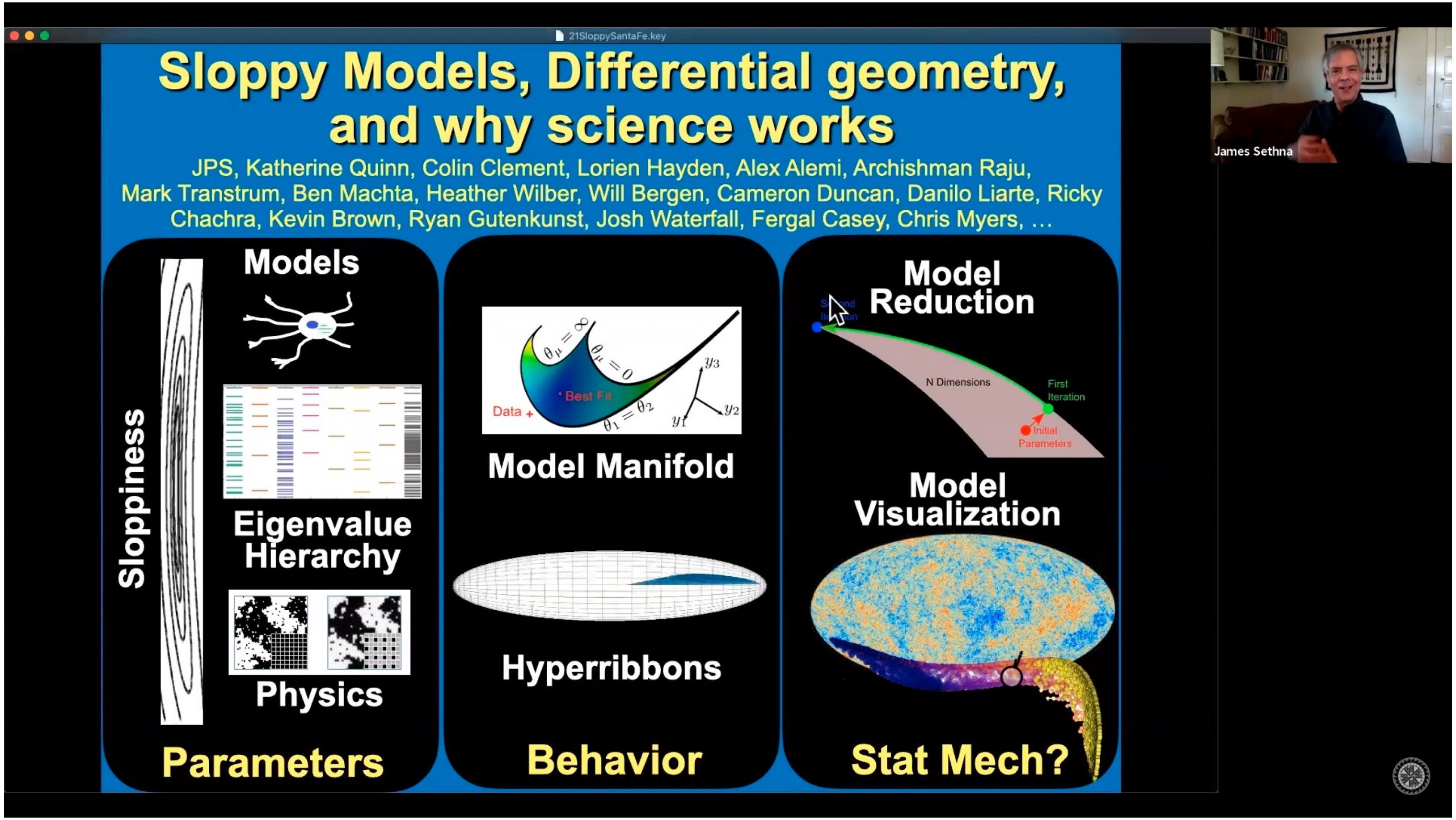
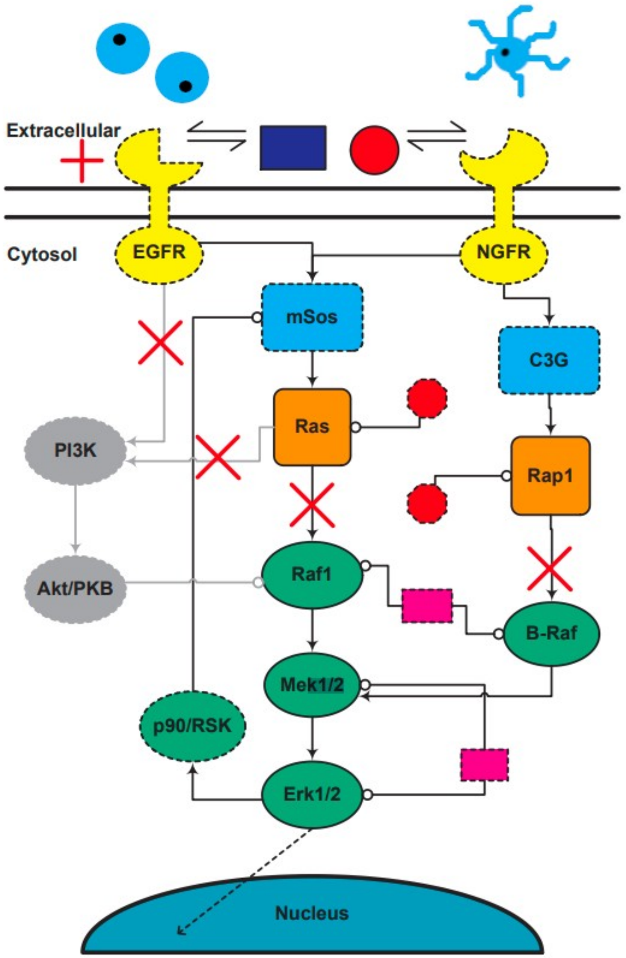
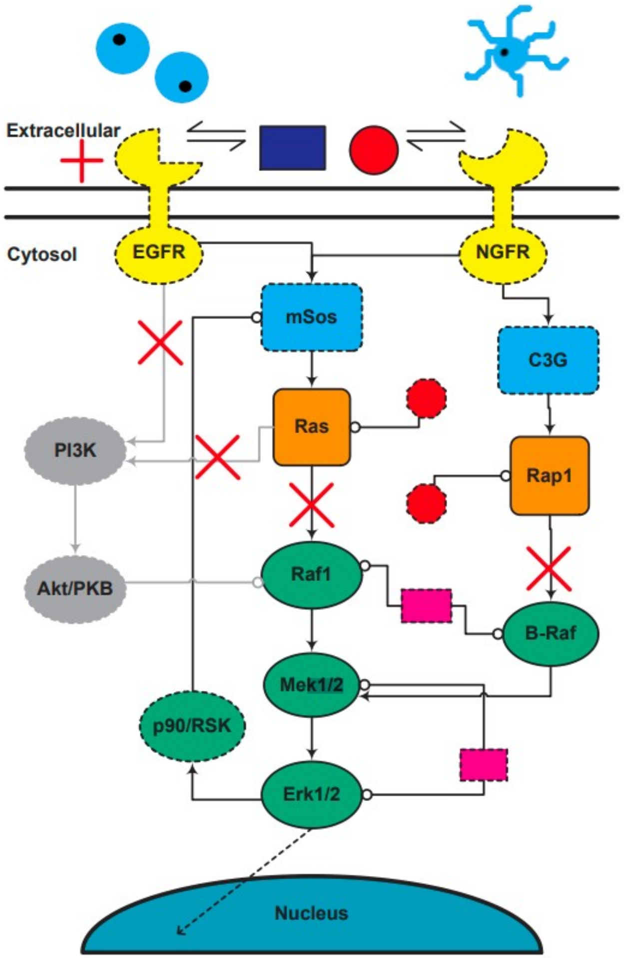


21SloppySantaFe.key
Sloppy Models, Differential geometry, and why science works
JPS, Katherine Quinn, Colin Clement, Lorien Hayden, Alex Alemi, Archishman Raju, Mark Transtrum, Ben Machta, Heather Wilber, Will Bergen, Cameron Duncan, Danilo Liarte, Ricky Chachra, Kevin Brown, Ryan Gutenkunst, Josh Waterfall, Fergal Casey, Chris Myers, …
Sloppiness
Models
Eigenvalue Hierarchy
Physics
Parameters
Data
Best Fit
$\theta_\mu = \infty$
$\theta_\mu = 0$
$\theta_1 = \theta_2$
y_1
y_2
y_3
Model Manifold
Hyperribbons
Behavior
Model Reduction
N Dimensions
First Iteration
Initial Parameters
Model Visualization
Stat Mech?
James Sethna



Extracellular
Cytosol
EGFR
NGFR
mSos
C3G
Ras
Rap1
PI3K
Akt/PKB
Raf1
B-Raf
Mek1/2
p90/RSK
Erk1/2
Nucleus


Extracellular
Cytosol
EGFR
NGFR
mSos
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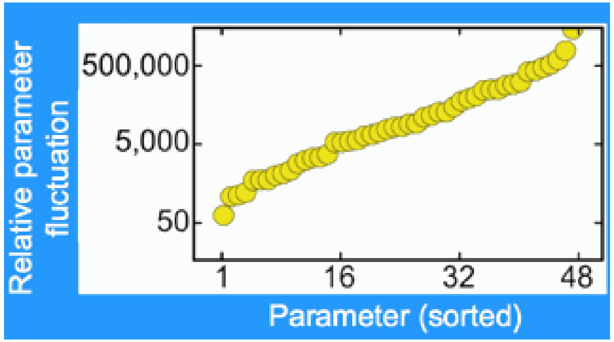
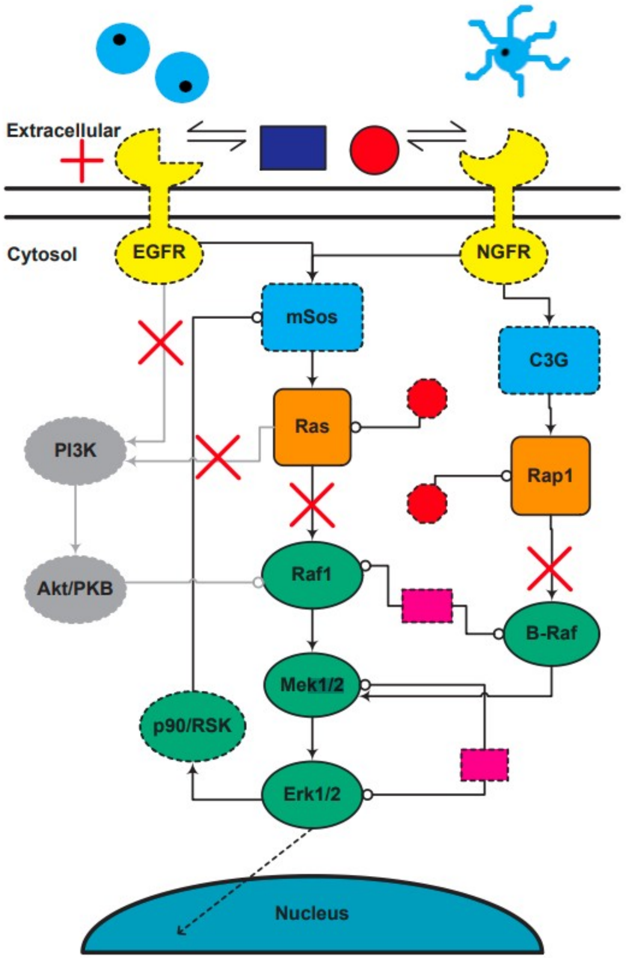
Ras
Rap1
PI3K
Akt/PKB
Raf1
B-Raf
Mek1/2
p90/RSK
Erk1/2
Nucleus


Relative parameter fluctuation
500,000
5,000
50
1
16
32
48
Parameter (sorted)


