



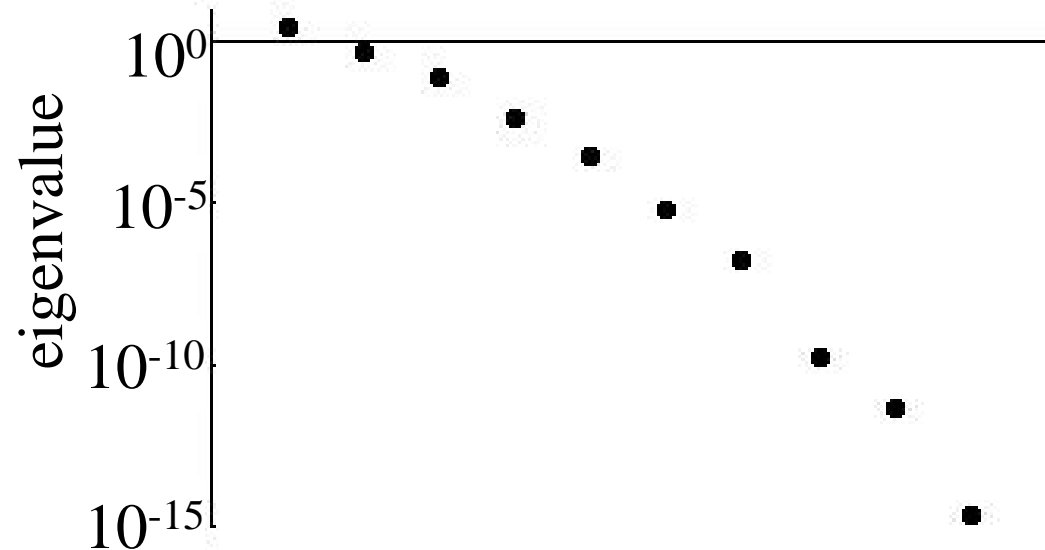
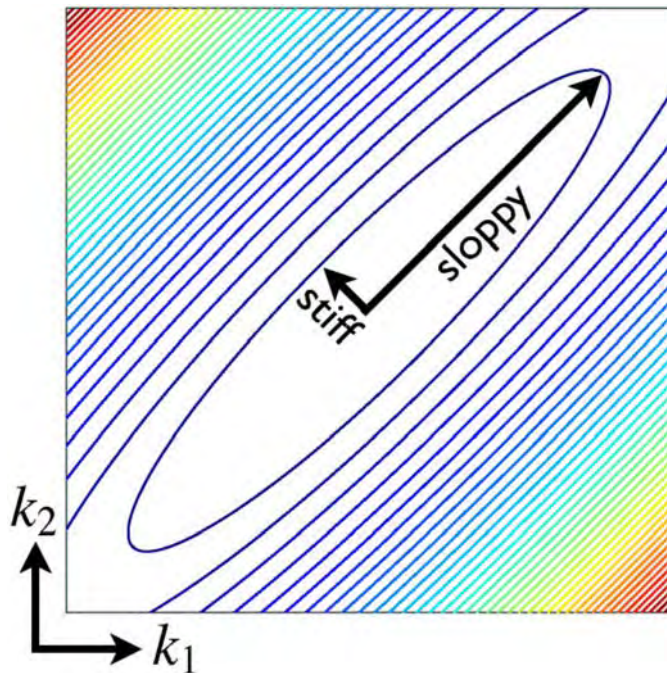
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Origins of sloppiness in biological networks

