Sloppiness in Multiparameter Models

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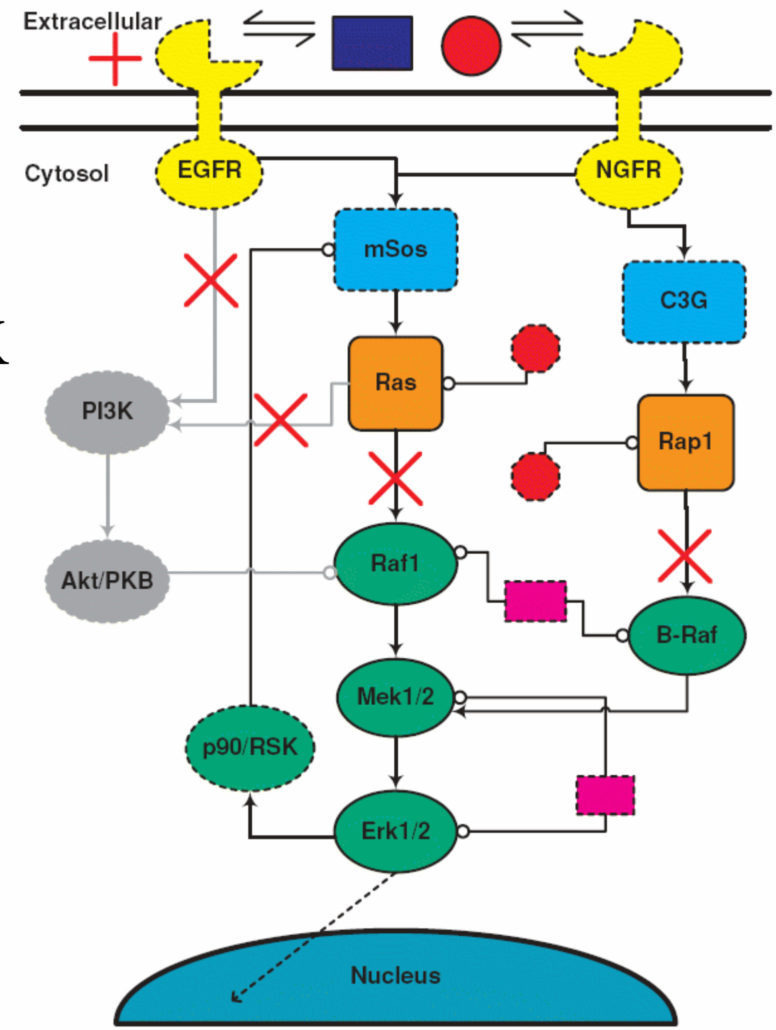
Motivation

› Biological models have lots of parameters, and they control the output in complex ways.

› It's often hard to measure these parameters.

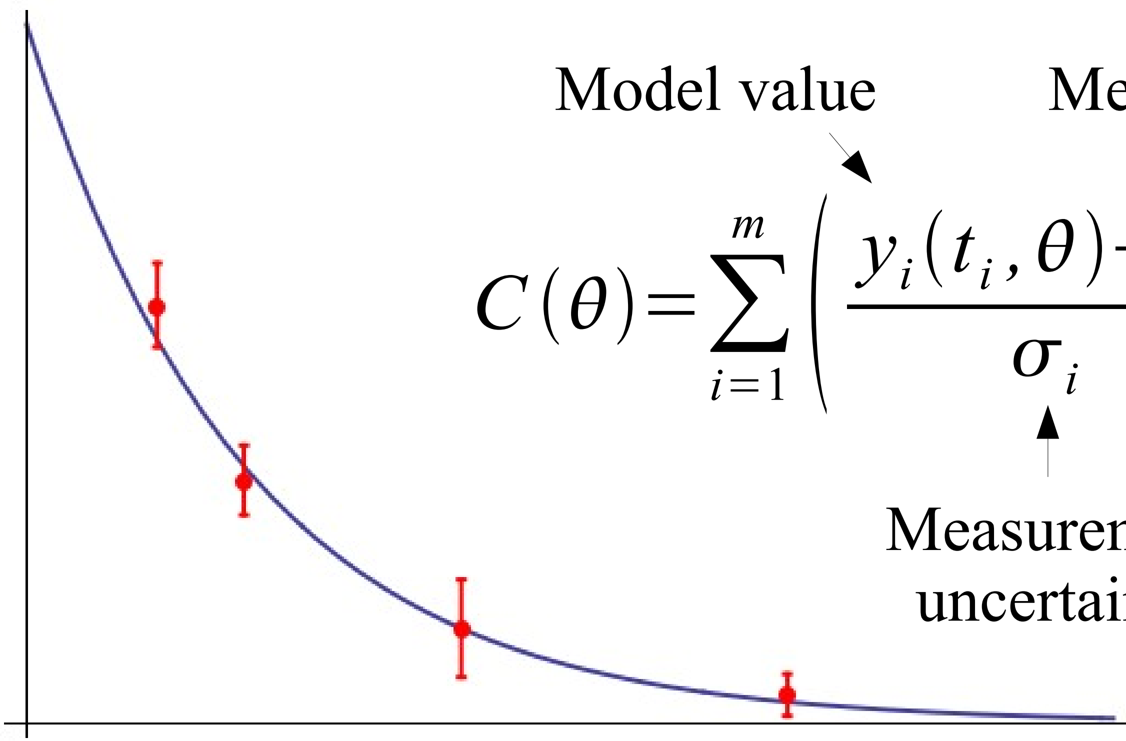
› How does this affect model predictions? What predictions can we trust?



Brown et al., Phys. Biol. 1: 184-195

Cost Landscape

- A set of parameters θ has a cost based on how well the model fits measured data.
- We usually use a squared residuals cost.



Model value

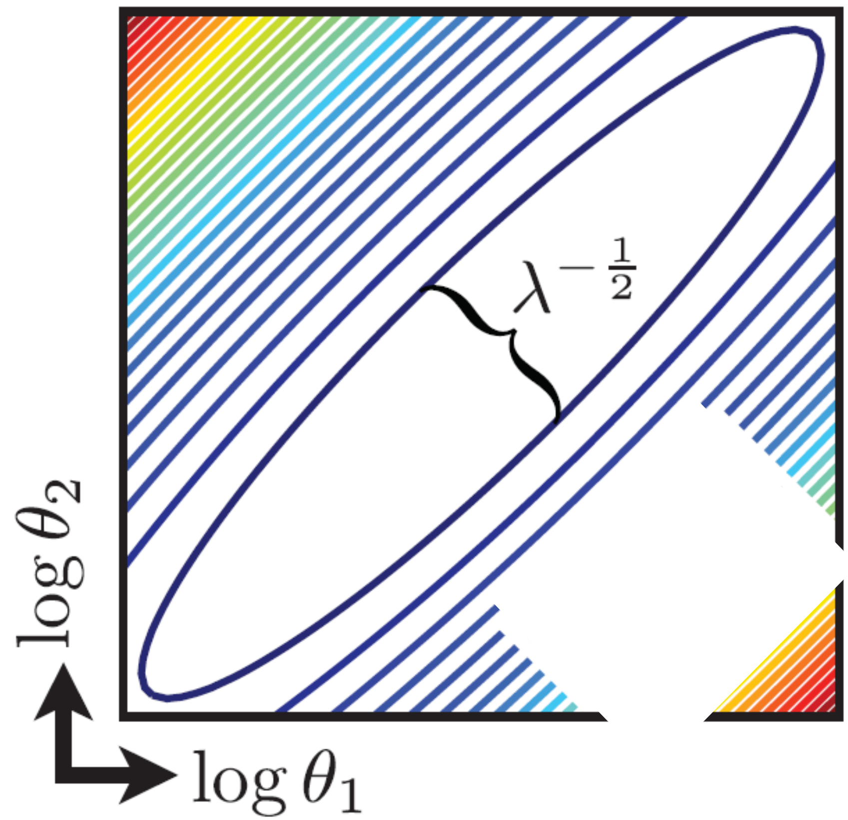
Measured value

$$C(\theta)=\sum_{i=1}^{m}\left(\frac{y_i(t_i,\theta)-d_i}{\sigma_i}\right)^2$$

Measurement uncertainty

Cost Landscape

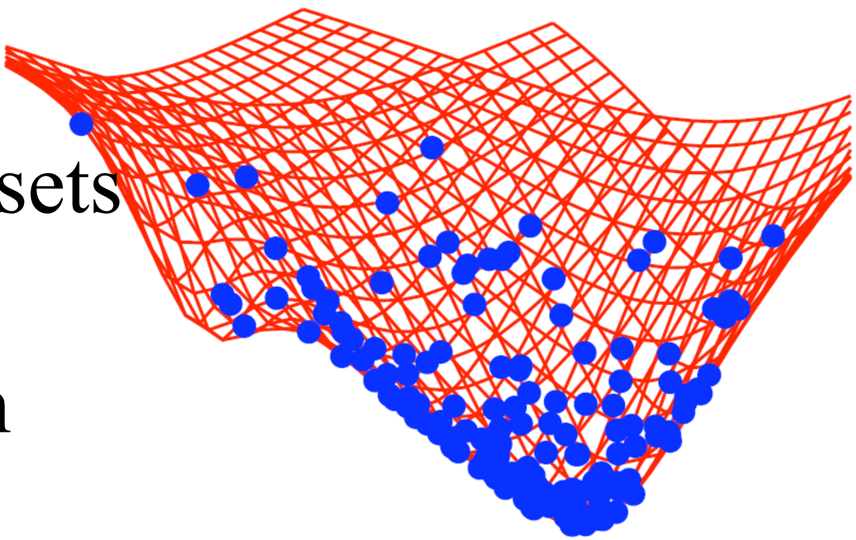
- Locally around the best-fit point we can approximate the cost as quadratic.
- The matrix of 2nd derivatives (Hessian) gives us the quadratic expansion.



Gutenkunst et al., PLoS Comput Biol 3(10): e189 (2007)

Making Sensible Error Bars

- Most thorough method: Bayesian analysis using Monte Carlo sampling
  1. Sample from all parameter sets that fit the data;
  2. Find prediction output from each;
  3. Calculate mean, standard deviation, etc.