Extracellular
Cytosol
EGFR
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Ras
Rap1
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Akt/PKB
Raf1
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Mek1/2
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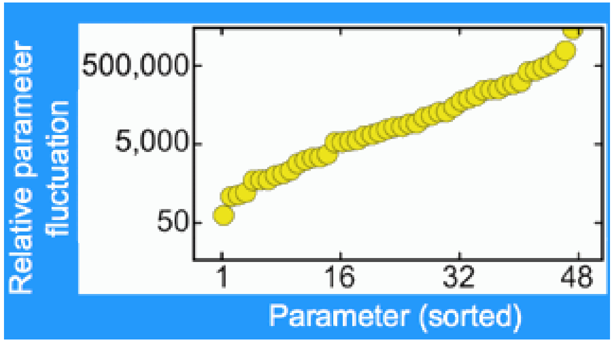
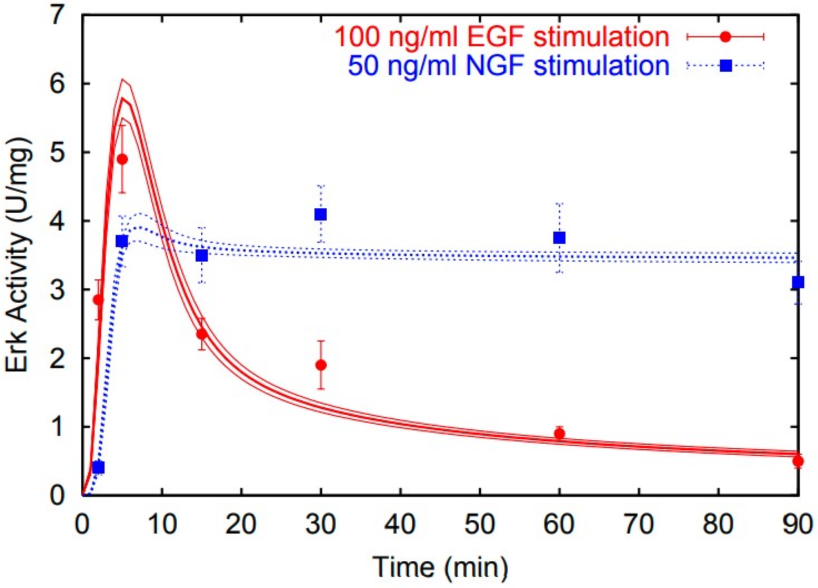
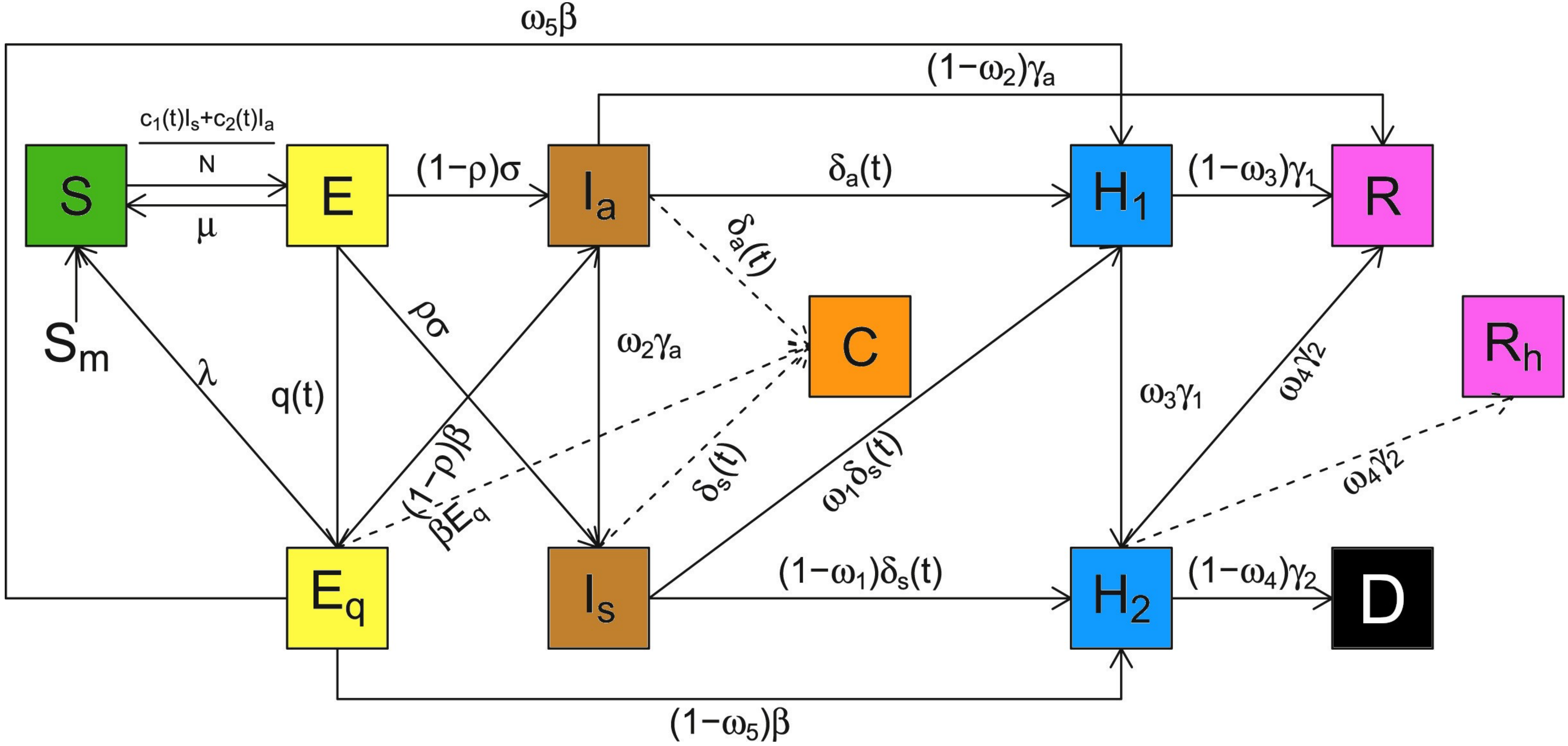
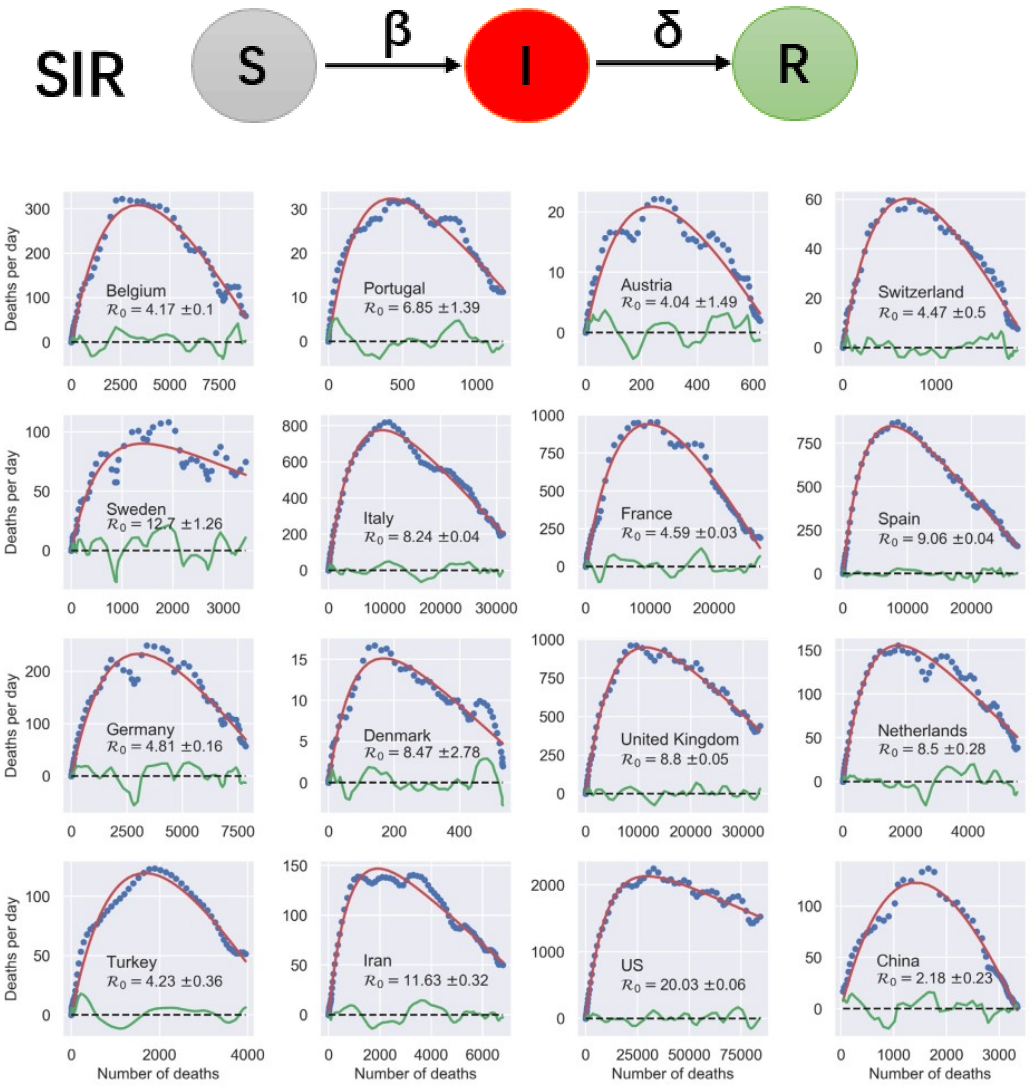
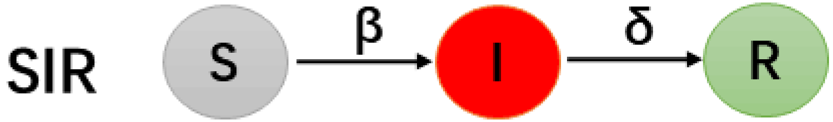

Relative parameter fluctuation
500,000
5,000
50
1
16
32
48
Parameter (sorted)

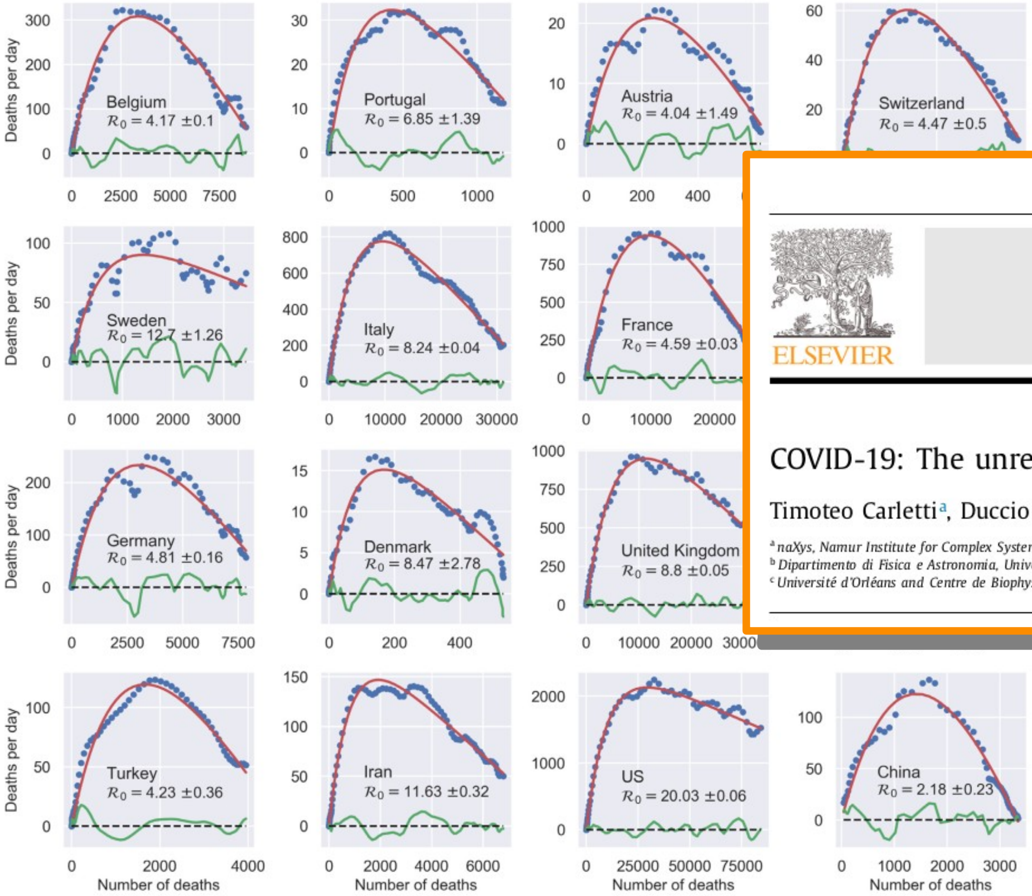

100 ng/ml EGF stimulation
50 ng/ml NGF stimulation
Erk Activity (U/mg)
Time (min)
0
1
2
3
4
5
6
7
10
20
30
40
50
60
70
80
90

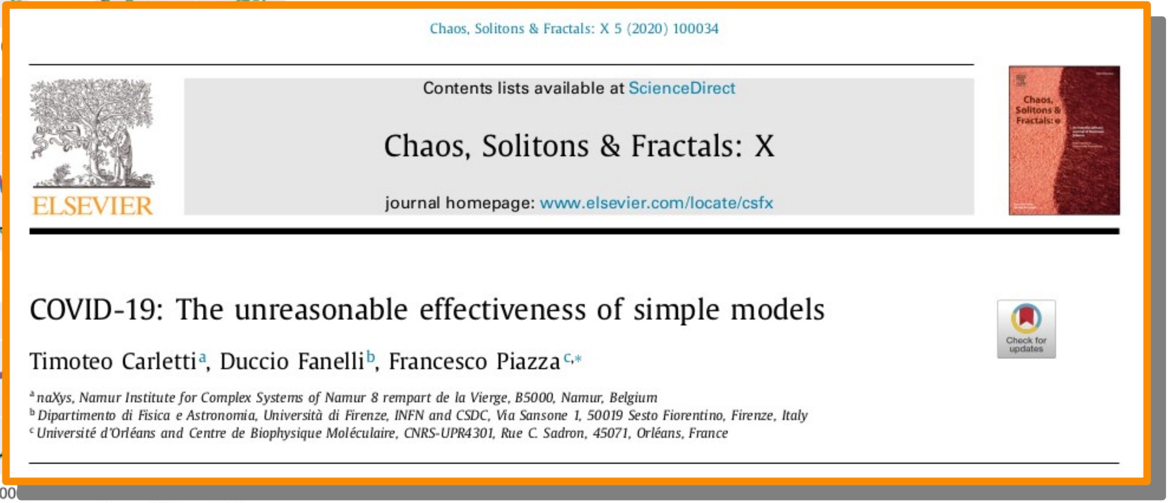


ω5β
(1−ω2)γa
c1(t)Is+c2(t)Ia
N
μ
(1−ρ)σ
δa(t)
(1−ω3)γ1
S
E
Ia
H1
R
Sm
ρσ
C
Rh
λ
q(t)
ω2γa
ω3γ1
ω4γ2
(1−ρ)β
βEq
δs(t)
ω1δs(t)
ω4γ2
Eq
Is
(1−ω1)δs(t)
H2
(1−ω4)γ2
D
(1−ω5)β


SIR
S
β
I
δ
R
Belgium
$\mathcal{R}_0 = 4.17 \pm 0.1$
Portugal
$\mathcal{R}_0 = 6.85 \pm 1.39$
Austria
$\mathcal{R}_0 = 4.04 \pm 1.49$
Switzerland
$\mathcal{R}_0 = 4.47 \pm 0.5$
Sweden
$\mathcal{R}_0 = 12.7 \pm 1.26$
Italy
$\mathcal{R}_0 = 8.24 \pm 0.04$
France
$\mathcal{R}_0 = 4.59 \pm 0.03$
Spain
$\mathcal{R}_0 = 9.06 \pm 0.04$
Germany
$\mathcal{R}_0 = 4.81 \pm 0.16$
Denmark
$\mathcal{R}_0 = 8.47 \pm 2.78$
United Kingdom
$\mathcal{R}_0 = 8.8 \pm 0.05$
Netherlands
$\mathcal{R}_0 = 8.5 \pm 0.28$
Turkey
$\mathcal{R}_0 = 4.23 \pm 0.36$
Iran
$\mathcal{R}_0 = 11.63 \pm 0.32$
US
$\mathcal{R}_0 = 20.03 \pm 0.06$
China
$\mathcal{R}_0 = 2.18 \pm 0.23$
Deaths per day
Number of deaths






Chaos, Solitons & Fractals: X 5 (2020) 100034

Contents lists available at ScienceDirect

Chaos, Solitons & Fractals: X

journal homepage: www.elsevier.com/locate/csfx

ELSEVIER

COVID-19: The unreasonable effectiveness of simple models

Timoteo Carletti[a], Duccio Fanelli[b], Francesco Piazza[c,*]

