Sloppiness, Robustness, and Evolvability

Bryan C. Daniels[1], Yan-Jiun Chen[1], James P. Sethna[1], Ryan N. Gutenkunst[2], and Christopher R. Myers[3]

Cornell University; [1]Laboratory of Atomic and Solid State Physics, [2]Department of Biological Statistics and Computational Biology, [3]Computational Biology Service Unit

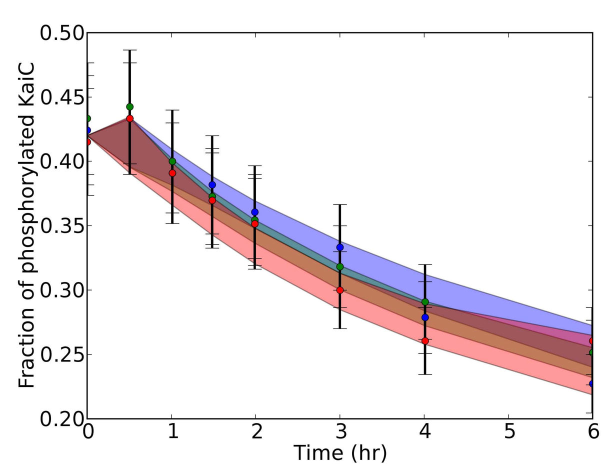
Robustness may be an inherent property of multiparameter systems.

The functioning of many biochemical networks is often robust -- remarkably stable under changes in external conditions and internal reaction parameters. Much recent work on robustness and evolvability has focused on the structure of neutral spaces, in which system behavior remains invariant to mutations. Recently we have shown that the collective behavior of multiparameter models is most often sloppy: insensitive to changes except along a few 'stiff' combinations of parameters, with an enormous sloppy neutral subspace.

Robustness is often assumed to be an emergent evolved property. We present an alternative hypothesis: robustness is linked to sloppiness, a natural feature of multiparameter systems.

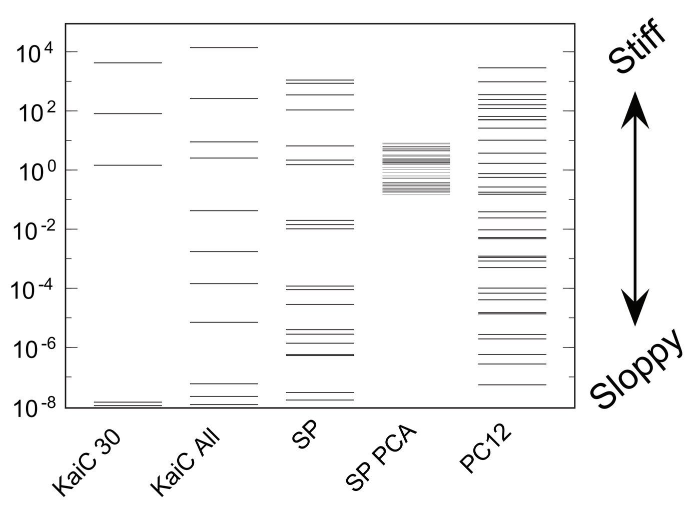
What is sloppiness?

Our group has noticed that multiparameter models tend to be sloppy: there are many *sloppy* directions in parameter space along which the model's parameters can change with very little effect on the output. There are only a few *stiff* directions that appreciably affect the system's behavior.

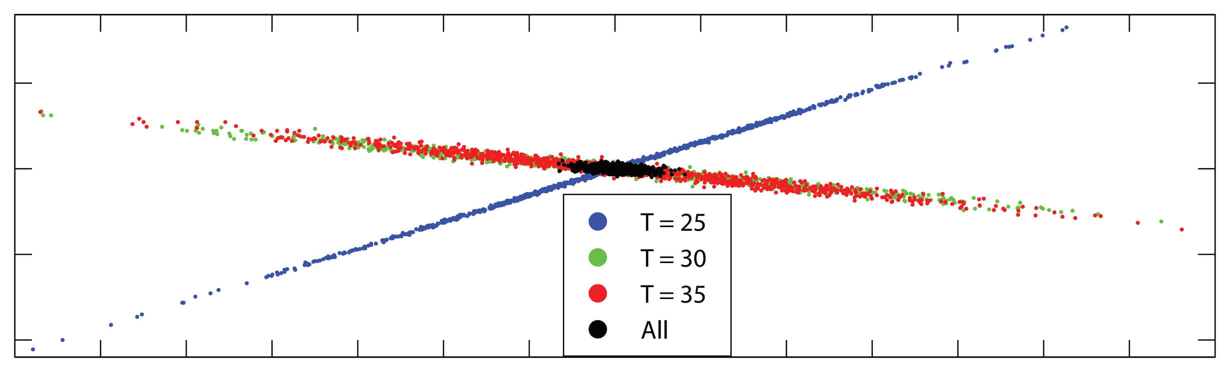


Parameter ensembles can be chosen to fit data within experimental error bars using a least-squares cost.

Sensitivity spectra: Eigenvalues of the quadratic expansion of the cost around the best fit reveal sloppiness. (Can you tell which ensemble is not sloppy?)



Robustness to environmental changes is not difficult if the model is sloppy.