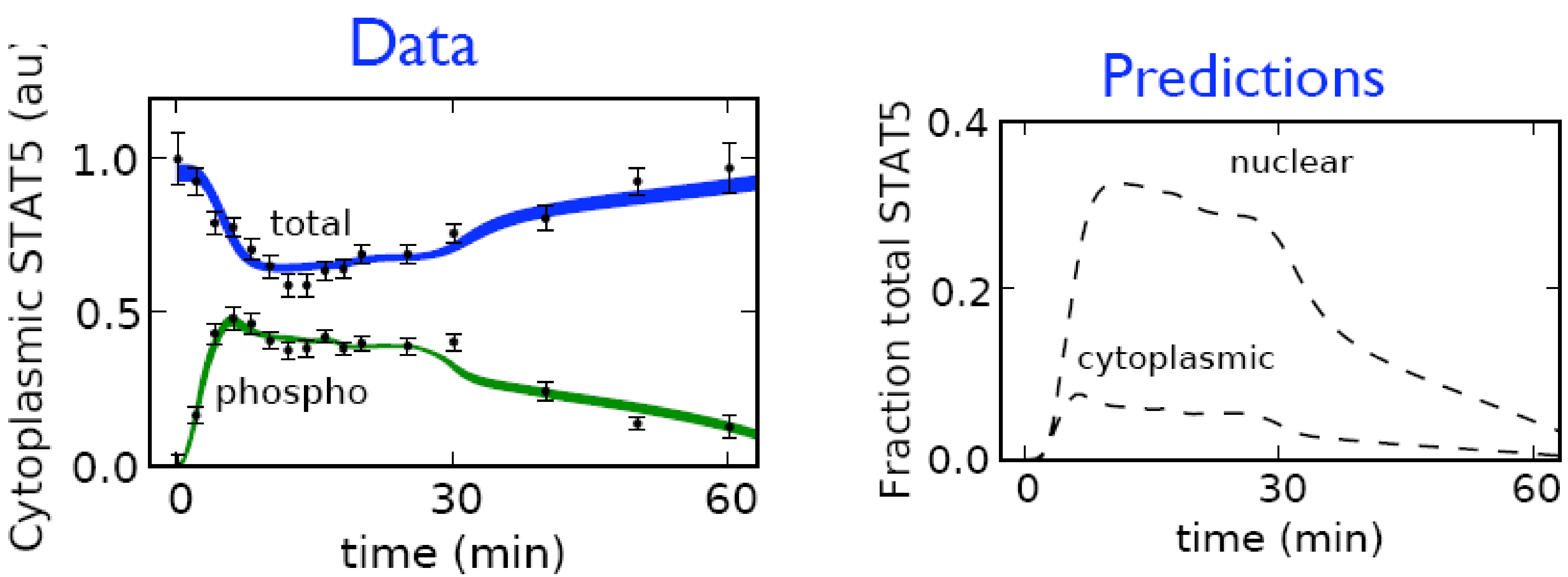


“Stat mech in model space”

Figure courtesy Ryan Gutenkunst

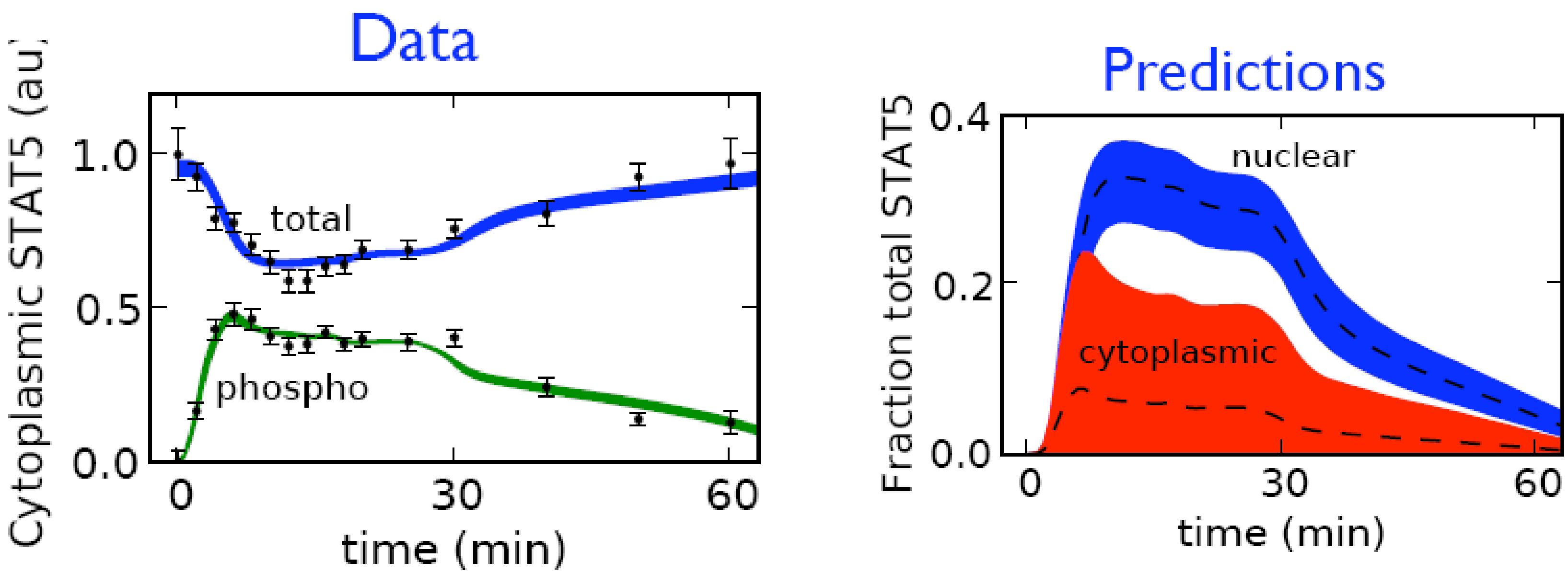
- Example: Brown et al., Phys. Biol. 1: 184-195

Making Sensible Error Bars



Figures courtesy Ryan Gutenkunst

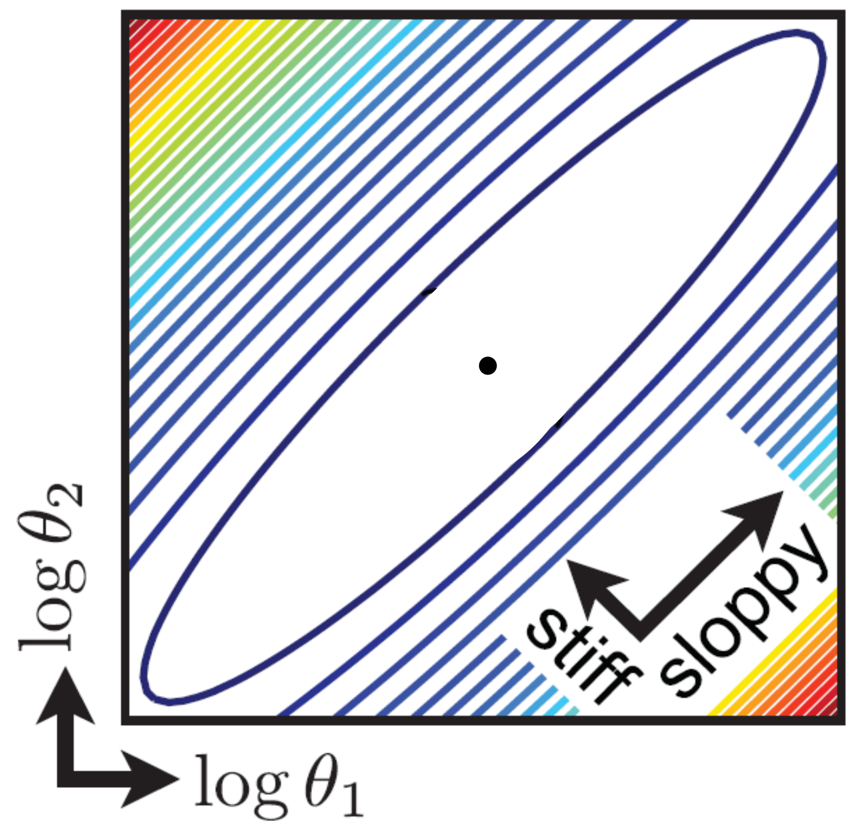
Making Sensible Error Bars



Figures courtesy Ryan Gutenkunst

“Sloppiness”

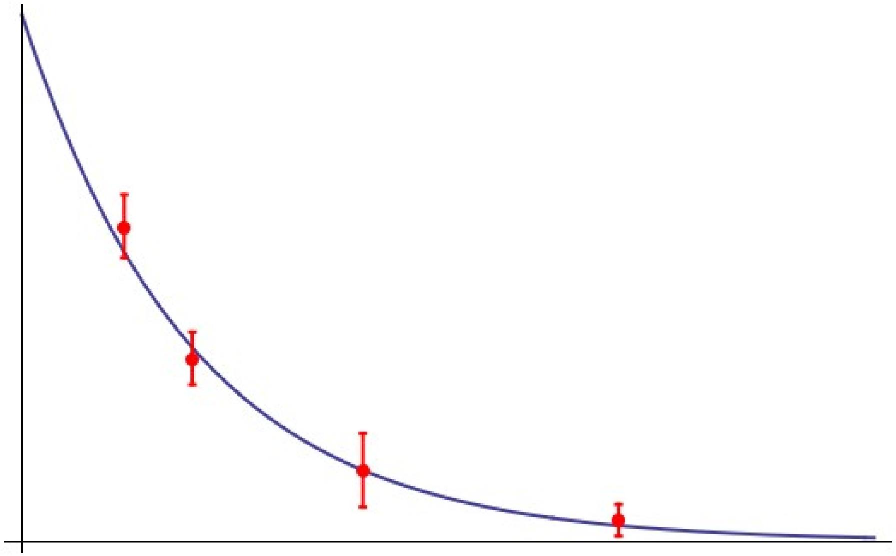
- Nonlinear multiparameter models are “sloppy”: orders of magnitude more sensitive to changes in certain directions in parameter space.



Gutenkunst et al., PLoS Comput Biol 3(10): e189

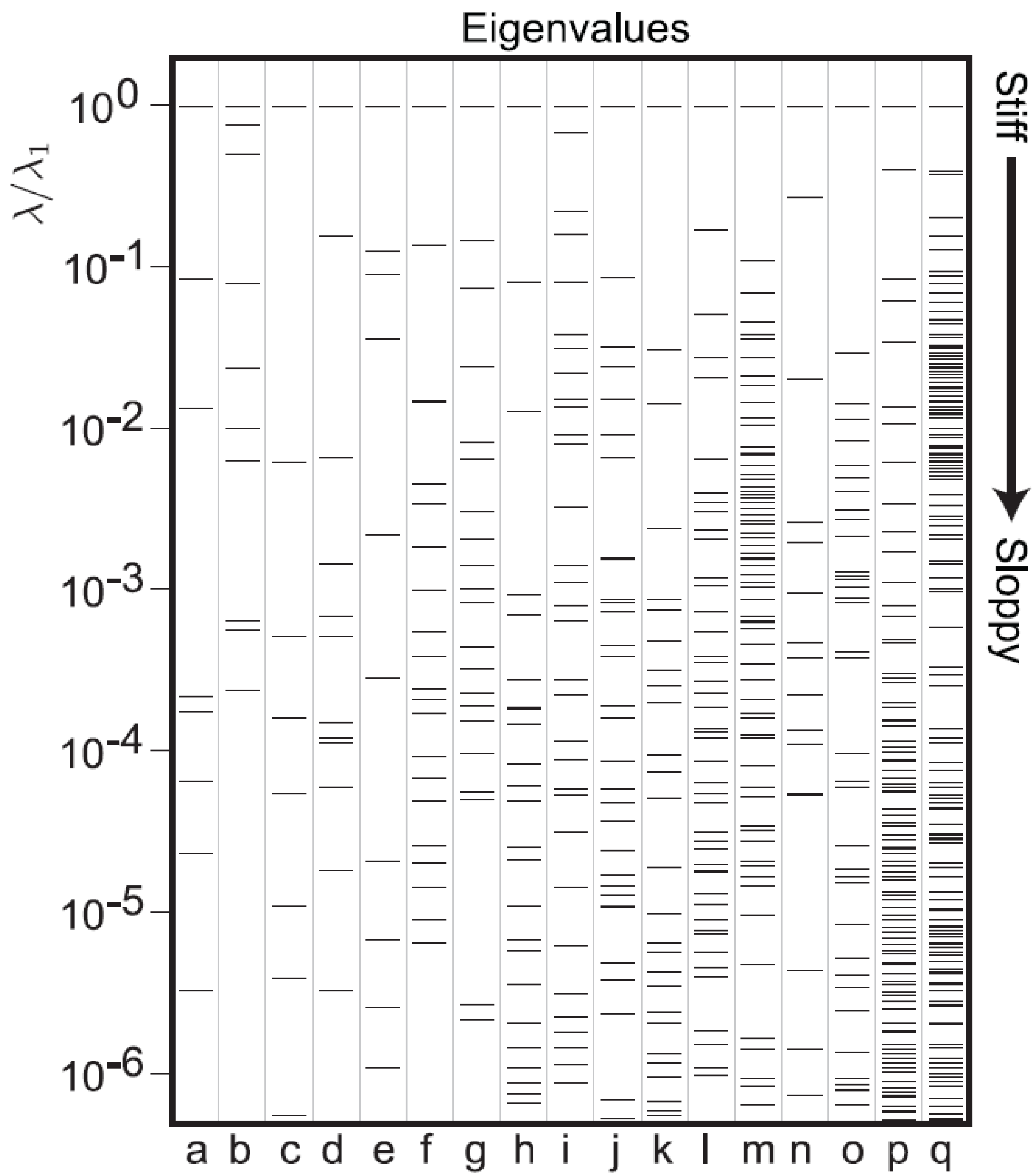
Measuring Sloppiness

1) Define cost – usually squared residuals
2) Find Hessian (2^{nd} derivative matrix of cost)



