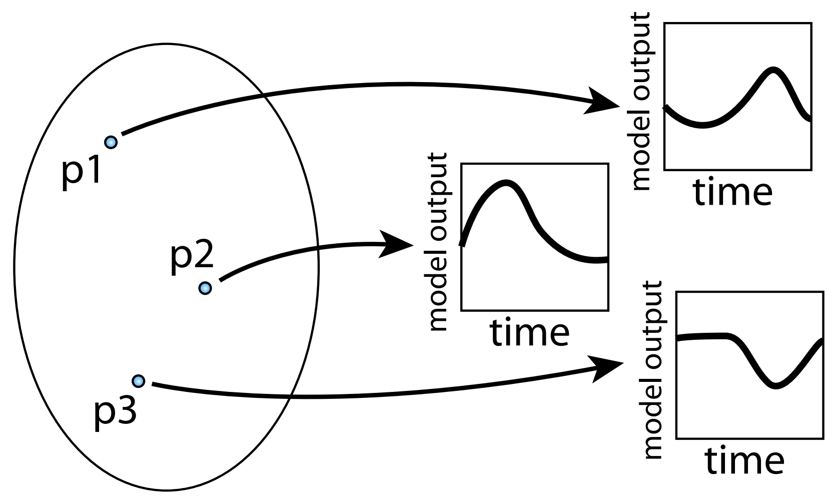
Introduction to Structural & Practical Identifiability

Marisa Eisenberg
University of Michigan, Ann Arbor

Identifiability

- Identifiability—Is it possible to uniquely determine the parameters from the data?

Parameters  Output/Data

- Important problem in parameter estimation

- Many different approaches - statistics, applied math, engineering/systems theory

Ollivier 1990, Ljung & Glad 1994, Evans & Chappell 2000, Audoly et al 2003, Hengl et al. 2007, Chis et al 2011

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IDENTIFIABILITY OF A LINEAR RELATION BETWEEN VARIABLES WHICH ARE SUBJECT TO ERROR[1]

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On Structural Identifiability

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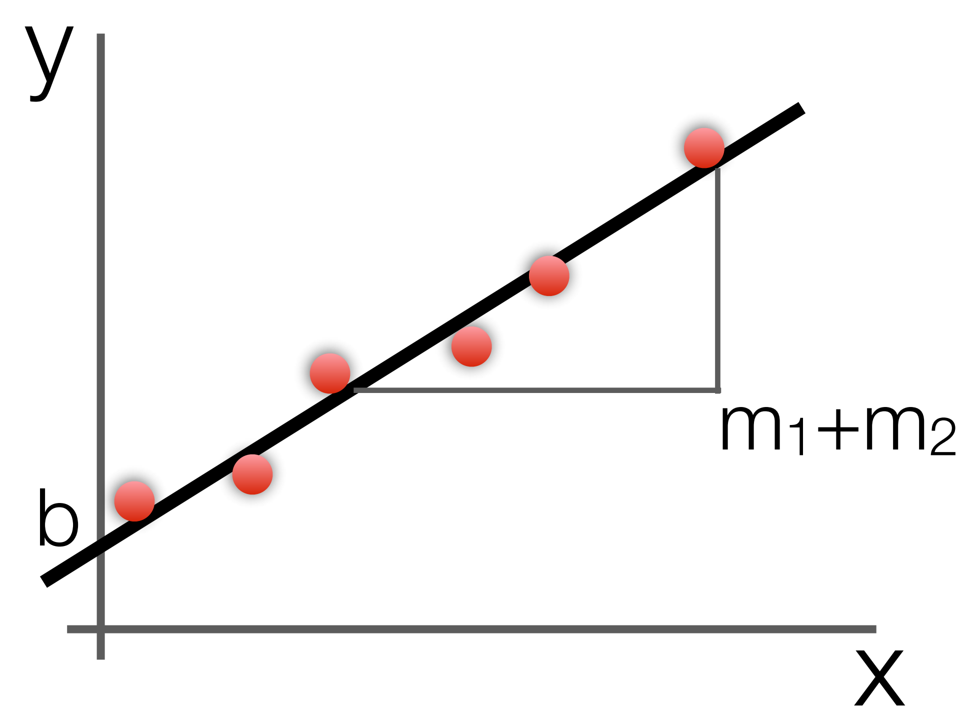
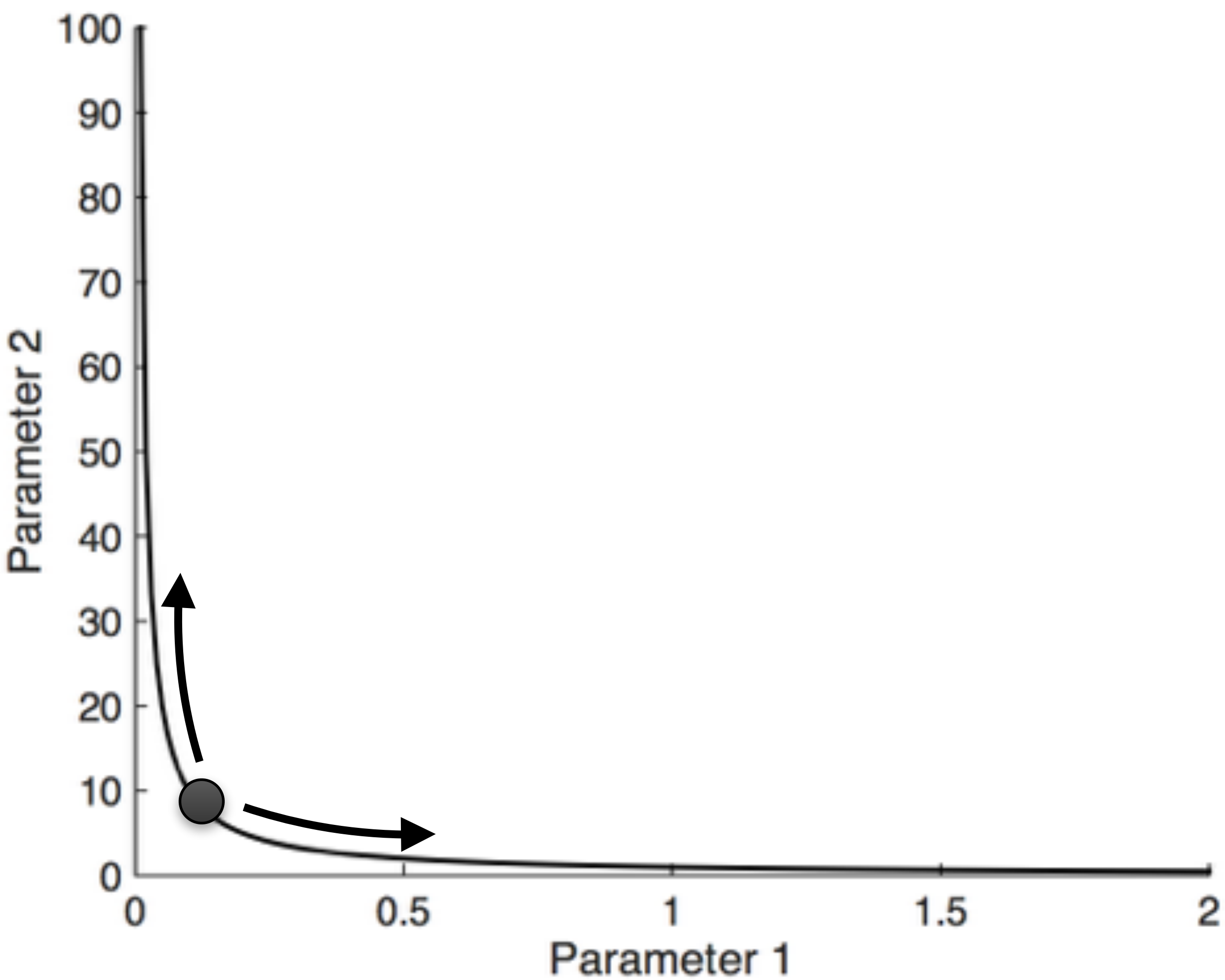
Identifiability

- Practical vs. Structural
  - Broad, sometimes overlapping categories
  - Noisy vs. perfect data
- Example: $y = (m_1 + m_2)x + b$
- Unidentifiability - can cause serious problems when estimating parameters
- Identifiable combinations





Parameter 2
Parameter 1
100
90
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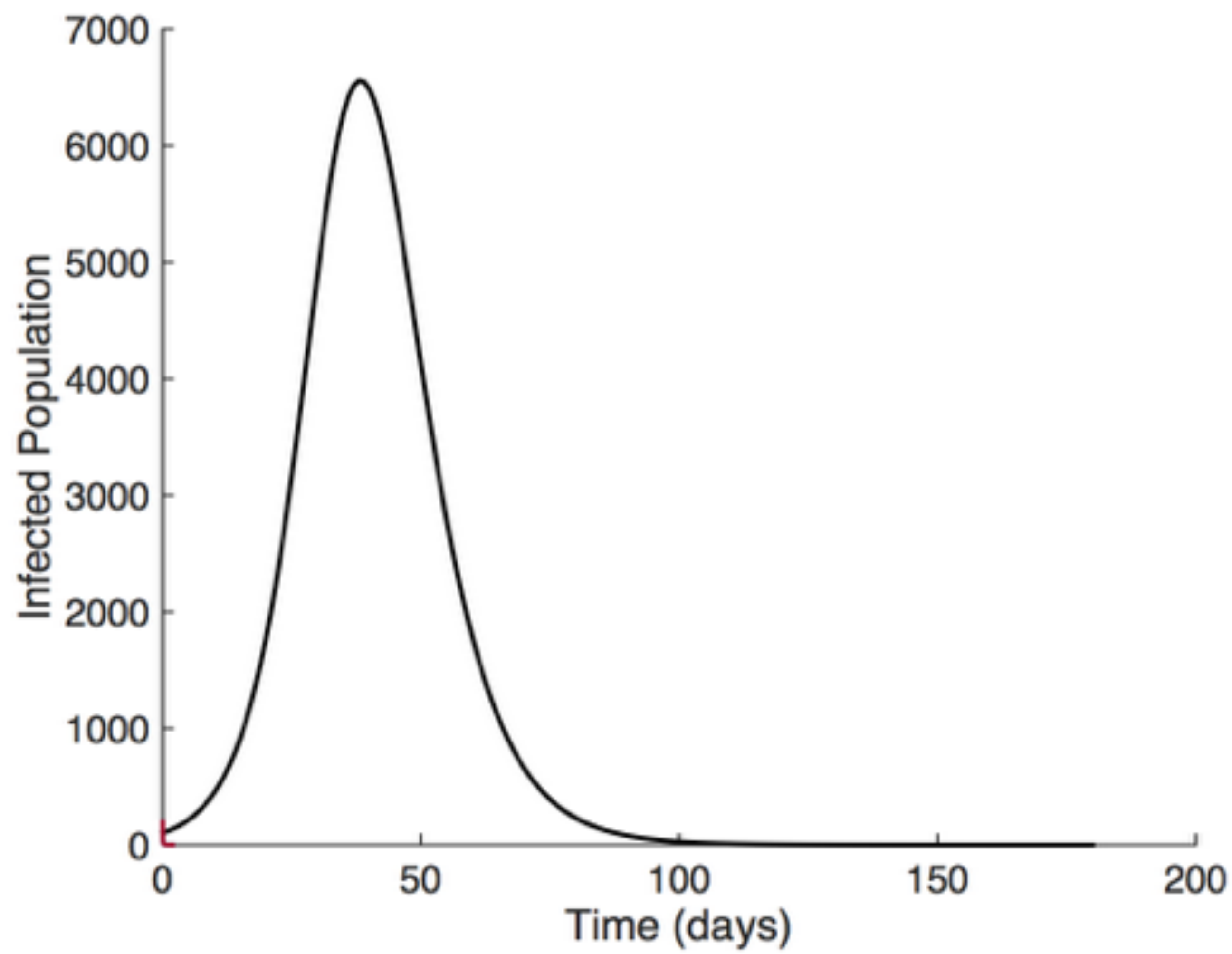

Infected Population
Time (days)
7000
6000
5000
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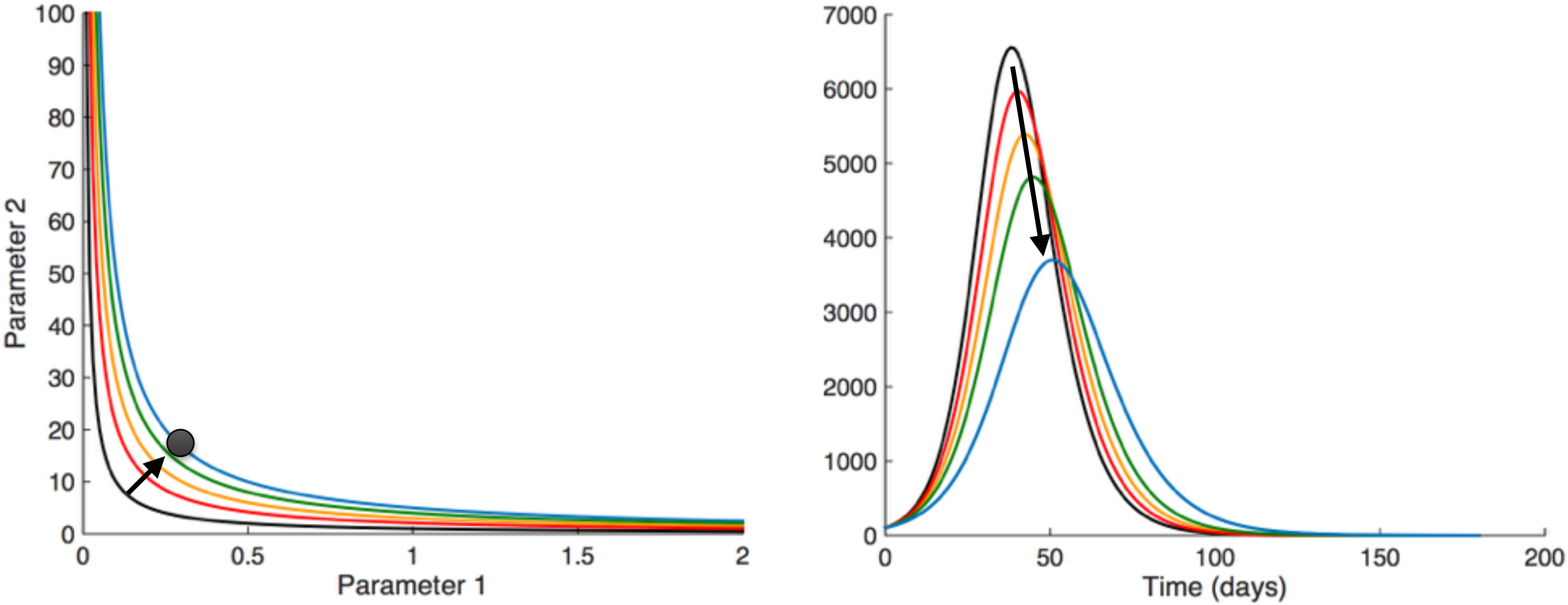

