Direct and reverse simulations of signal transduction pathways in PC12 cell - (session: Other)

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The objective of our work is to formulate a mathematical model of intracellular signal transduction in neuronal cells, in response to extracellular signals, 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 model network composed mainly by intracellualr protein kinases and phosphatases and activated by the binding of extracellular ligands to P75, Trk, EGFR, Fas receptors. The network is composed by N single proteins or protein complexes, each represented by one single node; every node can exist in two states, either active (usually phosphorylated) or inactive (usually dephosphorylated). The links connecting the nodes are the protein-protein interations, which can be unary, binary or multiple, mono or bidirectional. The interactions belong to different typologies: activation/deactivation, binding/unbinding, chemical processing, activation/deactivation of a second interaction, synthesis/degradation.
The model is composed by a set of (2N + Nk) first-order non-linear differential equations in time, in the N variables x(i), concentration of the active form of the protein/complex, the N variables n(i), concentration of the total amount of protein/complex, the Nk variables K(i,j), the kinetic interaction constants which are linear functions of { x(i) , i=1∑N }. Space is neglected in the model equations:

d[x(i)]/dt = Inter_x{x(j),n(j)} ˆ des(i)*x(i) , i=1∑.N
d[x(i)]/dt = Inter_n{x(j),n(j)} + gen(i) ˆ des(i)*n(i)
d[K(i,j)]/dt = Sum[Kint(r,i,j)*x(r)] , r=1∑.N

where (n(i)-x(i)) is the concentration of protein/complex (i) in the inactive state, Ka(j,i) the coefficient for activating connections of protein (j) acting on (i), gen(i) the rate of synthesis, des(i) the rate of degradation.

The form of the expressions Inter_x{x(j),n(j)} and Inter_n{x(j),n(j)} depends upon the types of interaction the node (i) is involved in, for example:

Activation: Inter_x{x(j),n(j)} = Ka(j,i)*(n(i)-x(i))*x(j)
Disactivation: Inter_x{x(j),n(j)} = ˆ Kd(j,i)*x(i)*x(j)
Complex aggregation: Inter_x{x(j),n(j)} = Inter_n{x(j),n(j)} = Kmulplus(i)*[x(k1)*∑*x(knp)]
∑∑∑∑∑∑∑.

The model can be used for direct simulations or for reverse engineering of the network. Direct simulations include the usual receptor induced activation of the signalling network, effects of perturbations such as weakening of single interactions or protein knock-out and determination of the output steady state. Effects of a drug on the pathway can be modelled as a new node in the network interacting with its targets.
Most of the kinetic parameters of the model are not available from the existing data repositories, thus to estimate them we realized a reverse engineering of the network by implementing a Genetic Algorithm (GA) on a parallel computational platform. If the unknown values, here the set of kinetic parameters {K(i,j)}, is considered to be the „genome‰ of the system, the GA exploits the laws of natural selection to generate the „genome‰ able to better fit the given constraints in the system, usually experimental data such as asymptotic concentrations of one or more protein species. Essentially, the GA works by making a large number Ni of „individuals‰ (i.e. replicas of the network), each containing a different „genome‰, „mating‰ in couples once per generation, thus crossing-over and mixing the genomes: the best individuals are selected for the next generation cycle, therefore pushing the sets {K(i,j)} towards values better describing the chosen constraints. Every generation cycle corresponds to performing Ni direct simulations, thus the advantage of the parallelization. The implementation is able to reasonably estimate the unknown parameters (Fig. 1)
We plan to expand the network to include other signalling pathways, genetic interactions and the space component.