- The **eigenvalues of the Hessian** tell you about sensitivity along eigendirections in parameter space
- Produces a "sensitivity spectrum"

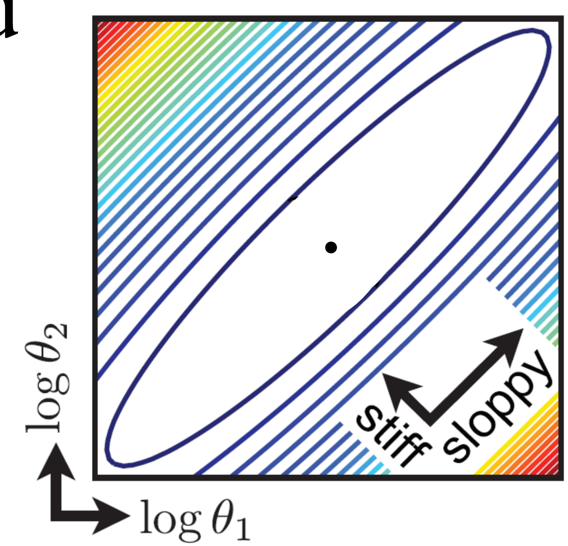
- Hallmarks of sloppiness:
  1. Large range of eigenvalues
  2. Eigenvalues roughly evenly spaced in log space



Gutenkunst et al., PLoS Comput Biol 3(10): e189

Implications of Sloppiness

- Large range means cost contour ellipsoids are routinely stretched by a factor of 1000 (the aspect ratio of a human hair).
- Even spacing means there is no well-defined cutoff between "important" and "unimportant".



Universality of sloppiness

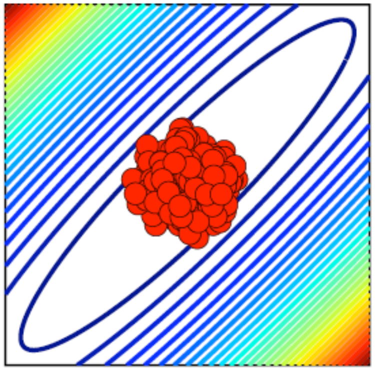
- Sloppiness has been found in every biological system analyzed (17 so far), and more:
  - Interatomic potentials, particle accelerator design, sums of exponentials...
- May be a “universal” feature of nonlinear multiparameter fitting problems.

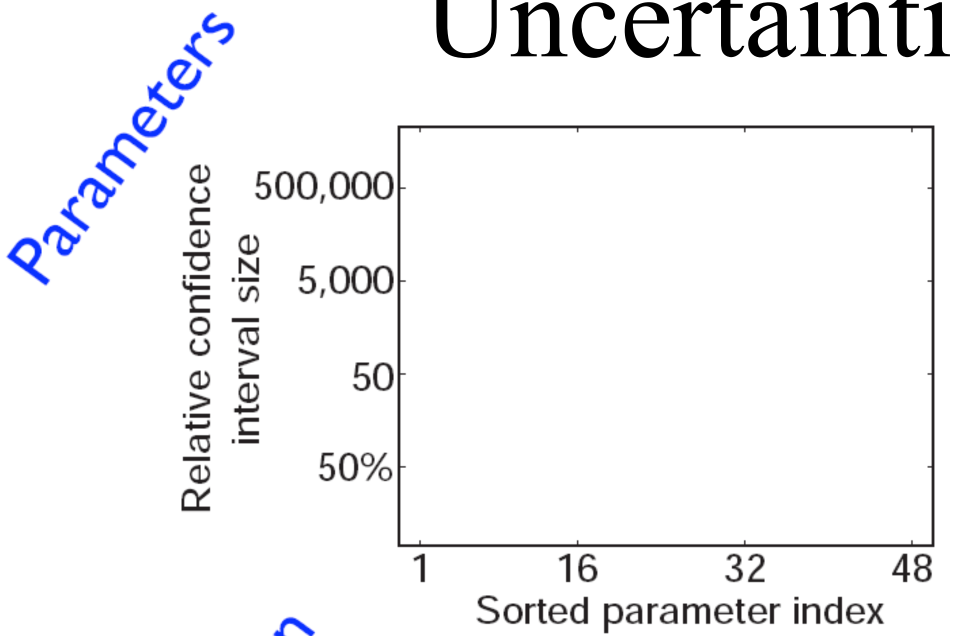
Parameter Uncertainty is Inevitable

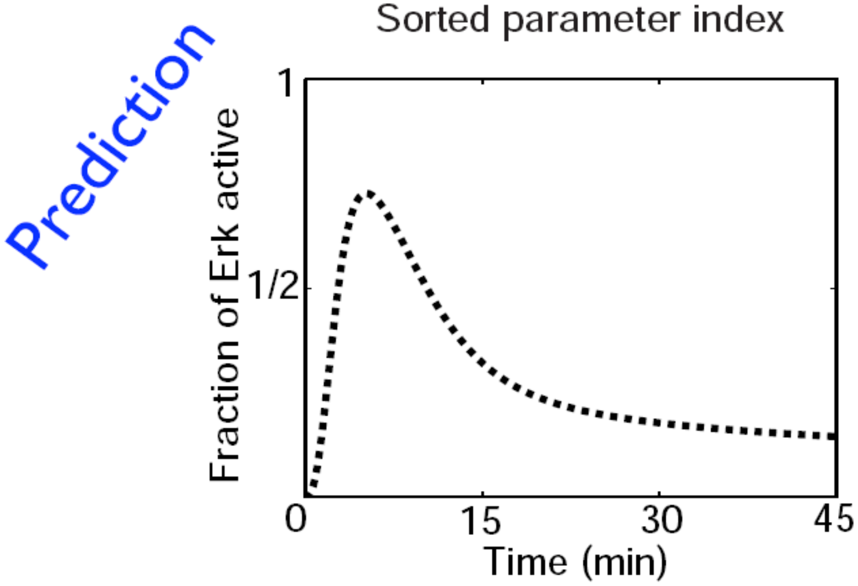
› Sloppiness provides an answer for why fits can lead to large uncertainties in parameter values.

› Large parameter uncertainty does not imply large uncertainty in predictions.

