Introduction to Parameter Uncertainty and Identifiability

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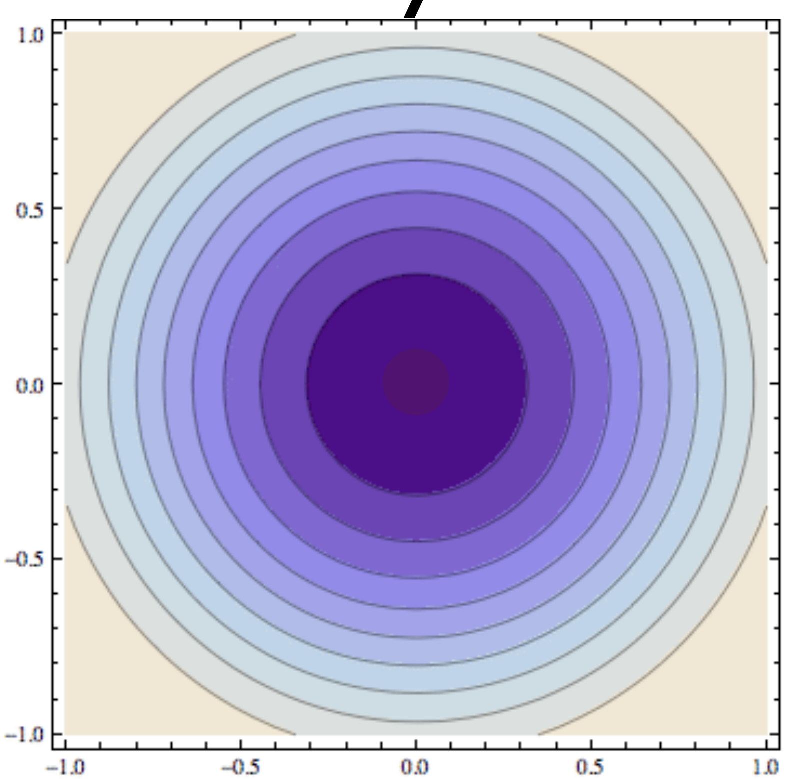
Epid 814

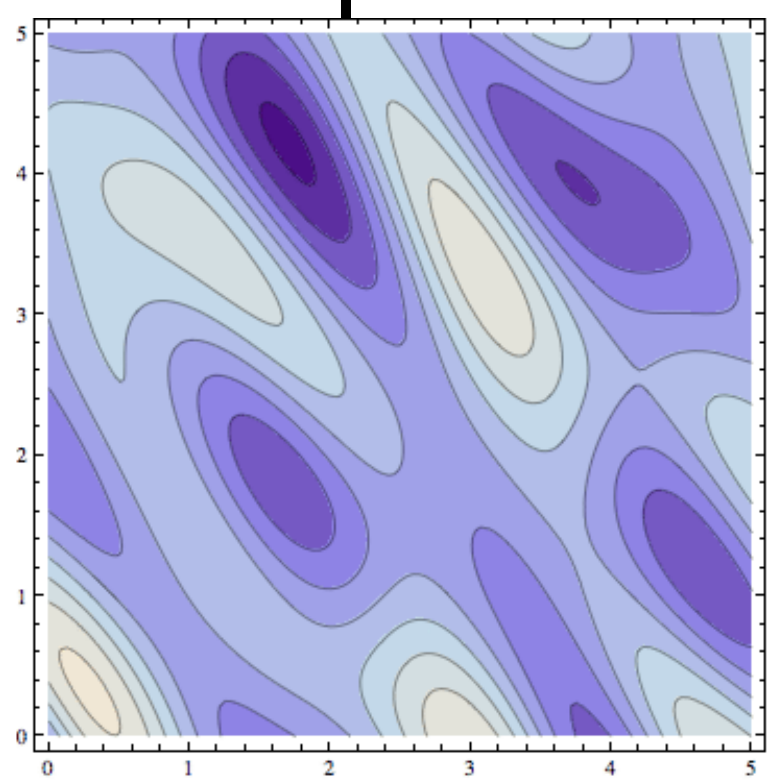
Parameter Estimation

- In general—search parameter space to find optimal fit to data
- Or to characterize distribution of parameters that matches data

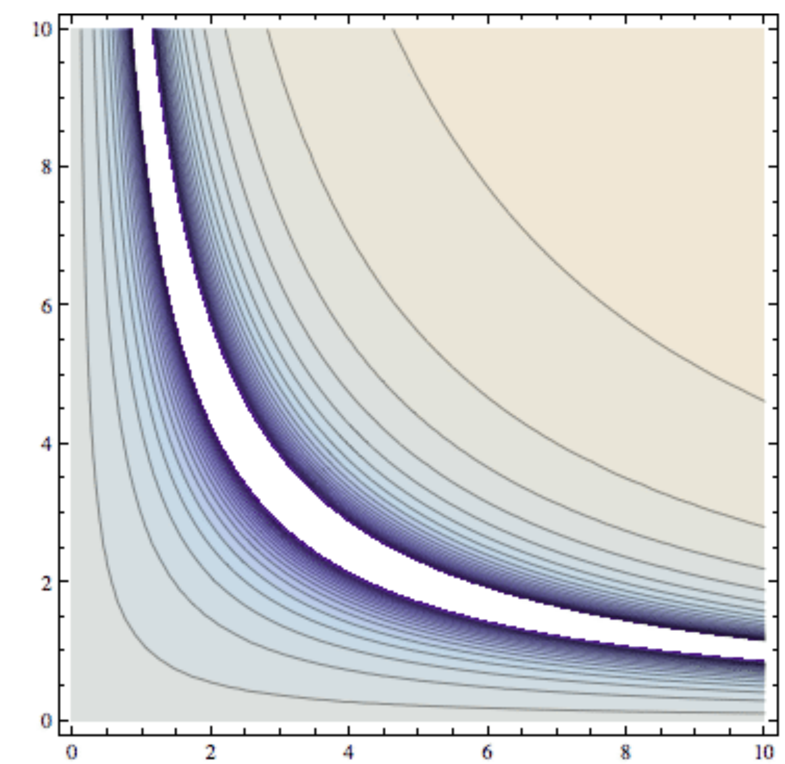
Yay!



Multiple Mins



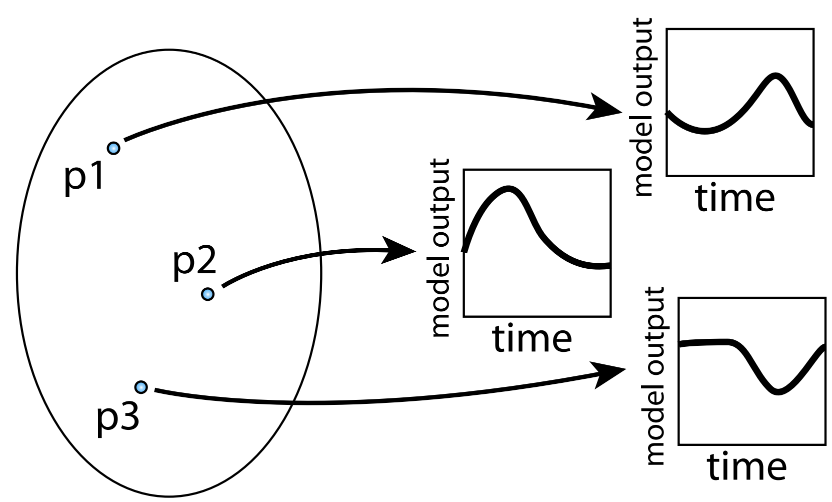
Struct. UnID



Identifiability

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

Parameters



Output/Data

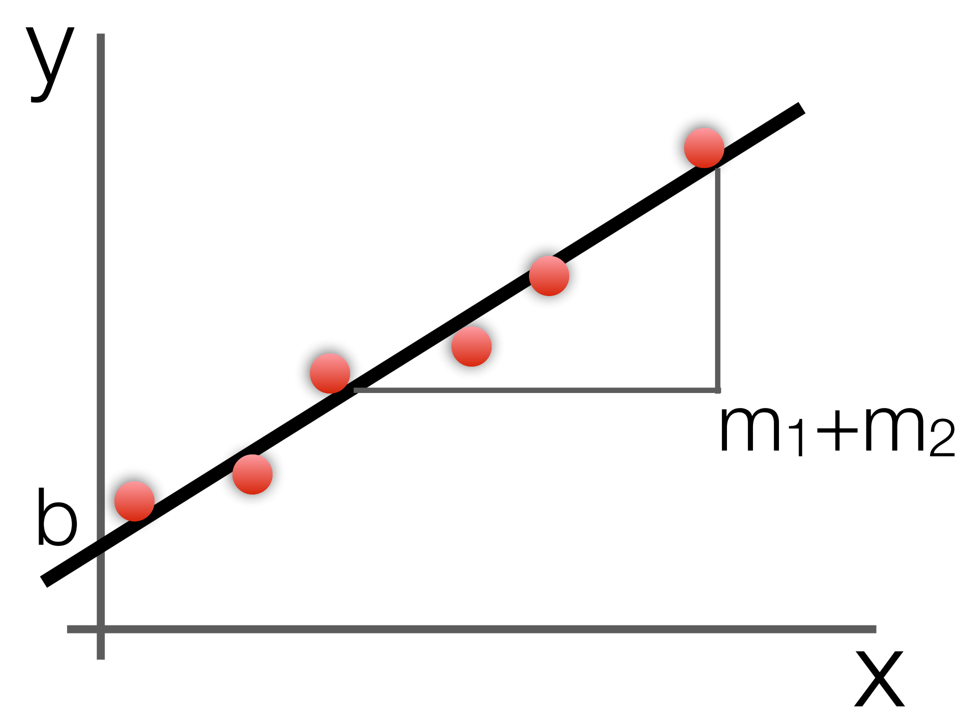
- Important problem in parameter estimation

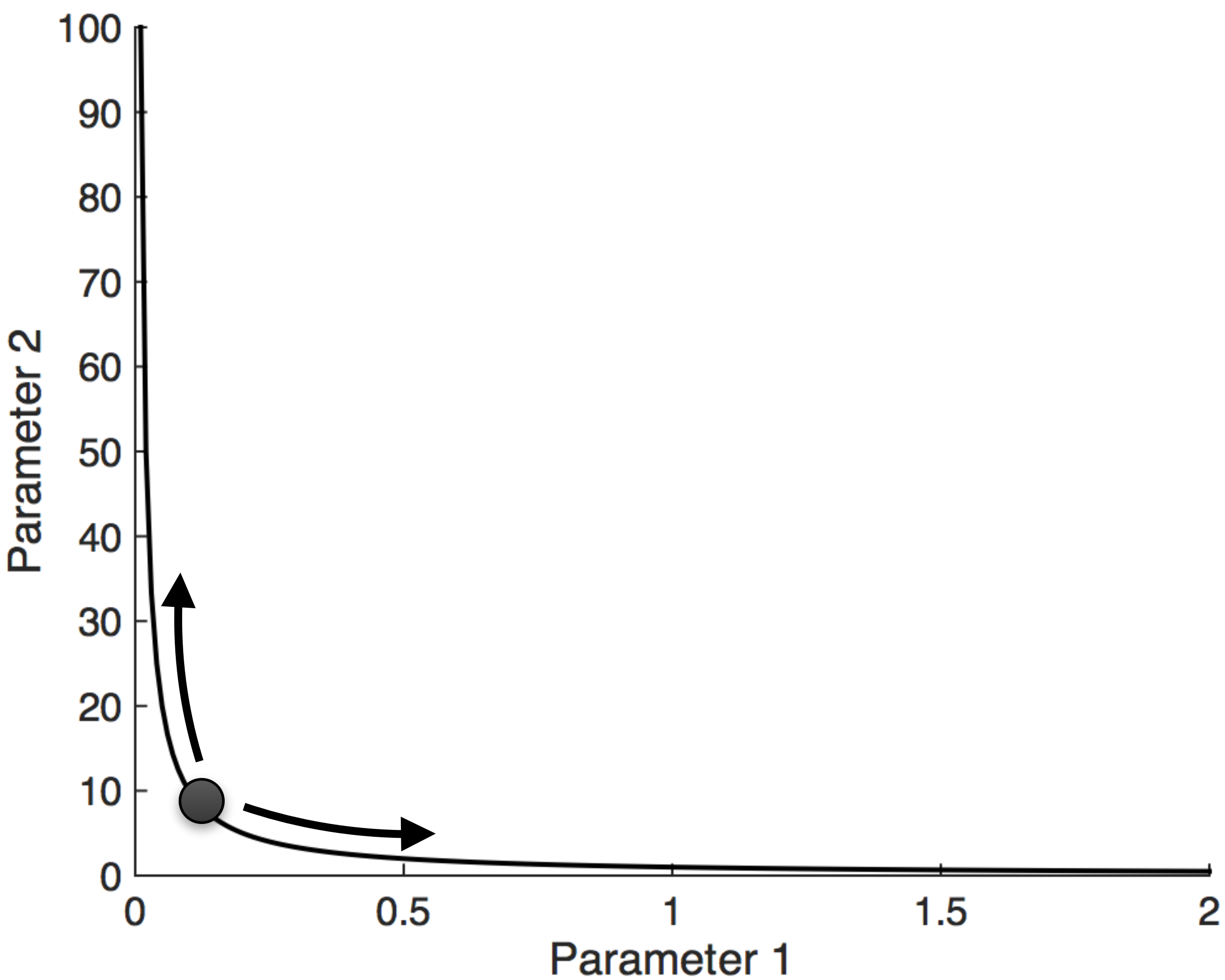
- Many different approaches - statistics, applied math, engineering/systems theory

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

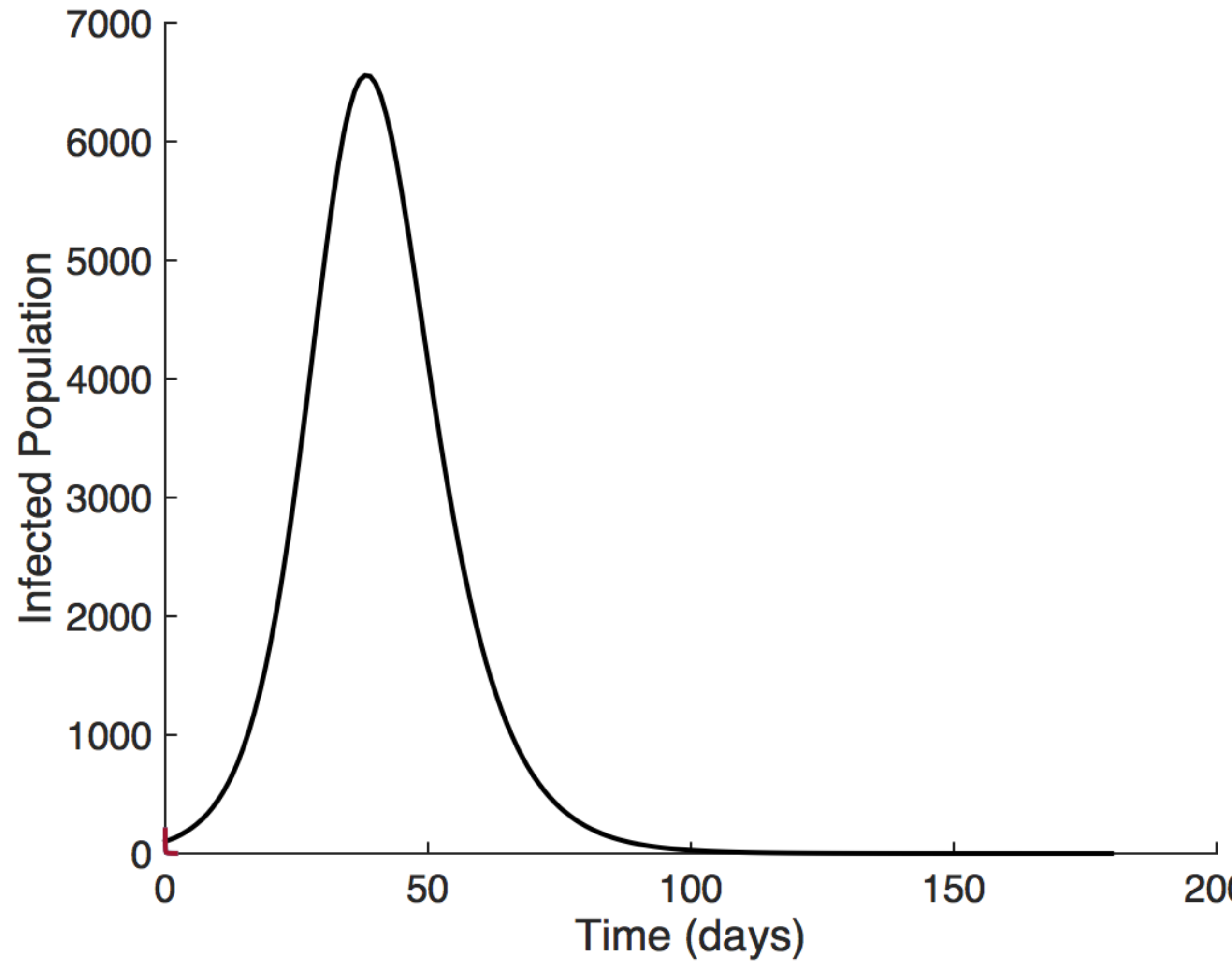
Identifiability

- Practical (estimability) vs. Structural (identifiability)
    - 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