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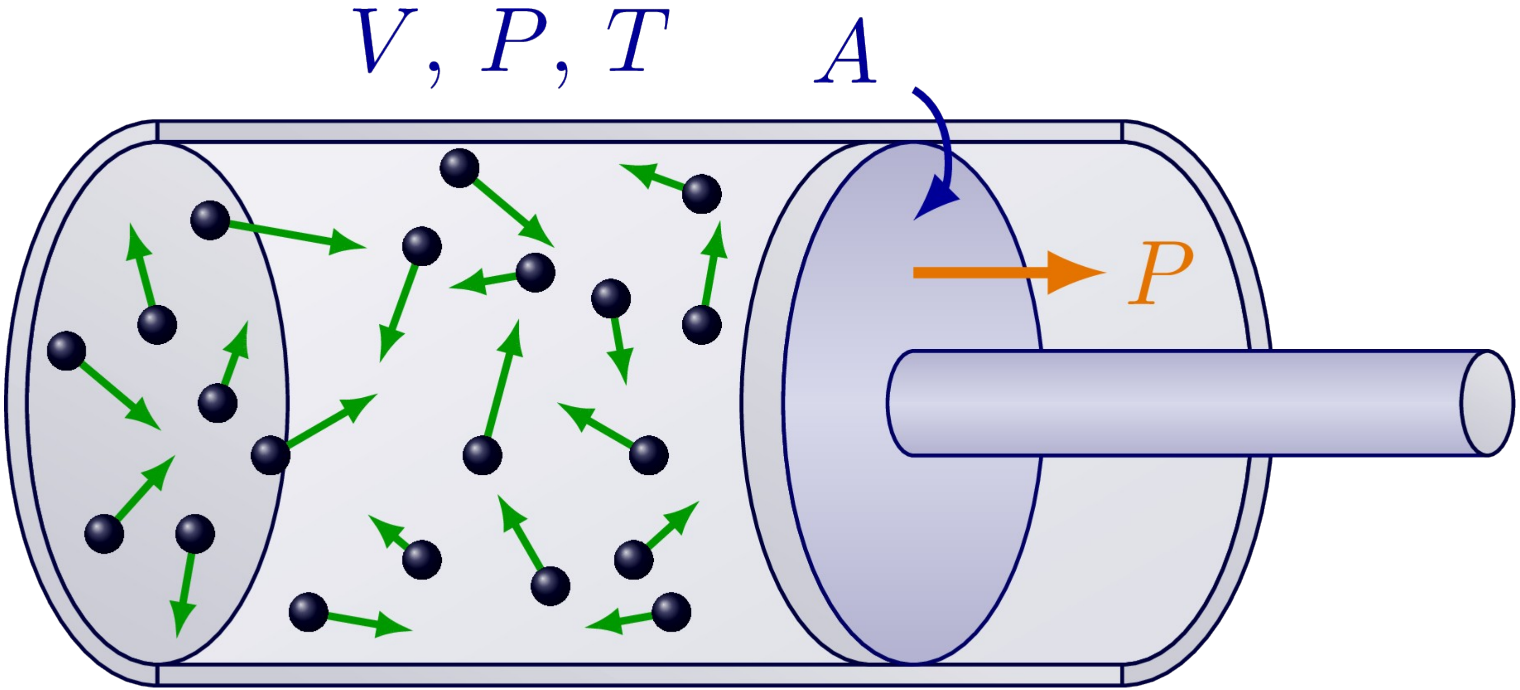
[b] Dipartimento di Fisica e Astronomia, Università di Firenze, INFN and CSDC, Via Sansone 1, 50019 Sesto Fiorentino, Firenze, Italy
[c] Université d'Orléans and Centre de Biophysique Moléculaire, CNRS-UPR4301, Rue C. Sadron, 45071, Orléans, France



$V,\, P,\, T$
A
P

information geometry of sloppy models

jose cuesta

uc3m
GISC

Reports on Progress in Physics
https://doi.org/10.1088/1361-6633/aca6f8

IOP Publishing
Rep. Prog. Phys. **86** (2023) 035901 (29pp)

Review

Information geometry for multiparameter models: new perspectives on the origin of simplicity

Katherine N Quinn[1], Michael C Abbott[2], Mark K Transtrum[3], Benjamin B Machta[4] and James P Sethna[5,*]

Parameter Space Compression Underlies Emergent Theories and Predictive Models

Benjamin B. Machta,[1,2] Ricky Chachra,[1] Mark K. Transtrum,[1,3] James P. Sethna[1*]

THE JOURNAL OF CHEMICAL PHYSICS **143**, 010901 (2015)

Perspective: Sloppiness and emergent theories in physics, biology, and beyond

Mark K. Transtrum,[1] Benjamin B. Machta,[2] Kevin S. Brown,[3,4] Bryan C. Daniels,[5] Christopher R. Myers,[6,7] and James P. Sethna[6]

PRL **104,** 060201 (2010) PHYSICAL REVIEW LETTERS

Why are Nonlinear Fits to Data so Challenging?

Mark K. Transtrum,* Benjamin B. Machta,† and James P. Sethna‡

PHYSICAL REVIEW E **83**, 036701 (2011)

Geometry of nonlinear least squares with applications to sloppy models and optimization

Mark K. Transtrum, Benjamin B. Machta, and James P. Sethna

PRL **113,** 098701 (2014) PHYSICAL REVIEW LETTERS week ending 29 AUGUST 2014

Model Reduction by Manifold Boundaries

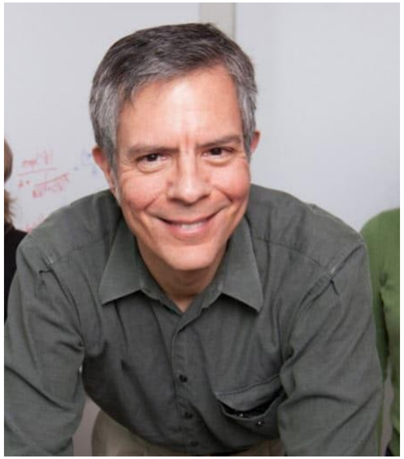
Mark K. Transtrum[1,*] and Peng Qiu[2]

PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Bridging Mechanistic and Phenomenological Models of Complex Biological Systems

Mark K. Transtrum[1*], Peng Qiu[2]



james sethna

mark transtrum

benjamin machta

katherine quinn

sloppyness $\longrightarrow$ hierarchy of parameter importance

relevant for:

- robustness and evolvability of complex biological systems
- effectiveness of simple models

  (the unreasonable success of spherical cows)
- developing coarse-grained descriptions of complex models
- parameter identifiability

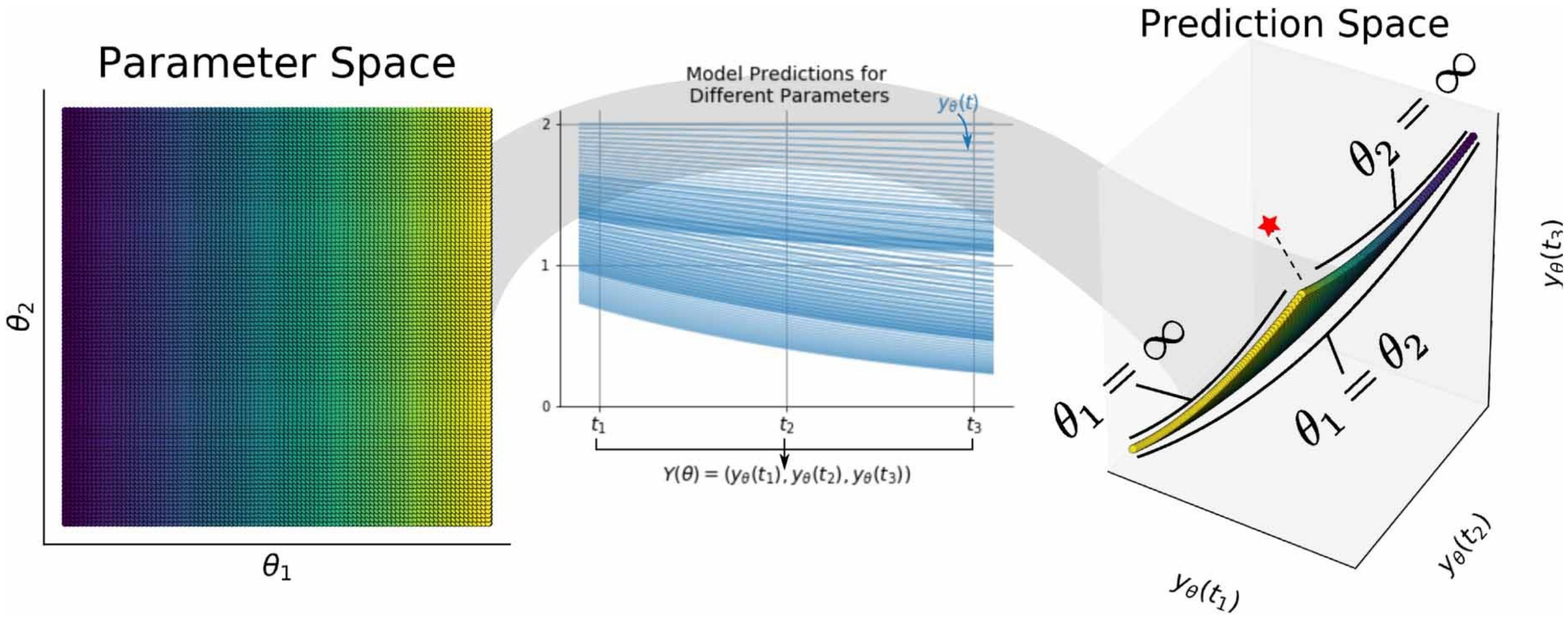
nonlinear least-squares

model: $x = y_\theta(t) \begin{cases} \text{data: } \{\mathbf{x}, \mathbf{t}\} \equiv \{(x_1, t_1), \ldots, (x_M, t_M)\} \\ \text{parameters: } \boldsymbol{\theta} \equiv (\theta_1, \theta_2, \ldots, \theta_D) \end{cases}$

$$\boxed{p(\mathbf{x}|\boldsymbol{\theta}) = \frac{1}{(2\pi\sigma^2)^{M/2}} \exp\left\{-\frac{1}{2\sigma^2}\sum_{i=1}^{M}\left[x_i - y_{\boldsymbol{\theta}}(t_i)\right]^2\right\}}$$

parameter manifold

$$y_\theta(t) = e^{-\theta_1 t} + e^{-\theta_2 t}, \qquad \theta_\mu \geqslant 0$$



deviations in parameter space

$$D_{\mathrm{KL}}(\boldsymbol{\theta}', \boldsymbol{\theta}) \equiv \sum_x \left[p(\mathbf{x}|\boldsymbol{\theta}) - p(\mathbf{x}|\boldsymbol{\theta}') \right] \log \left(\frac{p(\mathbf{x}|\boldsymbol{\theta})}{p(\mathbf{x}|\boldsymbol{\theta}')} \right)$$

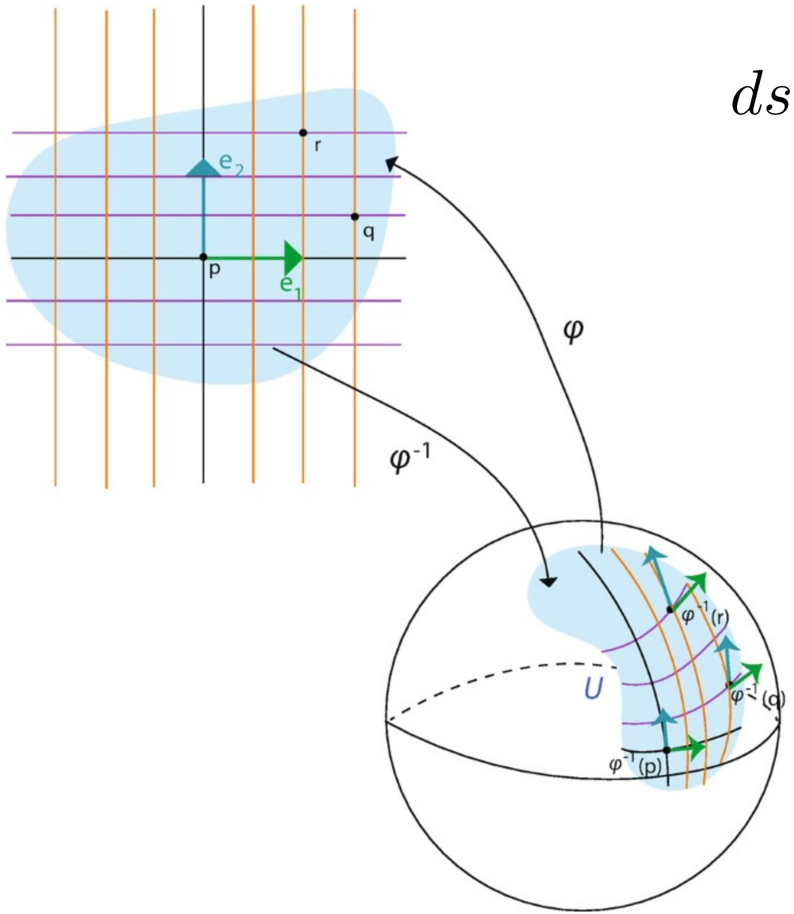
$$D_{\mathrm{KL}}(\boldsymbol{\theta}, \boldsymbol{\theta}) = 0 \qquad \frac{\partial D_{\mathrm{KL}}}{\partial \theta_\mu}(\boldsymbol{\theta}, \boldsymbol{\theta}) = 0$$

$$D_{\mathrm{KL}}(\boldsymbol{\theta} + d\boldsymbol{\theta}, \boldsymbol{\theta}) = \sum_{\mu,\nu=1}^{D} g_{\mu\nu}(\boldsymbol{\theta}) d\theta_\mu d\theta_\nu + \cdots$$

$$\boxed{g_{\mu\nu}(\boldsymbol{\theta}) = \sum_x p(\mathbf{x}|\boldsymbol{\theta}) \frac{\partial \log p(\mathbf{x}|\boldsymbol{\theta})}{\partial \theta_\mu} \frac{\partial \log p(\mathbf{x}|\boldsymbol{\theta})}{\partial \theta_\nu}}$$

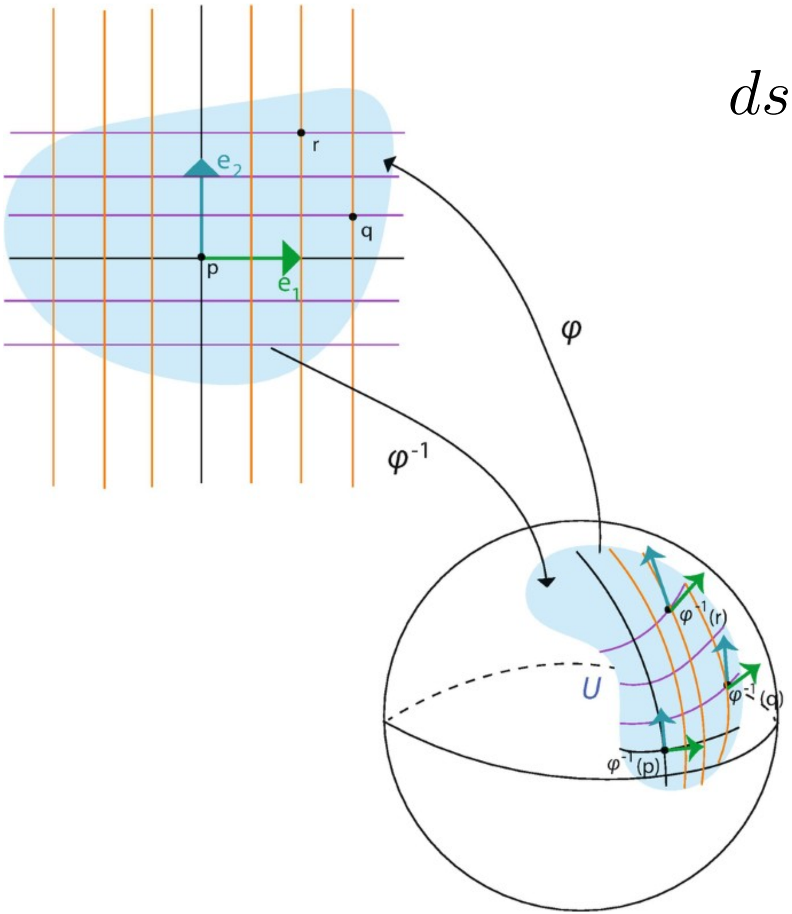
fisher's information matrix

riemannian geometry

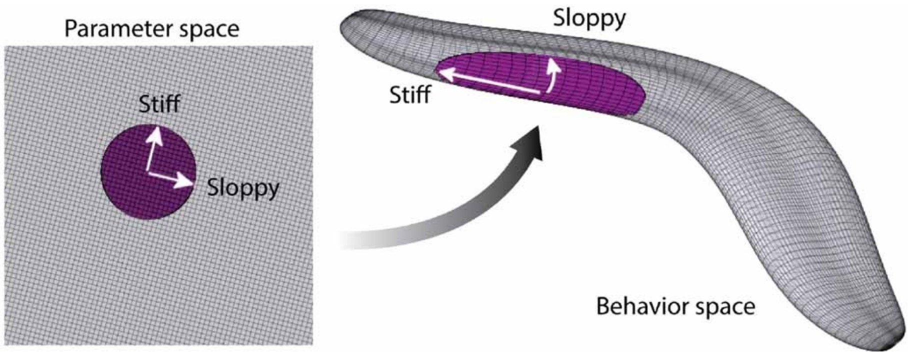


$$ds^2 = \sum_{\mu,\nu=1}^{D} g_{\mu\nu}(\boldsymbol{\theta}) d\theta_\mu d\theta_\nu$$