Uncertainties

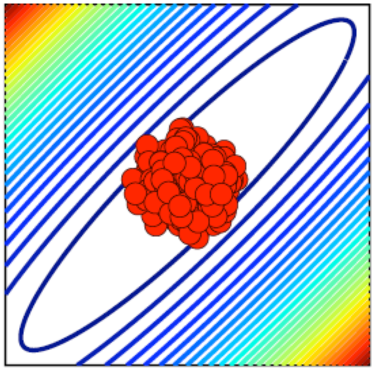




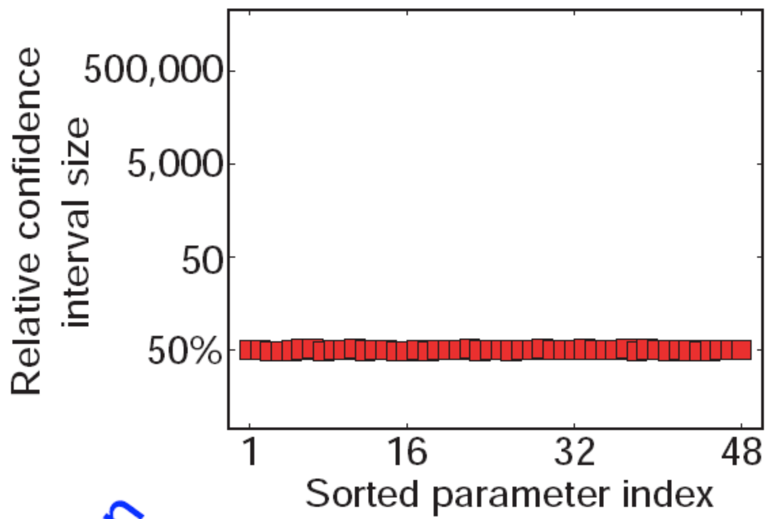


Slide courtesy Ryan Gutenkunst

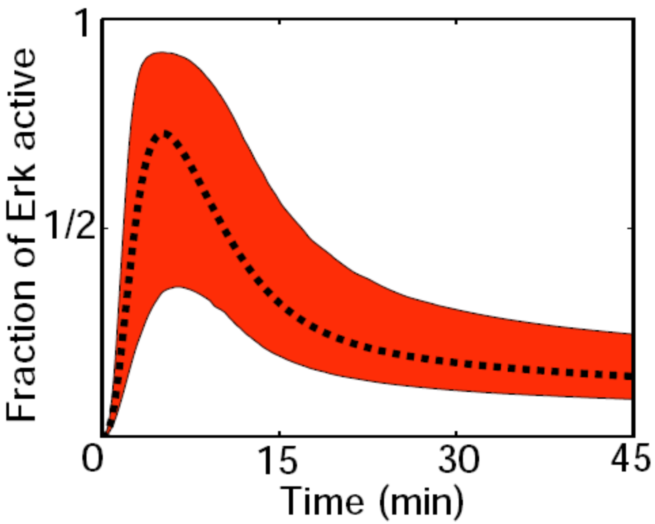
Uncertainties



Parameters



Prediction



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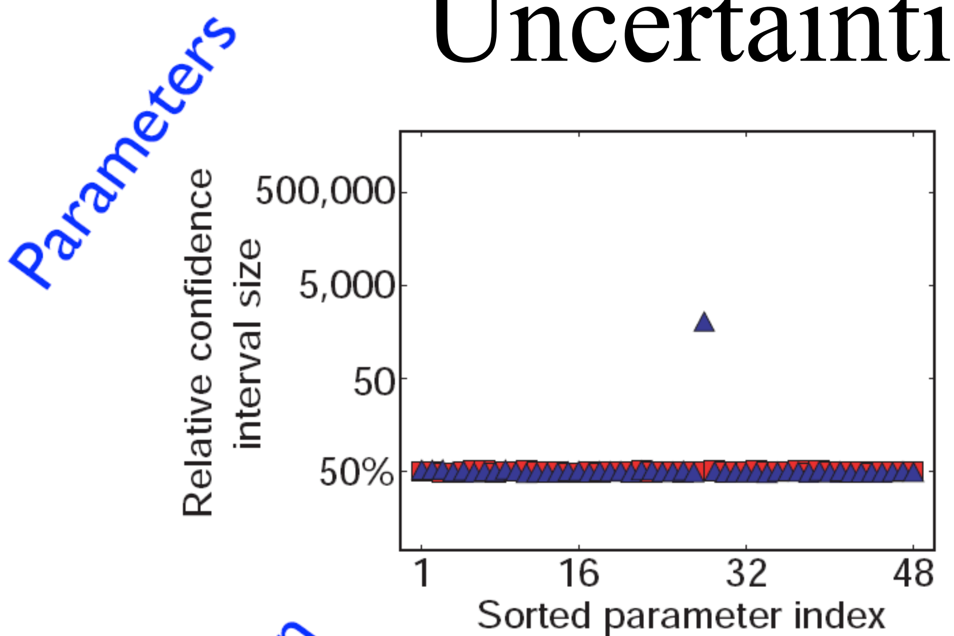
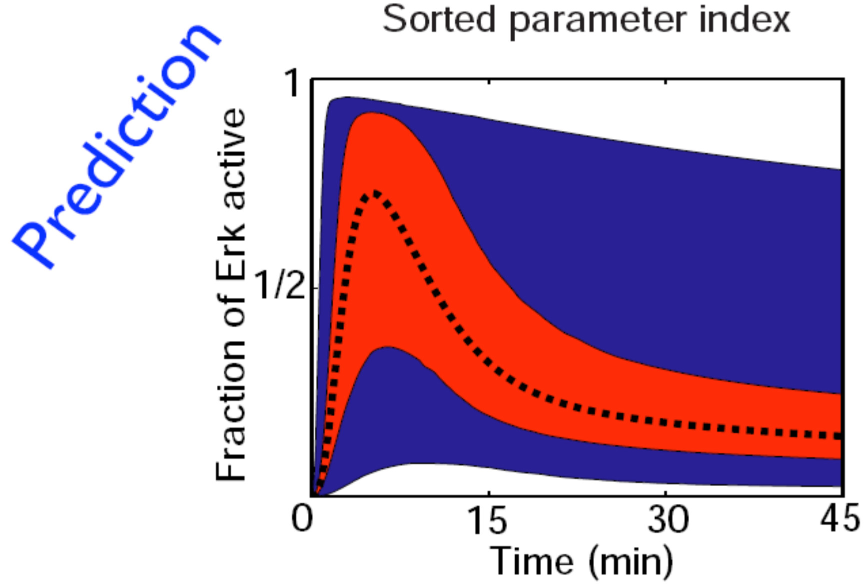
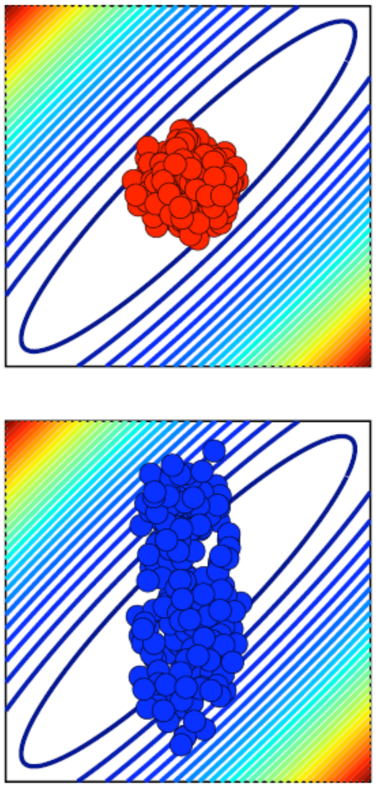
Uncertainties







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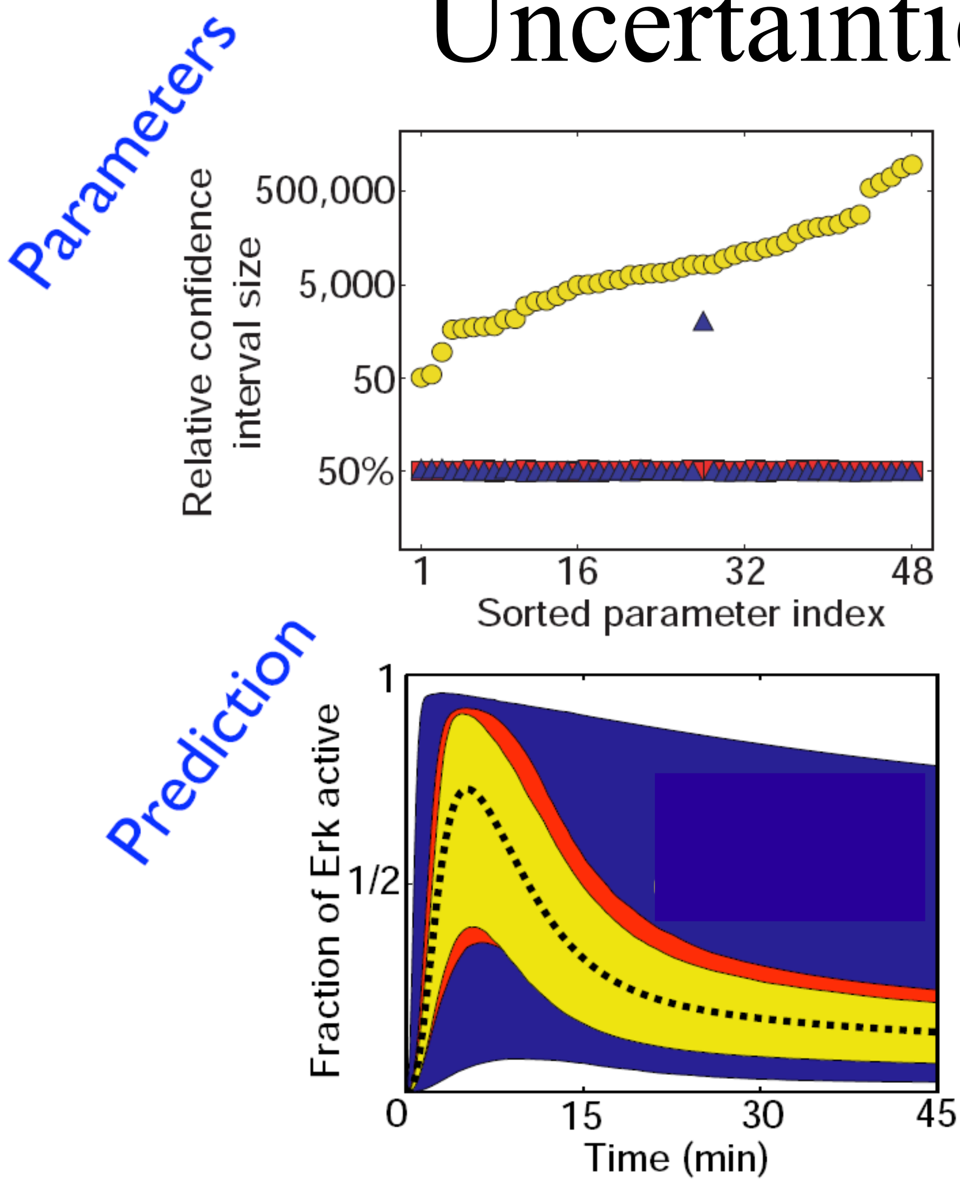
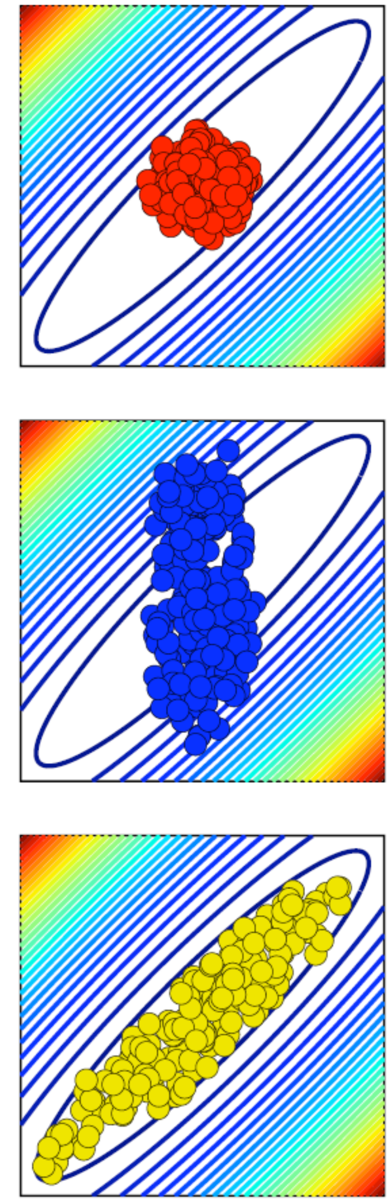




Slide courtesy Ryan Gutenkunst

Sloppiness is "Real"

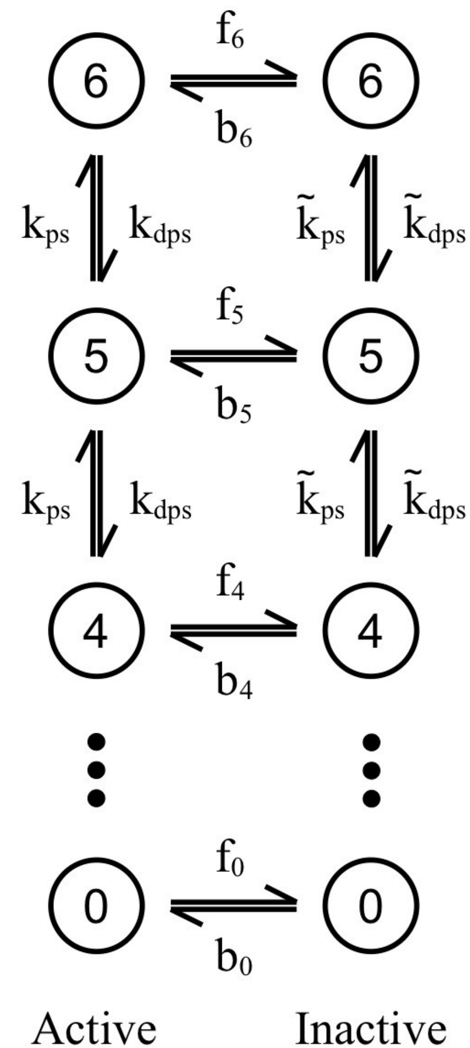
- Is it due to too few data points?
  - No; even for data the model can fit perfectly, sloppiness persists.
- Is it due to the local approximation?
  - No; principal component analysis of Monte Carlo ensembles still displays sloppiness.

SloppyCell

- Computing environment for simulating and analyzing biochemical networks (or any system of ODEs)
- Structure for optimization and efficient calculation of ensembles
- Supports Systems Biology Markup Language (SBML)
- Implemented in Python

Is robustness a delicate balancing act?