100
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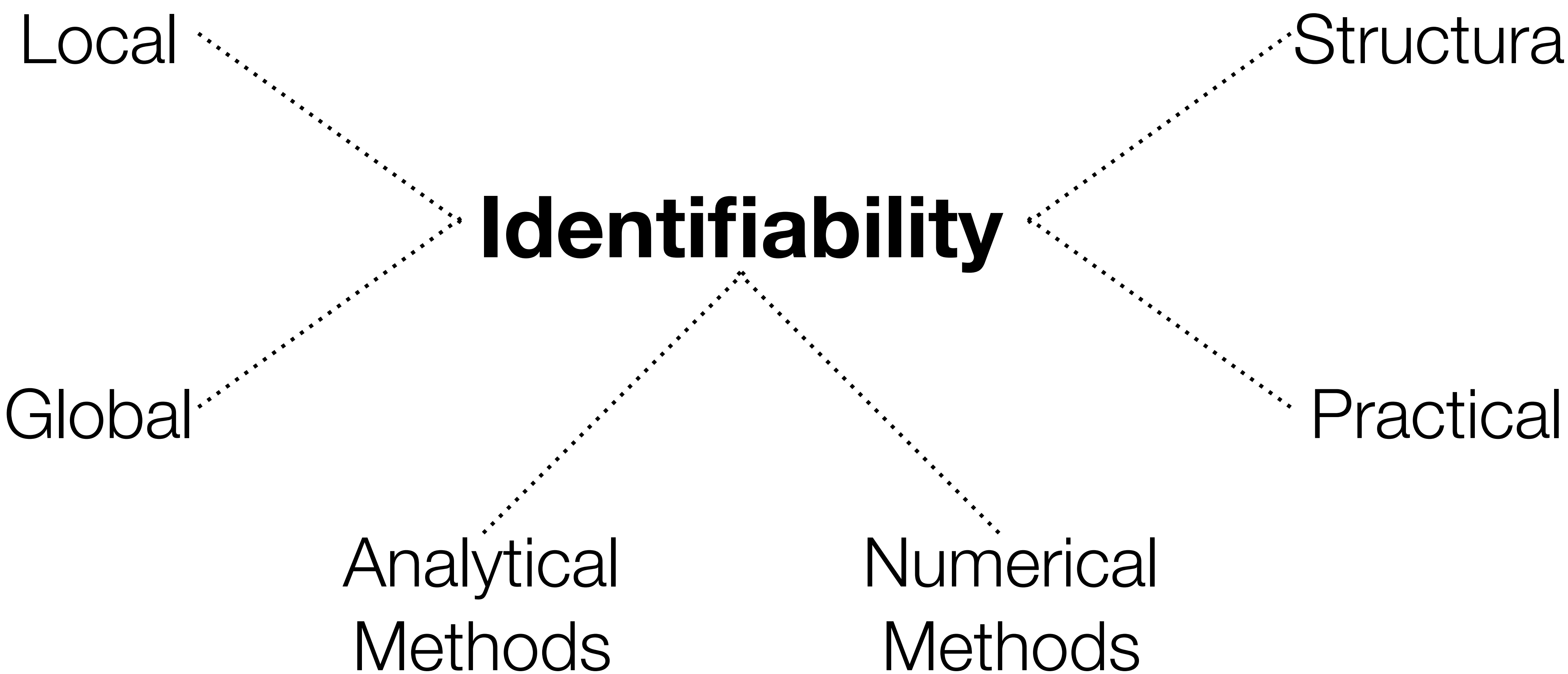
Parameter 1
7000
6000
5000
4000
3000
2000
1000
0
0
50
100
150
200
Time (days)

Structural Identifiability

- Assumes best case scenario - data is known perfectly at all times
- Unrealistic!
- But, necessary condition for practical identifiability with real, noisy data

Structural Identifiability

- Reveals identifiable combinations and how to restructure the model so that it is identifiable
- Can give a priori information, help direct experiment design


Local
Structural
Identifiability
Global
Practical
Analytical Methods
Numerical Methods

Key Concepts

- Identifiability vs. unidentifiability
  - Practical vs. structural, local vs. global
  - Can be in between, e.g. quasi-identifiable
- Identifiable Combinations
- Reparameterization
- Related questions: observability, distinguishability & model selection

Reparameterization

- Identifiable combinations - parameter combinations that can be estimated
- Once you know those, why reparameterize?
- Estimation issues - reparameterization provides a model that is input-output equivalent to the original but identifiable
- Often the reparameterized model has ‘sensible’ biological meaning (e.g. nondimensionalized, etc.)

Methods we'll talk about today

- Differential Algebra Approach - structural identifiability, global, analytical method
- Fisher information matrix - structural or practical, local, analytical or numerical method
- Profile likelihood - structural or practical, local, numerical method

Simple Methods

- Simulated data approach
- If you have a small system, you can even plot the likelihood surface (typically can't though—more on this with profile likelihoods)

Analytical Methods for Structural Identifiability

Methods for Structural Identifiability

- **Laplace transform** - linear models only
- **Taylor series approach** - more broad application, but only local info & may not terminate
- **Similarity transform approach** - difficult to make algorithmic, can be difficult to assess conditions for applying theorem
- **Differential algebra approach** - rational function ODE models, global info

Bellman 1970, Cobelli & DiStefano 1980, Evans & Chappell 2000, Ollivier 1990, Ljung & Glad 1994, Audoly et al 2003

Methods for Structural Identifiability

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Structural Identifiability Analysis

- Basic idea: use substitution & differentiation to eliminate all variables except for observed output (y)
- Clear (divide by) the coefficient for highest derivative term(s)
- This is called the **input-output equation(s)**
- Contains all structural identifiability info for the model

Structural Identifiability Analysis

- Use the coefficients to solve for identifiability of the model
- If unidentifiable, determine identifiable combinations
- Find identifiable reparameterization of the model?
- Easier to see with an example—

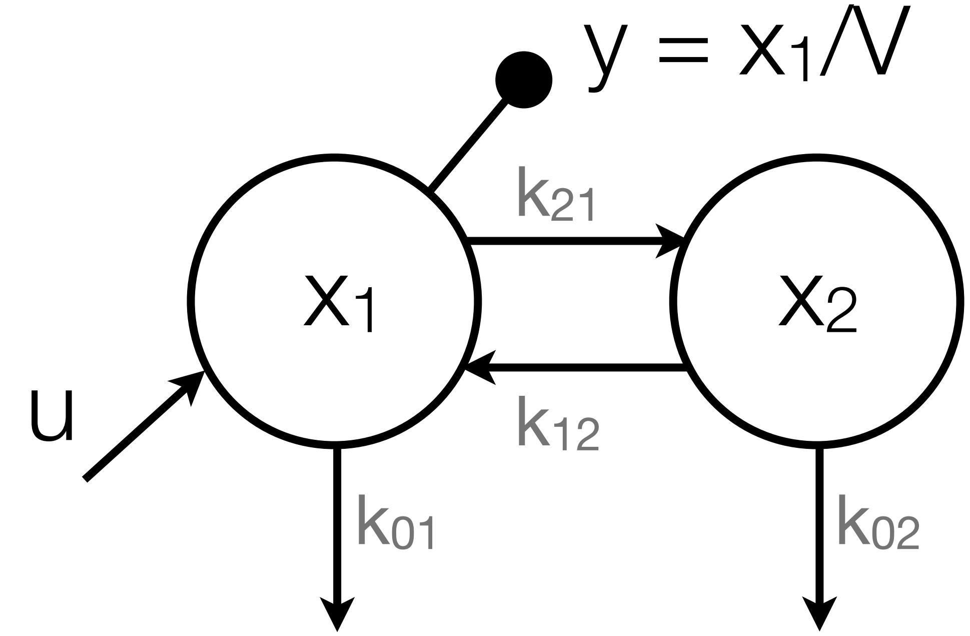
2-Compartment Example

- Linear 2-Comp Model

$$\dot{x}_1 = u + k_{12}x_2 - \left(k_{01} + k_{21}\right)x_1$$

$$\dot{x}_2 = k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2$$

$$y = x_1 / V$$



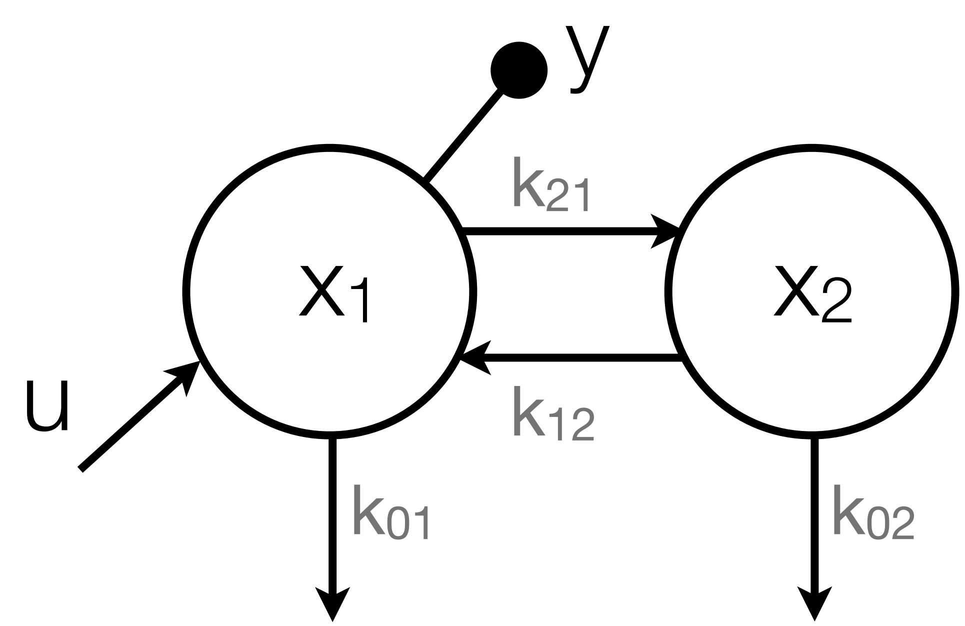
- state variables (x)
- measurements (y)
- known input (u) (e.g. IV injection)

2-Compartment Example

$$\dot{x}_1 = u + k_{12}x_2 - \left(k_{01} + k_{21}\right)x_1$$

$$\dot{x}_2 = k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2$$

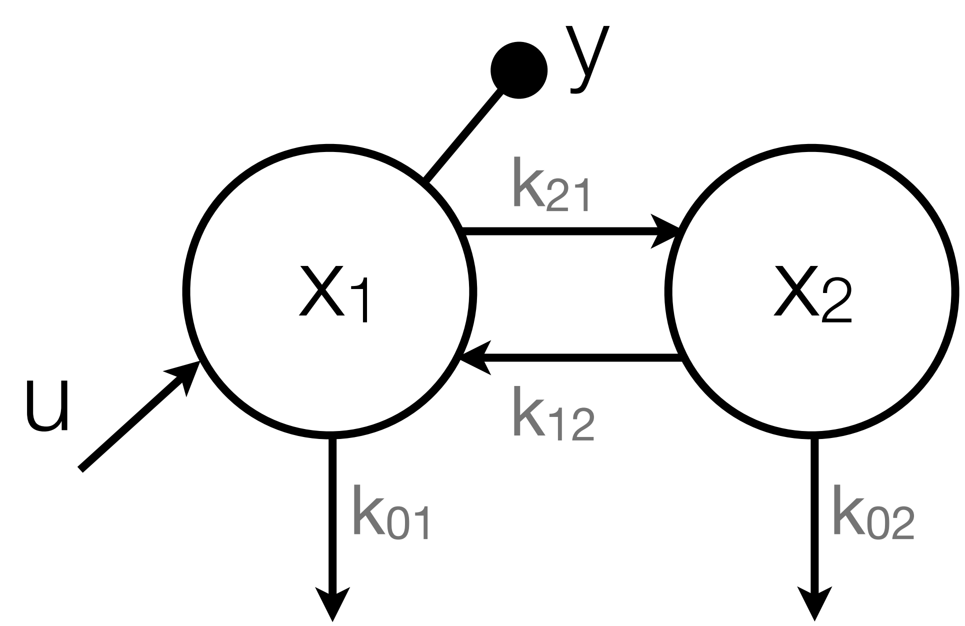
$$y = x_1 / V$$



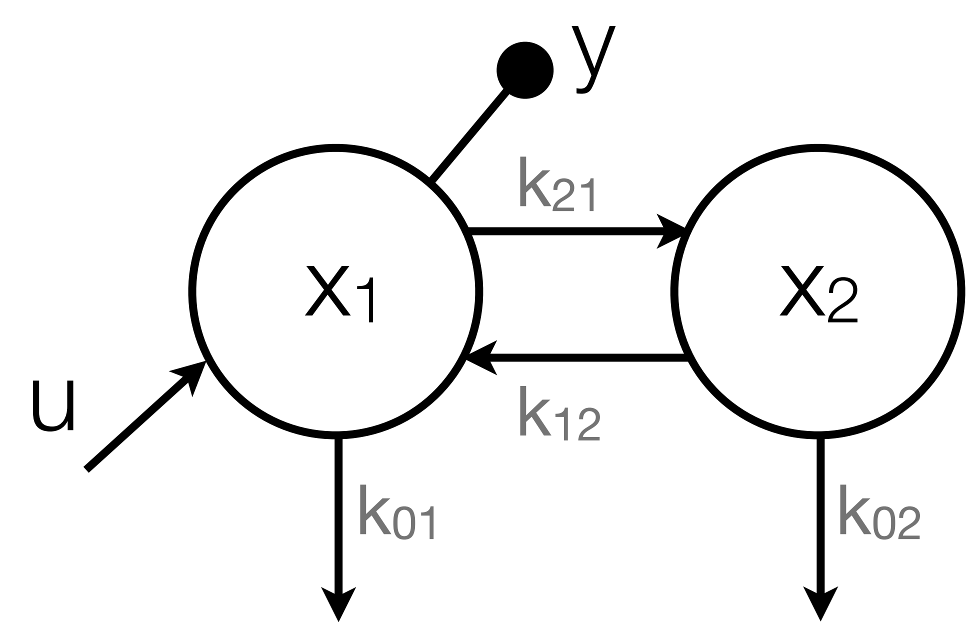
2-Compartment Example

$$\dot{y}V = u + k_{12}x_2 - \left(k_{01} + k_{21}\right)yV$$

$$\dot{x}_2 = k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2$$



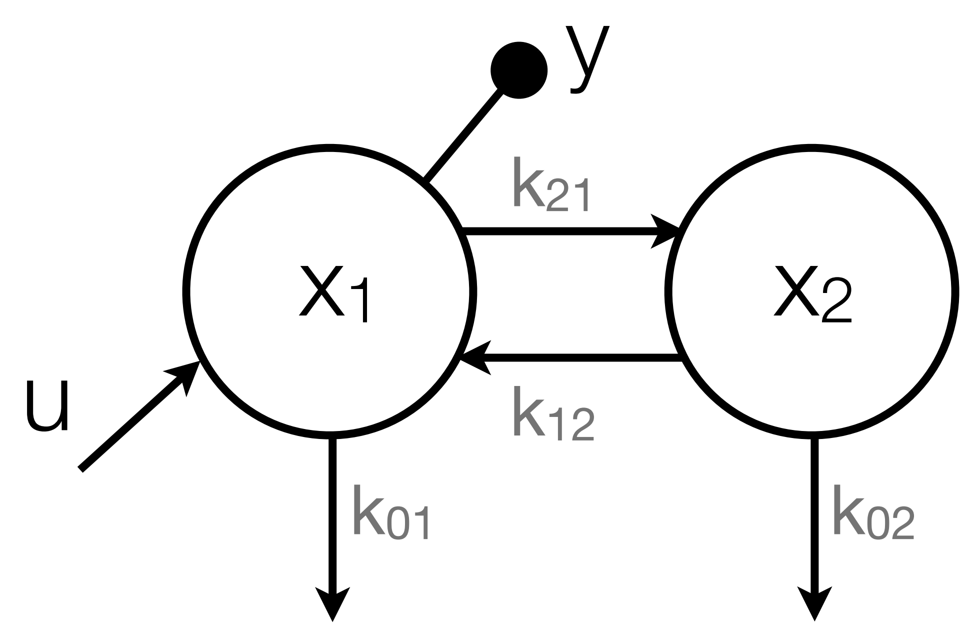
2-Compartment Example



$$\ddot{y} + \left(k_{01} + k_{21} + k_{12} + k_{02}\right)\dot{y} -$$

$$\left(k_{12}k_{21} - \left(k_{02} + k_{12}\right)\left(k_{01} + k_{21}\right)\right)y - u\left(k_{12} + k_{02}\right)/V - \dot{u}/V = 0$$

