Cornell University
Laboratory of
Atomic and Solid State Physics

Origins of sloppiness in biological networks

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DOE CSGF Meeting
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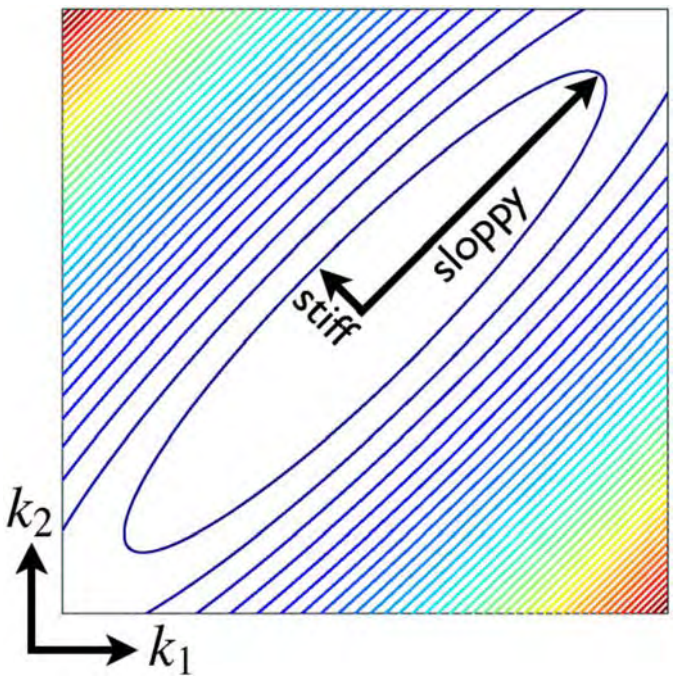
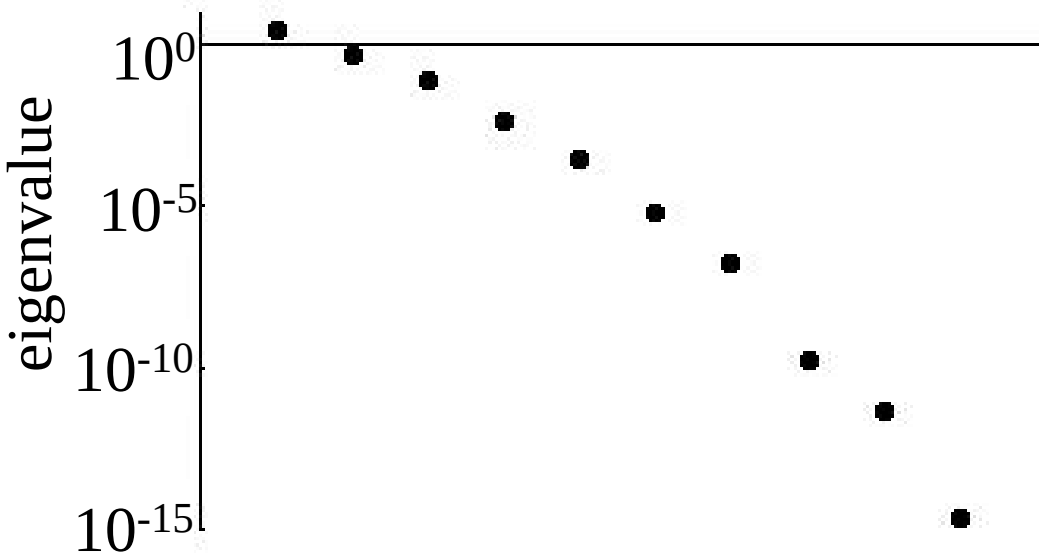
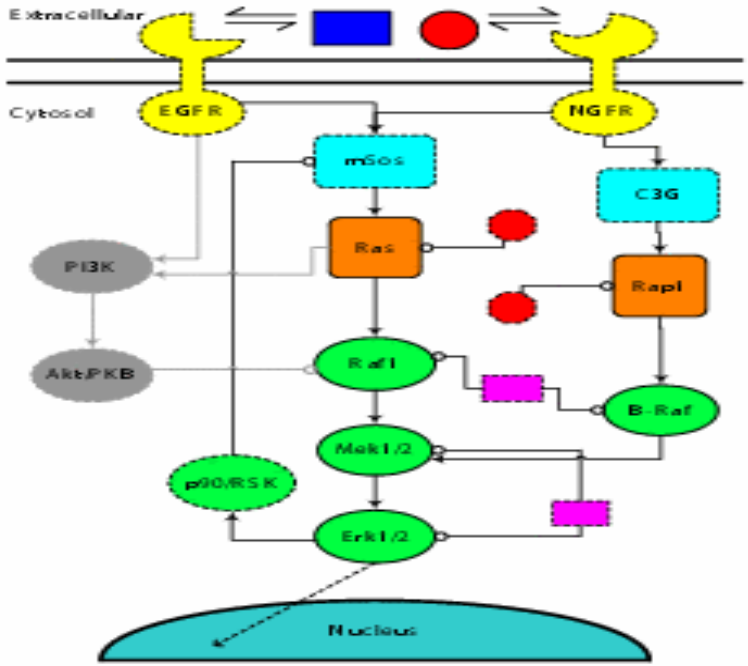




