

Dear Editors:

Please find attached a manuscript entitled “Dynamic Modeling of the Human Coagulation Cascade using Reduced Order Effective Kinetic Models” by Adithya Sagar and myself. This manuscript has been an invited submission to *Processes* for the special issue on Modeling of signal transduction processes.

In this study, we present a novel modeling approach which combines ordinary differential equation (ODE) modeling with logical rules to simulate an archetype biochemical network, the human coagulation cascade. The model consisted of five differential equations augmented with several logical rules describing regulatory connections between model components, and unmodeled interactions in the network. This formulation was more than an order of magnitude smaller than current coagulation models, because many of the mechanistic details of coagulation were encoded as logical rules. We estimated an ensemble of likely model parameters ( $N = 20$ ) from *in vitro* extrinsic coagulation data sets, with and without inhibitors, by minimizing the residual between model simulations and experimental measurements using particle swarm optimization (PSO). Each parameter set in our ensemble corresponded to a unique particle in the PSO. We then validated the model ensemble using thrombin data sets that were not used during training. The ensemble predicted thrombin trajectories for conditions not used for model training, including thrombin generation for normal and hemophilic coagulation in the presence of platelets (a significant unmodeled component). We then used flux analysis to understand how the network operated in a variety of conditions, and global sensitivity analysis to identify which parameters controlled the performance of the network. Taken together, the hybrid approach produced a surprisingly predictive model given its small size, suggesting the proposed framework could also be used to dynamically model other biochemical networks, including intracellular metabolic networks, gene expression programs or potentially even cell free metabolic systems.

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Best regards,

Jeffrey D. Varner