2-Compartment Example



$$1 / V = a_1$$

$$\left(k_{12} + k_{02}\right) / V = a_2$$

$$\left(k_{01} + k_{21} + k_{12} + k_{02}\right) = a_3$$

$$\left(k_{12}k_{21} - \left(k_{02} + k_{12}\right)\left(k_{01} + k_{21}\right)\right) = a_4$$

2-Compartment Example

$$1/V = a_1 \Rightarrow V = 1/a_1$$

$$\left(k_{12} + k_{02}\right)/V = a_2$$

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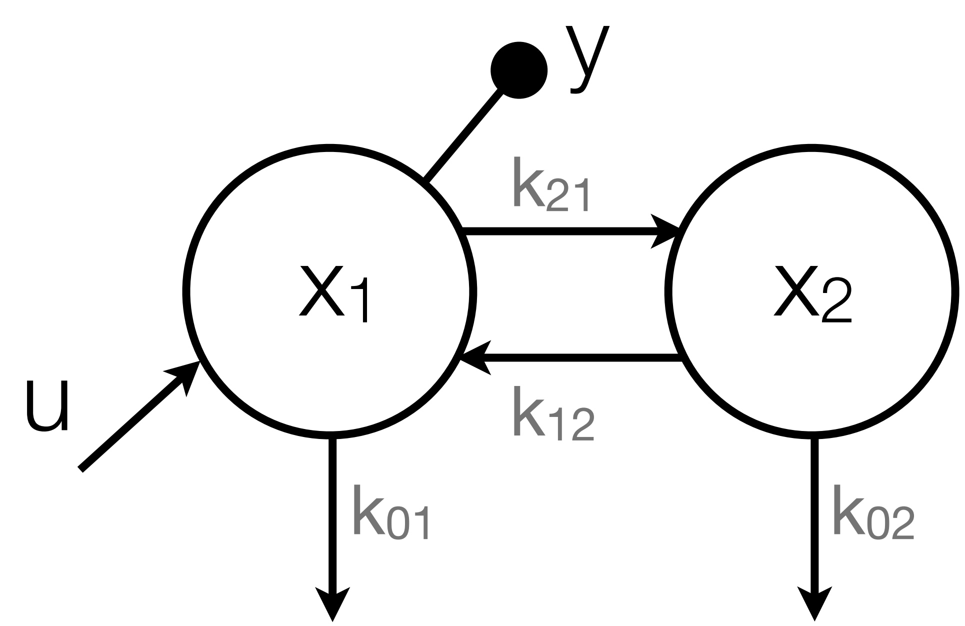
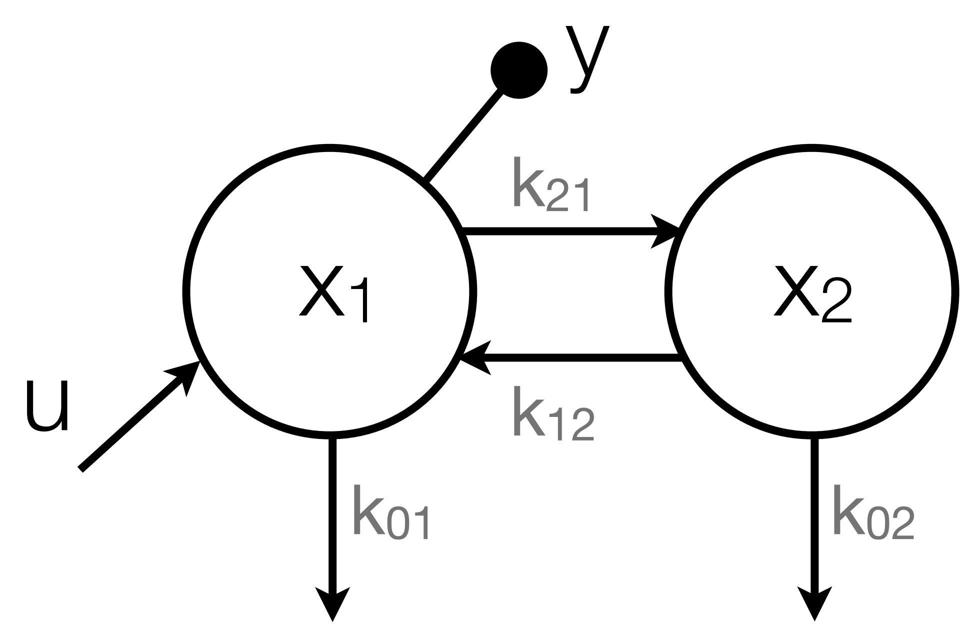


Unidentifiable

2-Compartment Example

$$\dot{x}_1 = u + k_{12}x_2 - \left(k_{01} + k_{21}\right)x_1$$
$$\dot{x}_2 = k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2$$
$$y = x_1 / V$$

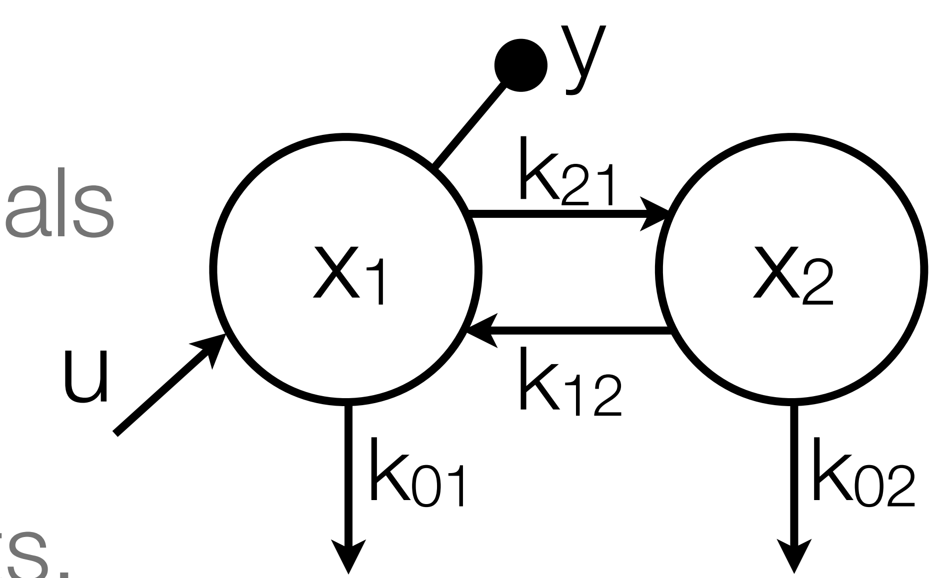


Let $\underline{x}_2 = k_{12}x_2$

$$\dot{x}_1 = u + \underline{x}_2 - \left(k_{01} + k_{21}\right)x_1$$
$$\dot{\underline{x}}_2 = k_{12}k_{21}x_1 - \left(k_{02} + k_{12}\right)\underline{x}_2$$
$$y = x_1 / V$$

Or add information about one of the parameters

Differential Algebra Approach



- View model & measurement equations as differential polynomials
- Reduce the equations using Gröbner bases, characteristic sets, etc. to eliminate unmeasured variables (x)
- Yields **input-output equation(s)** only in terms of known variables (y, u)
- Use coefficients to test model identifiability

Ollivier 1990, Ljung & Glad 1994, Audoly et al 2003, etc.

Differential Algebra Approach

- From the coefficients, can often determine:
    - Simpler forms for identifiable combinations
    - Identifiable reparameterizations for model
- Not always easy by eye—use Gröbner bases & other methods to simplify

Differential Algebra Approach

- Convenient as a way to prove identifiability results for relatively broad classes of models
  - Linear compartmental models & graph structure (with Nikki Meshkat & Seth Sullivant)
  - SIR-type models (with Tony Nance)
  - Hodgkin-Huxley-type models (with Olivia Walch)

Numerical Methods for Identifiability Analysis

Numerical Approaches to Identifiability

- Analytical approaches can be slow, sometimes have limited applicability
- Wide range of numerical approaches
  - Sensitivities/Fisher Information Matrix
  - Profile Likelihood
  - Many others (e.g. Bayesian approaches, etc.)

Numerical Approaches to Identifiability

- Most can do both structural & practical identifiability
- Wide range of applicable models, often (relatively) fast
- Typically only local

Simple Simulation Approach

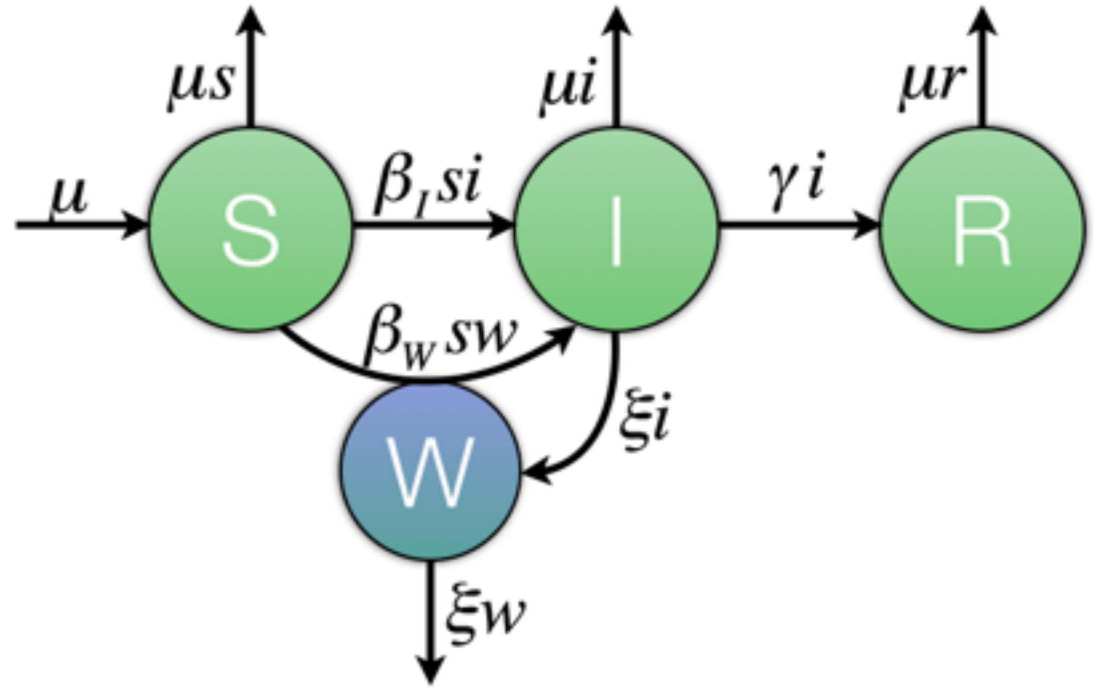
- Simulate data using a single set of ‘true’ parameter values
  - Without noise for structural identifiability
  - With noise for practical identifiability (in this case generate multiple realizations of the data)

Simple Simulation Approach

- Fit your simulated data from multiple starting points and see where your estimates land

- If they all return to the 'true' parameters, likely identifiable, if they do not, examine the relationships between the parameters

- Note—unidentifiability when estimating with 'perfect', noise-free simulated data is most likely structural



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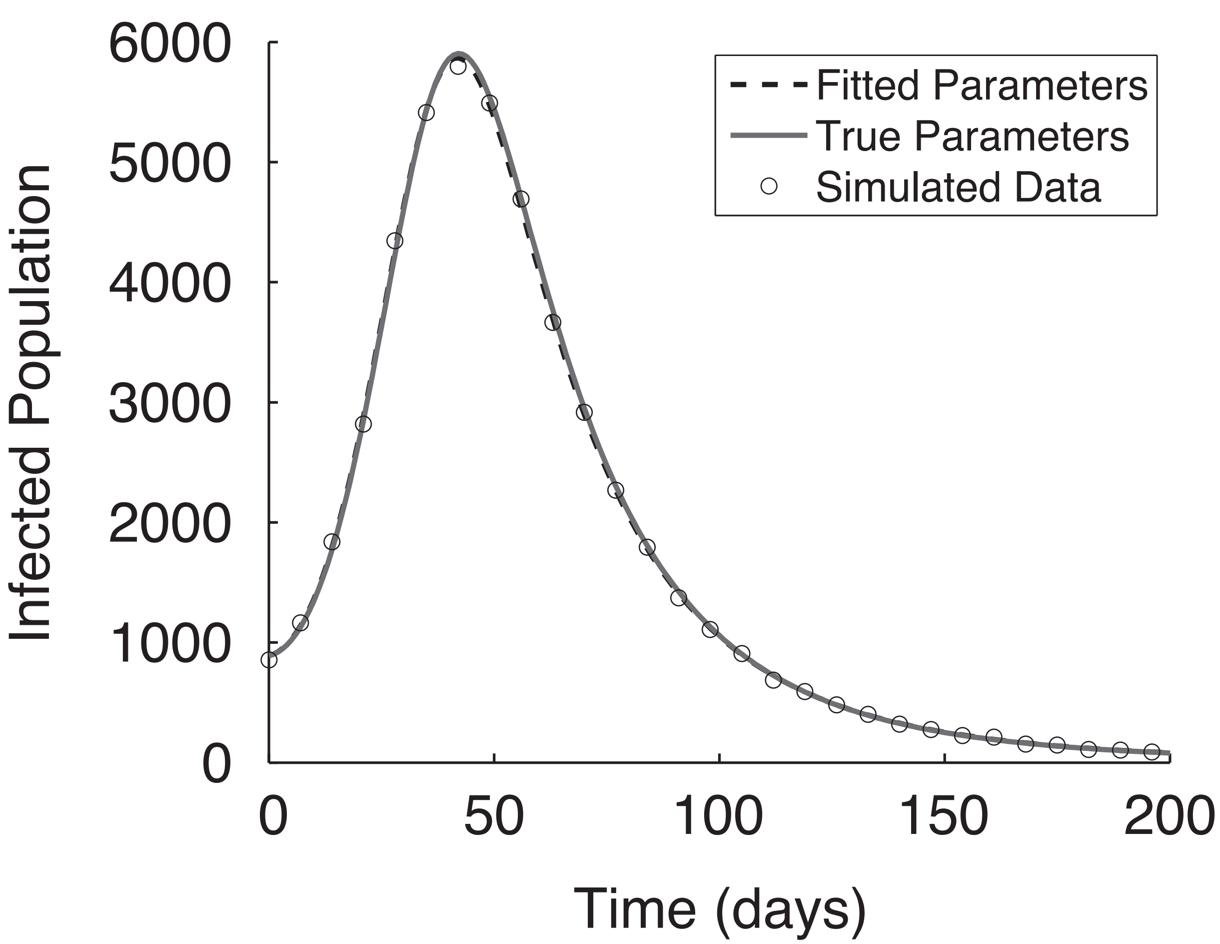
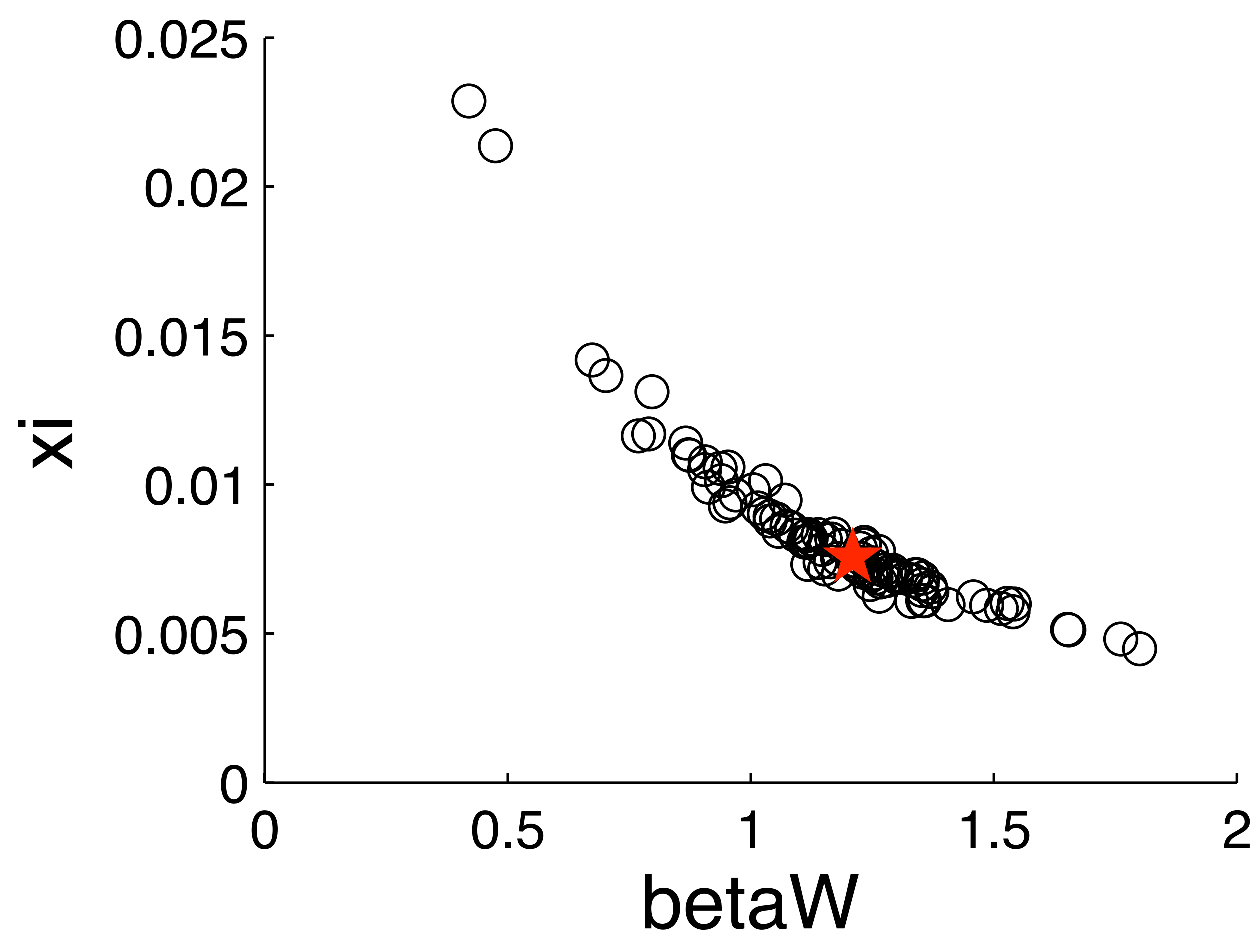