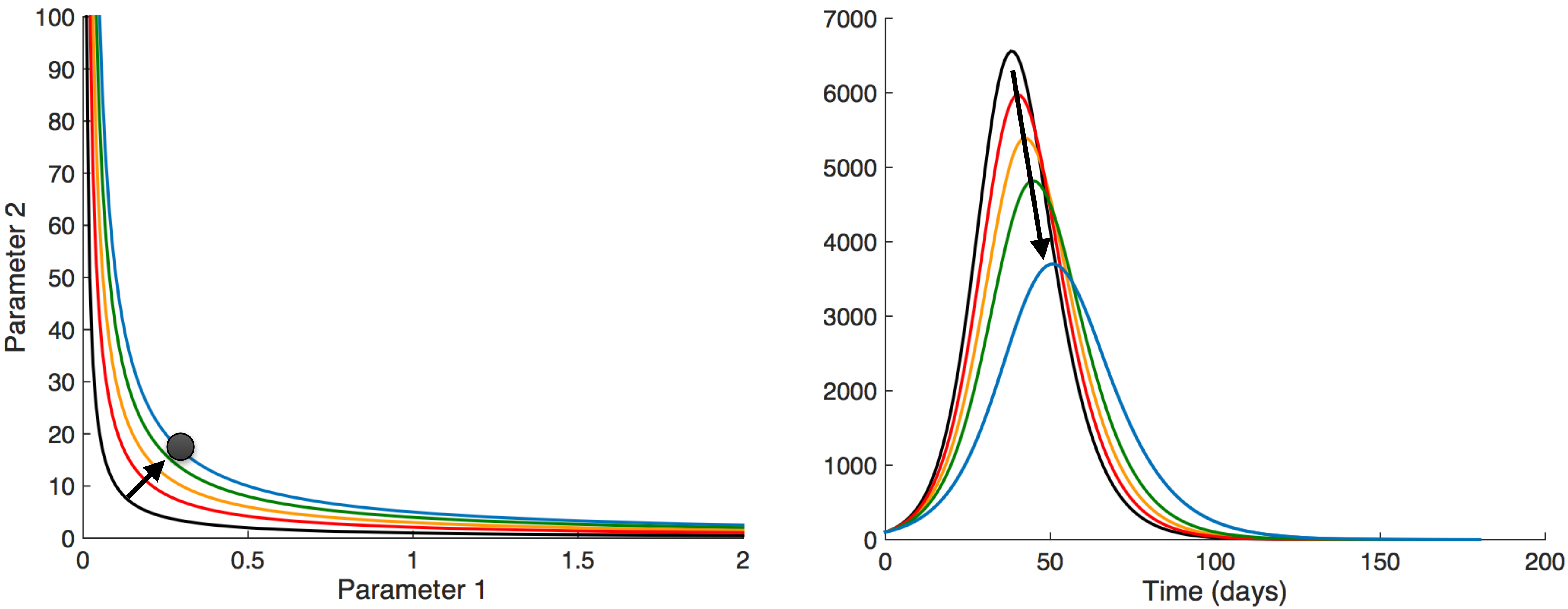




Parameter 2
Parameter 1
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2



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



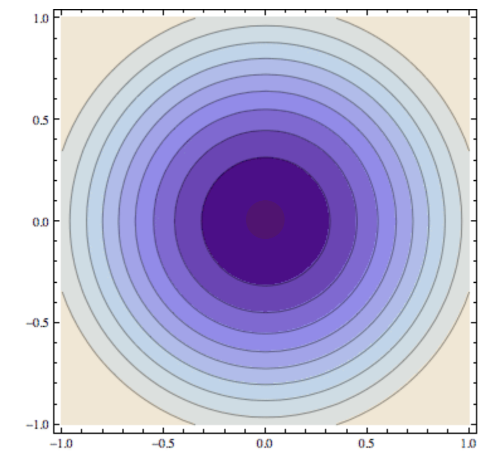
Parameter 2
Parameter 1
Time (days)

Structural Identifiability

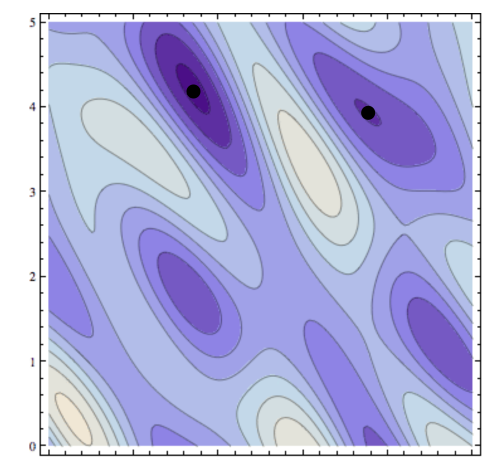
- Assumes best case scenario - data is known perfectly at all times
- Unrealistic!
- But, necessary condition for practical identifiability with real, noisy data

Structural identifiability

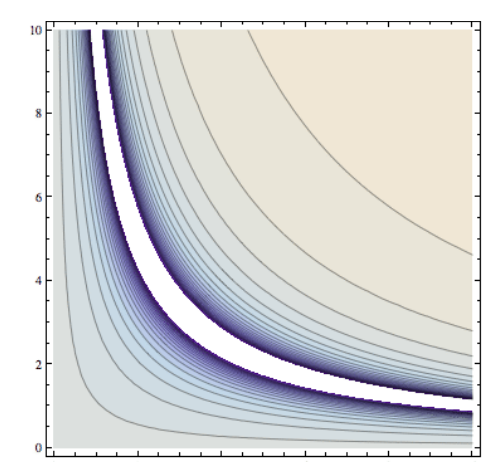
- *Globally (uniquely) structurally identifiable*: map from parameter space to outputs is one-to-one (i.e. only one parameter set will fit the data best)



- *Non-uniquely structurally identifiable*: map from parameters to outputs is finite-to-one (i.e. there exist finitely many parameter sets fit the data equally ‘best’)
    - Related concept: *Local identifiability*



- *Unidentifiable*: map from parameter space to outputs is infinite-to-one :(



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

Practical Identifiability

- Harder to define rigorously! Many different variations
- Many parameter sets fit the data very similarly well (or even equally well)
- There is something of a gradient of how poorly estimated a parameter can be—how bad is bad enough that we count it as practically unidentifiable?
- E.g. practical unidentifiability is sometimes defined as having infinite confidence intervals, but these may be finite for some levels of confidence and infinite for others
(see profile likelihood example later)

Categories to consider

- Structural vs. practical identifiability
- Analytical vs. numerical methods
- Global vs. local results (in parameter space)

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

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)

Some quick notation

- Model state variables: x
  - Variables describing the unobserved (unknown) dynamics of the system of interest
- Inputs: u
  - Known variables/functions that drive the system (e.g. forcing functions or covariates)
- Outputs: y
  - Observed (known) variables that we measure
  - Measurement equations $y = f(t,u,x,p)$

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
- **Observability Rank Condition** - fast! only local
- **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

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Differential Algebra Approach

- 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

Differential Algebra Approach

- 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—

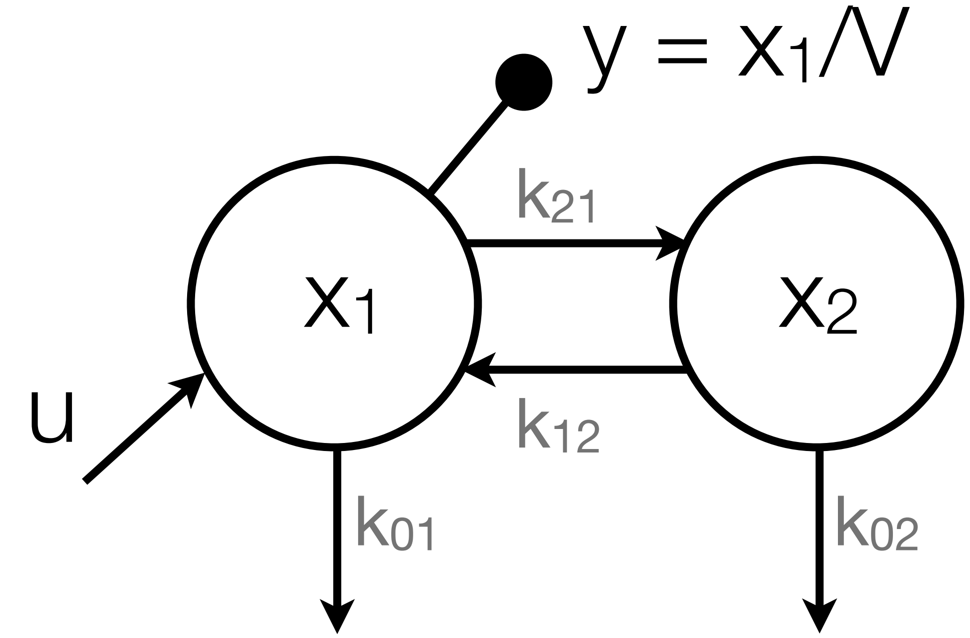
2-Compartment Example

- 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

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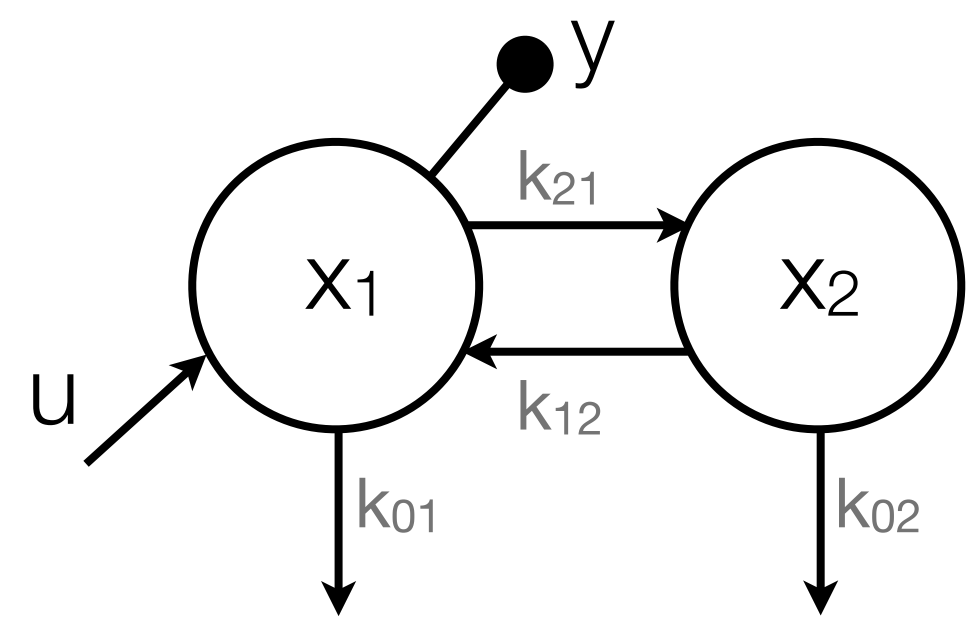

2-Compartment Example

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

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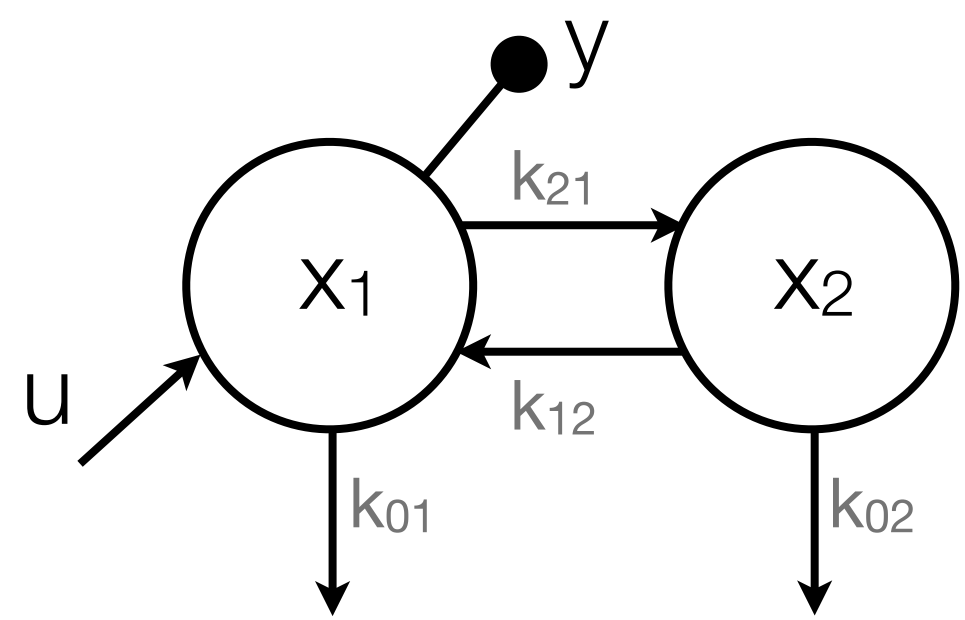
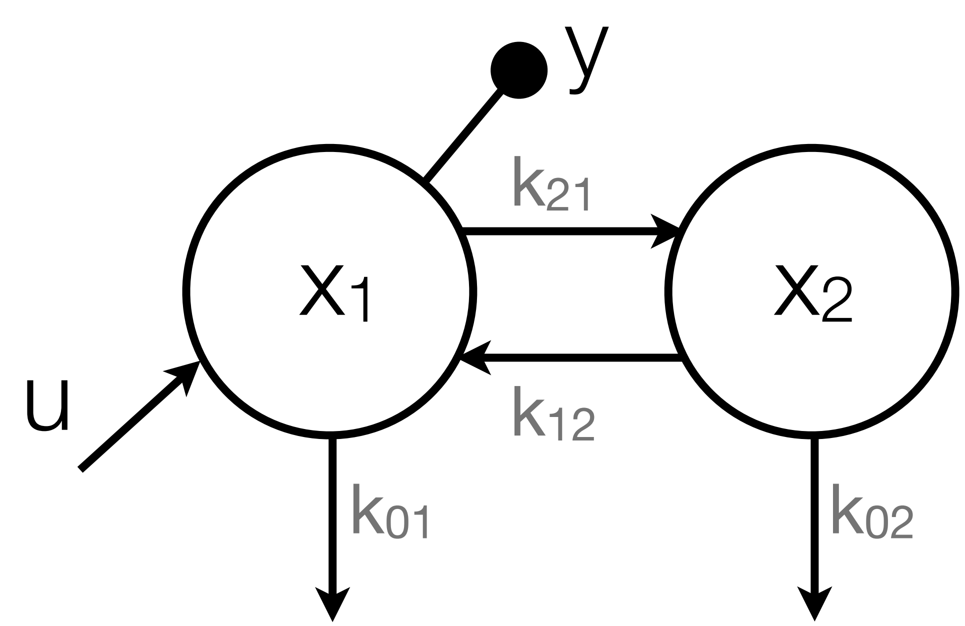


2-Compartment Example

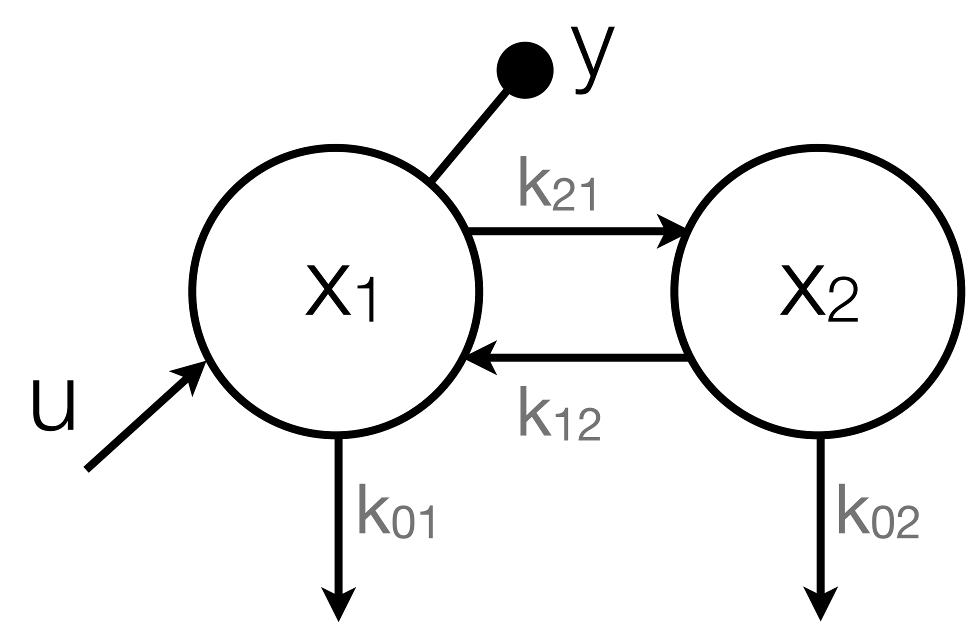
$$\dot{y}V = u + k_{12}x_2 - \left(k_{01} + k_{21}\right)yV$$
$$\dot{x}_2 = k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2$$



