THE MANIFOLD BOUNDARY APPROXIMATION METHOD (MBAM)

SUMMARY

To this point, we have discussed several ideas

- Practical Identifiability/Sloppiness (How to define?)
- Low-effective dimensionality (Manifold widths)
- Manifold boundaries
- Geodesics systematically explore model behavior space

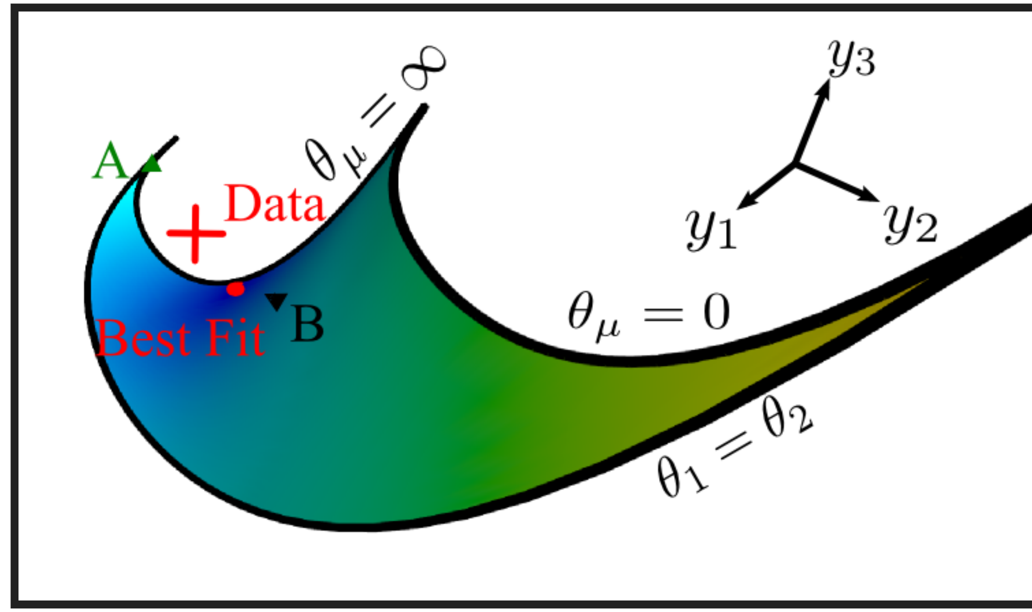
We are going to bring these ideas together to develop a method for constructing simpler models (fewer parameters) from complex ones.

WHAT ARE THE BOUNDARIES?

Example: $y = e^{-\theta_1 t} + e^{-\theta_2 t}$

Three boundaries:

- $\theta_\mu \to 0$
- $\theta_\mu \to \infty$
- $\theta_1 \to \theta_2$



The boundaries are physically interesting limiting approximations.

By choosing the boundary oriented with the long axis, can we find a low-dimensional approximation to the complicated model?

MODEL REDUCTION

Model reduction is a very old problem with many approaches:

- Mean field theory
- Renormalization Group
- Singular Perturbation
- Lots of methods for Dynamical Systems from Controls Community

Existing methods fall short for several reasons:

- Limited to specific functional forms
- Black box approximations
- Need to know which parameters are small *a priori*.