Infected Population
Time (days)
Fitted Parameters
True Parameters
Simulated Data
0
1000
2000
3000
4000
5000
6000
0
50
100
150
200



xi
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0.005
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0.015
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0.025
0
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1
1.5
2

Parameter Sensitivities

- Design matrix/output sensitivity matrix
- Closely related to identifiability
- Insensitive parameters
- Dependencies between columns

$$X = \begin{pmatrix} \frac{\partial y(t_1)}{\partial p_1} & \cdots & \frac{\partial y(t_1)}{\partial p_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial y(t_m)}{\partial p_1} & \cdots & \frac{\partial y(t_m)}{\partial p_n} \end{pmatrix}$$

Fisher Information Matrix

- FIM - N_P x N_P matrix
- Useful in testing practical & structural ID - represents amount of information that the output **y** contains about parameters **p**
- Cramer-Rao Bound: $FIM^{-1} \leq Cov(\mathbf{p})$
- Rank(FIM) = number of identifiable parameters/ combinations
- Identifiable Combinations

Fisher Information Matrix

- Special case when errors are normally distributed

$$F = X^T W X$$

W = weighting matrix

$$X = \begin{pmatrix} \frac{\partial y(t_1)}{\partial p_1} & \cdots & \frac{\partial y(t_1)}{\partial p_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial y(t_m)}{\partial p_1} & \cdots & \frac{\partial y(t_m)}{\partial p_n} \end{pmatrix}$$

Design Matrix

Fisher Information Matrix

- For looking at structural ID, often just use

$$F = X^T X$$

$$X = \begin{pmatrix} \frac{\partial y(t_1)}{\partial p_1} & \cdots & \frac{\partial y(t_1)}{\partial p_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial y(t_m)}{\partial p_1} & \cdots & \frac{\partial y(t_m)}{\partial p_n} \end{pmatrix}$$

Design Matrix

Identifiability & the FIM

- Covariance matrix/confidence interval estimates from Cramér-Rao bound: Cov ≥ FIM^{-1}
  - e.g. large confidence interval ⇒ probably unID
  - Often can detect structural unID as 'near-infinite' (gigantic) variances in Cov ~ FIM^{-1}

Identifiability & the FIM

- **Rank of the FIM** is number of identifiable combinations/parameters - can do a lot by testing sub-FIMs and versions of the FIM

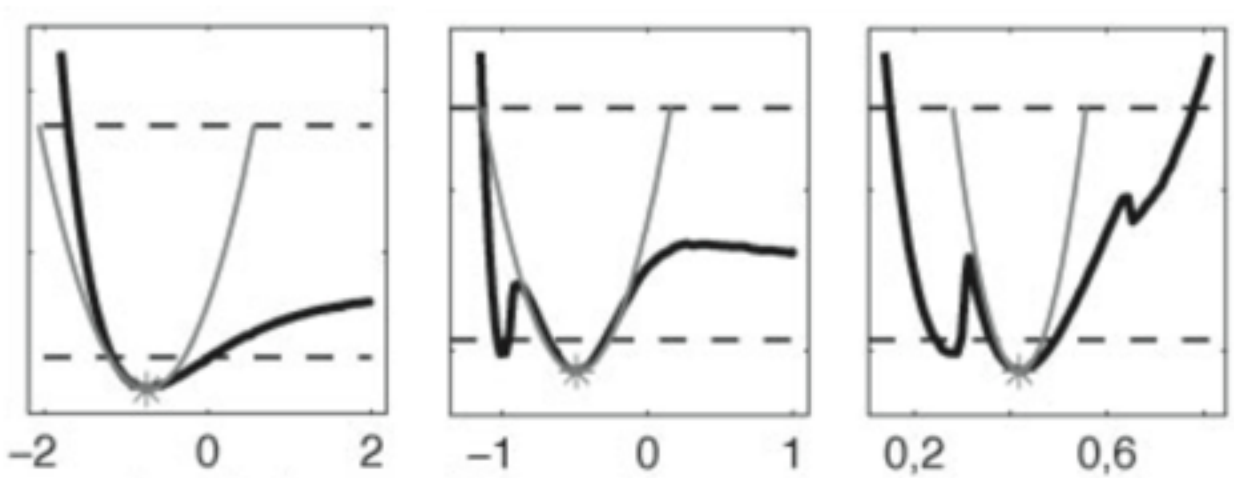
- Use FIM to find blocks of related parameters & how many to fix (not estimate)

- Identifiable combinations - can often see what parameters are related, but don’t know form

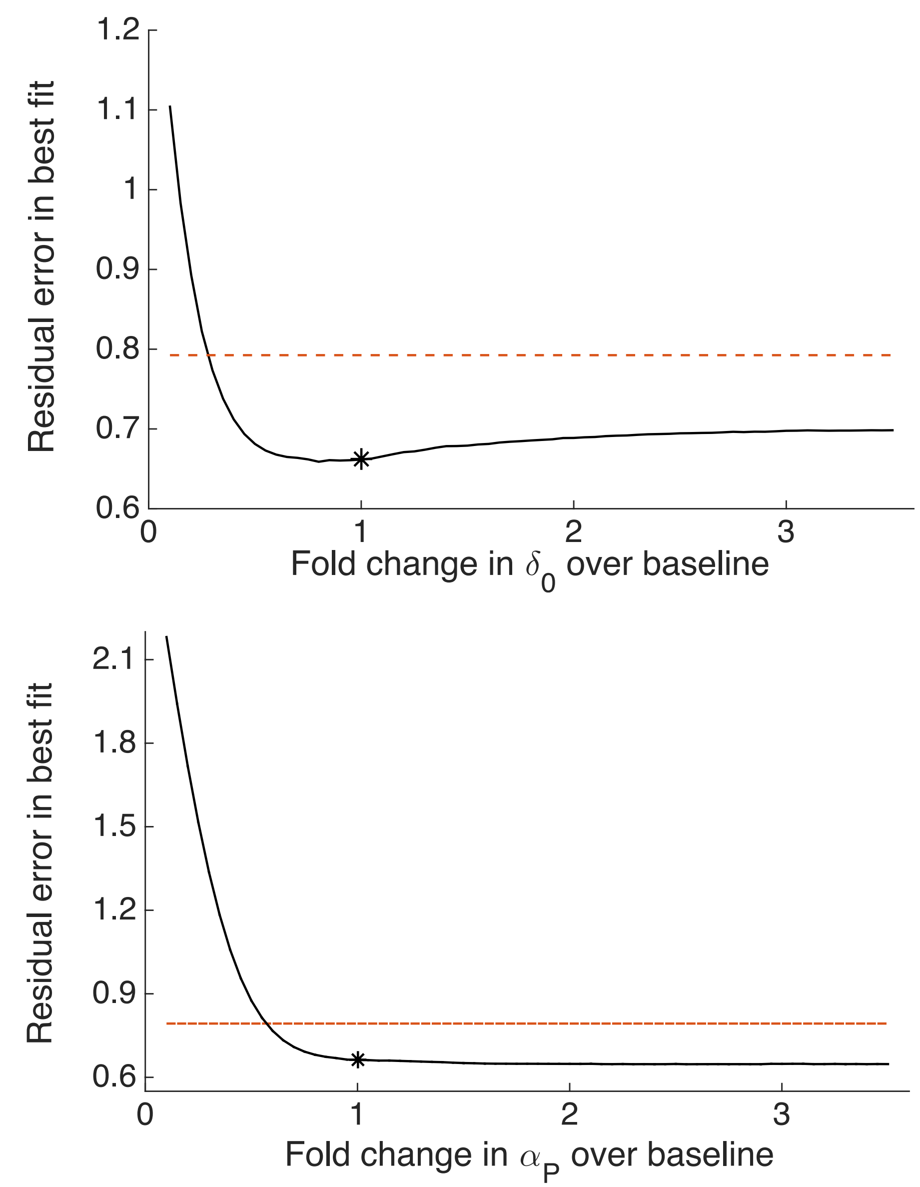
  - Interaction of combinations

Identifiability & the FIM

- But, be careful—FIM is local & asymptotic
- Local approximation of the curvature of the likelihood



Raue et al. 2010



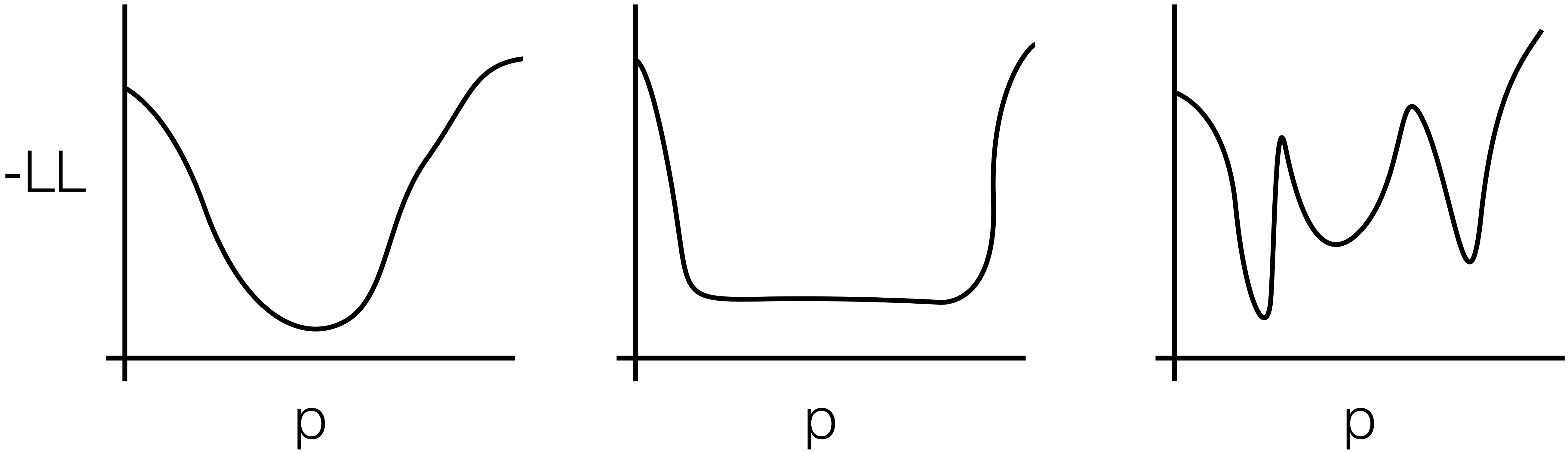
Profile Likelihood

- Want to examine likelihood surface, but often high-dimensional
- Basic Idea: ‘profile’ one parameter at a time, by fixing it to a range of values & fitting the rest of the parameters
- Gives best fit at each point
- Evaluate curvature of likelihood to determine confidence bounds on parameter (and to evaluate parameter uncertainty)

