

# **Fitting Decaying Exponentials**

# Classic ill-posed inverse problem

Given Geiger counter measurements from a radioactive pile, can we recover the identity of the elements and/or predict future radioactivity? Good fits with bad decay rates!



 $y(A, \gamma, t) = A_1 e^{-\gamma} {}_1^t + A_2 e^{-\gamma} {}_2^t + A_3 e^{-\gamma} {}_3^t$ **6 Parameter Fit** 

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### Biologists study which proteins talk to which. Modeling?



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Thursday, September 26, 13

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### **48 Parameter Fit!**



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### **48 Parameter Fit!**



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<u>d()9000000000000000000000000000000000000</u>		$\begin{split} & + \underline{b}_{2n} \left[ \text{PRRAderial} \right] & \frac{\text{pressure}}{\left[ \text{PRRAderial} \right] \times \left\{ 1 \le t \le$	a cPBMotion a (Athenion) (Athenion)
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### **48 Parameter Fit!**

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### **48 Parameter Fit!**

# **Ensemble of Models**

We want to consider not just minimum cost fits, but all parameter sets consistent with the available data. New level of abstraction: *statistical mechanics in model space*.

Don't trust predictions that vary



#### Cost is least-squares fit

$$C(\vec{\theta}) = \frac{1}{2} \sum_{i=1}^{N_D} \frac{(y(\vec{\theta}) - y_i)^2}{\sigma_i^2}$$

### Boltzmann weights exp(-C/T)

O is chemical concentration  $y(t_i)$ , or rate constant  $\theta_n$ ...

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$$\left\langle O\right\rangle = \frac{1}{N_E} \sum_{i=1}^{N_E} O(\vec{\theta_i})$$
$$\sigma_O^2 = \left\langle O^2(\vec{\theta_i}) \right\rangle - \left\langle O(\vec{\theta_i}) \right\rangle^2$$

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#### Cost is least-squares fit

$$C(\vec{\theta}) = \frac{1}{2} \sum_{i=1}^{N_D} \frac{(y(\vec{\theta}) - y_i)^2}{\sigma_i^2}$$

### Boltzmann weights exp(-C/T)

$$\left\langle O \right\rangle = \frac{1}{N_E} \sum_{i=1}^{N_E} O(\vec{\theta_i})$$
$$\sigma_O^2 = \left\langle O^2(\vec{\theta_i}) \right\rangle - \left\langle O(\vec{\theta_i}) \right\rangle$$

O is chemical concentration  $y(t_i)$ , or rate constant  $\theta_n$ ...



eigenparameter

0g<sub>e</sub>

All parameters vary by minimum factor of 50, some by a million
Not robust: four or five "stiff" linear combinations of parameters; 44 sloppy
Are predictions

possible?

5 stiff -5 sloppy -10 -15 -20 0 5 10 15 20 25 30 35 40 45 50

sorted eigenparameter number

# Predictions are Possible





# Model predicts that the left branch isn't important

Parameters fluctuate orders of magnitude, but still predictive!

# Parameter Indeterminacy and Sloppiness



Note: Horizontal scale shrunk by 1000 times Aspect ratio = Human hair

48 parameter fits are sloppy: Many parameter sets give almost equally good fits

A few 'stiff' constrained directions allow model to remain predictive



# **Sloppy Universality Outside Bio**

### Sloppy Systems

- Enormous range of eigenvalues
- Roughly equal density in log
- Observed in broad range of systems

From accelerator <sup>1</sup> design to insect flight, multiparameter fits are sloppy



# The Model Manifold

Two exponentials  $\theta_1$ ,  $\theta_2$ fit to three data points  $y_1$ ,  $y_2$ ,  $y_3$  $y_n = \exp(-\theta_1 t_n) + \exp(-\theta_2 t_n)$ 

**Parameter space** Stiff and sloppy directions Canyons, Plateaus





Data space Manifold of model predictions Parameters as coordinates Model boundaries  $\theta_n = \pm \infty$ ,  $\theta_m$ cause Plateaus Metric  $g_{uv}$  from distance to data

# Geodesics

### "Straight line" in curved space Shortest path between points



Easy to find cost minimum using polar geodesic coordinates Υ<sub>1</sub>, Υ<sub>2</sub>



Cost contours in geodesic coordinates nearly concentric circles! Use this for algorithms...

