Analysis of Regulatory Motifs Dynamics in Cellular Signaling Kinetic Models

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The cell uses complex networks of interacting components in order to process information in response to extracellular and intracellular environmental changes. These networks are made up of genes and proteins interacting in regulatory motifs. Regulatory motifs can be defined as simple patterns of activation and inhibition, such as positive and negative feedback loops. The dynamics of regulatory motifs are commonly modeled and analyzed with differential equations, but the topology of the interactions may not be explicit from the calculations. To create a more intuitive representation of how cellular components interact, we use Petri nets to build dynamic graphs to represent the dynamics of regulatory motifs. We create the interaction network representation of an ODE model, divide it into its topological signaling components and animate it with concentration and flux values in order to construct a dynamic network representation of numerical simulation data. We demonstrate the utility of this method using two established models of cellular regulatory systems: a model of the cell cycle (1) and a model of Ca^{2+}/calmodulin-dependent protein kinase (2). Results with the first model show that the arrangement of cyclin-dependent kinases in feed-forward loops (FFLs) allows for these loops to activate different proteins at different phases of the cell cycle depending on the effect of the regulatory steps of the FFL (+ or -). In the second system, we explore the interaction of multiple signaling pathways to form networks that have properties that individual pathways do not. A dynamic representation of the CaMKII network shows that bistability and sustained CAMKII activity is due to the interaction of the CAMKII pathway with the cAMP pathway and with a positive PKC-MAPK feedback loop within a nested feedforward motif.

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