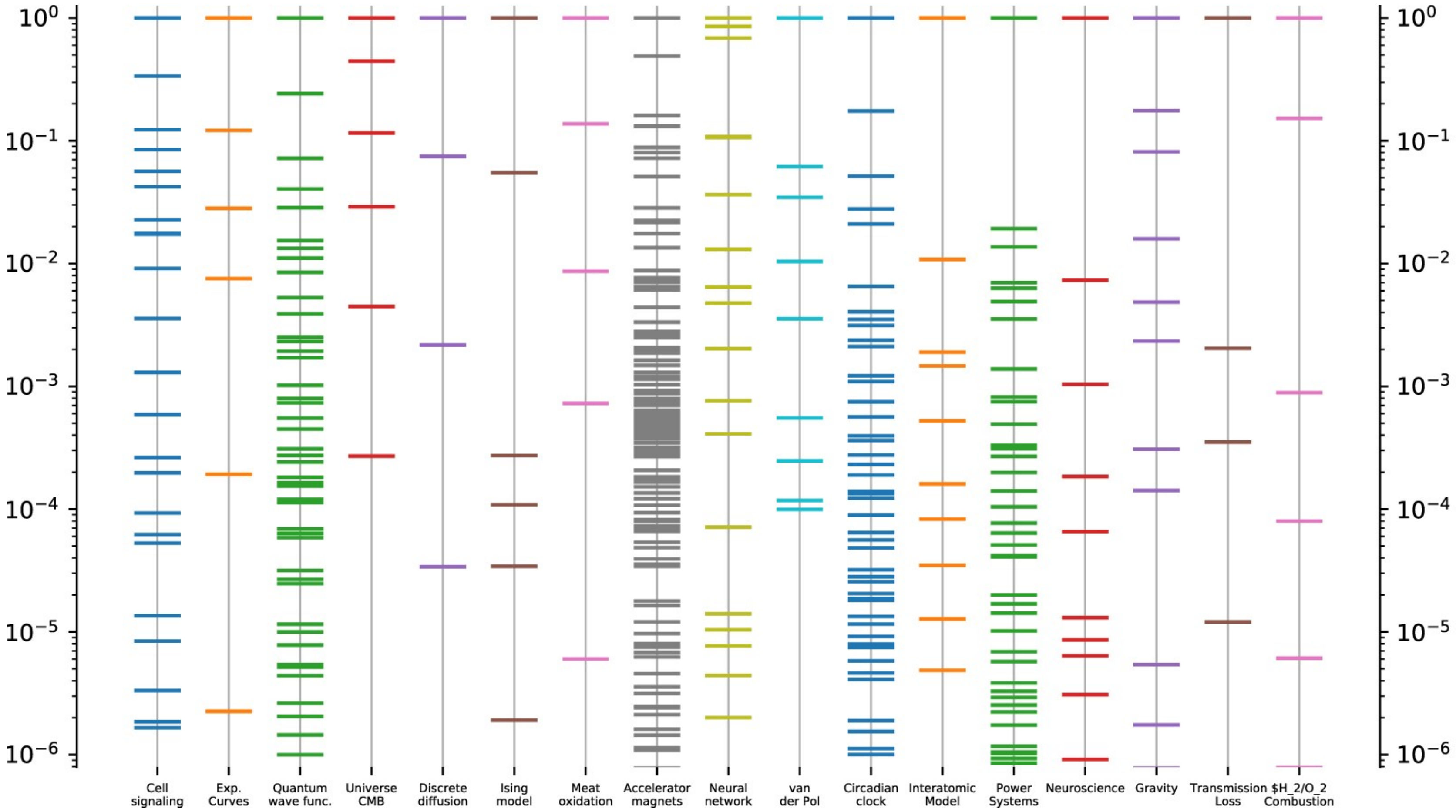
riemannian geometry



$$ds^2 = \sum_{\mu,\nu=1}^{D} g_{\mu\nu}(\boldsymbol{\theta})d\theta_\mu d\theta_\nu$$



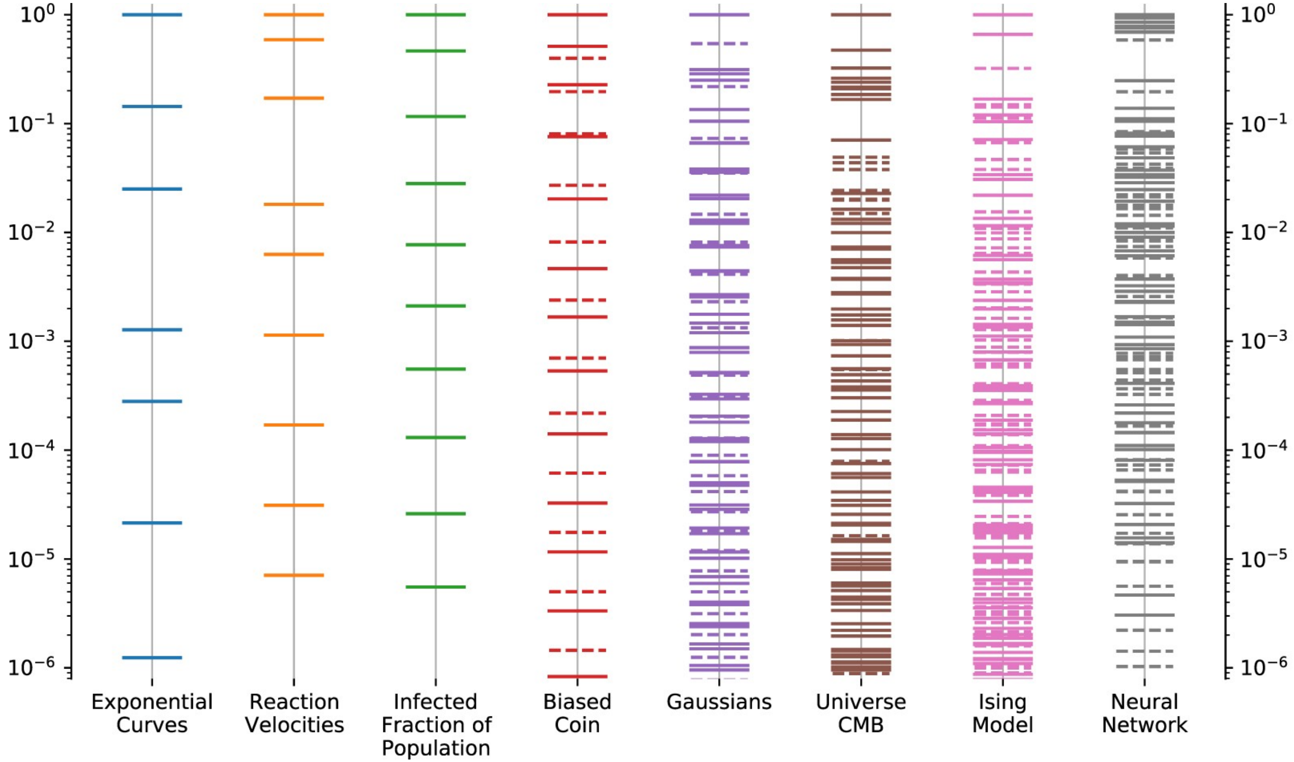
spectrum of the metric tensor



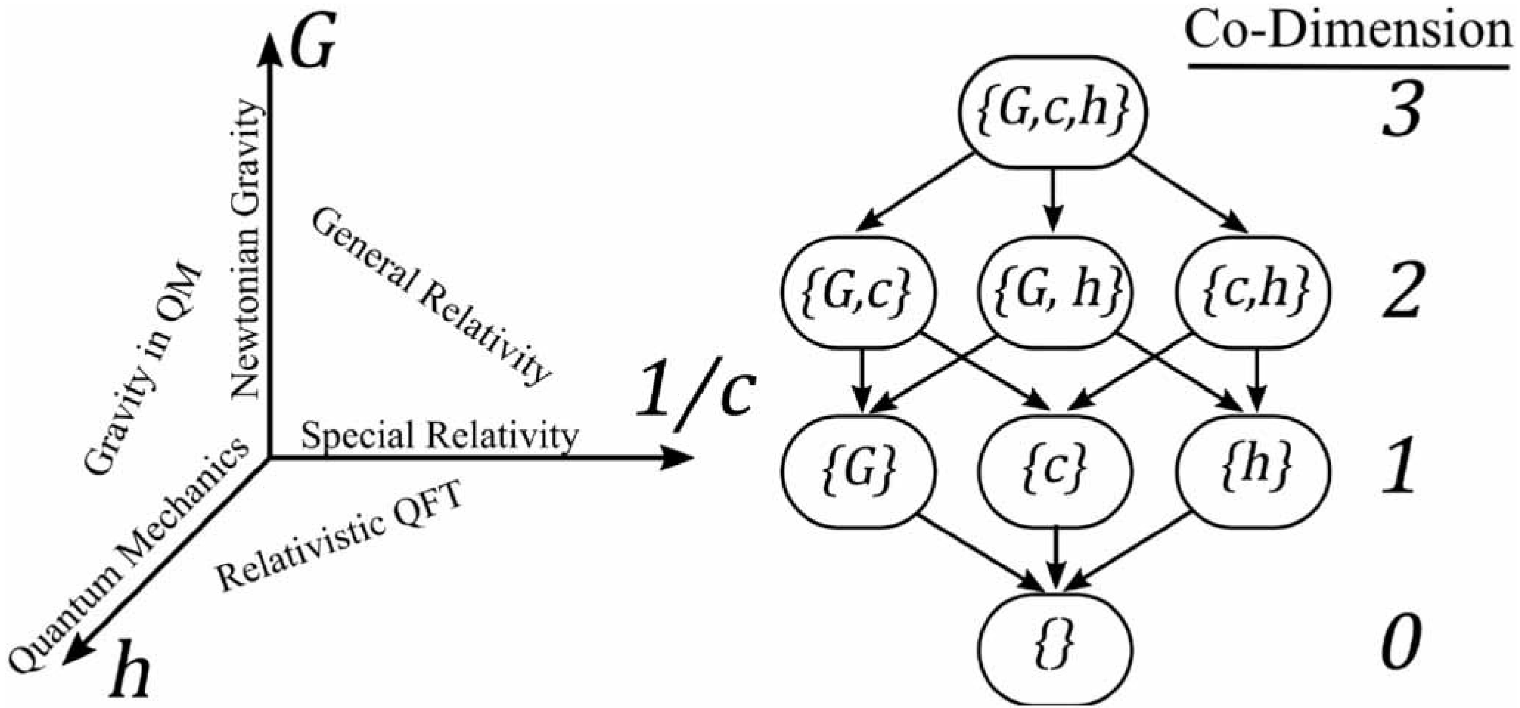
size of the manifold: hyperribbon

$$L = \int \sqrt{ds^2} = \int_0^1 d\tau \sqrt{\sum_{\mu,\nu} g_{\mu\nu}(\boldsymbol{\theta}) \frac{\partial \theta_\mu}{\partial \tau} \frac{\partial \theta_\nu}{\partial \tau}}$$

$\boldsymbol{\theta}(\tau)$ geodesic

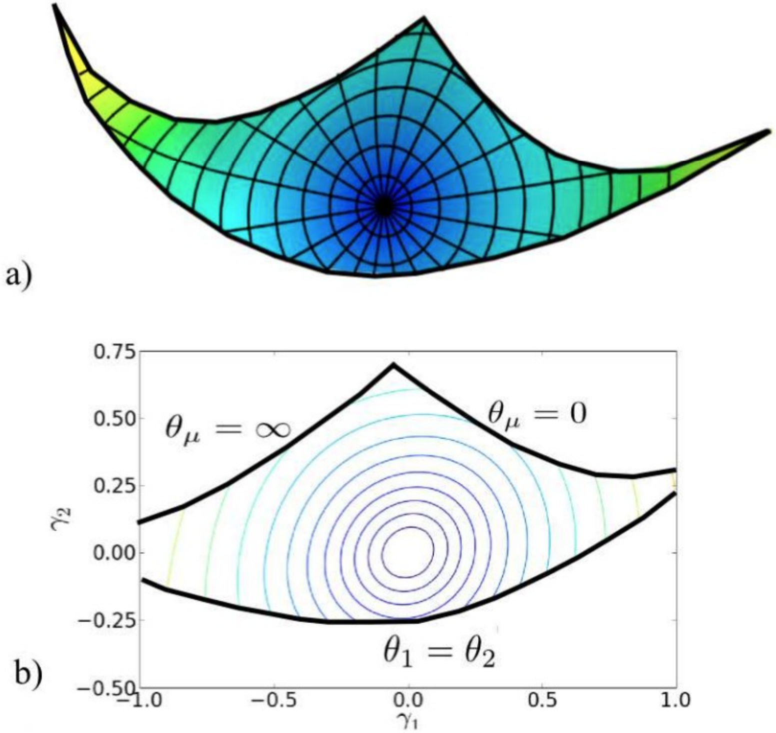


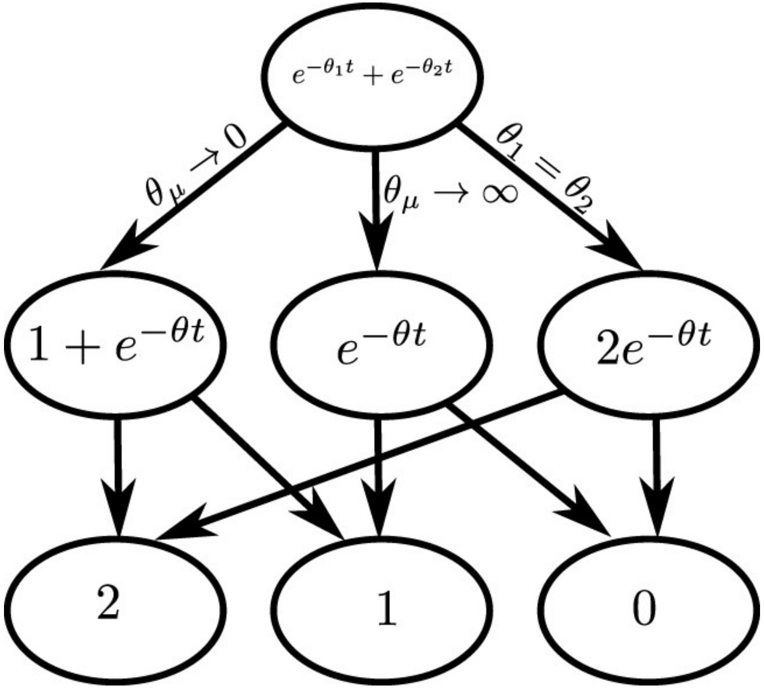
effective theories as manifold boundaries



