427e Stochastic Modeling of Extrinsic Blood Coagulation Dynamics

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Prediction of blood coagulation may enable blood fingerprinting and development of new drugs to assist with coagulation disorders including stroke and myocardial infarction. To enable this prediction, a kinetic Monte Carlo simulation was developed using the deterministic reaction network developed in the Mann laboratory for tissue factor (TF)-initiated blood coagulation. A stochastic model was chosen for its ability to model the stiff dynamics of the coagulation system where there are many reactions with time scales of reactions and concentrations varying over many orders of magnitude. This stochastic model favorably compares to the dynamics of the deterministic model presented by Mann. The model predicted thrombin dynamics in an experimental assay with 60 μL wells of recalcified whole blood (3-fold diluted) pretreated with convulxin (platelet GPVI activator) and picomolar levels of TF (1 to 14 pM). The model did not accurately predict experimental coagulation times at low concentrations of TF (0 to 0.7 pM) or without convulxin. The simulation revealed that ~0.2 pM TF was the critical concentration to cause a 50 % probability of 3-fold diluted whole blood reaching a clotting threshold of 0.05 U/mL thrombin by 1 hr with some simulations not reaching the threshold below ~0.3 pM and no simulations reaching the threshold below ~0.1 pM. Simulations of 1 nL of blood (5 pM TF) revealed small stochastic variations in thrombin initiation time, while 16.6 pL simulations were highly stochastic at this level of TF (50 molecules/16.6 pL). Further experiment and simulation will require evaluation of mechanisms of coagulation kinetics at sub-picomolar levels of TF.