- A subset of the circadian rhythm network in cyanobacteria
- The phosphorylation decay rate is measured to be robust to temperature change, even when individual (de)phosphorylation rates would double



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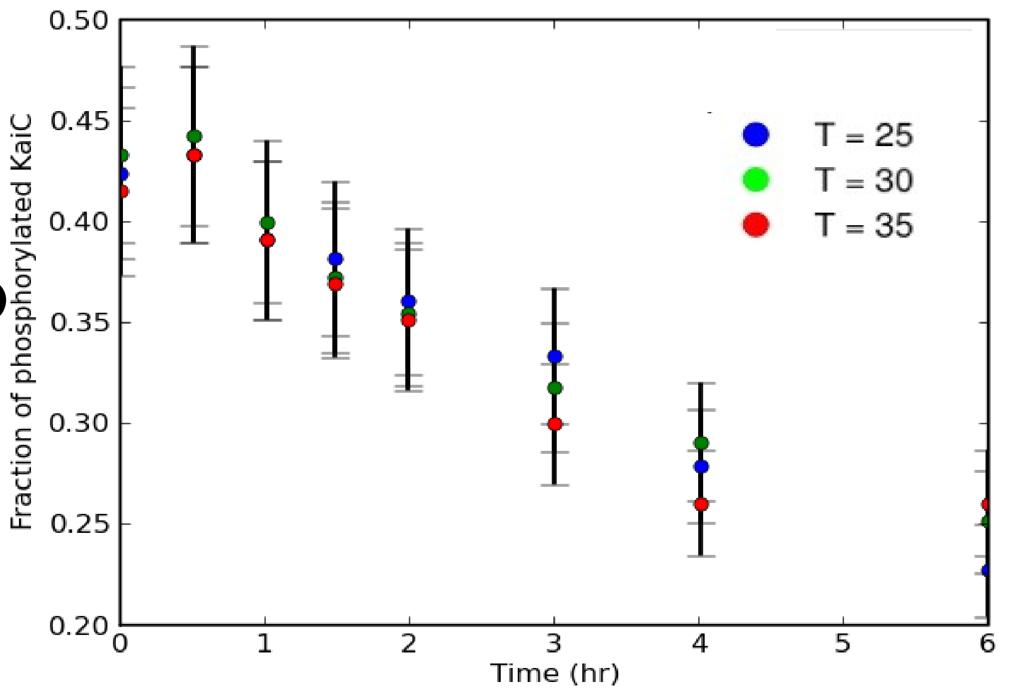

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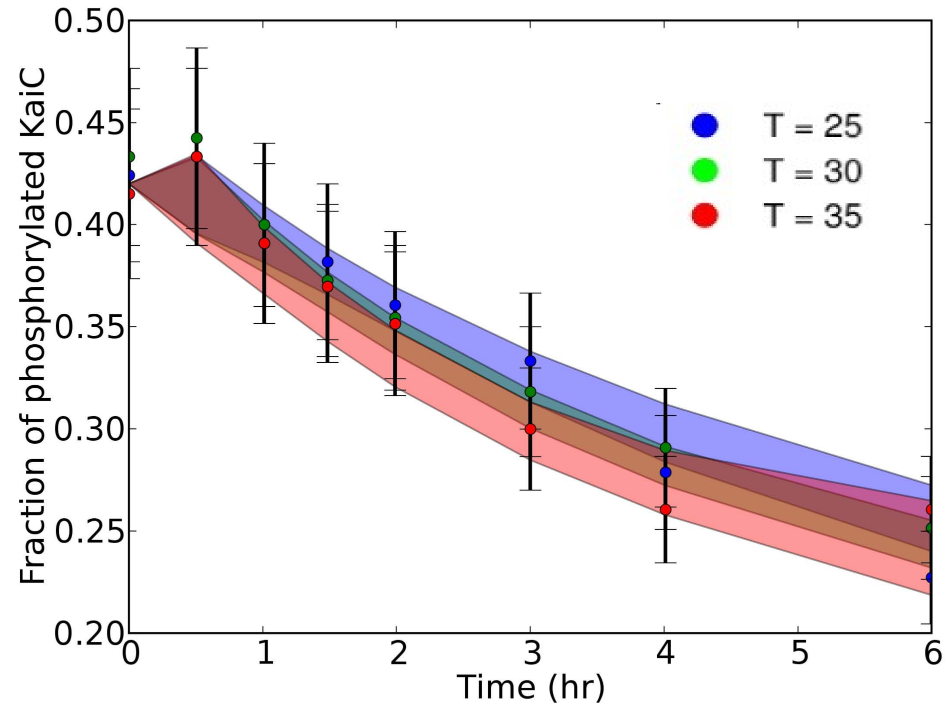

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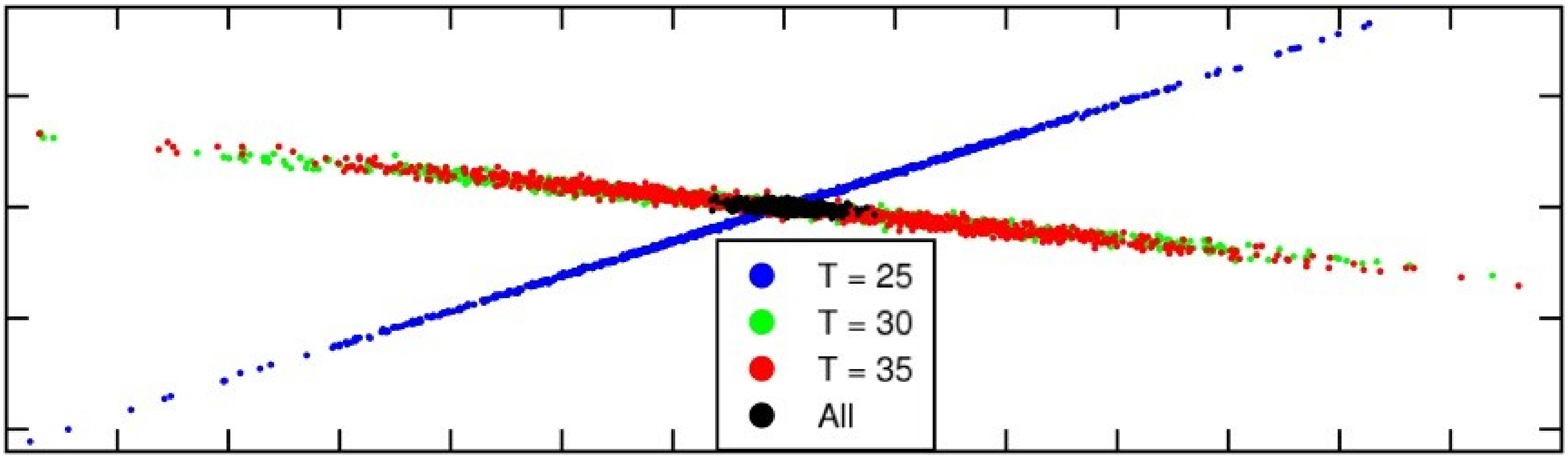


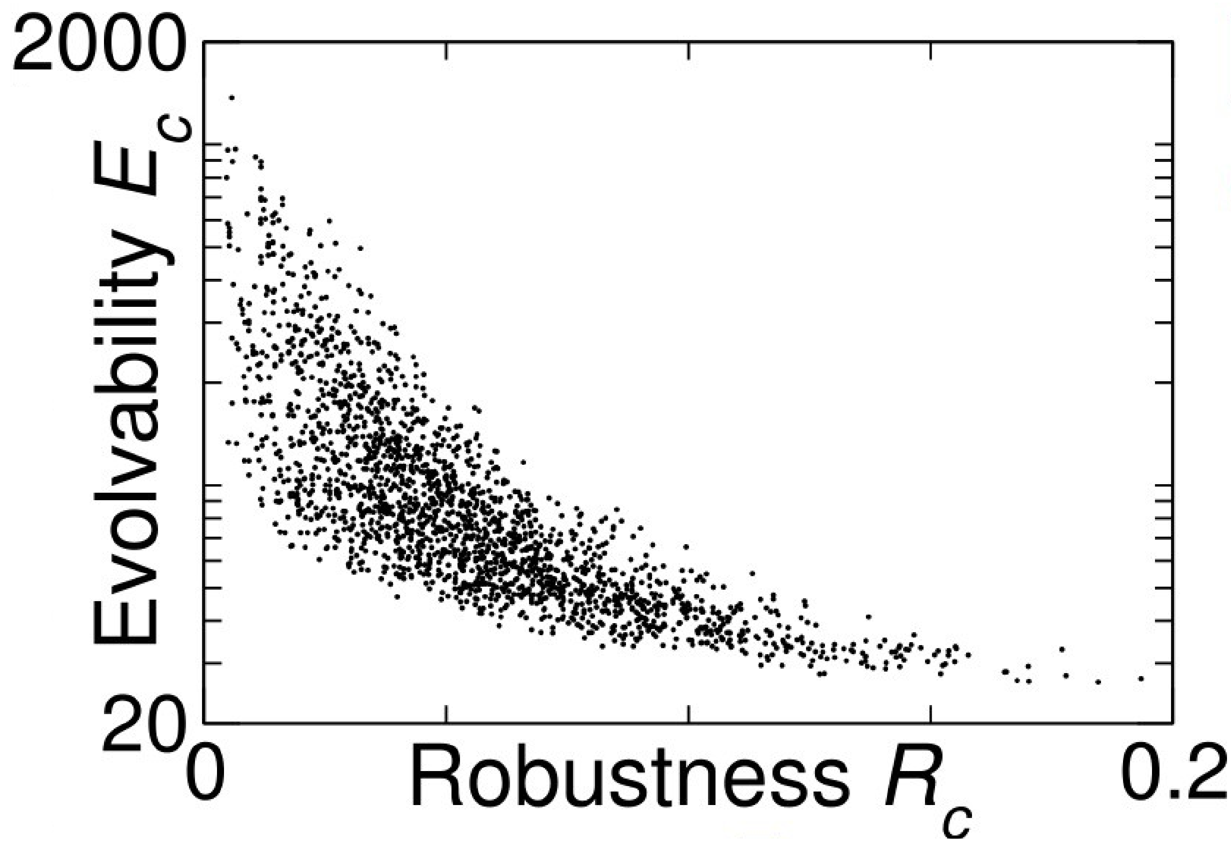
Robustness and Evolvability

Robustness and Evolvability

- Robustness: What fraction of a given volume in parameter space keeps the output reasonably constant?
- Evolvability: With a selection pressure to move in a certain direction in residual (output) space, how far can I move in that direction by varying my parameters by a fixed amount?