effective theories as manifold boundaries

$$y_\theta(t) = e^{-\theta_1 t} + e^{-\theta_2 t}, \qquad \theta_\mu \geq 0$$

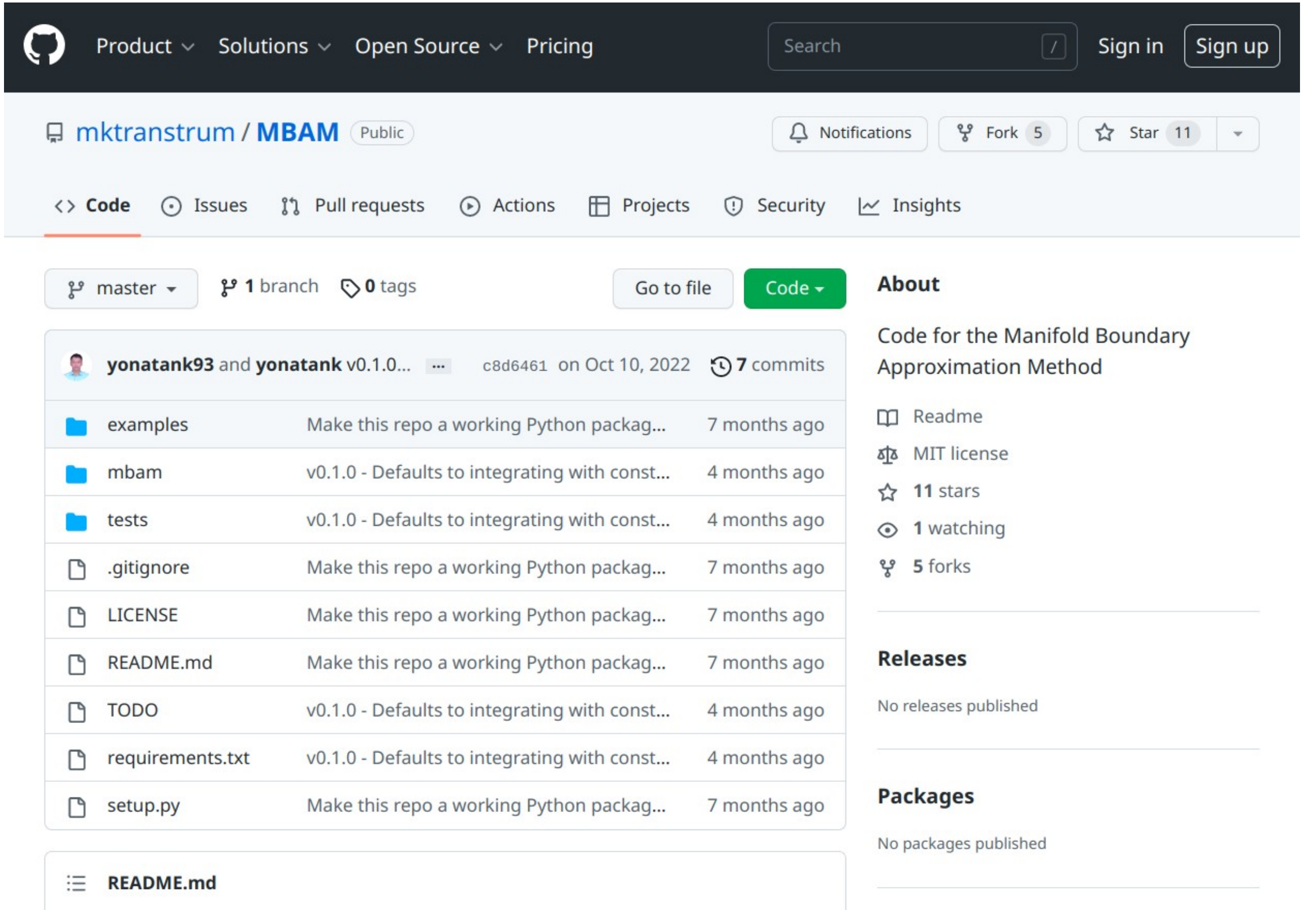




manifold boundary approximation method

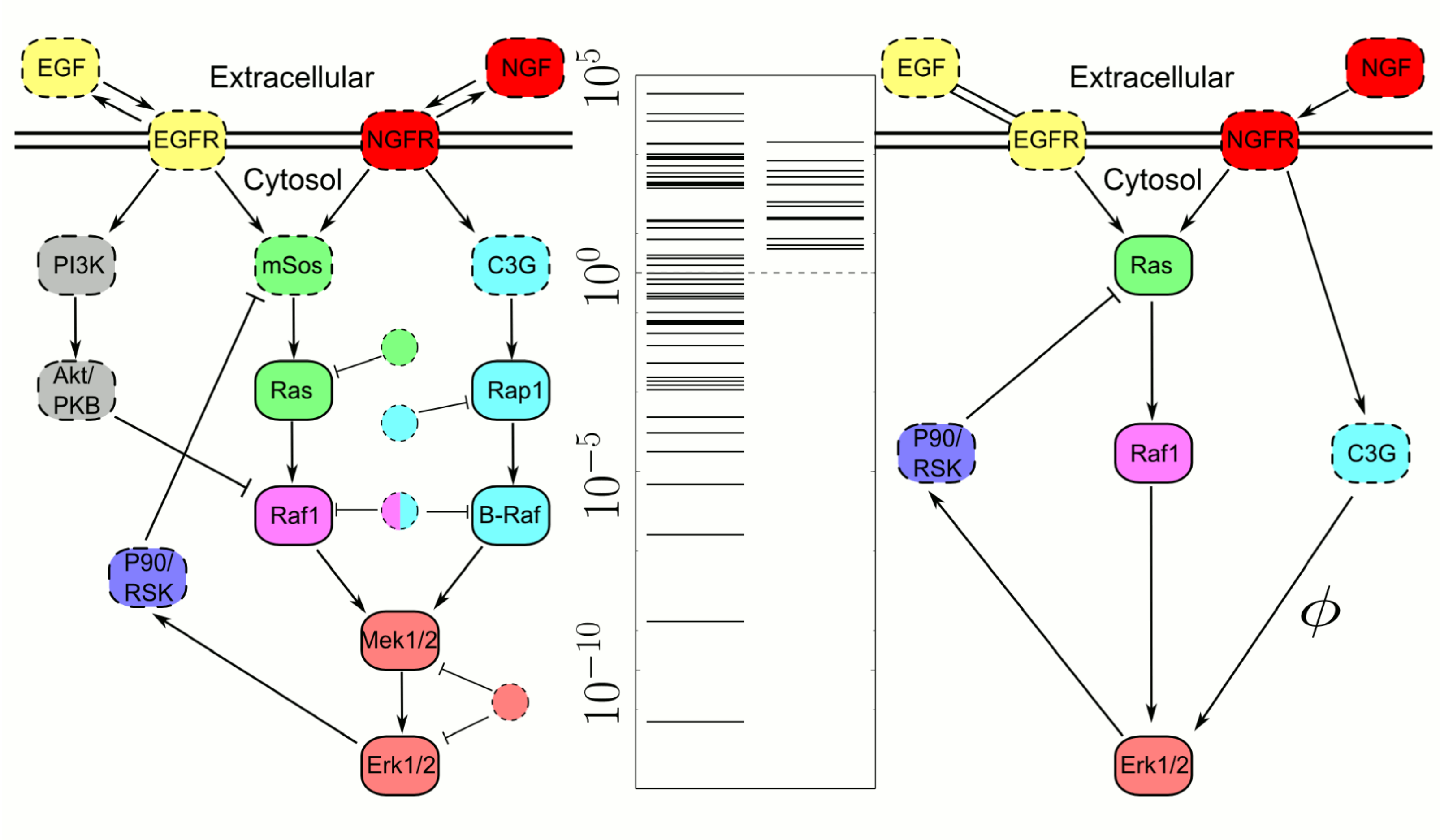
1. identify the **sloppiest direction** on the manifold
2. follow the **shortest geodesic path** to a **boundary**
3. use the **limiting combination of parameters** to simplify the model
4. **fit data** with the simplified model
5. **iterate**

manifold boundary approximation method



https://github.com/mktranstrum/MBAM

manifold boundary approximation method



manifold boundary approximation method

$$
\begin{aligned}
\frac{d}{dt}[\mathrm{EGF}] &= \mathrm{kruEGF}\cdot[\mathrm{bEGFR}] - \mathrm{krbEGF}\cdot[\mathrm{EGF}]\cdot[\mathrm{fGFR}]\\
\frac{d}{dt}[\mathrm{NGF}] &= \mathrm{kruNGF}\cdot[\mathrm{bNGFR}] - \mathrm{krbNGF}\cdot[\mathrm{NGF}]\cdot[\mathrm{fNGFR}]\\
\frac{d}{dt}[\mathrm{fEGFR}] &= \mathrm{kruEGF}\cdot[\mathrm{bEGFR}] - \mathrm{krbEGF}\cdot[\mathrm{EGF}]\cdot[\mathrm{fEGFR}]\\
\frac{d}{dt}[\mathrm{bEGFR}] &= \mathrm{krbEGF}\cdot[\mathrm{EGF}]\cdot[\mathrm{fEGFR}] - \mathrm{kruEGF}\cdot[\mathrm{bEGFR}]\\
\frac{d}{dt}[\mathrm{fNGFR}] &= \mathrm{kruNGF}\cdot[\mathrm{bNGFR}] - \mathrm{krbNGF}\cdot[\mathrm{NGF}]\cdot[\mathrm{fNGFR}]\\
\frac{d}{dt}[\mathrm{bNGFR}] &= \mathrm{krbNGF}\cdot[\mathrm{NGF}]\cdot[\mathrm{fNGFR}] - \mathrm{kruNGF}\cdot[\mathrm{bNGFR}]\\
\frac{d}{dt}[\mathrm{SosA}] &= \frac{\mathrm{kEGF}\cdot[\mathrm{bEGFR}]\cdot[\mathrm{SosI}]}{([\mathrm{SosI}]+\mathrm{KmEGF})} + \frac{\mathrm{kNGF}\cdot[\mathrm{bNGFR}]\cdot[\mathrm{SosI}]}{([\mathrm{SosI}]+\mathrm{KmNGF})} - \frac{\mathrm{kdSos}\cdot[\mathrm{P90RskA}]\cdot[\mathrm{SosA}]}{([\mathrm{SosA}]+\mathrm{KmdSos})}\\
\frac{d}{dt}[\mathrm{P90RskA}] &= \frac{\mathrm{kpP90Rsk}\cdot[\mathrm{ErkA}]\cdot[\mathrm{P90RskI}]}{([\mathrm{P90RskI}]+\mathrm{KmpP90Rsk})}\\
\frac{d}{dt}[\mathrm{RasA}] &= \frac{\mathrm{kSos}\cdot[\mathrm{SosA}]\cdot[\mathrm{RasI}]}{([\mathrm{RasI}]+\mathrm{KmSos})} - \frac{\mathrm{kRasGap}\cdot[\mathrm{RasGapA}]\cdot[\mathrm{RasA}]}{([\mathrm{RasA}]+\mathrm{KmRasGap})}\\
\frac{d}{dt}[\mathrm{Raf1A}] &= \frac{\mathrm{kRasToRaf1}\cdot[\mathrm{RasA}]\cdot[\mathrm{Raf1I}]}{([\mathrm{Raf1I}]+\mathrm{KmRasToRaf1})} - \frac{\mathrm{kdRaf1}\cdot[\mathrm{Raf1PPtase}]\cdot[\mathrm{Raf1A}]}{([\mathrm{Raf1A}]+\mathrm{KmdRaf1})} - \frac{\mathrm{kdRaf1ByAkt}\cdot[\mathrm{AktA}]\cdot[\mathrm{Raf1A}]}{([\mathrm{Raf1A}]+\mathrm{KmRaf1ByAkt})}
\end{aligned}
$$

$$
\begin{aligned}
\frac{d}{dt}[\mathrm{BRafA}] &= \frac{\mathrm{kRap1ToBRaf}\cdot[\mathrm{Rap1A}]\cdot[\mathrm{BRafI}]}{([\mathrm{BRafI}]+\mathrm{KmRap1ToBRaf})} - \frac{\mathrm{kdBRaf}\cdot[\mathrm{Raf1PPtase}]\cdot[\mathrm{BRafA}]}{([\mathrm{BRafA}]+\mathrm{KmdBRaf})}\\
\frac{d}{dt}[\mathrm{MekA}] &= \frac{\mathrm{kpRaf1}\cdot[\mathrm{Raf1A}]\cdot[\mathrm{MekI}]}{([\mathrm{MekI}]+\mathrm{KmpRaf1})} + \frac{\mathrm{kpBRaf}\cdot[\mathrm{BRafA}]\cdot[\mathrm{MekI}]}{([\mathrm{MekI}]+\mathrm{KmpBRaf})} - \frac{\mathrm{kdMek}\cdot[\mathrm{PP2AA}]\cdot[\mathrm{MekA}]}{([\mathrm{MekA}]+\mathrm{KmdMek})}\\
\frac{d}{dt}[\mathrm{ErkA}] &= \frac{\mathrm{kpMekCytoplasmic}\cdot[\mathrm{MekA}]\cdot[\mathrm{ErkI}]}{([\mathrm{ErkI}]+\mathrm{KmpMekCytoplasmic})} - \frac{\mathrm{kdErk}\cdot[\mathrm{PP2AA}]\cdot[\mathrm{ErkA}]}{([\mathrm{ErkA}]+\mathrm{KmdErk})}\\
\frac{d}{dt}[\mathrm{PI3KA}] &= \frac{\mathrm{kPI3K}\cdot[\mathrm{bEGFR}]\cdot[\mathrm{PI3KI}]}{([\mathrm{PI3KI}]+\mathrm{KmPI3K})} + \frac{\mathrm{kPI3KRas}\cdot[\mathrm{RasA}]\cdot[\mathrm{PI3KI}]}{([\mathrm{PI3KI}]+\mathrm{KmPI3KRas})}\\
\frac{d}{dt}[\mathrm{AktA}] &= \frac{\mathrm{kAkt}\cdot[\mathrm{PI3KA}]\cdot[\mathrm{AktI}]}{([\mathrm{AktI}]+\mathrm{KmAkt})}\\
\frac{d}{dt}[\mathrm{C3GA}] &= \frac{\mathrm{kC3GNGF}\cdot[\mathrm{bNGFR}]\cdot[\mathrm{C3GI}]}{([\mathrm{C3GI}]+\mathrm{KmC3GNGF})}\\
\frac{d}{dt}[\mathrm{Rap1A}] &= \frac{\mathrm{kC3G}\cdot[\mathrm{C3GA}]\cdot[\mathrm{Rap1I}]}{([\mathrm{Rap1I}]+\mathrm{KmC3G})} - \frac{\mathrm{kRapGap}\cdot[\mathrm{RapGapA}]\cdot[\mathrm{Rap1A}]}{([\mathrm{Rap1A}]+\mathrm{KmRapGap})}
\end{aligned}
$$

15 independent diff. eqs.

