Notes on ODE parameter optimization

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These are brief notes and questions on some papers about parameter optimization, including the two papers about parameter optimization in *E-Cell* that Koichi circulated.

One of the papers, Moles, Mendes et al. *Parameter estimation in biochemical...* could be construed as a review by experts in the field; at least I take Mendes to be a sort of expert. They set out a variety of alternatives, but in the end they endorse two algorithms of a kind very similar to the genetic algorithm in the *E-Cell* paper.

The Institute seems to be gravitating toward *E-Cell* for simulation, optimization, and other such purposes. This is a natural result of *E-Cell's* present availability to MSI, its presumptive ease of use and integration of many tools, as well as its extensive support structure, both at MSI and in Japan. That experts outside of *E-Cell* approve of related approaches to parameter optimization is therefore reassuring.

1 Kikuchi et al. *Dynamic modeling...*

1. I note that this algorithm optimizes over the S-system class of equations:

$$\frac{dX_i}{dt} = \alpha_i \prod_{j=1}^{n} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n} X_j^{h_{ij}}, \tag{1}$$

   which includes but is not limited to reaction equations.

   - Do we want to be able to express the results of operations such as this in terms of chemical reactions? Not doing so would represent some departure from our previous, reductionistic view of this question.
   - More fundamentally, how do the biologists feel about letting ODE optimization change the equations at all? This feeds into the same general question about machine learning in the Bayesian network context.

     Why would one feel good about rate estimation, but bad about structure selection? Given that rate estimation, in a sense, trumps or includes structure selection?

- We would probably be limited to functions similar to the rhs of Eq. 1 for stimulus functions ("time-dependent input.") Similar to the Fourier analysis situation, we probably would not be able to combine functions of this kind to create more varied "input waveforms."

  On the other hand, general ODE solvers are still at our disposal.

- Perhaps the genetic algorithm can be (or already has been) adapted to operate with chemical reactions only. Perhaps one would even want to restrict to unary and binary reactions; this sort of thing is probably already possible in *E-Cell.* See also notes on the Runarsson and Yao paper below.

2. Do the experimentalists feel comfortable with the number (50) of timeseries that they used in this? What about collecting 50 timeseries by quantitative Western, starting from different initial conditions, as Kikuchi et al. did in simulation?

3. (Personal note.) Are their expressions "Gaussian regularization term" and "Laplace regularization term" just ways of avoiding saying "prior distribution?" I note that the references connected with these expressions are both Bayesian statistical papers.

4. Their approach seems to be a "shooting" approach, by which I mean loosely that ODE solution and parameter search are essentially independent algorithms operating in tandem, rather than a "relaxation" approach, by which I mean loosely an approach in which ODE solution and parameter optimization are an integrated operation. But I have only seen the latter discussed in connection with boundary-value problems.

   Are all modern parameter estimation techniques based on shooting? Recent survey by Mendes (*Gepasi*) and others also points to this being the case.

2 Sugimoto et al. *Distributed...Simulations...E-Cell*

1. Note again "...kinetic parameter estimation...require(s) a large number of repetitive runs with different input parameters," which somewhat implies a shooting paradigm.

3 Kimura et al. *OBIYagns: a grid based...*

1. They use a genetic algorithm (not described in the paper) and shooting, as in Kikuchi et al.

2. This software seems to allow the user to restrict to certain classes of reaction equations. This exposition does not actually seem to say whether

the reaction network itself is optimized, but otherwise, this "menu item" would be meaningless.

3. This article's focus is distributed computing, rather than the simulation algorithm or the optimization algorithm.

4 Moles, Mendes et al. *Parameter estimation in biochemical...*

1. This is an interesting survey and performance comparison of global ODE parameter optimization methods for biochemical simulation, including some similar to the GA methods described in the *E-Cell* paper.

2. Their test system is a 3-stage biochemical pathway, an apparently suitable "test subject" from out point of view.

3. The two methods that "win" their contest are both of the same type, and are both GA's: the uEs ("unconstrained Evolution Strategy") and SRES ("stochastic ranking Evolution Strategy.") of Runarsson and Yao.

5 Runarsson and Yao *Stochastic...Optimization*

1. This paper is primarily concerned with balancing the objective function (to be optimized) with penalty functions designed to enforce constraints (generally, algebraic inequalities and equations) in the parameter domain.

2. To what extent does it pay to consider our reaction rate optimization as a constrained problem? Do we have to? (Rates do have to be positive, after all.)

   Referring back to the "S-system" question above causes me to wonder about treating the constraint of "must be a mass-action equation" in this way. I imagine that constraints of that kind should be built in to the algorithm, rather than treated as additional input to every run.