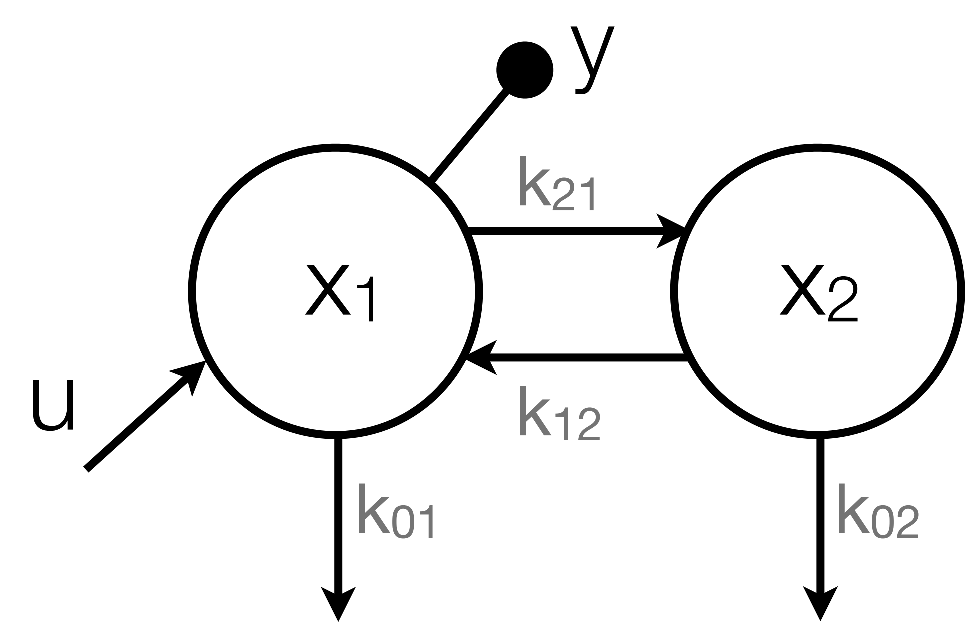
2-Compartment Example

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

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



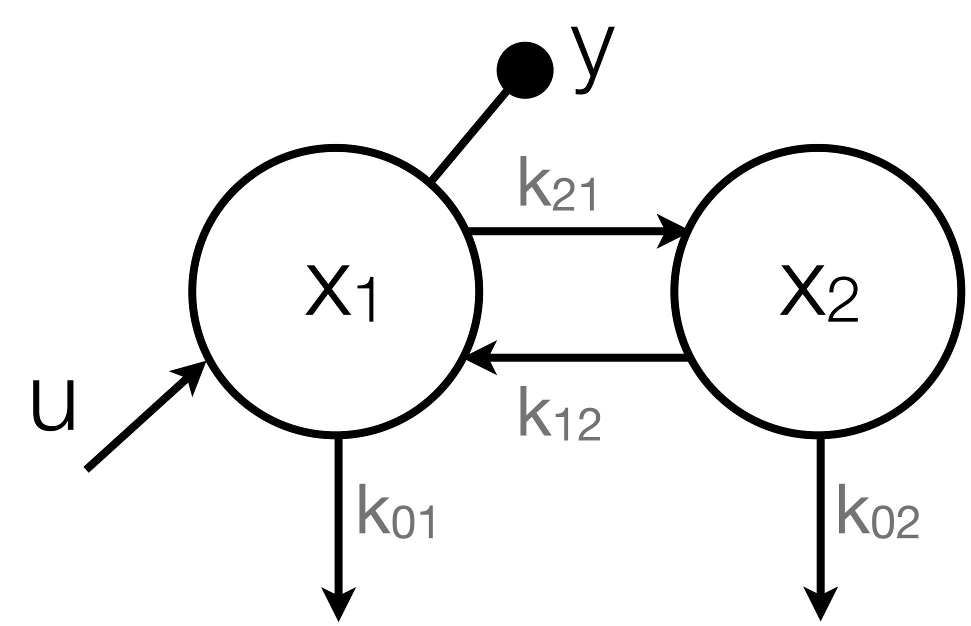
2-Compartment Example



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

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

2-Compartment Example



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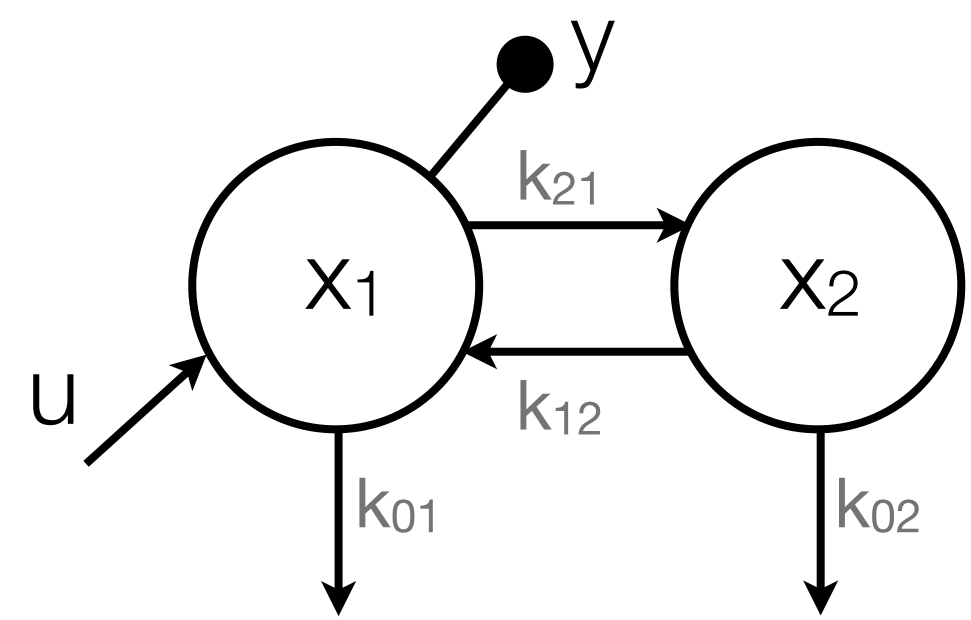

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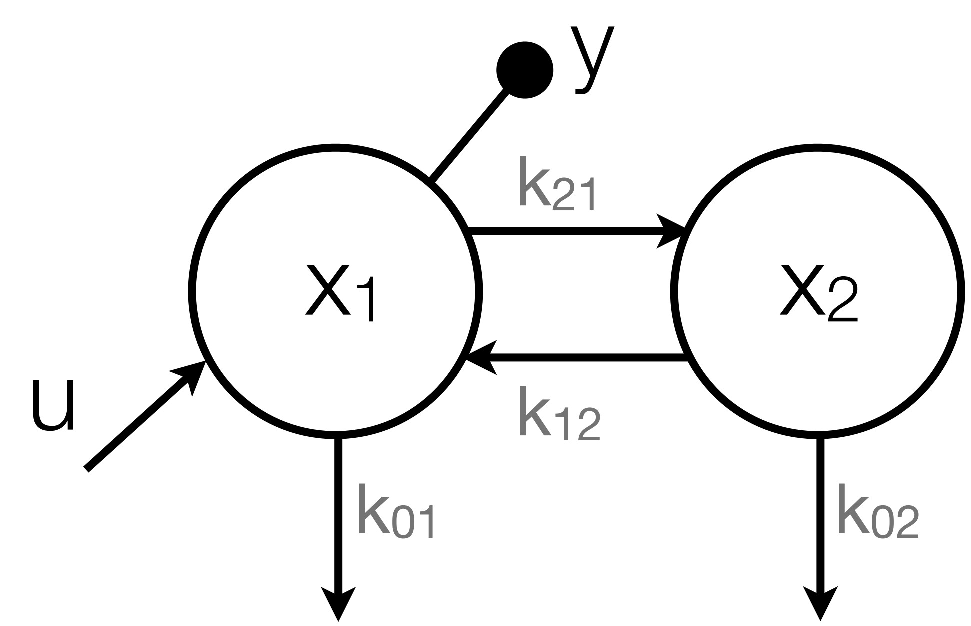
$$\left(k_{01} + k_{21} + k_{12} + k_{02}\right) \qquad \left(k_{12} + k_{02}\right)/V$$

$$\left(k_{12}k_{21} - \left(k_{02} + k_{12}\right)\left(k_{01} + k_{21}\right)\right) \qquad 1/V$$

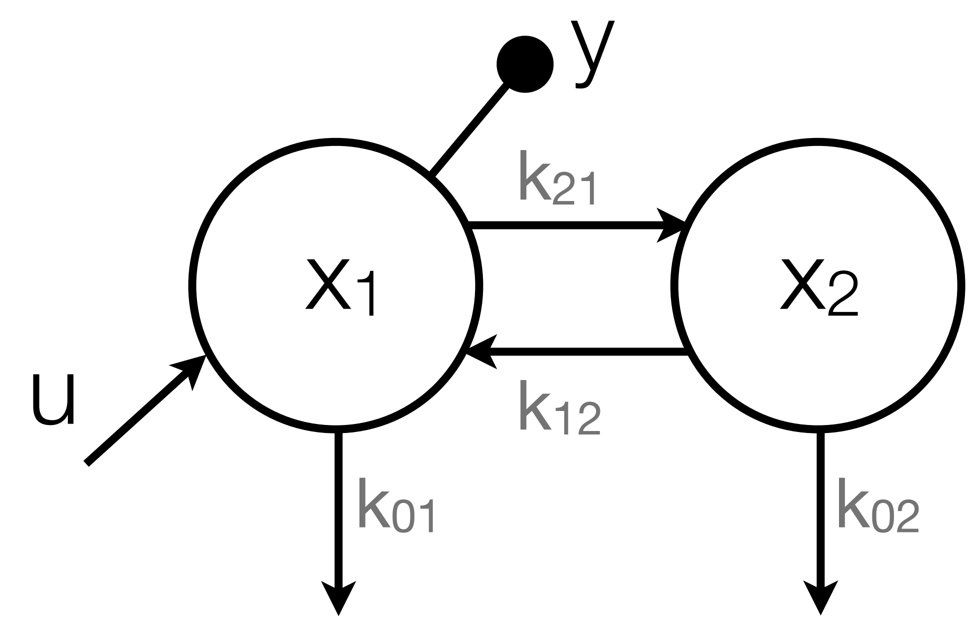
2-Compartment Example



$$\left(k_{01}+k_{21}+k_{12}+k_{02}\right) \qquad \left(k_{12}+k_{02}\right)/V$$

$$\left(k_{12}k_{21}-\left(k_{02}+k_{12}\right)\left(k_{01}+k_{21}\right)\right) \qquad 1/V$$

2-Compartment Example



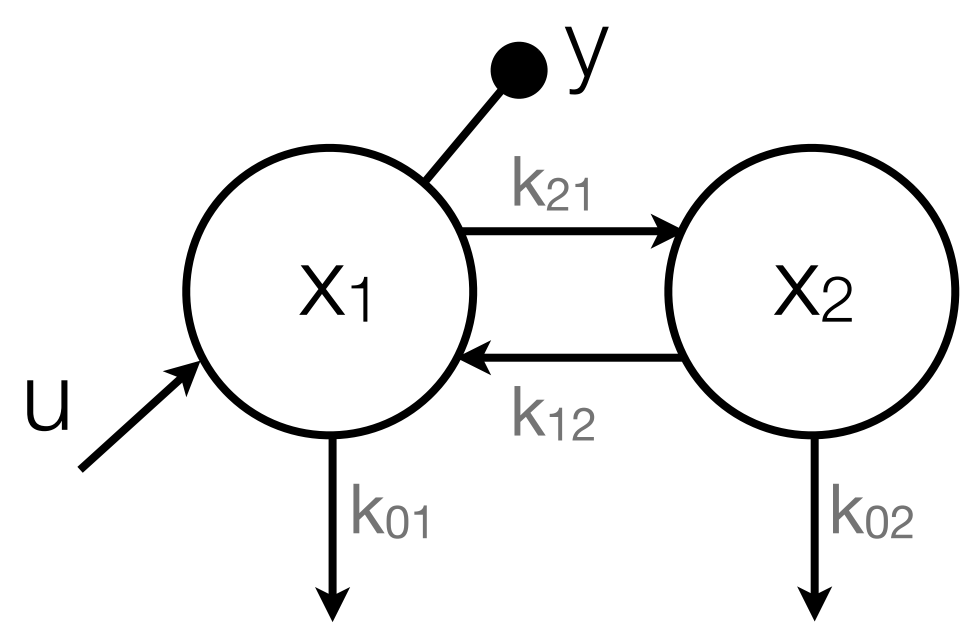
$$1 / V$$

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

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

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

2-Compartment Example



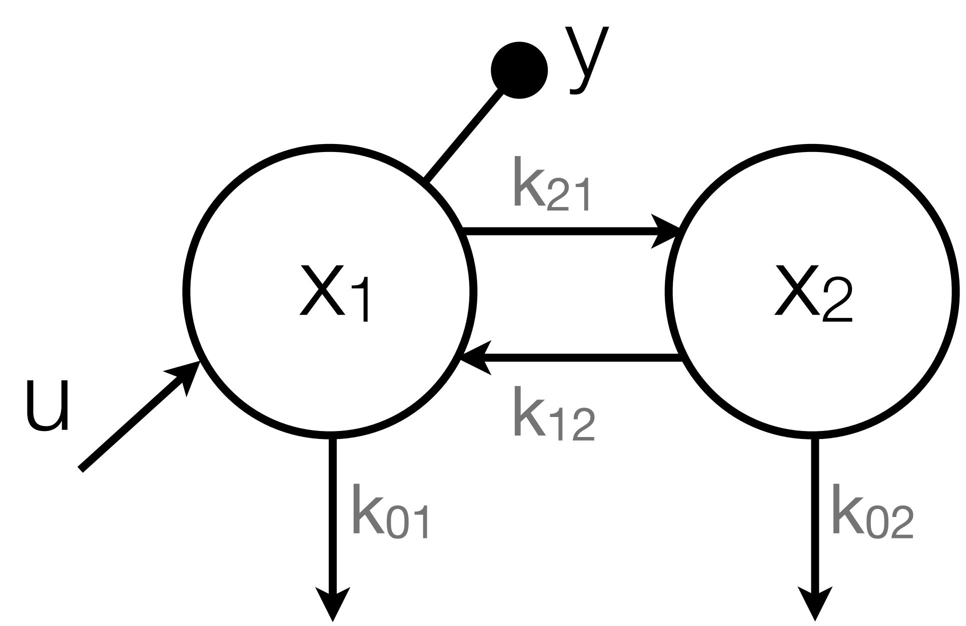
$$1/V = a_1$$

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

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

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

2-Compartment Example



$$\boxed{1/V = a_1 \Rightarrow V = 1/a_1}$$

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

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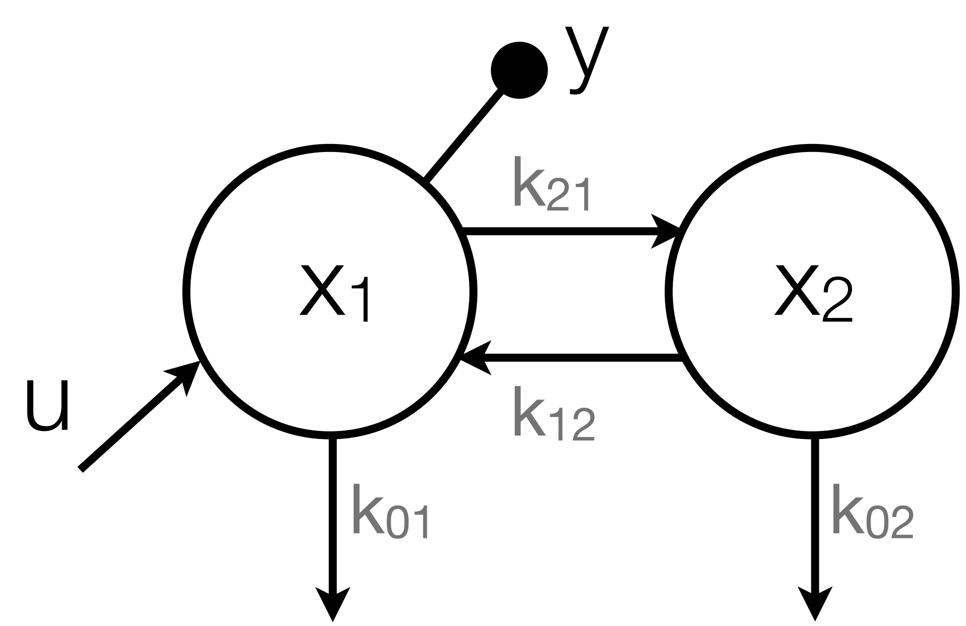

Unidentifiable

2-Compartment Example

$$\boxed{1/V = a_1 \Rightarrow V = 1/a_1}$$

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

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

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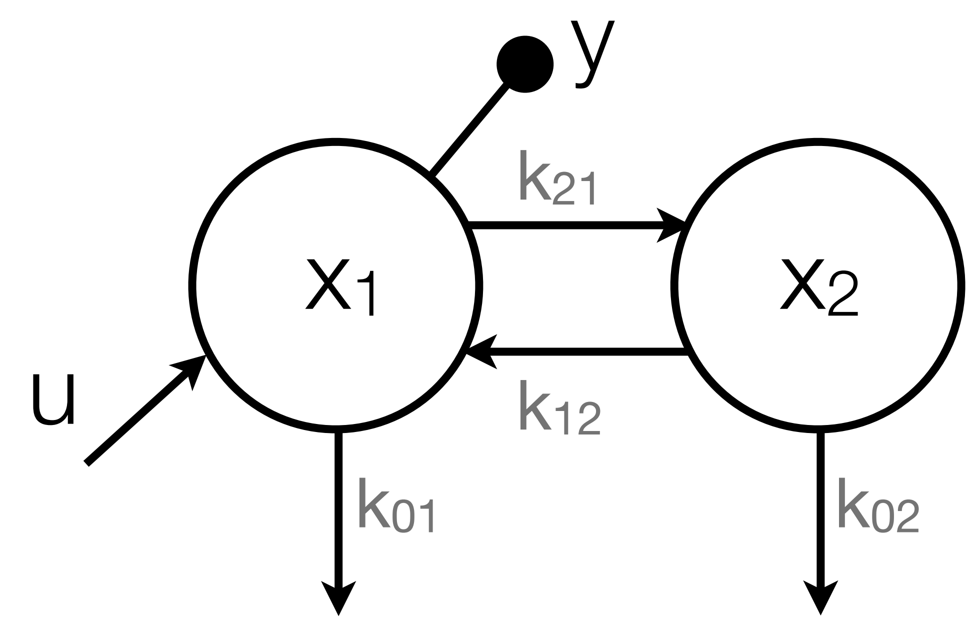

Unidentifiable

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

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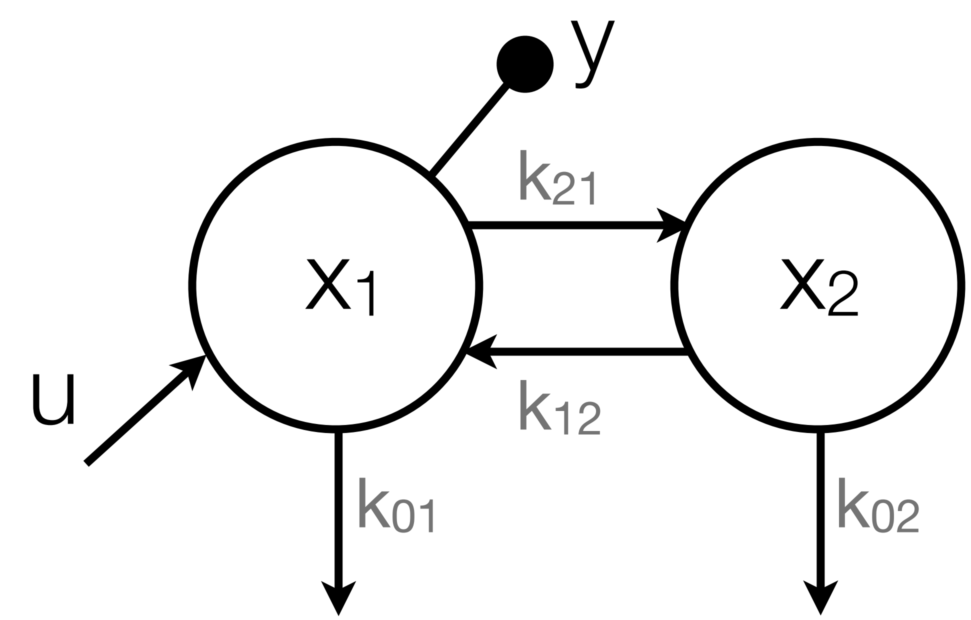

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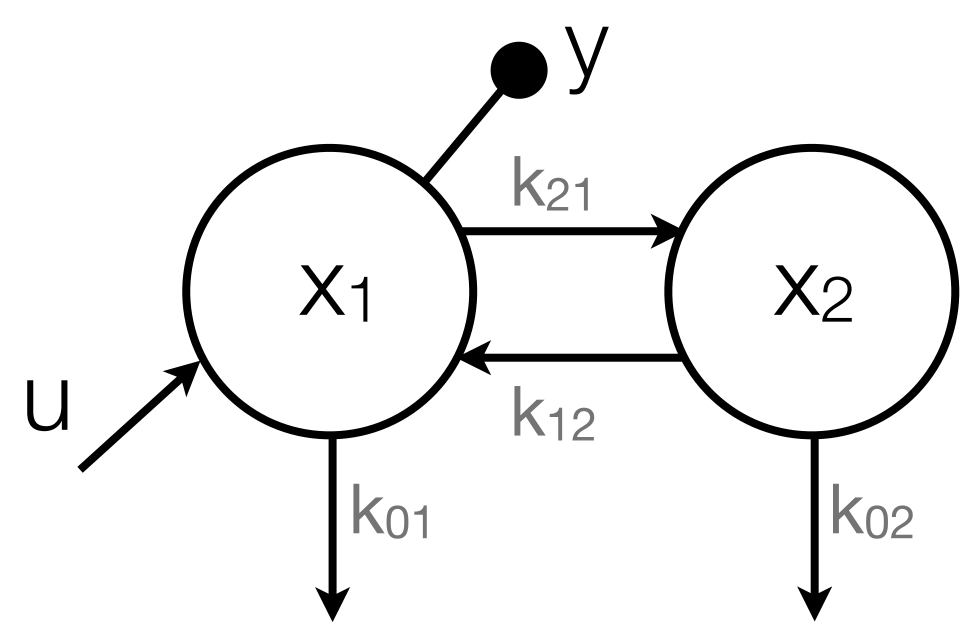