48 parameters

uncertainties up to **500 %** !

manifold boundary approximation method

$$
\begin{aligned}
\frac{d}{dt}[\mathrm{NGF}] &= -\theta_1[\mathrm{NGF}][\mathrm{fNGFR}] \\
\frac{d}{dt}[\mathrm{bNGFR}] &= \theta_1[\mathrm{NGF}][\mathrm{fNGFR}] \\
[\mathrm{bEGFR}] &= \begin{cases} 1 & \text{EGF Present} \\ 0 & \text{Otherwise} \end{cases} \\
\frac{d}{dt}[\mathrm{RasA}] &= \theta_2[\mathrm{bEGFR}] + \theta_3[\mathrm{bNGFR}] - [\widetilde{\mathrm{P90}}][\mathrm{RasA}] \\
\frac{d}{dt}[\widetilde{\mathrm{Raf1A}}] &= \theta_4[\mathrm{RasA}] - \theta_5\frac{[\widetilde{\mathrm{Raf1A}}]}{[\widetilde{\mathrm{Raf1A}}] + \theta_6} \\
\frac{d}{dt}[\mathrm{C3GA}] &= \theta_7[\mathrm{bNGFR}][\mathrm{C3GI}] \\
[\mathrm{Rap1A}] &= \theta_8[\mathrm{C3GA}] \\
[\mathrm{MekA}] &= [\widetilde{\mathrm{Raf1A}}][\mathrm{MekI}] + \theta_9[\mathrm{Rap1A}] \\
\frac{d}{dt}[\mathrm{ErkA}] &= -\theta_{10}[\mathrm{ErkA}] + \theta_{11}[\mathrm{MekA}][\mathrm{ErkI}] \\
\frac{d}{dt}[\widetilde{\mathrm{P90}}] &= \theta_{12}[\mathrm{ErkA}].
\end{aligned}
$$

$$
\begin{aligned}
\theta_1 &= \mathrm{krbNGF} \\
\theta_2 &= \frac{[\mathrm{SosI}](\mathrm{kEGF})(\mathrm{KmRasGap})(\mathrm{kSos})}{[\mathrm{RasGapA}](\mathrm{KmEGF})(\mathrm{kRasGap})} \\
\theta_3 &= \frac{[\mathrm{SosI}](\mathrm{kNGF})(\mathrm{KmRasGap})(\mathrm{kSos})}{[\mathrm{RasGapA}](\mathrm{KmNGF})(\mathrm{kRasGap})} \\
\theta_4 &= \frac{(\mathrm{kRasToRaf1})(\mathrm{kpRaf1})(\mathrm{KmdMek})}{[\mathrm{PP2AA}](\mathrm{kdMek})(\mathrm{KmpRaf1})} \\
\theta_5 &= \frac{[\mathrm{Raf1PPtase}](\mathrm{kdRaf1})(\mathrm{kpRaf1})(\mathrm{KmdMek})}{[\mathrm{PP2AA}](\mathrm{kdMek})(\mathrm{KmpRaf1})} \\
\theta_6 &= \frac{(\mathrm{KmdRaf1})(\mathrm{kpRaf1})(\mathrm{KmdMek})}{[\mathrm{PP2AA}](\mathrm{kdMek})(\mathrm{KmpRaf1})} \\
\theta_7 &= \mathrm{kC3GNGF}/\mathrm{KmC3GNGF} \\
\theta_8 &= \frac{(\mathrm{KmRapGap})(\mathrm{kC3G})}{[\mathrm{RapGapA}](\mathrm{kRapGaP})} \\
\theta_9 &= \frac{[\mathrm{BRafI}](\mathrm{kRap1ToBRaf})(\mathrm{KmdBRaf})(\mathrm{kpBRaf})(\mathrm{KmdMek})}{[\mathrm{PP2AA}][\mathrm{Raf1PPtase}](\mathrm{kdBRaf})(\mathrm{KmRap1ToBRaf})(\mathrm{kdMek})} \\
\theta_{10} &= [\mathrm{PP2AA}](\mathrm{kdErk})/\mathrm{KmdErk} \\
\theta_{11} &= \mathrm{kpMekCytoplasmic}/\mathrm{KmpMekCytoplasmic} \\
\theta_{12} &= \frac{[\mathrm{P90/RSKI}](\mathrm{kpP90Rsk})(\mathrm{kdSos})}{(\mathrm{KmpP90Rsk})(\mathrm{KmdSos})}.
\end{aligned}
$$

7 independent diff. eqs.

12 “effective” parameters

manifold boundary approximation method

$$\begin{aligned}
\frac{d}{dt}[\mathrm{NGF}] &= -\theta_1[\mathrm{NGF}][\mathrm{fNGFR}] \\
\frac{d}{dt}[\mathrm{bNGFR}] &= \theta_1[\mathrm{NGF}][\mathrm{fNGFR}] \\
[\mathrm{bEGFR}] &= \left\{\begin{smallmatrix} 1 & \text{EGF Present} \\ 0 & \text{Otherwise} \end{smallmatrix}\right. \\
\frac{d}{dt}[\mathrm{RasA}] &= \theta_2[\mathrm{bEGFR}] + \theta_3[\mathrm{bNGFR}] - [\widetilde{\mathrm{P90}}][\mathrm{RasA}] \\
\frac{d}{dt}[\widetilde{\mathrm{Raf1A}}] &= \theta_4[\mathrm{RasA}] - \theta_5\frac{[\widetilde{\mathrm{Raf1A}}]}{[\widetilde{\mathrm{Raf1A}}] + \theta_6} \\
\frac{d}{dt}[\mathrm{C3GA}] &= \theta_7[\mathrm{bNGFR}][\mathrm{C3GI}] \\
[\mathrm{Rap1A}] &= \theta_8[\mathrm{C3GA}] \\
[\mathrm{MekA}] &= [\widetilde{\mathrm{Raf1A}}][\mathrm{MekI}] + \theta_9[\mathrm{Rap1A}] \\
\frac{d}{dt}[\mathrm{ErkA}] &= -\theta_{10}[\mathrm{ErkA}] + \theta_{11}[\mathrm{MekA}][\mathrm{ErkI}] \\
\frac{d}{dt}[\widetilde{\mathrm{P90}}] &= \theta_{12}[\mathrm{ErkA}].
\end{aligned}$$

parameter	Reduced Model Value	Uncertainty
θ_1	2.37×10^{-3}	1.1×10^{-3}
θ_2	9.34×10^{-2}	2.7×10^{-2}
θ_3	7.57×10^{-1}	3.9×10^{-1}
θ_4	9.88×10^{-1}	5.4×10^{-1}
θ_5	3.40×10^{-1}	2.1×10^{-1}
θ_6	2.70×10^{-1}	1.9×10^{-1}
θ_7	1.11×10^{0}	7.8×10^{-1}
θ_8	1.30×10^{-1}	3.6×10^{-2}
θ_9	1.75×10^{0}	5.5×10^{-1}
θ_{10}	2.56×10^{-1}	1.0×10^{-1}
θ_{11}	4.51×10^{0}	1.6×10^{0}
θ_{12}	8.21×10^{-1}	3.5×10^{-1}

7 independent diff. eqs.

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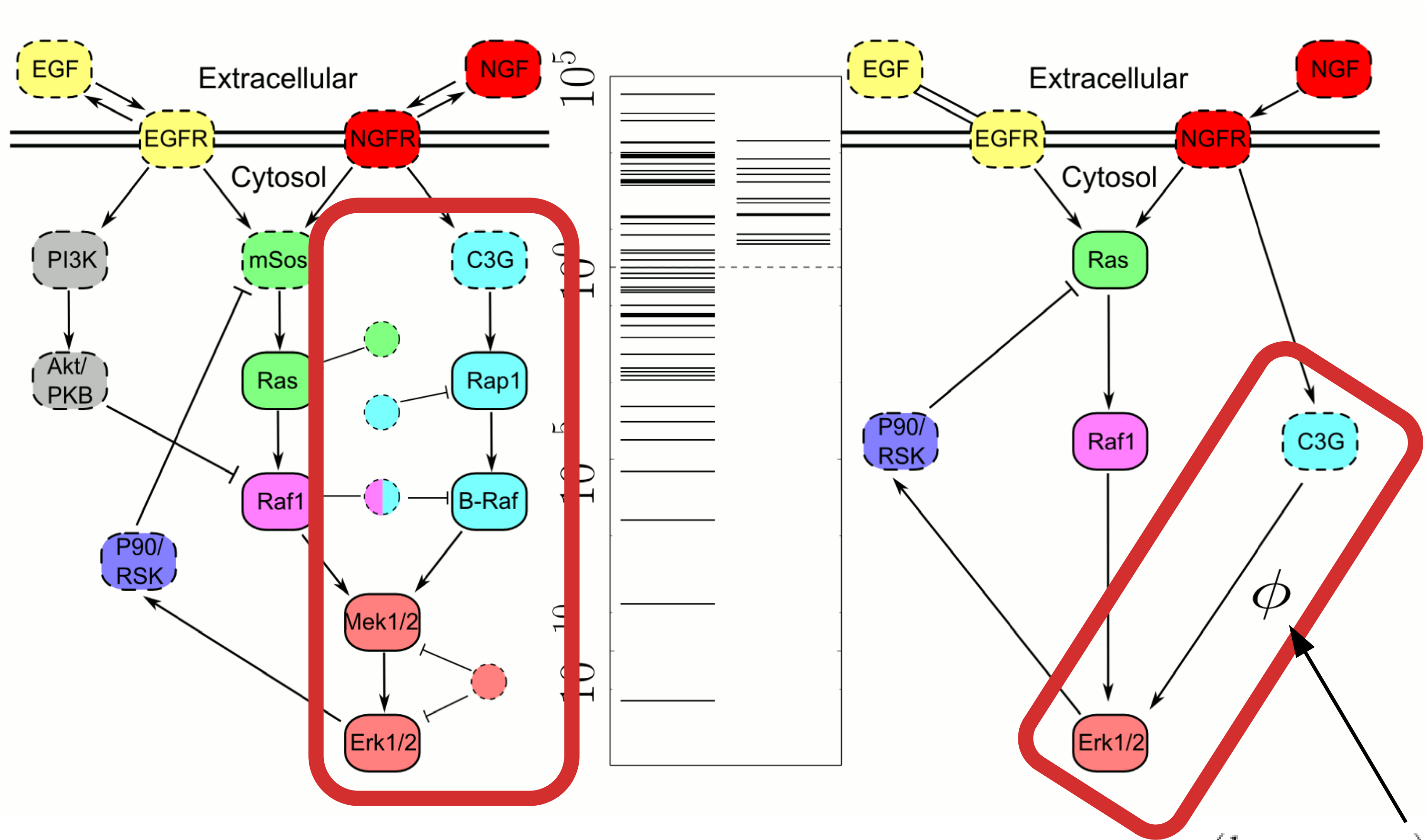
manifold boundary approximation method



$$\phi = \frac{(k_{\text{Rap1ToBRaf}})(K_{\text{mdBRaf}})(k_{\text{pBRaf}})(K_{\text{mdMek}})}{(k_{\text{dBRaf}})(K_{\text{mRap1ToBRaf}})(k_{\text{dMek}})}$$

example 1: sum of exponentials

$$y(t, \mathbf{A}, \boldsymbol{\lambda}) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t} + A_4 e^{-\lambda_4 t}, \qquad \boldsymbol{\theta} = (A_\mu, \lambda_\mu) \geqslant 0$$

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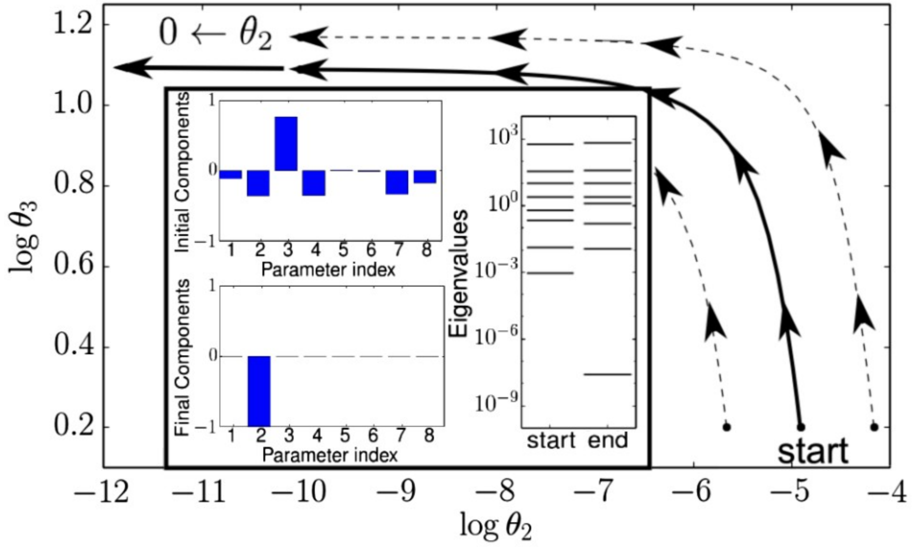

$$\ddot{\theta}^\mu + \Gamma^\mu_{\alpha,\beta} \dot{\theta}^\alpha \dot{\theta}^\beta = 0$$

$$\Gamma^\mu_{\alpha\beta} = \frac{1}{2} g^{\mu\nu} \left(\frac{\partial g_{\nu\beta}}{\partial \theta^\alpha} + \frac{\partial g_{\nu\alpha}}{\partial \theta^\beta} - \frac{\partial g_{\alpha\beta}}{\partial \theta^\nu} \right)$$