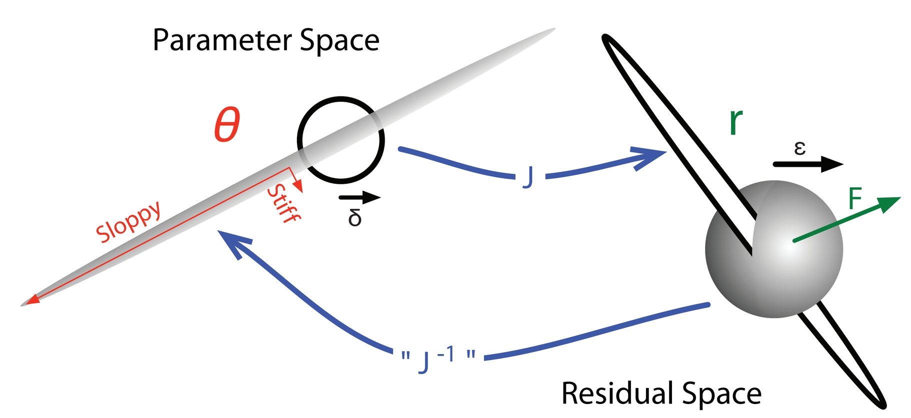


The biochemical network that controls circadian oscillations in cyanobacteria outputs a robust 24 hour period, even when the temperature changes enough to double the rates of individual reactions. Will this require a delicate balancing act?

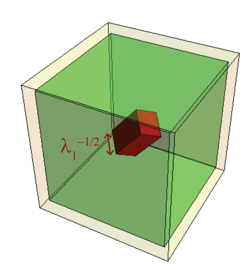
This is a two-dimensional projection of model parameters that fit experimental data. The colored dots represent parameters that work at a single temperature, whereas parameters in the black region work for all three temperatures.

Ensembles only have to fit a few constraints imposed in the stiff directions. The huge ranges in the other directions mean we are likely to always have an intersection that is robust to a given environmental change.

How can we define robustness and evolvability in terms of sloppiness?



Robustness: What fraction of a given volume in parameter space keeps the output reasonably constant?



$$R_c = \prod_{\lambda_n > \lambda_{crit}} \sqrt{\frac{\lambda_{crit}}{\lambda_n}}$$

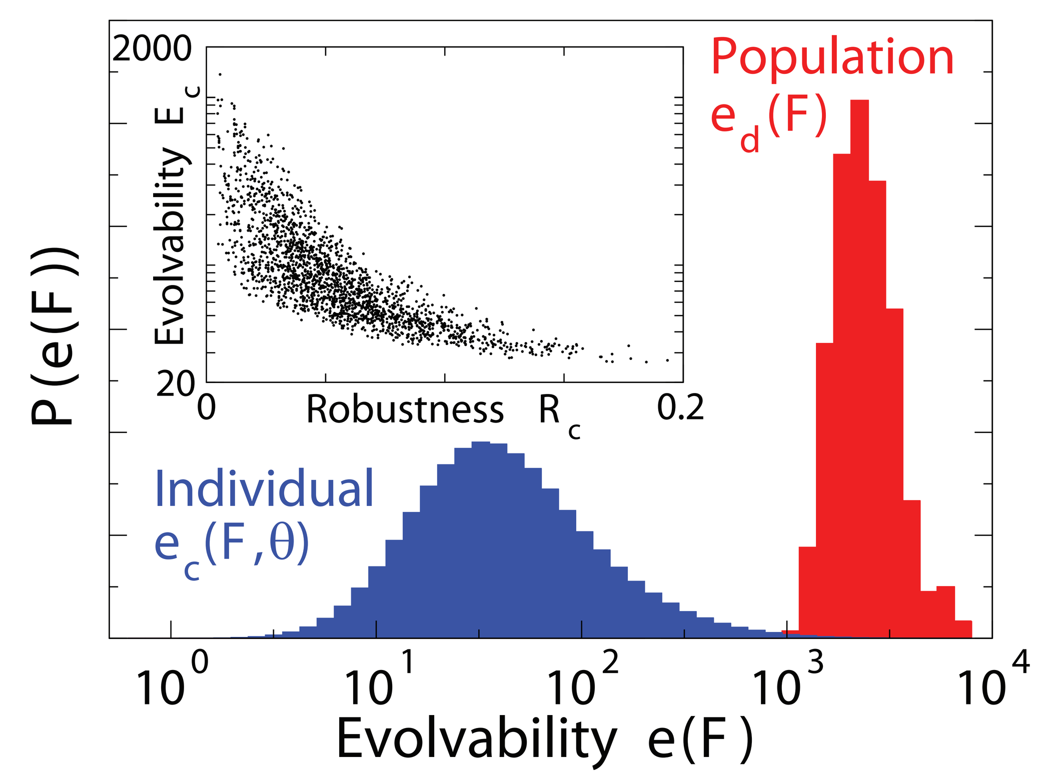
Evolvability: With a pressure to move in a direction **F** in residual (output) space, how far can I move in that direction by varying parameters by a fixed amount?

$$e_c(\mathbf{F}, \boldsymbol{\theta}) = \sqrt{\mathbf{F}^T J J^T \mathbf{F}}\, \delta$$

Evolvable populations can easily change to produce many different types of outputs.

We say that a system is more evolvable if movements in parameter space create larger changes in the output. Isn't evolvability the opposite of robustness?

Yes, for an individual, evolvability and robustness are inversely related (see figure inset). But a population filling a large sloppy ensemble can reach many different types of behaviors (being able to move in different directions in residual space), such that the population can respond favorably to a random evolutionary force much more easily than a typical individual.



Conclusions

- Robustness can be linked to sloppiness, a ubiquitous feature of multiparameter models.
- In the sloppy model we tested, individual robustness and evolvability are inversely related, and population evolvability is typically much larger than individual evolvability.

Learn more

- http://www.lassp.cornell.edu/sethna/Sloppy
- http://arxiv.org/abs/0805.2628 (in press, Current Opinon in Biotechnology)
- Circadian oscillation model: van Zon JS, Lubensky DK, Altena PRH, ten Wolde PR: Proc Natl Acad Sci USA 2007, 104:7420-7425.