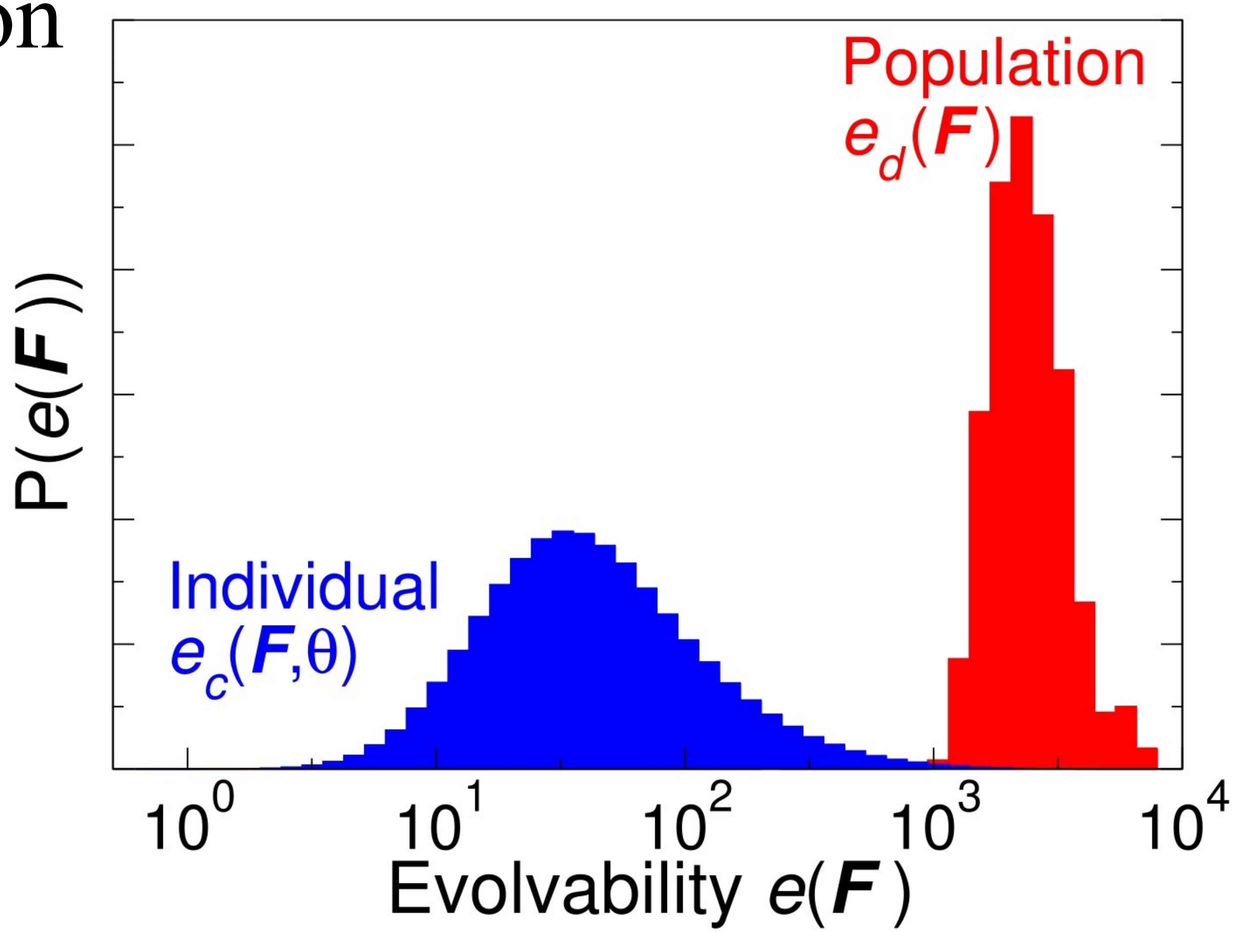
Robustness and Evolvability

› Individual evolvability decreases with robustness in example biological model



Individual and Population Evolvability

- Sloppiness may increase the variety of behaviors available to a population through mutation



Future work?

- Use information from multiple experiments / multiple systems to create ensembles
- Network structure
  1. Can we vary uncertain network connections in a similar way as parameters?
  2. Can we predict which experimental data would best constrain the network structure?

Conclusions

› Varying parameters provides important information about model uncertainty.

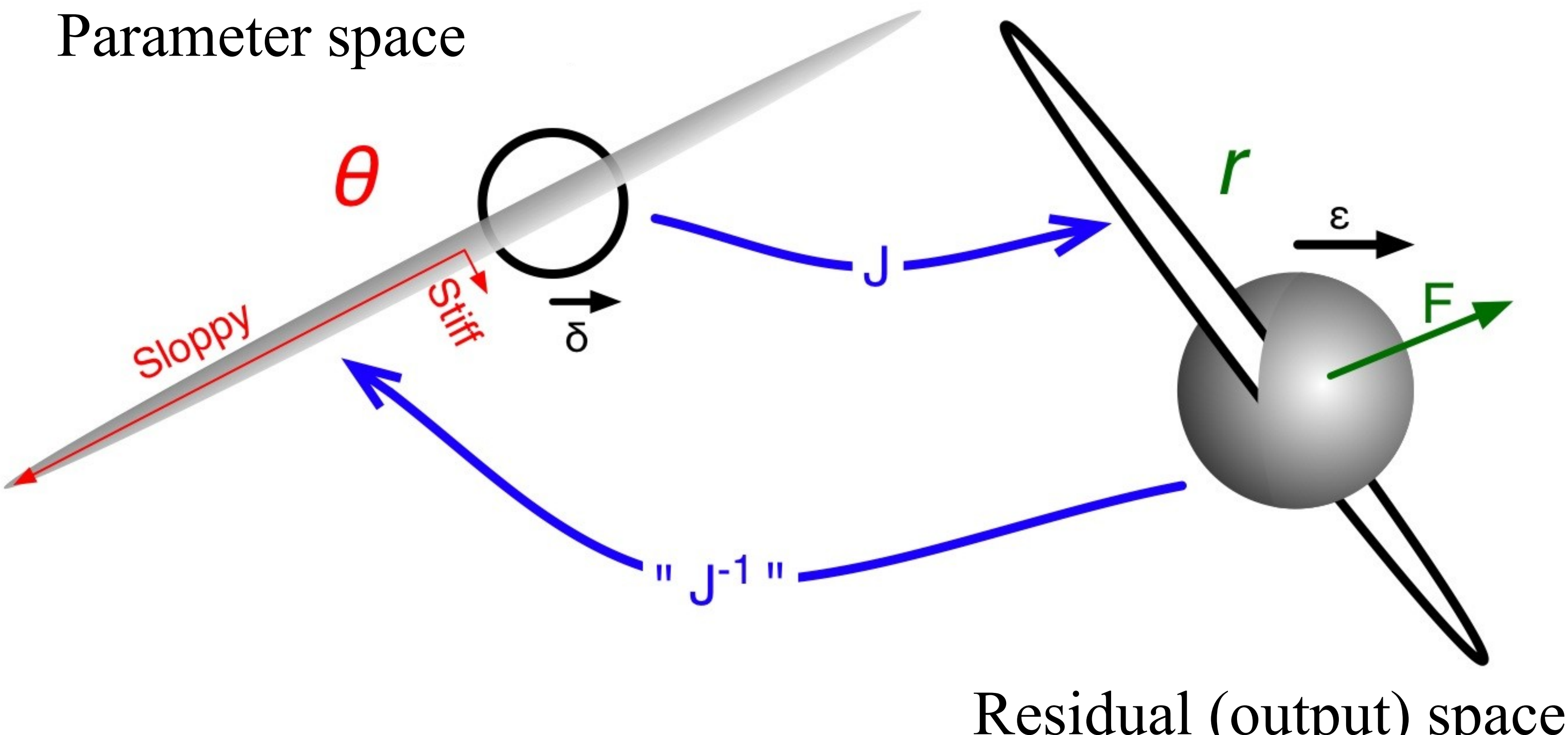
› Sloppiness is a common feature in large multiparameter models.

1. Precise measurements of constants are not as important; instead optimize experiments to provide well-constrained predictions.
2. Sloppiness can have important implications for robustness and evolvability.

Thanks!

- Jim Sethna
- Ryan Gutenkunst
- Chris Myers
- YJ Chen
- Ben Machta
- Mark Transtrum

Mapping parameters to residuals



Universality of Sloppiness

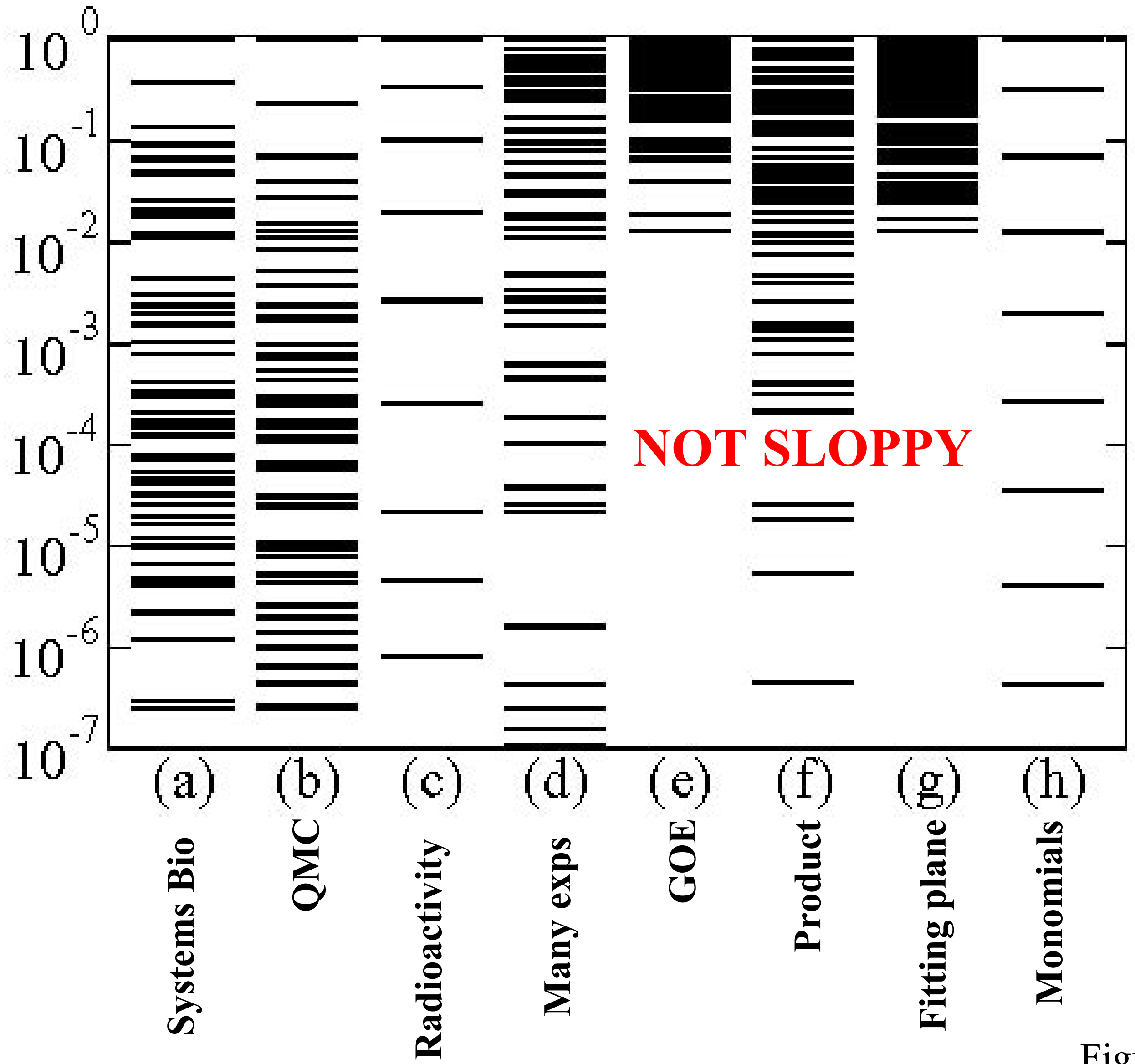
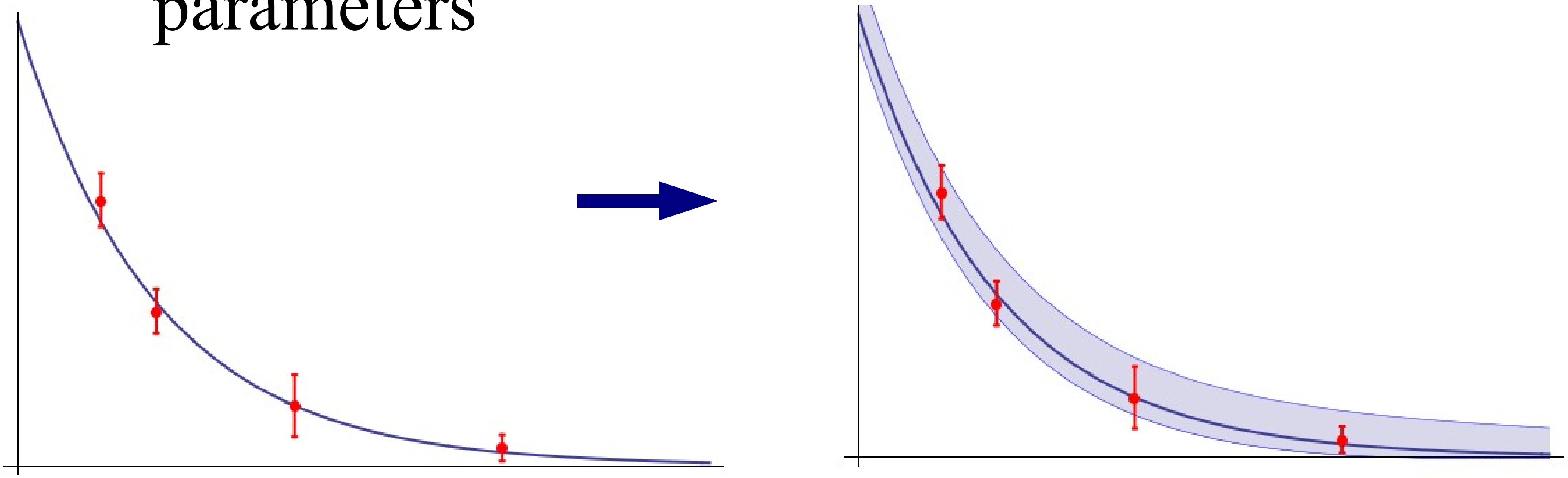