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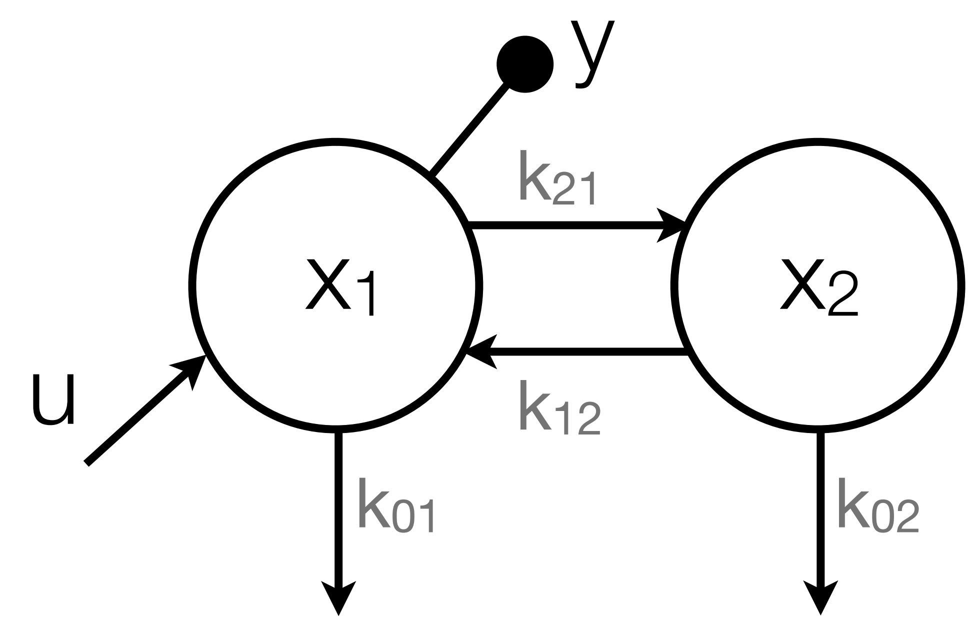

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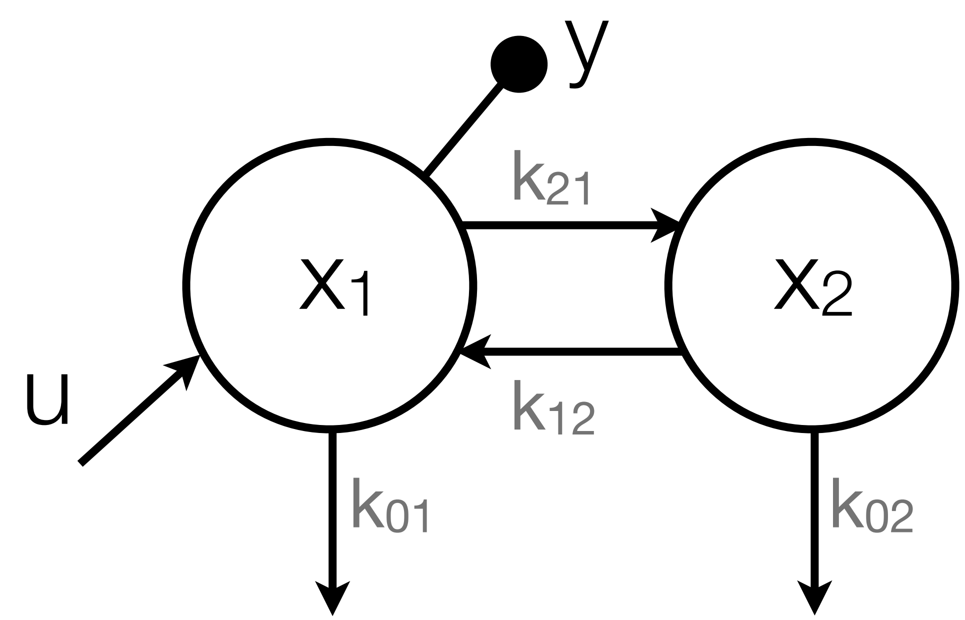
Let $\underline{x}_2 = k_{12}x_2$



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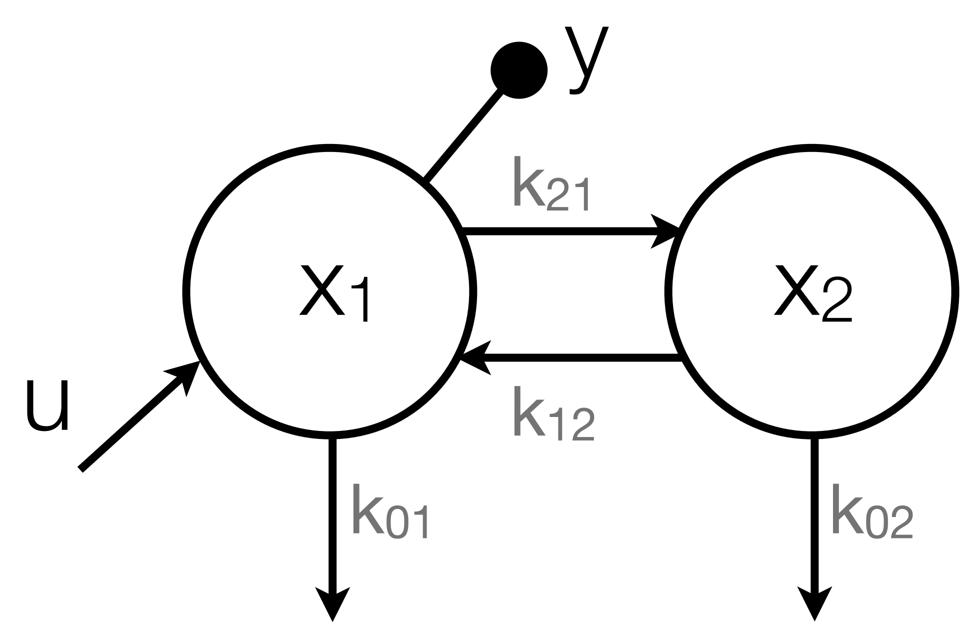


Let $\underline{x}_2 = k_{12}x_2$

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

Or add information about one of the parameters

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.)

In Summary: Differential algebra approach

- View model & measurement equations as differential polynomials

- Reduce the equations to eliminate unmeasured variables (x) (e.g. using characteristic sets, Groebner bases, etc.)

- Yields **input-output equation(s)** only in terms of known variables (y, u)

In Summary: Differential algebra approach

- Assuming the output & input dynamics give sufficiently many distinct/independent points, we can determine the coefficients of the input-output equations uniquely (solvability)

- Then the injectivity of the model map can be evaluated by examining the map from the parameters to the coefficients
  $p \mapsto c(p)$

- Coefficients are identifiable combinations and contain all identifiability information for the model

In Summary: 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
- Note about scaling as a useful first step (cf. nondimensionalization)

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

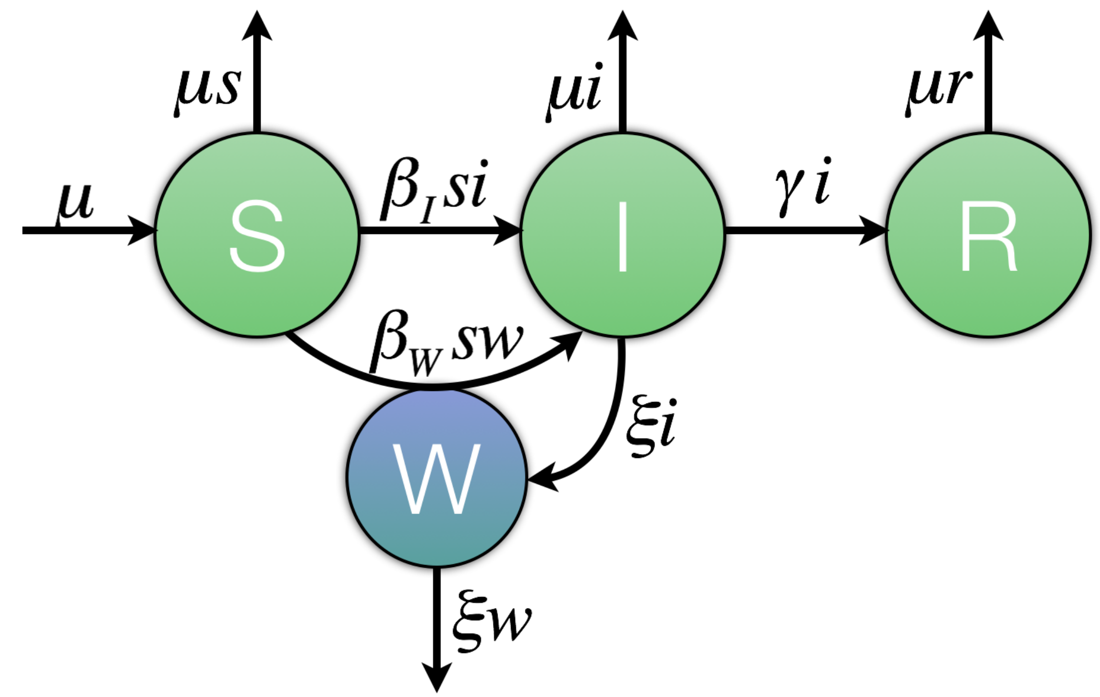
- Most can do both structural & practical identifiability
- Wide range of applicable models, often (relatively) fast
- Typically only local

Simple Simulation Approach

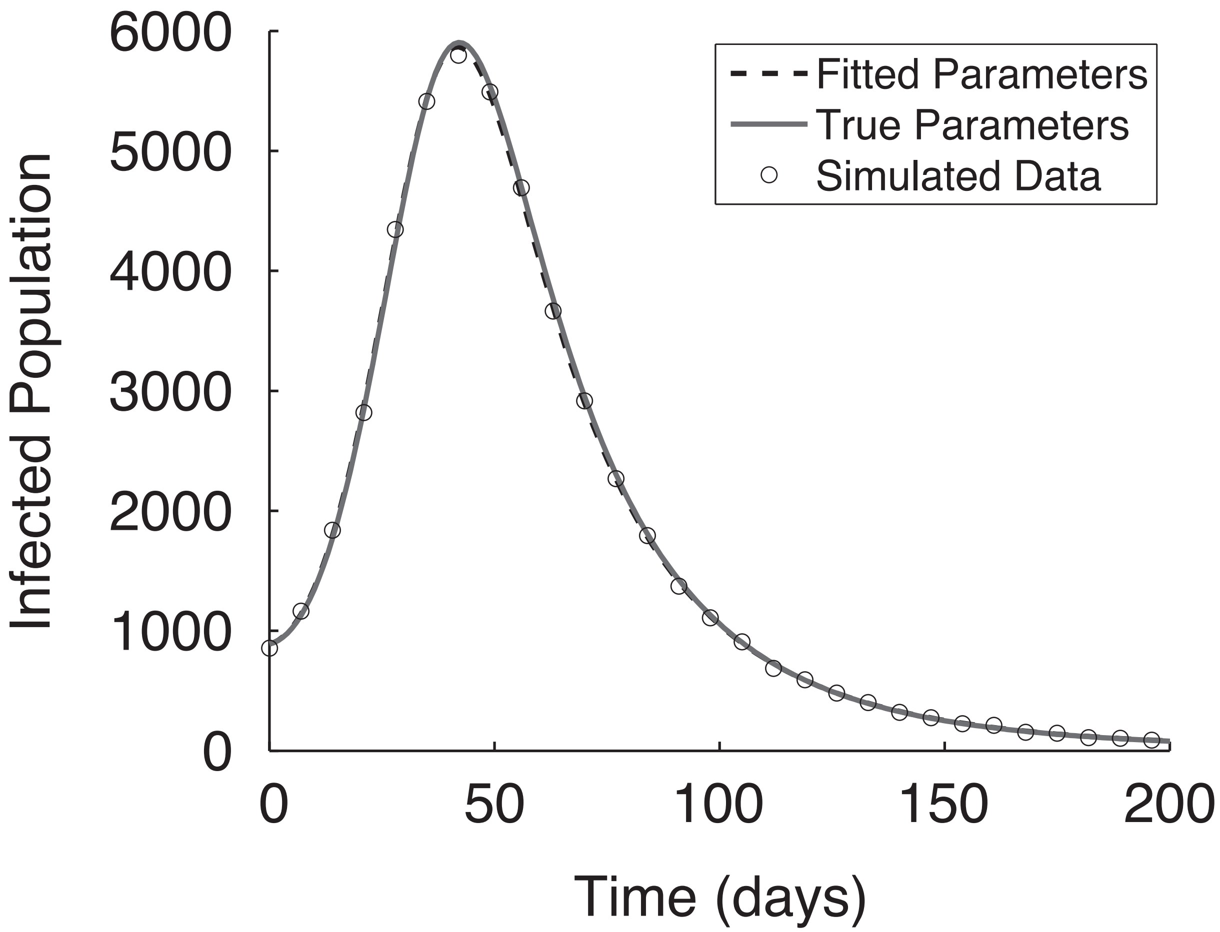
- Simulate data using a single set of ‘true’ parameter values
  - Without noise for structural identifiability
  - With noise for practical identifiability (in this case generate multiple realizations of the data)

Simple Simulation Approach

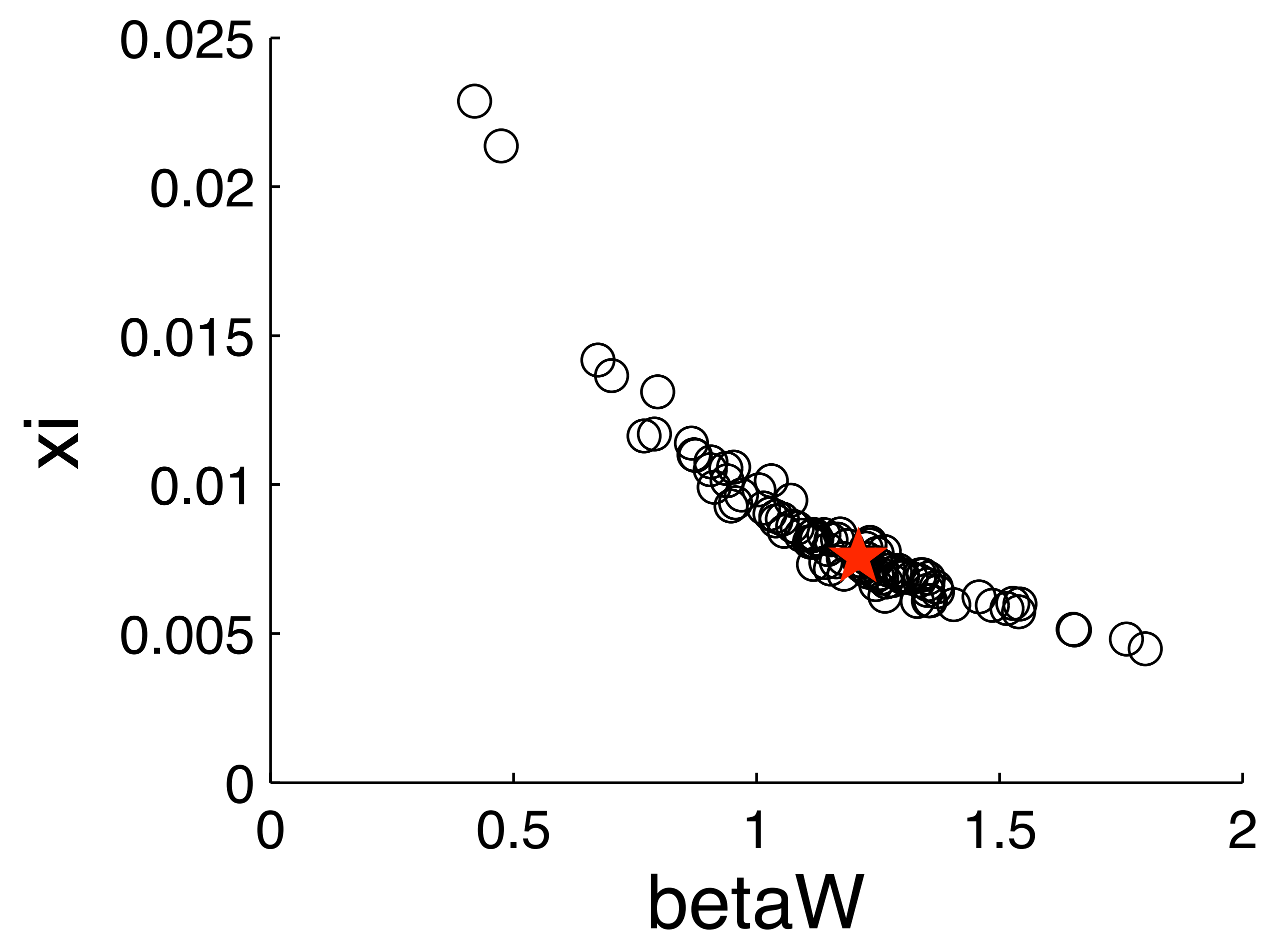
- Fit your simulated data from multiple starting points and see where your estimates land
- If they all return to the ‘true’ parameters, likely identifiable, if they do not—may be problems
- Note—unidentifiability when estimating with ‘perfect’, noise-free simulated data is most likely structural



μs
μi
μr
μ
S
β_I si
I
γ i
R
β_W sw
ξi
W
ξw



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



xi
betaW
0
0.005
0.01
0.015
0.02
0.025
0
0.5
1
1.5
2

Parameter Sensitivities

- Output sensitivity matrix (design matrix)
- Closely related to identifiability
- Insensitive parameters
- Undentifiability as dependencies between columns
  - Matrix rank indicates number of identifiable parameters/combinations

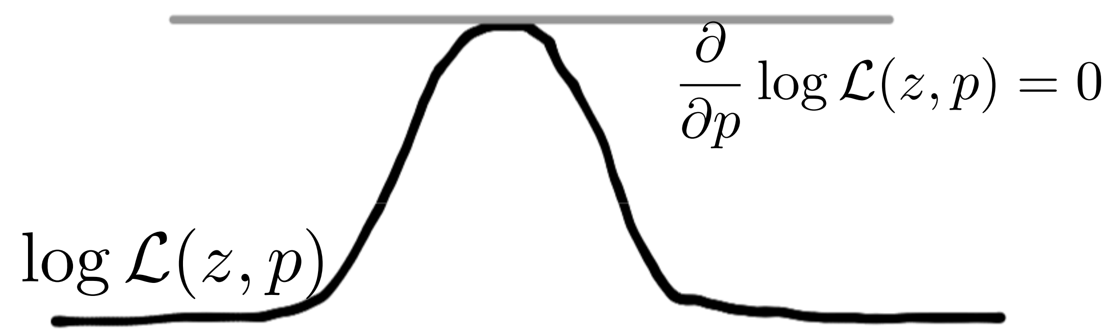
$$X = \begin{pmatrix} \dfrac{\partial y(t_1)}{\partial p_1} & \cdots & \dfrac{\partial y(t_1)}{\partial p_n} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial y(t_m)}{\partial p_1} & \cdots & \dfrac{\partial y(t_m)}{\partial p_n} \end{pmatrix}$$

Fisher Information Matrix

- Useful in testing practical & structural ID - represents amount of information that the output y contains about parameters p
- Relates to sensitivities via the score: $\frac{\partial}{\partial p} \log \mathcal{L}(z, p)$
  - Sensitivity of the log likelihood
  - Gives us a sense of how the likelihood changes as we change p

Fisher Information Matrix

- At the true parameter value, the expected value of the score is 0



- The variance of the score is the Fisher information:

$$\mathcal{I}(p) = \mathbb{E}\left[\left(\frac{\partial}{\partial p} \log \mathcal{L}(z,p) \right)^2 \middle| p \right]$$

$$= \int \left(\frac{\partial}{\partial p} \log \mathcal{L}(z,p) \right)^2 \mathcal{L}(z,p) dz$$

- Why the variance?