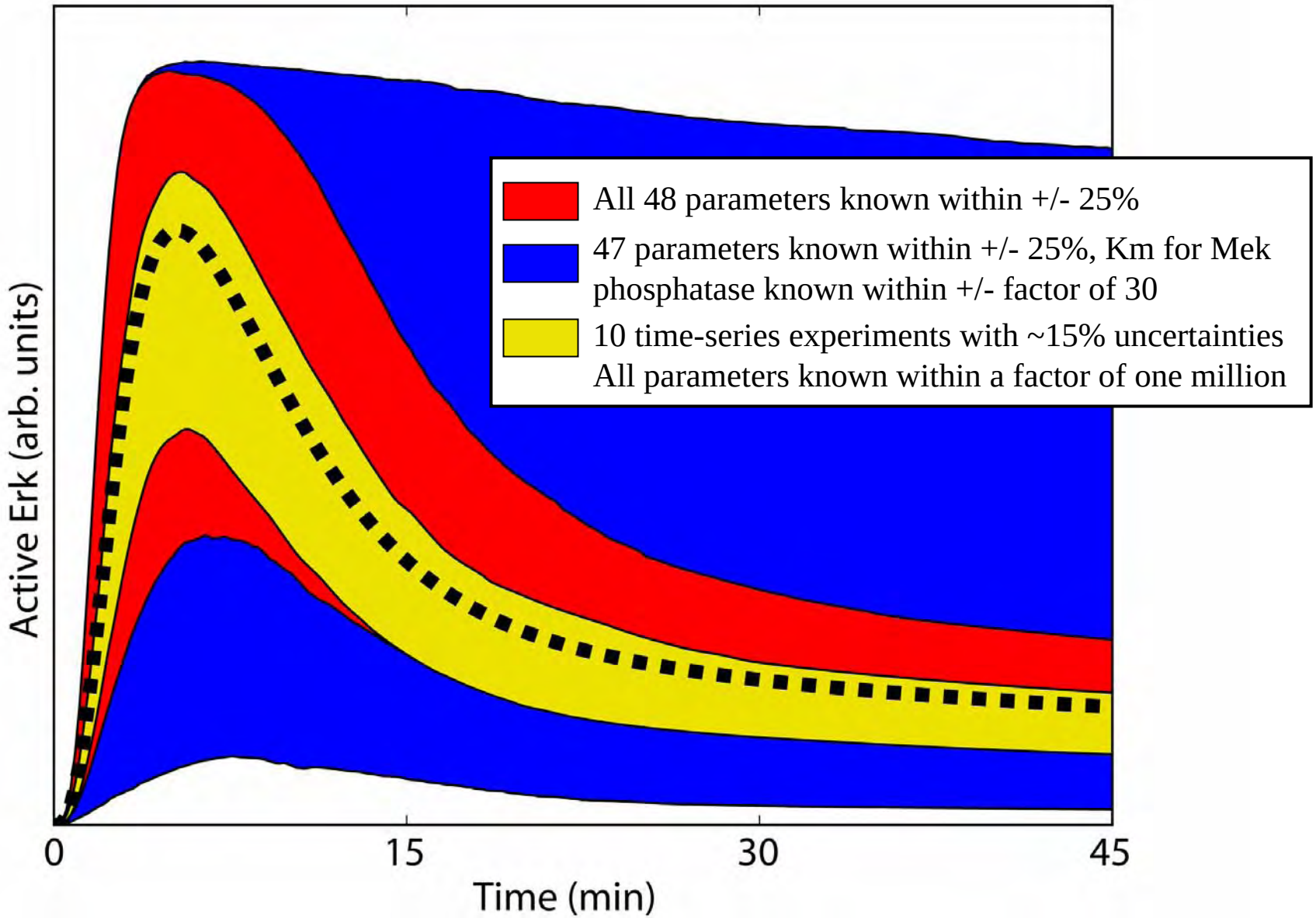
Biological networks



Growth factor signaling in PC12 cells

$$\frac{d[SOSActive]}{dt} = \frac{k_{EGF}[boundEGFR][SOSInactive]}{[SOSInactive] + K_{mEGF}}$$

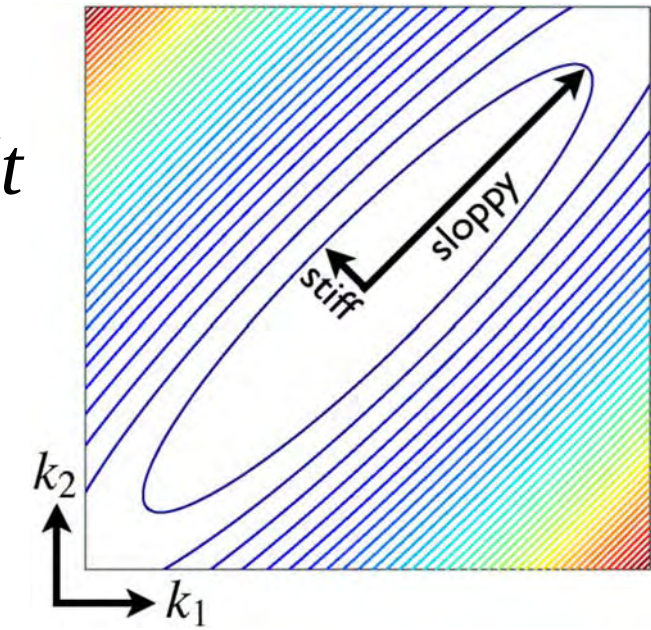
Prediction for Erk activation by EGF with PI3K inhibitor

