Unfolding the Rolling Stone

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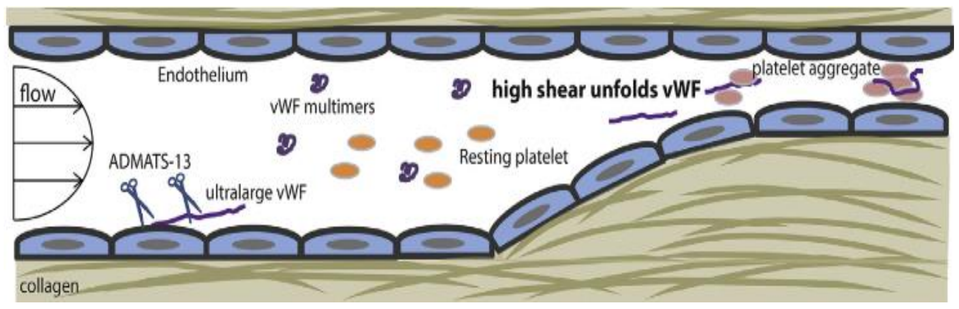
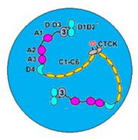
Background

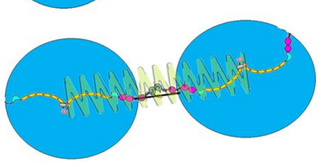
Von Willebrand Factor (vWF), a huge multimeric protein, plays a key role in the formation of arterial thrombus, which can lead to complications with a low rate of survival. Nowadays, thrombus-related complications remain the leading cause of morbidity and mortality in developing countries, but the underlying mechanism of thrombus formation is still unclear. Proposed mechanism is coupled with vWF unfolding in extreme hydrodynamic conditions within vessel stenosis[1,2]. In this study we have used computational models with experimental data to take a closer look at the dynamics of vWF in different flow conditions in order to understand the processes driving the formation of pathological thrombus in stenosis.

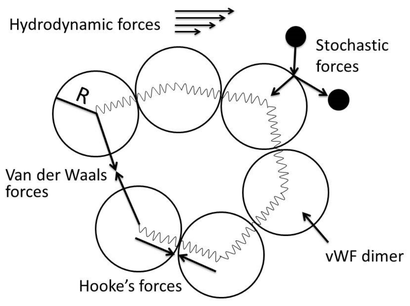


Methods



Schematic representation of our computational model.
VWF multimer is represented by N dimers connected with each other by Hooke's spring. It is believed that physiologically relevant are multimers with[3] N > 20.

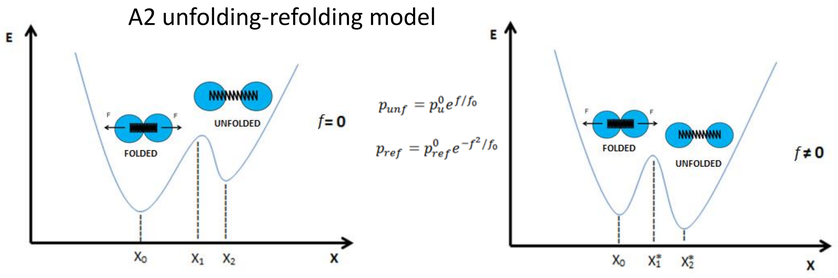




$$\vec{F} = \vec{F}_{hydrodynamic} + \vec{F}_{random} + \vec{F}_{VdW} + \vec{F}_{Hook's}$$

