A Quantitative Molecular Signaling Model of Calcium Regulation in a Homeostatic and Activated Platelet

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Platelets are the body's first response to vascular damage; upon injury to the endothelium platelets react to the exposed extracellular matrix and undergo a host of intracellular changes enabling them to activate and form a "plug" at the site of injury. Because of their simplistic nature, such as small size and lack of a nucleus, platelets are readily amenable to study using computational models.

In order to unify the myriad of molecular details of platelet metabolism available in the literature, our lab has developed a multi-compartment computational model of intracellular calcium signaling consisting of a system of ordinary differential equations which accurately reproduces platelet calcium response to the agonist adenosine diphosphate (ADP). However, the model thus far has treated the platelet as a closed system. In order to allow for calcium flux across the plasma membrane we are focused on adding mechanisms for the plasma membrane calcium ATP-ase (PMCA) and store-operated calcium entry (SOCE); both are processes conserved across many cell types. We obtained mechanistic data on these two pathways from the literature. Using both biological intuition and existing knowledge we constructed a search space for the new unknown parameters and species and used an optimization technique previously developed by our to calibrate the model to time course data on platelets in EDTA stimulated with thapsigargin (TG).

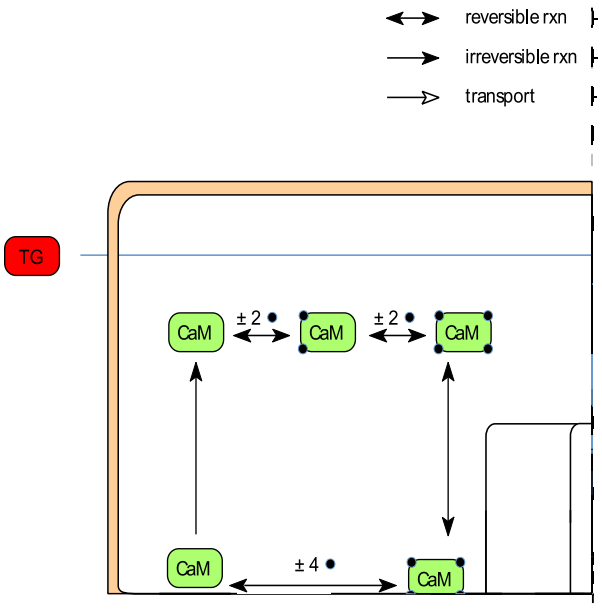

Figure 1. A schematic of the calcium module topology showing all mechanisms in the model responsible for regulating calcium levels in the cytosol and dense tubular system (DTS). This module contains 34 species, 37 reactions, and 70 parameters spanning five compartments.