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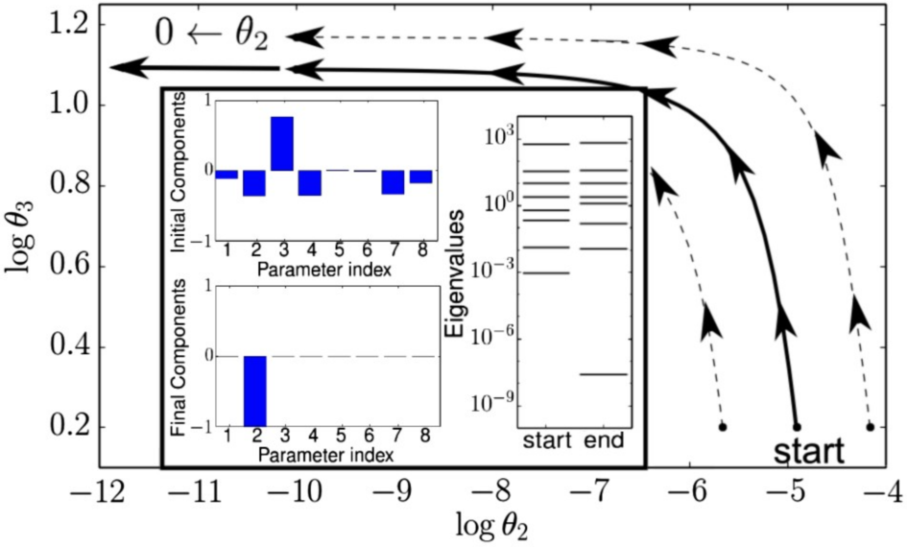

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$$\tilde{y}(t, \tilde{\mathbf{A}}, \tilde{\boldsymbol{\lambda}}) = \tilde{A}_2 + \tilde{A}_1 e^{-\tilde{\lambda}_2 t} + \tilde{A}_3 e^{-\tilde{\lambda}_3 t} + \tilde{A}_4 e^{-\tilde{\lambda}_4 t}$$

example 2: kinetics of enzymatic reaction

$$y(u, \boldsymbol{\theta}) = \frac{\theta_1(u^2 + \theta_2 u)}{u^2 + \theta_3 u + \theta_4}$$

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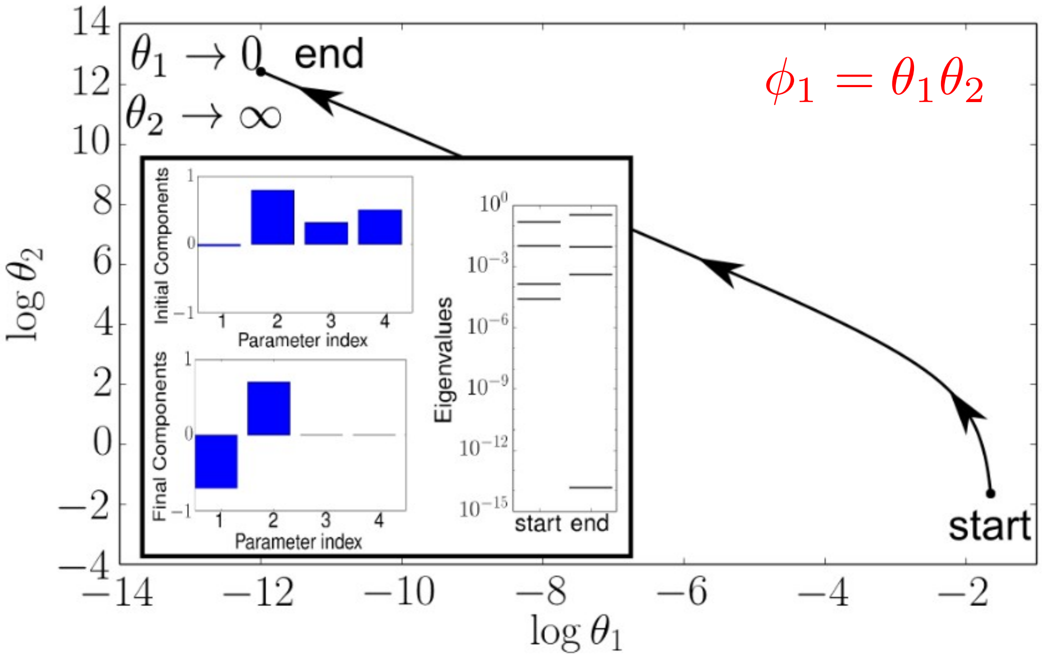

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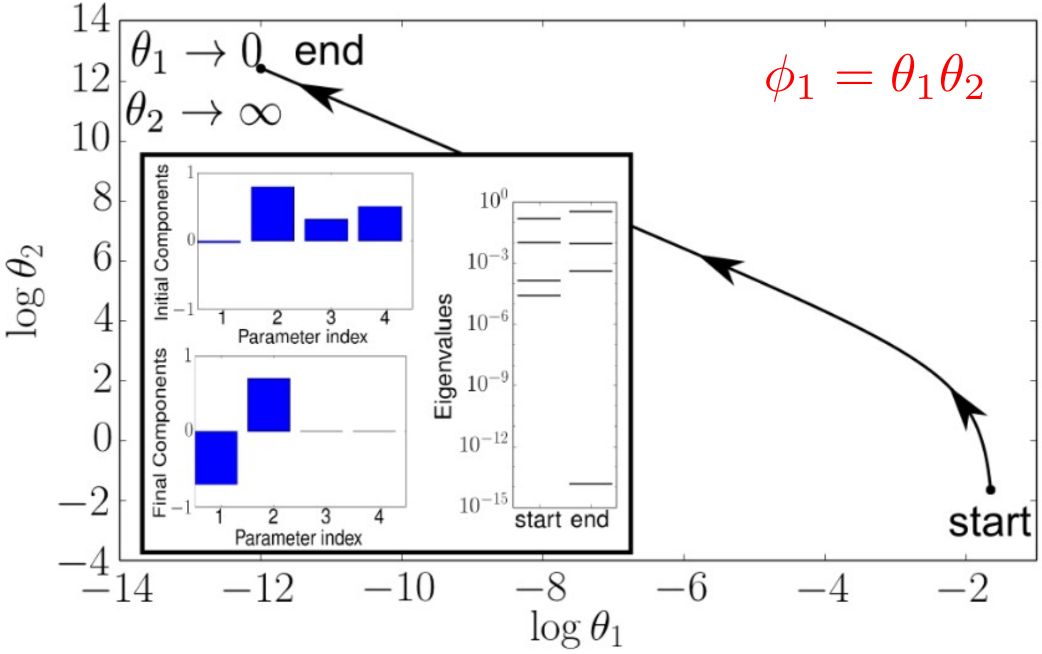

$$y(u, \phi) = \frac{\phi_1 u}{u^2 + \phi_2 u + \phi_3}$$

example 3: thermal isomerisation of α-pinene

$$\dot{y}_1 = -(\theta_1 + \theta_2) y_1$$
$$\dot{y}_2 = \theta_1 y_1$$
$$\dot{y}_3 = \theta_2 y_1 - (\theta_3 + \theta_4) y_3 + \theta_5 y_5$$
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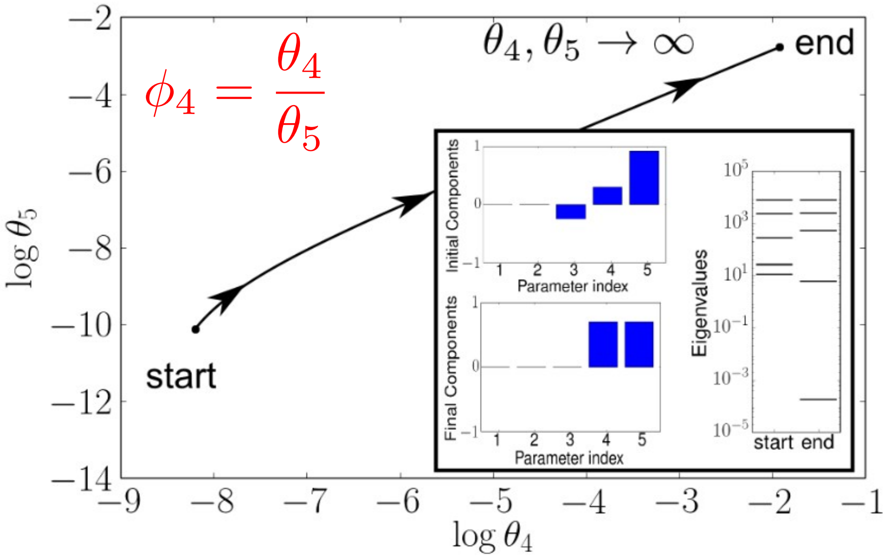

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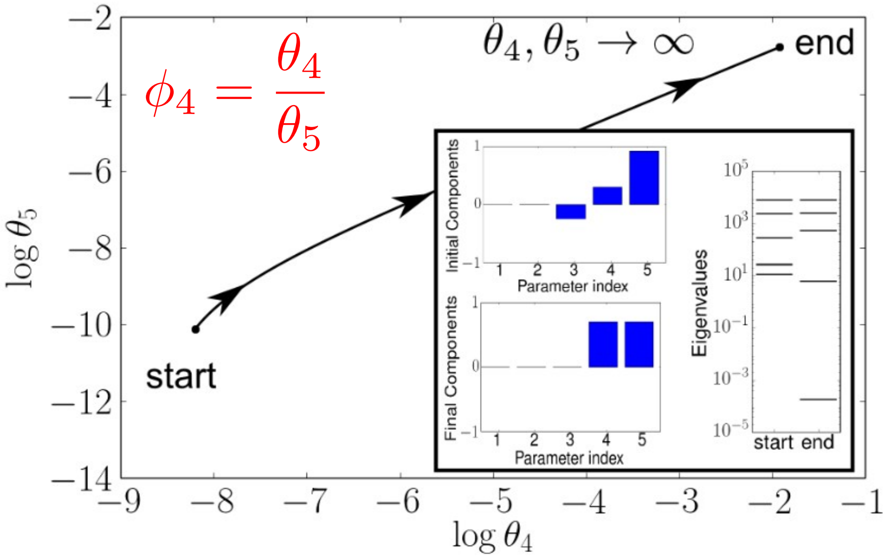

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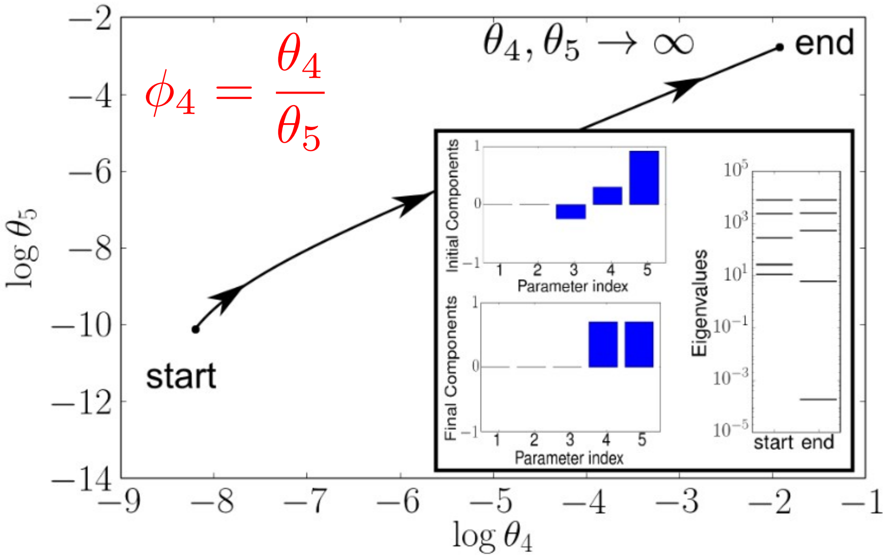
$$0 = \phi_4 y_3 - y_5$$



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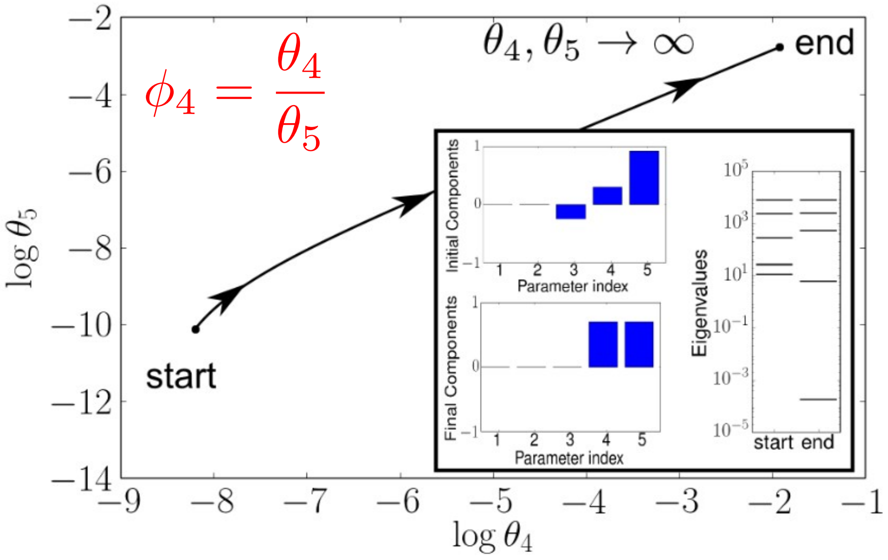

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$$\dot{y}_3 + \dot{y}_5 = \phi_2 y_1 - \phi_3 y_3$$

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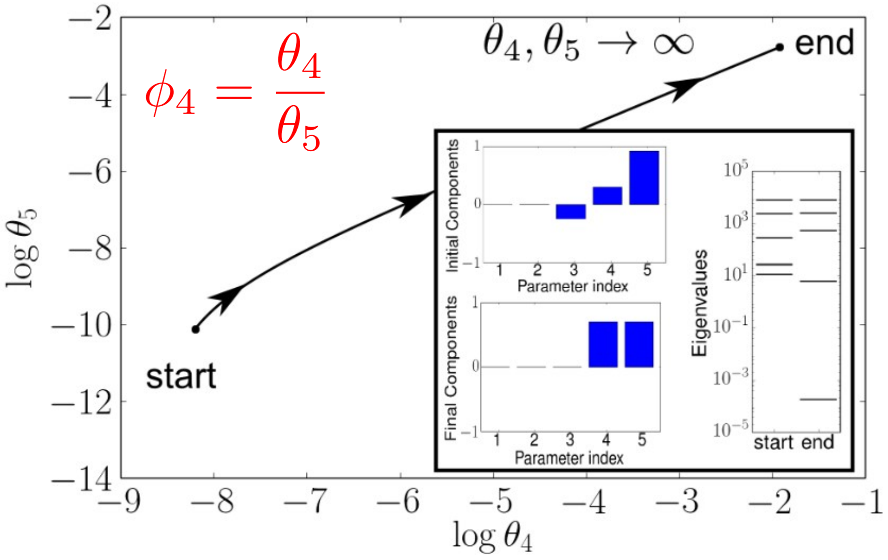

