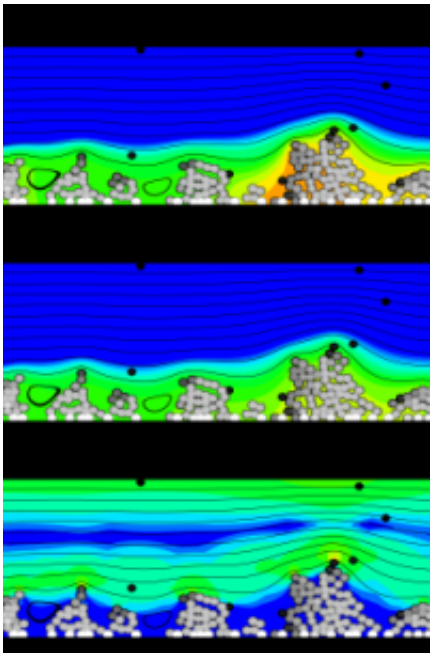
Scientists develop large-scale simulation of human blood

May 1 2012



A visulation of simulated platelets under flow conditions

(Medical Xpress) -- Having a virtual copy of a patient's blood in a computer would be a boon to researchers and doctors. They could examine a simulated heart attack caused by blood clotting in a diseased coronary artery and see if a drug like aspirin would be effective in reducing the size of such a clot.

Now, a team of biomedical engineers and hematologists at the University

of Pennsylvania has made large-scale, patient-specific simulations of blood function under the flow conditions found in blood vessels, using robots to run hundreds of tests on human platelets responding to combinations of activating agents that cause clotting.

Their work was published in the journal *Blood*.

Patient-specific information on how platelets form blood clots can be a vital part of care. Normally, clots prevent bleeding, but they can also cause heart attacks when they form in plaque-laden coronary arteries. Several drugs, including aspirin, are used to reduce the size of such clots and prevent heart attacks, but, as platelets differ from person to person, the efficacy of such drugs differs as well.

“Blood platelets are like computers in that they integrate many signals and make a complex decision of what to do,” said senior author Scott Diamond, professor of chemical and biomolecular engineering in the School of Engineering and Applied Science. “We were interested to learn if we could make enough measurements in the lab to detect the small differences that make each of us unique. It would be impossible to do this with the cells of the liver, heart or brain. But we can easily obtain a tube of blood from each donor and run tests of platelet calcium release.”

When blood platelets are exposed to the conditions of a cut or, in a more dangerous situation, a ruptured atherosclerotic plaque, they respond by elevating their internal calcium, which causes release of two chemicals, thromboxane and ADP. These two activating agents further enhance calcium levels and are the targets of common anti-platelet drugs such as aspirin or clopidogrel, also known as Plavix. By preventing platelets from increasing their calcium levels, these drugs make them less able to stick together and block blood vessels, decreasing the likelihood of a heart attack.

Since blood is a liquid, the liquid-handling robots originally developed for drug screening tests were ideal to test platelet function.

“We used a technique developed in our lab called ‘pairwise agonist scanning’ on platelets from three different donors to generate a massive data set of how their cells responded to all different pairs of these activating agents,” Diamond said. “Then we trained neural network models for each donor based on this data to simulate how each and every cell in a blood clot is responding.”

Neural networks are a way of looking at the relationship between inputs and outputs for very complex processes, rather than at the details of the process.

“They summarize the overall function of all the chemical reaction networks that are occurring within a single platelet,” Diamond said.

Graduate student and lead author Matt Flamm developed a powerful multi-scale computer model that populates a simulation of blood flowing over a site of vessel damage with thousands of platelets whose behaviors derive from the neural network model developed for each patient.

“This is the first time that it has been possible to predict blood clotting under flow using patient-specific platelets,” Flamm said. “We were able to predict the ranked potency of several drugs.”

To show that the computer simulations allowed them to make accurate predictions about an individual donor’s platelet behavior, the researchers performed physical test as well. Using microfluidic devices, they ran scores of blood tests with each blood sample at venous and arterial flow conditions using different drugs.

The multi-scale computer simulation for each donor predicted the drug

responses very accurately.

“We even identified one person who was resistant to aspirin,” Diamond said, “and then discovered a novel genetic mutation in their thromboxane receptor gene. The computer simulation for that donor identified the functional defect before we even sequenced the gene.”

Multi-scale, patient-specific simulation of blood function is an example in the rapidly growing field of systems biology. Multi-scale models require the understanding of the intracellular signaling in thousands of individual cells activating at the site of damaged blood vessel as well as detailed calculations of blood flow and molecular diffusion.

“Fields like weather prediction and airplane design simulate the flow of air,” Diamond said, “In cardiovascular medicine, we encounter the individually unique and complex fluid of human blood. Research areas involving traumatic bleeding, stroke and deep vein thrombosis may benefit advanced simulations of blood function.”

The development of equations and algorithms to model reactive blood flow will be very helpful in predicting clinical risks, drug responses and new disease mechanisms and in designing biomedical devices.

The research was conducted by professors Diamond and Talid Sinno and graduate students Flamm, Tom Colace and Manash Chatterjee of the Chemical and Biomolecular Engineering Department in the School of Engineering and Applied Science. Lawrence F. Brass of Penn’s Perelman School of Medicine Department of Hematology and Oncology also contributed to the research.

More information: *Blood* April 18, 2012 doi: 10.1182/blood-2011-10-388140

Provided by University of Pennsylvania