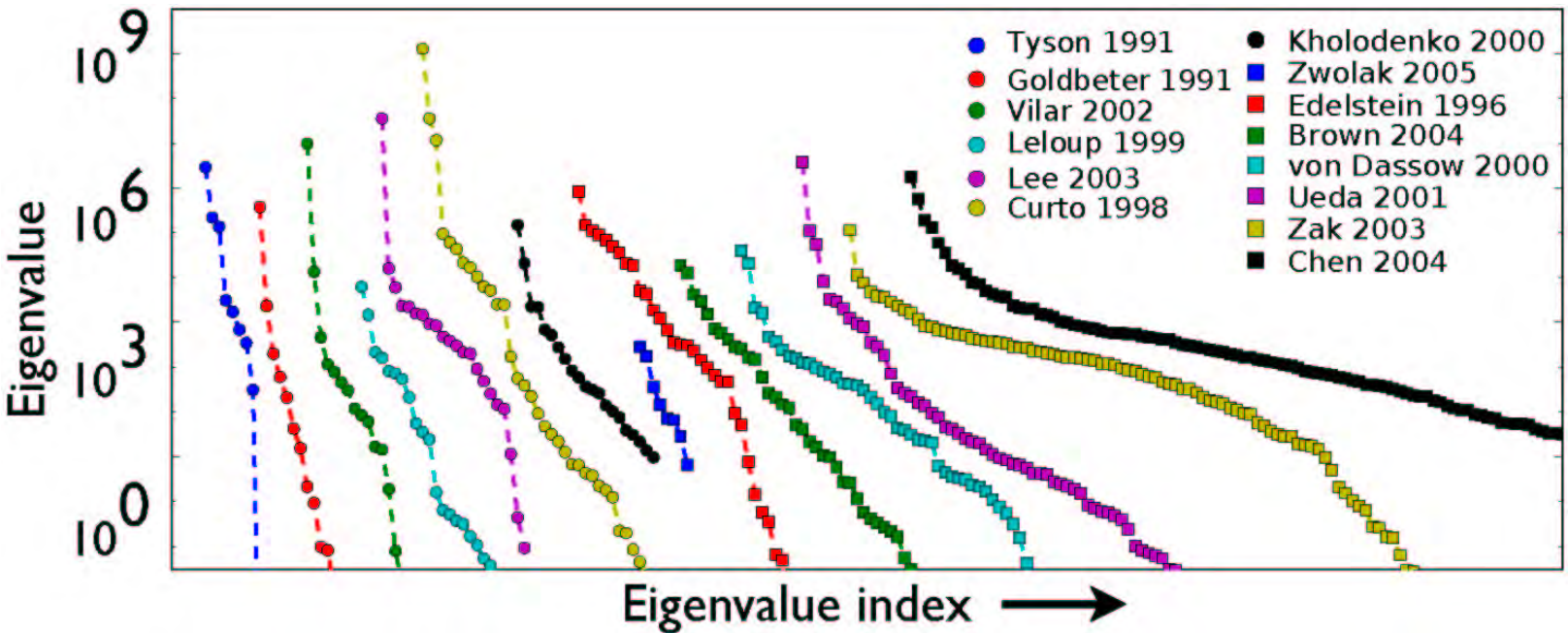


Parameter Fluctuations and Systems Fluctuations

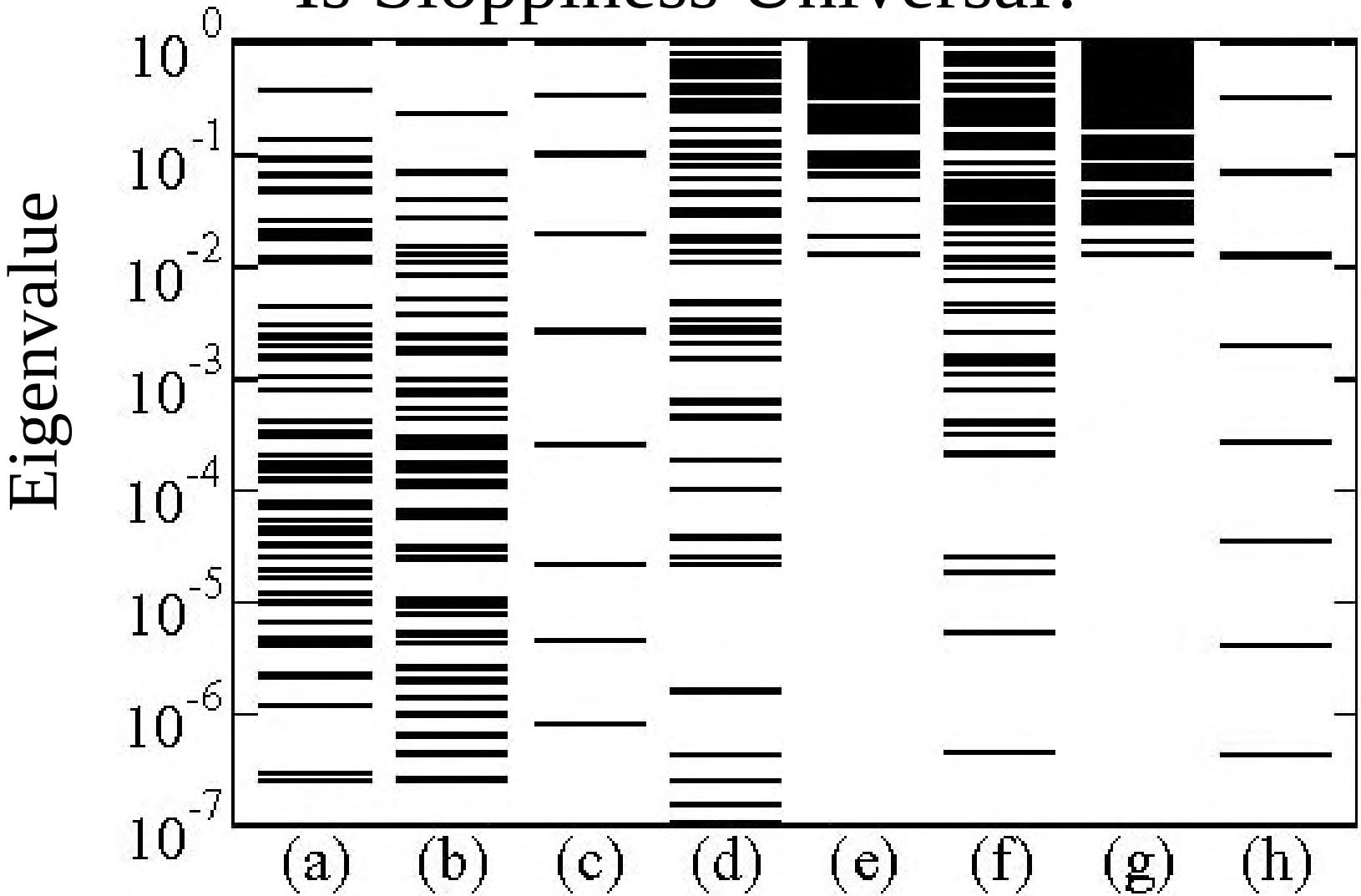
$$\chi^2(\theta) = \sum_{\text{species}} \frac{1}{T}\int_0^T \frac{(y(\theta,t) - y(\theta_0,t))^2}{\sigma^2}\,dt$$