$$\vec{V} = \frac{\vec{F}}{\eta}$$

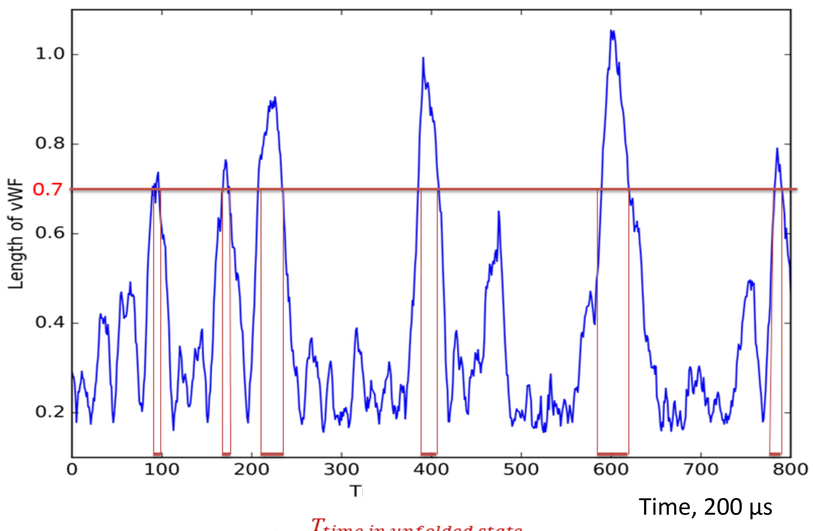
A2 unfolding-refolding model



$$p_{unf} = p_u^0 e^{f/f_0}$$

$$p_{ref} = p_{ref}^0 e^{-f^2/f_0}$$

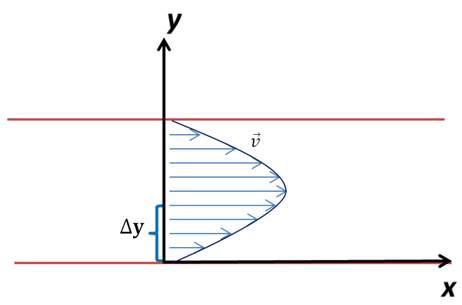
Representation of the multiple stable states in our model. We exploit 2-state model with unfolding probability exponentially increasing with unfolding force and refolding probability decreasing with force. The parameters of the model were inferred from experimental data obtained in[4]



$$unf = \frac{T_{time\ in\ unfolded\ state}}{T_{total\ time}}$$

Aims

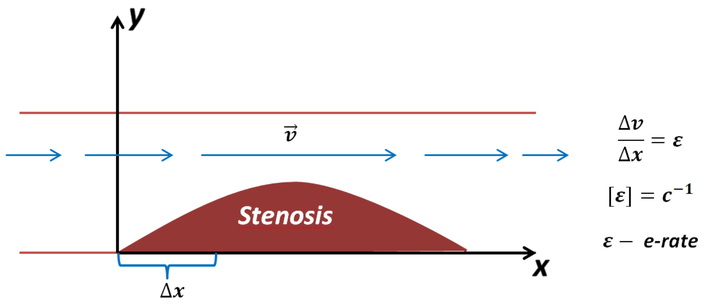
Our basic aim was to figure out whether unfolding of A2 domains of vWF multimers can influence its conformational dynamics in various flow conditions. That is why we were aimed at building and further analysis of a new model of vWF which includes possibility of A2 domain unfolding.



$$\frac{\Delta v}{\Delta y} = \gamma$$

$$[\gamma] = c^{-1}$$

γ – s-rate



$$\frac{\Delta v}{\Delta x} = \varepsilon$$

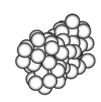
$$[\varepsilon] = c^{-1}$$

ε – e-rate

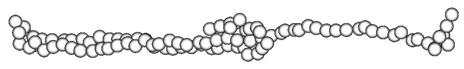
Local blood flow can be described by several parameters: shear rate and elongation rate are the most important of them. Elongational flow is found near stenosed part of the vessel.

Results

In order to compare the new model with classical one we performed massive computations of vWF dynamics under various hydrodynamic conditions for both models. The results of our simulations show that A2 unfolding might influence the conformational dynamics of larger vWF multimers, increasing their unfolding probability under both shear and elongational flows.