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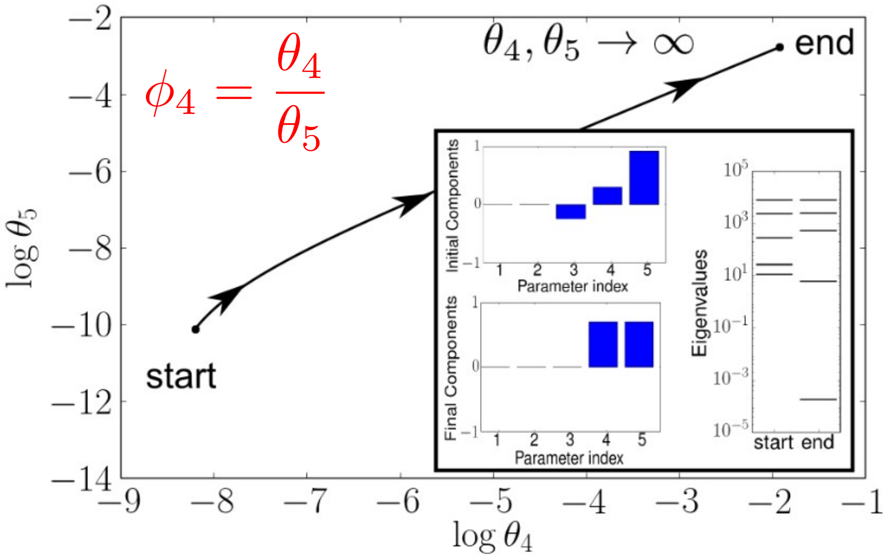
$$\dot{y}_3 = \frac{\phi_2}{1+\phi_4} y_1 - \frac{\phi_3}{1+\phi_4} y_3$$



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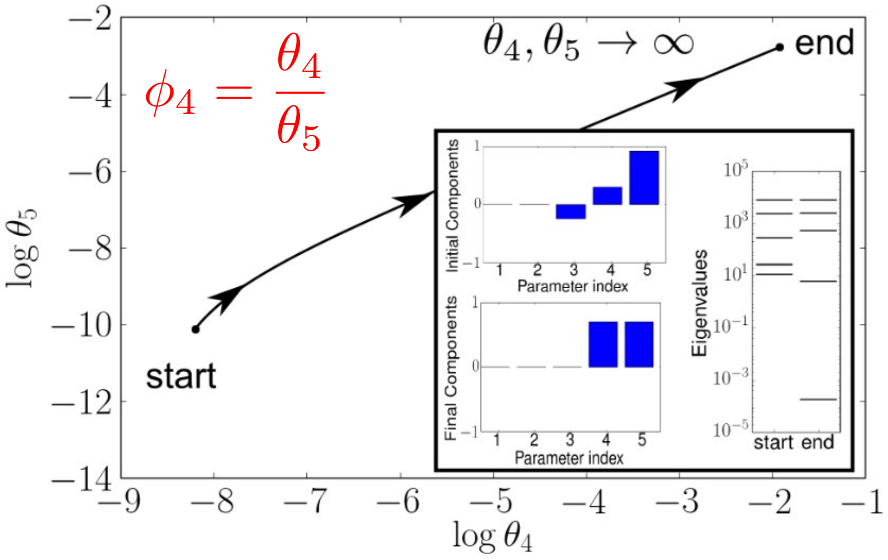

example 4: michaelis-menten

$$
\begin{aligned}
[\dot{E}] &= -\theta_1[E][S] + (\theta_2 + \theta_3)[ES] \\
[\dot{S}] &= -\theta_1[E][S] + \theta_2[ES] \\
[\dot{ES}] &= \theta_1[E][S] - (\theta_2 + \theta_3)[ES] \\
[\dot{P}] &= \theta_3[ES]
\end{aligned}
$$

example 4: michaelis-menten

$$
\begin{aligned}
[\dot{S}] &= -\theta_1[E][S] + \theta_2[ES] \\
[\dot{P}] &= \theta_3[ES] \\
E_0 &= [E] + [ES] \\
S_0 &= [S] + [ES] + [P]
\end{aligned}
$$

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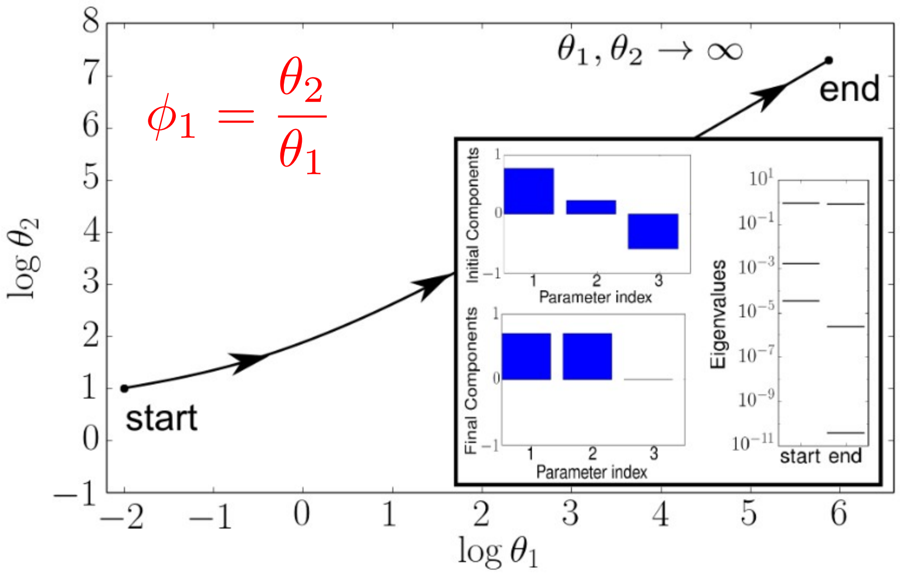

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$$[\dot{P}] = \theta_3[ES]$$

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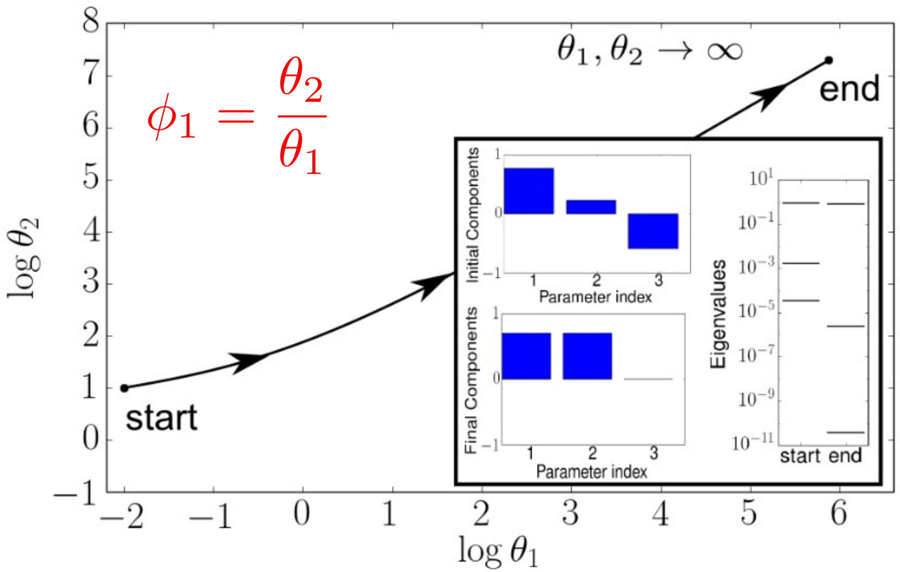


example 4: michaelis-menten

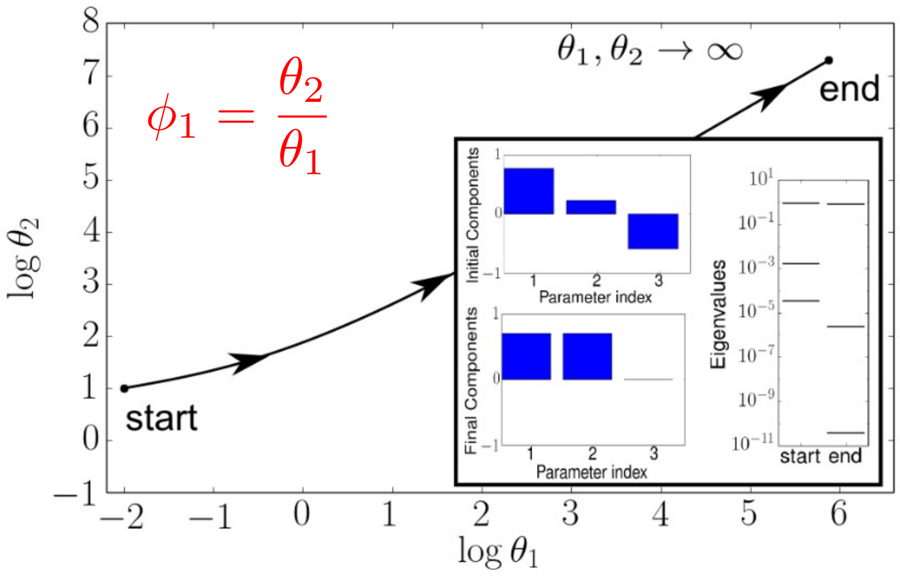
$$0 = -[E][S] + \phi_1[ES]$$

$$[\dot{P}] = \theta_3[ES]$$

$$E_0 = [E] + [ES]$$

$$S_0 = [S] + [ES] + [P]$$

$$\phi_1 = \frac{\theta_2}{\theta_1}$$



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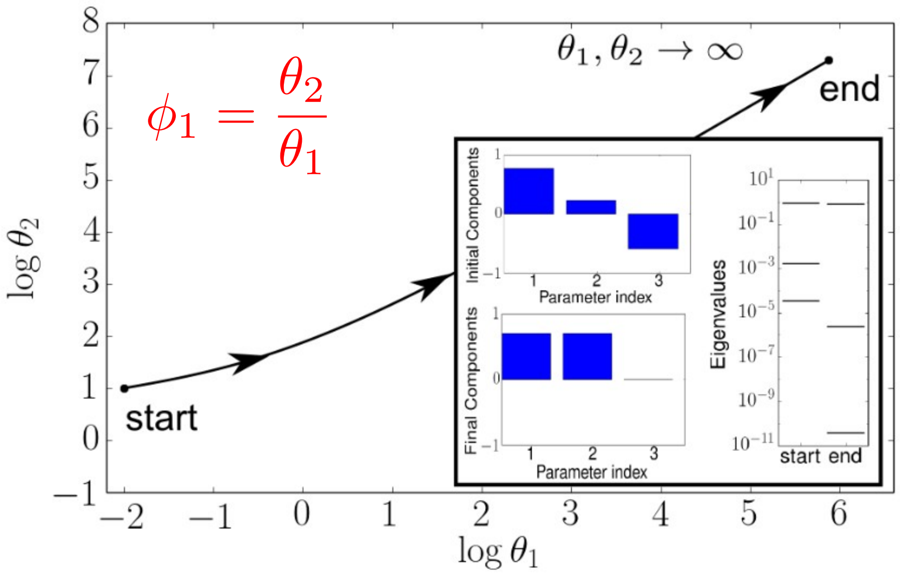

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$$[\dot{P}] = \theta_3 [ES]$$

$$[E] = \frac{\phi_1 E_0}{\phi_1 + [S]}$$

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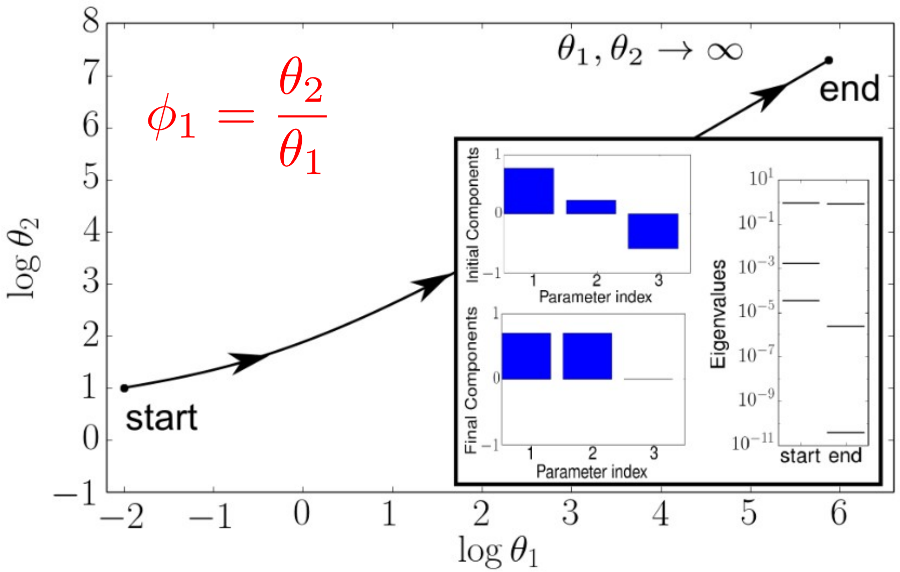

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$$[\dot{P}] = \theta_3 E_0 \frac{[S]}{\phi_1 + [S]}$$

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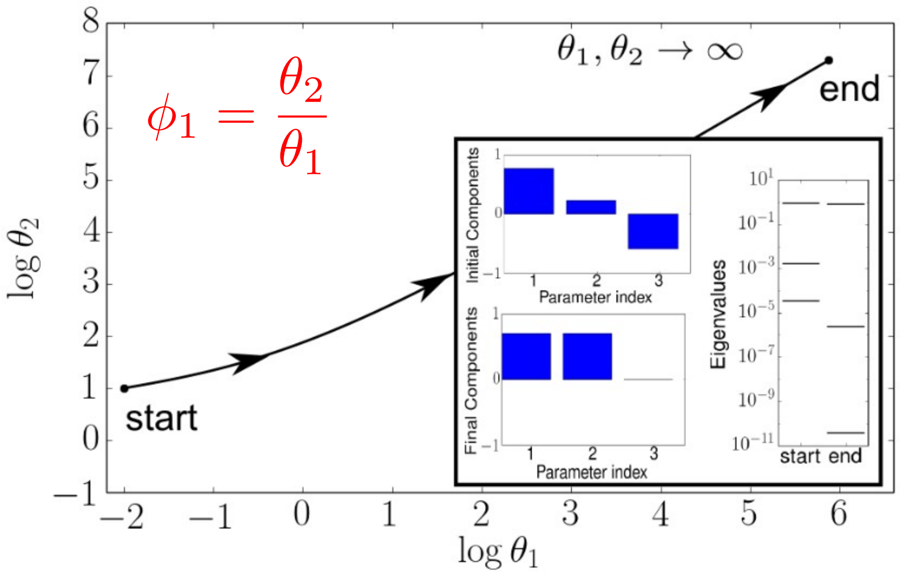

conclusions

- complex models with many parameters **neither** increase our understanding **nor** provide the best description of a system
- spherical cows work **not** because nature is simple, **but** because most complexity is irrelevant
- **mbam** provides a systematic method to achieve simpler descriptions of complex models