# The Model Manifold is a *Hyper-Ribbon*

•Hyper-ribbon: object that is longer than wide, wider than thick, thicker than ...

•Thick directions traversed by stiff eigenparameters, thin as sloppy directions varied.



# Widths along geodesics track eigenvalues almost perfectly!

Sum of many exponentials, fit to y(0), y(1)data predictions at y(1/4), y(1/2), y(3/4)

# Edges of the model manifold

*Fitting Exponentials* Top: Flat model manifold; articulated edges = plateau Bottom: Stretch to uniform aspect ratio (Isabel Kloumann)





# Edges of the model manifold

*Fitting Exponentials* Top: Flat model manifold; articulated edges = plateau Bottom: Stretch to uniform aspect ratio (Isabel Kloumann)









# Why is it so thin and flat?

Model  $f(t, \theta)$  analytic:  $f^{(n)}(t)/n! \leq R^{-n}$ Polynomial fit  $P_{m-1}(t)$ to  $f(t_1), ..., f(t_m)$ Interpolation convergence theorem  $\Delta f_{m+1} = f(t) - P_{m-1}(t)$  $< (t-t_1) (t-t_2) \dots (t-t_m) f^{(m)}(\xi)/m!$  $\sim (\Delta t / R)^m$ More than one data per R





**Hyper-ribbon:** Cross section constraining m points has width  $W_{m+1} \sim \Delta f_{m+1} \sim (\Delta t / R)^m$ 

**Extrinsic flatness:** N=M trivially flat, extra data deviates  $\varepsilon \sim \Delta f_{N+1}$ , so curvature  $K \sim \varepsilon / W_j^2 \sim (\Delta t/R)^{N+1-j} / W_j$ 

Thursday, September 26, 13

### Which Rate Constants are in the Stiffest Eigenvector?



Eigenvector components along the bare parameters reveal which ones are most important for a given eigenvector.



### Physics: Sloppiness and Emergence Ben Machta, Ricky Chachra

### Emergence of distilled laws from microscopic complexity



Ising: long bonds Diffusion: long hops Irrelevant on macroscale



### Both sloppy at long-wavelengths









### Physics: Sloppiness and Emergence Ben Machta, Ricky Chachra

Kullback-Liebler divergence metric Sloppy after coarse graining (in space for Ising, time for diffusion)







# **Generation of Reduced Models**

#### Mark Transtrum (not me)

Can we coarse-grain sloppy models? If most parameter directions are useless, why not remove some?

- Transtrum has *systematic* method!
- (1) Geodesic along sloppiest direction to nearby point on manifold boundary
  (2) Eigendirection simplifies at model boundary to chemically reasonable simplified model

Coarse-graining = boundaries of model manifold.



### **Generation of Reduced Models** Mark Transtrum (not me)



#### 48 params **29 ODEs**



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### Generation of Reduced Models Mark Transtrum (not me)



12 params 6 ODEs  $10^{3}$  $10^{1}$  $10^{-1}$  $10^{-3}$  $10^{-5}$  $10^{-7}$  $10^{-9}$  $10^{-11}$  $10^{-13}$ d