Profile Likelihood

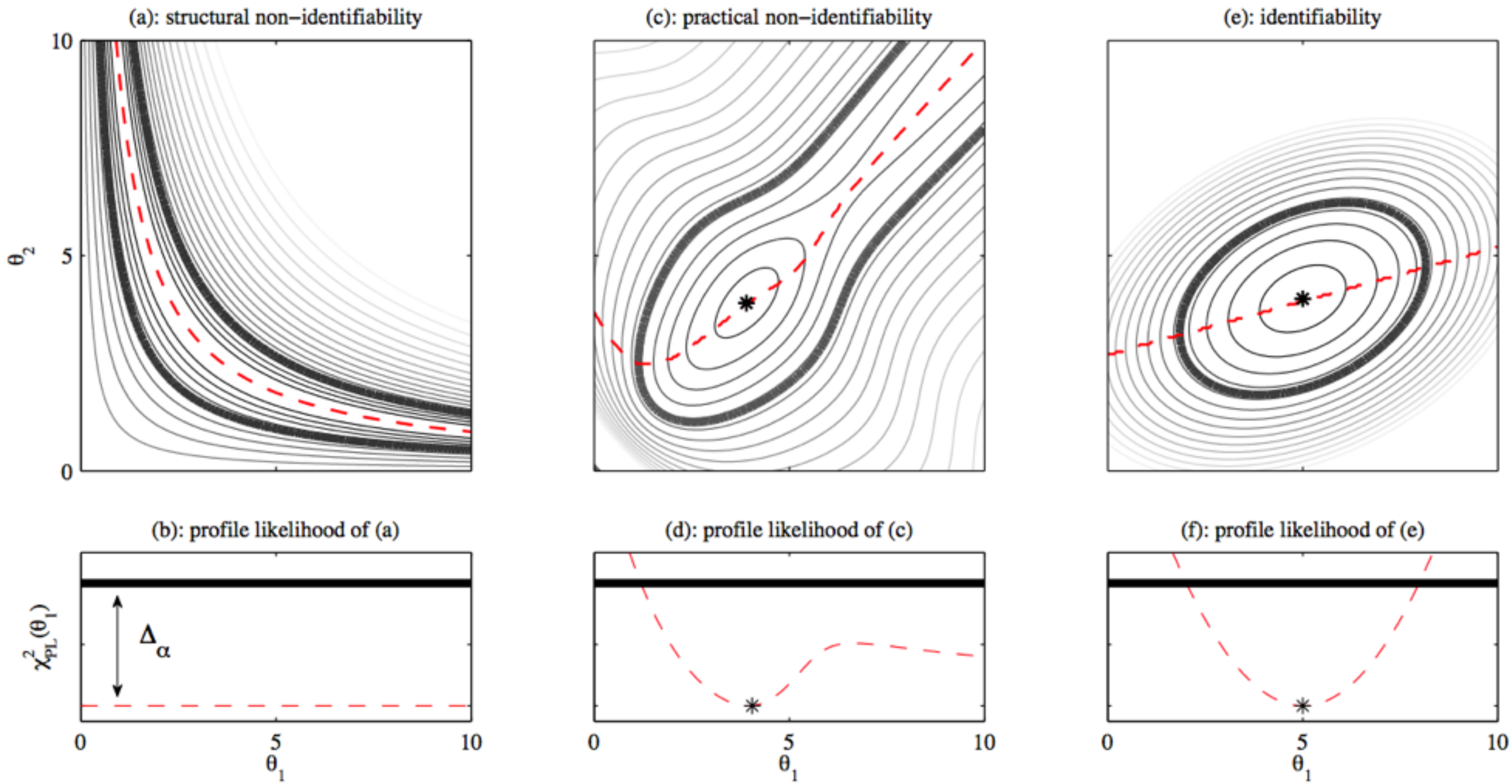
- Choose a range of values for parameter p_i
- For each value, fix p_i to that value, and fit the rest of the parameters
- Report the best likelihood/RSS/cost function value for that p_i value
- Plot the best likelihood values for each value of p_i — this is the profile likelihood

Profile Likelihood



Profile Likelihood & ID

- Can generate confidence bounds based on the curvature of the profile likelihood
- Flat or nearly flat regions indicate identifiability issues
- Can generate simulated ‘perfect’ data to test structural identifiability

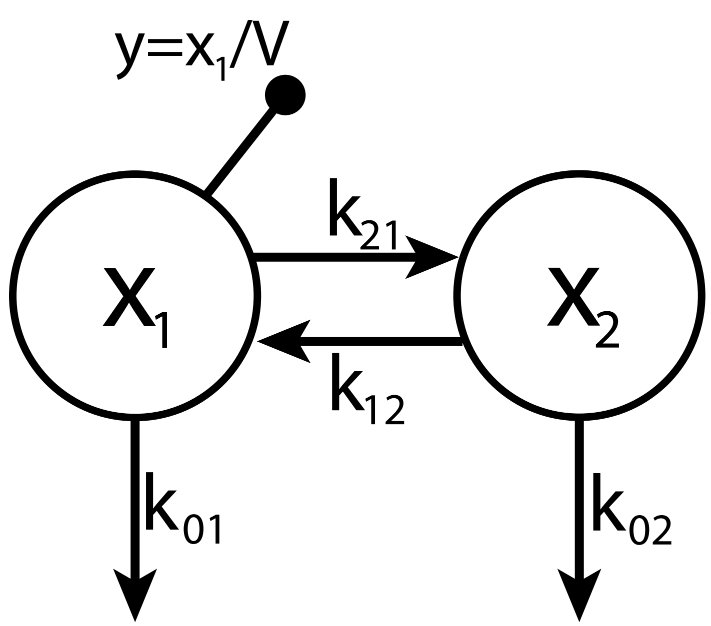


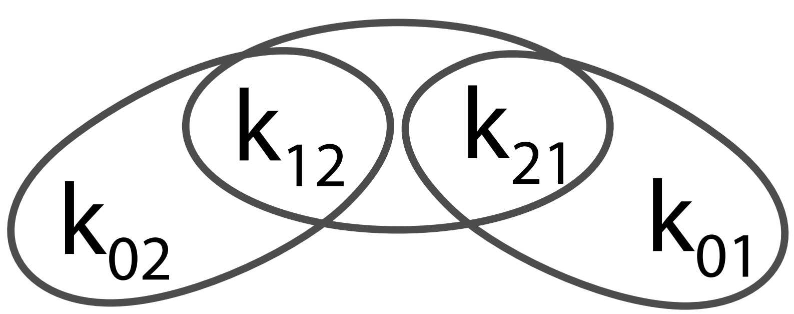
Raue et al. 2010

Profile Likelihood

- Can also help reveal the form of identifiable combinations
- Look at relationships between parameters when profiling
- However, can be problematic when too many degrees of freedom

2-Compartment Example





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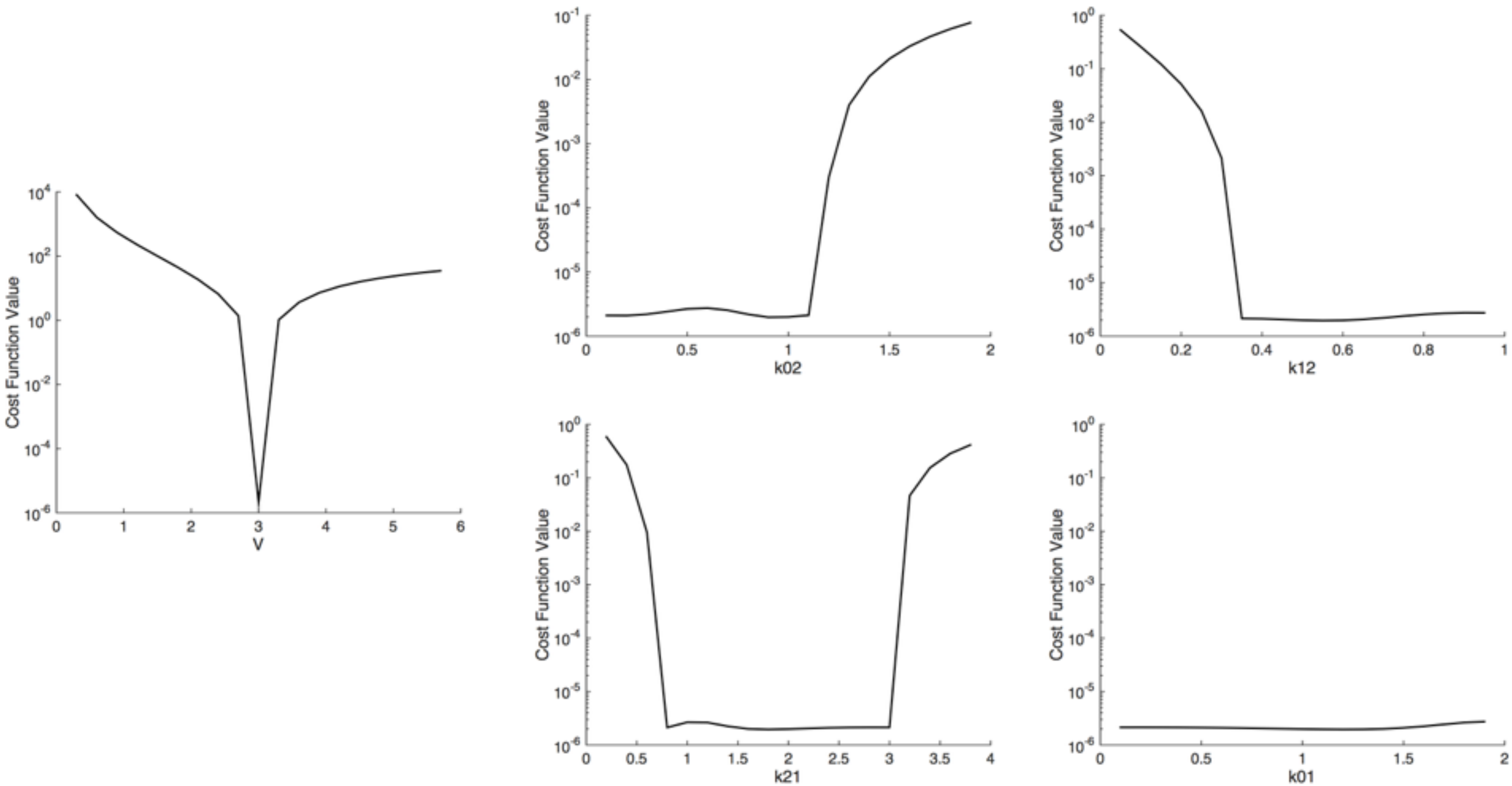
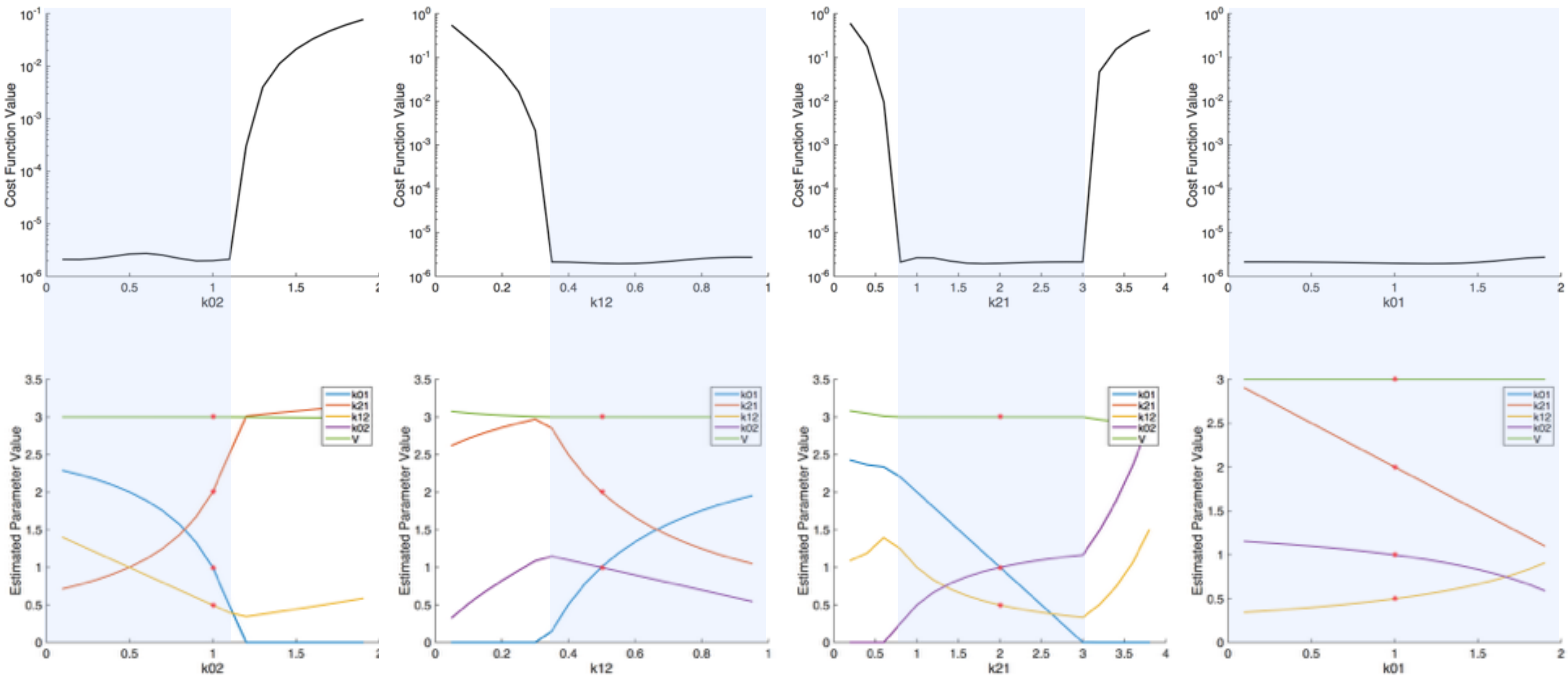
Eisenberg & Hayashi, Math Biosciences 2014

Profile Likelihoods



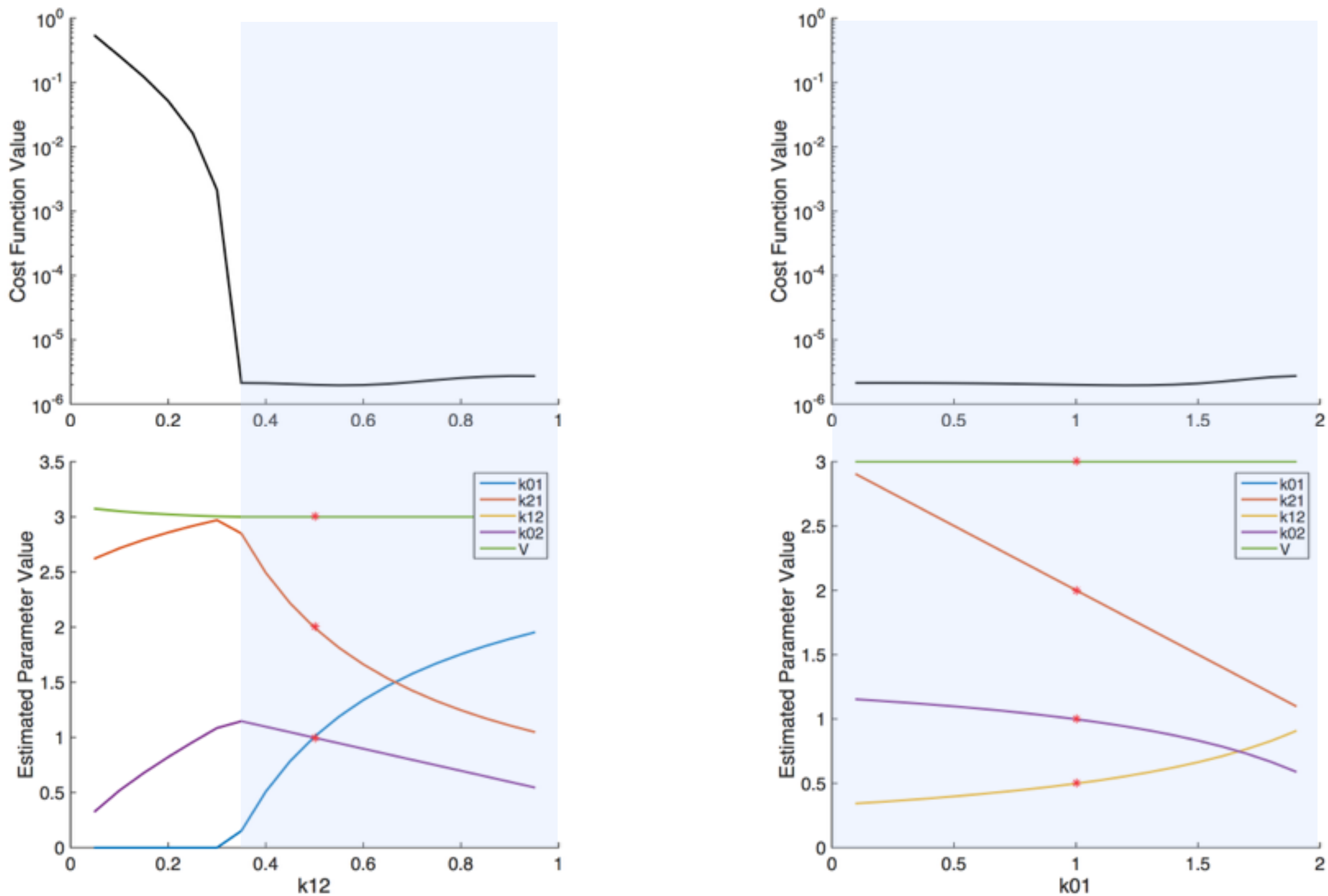
Eisenberg & Hayashi, Math Biosciences 2014

