Virtual Blood Vessels : A Practical Modeling Approach to Understanding Coagulopathy

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Introduction

When a blood vessel is damaged, the body responds with a long sequence of reactions called the coagulation cascade. Coagulopathy is the term used to describe a problem occurring with the process of coagulation. Coagulopathy is often seen in emergency rooms as a result of trauma. However, the molecular mechanisms are not clearly understood. In this project we look to create a "virtual blood vessel" that can accurately model the dynamics of a blood vessel in the event of an injury. We use this model to predict the outcomes of in vitro blood flow experiments.

How does coagulation work?

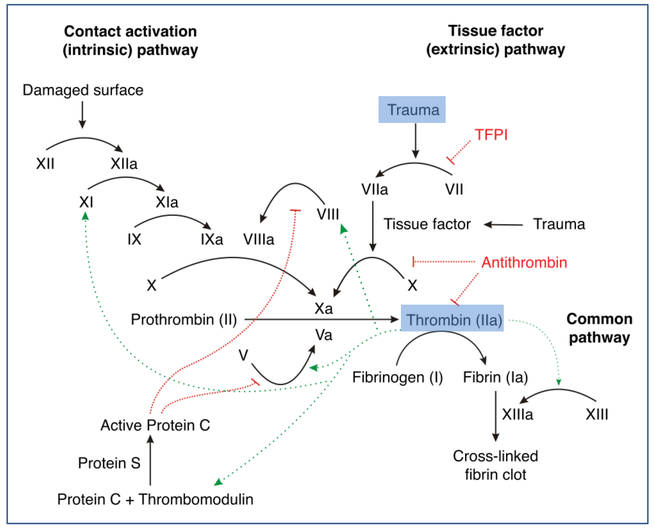
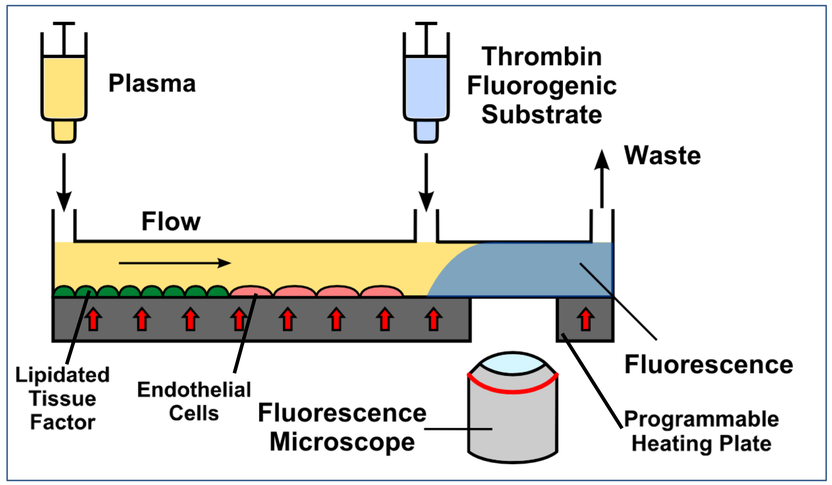


Diagram illustrating the coagulation cascade

When a blood vessel is damaged, the cells in the vessel wall express tissue factor to initiate the cascade. The pro-coagulants in the blood (listed as roman numerals) combine with the tissue factor to produce a protein called thrombin. Thrombin plays a critical role in the clotting process; it converts fibrinogen into fibrin as well as activates platelets to repair the vessel. Therefore, thrombin concentration is a good indicator of the blood's ability to clot. In addition to the pro-coagulants in the blood, anti-coagulants (red text) are present to regulate the clotting activity. These prevent the blood clot from possibly growing too large and disrupting blood flow in the vessel. The delicate balance between these two forces usually allow for healthy blood vessel repair.

Experimental Set-up

Pooled normal plasma is pumped into the 20mm long channel at shear rates ranging from $20s^{-1}$ to $1000s^{-1}$. The channel is 0.1mm high and 1mm wide and contains a patch of lipidated tissue factor, followed by a patch of endothelial cells. This set-up allows the experimentalists to observe thrombin being generated in flow like in a blood vessel. The channel is approximately the same thickness as the intermediate vessels that connect the larger veins and arteries to the much smaller capillaries. A fluorescent substrate is added to detect the thrombin concentration with a fluorescence microscope.