$$H_{ij} = \frac{\partial^2 \chi^2}{\partial \log\theta_i \partial \log\theta_j}$$





Is Sloppiness Universal?



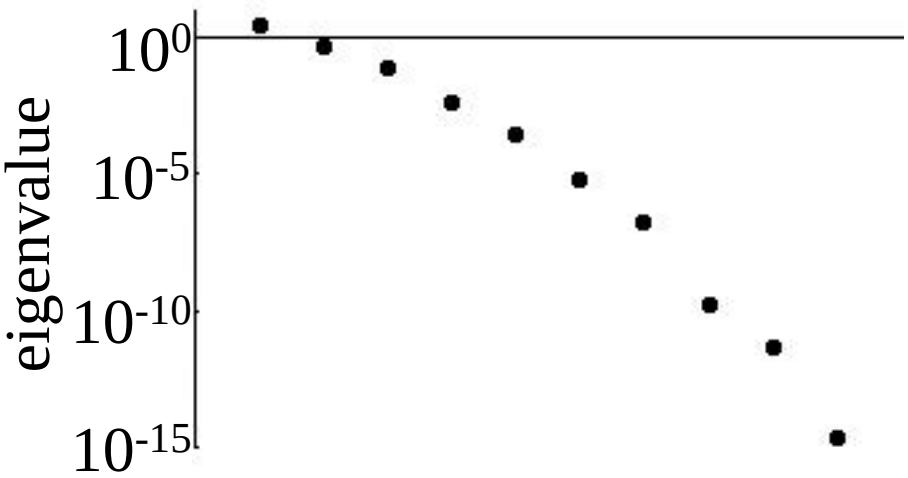
(a) Growth factor signaling in PC12 cells, (b) Quantum Monte Carlo (Jastrow parameters), (c) radioactivity from pharmaceutical isotopes, (d) 48 random exponentials from log uniform(± 25.), (e) random symmetric matrix (GOE), (f) products of GOE random matrices, (g) Wishart matrix, (h) fitting monomials (Hilbert matrix)