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DOE CSGF Meeting

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Biological networks

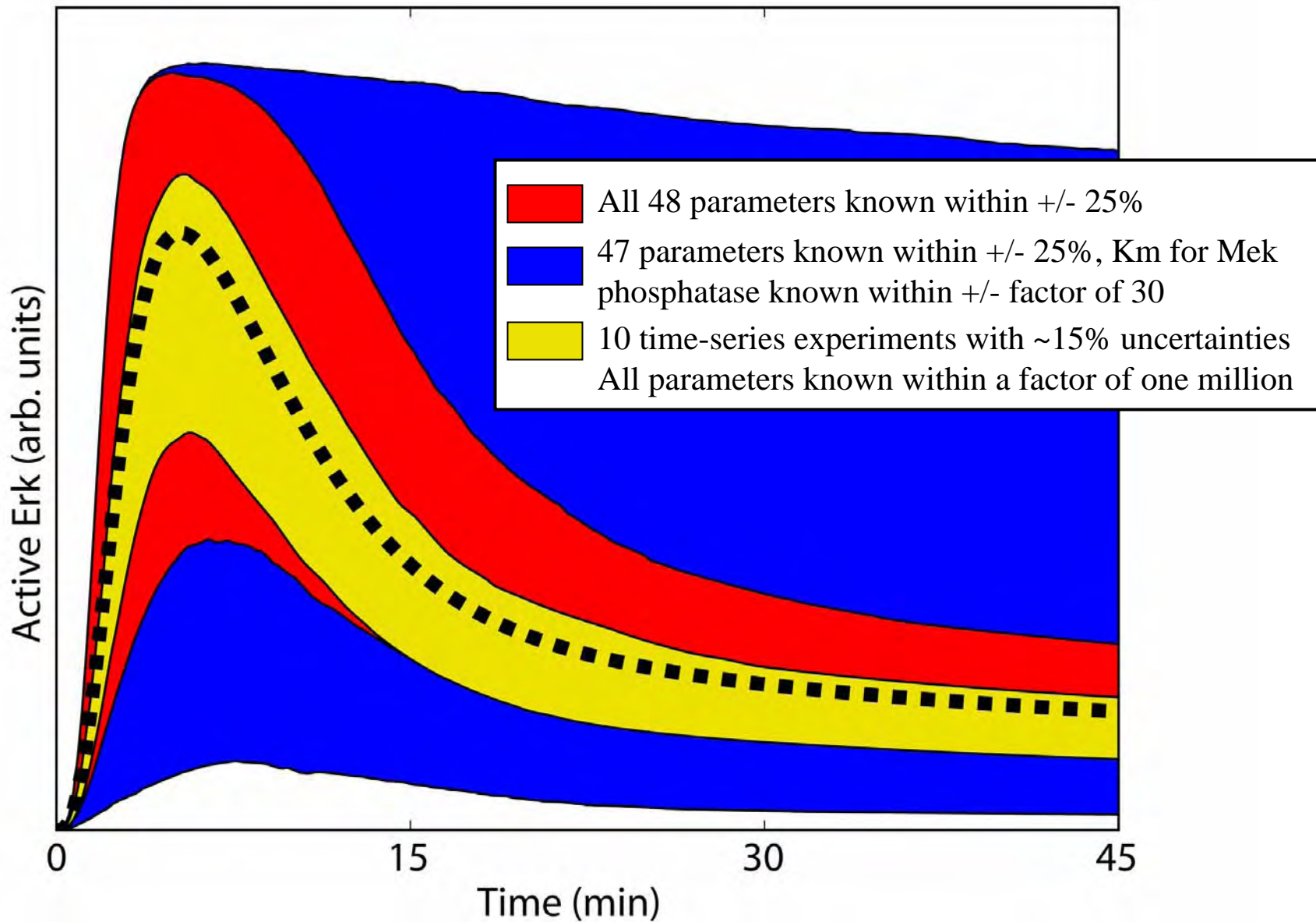


Growth factor signaling in PC12 cells

$$\begin{aligned} \frac{dEGF}{dt} &= -(krbEGF \times EGF \times freeEGFReceptor) + kruEGF \times boundEGFReceptor \\ \frac{dNGF}{dt} &= -(krbNGF \times NGF \times freeNGFReceptor) + kruNGF \times boundNGFReceptor \\ \frac{dfreeEGFReceptor}{dt} &= -(krbEGF \times EGF \times freeEGFReceptor) + kruEGF \times boundEGFReceptor \\ \frac{dboundEGFReceptor}{dt} &= krbEGF \times EGF \times freeEGFReceptor - kruEGF \times boundEGFReceptor \\ \frac{dfreeNGFReceptor}{dt} &= -(krbNGF \times NGF \times freeNGFReceptor) + kruNGF \times boundNGFReceptor \\ \frac{dboundNGFReceptor}{dt} &= krbNGF \times NGF \times freeNGFReceptor - kruNGF \times boundNGFReceptor \\ \frac{dSosInactive}{dt} &= -\left(\frac{kEGF \times boundEGFReceptor \times SosInactive}{SosInactive + KmEGF}\right) - \frac{kNGF \times boundNGFReceptor \times SosInactive}{SosInactive + KmNGF} \\ \frac{dSosActive}{dt} &= \frac{kEGF \times boundEGFReceptor \times SosInactive}{SosInactive + KmEGF} + \frac{kNGF \times boundNGFReceptor \times SosInactive}{SosInactive + KmNGF} \\ \frac{dP90RskInactive}{dt} &= -\left(\frac{kpP90Rsk \times ErkActive \times P90RskInactive}{P90RskInactive + KmP90Rsk}\right) \\ \frac{dP90RskActive}{dt} &= \frac{kpP90Rsk \times ErkActive \times P90RskInactive}{P90RskInactive + KmP90Rsk} \\ \frac{dRasInactive}{dt} &= -\left(\frac{kSos \times SosActive \times RasInactive}{RasInactive + KmSos}\right) + \frac{kRasGap \times RasGapActive \times RasActive}{RasActive + KmRasGap} \\ \frac{dRasActive}{dt} &= \frac{kSos \times SosActive \times RasInactive}{RasInactive + KmSos} - \frac{kRasGap \times RasGapActive \times RasActive}{RasActive + KmRasGap} \\ \frac{dRasGapActive}{dt} &= 0 \\ \frac{dRaf1Inactive}{dt} &= -\left(\frac{kRasToRaf1 \times RasActive \times Raf1Inactive}{Raf1Inactive + KmRasToRaf1}\right) + \frac{kdRaf1 \times Raf1PPtase \times Raf1Active}{Raf1Active + KmDraf1} \\ \frac{dRaf1Active}{dt} &= \frac{kRasToRaf1 \times RasActive \times Raf1Inactive}{Raf1Inactive + KmRasToRaf1} - \frac{kdRaf1 \times Raf1PPtase \times Raf1Active}{Raf1Active + KmDraf1} \\ \frac{dBraf1Inactive}{dt} &= -\left(\frac{kRap1ToBraf1 \times Rap1Active \times Braf1Inactive}{Braf1Inactive + KmRap1ToBraf1}\right) + \frac{kdBraf1 \times Braf1PPtase \times Braf1Active}{Braf1Active + KmDBraf1} \\ \frac{dBraf1Active}{dt} &= \frac{kRap1ToBraf1 \times Rap1Active \times Braf1Inactive}{Braf1Inactive + KmRap1ToBraf1} - \frac{kdBraf1 \times Braf1PPtase \times Braf1Active}{Braf1Active + KmDBraf1} \\ \frac{dMekInactive}{dt} &= -\left(\frac{kpRaf1 \times Raf1Active \times MekInactive}{MekInactive + KmPraf1}\right) - \frac{kpBRaf1 \times BRaf1Active \times MekInactive}{MekInactive + KmPBRaf1} \\ \frac{dMekActive}{dt} &= \frac{kpRaf1 \times Raf1Active \times MekInactive}{MekInactive + KmPraf1} + \frac{kpBRaf1 \times BRaf1Active \times MekInactive}{MekInactive + KmPBRaf1} \end{aligned}$$