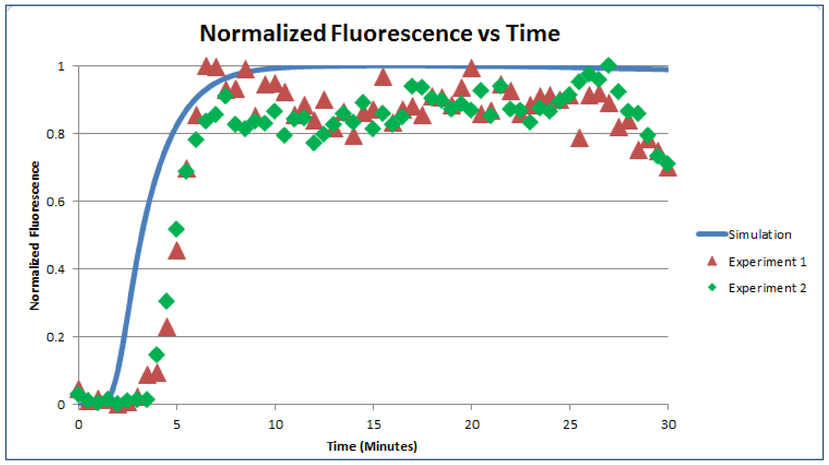


Schematic of microfluidics experiment

Computational Model

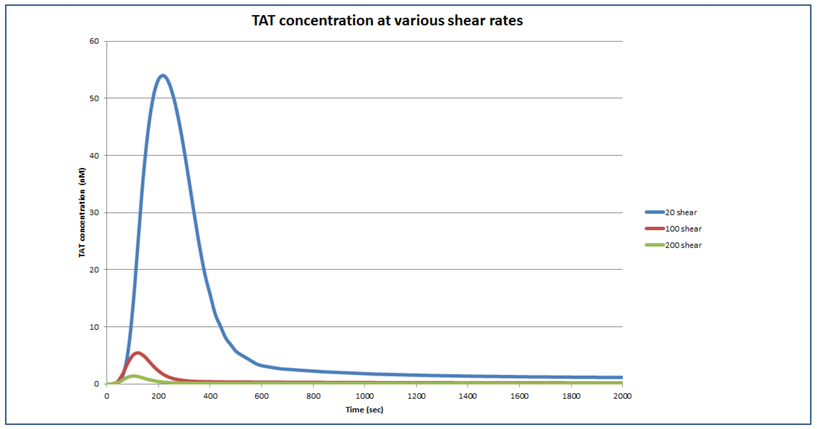
Our chemistry model is based on the ODE model in Brummel et al. 2012[1]. We converted the model to a 2D spatial model in COMSOL[2] by separating the reactions into surface and fluid reactions. Additional reactions and species were necessary to model the dynamics between the surface and fluid species. The convection profile is obtained by solving the 2D Navier-Stokes equation for incompressible, laminar flow first. Then the complete solution is obtained by solving the convection-reaction-diffusion problem for the entire channel.

Model Validation



Validation plot of Simulations vs. Experiments shows a close match between the experimental results and our model

Results



Thrombin generation depends greatly on shear rate

Conclusions

Shear rate is an important factor in the generation of thrombin, particularly when we consider that shear rates in human blood vessels span two orders of magnitude (from very low in large vessels like the aorta and vena cava, to very large in small capillaries).

Future Plans

We are in the process of developing our own PDE code that will be faster and more robust than COMSOL, as well as extendable to a more flexible problem statement.

Acknowledgements

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References

1. Brummel-Ziedins KE, Orfeo T, Callas PW, Gissel M, Mann KG, et al. (2012) The Prothrombotic Phenotypes in Familial Protein C Deficiency Are Differentiated by Computational Modeling of Thrombin Generation. PLoS ONE 7(9): e44378.
2. COMSOL Multiphysics® 4.3a. www.comsol.com.