$$\begin{split} [\mathrm{bEGFR}] &= \left\{ \begin{smallmatrix} 1 & \mathrm{EGF} & \mathrm{Present} \\ 0 & \mathrm{Otherwise} \end{smallmatrix} \right. \\ &\frac{d}{dt} [\mathrm{bNGFR}] = \theta_1 [\mathrm{NGF}] [\mathrm{fNGFR}] \\ &\frac{d}{dt} [\mathrm{bNGFR}] = -\theta_1 [\mathrm{NGF}] [\mathrm{fNGFR}] \\ &\frac{d}{dt} [\mathrm{RasA}] = -[\mathrm{RasA}] [\widetilde{\mathrm{P90RskA}}] + \theta_2 [\mathrm{bEGFR}] + \theta_3 [\mathrm{bNGFR}] \\ &\frac{d}{dt} [\widetilde{\mathrm{RasA}}] = -[\mathrm{RasA}] [\widetilde{\mathrm{P90RskA}}] + \theta_2 [\mathrm{bEGFR}] + \theta_3 [\mathrm{bNGFR}] \\ &\frac{d}{dt} [\widetilde{\mathrm{Raf1A}}] = \theta_4 [\mathrm{RasA}] - \theta_5 [\widetilde{\mathrm{Raf1A}}] / ([\widetilde{\mathrm{Raf1A}}] + \theta_6) \\ &\frac{d}{dt} [\mathrm{C3GA}] = \theta_7 [\mathrm{bNGFR}] [\mathrm{C3GI}] \\ &[\mathrm{Rap1A}] = \theta_8 [\mathrm{C3GA}] \\ &[\mathrm{MekA}] = [\widetilde{\mathrm{Raf1A}}] [\mathrm{MekI}] + \theta_9 [\mathrm{Rap1A}] \\ &\frac{d}{dt} [\mathrm{Erk}] = -\theta_{10} [\mathrm{ErkA}] + \theta_{11} [\mathrm{MekA}] [\mathrm{ErkI}] \\ &\frac{d}{dt} [\mathrm{P90RskA}] = \theta_{12} [\mathrm{ErkA}] \end{split}$$

# Reduced model fits all experimental data

 $\theta_9 = \frac{[\text{BRafI}]\,\text{kRap1toBRaf}\,\text{KmdBRAF}\,\text{kpBRaf}\,\text{KmdMek}}{[\text{PP2AA}]\,[\text{Raf1PPtase}]\,\text{kdBRaf}\,\text{KmRap1toBRaf}\,\text{kdMek}}$ 

Effective 'renormalized' params

# **Sloppy Applications** Several applications emerge



A. Fitting data vs. measuring parameters (Gutenkunst)

B. Finding best fits by geodesic acceleration (Transtrum)



C. Optimal experimental design (Casey)



E. Estimating systematic errors: DFT and interatomic potentials (Jacobsen et al.) D. Sloppy fitness and evolution (Gutenkunst)



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- Easy to Fit (14 expts); Measuring huge job (48 params, 25%)
- One missing parameter measurement = No predictivity
- Sloppy Directions = Enormous Fluctuations in Parameters
- Sloppy Directions often do not impinge on predictivity



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### **B. Finding best fits: Geodesic acceleration**

10





Model Graph add weight λ of parameter metric yields Levenberg-Marquardt: Step size now limited by curvature

Geodesic Paths nearly circles Follow local geodesic velocity?  $\delta \theta^{\mu} = -g_{\mu\nu} \nabla_{\nu} C$  $\rightarrow$  Gauss-Newton

→ Hits manifold boundary



Algorithm	Success Rate	Mean njev	Mean nfev
Traditional $LM + accel$	65%	258	1494
Traditional LM	33%	2002	4003
Trust Region LM	12%	1517	1649
BFGS	8%	5363	5365

Follow parabola, *geodesic acceleration* Cheap to calculate; faster; more success

# B. Finding best fits: Model manifold dynamics (Isabel Kloumann)

Dynamics on the model manifold: Searching for the best fit

- Jeffrey's prior plus noise
- Big noise concentrates on manifold edges
- Note scales: flat
- Top: Levenberg-Marquardt
- Bottom: Geodesic acceleration
- Large points: Initial conditions which fail to converge to best fit

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### C. EGFR Trafficking Model Fergal Casey, Cerione lab

Active research, Cerione lab: testing hypothesis, experimental design (Cool1Ξβ-PIX)
41 chemicals, 53 rate constants; only 11 of 41 species can be measured
Does Cool-1 triple complex sequester Cbl, delay endocytosis in wild type NIH3T3 cells?



### **C. Trafficking: experimental design** Which experiment best reduces prediction uncertainty?

- Amount of triple complex was not well predicted
- V-optimal experimental design: single & multiple measurements
- Total active Cdc42 at 10 min.; Cerione independently concurs
- Experiment indicates significant sequestering in wild type
- Predictivity without decreasing parameter uncertainty





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# D. Evolution in Chemotype space Implications of sloppiness?