MODEL REDUCTION

There are several challenges to doing parameter reduction in sloppy systems

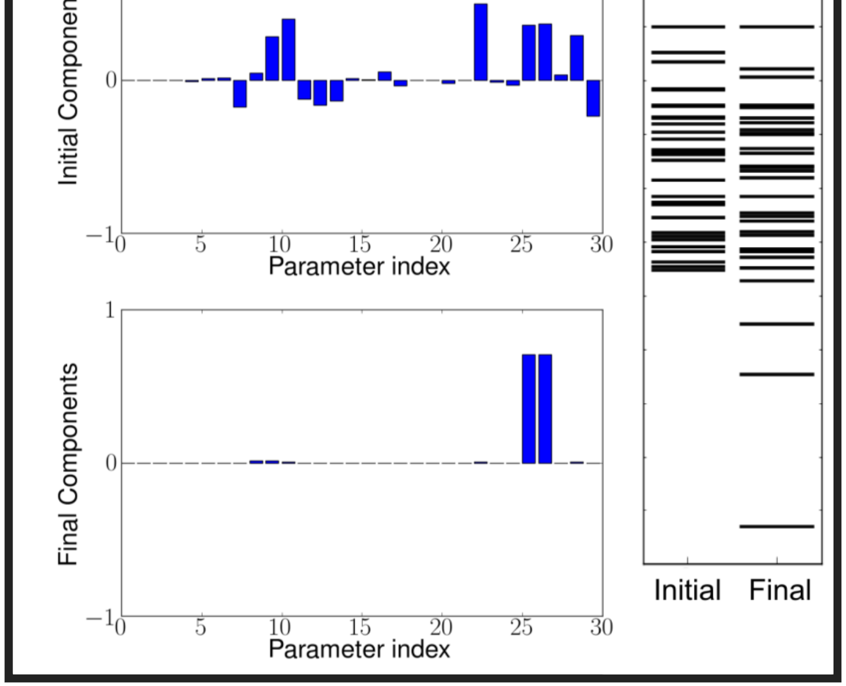
- Need to find (nonlinear) combinations of parameters.
- How to remove a parameter combination from the model?
  - Fixing parameters to predetermined values does not simplify the model (e.g., does not reduce the dynamical order)

MBAM

1. Choose an initial direction: eigenvector of $\mathcal{I}$ with smallest eigenvalue
    - Choose the orientation so that the parameter space norm will grow when following the geodesic.
    - This direction is usually involves a complicated combination of most parameters.
2. Solve the geodesic equation numerically
3. Monitor the behavior of the parameters in the geodesic to identify a limiting approximation.
    - Requires some human intervention/insight.
    - Evaluate the limit to remove one parameter combination.
4. Fit the behavior of the new model to original behavior.

GEODESICS NEAR THE BOUNDARIES

- The initial direction can be a complicated combination of parameters.
- Near the boundary, the geodesic rotates to reveal a limiting approximation.
- The smallest eigenvalues approach zero at the boundary.



WORKED EXAMPLE: ENZYME REACTION

$$E + S \rightleftarrows C \rightarrow E + P$$

$$\frac{d}{dt}[E] = -k_f[E][S] + k_r[C] + k_c[C]$$

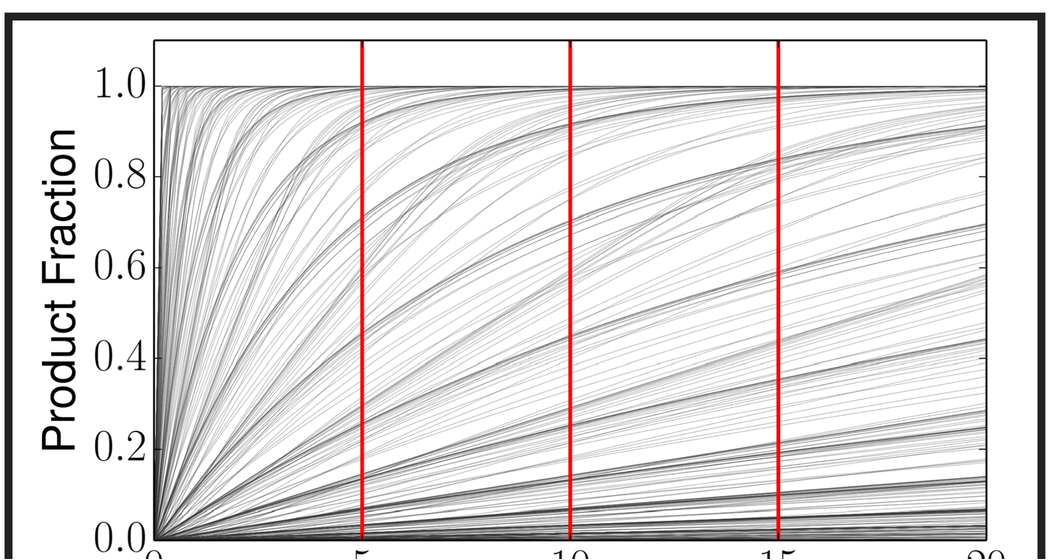
$$\frac{d}{dt}[S] = -k_f[E][S] + k_r[C]$$