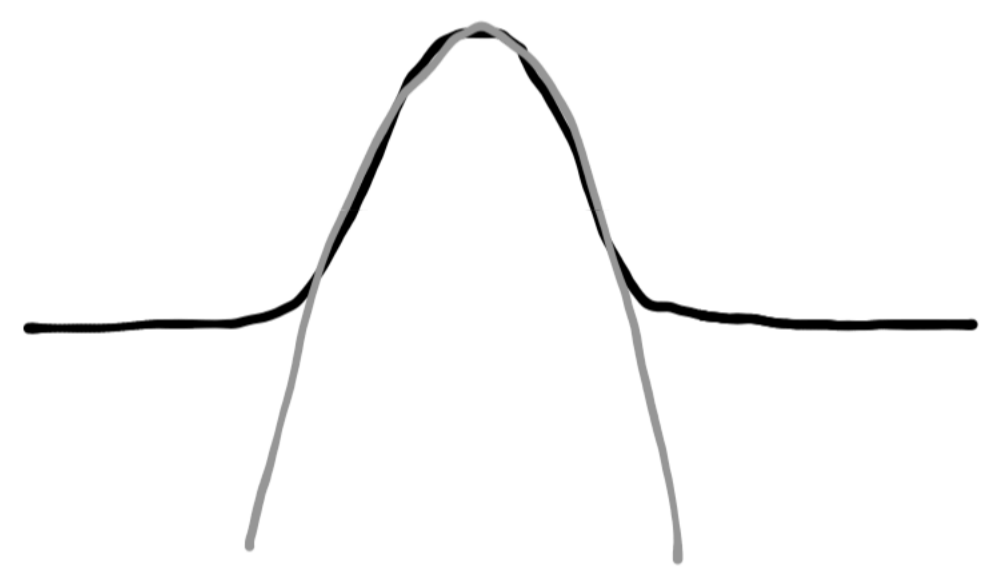
Fisher information matrix

- In matrix form:

$$[\mathcal{I}(p)]_{ij} = \mathbb{E}\left[\left(\frac{\partial}{\partial p_i}\log\mathcal{L}(z,p)\right)\left(\frac{\partial}{\partial p_j}\log\mathcal{L}(z,p)\right)\bigg|p\right]$$

- FIM - N_P x N_P matrix

- Under certain conditions, the FIM can be written as the Hessian (2nd derivative matrix), allowing us to interpret it as the curvature or a quadratic approximation of the likelihood



Fisher Information Matrix

- Special case when errors are normally distributed with constant

$$F = X^T W X$$

W = weighting matrix

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

Fisher Information Matrix

- For looking at structural ID, often just use

$$F = X^T X$$

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

Fisher information matrix

- **Cramer-Rao Bound**: $FIM^{-1} \leq Cov(p)$
  - Diagonal of the covariance matrix gives variances for the parameters (use to calculate confidence intervals)
- Also used for a wide range of other applications—Jeffries prior, model dimension reduction, etc.
- Rank(FIM) = number of identifiable parameters/ combinations

Identifiability & the FIM

- Covariance matrix/confidence interval estimates from Cramér-Rao bound: Cov ≥ FIM^{-1}
  - e.g. large confidence interval ⇒ probably at least practically 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

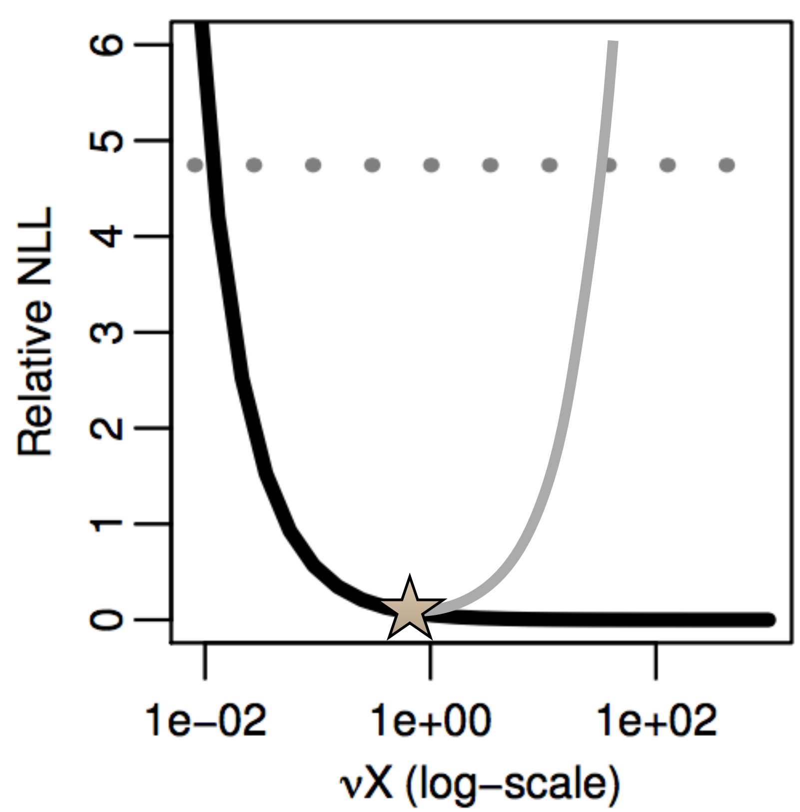
- Use FIM to find blocks of related parameters & how many to fix (not estimate)

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

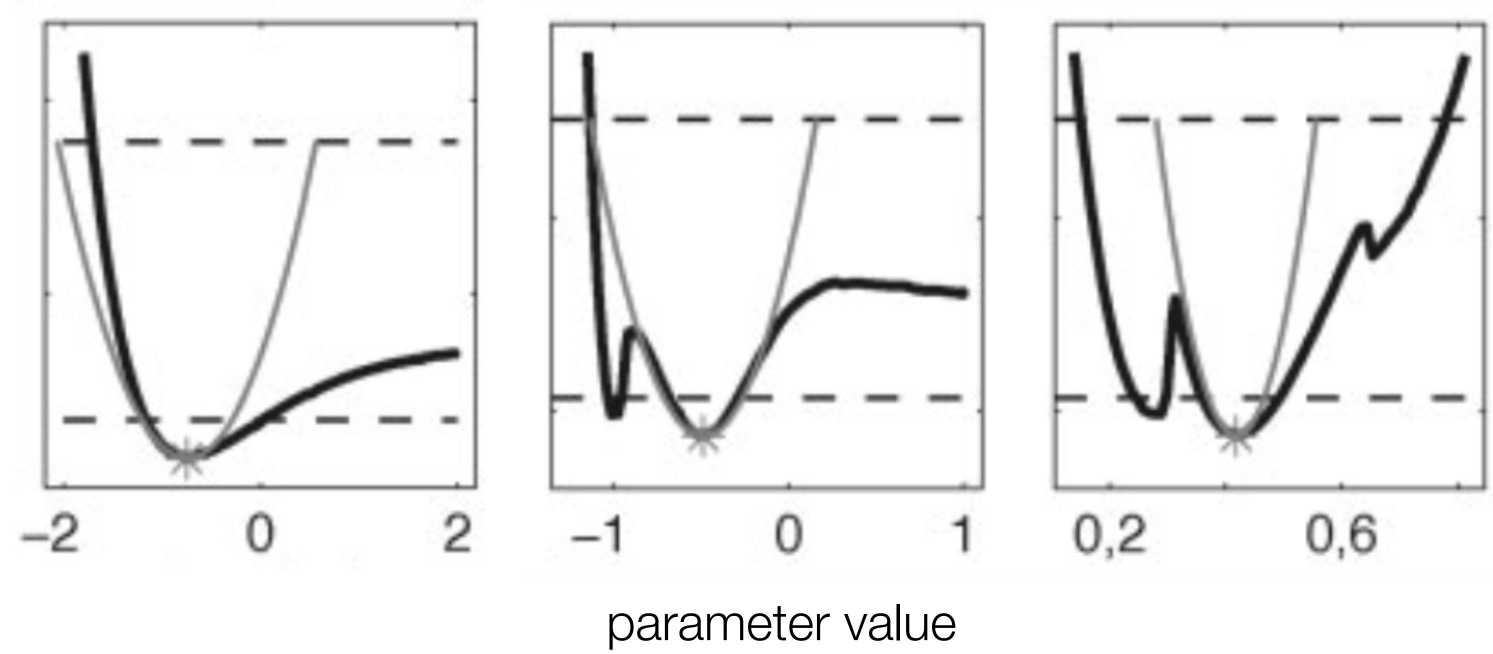
  - Interaction of combinations

Identifiability & the FIM

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



Brouwer, Meza, Eisenberg 2017



Raue et al. 2010

Profile Likelihood

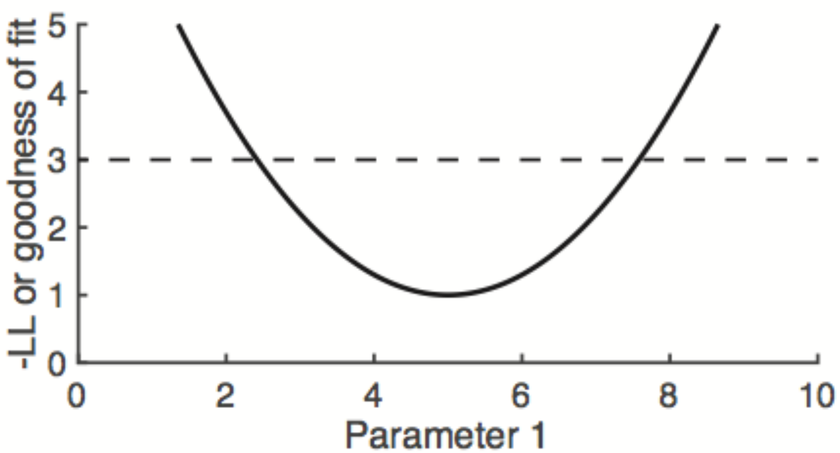
- Want to examine likelihood surface, but often high-dimensional
- Basic Idea: ‘profile’ one parameter at a time, by fixing it to a range of values & fitting the rest of the parameters
- Gives best fit at each point
- Evaluate curvature of likelihood to determine confidence bounds on parameter (and to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

Profile Likelihood

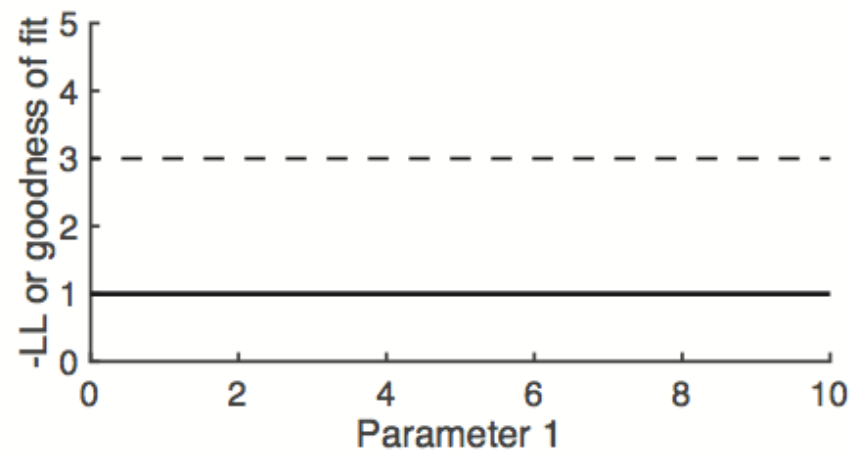
- Choose a range of values for parameter p_i
- For each value, fix p_i to that value, and fit the rest of the parameters
- Report the best likelihood/RSS/cost function value for that p_i value
- Plot the best likelihood values for each value of p_i— this is the profile likelihood

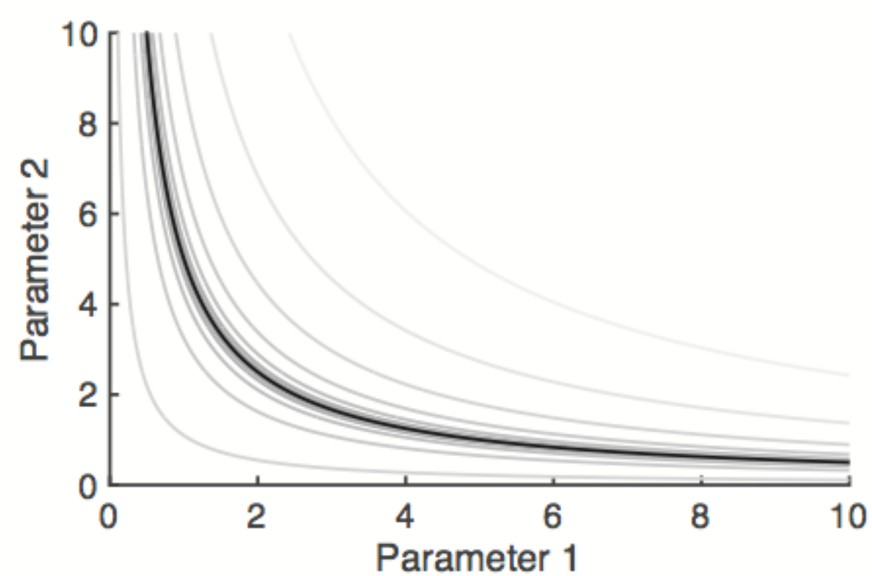
Profile Likelihoods

identifiable

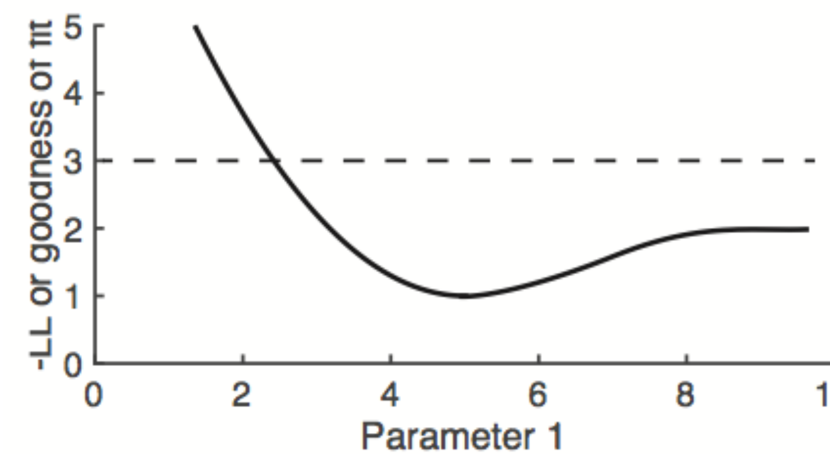


structurally unidentifiable





practically unidentifiable



Profile Likelihood & ID

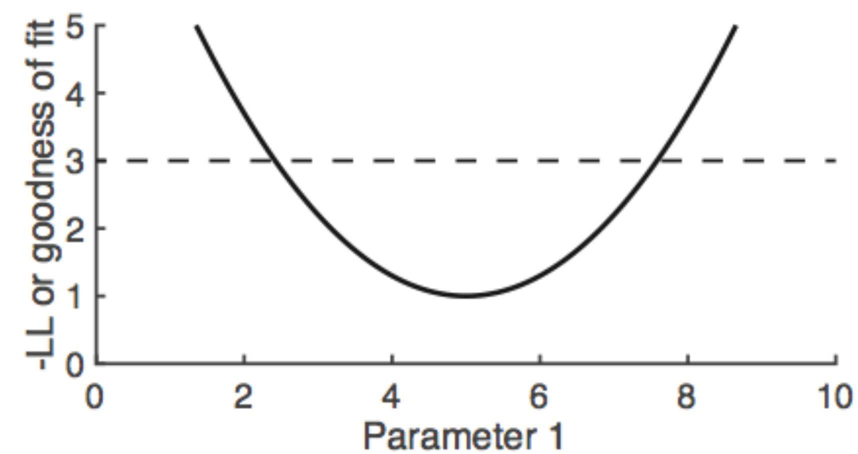
- Can generate confidence bounds based on the curvature of the profile likelihood
- Flat or nearly flat regions indicate identifiability issues
- Can generate simulated ‘perfect’ data to test structural identifiability