Figure courtesy Jim Sethna

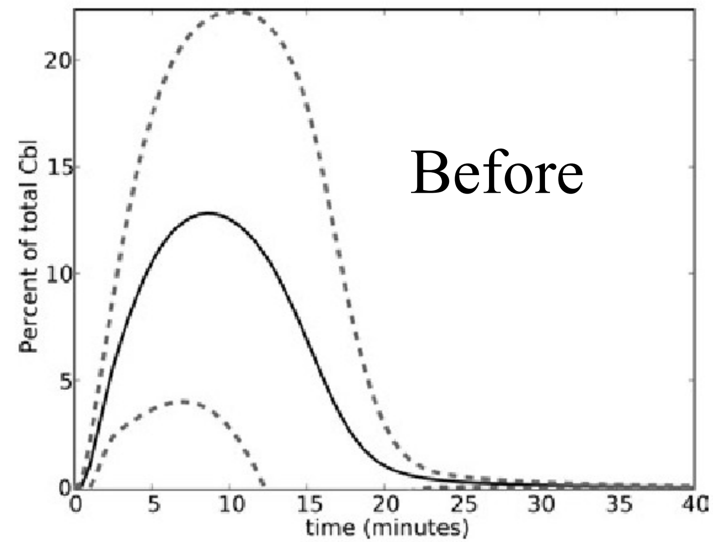
Making Sensible Error Bars

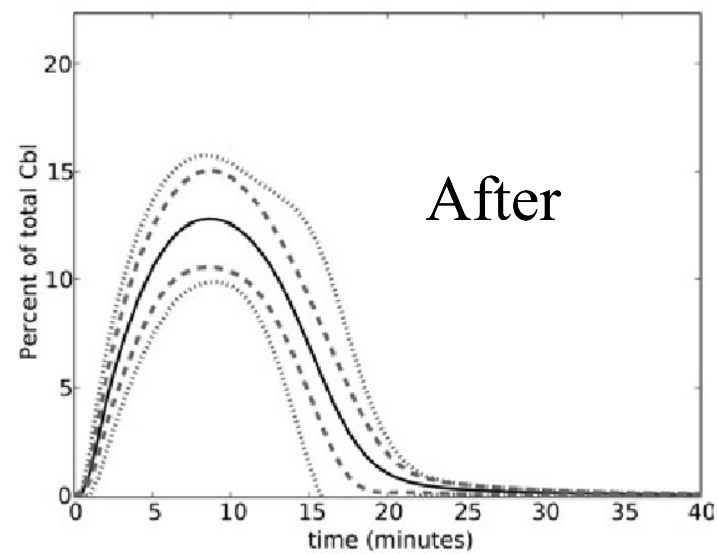
- Quickest method: Linear covariance analysis
- Two approximations:
  1. Quadratic expansion around best-fit
  2. Linear response of output to changes in parameters



Experimental Optimization

- We can ask what new measurement will reduce the uncertainty of a specific output.
- Example: Adding a single measurement of a different protein concentration.
- Must use linear approx.





Fergel Casey et al., IET Sys. Biol. 1 (3), 190 (2007)

Sloppiness

› What does understanding sloppiness buy you? How can you use these ideas?

1. More efficient Monte Carlo sampling of parameter space;
2. Hints at the most important reactions in a network;
3. An appreciation of the futility of thinking in terms of individual parameters;
4. Model simplifications?

More Efficient Sampling

- Using a Metropolis Monte Carlo algorithm, we can make use of our knowledge about the local shape of the cost function.
- Big steps in sloppy directions, small steps in stiff directions.

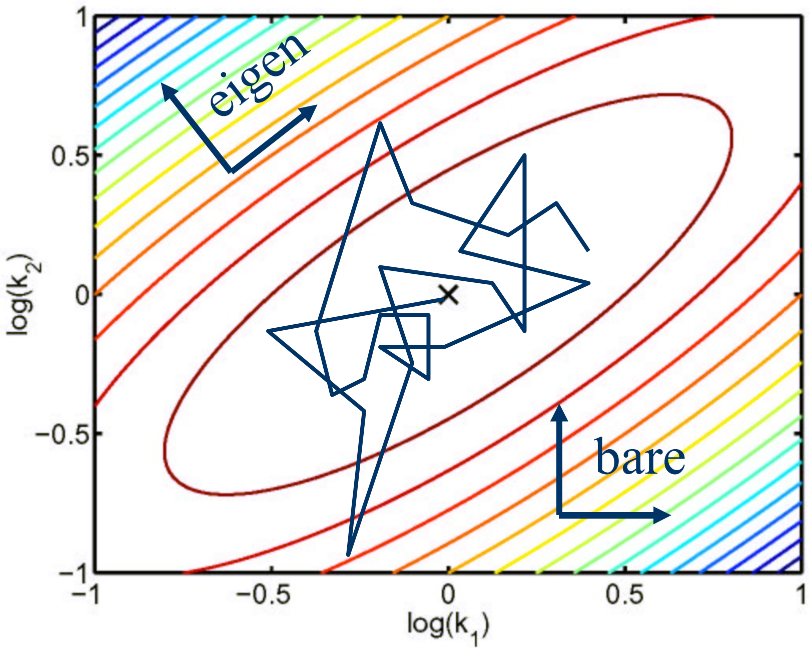
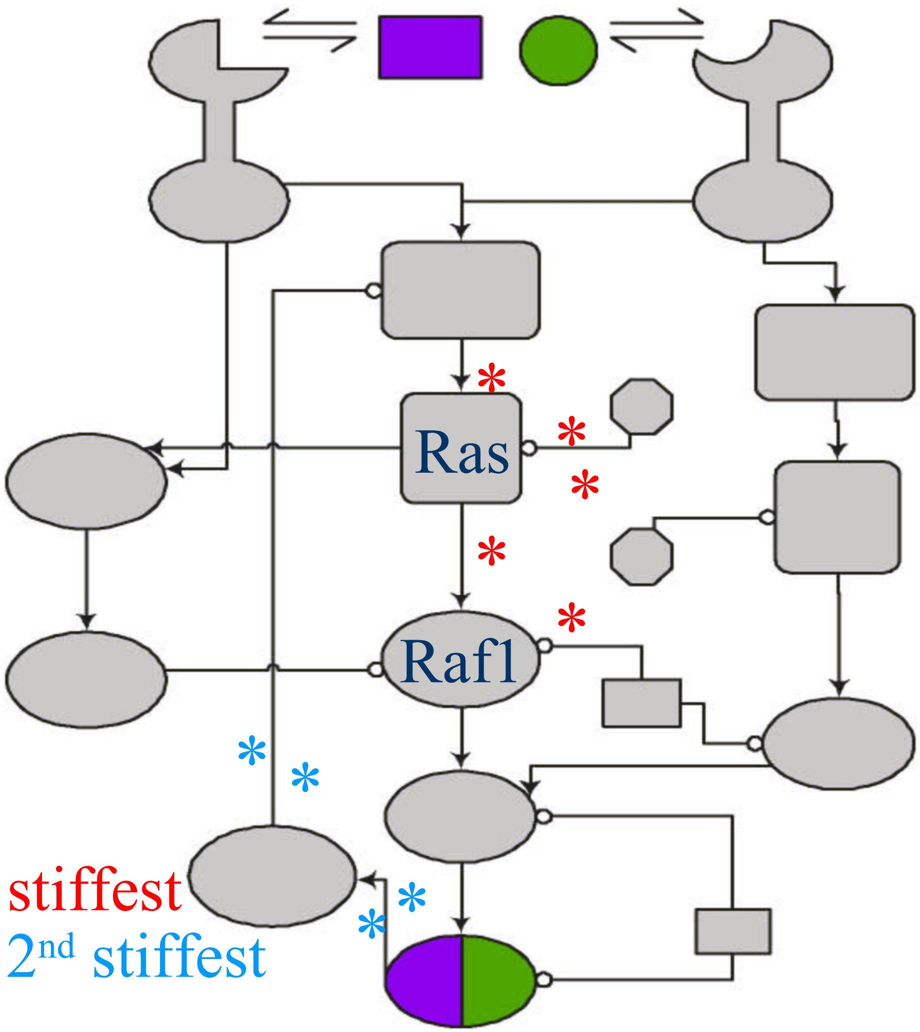


Figure courtesy Jim Sethna

Stiffest Directions

› The parameters with large components in the stiffest eigenvectors are in some sense more important.

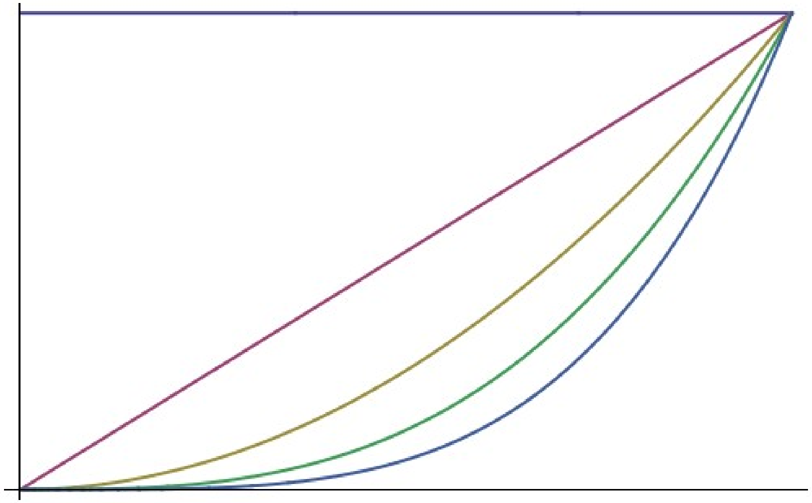


Current Projects

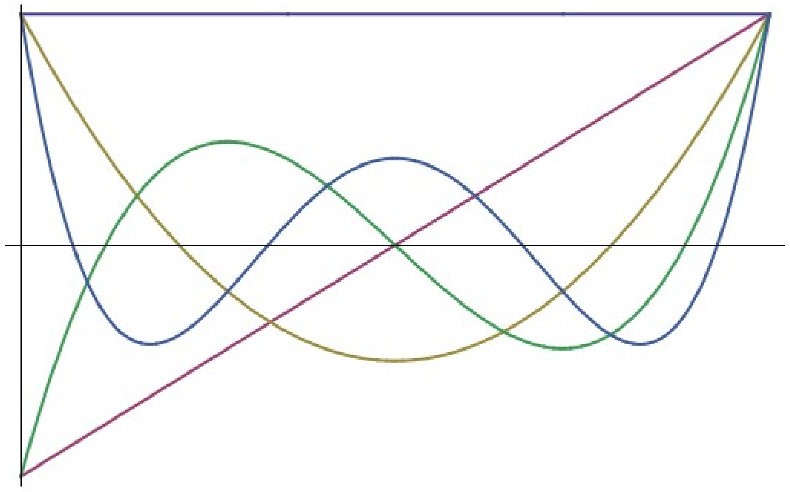
- SloppyCell
- Origin of sloppiness
- Curved manifolds: connections to GR?
- Model simplification?
- New systems to implement

Where does sloppiness come from?