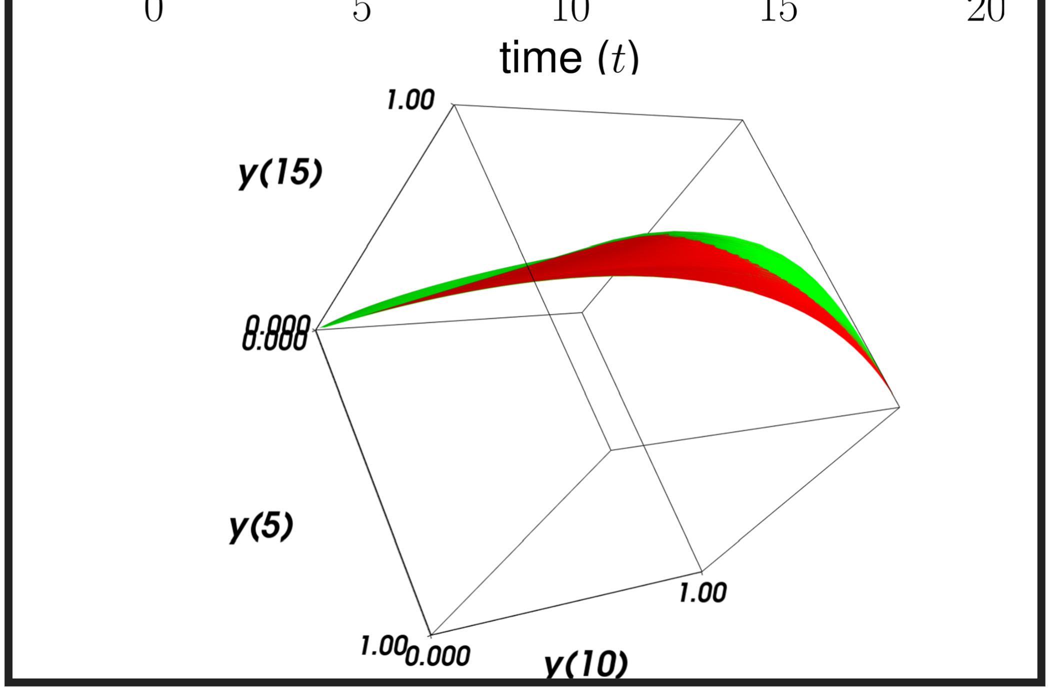
$$\frac{d}{dt}[C] = k_f[E][S] - k_r[C] - k_c[C]$$

$$\frac{d}{dt}[P] = k_c[C]$$

Three parameters: k_f, k_r, k_c.

