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Using mathematical modeling to understanding the role of diacylglycerol (DAG) as a second messenger

Diacylgylcerol (DAG) plays a key role in cellular signaling as a second messenger. In particular, it regulates a variety of cellular processes and the breakdown of the signaling pathway that involves DAG contributes to the development of a variety of diseases, including cancer. We present a mathematical model of the G-protein signaling pathway in RAW 264.7 macrophages downstream of P2Y6 activation by the ubiquitous signaling nucleotide uridine 5'-diphosphate. Our primary goal is to better understand the role of diacylglycerol in the signaling pathway and the underlying biological dynamics that cannot always be easily measured experimentally. The model is based on time-course measurements of P2Y6 surface receptors, inositol trisphosphate, cytosolic calcium, and with a particular focus on differential dynamics of multiple species of diacylglycerol. When using the canonical representation, the model predicted that key interactions were missing from the current pathway structure. Indeed, the model suggested that to accurately depict experimental observations, an additional branch to the signaling pathway was needed, whereby an intracellular pool of diacylglycerol is immediately phosphorylated upon stimulation of an extracellular receptor for uridine 5'-diphosphate and subsequently used to aid replenishment of phosphatidylinositol. As a result of sensitivity analysis of the model parameters, key predictions can be made regarding which of these parameters are the most sensitive to perturbations and are therefore most responsible for output uncertainty.