Sums of exponentials

$$y(x) = \sum_{i=0}^{n} e^{-\gamma_i x}$$

$$H_{ij} = \frac{2\gamma_i \gamma_j}{(\gamma_i + \gamma_j)^3}$$

SLOPPY



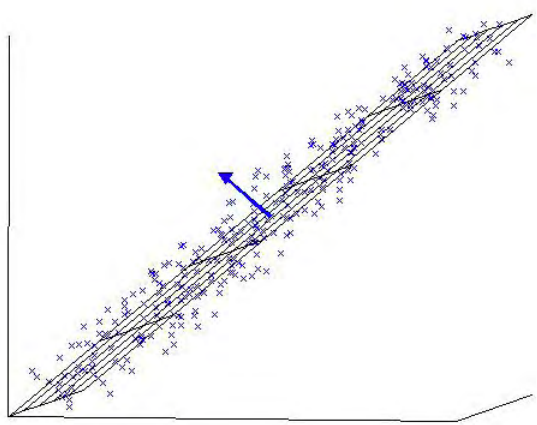
Linear Correlations

$$a(\vec{p}) = \vec{n} \cdot \vec{p}$$

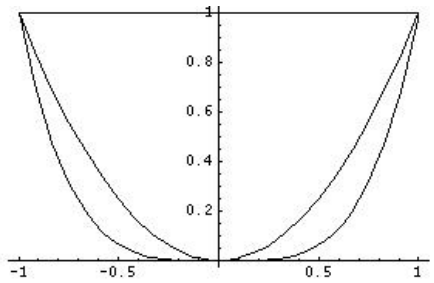
Hessian is covariance matrix of data.
Wishart statistics for eigenvalues.

$$H = \sum_i \vec{p}_{(i)} \vec{p}^{\,T}_{(i)}$$

NOT SLOPPY

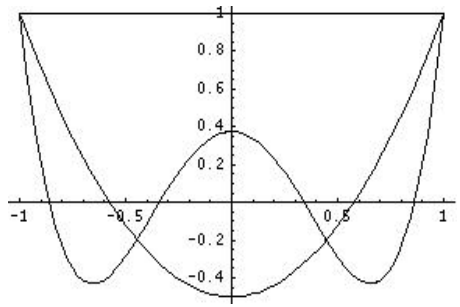


Sums of monomials



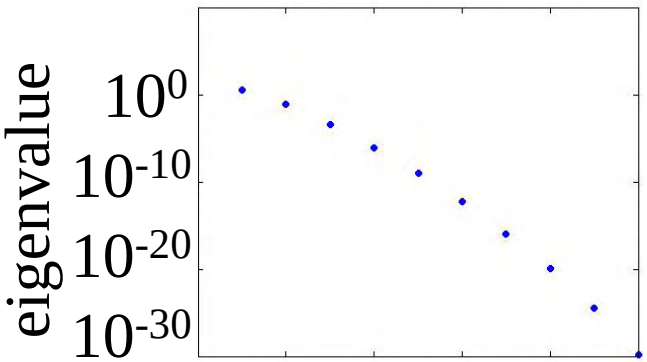
$\sqrt{|H|}$ = volume change under basis transformation

Sums of Shifted Legendre polynomials



Hessian = Hilbert matrix

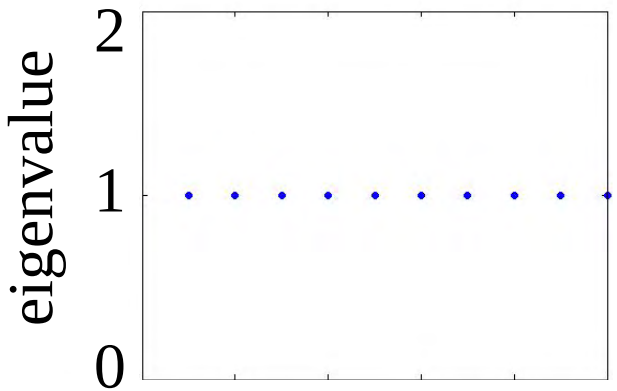
$$H_{ij} = \frac{2}{i + j + 1}$$



SLOPPY

Hessian = Identity matrix

$$H_{ij} = \delta_{ij}$$



NOT SLOPPY

The Vandermonde Ensemble

Assumptions for proof:

i. Parameters are nearly degenerate.
ii. Cost function is sum of squares of residuals.
iii. Each residual is a symmetric function of all the parameters.