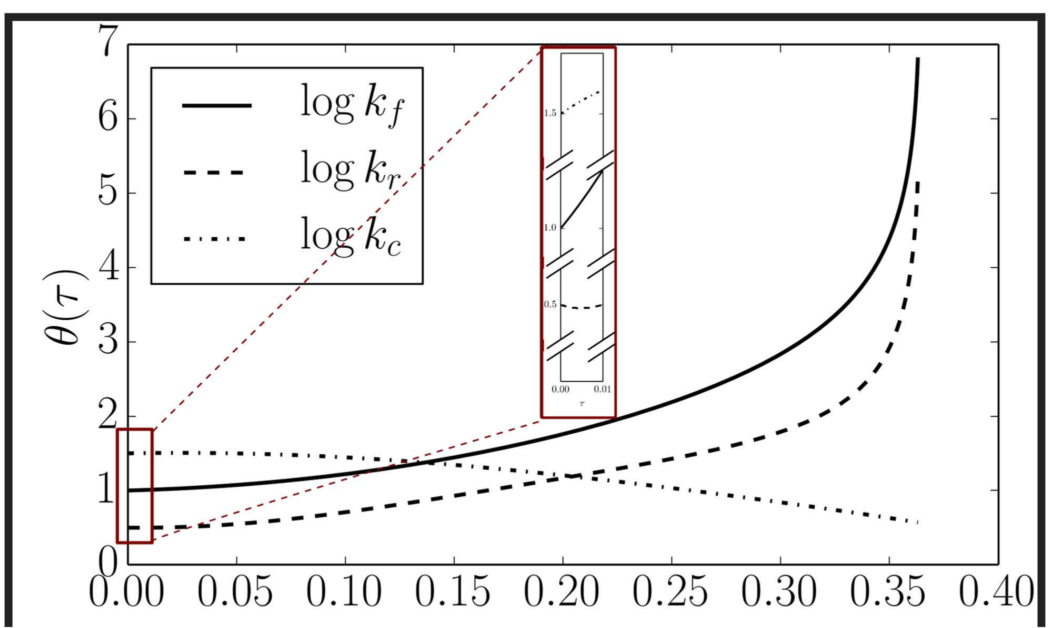
MODEL MANIFOLD



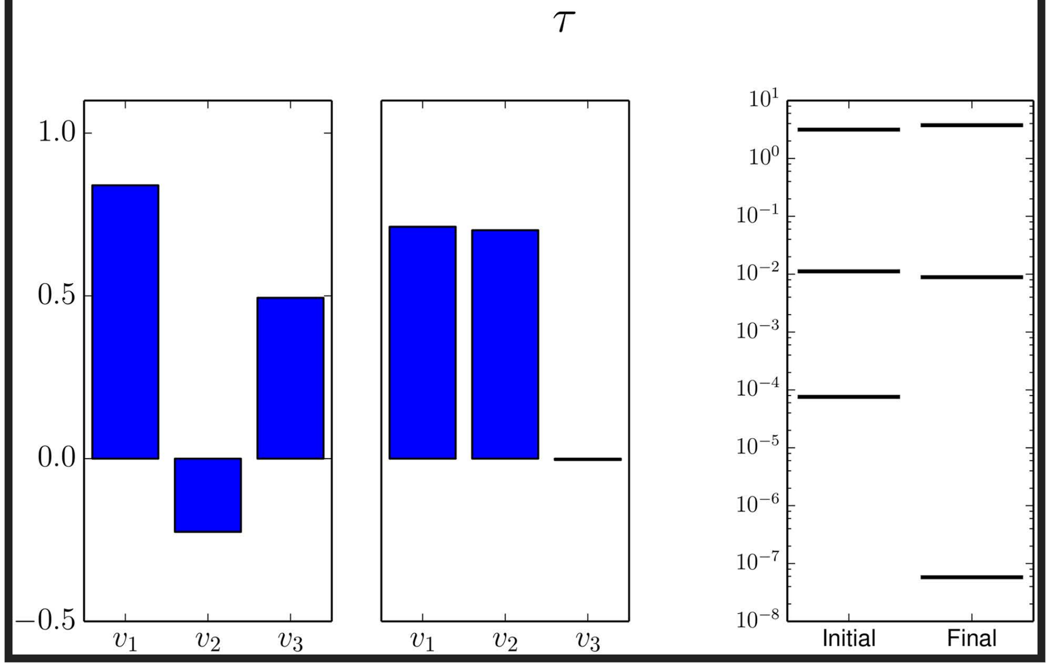


- 3 Dimensional Model Manifold
- Two boundaries (red and green)

GEODESIC



- Geodesic finds boundary at $\tau = 0.37$
- Two parameters become



infinite:

$$k_f, k_r \to \infty$$

FINDING THE REDUCED MODEL

Focus on the equation for $[S]$

$$\frac{d}{dt}[S] = -k_f[E][S] + k_r[C]$$

$$\frac{1}{k_r}\frac{d}{dt}[S] = -\frac{k_f}{k_r}[E][S] + [C]$$

$$\to_{k_f, k_r \to \infty} \; 0 = -\frac{1}{K_d}[E][S] + [C]$$

$$\implies [C] = \frac{1}{K_d}[E][S]$$

FINDING THE REDUCED MODEL

$$\boxed{K_d[C] = [E][S]}$$

$$\begin{aligned} E_0 &= [E] + [C] \\ &= \frac{K_d[C]}{[S]} + [C] \\ \Longrightarrow \quad [C] &= \frac{E_0[S]}{K_d + [S]} \end{aligned}$$

$$\Longrightarrow \quad \frac{d}{}[P] = k_c[C] = \frac{k_c E_0[S]}{}$$

$$\implies \frac{d}{dt}[P] = k_c[C] = \frac{}{K_d + [S]}$$

which is the famous Michalies-Menten equation.

COMMENTS

- Michaelis and Menten originally assumed an equilibrium approximation:.
  - $d[S]/dt = 0 \implies K_d[C] = [E][S]$
  - Formally valid if $k_f, k_r \gg k_c$
  - Equivalent to the boundary.
  - If $d[S]/dt = 0$, then k_f and k_r are structurally unidentifiable. K_d is the identifiable combination.
- Michaelis and Menten applied their deep physical insight into

the system behavior.