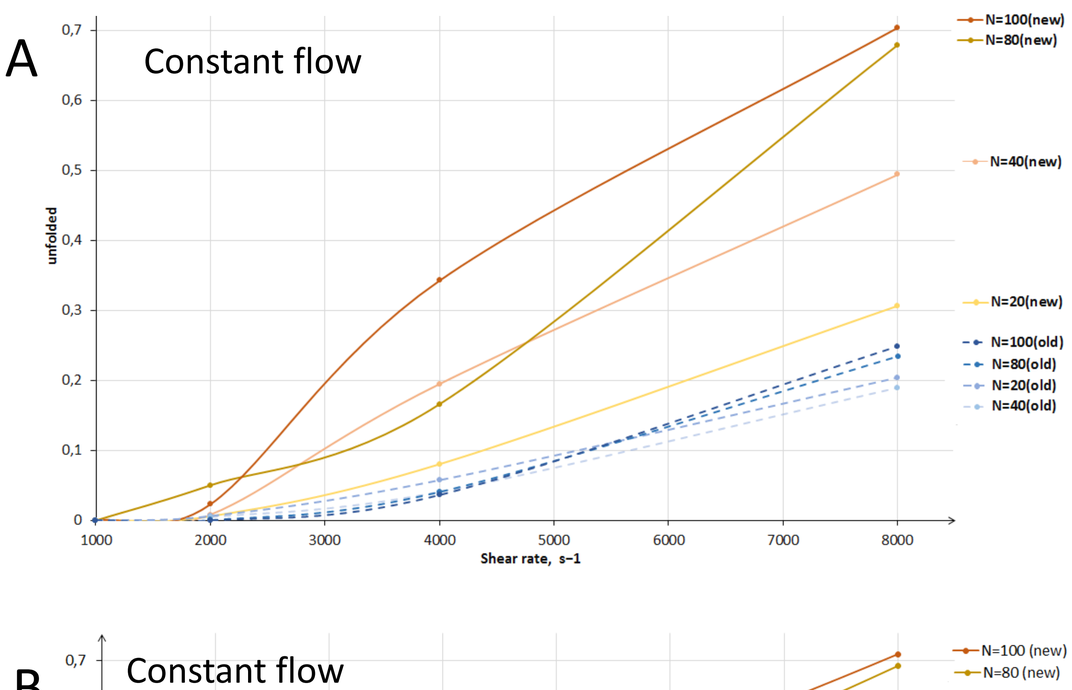


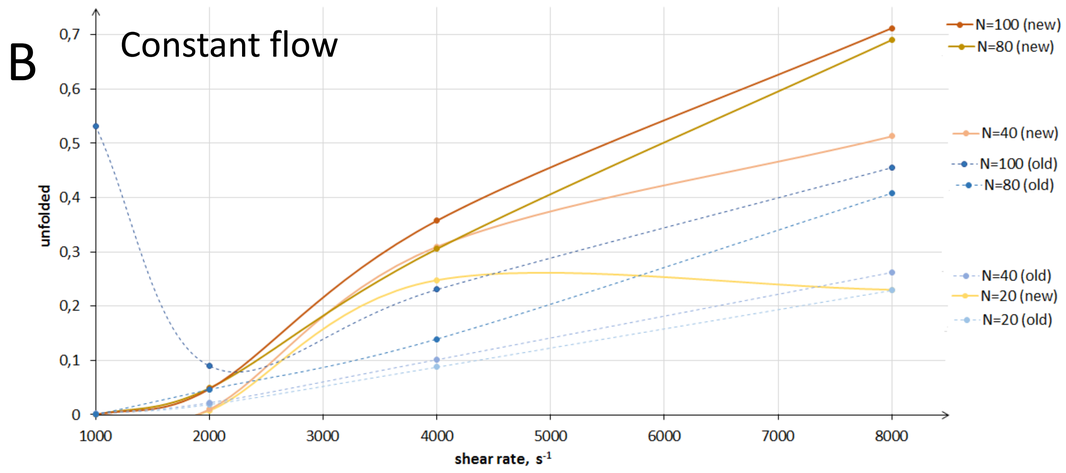
Folded vWF



Partially unfolded vWF

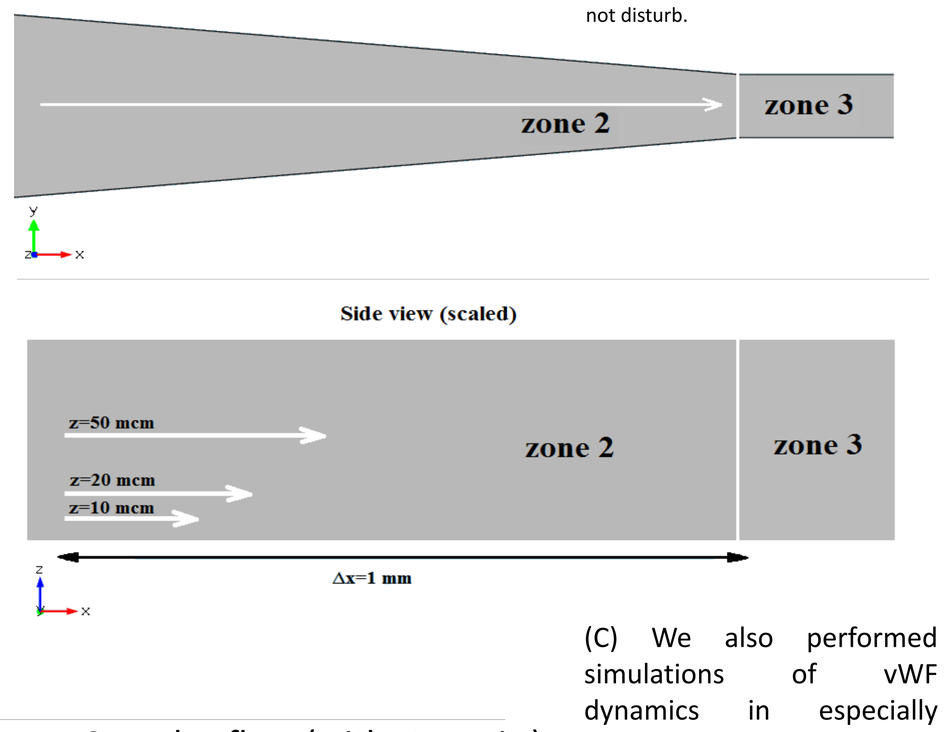
The fraction of time which protein spends in unfolded state *(unf)* is an important value which describes it's average conformational dynamics in given environment.