Parameter Relationships



Eisenberg & Hayashi, Math Biosciences 2014

Parameter Relationships



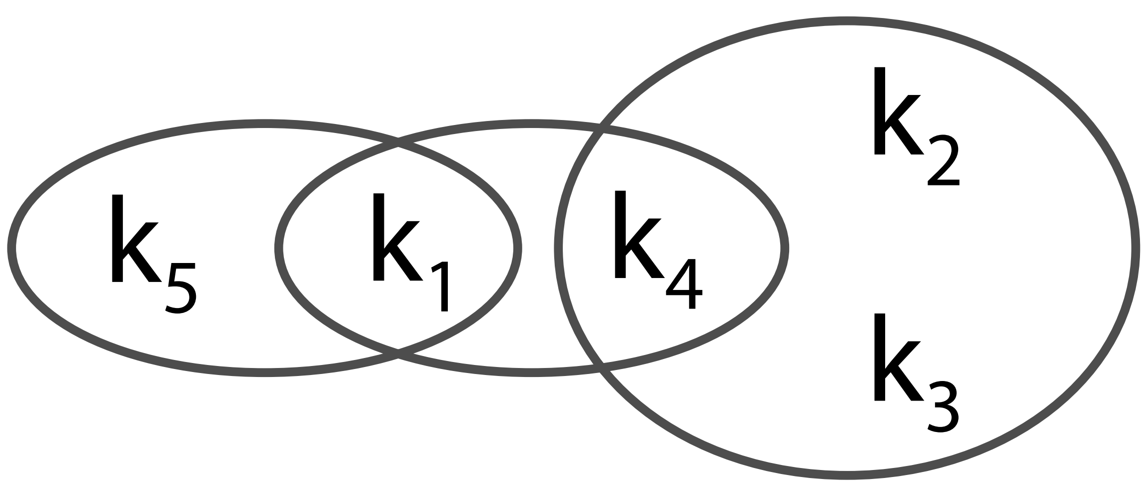
Eisenberg & Hayashi, Math Biosciences 2014

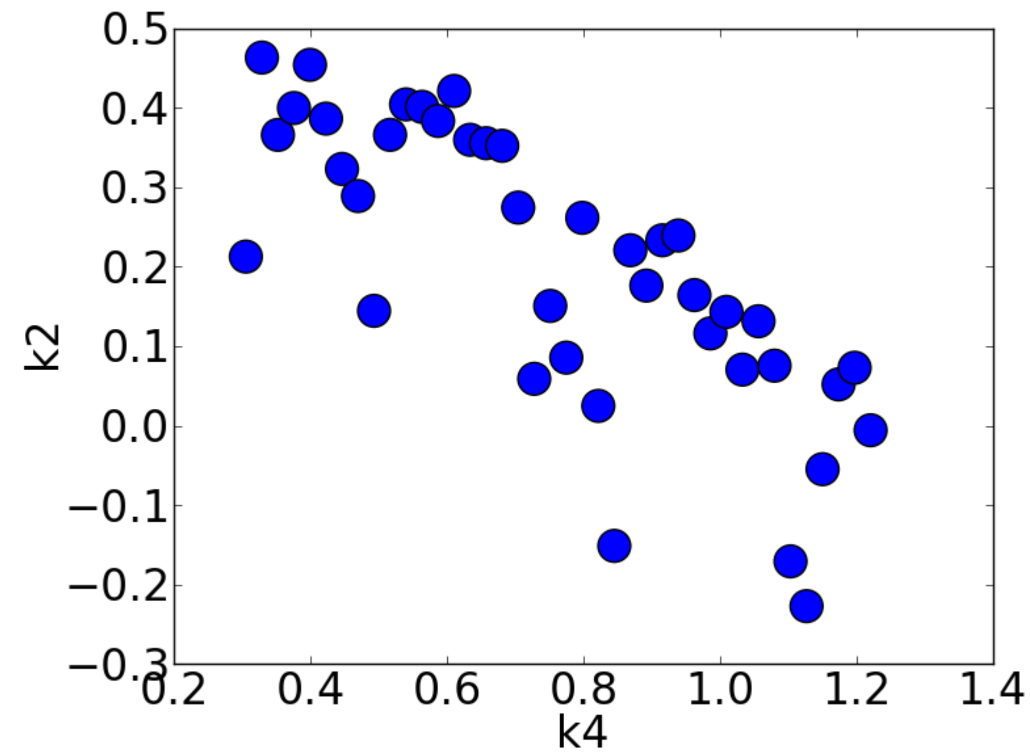
Likelihood Profiling Example

$$\dot{x}_1 = k_1 x_2 - (k_2 + k_3 + k_4) x_1$$

$$\dot{x}_2 = k_4 x_1 - (k_5 + k_1) x_2$$

$$y = x_1 / V$$

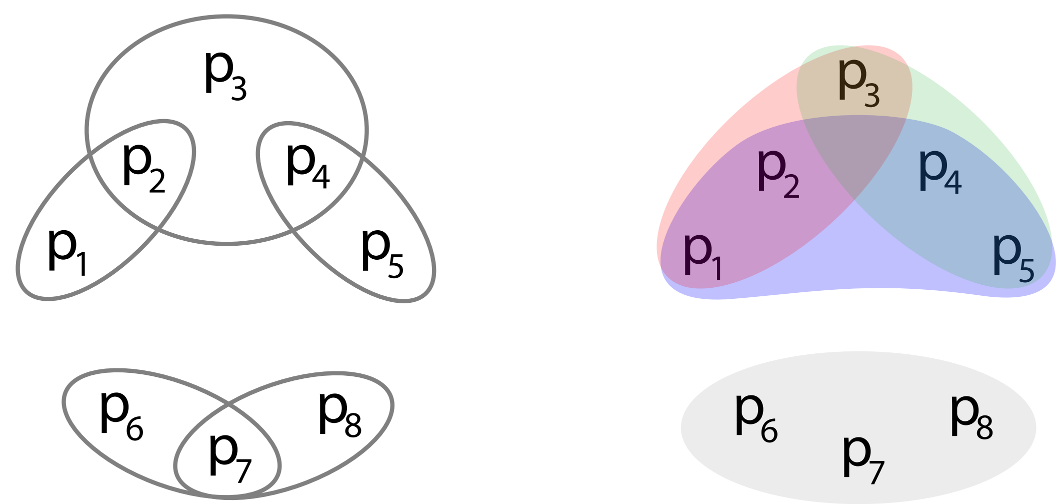




Eisenberg & Hayashi, Math Biosciences 2014

FIM Subset Approach

- Basic idea - evaluate the rank of the FIM for subsets of parameters to elucidate the structure of the identifiable combinations



- Can then combine this with profile likelihood approach by Raue et al. to determine the form of the combinations

Eisenberg & Hayashi, Math Biosciences 2014

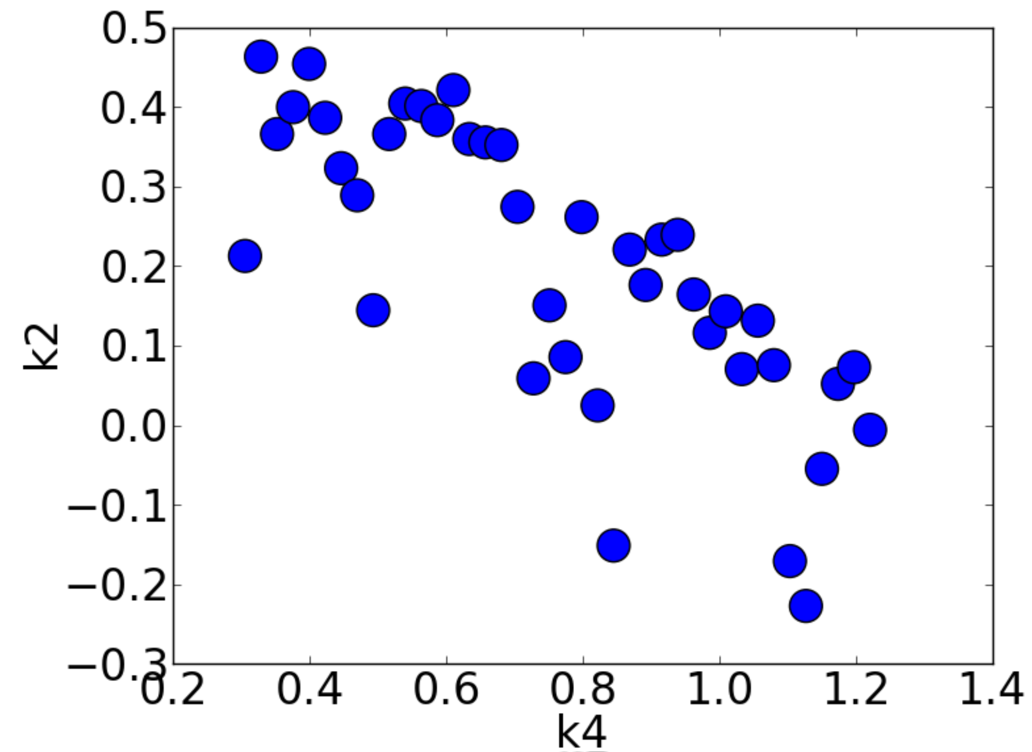
FIM Subset Approach

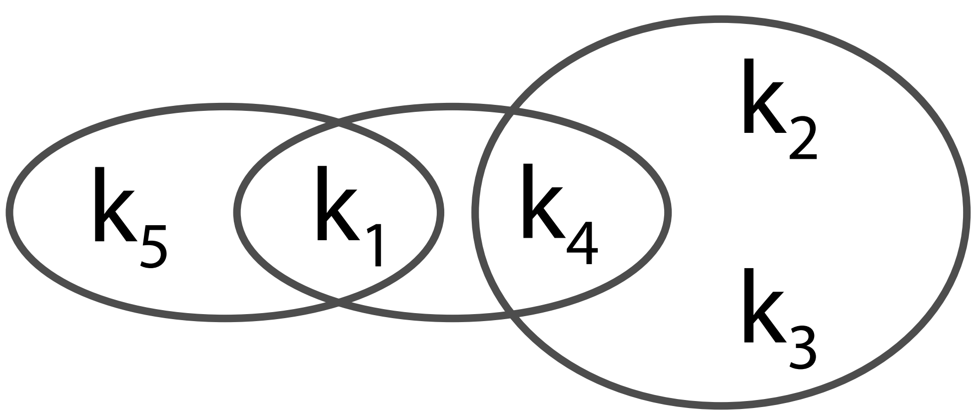
- Use the FIM rank to select subsets of parameters which are *nearly full rank* (i.e. which become full rank if any single parameter is fixed)
- Use these subsets when likelihood profiling to determine all parameter relationships
- Polynomial interpolation to recover identifiable combinations

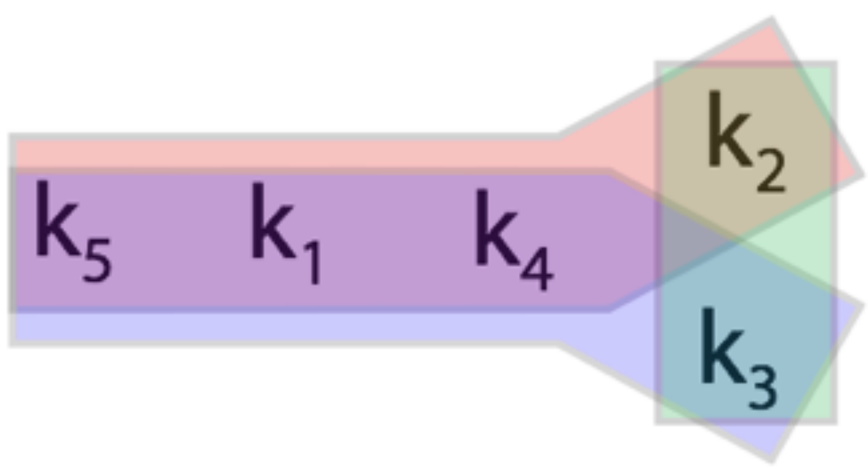
Eisenberg & Hayashi, Math Biosciences 2014

Example Model

$$\dot{x}_1 = k_1 x_2 - (k_2 + k_3 + k_4) x_1$$
$$\dot{x}_2 = k_4 x_1 - (k_5 + k_1) x_2$$
$$y = x_1 / V$$