- MBAM extracts the physical insight from the identifiablility analysis.

PRACTICE: NEGATIVE FEEDBACK ADAPTATION

$$\frac{dA}{dt} = k_{IA} I \frac{1-A}{1-A+K_{IA}} - F_A k_{FA} \frac{A}{A+K_{FA}}$$

$$\frac{dB}{dt} = k_{CB} C \frac{1-B}{1-B+K_{CB}} - F_B k_{FB} \frac{B}{B+K_{FB}}$$

$$\frac{dC}{dt} = k_{AC} A \frac{1-C}{1-C+K_{AC}} - k_{BC} B \frac{C}{C+K_{BC}}$$

The first three MBAM limits are

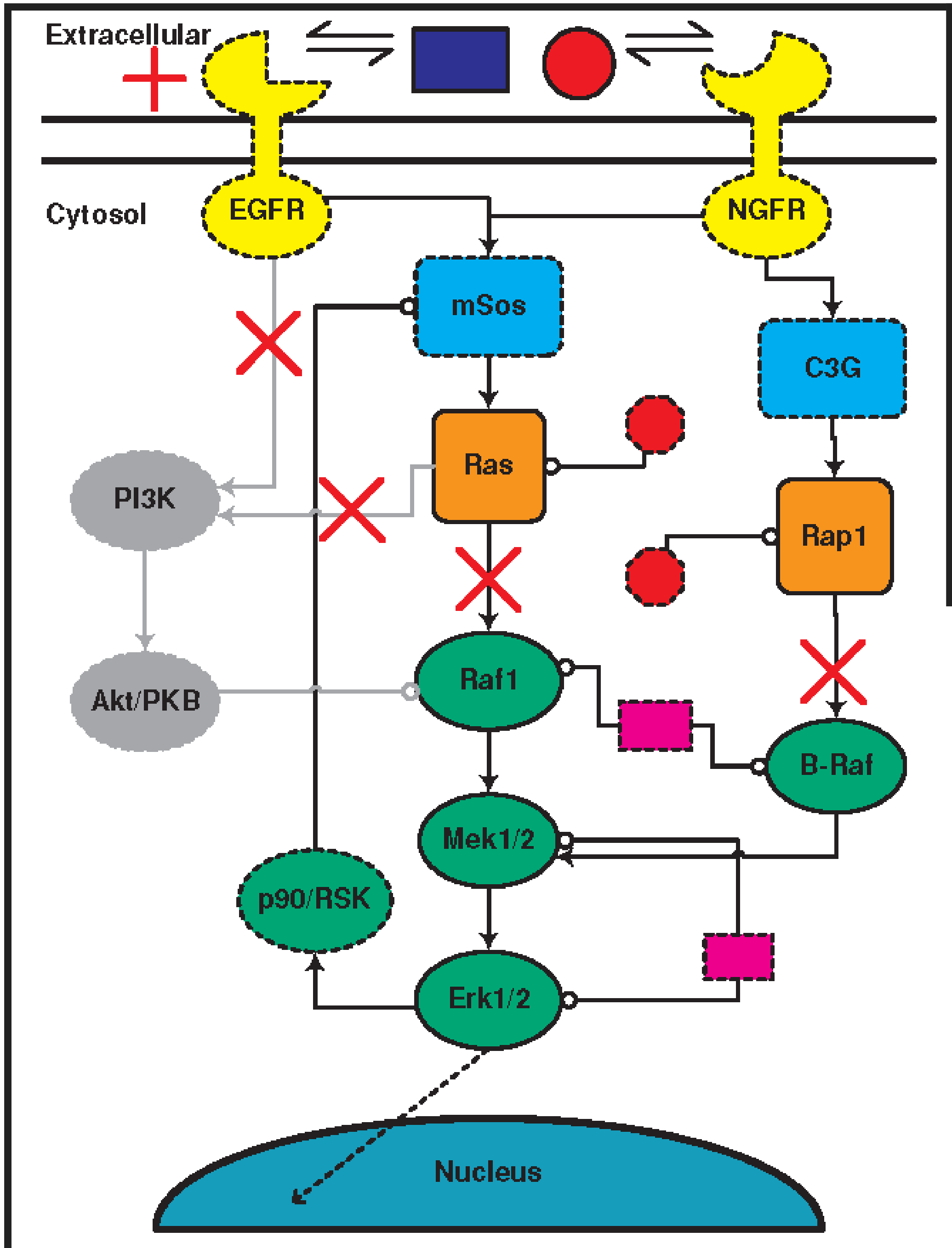
1. $k_{FA}, K_{FA} \to \infty$
2. $k_{CB}, K_{CB} \to \infty$
3. $(k_{CB}/K_{CB}), k_{FB}, K_{FB}, 1/k_{BC} \to 0$

