Multiscale prediction of patient-specific clotting function under flow.

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Predicting tissue function based upon an individual's unique cells requires a multiscale Systems Biology approach to understand the coupling of intracellular signaling with spatiotemporal gradients of extracellular biochemicals controlled by convective-diffusive transport. During thrombotic or hemostatic episodes, platelets bind collagen and release ADP and thromboxane-A_2 (TXA_2) to facilitate the recruitment of additional platelets to a growing deposit that distorts the flow field. Calcium dye-loaded platelets in PPACK and indomethacin-treated plasma (thus lacking thrombin and TXA_2) from 3 healthy donors were subjected to Pairwise Agonist Scanning where platelets were exposed to all pairwise combinations of ADP, U46619, and convulxin (at 0, 0.1, 1, 10 x EC_{50}) to activate $P2Y_1$/$P2Y_{12}$, TP, and GPVI receptors, respectively, in the presence or absence of the IP receptor agonist, iloprost. A set of 74 calcium responses allowed training of a neural network (NN) model of platelet calcium mobilization for each donor. Each NN model was then imbedded into a kinetic Monte Carlo/finite element/lattice Boltzmann simulation of platelet deposition under flow. Simulations predicted the measured clot buildup dynamics for each donor for PPACK-treated whole blood flowing over collagen at 200 s^{-1} wall shear rate in the presence of indomethacin, iloprost, or MRS-2917 (a $P2Y_1$ inhibitor). Consistent with measurement and simulation, one donor displayed larger clots than the other two donors, while another donor was distinguished by combined indomethacin-resistance and U46619-insensitivity (allowing the discovery of a novel TP mutation). In silico representations of an individual's platelet phenotype allows prediction of blood function, essential to prioritizing patient-specific cardiovascular risk and drug response or to identify unsuspected gene mutations.