Simulations of signal transduction pathways in PC12 cell

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The objective of our work is to formulate a mathematical model of extracellular signal transduction in neuronal cells, based on protein-protein interaction information from existing databases and literature. The first step has been to describe the propagation of a signal through a network of protein kinases and phosphatases activated by EGF and NGF receptors. The network is composed by N proteins each representing one single node; every protein can exist in two states, active or inactive. The edges connecting the nodes are the protein-protein interations, which are always binary, unidirectional and can be either activating or disactivating.
The model is composed by a set of N time first-order differential equations of the type:

$$Dt(x(i)) = SUM(j=1.N)[\ Ka(j,i)*(n(i)-x(i))*x(j) - Kd\ (j,i)*x(i)*x(j)\ ] +\ gen(i) - des(i)*x(i)\ ,\ \ i=1.N$$

where N is the number of different protein species, n(i) is the total concentration of protein species (i), x(i) is the concentration of protein (i) in the active state, (n(i)-x(i)) the concentration of protein (i) in the inactive state, Ka(j,i) the coefficient for activating connections of protein (j) acting on (i), Kd(j,i) the coefficient for disactivating connections of protein (j) acting on (i), gen(i) is the trascription rate and des(i) the destruction rate.
The model can be easily used for direct simulations or for reverse engineering of the network. Direct simulation include the usual receptor induced activation of the signalling network, effects of perturbations such as weakening of single interactions or protein knock-out: for example we could successifully describe the MEK and ERK kinase time pattern of activation, following a ligand binding to the receptors (Fig.1) and suggest how these patterns would change after knocking-out single nodes (Fig.2). Effects of a drug on the pathway can be modelled as a new node in the network interacting with its targets.
Little information is available in the literature about kinetic parameters: estimating quantitatively the kinetic constants describing the interactions is a reverse engineering problem. Given some constraints in the system, usually experimental data such as asymptotic concentrations of one or more protein species, we used the 'simulated annealing' method to estimate the strength of some connections in the network. Simulated annealing is a Monte Carlo approach for minimizing multivariate functions, such as energy lanscapes: in this case we acted on the parameters space to push the system to approach the chosen state. We plan to expand the network to include pathways activated by other neurotrophic receptors, as well as other death and survival pathways.