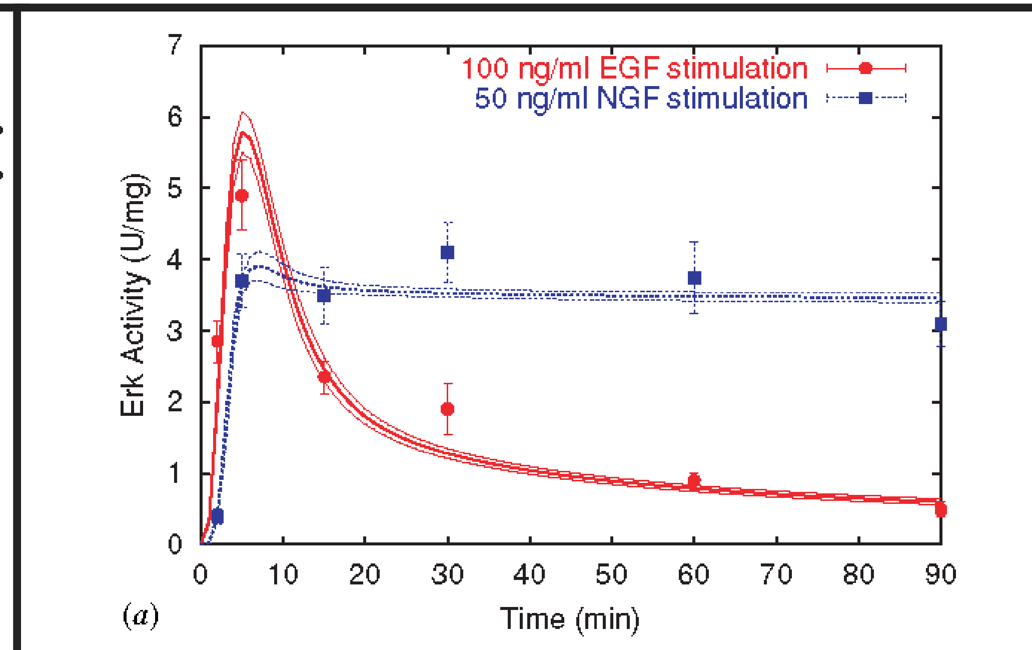
Exercise: Find the model after evaluating these three limits.

SOLUTION:

$$
\begin{aligned}
\frac{dA}{dt} &= k_{IA} I \frac{1-A}{1-A+K_{IA}} - \left(\frac{k_{FA}}{K_{FA}}\right) F_A A \\
\frac{d\tilde{B}}{dt} &= \left(\frac{k_{CB} k_{BC}}{K_{BC}}\right) C - F_B \left(k_{FB} k_{BC}\right) \frac{\tilde{B}}{\tilde{B} + \left(K_{FB} k_{BC}\right)} \\
\frac{dC}{dt} &= k_{AC} A \frac{1-C}{1-C+K_{AC}} - \tilde{B} \frac{C}{C+K_{BC}} \\
\tilde{B} &= k_{BC} B
\end{aligned}
$$

