Title: A Quantitative 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. The signaling cascades involved in the activation process are complex at both the extracellular and intracellular level. But, as has been seen in many biological systems, calcium plays a critical role, frequently being the focal point of a signaling network diagram. A sharp rise in cytosolic calcium triggers a series of chemical and morphological changes which are critical to platelet activation and clot propagation. In order to unify the myriad of molecular details of platelet metabolism available in the literature, our lab has developed a compartmentalized model of intracellular calcium signaling in the human platelet. The model consists of a system of coupled ordinary differential equations1 comprising 84 species, 87 reactions, and 154 rate parameters and spans five well mixed compartments. Calcium balance in the cytosol is determined by the opposing actions of calcium channels and ATPase pumps in the plasma membrane and inner membrane surrounding the platelet's calcium stores. IP3 mediated channels facilitate calcium release from the stores in response to extracellular agonists such as ADP. Store-operated calcium entry (SOCE) channels in the plasma membrane open to allow calcium entry into the cytosol in response to store depletion. A complete understating of SOCE, a ubiquitous calcium entry pathway seen in many cells types, is still lacking. We have synthesized results from the literature to create a model for SOCE regulation consisting of diffusion-limited dimerization of the calcium sensor STIM1, followed by fast, cytosolic calcium-dependent association of STIM1 dimers with trapped Orai channels in the plasma membrane resulting in graded channel activation2.Appropriate resting states were characterized using a dense Monte Carlo technique on an initial condition sampling space constrained by available data on species concentrations and protein copy number. From this set of resting states we then selected for states exhibiting expected dynamic behavior based on responses to physiologic IP3 stimuli. We also selected for states presenting significant SOCE current based on differences in cytosolic calcium between simulations run with and without extracellular calcium. Low resting levels of IP3 are required for system robustness and for appropriate dynamic response to physiologic agonists.

References:

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