Profile-based Confidence Intervals

- The shape of the likelihood—more specifically, the likelihood ratio:

$$2(NLL(p) - NLL(\hat{p}))$$

is approximately χ^2-distributed when the sample size is large



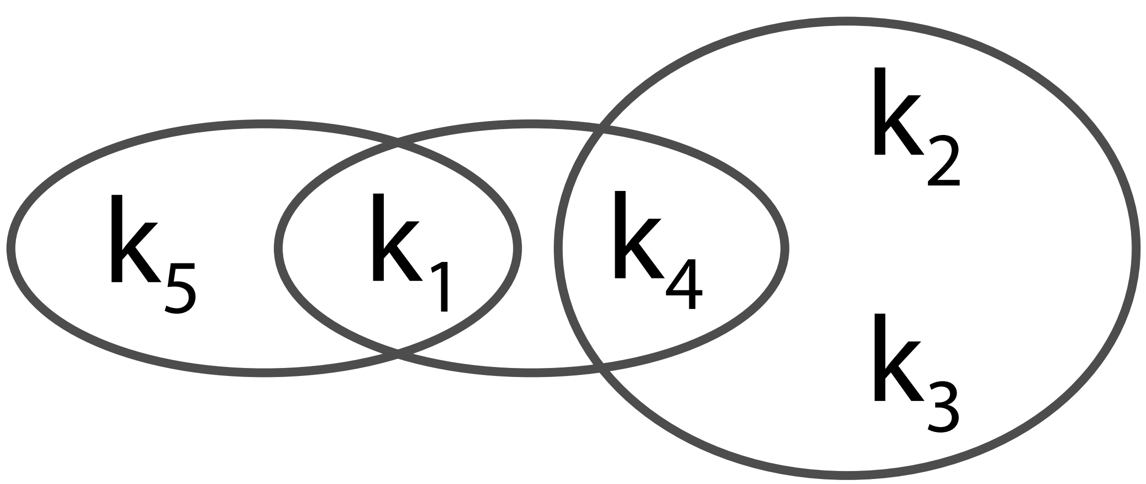
- From this, we can calculate a threshold to define a confidence interval, based on the appropriate percentile of the χ^2

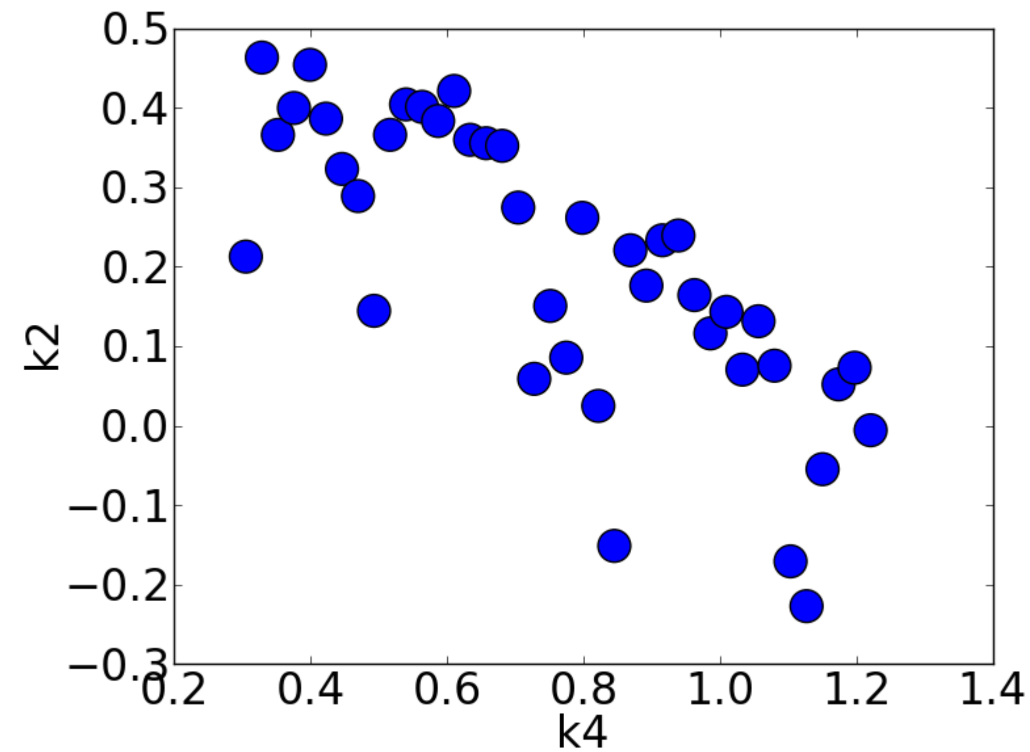
Profile Likelihood

- 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
- Similar to pairwise plots with sampling-based methods (e.g. MCMC)

Some potential issues

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

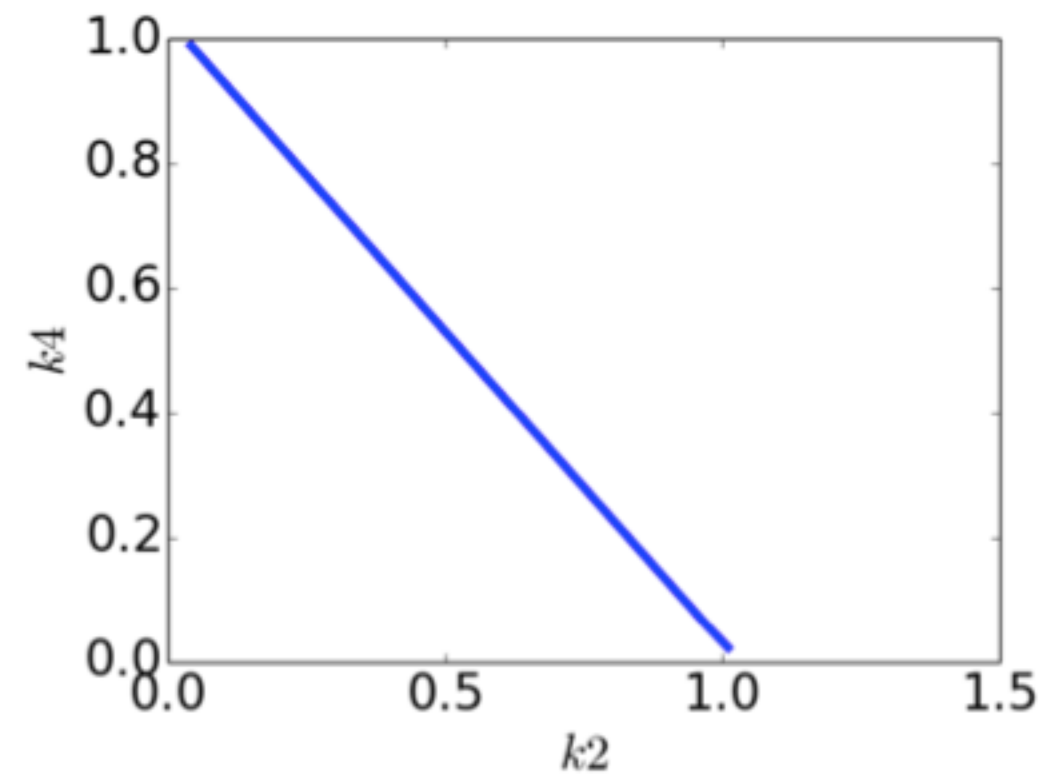


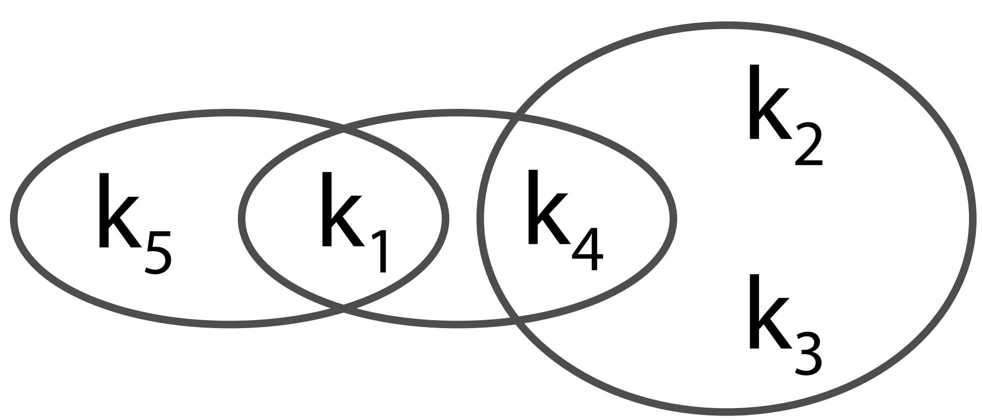


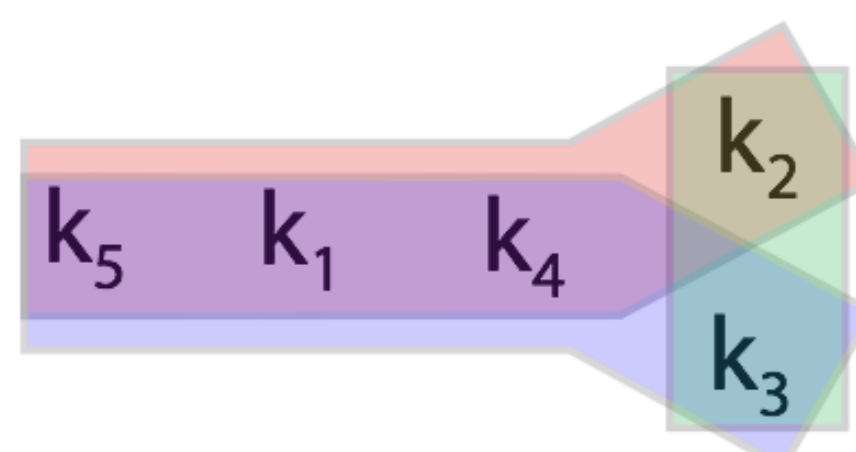
Eisenberg & Hayashi, Math Biosciences 2014

Example Model

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

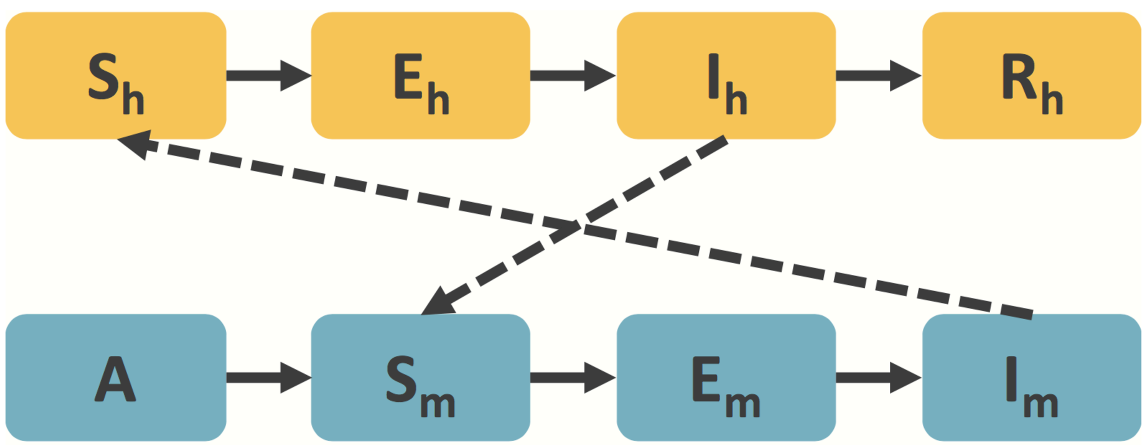






Eisenberg & Hayashi 2014, *Math Biosciences*

Dengue Model Example

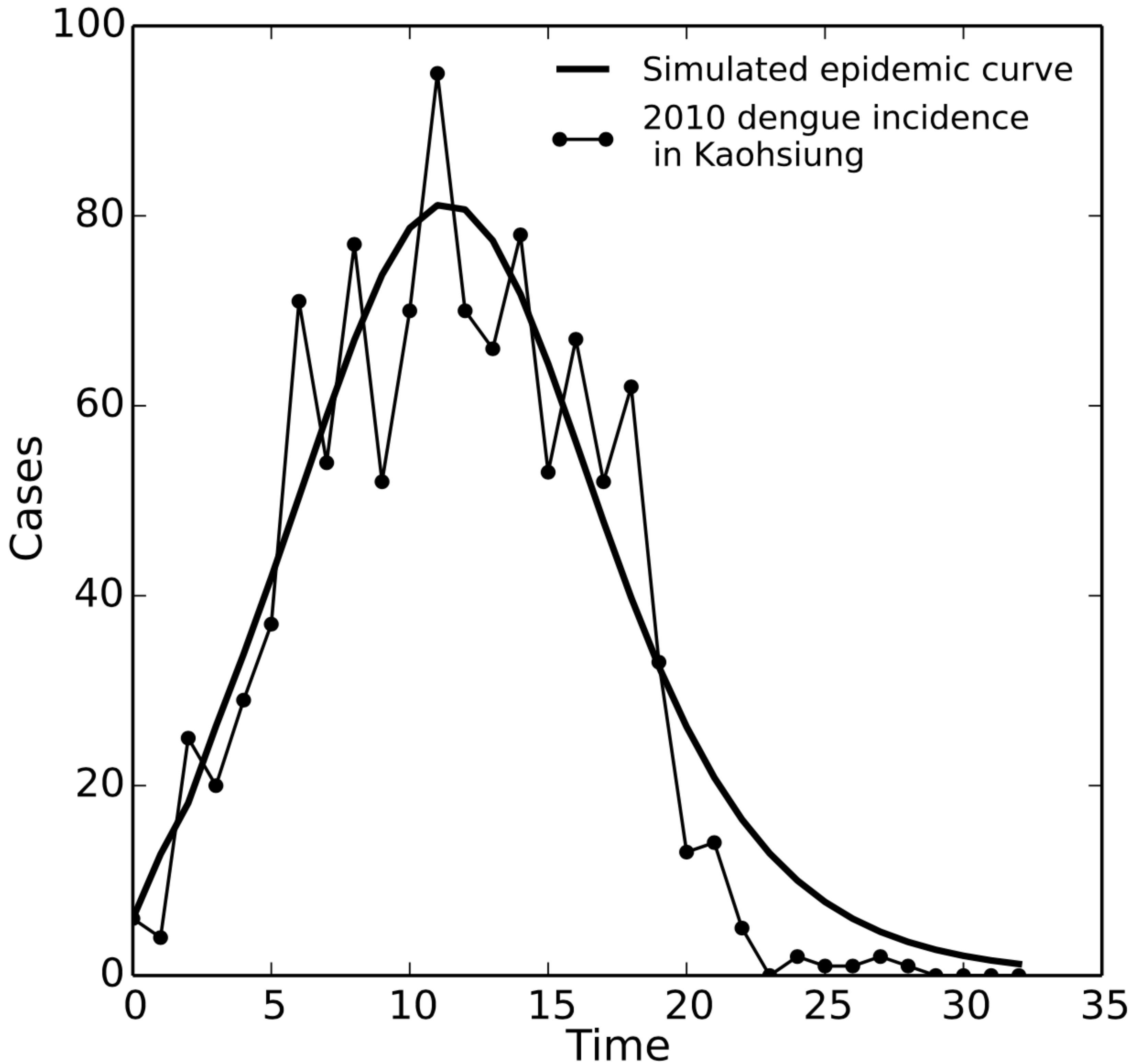


$$\frac{dS_h}{dt} = \mu(1 - S_h) - \beta^*_{mh} S_h I_m$$
$$\frac{dE_h}{dt} = \beta^*_{mh} S_h I_m - \alpha E_h - \mu E_h$$
$$\frac{dI_h}{dt} = \alpha E_h - \eta I_h - \mu I_h$$
$$\frac{dR_h}{dt} = \eta I_h - \mu R_h$$
$$\frac{dA}{dt} = \xi^*(S_m + E_m + I_m)(1 - A) - \mu^*_a A$$
$$\frac{dS_m}{dt} = A - \beta_{hm} S_m I_h - \mu_m S_m$$
$$\frac{E_m}{dt} = \beta_{hm} S_m I_h - \gamma E_m - \mu_m E_m$$
$$\frac{I_m}{dt} = \gamma E_m - \mu_m I_m$$

Measurement Model & Structural Identifiability

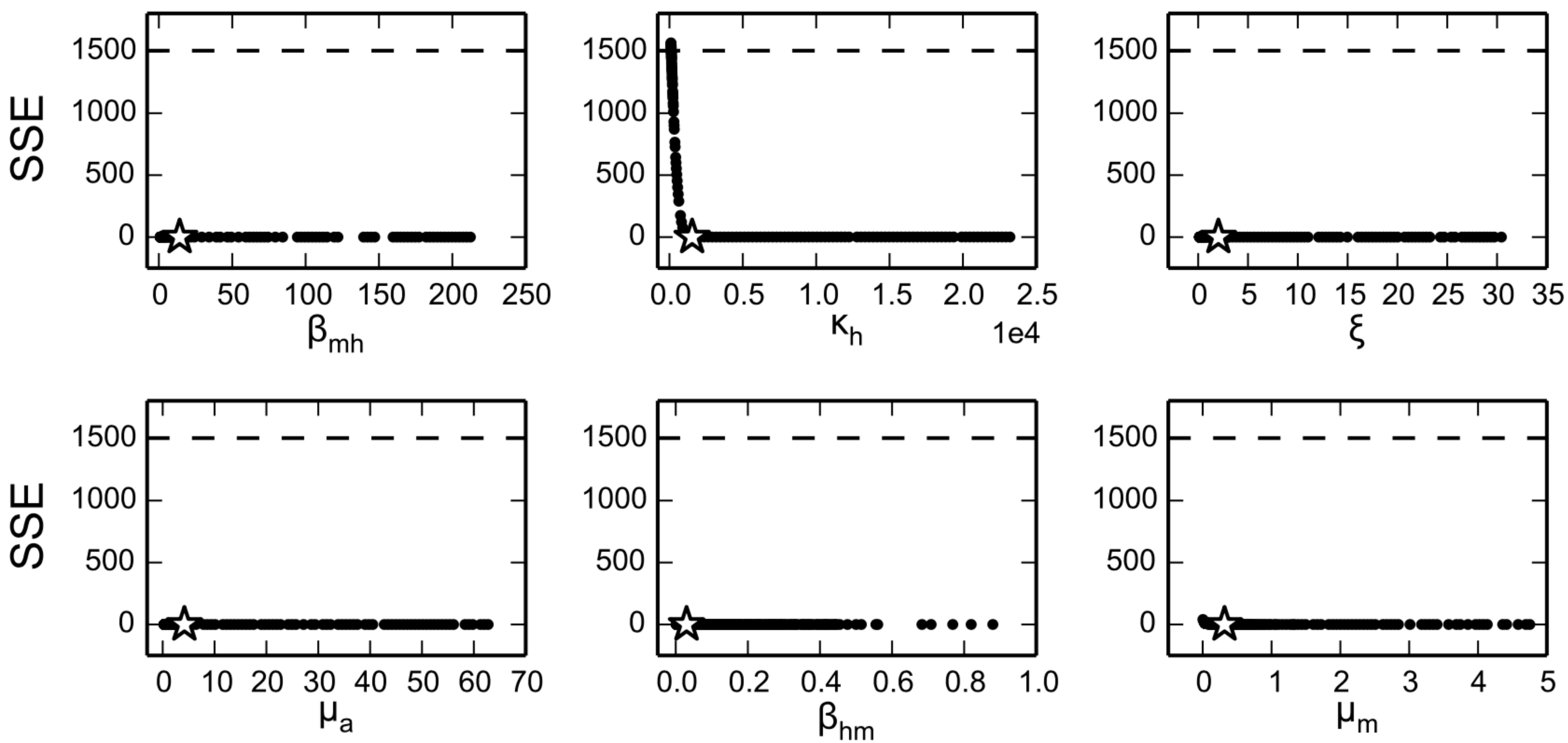
- Measure human incidence data, $y = \kappa_h \alpha E_h$, integrated to weekly incidence

