# Bioengineers create simulator to test blood platelets in virtual heart attacks

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A team of bioengineers from the University of Pennsylvania Institute for Medicine and Engineering have trained a computer neural network model to accurately predict how blood platelets would respond to complex conditions found during a heart attack or stroke.

Using an automated, robotic system, they exposed human blood platelets to hundreds of different combinations of biological stimuli like those experienced during a heart attack. This was done by fingerprinting each platelet sample with 34,000 data points obtained in response to all possible pairs of stimuli.

The team applied the system to predict intracellular calcium signaling responses of human platelets to any combination of up to six different agonists used at different dosages and even applied at different times. The model predicted platelet responses accurately, even distinguishing between 10 blood donors, demonstrating an efficient approach for predicting complex chemical responses in a patient-specific disease milieu.

The strategy involves selecting molecules that react with blood platelets under high-risk situations, such as a heart attack, measuring the cellular responses to all pairwise combinations of stimuli in a high-throughput manner and then training a two-layer, nonlinear, neural network with the measured cellular responses. For platelets, it was discovered that the complexity of integrating numerous signals can be built up from the responses to simpler conditions involving only two stimuli.

"With patient-specific computer models, it is now possible to predict how an individual's platelets would respond to thousands of 'in silico' heart-attack scenarios," said Scott L. Diamond, professor of chemical and biomolecular engineering and the director of the Penn Center for Molecular Discovery. "With this information we can identify patients at risk of thrombosis or improve upon current forms of anti-platelet therapies."

The research team developed its experimental/computational technique, called Pairwise Agonist Scanning, or PAS, to define platelet response to combinations of agonists, chemicals that bind in this case to platelet cells, initiating a cellular response. Future research would include the application of PAS to clinical stimuli that platelets encounter such as epinephrine, serotonin and nitric oxide, which would map a major portion of the entire platelet response. The use of PAS with certain pharmacological agents would allow further assessment of individual clinical risk, or sensitivity to therapy.

Platelet cells respond in a patient-specific manner to multiple signals, and their reaction to thrombotic signals is central to the 1.74 million heart attacks and strokes, 1.115 million angiograms and 0.652 million stent placements in the United States each year. For Diamond, platelets are also ideal cellular systems for quantifying the effects of multiple signaling pathways because they are anucleate, easily obtained from donors and amenable to automated liquid handling. Few experimental or computational tools are available for building a global understanding of how the platelet integrates multiple stimuli present at varying levels.

Researchers working in systems biology seek to understand blood as a reactive biological fluid whose function changes through a variety of physical and chemical stimuli such as hemodynamics, vessel-wall characteristics, platelet metabolism, numerous coagulation factors in plasma and small molecules released during thrombosis.

Because platelet cells respond to numerous signals and chemical doses and integrate their responses to these stimuli, efficient and speedy computational methods are needed to survey such high-dimensional systems. Evaluating the cellular response to merely pairs of stimuli offers a direct and rapid sampling of the cellular response, which can be built up to predict even more complex situations and may eventually lead to a predictive clinical tool for cardiovascular disease.

The study, published in the current issue of *Nature Biotechnology*, was conducted by Diamond and Manash S. Chatterjee of the Department of Chemical and Biomolecular Engineering, Jeremy E. Purvis of the Department of Genomics and Computational Biology and Lawrence F. Brass of the Department of Medicine at Penn.

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