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An Integrated Approach to Modeling the TCR-Activated MAPK Pathway

Zheng, Y., Harrison, M., Geahlen, R., Balakrishnan, V., Rundell, A.*
Purdue University, West Lafayette, IN, USA

Quantifying the T-cell signaling pathway through mathematical models will impact the understanding and potential treatment design for several immunologically related and malignant diseases. Currently most T-cell signaling pathways have been mapped out in terms of their dominant interactions and key participating elements; however, the quantification of these pathways and their regulation mechanisms remain to be identified. Engagement of plasma membrane-bound T cell receptors (TCRs) by antigen leads to T-cell activation through various signaling pathways including the Ras-MAP kinase pathway. A mathematical model of the T-cell MAPK signaling pathway has been constructed to assist in this quantification and delineation this pathway. This model is a deterministic module composed of nonlinear differential equations to simulate the induced MAPK activation. Intracellular signaling pathways are usually modeled as well-mixed systems despite the fact that signals are often initiated at the plasma membrane and propagate to the cytosol or even nucleus via second messengers. This discrepancy, which can cause an overestimation of the system behaviors, is diminished in our detailed kinetic model for the TCR-activated MAPK pathway by a two-compartment approximation for the subcellular localization of signaling molecules. The model is continuously refined using an integrated approach that combines *in silico* analysis with *in vitro* experimentation. The time-dependent responses of observable signaling intermediates are measured using biochemical techniques and compared to model simulations with reasonable parameter ranges. Initially a large discrepancy was found between the predicted steady-state and observed damped responses. Based on model analysis, hypotheses of possible inhibitory feedback from the MAP kinase, Erk, to Lck was proposed and confirmed experimentally using a MEK inhibitor. Currently additional hypotheses are being explored to improve the fit between the experimental and simulated results. This work demonstrates how model analysis and simulation provide a systematic means to design experiments for distinguishing between hypotheses and refinement of the quantitative model.