- Differential algebra approach and FIM-based approaches show structural identifiability

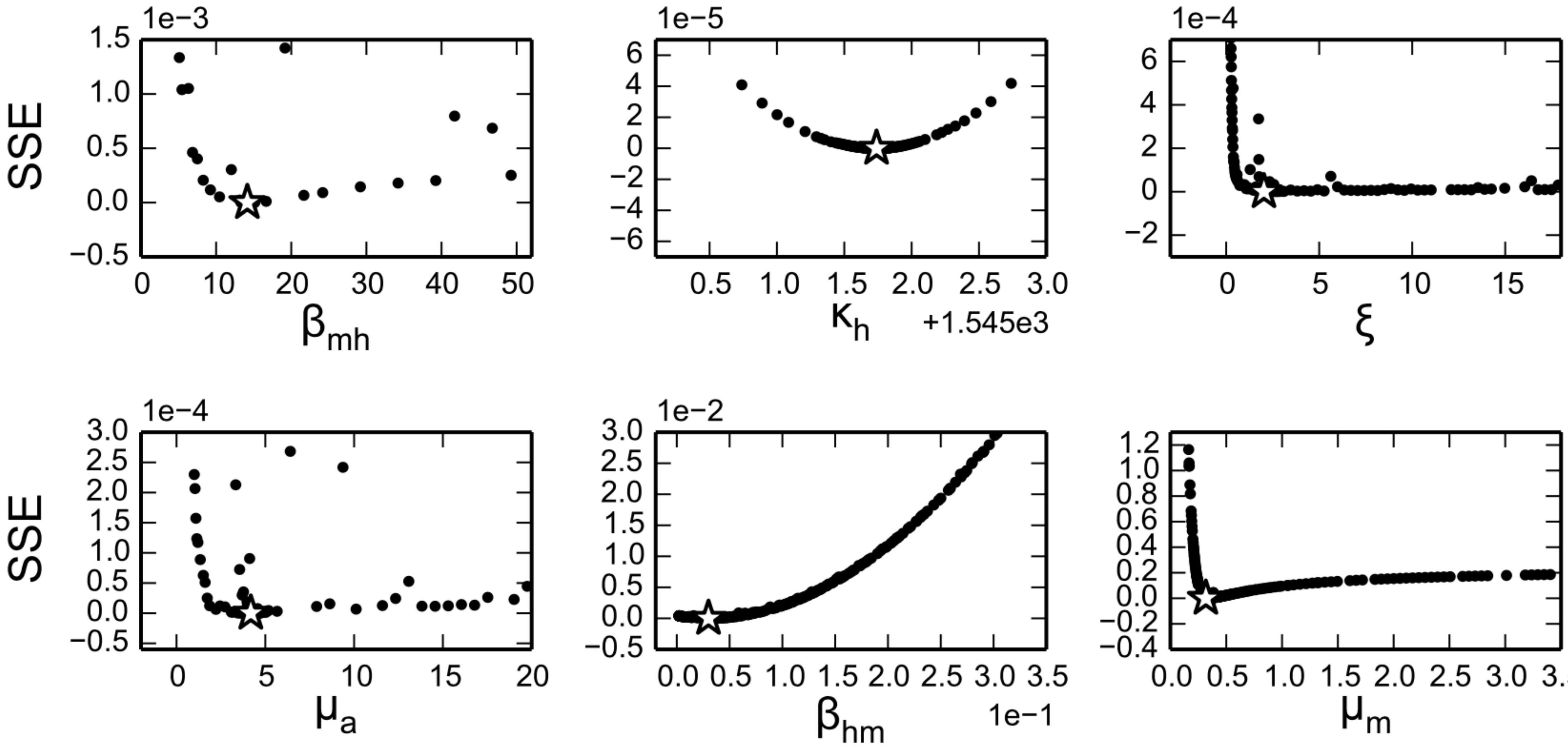


$\beta_{mh} = 14.15$
$\xi = 2.03$
$\beta_{hm} = 0.03$
$\mu_a = 4.18$
$\mu_m = 0.32$
$\kappa_h = 1546.74$

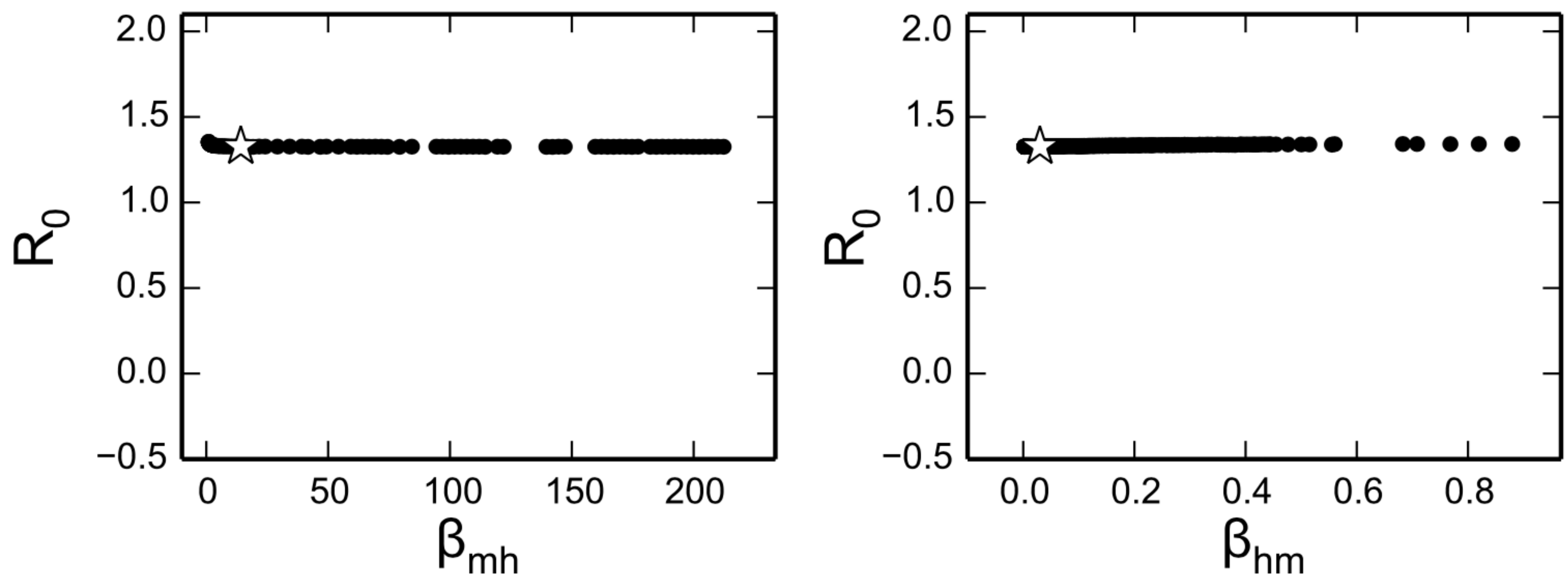
What about practical identifiability?



What about practical identifiability?

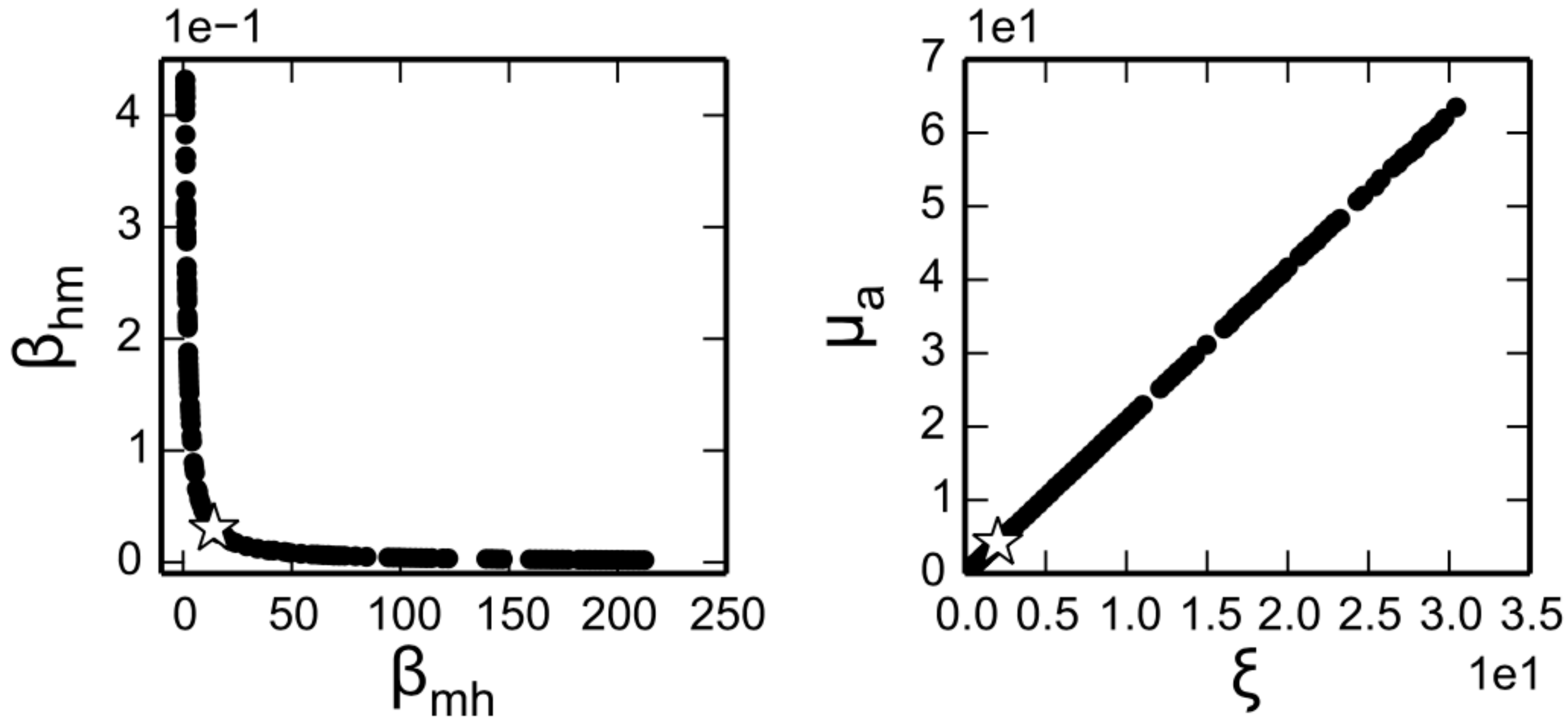


How does this affect R0?



$$\mathcal{R}_0 = \sqrt{\frac{S_m \alpha \beta_{hm} \beta_{mh} \gamma}{(\alpha + \mu)(\eta + \mu)(\gamma + \mu_m)\mu_m}}.$$

Practically Identifiable Combinations

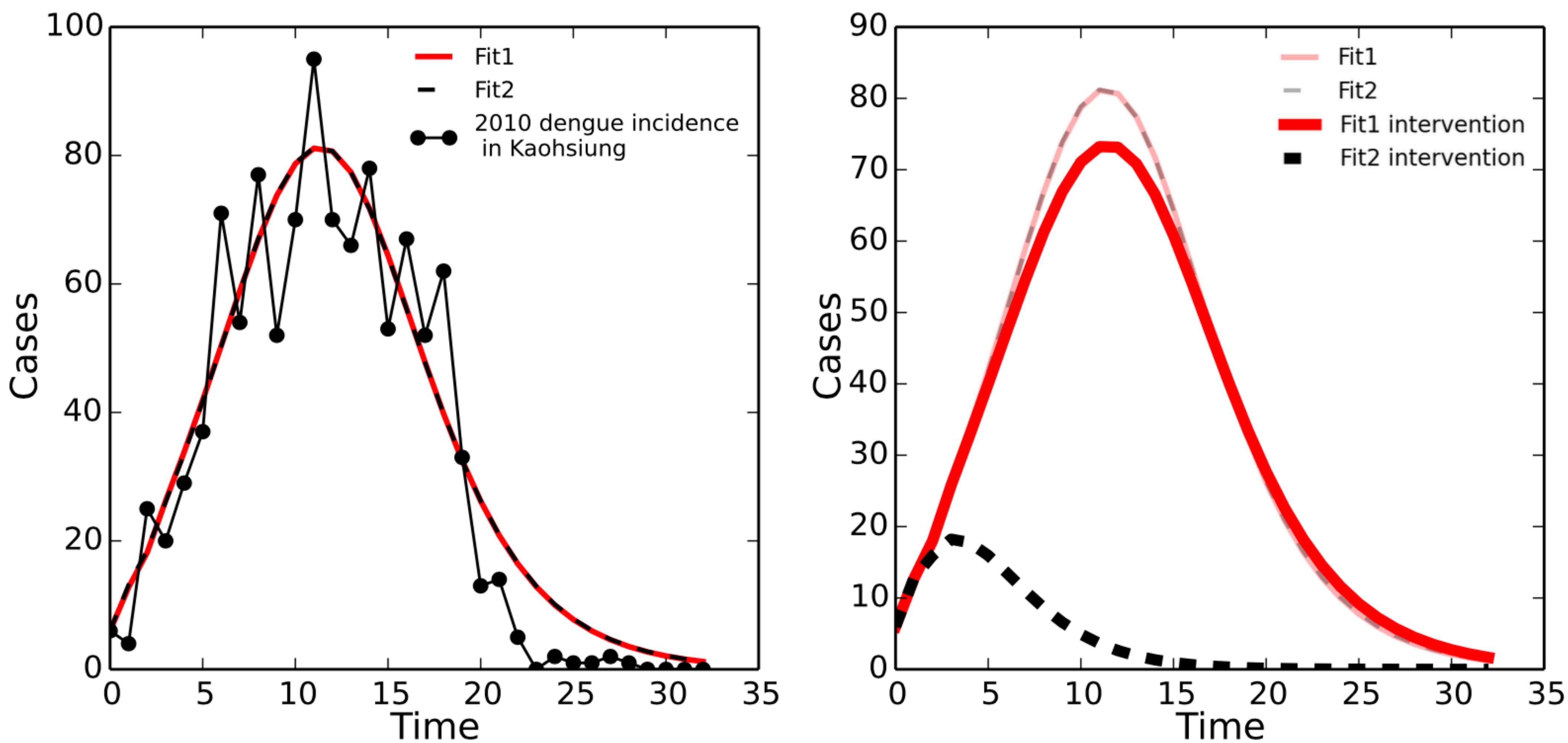


$$\mathcal{R}_0 = \sqrt{\frac{S_m \alpha \beta_{hm} \beta_{mh} \gamma}{(\alpha + \mu)(\eta + \mu)(\gamma + \mu_m)\mu_m}}.$$

Intervention predictions

Fit1:
β_{mh} = 14.15
ξ = 2.03
β_{hm} = 0.03
μ_a = 4.18
μ_m = 0.32
κ_h = 1546.74

Fit2:
β_{mh} = 38.10
ξ = 0.13
β_{hm} = 0.02
μ_a = 0.15
μ_m = 0.42
κ_h = 1625.42



Kao & Eisenberg, *Epidemics*, 2018.

