Image-Based Modeling as Simple Approach to Studying Thrombosis

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The assembly of platelet deposits and fibrin polymerization results in over one million heart attacks and strokes each year in the US. Conversely, deficiencies in these processes result in bleeding risks that confront surgeons on a regular basis. Therefore, a fundamental understanding of thrombosis is desired, since it would advance the current state of medicine via more effective treatments and forecasting methods. However, due to the complicated nature of the problem (hundreds of coupled chemical reactions occuring simultaneously, boundary conditions that are difficult to describe mathematically, small scales that are pushing the limits of experimental technology), investigations of thrombosis have proven to be challenging and the complete mechanism of thrombogenesis remains poorly understood.

Image-based modeling is an emerging multi-disciplinary field that finds numerous applications in many diverse industries ranging from Biomedicine to Enhanced Oil Recovery. By using state-of-the-art imaging techniques in conjunction with high performance computer modeling the image-based approach enables researchers to gain insights into systems that otherwise would have been inaccessible. In the case of studying thrombosis, image-based modeling allows one to bypass the dependence on highly complicated models of thrombus formation. Instead, we use confocal fluorescent microscopy of in-vivo laser injury experiments in mice in order to obtain the 3D thrombus structure. This way the structure is based on actual experimental data, and does not need to be generated mathematically. Once the thrombus structure is obtained, we use simple well-developed simulation methods in order to "reverse engineer" biologically-important results: we perform flow dynamics (Lattice Boltzmann Method) and chemo-transport simulations (Lagrangian Scalar Tracking) in order to calculate local stresses, permeability, fluxes and diffusivities of the key soluble species within the thrombus.

The obtained structural characteristics of the heterogeneous thrombus structure are: specific surface area to platelet volume ratio ~ 17,000 cm-1 and the porosity varies from between 0.3-0.4 in the inner thrombus "core" to 0.7-0.8 at its outer "shell". The average velocity within a 30 micron diameter mouse blood vessel is measured to be approximately 2 mm /sec (Re = 0.08). Due to the heterogeneity of the thrombus structure and because of the constriction that it creates in the blood vessel, it's outer and less porous layers experience higher stress due to fluid shear (~20Pa) and can be observed to be changing structure dynamically in time. The thrombus core, on the other hand, is more rigid and is less prone to deformation due to flow, as it experiences much smaller fluid shear. The latter can be deduced from fluid dynamics simulations that show that convection plays a negligible role within the thrombus porosity. Chemotransport within the thrombus is likewise affected by its heterogeneous structure: platelets in the core of the thrombus become activated and release their contents, which in turn catalyze the coagulation cascade. These chemicals move less freely within the more compact thrombus core and are thus more concentrated in that region.

The outcomes of our work could potentially provide insight towards understanding clot generation, structure and stability relevant to thrombosis, thromboembolism and coagulopathy, ideally to reduce risks of occlusion and embolism.