Eisenberg & Hayashi 2014, *in review*

Example Model

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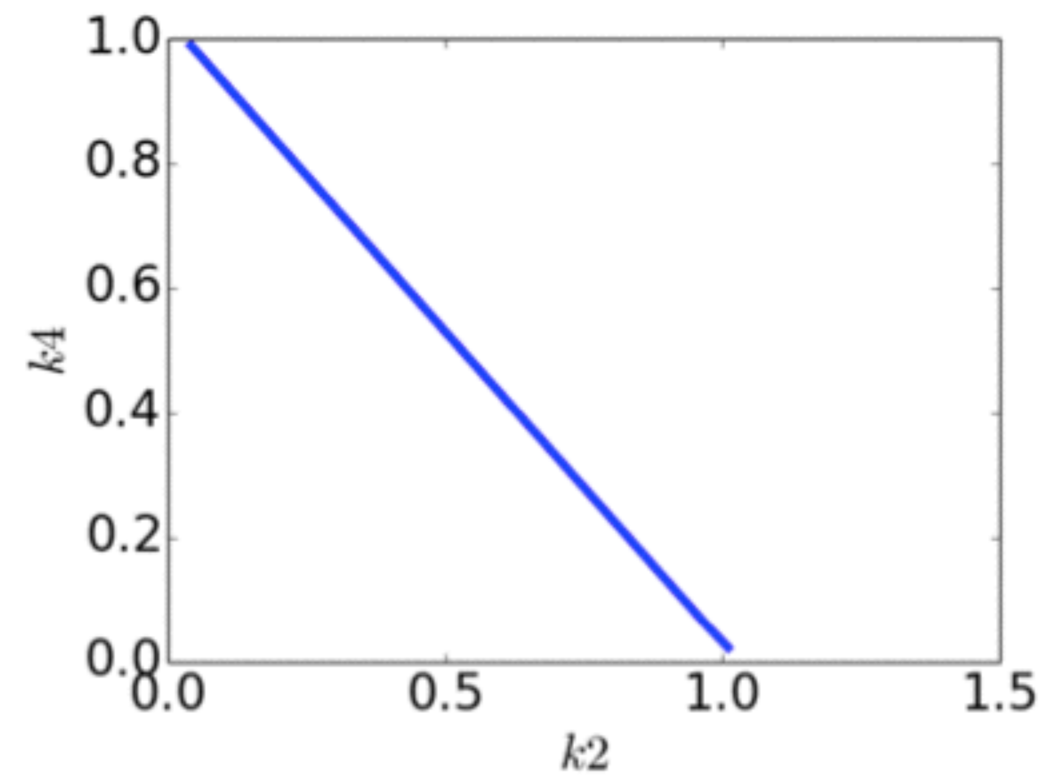
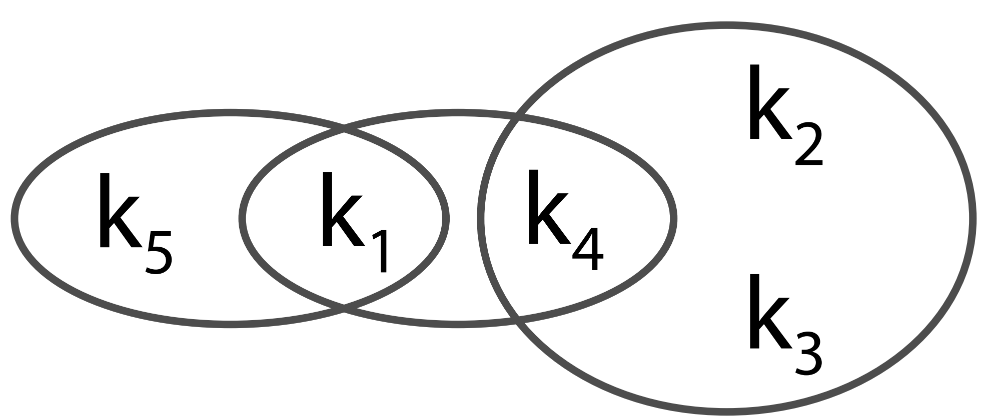
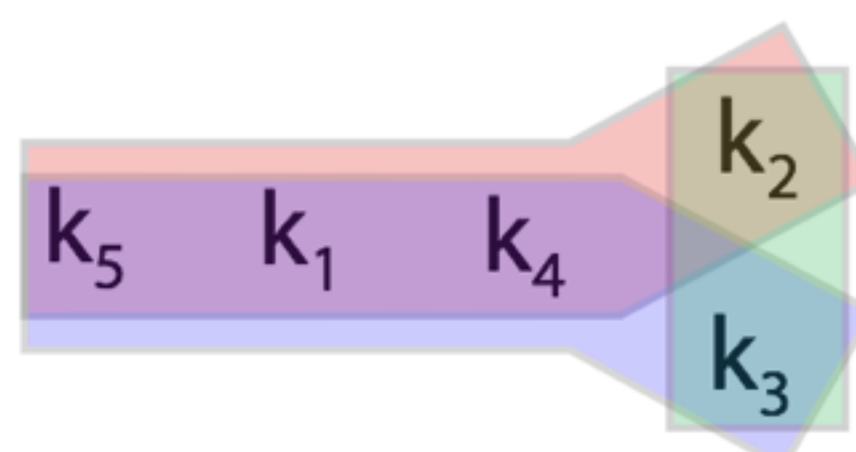
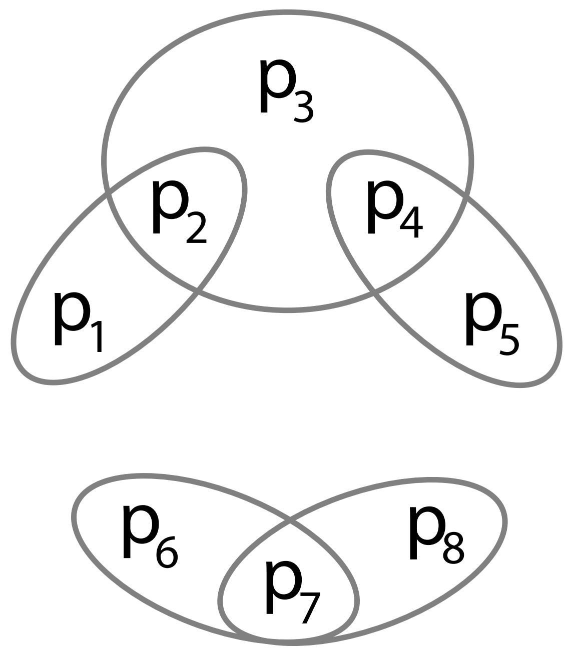


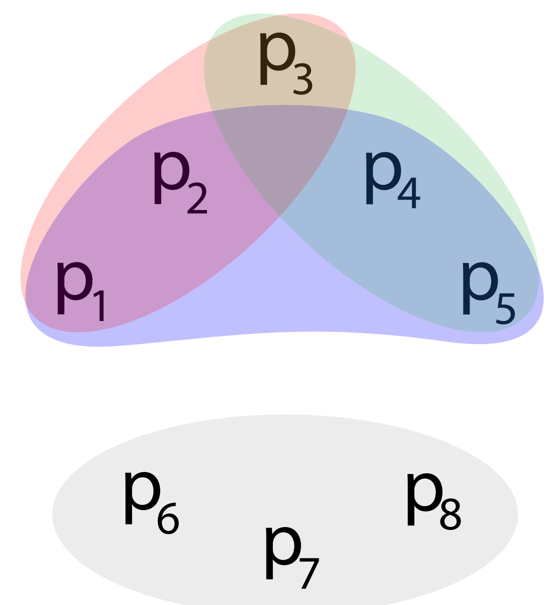


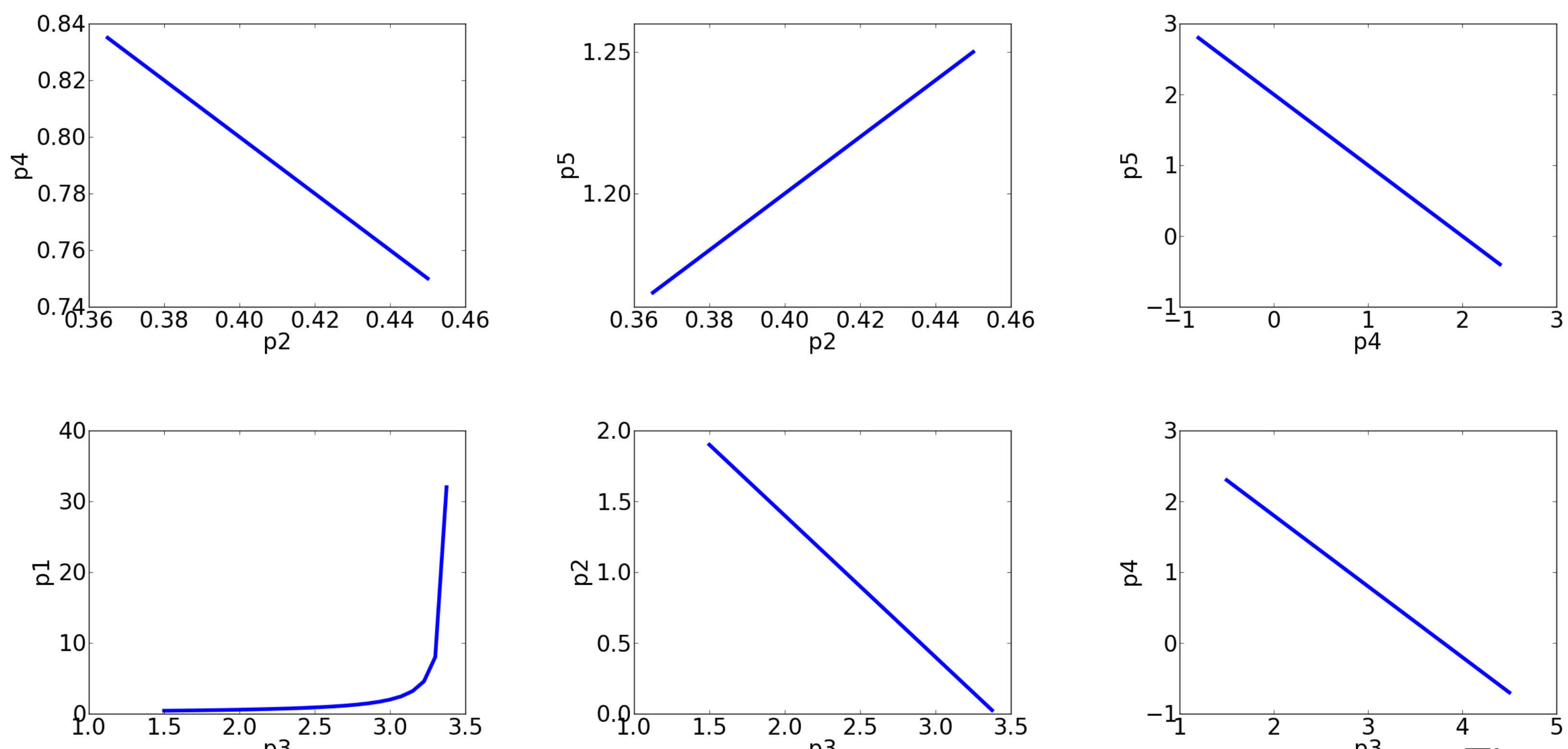


Eisenberg & Hayashi 2014, *in review*

Example Model







$p_1 p_2$

$p_2 + p_3 + p_4$

$p_4 + p_5$

$p_6 + p_7$ $p_7 + p_8$

Eisenberg & Hayashi, Math Biosciences 2014

Conclusions

- Many related questions and potential issues when connecting models to data: observability, distinguishability & model selection, reparameterization & model/parameter reduction, and more

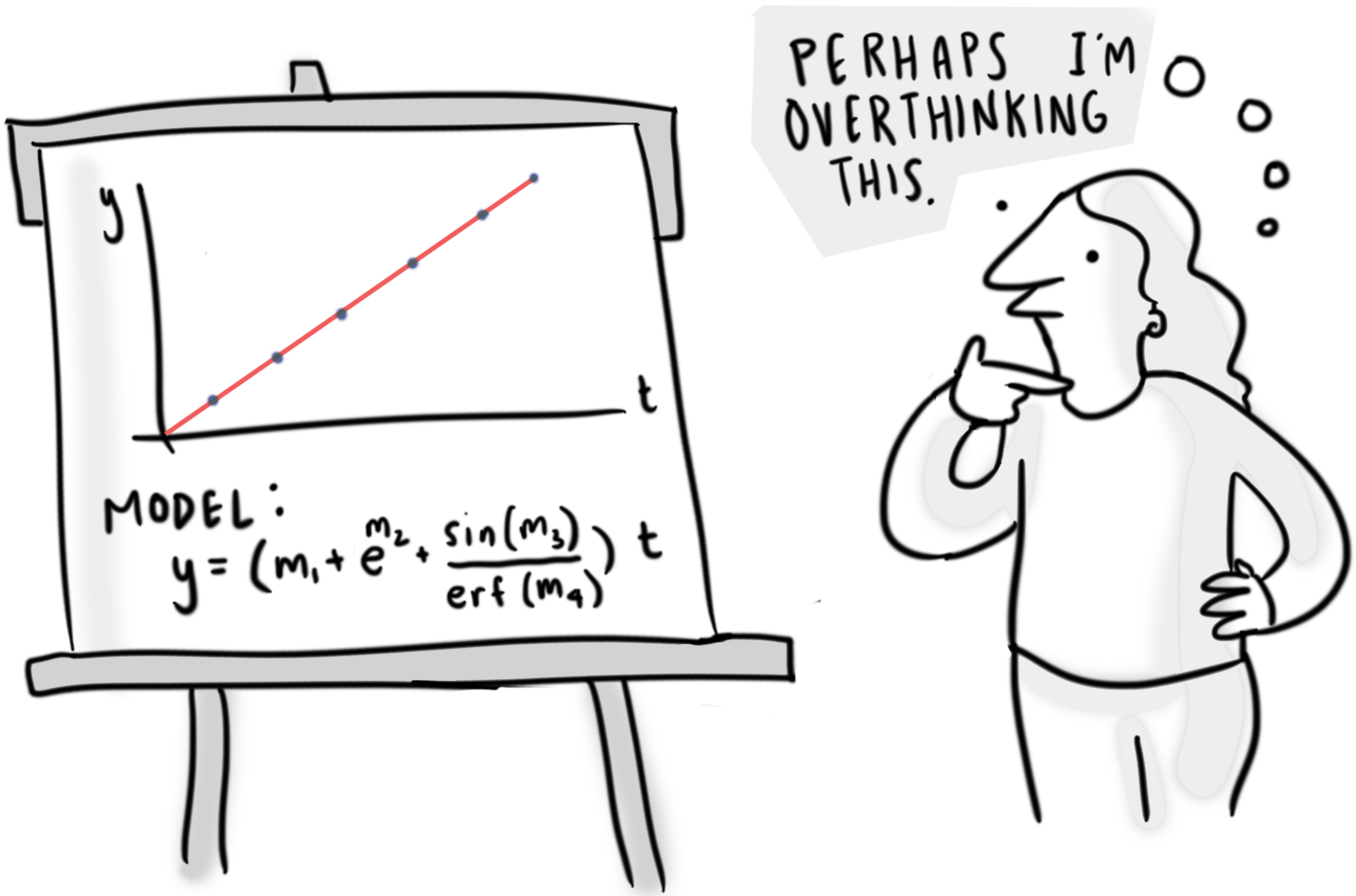
- Many other methods! (eigenvalues of FIM, sloppy models, active subspaces, Bayesian methods, & more)

- Depending on amount of data, model complexity, model type, and more, different approaches may work in different circumstances

Conclusions

- Identifiability—an important question to address when estimating model parameters
- Common problem in math bio (identifiability-robustness tradeoff)
- Many approaches, both numerical and analytical

Questions?