Sidenote: Identifiability in a Bayesian Context

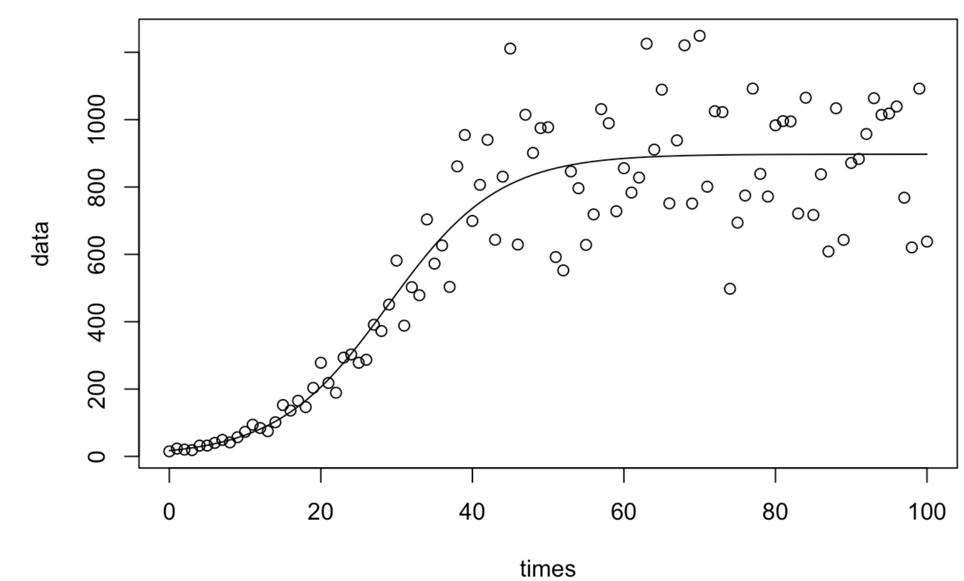
- Unidentifiability can affect the performance of MCMC and other sampling methods, and can lead to broad, flat posteriors or heavy reliance on the prior

- Simple unidentifiable model example:

$$\frac{dS}{dt} = -\beta S I + \gamma I$$

$$\frac{dI}{dt} = \beta S I - \gamma I$$

$$y = kNI$$



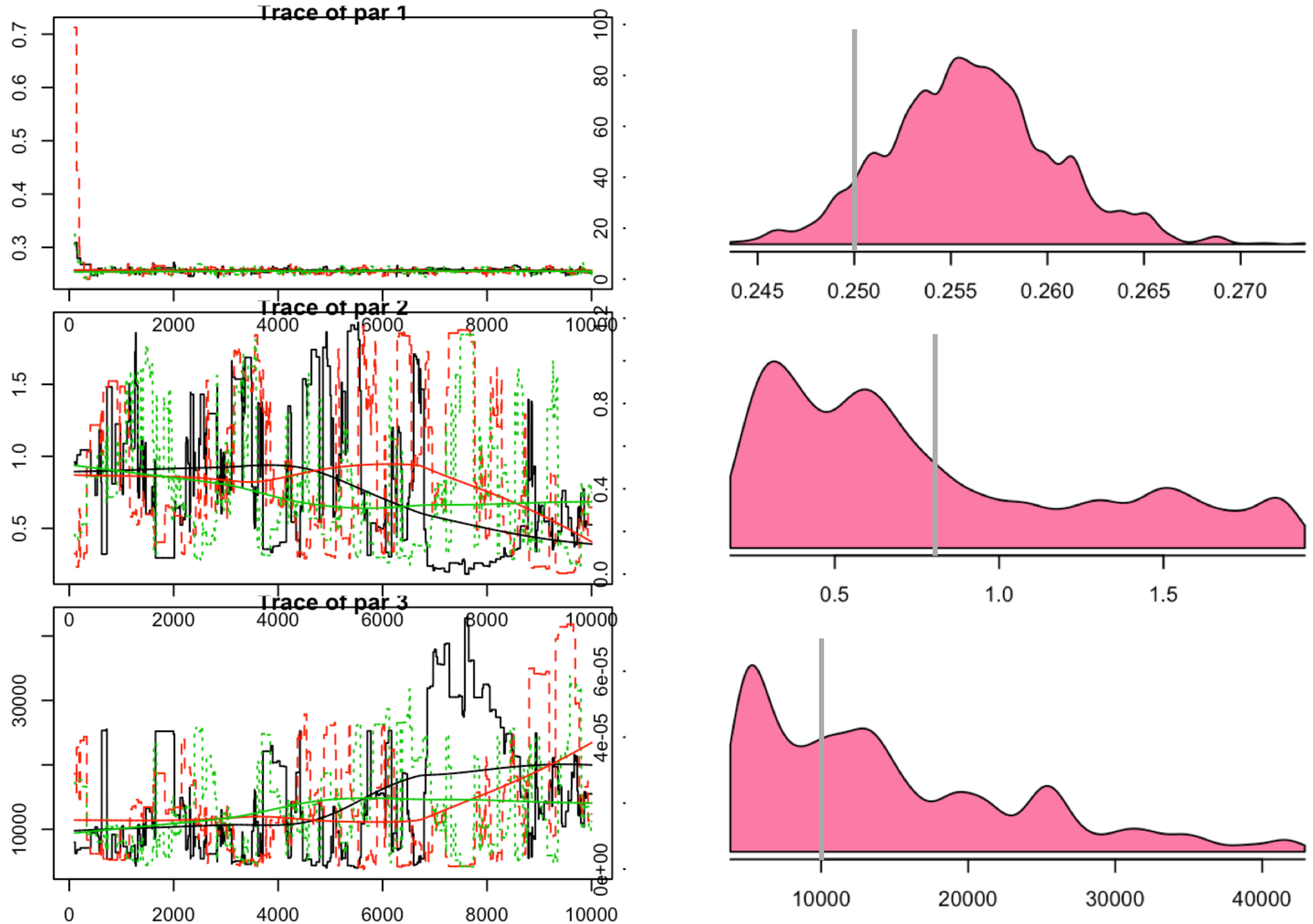
- Try MCMC (e.g. with Metropolis-Hastings or variants of)

Unidentifiable model

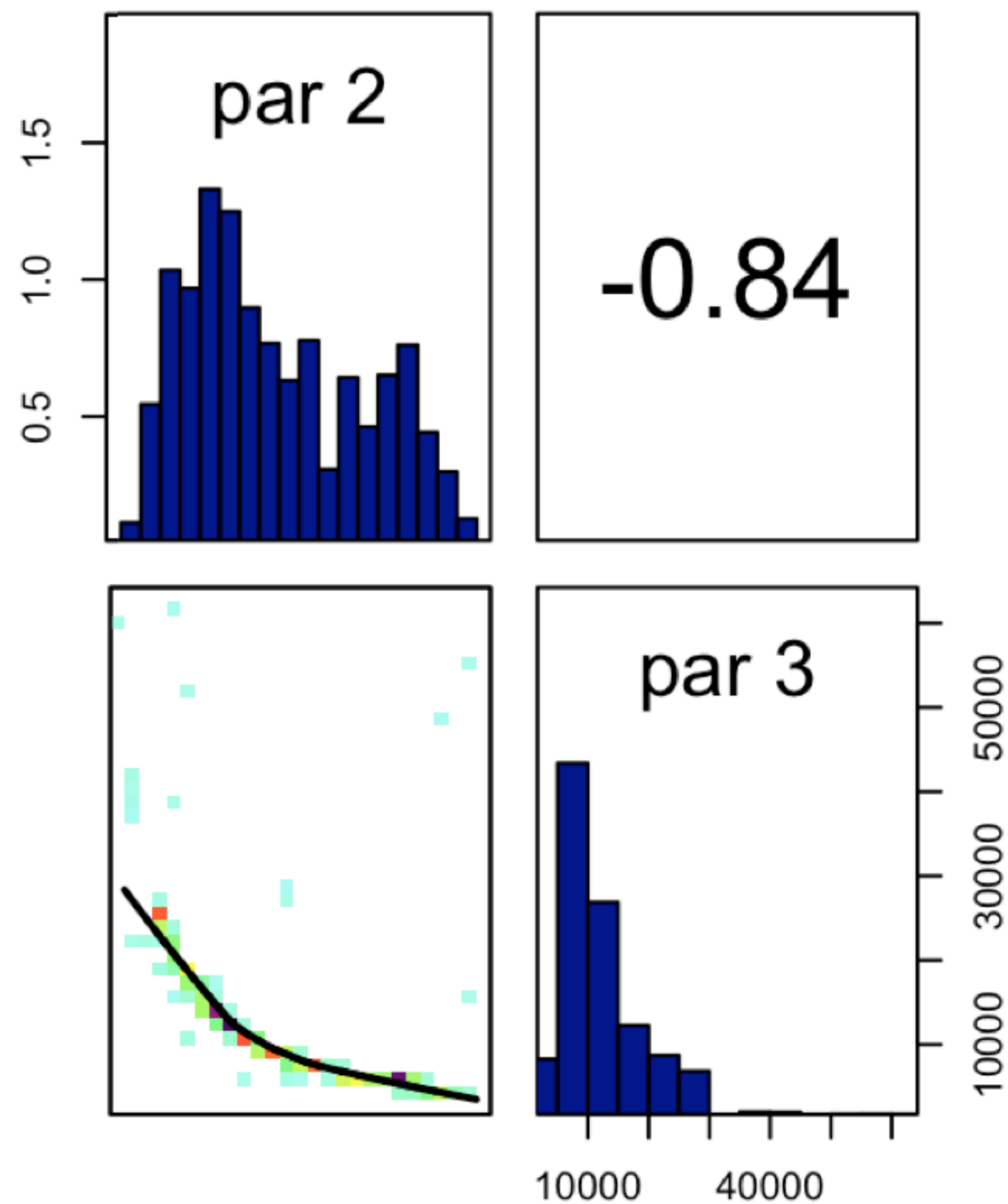
ß

k

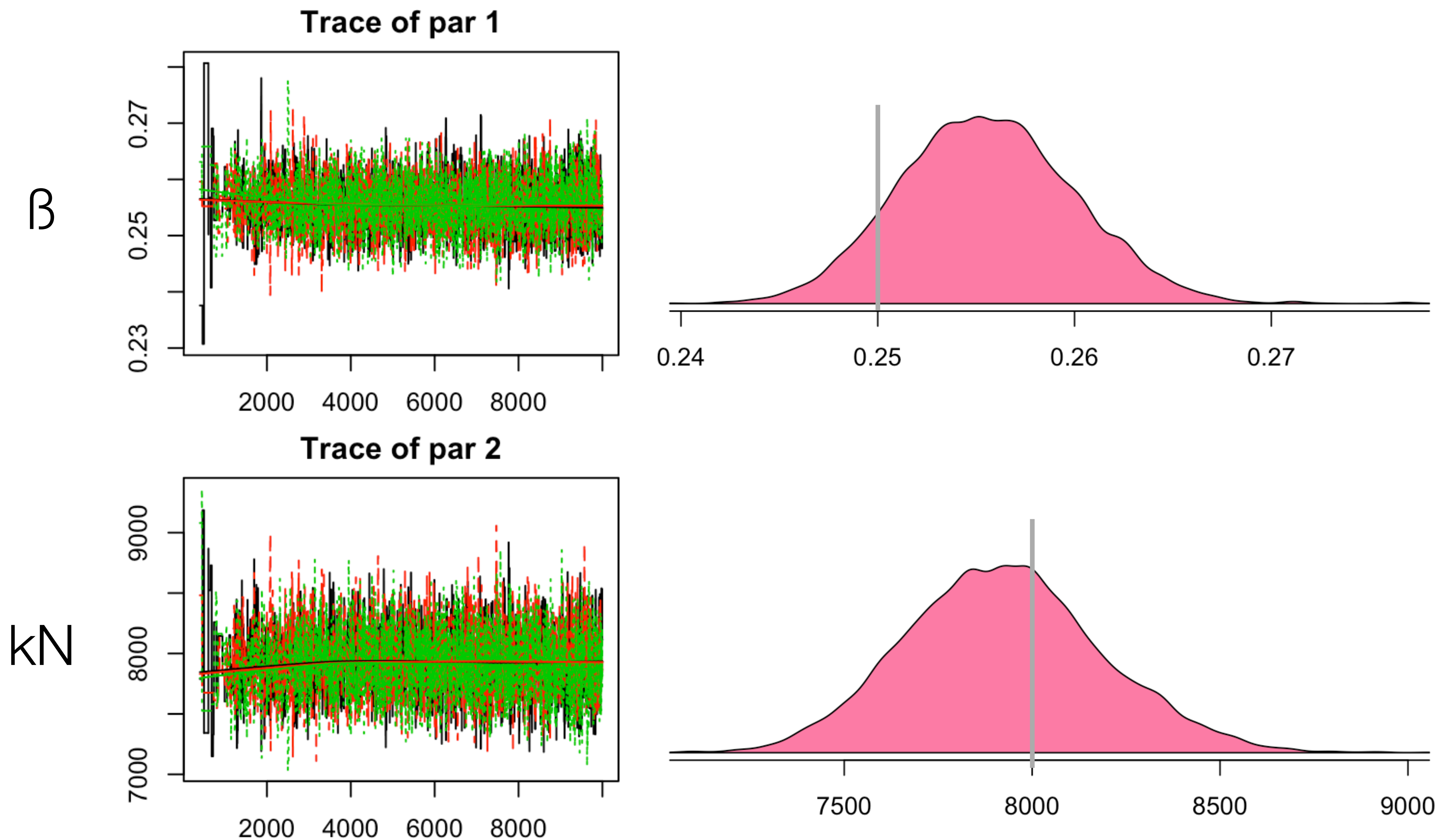
N



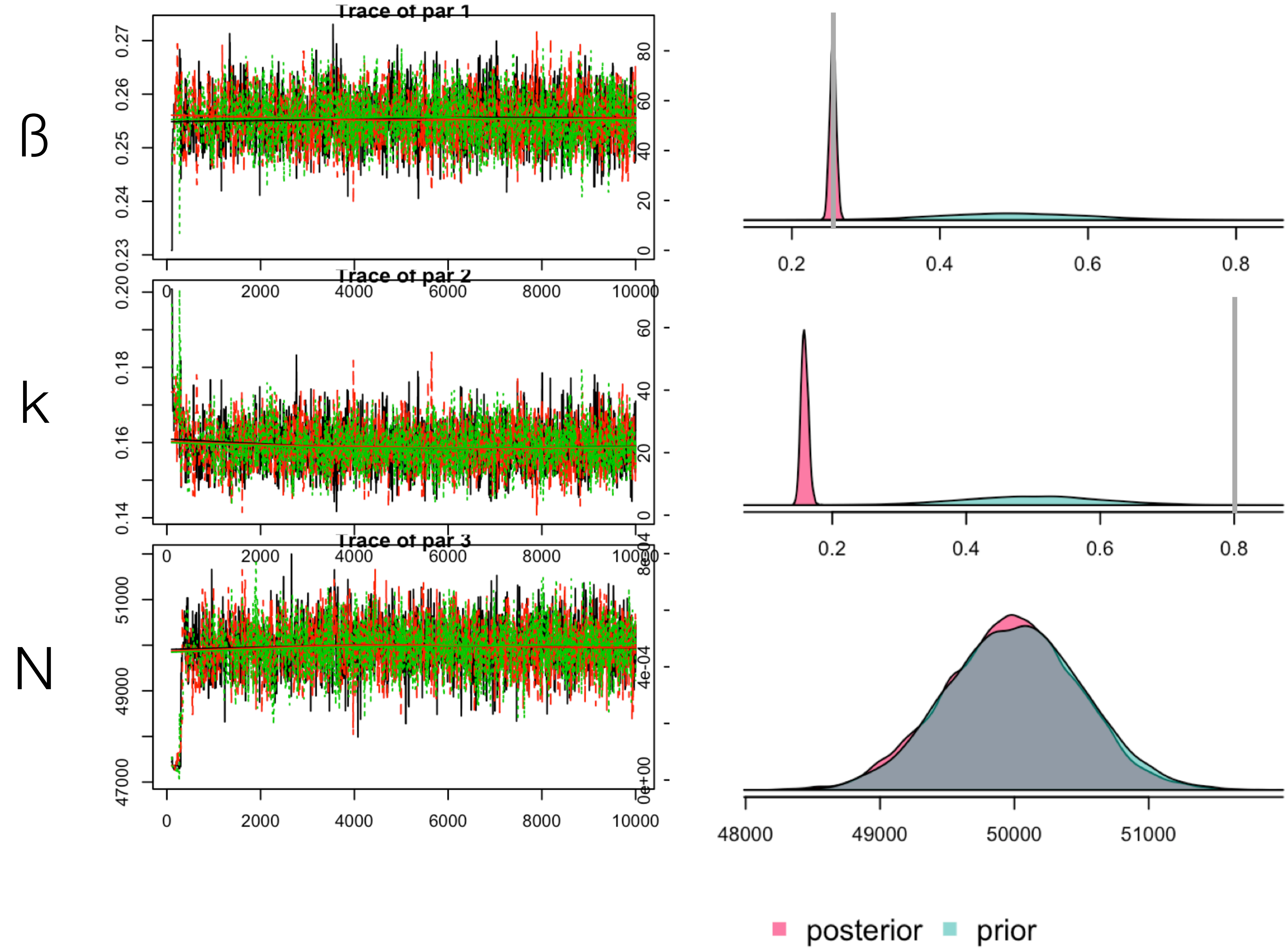
Correlation between k and N



Reparameterize to make the model identifiable



Adding a strong prior



Conclusions

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

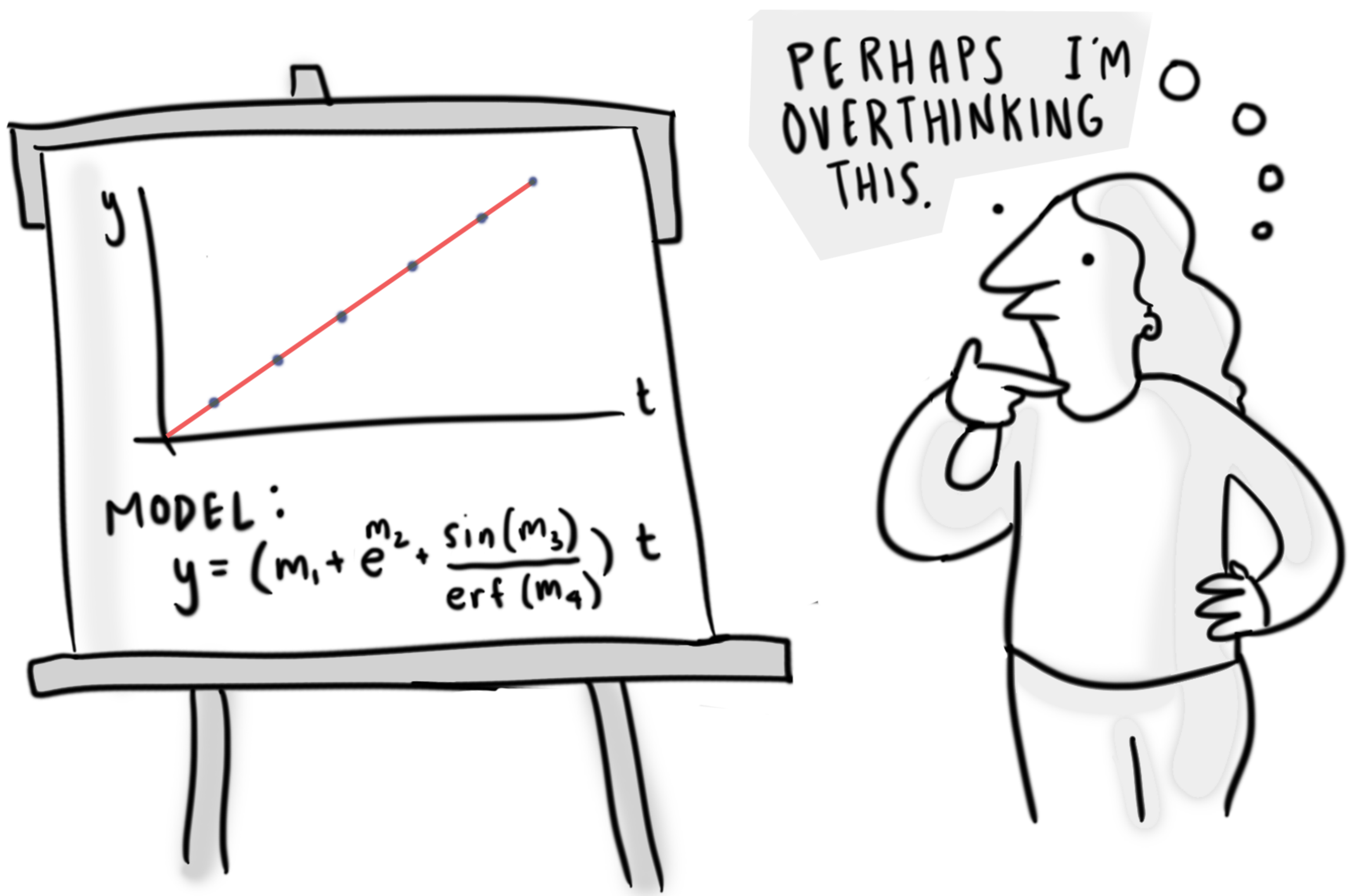
- Many other methods! (eigenvalues of FIM, sloppy models, active subspaces, Bayesian methods, & more)

- 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