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

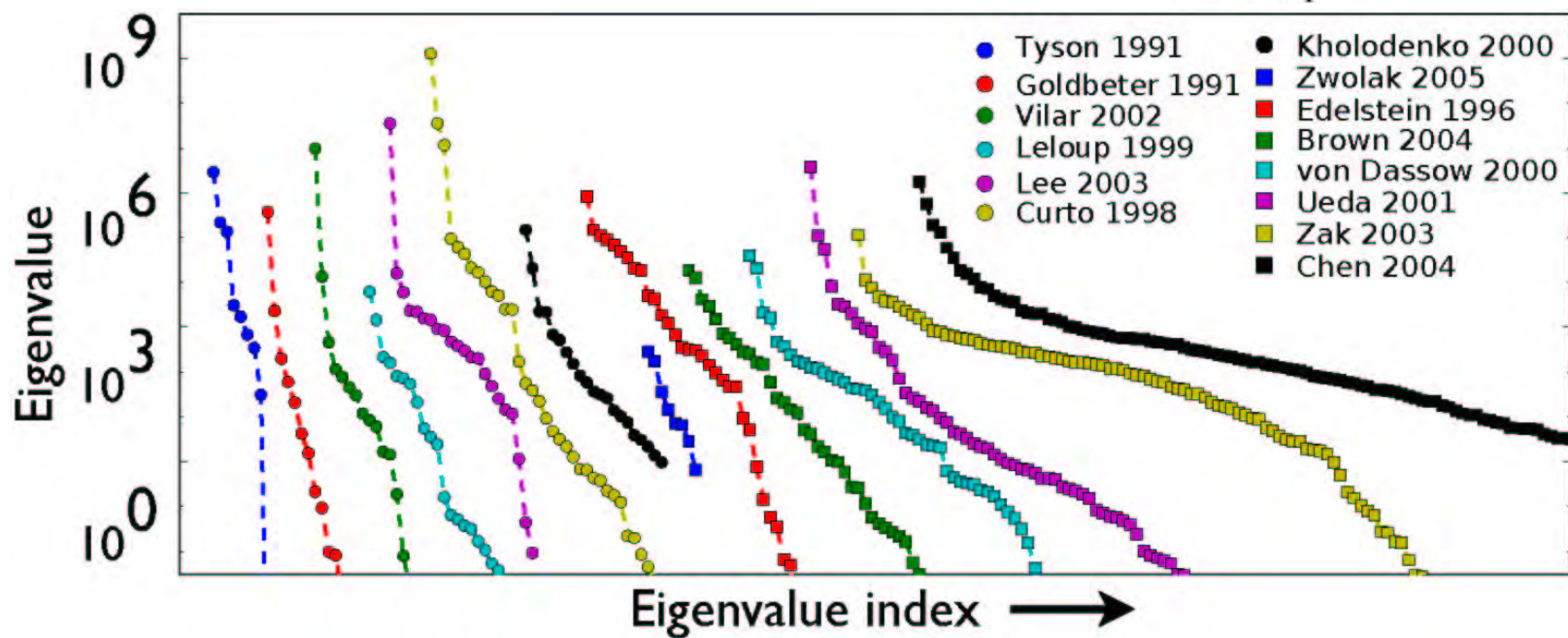
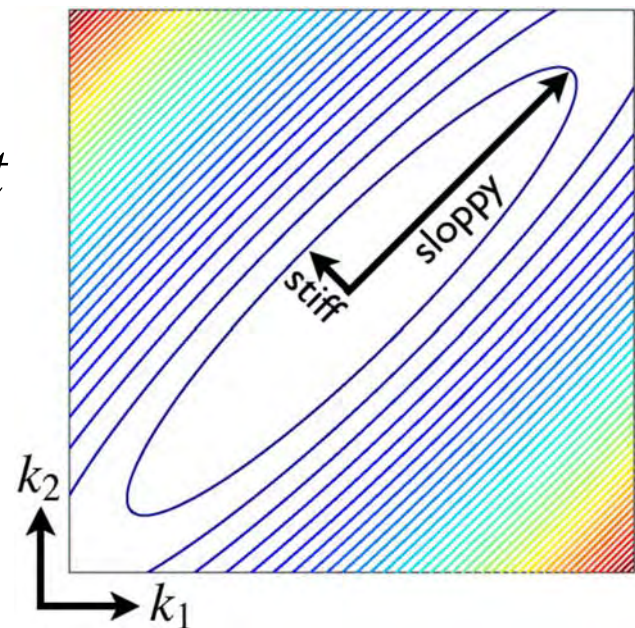
Prediction for Erk activation by EGF with PI3K inhibitor



