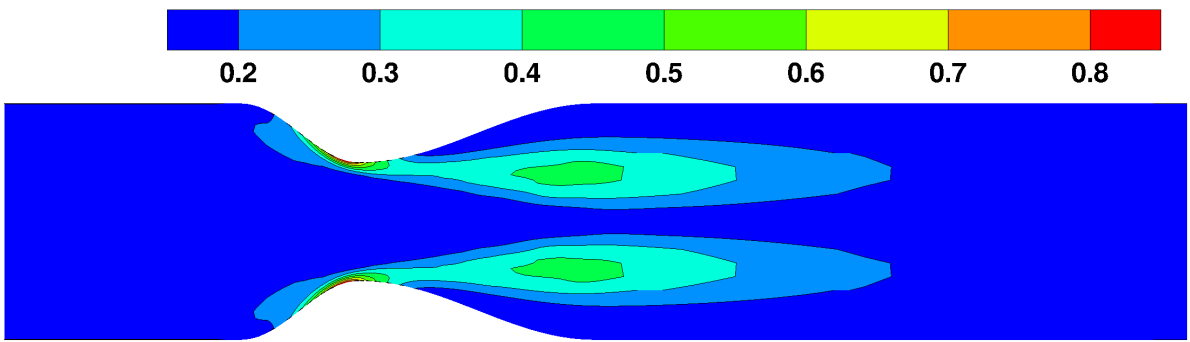
Stress-induced activation test

In this case an axisymmetric stenosis geometry is used to demonstrate the ability of the activation function to react to supra-critical stress levels.



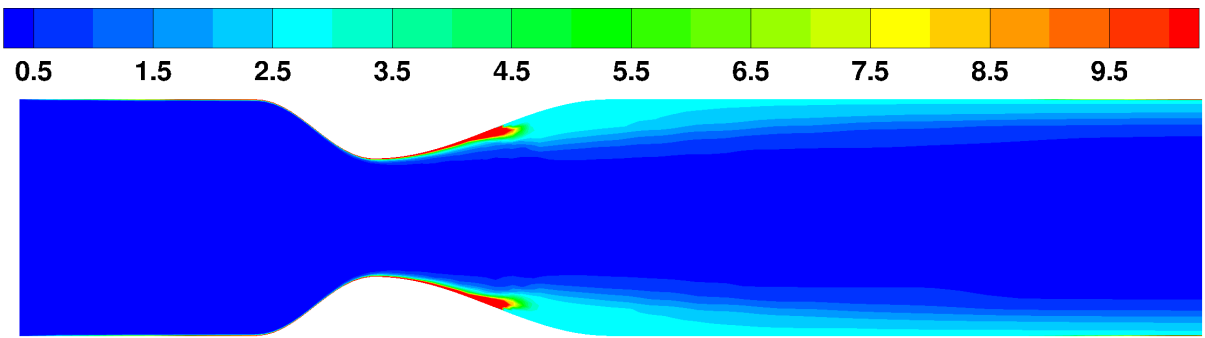
Flow structure in the stenosis (axial cut of the 3D domain).

The large flow separation and recirculation follows the rapid flow acceleration in the stenosed region. This is responsible for the local increase of stress shown in the following figure. The scalar measure of stress was evaluated using the symmetric part of velocity gradient D as $\tau = \mu\sqrt{2D : D}$.



Stress contours in the axial cut.

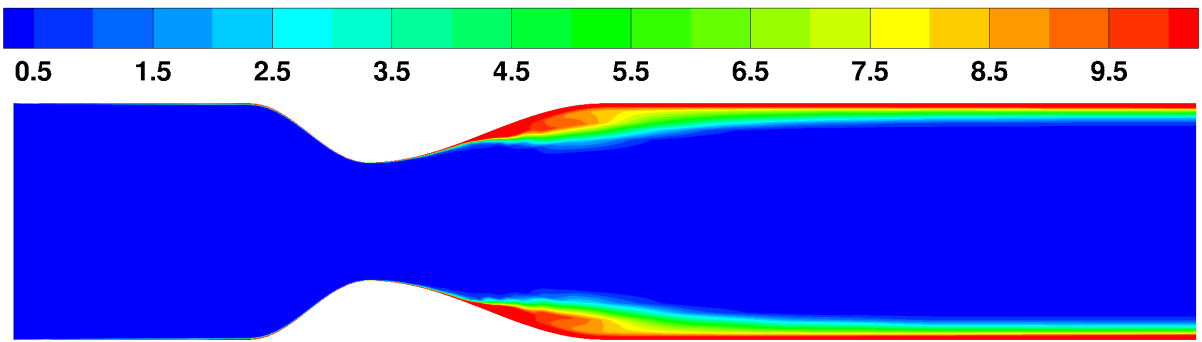
The critical stress level was set to $\tau_c = 0.2Pa$. Above this level, the stress is considered as excessive and contributes to the platelet accumulated stress $A(\boldsymbol{x}, t)$ shown in the following figure



