Combining data-driven neural network models of cellular signaling with large scale ODE models of extracellular protease cascades:

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Background: Systems biology models of blood coagulation are classified as bottom-up (mechanistic) or top-down (input-output correlation) models. Many models for coagulation are mechanistic, and are either homogeneous, pseudo-homogeneous, or heterogeneous depending on their treatment of activated platelets. Few models satisfactorily combined platelet signaling during thrombin (Factor IIa, FIIa) production owing to the number of equations required. Realistic bottom-up ODE descriptions of platelet signaling would require ~$\boldsymbol{O}(10^3)$ parameters. For example, recent ODE models of ADP activation of P2Y1 and store operated calcium entry require over 200 parameters. A computationally and experimentally efficient route is to combine a top-down data-driven description (using neural networks) of platelet activation with a mechanistic description (using ODEs) for thrombin production.

Method: Pair-wise agonist scan data of platelet activation can be used to train and validate a neural network that describes platelet response to multiple combinations of agonists. We use this approach to generate a neural network that uses instantaneous agonist concentrations (ADP, CVX, IIa, TxA_2), and calcium concentration history, as inputs and then computes the instantaneous intracellular calcium concentration, $[Ca(t)]_i$, at the next instant. The enzymatic cascade of reactions leading to FIIa production is then modeled using a set of 75 ODEs obtained from a published pseudo-homogeneous model. These ODEs contain a term for active platelets concentration (i.e. extent of phosphatidylserine (PS) expression) that are obtained at each instant from the neural network output of $[Ca(t)]_i$. We integrate $[Ca(t)]_i$ with time: the resultant value, denoted as ξ, must exceed a critical value to initiate PS expression. The extent of PS expression is obtained using a coarse-grained expression obtained by fitting earlier data. The combined neural network-ODE equations are solved using solvers available in MATLAB.

Results: For isotropic clotting of platelet rich plasma, the combined NN-ODE model of platelet activation and triggered clotting displayed a threshold response to the concentration of tissue factor (TF), as well as to the platelet count. Varying [TF], we find that, as expected, the final concentration of activated platelets is less for 1pM TF than for 5pM TF. We also simulate the inhibition of platelet activation through the individual receptors for ADP, TxA2, FIIa, as well as for all three. These tests show that inhibition of ADP-driven platelet activation leads to greatest delay in quantitative thrombin production, whereas inhibition of TxA2 delays it the least. Inhibition of IIa-driven platelet activation leads to the greatest fall in subsequent levels of activated platelets.

Conclusions: The results from combining data-driven neural-network model for platelet activation with a large-scale ODE model are promising. This is a potential tool to match patient-specific platelet data with clotting assay results.