EGFR REVISITED

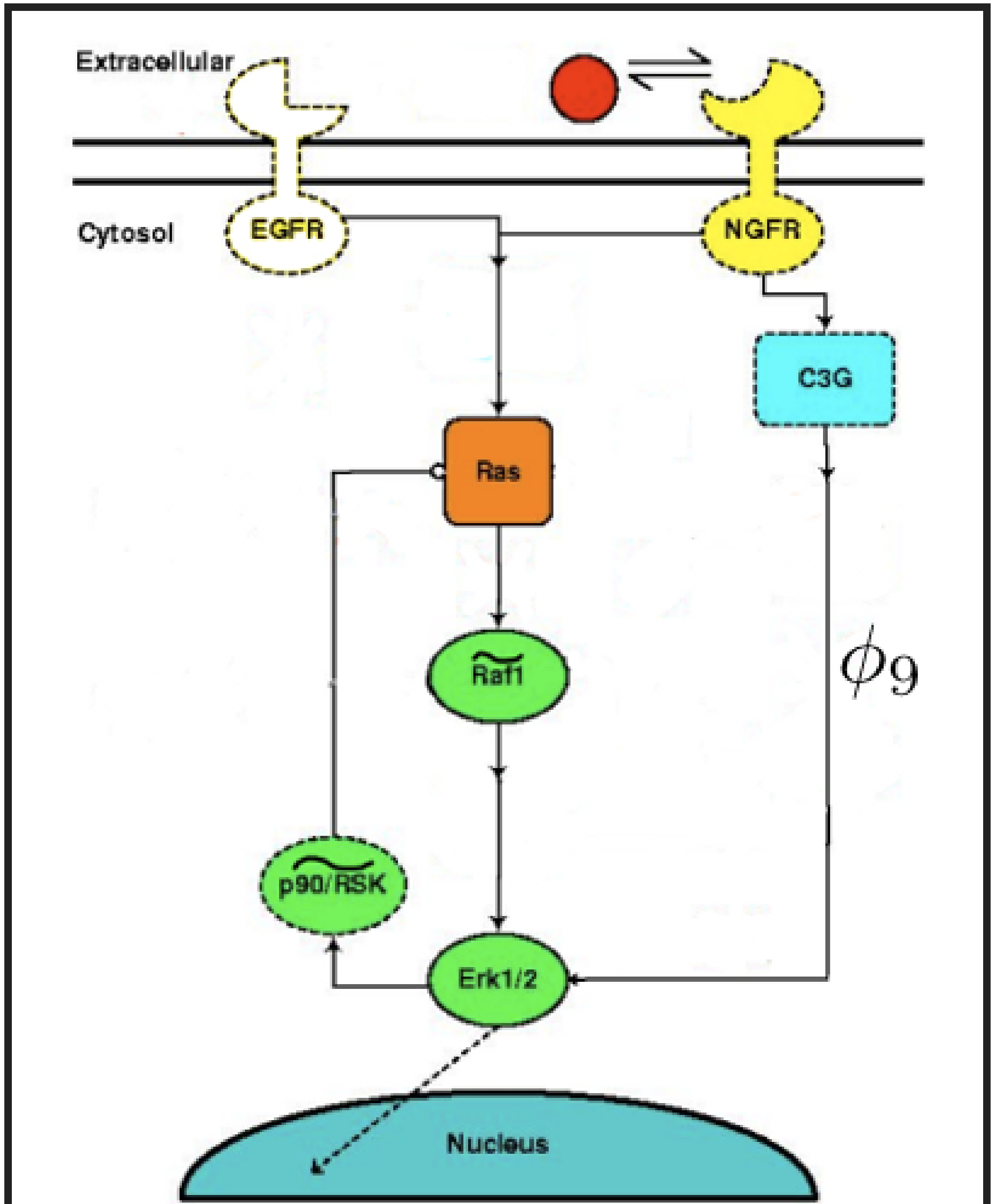




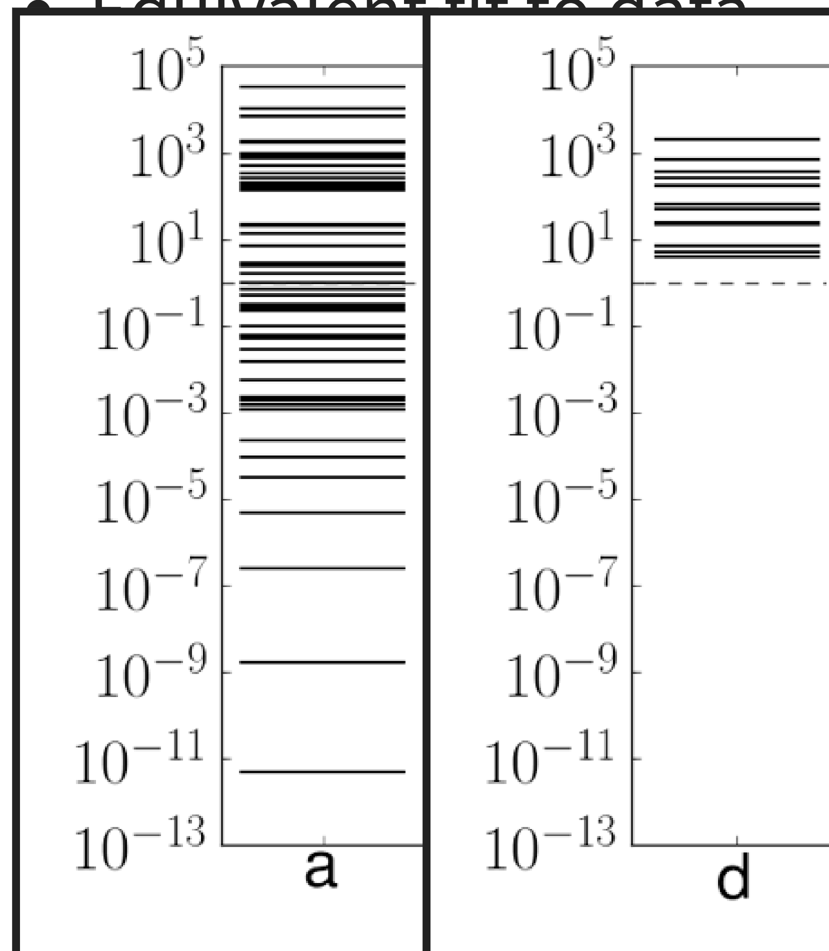
- 48 Parameters
- 29 Differential Equations
- 68 data points

REDUCED NETWORK

REDUCED NETWORK



- 12 Parameters
- 6 Differential Equations
- Equivalent fit to data



INTERPRETING THE REDUCED MODEL

- Effective "renormalized" parameters
$$\phi_9 = \frac{[BRafI](kRap1ToBRaf)(KmdBRaf)(kpBRaf)(KmdM}{[PP2AA][Raf1PPtas](kdBRaf)(KmRap1ToBRaf)(kdM}$$
  - Interpretation: effective rate of information flow through the channel
  - Emergent control knob
  - No black box
  - Effect of changes to microscopic parameters can be predicted
- Dynamical Variables: Functional, biological module
- The character of the model has changed
  - Proteins → Signaling
  - Chemistry → Biology

ISING MODEL

$$\mathcal{H} = -\sum_{nn} J_{ij} s_i s_j - h \sum s_i$$

- One parameter for each nearest-neighbor bond.
- Boundaries: $J_{ij} \rightarrow \infty$
  - $P(s_i \neq s_j) = 0$
  - Two spins cluster into a single, larger spin
  - For each parameter reduction, there is an analogous coarse-graining (general result)
- Iterating clusters more spins into effective "blocks" of spin
- Result: model relating effective relationships among large-scale domains

ISING MODEL

$$\mathcal{H} = -J_1 \sum s_i s_j - J_2 \sum s_i s_j - \ldots$$

$${}_1\sum_{nn} {}_i\, {}_j \qquad {}_2\sum_{nnn} {}_i\, {}_j$$

- Boundaries: $\tilde{J}_i \rightarrow \infty$ (Fourier transform of J's)