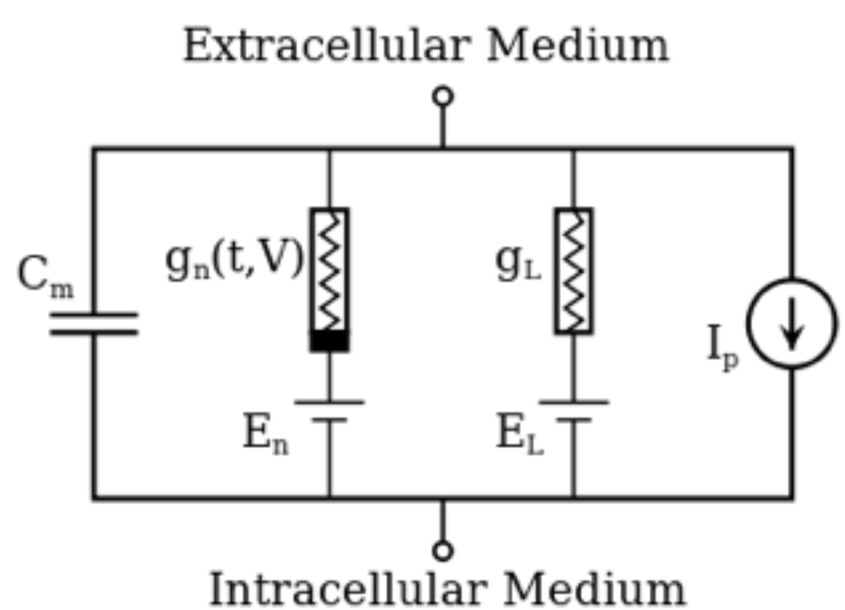
comic by Olivia Walch (UM):
http://imogenquest.net

Identifiability of Hodgkin-Huxley Models

Joint work with Olivia Walch (UM)

Hodgkin-Huxley Model

- Hodgkin & Huxley - Nobel 1963
- Classic model of neuronal firing & dynamics
- The basis for many modern neuronal models
- Treats each component of cell as an electrical element



Hodgkin-Huxley Equations

$$I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 \left(V_m - V_K\right) + \bar{g}_{Na} m^3 h \left(V_m - V_{Na}\right) + \bar{g}_L \left(V_m - V_L\right)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}$$

Retinal subconscious vision cells

$$C_m \frac{dV}{dt} = -g_{Na} m^3 h (V - E_{Na}) - g_K n^4 (V - E_K) - g_{Ca} r f (V - E_{Ca}) - g_L (V - E_L) + I_{app} \qquad \frac{dw}{dt} = \frac{w_\infty - w}{\tau_w}$$

$$m_\infty = \frac{1}{e^{0.126582(24.8 - 2(V+30))} + 1}$$

$$h_\infty = \frac{1}{78647.2 e^{0.363636V} + 1}$$

$$r_\infty = \frac{1}{0.035674 e^{-0.266667V} + 1}$$

$$f_\infty = \frac{1}{e^{\frac{2V}{65}+4} + 1}$$

$$n_\infty = \frac{1}{\sqrt[4]{e^{-\frac{2}{17}(V-7)} + 1}}$$

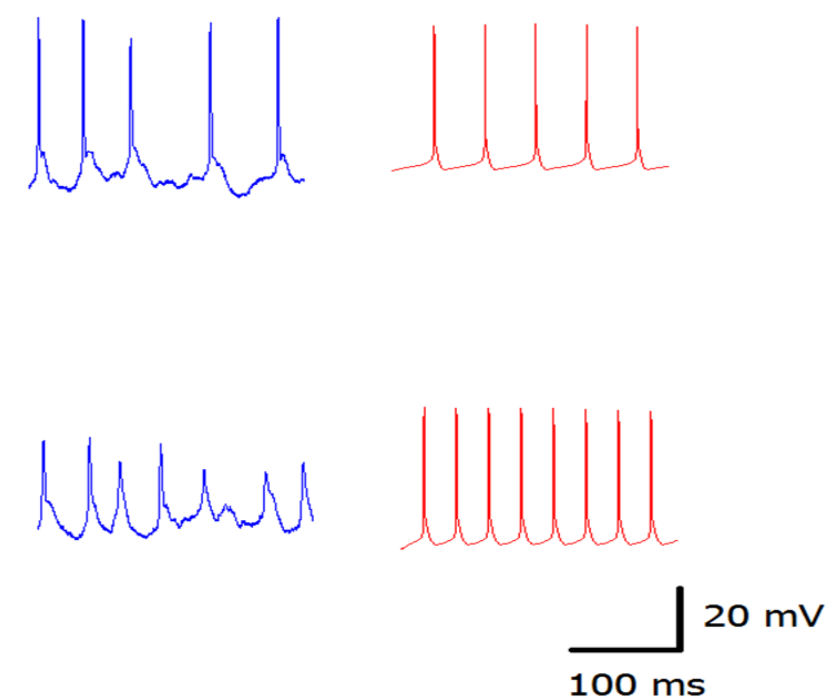
$$\tau_m = \frac{5}{21} e^{\frac{1}{80}(-V-143)}$$

$$\tau_h = 0.121429 + 0.00561921 e^{-0.28169V}$$

$$\tau_r = 0.738$$

$$\tau_f = 1.79158 e^{-V/110}$$

$$\tau_n = \frac{5}{21} e^{\frac{1}{68}(67-2V)}$$



$$m_\infty = \frac{1}{0.0336138 e^{-0.12383V} + 1}$$

$$h_\infty = \frac{1}{17086.4 e^{0.177865V} + 1}$$

$$r_\infty = \frac{1}{0.109289 e^{-0.130435V} + 1}$$

$$f_\infty = \frac{1}{e^{\frac{36V+9259}{2392}} + 1}$$

$$n_\infty = \frac{1}{\sqrt[4]{e^{\frac{4121-180V}{3128}} + 1}}$$

$$\tau_m = 0.0112252 e^{-9V/1472}$$

$$\tau_h = 0.0324545 + 0.00490052 e^{-0.137783V}$$

$$\tau_r = 0.1973$$

$$\tau_f = 0.547216 e^{-9V/2024}$$

$$\tau_n = 0.4821 e^{-45V/3128}$$

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REVIEW

5,632 VIEWS

The What and Where of Adding Channel Noise to the Hodgkin-Huxley Equations

Joshua H. Goldwyn, Eric Shea-Brown

J Physiol 580.1 (2007) pp 15–22

Hodgkin–Huxley–Katz Prize Lecture

heart

J Neurophysiol 91: 2541–2550, 2004;
10.1152/jn.00646.2003.

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e, Silicon Neurons

[A quantitative description of membrane current and its application to conduction and excitation in nerve]

AL **Hodgkin**, AF **Huxley** - The Journal of physiology, 1952 - ncbi.nlm.nih.gov

The nature ofthe permewablity change8 At present the thickness and composition of the excitable membrane are unknown. Our experiments are therefore unlikely to give any certain information about the nature of the molecular events underlying changes in perme- ...

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Ghostbursting: A Novel Neuronal Burst Mechanism

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Received June 8, 2001; Revised October 17, 2001; Accepted November 1, 2001

Action Editor: John Rinzel

J Physiol 590.11 (2012) pp 2569–2570

EDITORIAL

Hodgkin and Huxley and the basis for electrical signalling: a remarkable legacy still going strong

Jamie I. Vandenberg[1,2]
and Stephen G. Waxman[3,4]

Voltage Clamp

- Common method for collecting current data from neurons & other excitable cells (e.g. cardiac cells)
- Uses electrodes to maintain constant voltage, then can measure the resulting current dynamics
- Often do multiple runs with different voltage levels
- Can measure individual channel currents by blocking channels

Parameter Estimation for HH-Type Models

- Estimate parameters for HH-type model using voltage clamp data

- Break down estimation by each type of ion current

- Wide range of models use this formalism & data type

- Are the parameters identifiable?

Generalized HH for One Channel

current, max conductance, voltage, reversal potential

$$I(t) = g(V - E)m_1^{p_1} \cdots m_n^{p_n}$$

$$m_i'(t) = \frac{m_{i,\infty}(V) - m_i}{\tau_i(V)}$$

Generalized HH Identifiability

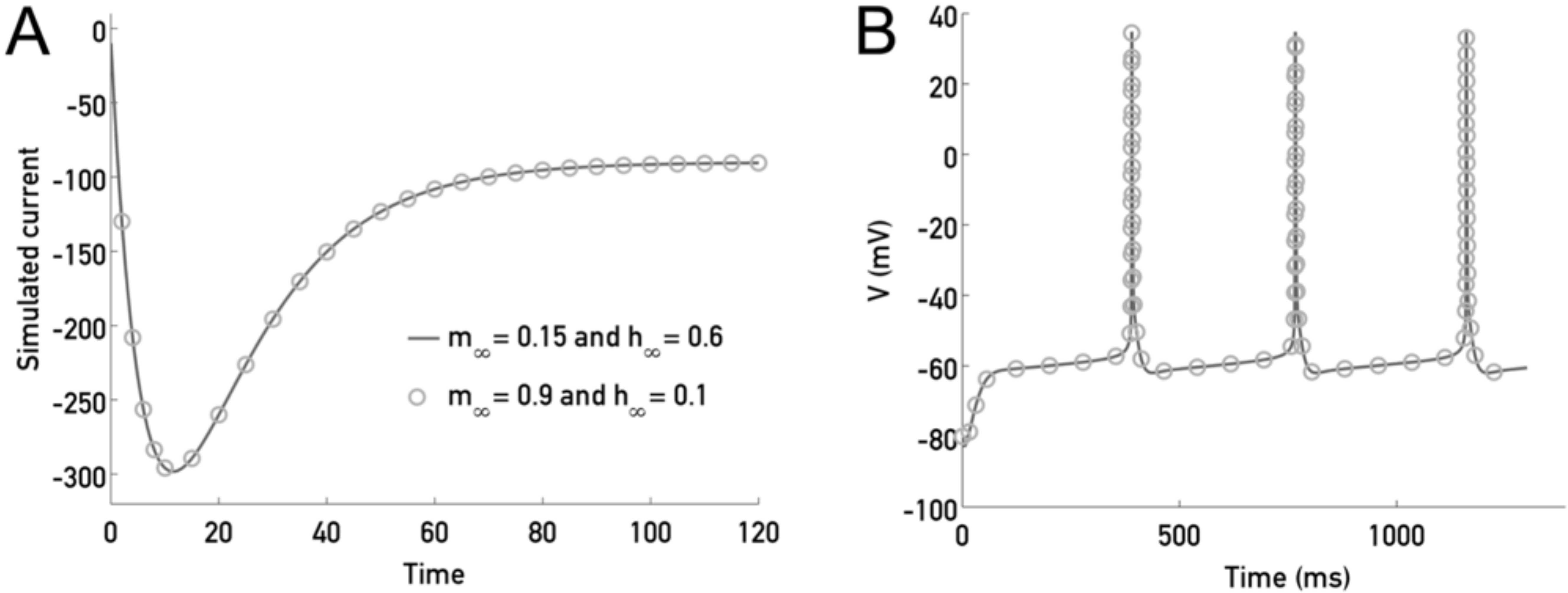
- Theorem. The time constants for the gating variable kinetics, τ_i, are identifiable from voltage clamp data.
- Approach: re-scale the system s.t. we can rewrite derivatives of I(t) using a Vandermonde matrix

$$
\begin{pmatrix}
1 & 1 & \cdots & 1 \\
\lambda_1 & \lambda_2 & \cdots & \lambda_{2^n-1} \\
\lambda_1^2 & \lambda_2^2 & \cdots & \lambda_{2^n-1}^2 \\
\vdots & \vdots & \vdots & \vdots \\
\lambda_1^{2^n-2} & \lambda_2^{2^n-2} & \cdots & \lambda_{2^n-1}^{2^n-2}
\end{pmatrix}
\begin{pmatrix}
-\tau_1 \dot{z}_1 \\
\vdots \\
(-1)^k \tau_{j_1} \cdots \tau_{j_k} \dot{z}_{j_1} \cdots \dot{z}_{j_k} \\
\vdots \\
(-1)^n \tau_1 \cdots \tau_n \dot{z}_1 \cdots \dot{z}_n
\end{pmatrix}
=
\begin{pmatrix}
\tilde{I} \\
\hat{I}'(t) \\
\vdots \\
\hat{I}^{(p)}(t) \\
\vdots \\
\hat{I}^{(2^n-1)}(t)
\end{pmatrix}
$$

Generalized HH Identifiability

- Theorem. The conductance term g and the steady state parameters $m_{i,\infty}$ are not identifiable from voltage clamp data
- The product $g\prod_{i=1}^{n} m_{i,\infty}^{p_i}$ is an identifiable combination
- But! if initial conditions $m_i(0)$ are known, then the $m_{i,\infty}$ become identifiable

Examples

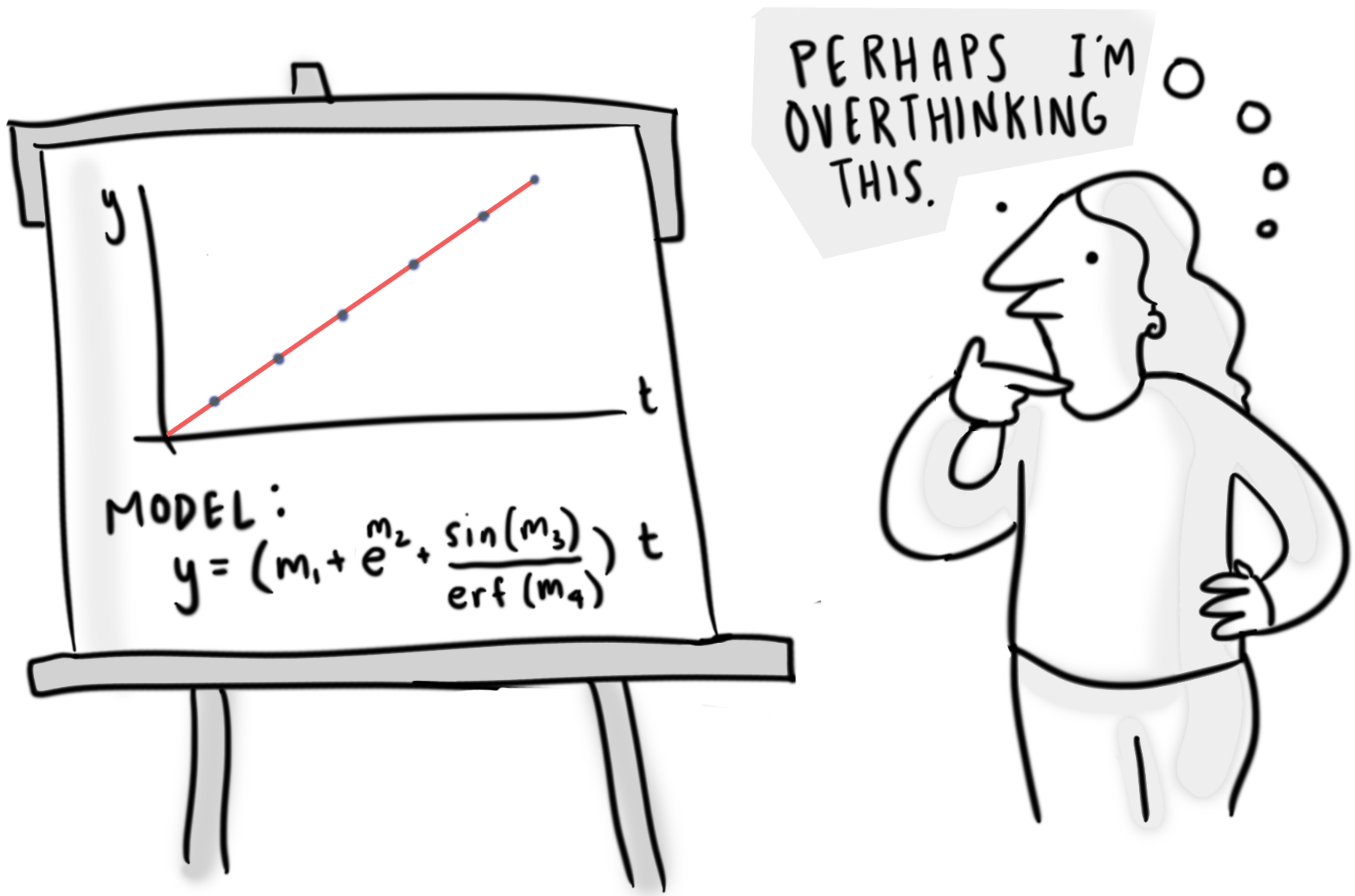


A
0
-50
-100
-150
-200
-250
-300
Simulated current
0
20
40
60
80
100
120
Time
m∞ = 0.15 and h∞ = 0.6
m∞ = 0.9 and h∞ = 0.1
B
40
20
0
-20
-40
-60
-80
-100
V (mV)
0
500
1000
Time (ms)

Generalized HH Conclusions

- HH models unidentifiable from voltage clamp data
- However, can estimate time constants τ_i, and identifiability is resolved if gating variable initial conditions are known
- May help to explain some observed issues with HH model parameter estimation
- Also seen in biological data—'experimental evidence suggests that biological neurons can achieve similar firing patterns with a continuum of different membrane conductances' (Prinz et al. 2003)

Questions?



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