Accumulated stress induced damage function $A(\boldsymbol{x}, t)$.

The highest levels of A can be found in the near wall boundary layer with peak close to the stenosis, at the separation point downstream from the narrowest cross-section of the vessel.

Setting the critical value of A, e.g. to $A_c = 2.0Pa \cdot s$, leads to transition to the next stage of the activation algorithm, to the aging (or delay) phase. The following figure shows the (delay) time of fluid parcels since the moment they accumulated the critical amount of excessive stress A.



Contours of the delay time function $B(\boldsymbol{x}, t)$.

Depending on the value of desired activation time (delay) t_{act}, the regions of resting and activated platelets can easily be determined.

2. Conclusions & Remarks

- The numerical tests presented above have demonstrated the applicability of the newly formulated model in simple situations. Its implementation has turned out to be very simple, especially in comparison to its Lagrangian counterpart.
- Platelet activation depends on many other physical, biochemical and biological interactions. Such processes can be added as additional stages into the above described (purely mechanical) model.
- The multistage approach to the platelet activation can profit from splitting the highly complex process into a sequence of simpler stages, where model parameters can be found easier.
- This newly formulated model can be seen as a prototype of a much wider class of multistage (sequential) models. This model is easy to implement as a straightforward extension of existing CFD codes and underlying mathematical models.

THE END

References

ANAND, M. & RAJAGOPAL, K.: A mathematical model to describe the change in the constitutive character of blood due to platelet activation. *Comptes Rendus - Mecanique*, vol. 330, no. 8: (2002) pp. 557–562.

ANAND, M., RAJAGOPAL, K., & RAJAGOPAL, K.: A model incorporating some of the mechanical and biochemical factors underlying clot formation and dissolution in flowing blood. *Journal of Theoretical Medicine*, vol. 5, no. 3-4: (2003) pp. 183–218.

BODNÁR, T.: On the Eulerian formulation of a stress induced platelet activation function. *Mathematical Biosciences*, vol. 257: (2014) pp. 91–95.

GARON, A. & FARINAS, M.-I.: Fast three-dimensional numerical hemolysis approximation. *Artificial Organs*, vol. 28, no. 11: (2004) pp. 1016–1025.

GRIGIONI, M., DANIELE, C., MORBIDUCCI, U., D'AVENIO, G., DI BENEDETTO, G., & BARBARO, V.: The power-law mathematical model for blood damage prediction: Analytical developments and physical inconsistencies. *Artificial Organs*, vol. 28, no. 5: (2004) pp. 467–475.

GRIGIONI, M., MORBIDUCCI, U., D'AVENIO, G., DI BENEDETTO, G., & DEL GAUDIO, C.: A novel formulation for blood trauma prediction by a modified power-law mathematical model. *Biomechanics and Modeling in Mechanobiology*, vol. 4, no. 4: (2005) pp. 249–260.

HUND, S., ANTAKI, J., & MASSOUDI, M.: On the representation of turbulent stresses for computing blood damage. *International Journal of Engineering Science*, vol. 48, no. 11: (2010) pp. 1325–1331.

NOBILI, M., SHERIFF, J., MORBIDUCCI, U., REDAELLI, A., & BLUESTEIN, D.: Platelet activation due to hemodynamic shear stresses: Damage accumulation model and comparison to in vitro measurements. *ASAIO Journal*, vol. 54, no. 1: (2008) pp. 64–72.

YELESWARAPU, K., ANTAKI, J., KAMENEVA, M., & RAJAGOPAL, K.: A mathematical model for shear-induced hemolysis. *Artificial Organs*, vol. 19, no. 7: (1995) pp. 576–582.