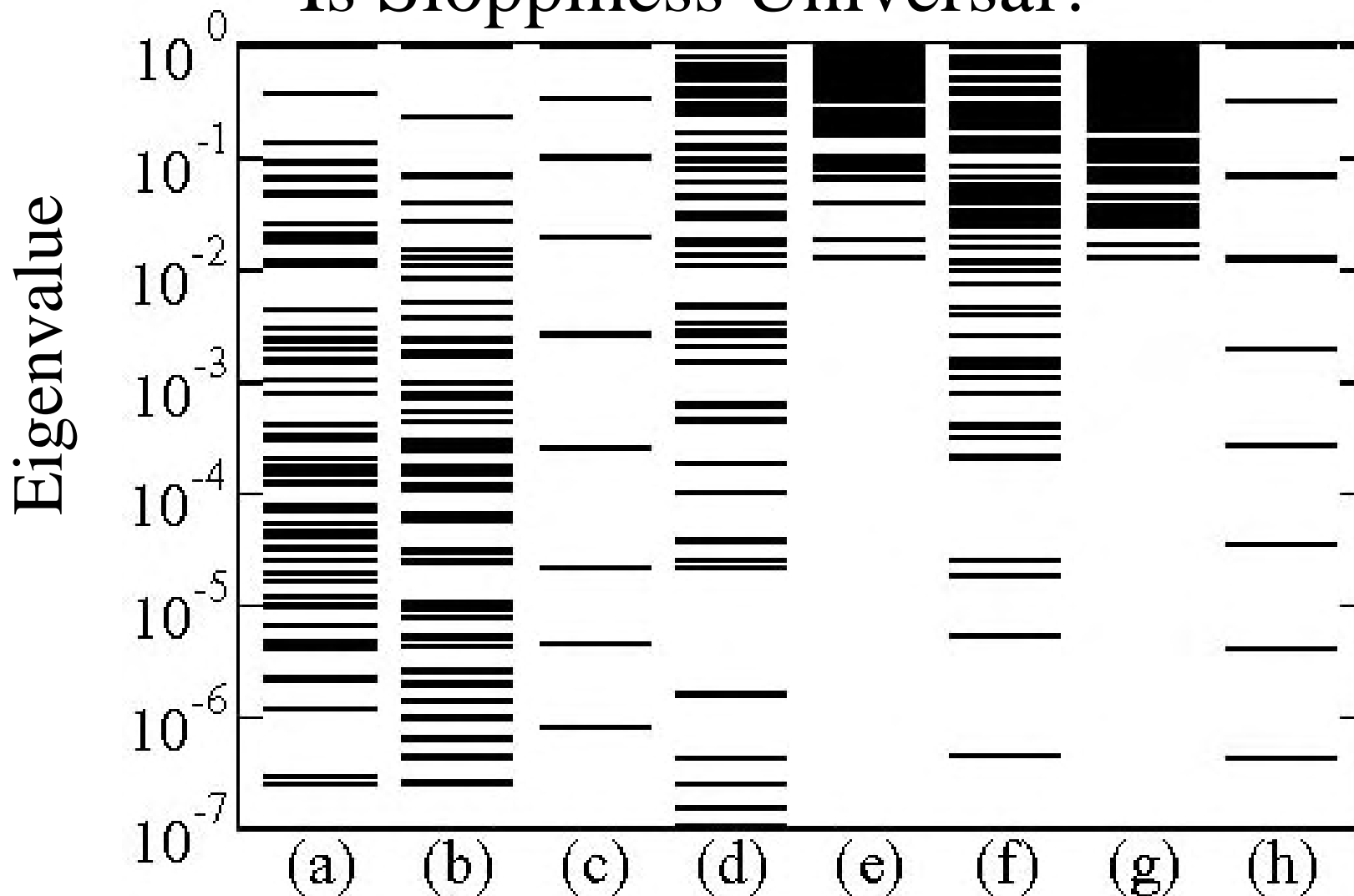
Parameter Fluctuations and Systems Fluctuations