Fitness gain from first successful mutation

- Culture of identical bacteria, one mutation at a time
- Mutation changes one or two rate constants (no *pleiotropy*): orthogonal moves in rate constant (chemotype) space
- Cusps in first fitness gain (one for each rate constant, big gap)
- Multiple mutations get stuck on ridge in sloppy landscape

### **E. Bayesian Errors for Atoms** 'Sloppy Model' Approach to Error Estimation of Interatomic Potentials Søren Frederiksen, Karsten W. Jacobsen, Kevin Brown, JPS



Quantum Electronic Structure (Si) 90 atoms (Mo) (Arias)



Atomistic potential 820,000 Mo atoms (Jacobsen, Schiøtz)

### **Interatomic Potentials** $V(r_1, r_2, ...)$

- Fast to compute
- Limit  $m_e/M \rightarrow 0$  justified
- Guess functional form
   Pair potential ∑ V(r<sub>i</sub>-r<sub>j</sub>) poor
   Bond angle dependence
   Coordination dependence
- Fit to experiment (old)
- Fit to forces from electronic structure calculations (new)

### **17 Parameter Fit**

# Ensemble of Acceptable Fits to Data

### Not transferable

Unknown errors

- 3% elastic constant
- 10% forces
- 100% fcc-bcc, dislocation core

Best fit is *sloppy*: ensemble of fits that aren't much worse than best fit. **Ensemble in Model Space!**  $T_0$  set by equipartition energy = best cost

> Error Bars from quality of best fit



#### Green = DFT, Red = Fits

# E. Interatomic Potential Error Bars Ensemble of Acceptable Fits to Data

### Not transferable

Unknown errors

- 3% elastic constant
- 10% forces
- 100% fcc-bcc, dislocation core



Best fit is *sloppy*: ensemble of fits that aren't much worse than best fit. **Ensemble in Model Space!**  $T_0$  set by equipartition energy = best cost

> Error Bars from quality of best fit



### Sloppy Molybdenum: Does it Work? Estimating *Systematic* Errors Bayesian error $\sigma_i$ gives total error if ratio $r = \text{error}_i/\sigma_i$ distributed as a Gaussian: cumulative distribution $P(r) = Erf(r/\sqrt{2})$



### Systematic Error Estimates for DFT GGA-DFT as Multiparameter Fit? J. J. Mortensen, K. Kaasbjerg, S. L. Frederiksen, J. K. Nørskov, JPS, K. W. Jacobsen, (Anja Tuftelund, Vivien Petzold, Thomas Bligaard)



Enhancement factor  $F_x(s)$ in the exchange energy  $E_x$ Large fluctuations



Actual error / predicted error Deviation from experiment well described by ensemble!



# Where is Sloppiness From? Fitting Polynomials to Data



Fitting Monomials to Data  $y = \sum a_n x^n$ Functional Forms Same Hessian  $H_{ij} = 1/(i+j+1)$ Hilbert matrix: famous



Orthogonal Polynomials  $y = \sum b_n L_n(x)$ Functional Forms Distinct Eigen Parameters *Hessian*  $H_{ii} = \delta_{ii}$ 

Sloppiness arises when bare parameters skew in eigenbasis

Small Determinant!  $|H| = \prod \lambda_n$ 

# Proposed universal ensemble Why are they sloppy?

**Assumptions:** (Not one experiment per parameter) **i. Model predictions all depend on every parameter,** *symmetrically*:  $y_i(\theta_1, \theta_2, \theta_3) = y_i(\theta_2, \theta_3, \theta_1)$ 

ii. Parameters are nearly degenerate:  $\theta_{i} = \theta_{0} + \varepsilon_{i}$ 

$$H = J^{T}J = V^{T}A^{T}AV$$

$$V = \begin{bmatrix} 1 & 1 & \cdots & 1 \\ \epsilon_{1} & \epsilon_{2} & \cdots & \epsilon_{N} \\ \vdots & \vdots & \ddots & \vdots \\ \epsilon_{1}^{d} & \epsilon_{2}^{d} & \cdots & \epsilon_{N}^{d} \end{bmatrix}$$
Vandermonde  
Matrix
$$det(V) = \prod_{i < j} (\epsilon_{i} - \epsilon_{j}) \propto \epsilon^{N(N-1)/2}$$

