Conceptual sensitivity project

Larry Lok

February 6, 2006

The basic idea of the project is to employ a genetic algorithm or other global optimization method to find time-dependent input to a given biochemical model that maximizes the sensitivity of the model response to changes in a given model parameter (usually a reaction rate).

Suppose, for example, that we are working with a Shokat inhibitor of Ste11 whose application by "flowing in and washing out" we wish to use to "bring out" the sensitivity of the the alpha response to the rate r at which Ste7 phosphorylates Fus3. The genetic algorithm would search through many profiles of "flowing in and out" of the inhibitor, examining simulation results generated with r low and simulation results generated with r high. The algorithm would, according its "evolutionary" metaphor, selectively favor those profiles where the simulation results differed greatly between r low and r high.

A genetic algorithm consists of several standard steps:

1. A population of candidates, in this case, a population of input profiles.

2. A fitness measure for candidates; in this case, the least-squares distance between the responses for r low and r high.

3. A way of selecting a favored subpopulation to be retained from one "generation" to the next. Here, one usually just retains some percentage, say, the most-fit 50 percent of the population of candidates.

4. Ways of "mutating" and/or "recombining" less-fit candidates, hopefully producing more-fit candidates.

The initial population of candidates is usually produced by sampling some chosen distribution, and the "mutation" and "recombination" operations are generally stochastic.

The above components are analogous to those needed for optimization by, say, simulated annealing, so that some of this work would not be completely "wedded" to a genetic algorithms approach.

I think of the candidates as "living" in an overall space of possible candidates, and the "mutation" and "recombination" operations as ways of selecting new points in the space. One needs to decide on the nature of this space of possible candidates prior to deciding on the kinds of "mutation" and "recombination" operations. And these operations must effectively explore the chosen space of candidates, in our case, a space of input profiles for the Shokat inhibitor.

One simple choice for the space of possible input profiles is just square-wave "wash-in, wash-out" cycles of Shokat inhibitor (or whatever the "input signal.") We can parameterize this space just by giving the change times, at which the inhibitor goes from low to high or vice versa.

The "mutations" will probably need to include the addition or removal of a transition point. (One could always bisect previously-existing steady intervals with new transition points, for example.) Another might be to reverse the temporal sequence of the transitions. A possible "recombination" would be to combine the lower half of one sequence of transitions with the upper half of another sequence of transitions from the population. It's hard to say how well these or other reasonable-sounding "genetic events" would really explore the space of stimulus sequences, but as noted above, the "genetic" approach is just one of the possibilities.