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

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



Is Sloppiness Universal?



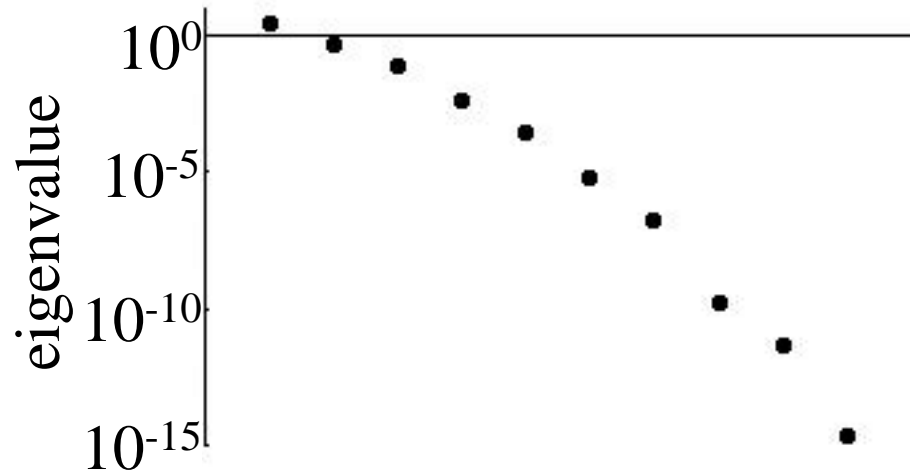
(a) Growth factor signaling in PC12 cells, (b) Quantum Monte Carlo (Jastrow parameters), (c) radioactivity from pharmaceutical isotopes, (d) 48 random exponentials from log uniform(± 25), (e) random symmetric matrix (GOE), (f) products of GOE random matrices, (g) Wishart matrix, (h) fitting monomials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

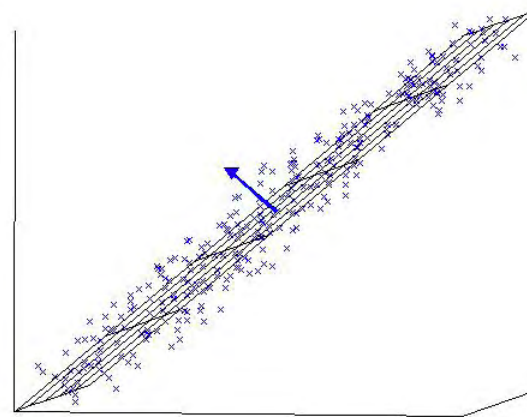
$$a(\vec{p}) = \vec{n} \cdot \vec{p}$$

Hessian is covariance matrix of data.

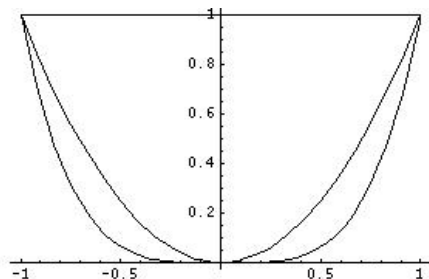
Wishart statistics for eigenvalues.