Implies enormous range of eigenvalues
Implies equal spacing of log eigenvalues
Like universality for random matrices

# 48 Parameter "Fit" to Data

### Cost is Energy

$$C(\vec{\theta}) = \frac{1}{2} \sum_{i=1}^{N_D} \frac{(y(\vec{\theta}) - y_i)^2}{\sigma_i^2}$$

### Ensemble of Fits Gives Error Bars





Exploring Parameter Space Rugged? More like Grand Canyon (Josh)

Glasses: Rugged Landscape Metastable Local Valleys Transition State Passes Optimization Hell: Golf Course Sloppy Models Minima: 5 stiff, N-5 sloppy Search: Flat planes with cliffs







# **Climate Change**

Climate models contain many unknown parameters, fit to data

- General Circulation Model (air, oceans, clouds), exploring doubling of  $CO_2$
- 21 total parameters
- Initial conditions and (only)
- 6 "cloud dynamics" parameters varied
- Heating typically 3.4K, ranged from
   2K to > 11K

Stainforth et al., *Uncertainty in predictions of the climate response to rising levels of greenhouse gases*, **Nature 433**, 403-406 (2005)



Thursday, September 26, 13

# **Neural Networks**

#### Mark Transtrum



. . .

Neural net "trained" to predict Black-Scholes output option price OP, given inputs volatility V, time t, and strike S
Each circular "neuron" has sigmoidal response signal s<sub>j</sub> to input signals s<sub>i</sub>:

 $s_j = \tanh(\sum_i w_{ij} s_i)$ 

Inputs and outputs scaled to [-1,1]
101 parameters w<sub>ij</sub> fit to 1530 data points

Mark Transtrum

(http://www.scientific-consultants.com/nnbd.html)

# Curvatures

### Intrinsic curvature $R^{\mu}_{\nu\alpha\beta}$

- determines geodesic shortest paths
- independent of embedding, parameters

### **Extrinsic curvature**

- also measures bending in embedding space (i.e., cylinder)
- independent of parameters
- Shape operator, geodesic curvature

### **Parameter effects**

"curvature"

- Usually much the largest
- Defined in analogy to Geo extrinsic curvature (projecting Cur out of surface, rather than into)



# No intrinsic curvature





Geodesic

Curvature



# Why is it so thin?

Model  $f(t, \theta)$  analytic:  $f^{(n)}(t)/n! \leq R^{-n}$ Polynomial fit  $P_{m-1}(t)$ to  $f(t_1), ..., f(t_m)$ Interpolation convergence theorem  $\Delta f_{m+1} = f(t) - P_{m-1}(t)$  $< (t-t_1)...(t-t_m) f^{(m)}(\xi)/m!$  $\sim (\Delta t / R)^m$ More than one data per R



*Hyper-ribbon:* Cross-section constraining m points has width  $W_{m+1} \sim \Delta f_{m+1} \sim (\Delta t/R)^m$ 

# B. Finding sloppy subsystems Model reduction?

- Sloppy model as multiple redundant parameters?
- Subsystem = subspace of parameters p<sub>i</sub> with similar effects on model behavior
- Similar = same effects on residuals r<sub>i</sub>
- Apply clustering algorithm to rows of  $J_{ij} = \partial r_i / \partial p_i$

Continuum mechanics, renormalization group, Lyapunov exponents can also be viewed as sloppy model reduction





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"Sloppy systems biology: tight predictions with loose parameters", Ryan N. Gutenkunst, Joshua J. Waterfall, Fergal P. Casey, Kevin S. Brown, Christopher R. Myers & James P. Sethna (submitted).

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"SloppyCell" systems biology modeling software, Ryan N. Gutenkunst, Christopher R. Myers, Kevin S. Brown, Joshua J. Waterfall, Fergal P. Casey, James P. Sethna http://www.lassp.cornell.edu/sethna/GeneDynamics/, SourceForge repository at http://sloppycell.sourceforge.net/