- Spin configuration of the i^{th} frequency has probability zero.
- Iterating removes spin configuration of highest frequencies
- Result: model relating the effective relationships among configuration with long-length scale correlations.

LIMITATIONS OF THE MBAM

- Not fully automatic
- Computational challenges

Computational challenges
    - Ill-conditioned metric (not a problem in practice?)
    - Geodesics can be expensive
    - Successfully applied on models with 100s of parameters and dynamical variables.
    - This is likely the limit with current techniques.
- Does not remove structural unidentifiabilities (more on that to come)
- Requires a hierarchy of boundaries (more on that to come)
    - Models without boundaries include linear least squares
    - Many models are unbounded in some direcions but included bounded cross sections.
    - MBAM works in these cases.

WHERE IS IT KNOWN TO WORK

- Chemical/Biochemical kinetics (Conservation of mass)
- Compartment models (Conservation of mass)
- Power system Transients (Singular Perturbation)
- Stable Linear Time Invariant Systems (Balanced Truncation)
- Composition of elementary functions (exponential, rational polynomial, etc.)
- Bayesian networks/Markov Chains/Markov Random Fields (Conservation of Probability)
- Molecular dynamic with harmonic potentials (Conservation of energy)
- Neural Networks
- Exponential Families (e.g., Ising Model)
- Models with discrete symmetries (Orbifolds)
- Hogdkin-Huxley Neurons