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

NOT SLOPPY

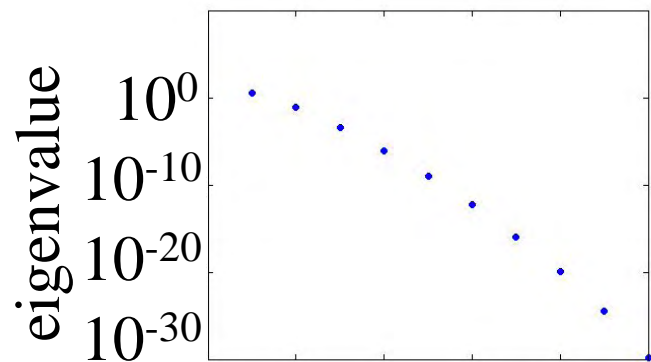


Sums of monomials



Hessian = Hilbert matrix

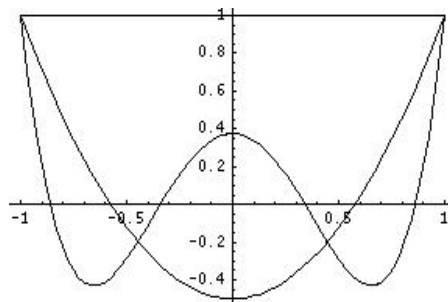
$$H_{ij} = \frac{2}{i+j+1}$$



SLOPPY

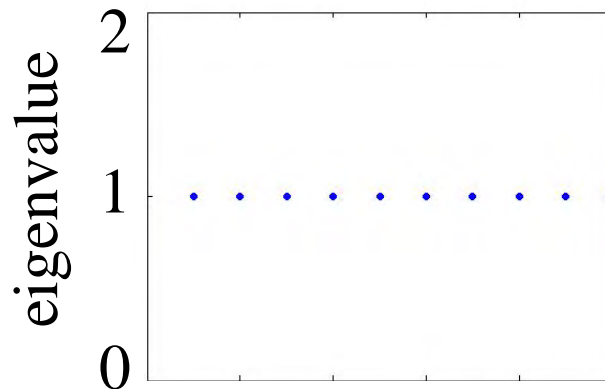


Sums of Shifted Legendre polynomials



Hessian = Identity matrix

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



NOT SLOPPY

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



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.

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

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

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

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

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

The Vandermonde Ensemble

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

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

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

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

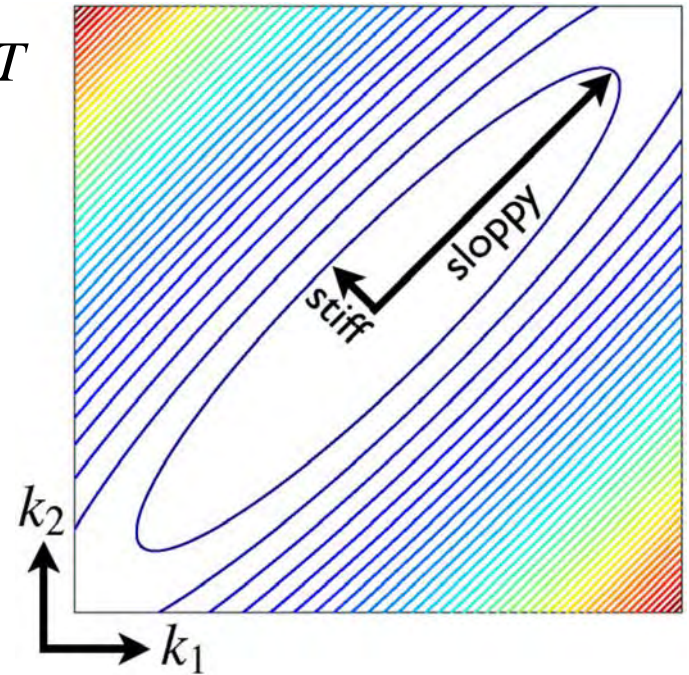
$$\tilde{\lambda}^{(i)} = O(\varepsilon^{2(i-1)})$$

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



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

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



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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