Biological network properties:

i. Dozens to hundreds of biochemical parameters in limited range.
ii. χ^2 measure of system behavior variation.
iii. Similar biochemical reactions repeated throughout network.

$$\theta_i = \theta_0 + \varepsilon_i \qquad C(\vec{\theta}) = \sum_k r_k^2(\{m_i\}) \qquad m_i = \sum_j \varepsilon_j^i$$

$$J_{ij} = \frac{\partial r_i}{\partial \theta_j} = \sum_k \frac{\partial r_i}{\partial m_k} k\varepsilon_j^{k-1} = A_{ik}V_{kj}$$

$$H = J^T J = V^T A^T A V$$

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

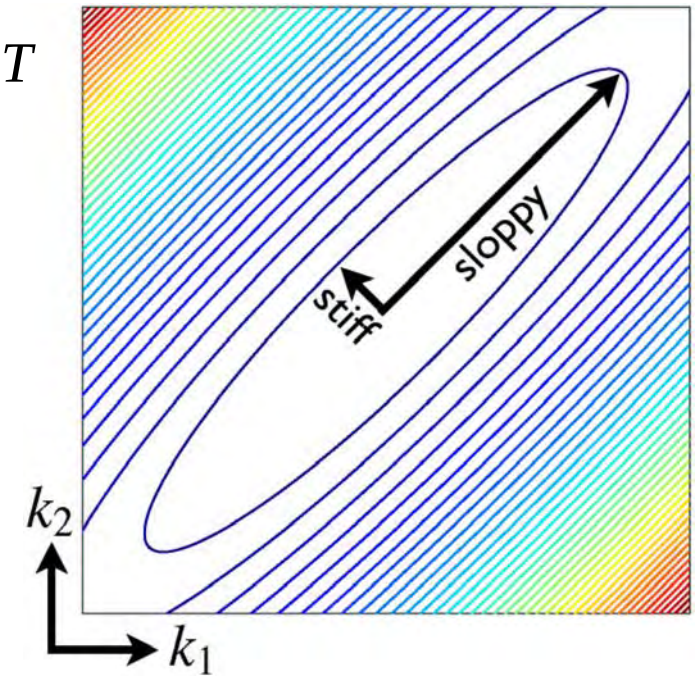
$$\det(V) = \prod_{i<j} (\varepsilon_i - \varepsilon_j) \propto \varepsilon^{N(N-1)/2}$$

The Vandermonde Ensemble

$$H = J^T J = V^T A^T A V = W \tilde{H} W^T$$

$$\Sigma \quad U^T A^T A U \quad \Sigma \quad = \quad \tilde{H}$$

$$\begin{bmatrix} \varepsilon^0 & & \\ & \ddots & \\ & & \varepsilon^{n-1} \end{bmatrix} \begin{bmatrix} & & \\ & \blacksquare & \\ & & \end{bmatrix} \begin{bmatrix} \varepsilon^0 & & \\ & \ddots & \\ & & \varepsilon^{n-1} \end{bmatrix} = \begin{bmatrix} & & \\ & /// & \\ & & \end{bmatrix}$$



$$\tilde{H}_{ij} = O(\varepsilon^{i+j-2})$$

$$\tilde{\lambda}^{(i)} = O(\varepsilon^{2(i-1)})$$

$$\tilde{v}_j^{(i)} = \delta_{ij} + O(\varepsilon^{|i-j|})$$

$$\lambda^{(i)} = O(\varepsilon^{2(i-1)})$$

$$v_j^{(i)} = W_{ij} + O(\varepsilon)$$

Conclusions

• Large biological networks are governed by a small number of combinations of parameters.

• The origin of this sloppiness is the **redundant behavior** of the constituent biochemical reactions.

• We have found a **new class of "sloppy" models**, which includes those of biological networks, and are defined by being a Vandermonde transformation of a random symmetric matrix.

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