Numerical simulation of a kinase/phosphatase network for signal transduction in PC12 cells

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Recent genetic, biochemical and structural data has focused the attention on conserved protein modules that regulate signal transduction trough their ability to mediate protein-protein interactions. These conserved modules represent common regulatory features of many distinct signalling pathways which are used to build up complex networks of interacting proteins. Many extracellular polypeptide signaling hormones, such as growth factors, trigger intracellular cascades of phophorylation/dephosphorylation events, mediated by kinases and phosphatases. With the idea of modeling these signaling pathways, we have studied the time evolution of protein networks made of kinases and phosphatases. These protein networks formally resemble attractor neural networks (ANNs), and, like ANN, their steady states can be thought of as encoding the input. Inputs will be recognized as different, if they lead the network into different steady states. Equations for the kinase networks were derived, based on simple enzyme kinetics considerations, and the general properties of the solutions were studied with the tools of qualitative analysis of dynamical systems. A specific network, describing many of the known signal transduction proteins activated by the polypeptide growth factors EGF and NGF in the cell line PC12, was simulated, and the solutions studied by numerical analysis. These cells use a largely overlapping set of signal transduction proteins to respond to the two factors in two opposing ways, proliferation (with EGF) and differentiation and mitotic arrest (with NGF). The results obtained from the simulations were in striking agreement with many experimental data, even with most parameters chosen over a wide interval, showing a great robustness of the property of the network to discriminate between to stimuli. sWith the forthcoming completion of genome sequence projects, and the undertaking of genome-wide protein linkage mapping studies, we believe that the quantitative study of assemblies and networks of proteins will represent a fundamental aspect of their understanding.