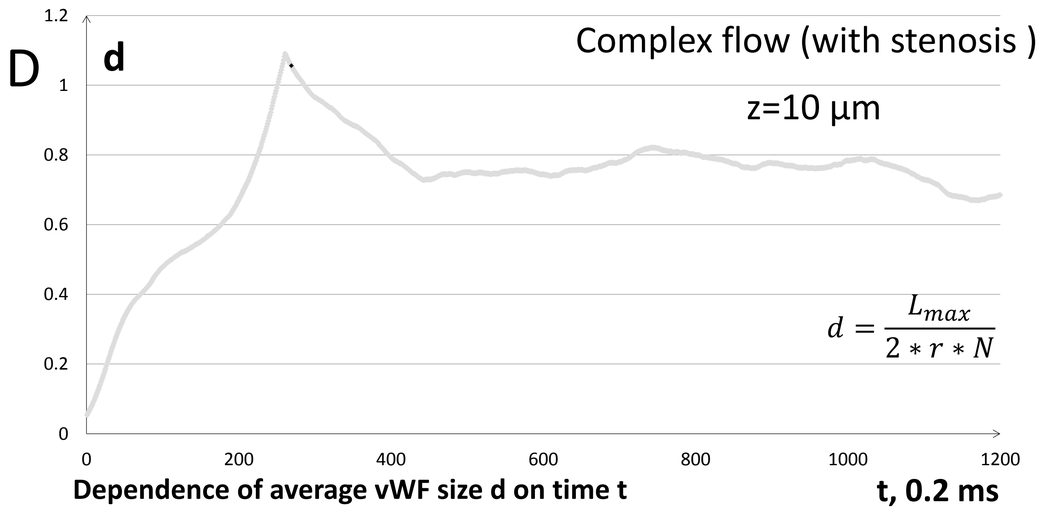


(A) Relation between unfolding rates in the new model (continuous line) and old model (discontinuous line). The unfolding is shown in the y-axis and the shear rate in the x-axis. Higher unfolding values in the new model are caused by A2 domain unfolding. Higher unfolding rates are also observed with increase of the shear rate and the number of dimers in the model with the lack of elongation rate.

(B) Relation between unfolding and an increase of shear rate and constant elongation rate of 50 s^{-1} within the old and the new models. Higher values for unfolding seen in the new model are due to A2 domain unfolding.



(C) We also performed simulations of vWF dynamics in especially designed flow chambers which model stenosis.



(D) Simulations show that vWF has maximum elongation at the entrance to stenosis region, however under given model parameters almost no A2 unfolding took place at this site.

Conclusions

Our results show that A2 domain unfolding of von Willebrand factor can influence the conformational dynamics of vWF multimers under a wide range of hydrodynamic conditions, especially those expected in stenosed arteries.

In order to get insight into interaction of vWF multimers with vessel wall and vWF-vWF interactions we built corresponding models which will be used in further work. The videos showing vWF dynamics can be found on the website using the QR code to the right

References

1)Springer, Timothy A. "von Willebrand factor, Jedi knight of the bloodstream." *Blood* 124, no. 9 (2014): 1412-1425.
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3)Lippok, Svenja, Tobias Obser, Jochen P. Müller, Valentin K. Stierle, Martin Benoit, Ulrich Budde, Reinhard Schneppenheim, and Joachim O. Rädler. "Exponential size distribution of von Willebrand factor." *Biophysical journal* 105, no. 5 (2013): 1208-1216.
4)Zhang, Xiaohui, Kenneth Halvorsen, Cheng-Zhong Zhang, Wesley P. Wong, and Timothy A. Springer. "Mechanoenzymatic cleavage of the ultralarge vascular protein von Willebrand factor." *Science* 324, no. 5932 (2009): 1330-1334.

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