Sloppiness in Biochemical Modeling and Evolution

Ryan N. Gutenkunst[1], Joshua J. Waterfall[2], Fergal P. Casey[3], Kevin S. Brown[4], Christopher R. Myers[5] and James P. Sethna[6]

***Short Abstract* — The dynamics of biochemical networks typically depend on many parameters (e.g. reaction rate constants). We show that models of such networks exhibit a universal "sloppy" pattern of parameter sensitivities; their dynamics are exponentially more sensitive to changes in some combinations of parameters than others. For model builders this suggests that predictions will be much more efficiently constrained by fitting parameters than by directly measuring them. We also briefly explore the evolutionary consequences of sloppiness, showing that it has little affect on the first step in an adaptive walk, but that it may substantially slow the long-term pace of adaptation.**

***Keywords* — sloppiness, parameter estimation, prediction uncertainty, evolution, geometrical model**

I. Sloppiness and Modeling

Quantitative computational models are powerful tools for building and testing hypotheses about complex biological systems. Dynamic models often involve many numerical parameters, such as reaction rate constants. For many systems of interest, few of these parameters have been directly measured, and fitting them to other data often yields large uncertainties [1]. Nevertheless, we have shown, in a model of growth-factor signaling in PC12 cells, that useful predictions can be made by integrating over even a very large region of parameter uncertainty [2,3].

We attribute this contrast between tightly constrained predictions and very loosely constrained parameters to the PC12 model's *sloppy* pattern of parameter sensitivities; the eigenvalues of the parameter sensitivity matrix span many decades roughly evenly [2]. This implies that the model dynamics are very sensitive to a few "stiff" combinations of parameters and very insensitive to many other "sloppy" combinations. Fluctuations of sloppy combinations yield the large parameter uncertainties often found in fits, but fits can yield tight predictions if they constrain fluctuations of the stiff combinations.

To test the commonality of sloppiness, we recently analyzed a collection of models from the systems biology literature, showing that they all exhibit sloppy parameter sensitivity spectra [4]. We also demonstrated that direct parameter measurements must be very precise to tightly constrain predictions in sloppy systems [4].

Taken together, our results suggest that modelers would be wise focus on prediction uncertainties rather than parameter uncertainties and that collective parameter fitting can be an efficient path to useful predictions.

II. Sloppiness and Evolution

Directly testing real biological systems for sloppiness is difficult; quantitatively perturbing a rate constant is even hard than directly measuring it. The process of evolution, however, tweaks biochemical parameters, and so we seek signatures of sloppiness that might arise in experimental evolution.

A common evolution experiment is to observe the fixation of adaptive mutations in a microbial population and to measure their fitness advantage. Using a variant of Fisher's geometrical model, we show that sloppiness will have little effect on the first few mutations fixed in such an experiment [5], but sloppiness may play an important role over longer periods [6].

While our analysis suggests that sloppiness may leave little signature in evolution experiments, it also shows that a surprisingly large fraction of the fittest mutations should all involve a single biochemical parameter. This fact that may be important for parallel evolution.

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[1]Department of Biological Statistics and Computational Biology, Cornell University. E-mail: rng7@cornell.edu

[2]Department of Molecular Biology and Genetics, Cornell University. E-mail: jjw36@cornell.edu

[3]Conway Institute of Biomolecular and Biomedical Research, University College Dublin. E-mail: fergal.casey@ucd.ie

[4]Department of Physics and Institute for Collaborative Biotechnologies, University of California, Santa Barbara. E-mail: brown@physics.ucsb.edu

[5]Cornell Center for Advanced Computing, Cornell University. E-mail: crm17@cornell.edu

[6]Laboratory of Atomic and Solid State Physics, Cornell University. E-mail: sethna@lassp.cornell.edu

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