- Related to the interchangeability of different sets of parameters
- Using the wrong parameterization
- Example: fit polynomial function on [0,1]



monomials: sloppy



Legendre polynomials: not sloppy

Origin of Sloppiness

› With two idealizations, get "perfect" sloppiness:

1. Parameters are exactly interchangable.
2. Parameters are nearly degenerate.

$$H = V^T A^T A V \qquad V = \begin{bmatrix} 1 & 1 & \cdots & 1 \\ \varepsilon_1 & \varepsilon_2 & \cdots & \varepsilon_N \\ \vdots & \vdots & \ddots & \vdots \\ \varepsilon_1^d & \varepsilon_2^d & \cdots & \varepsilon_N^d \end{bmatrix}$$

$$\det(V) = \prod_{i<j} (\varepsilon_i - \varepsilon_j) \propto \varepsilon^{N(N-1)/2}$$

Curved Manifolds

- Anharmonic effects seem to be important.
- To efficiently explore parameter space, we may need curved coordinates.

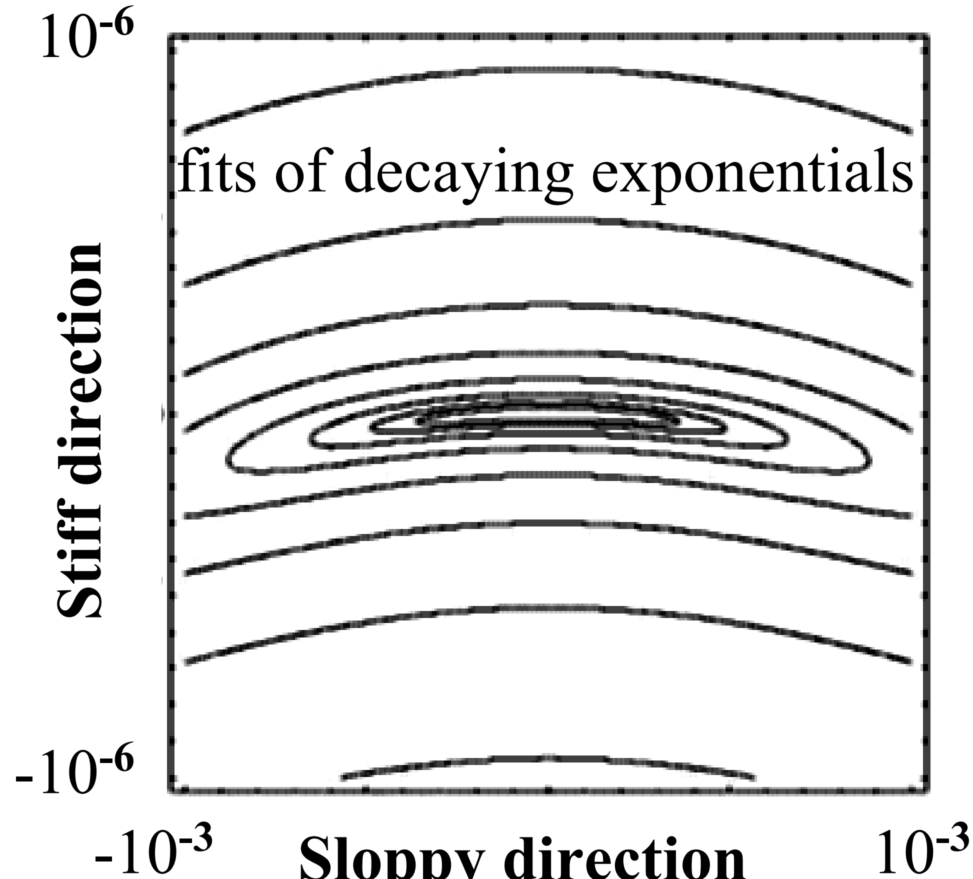
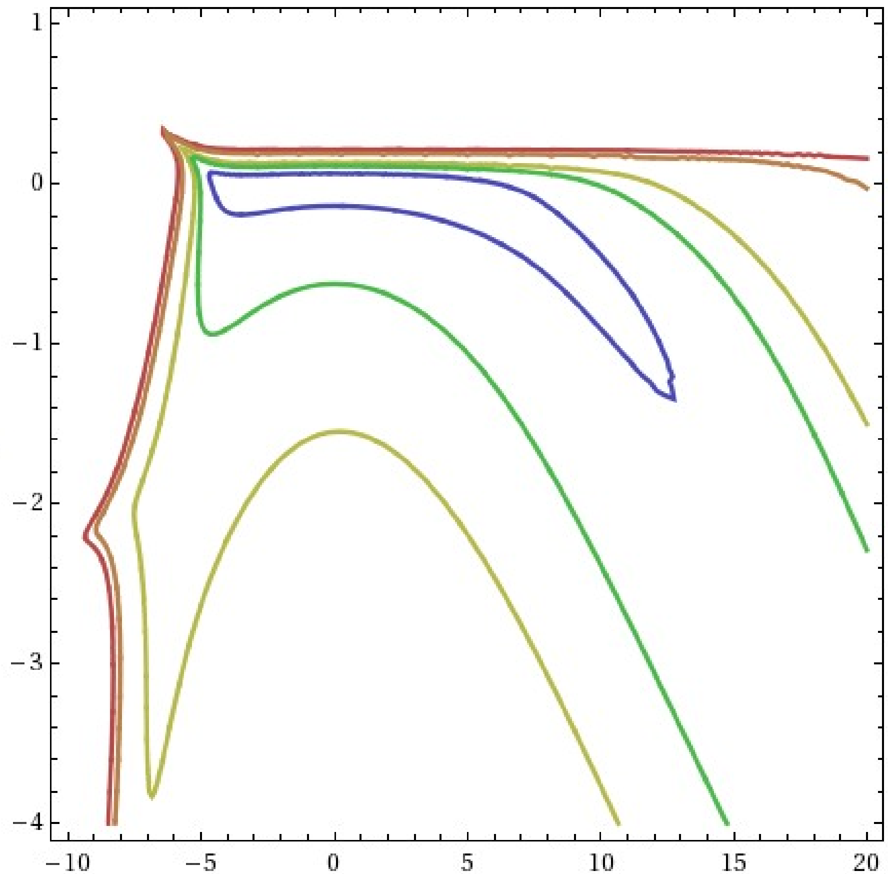


Figure courtesy Jim Sethna

Curved Manifolds

› Example: sum of exponentials problem



Model Simplification

- Figure: Correlated parameter clusters
- When sets of parameters have the same effect on output:
  1. We see sloppiness;
  2. It suggests we could simplify the model...

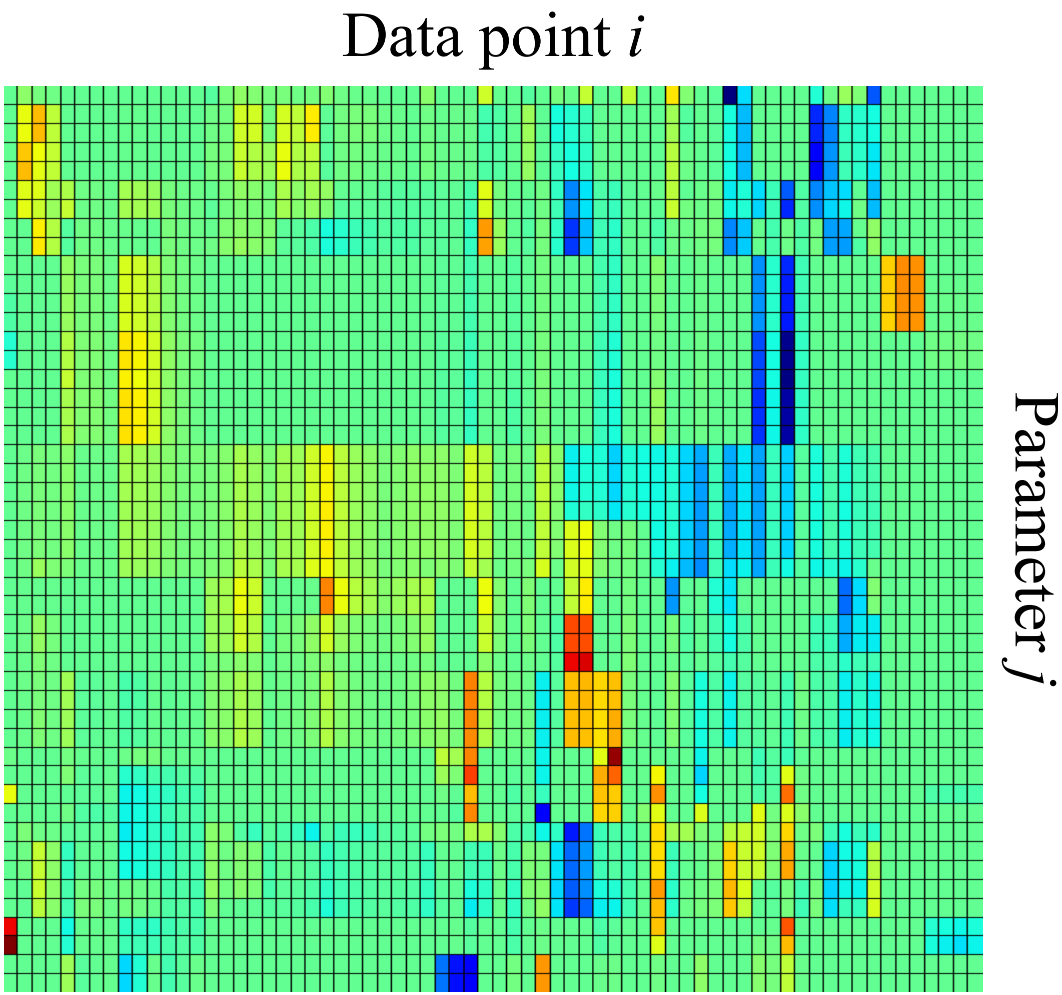


Figure courtesy Josh Waterfall/Jim Sethna

New Systems to Implement

› To avoid getting too abstract, we are on the lookout for real-world problems to implement...

1. Climate modeling
2. Economic models
3. Physics models (CMB, accelerator design)
4. Other systems biology problems

Conclusions

- Varying parameters provides important information about model uncertainty.
- Sloppiness is a common feature in large multiparameter models.
  1. Precise measurements of constants are not as important; instead optimize experiments to provide well-constrained predictions.
  2. Simplification schemes may be fruitful.