

# Introduction to Parameter Identifiability & Uncertainty

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Complex Systems 530

# Logistics Miscellaneous

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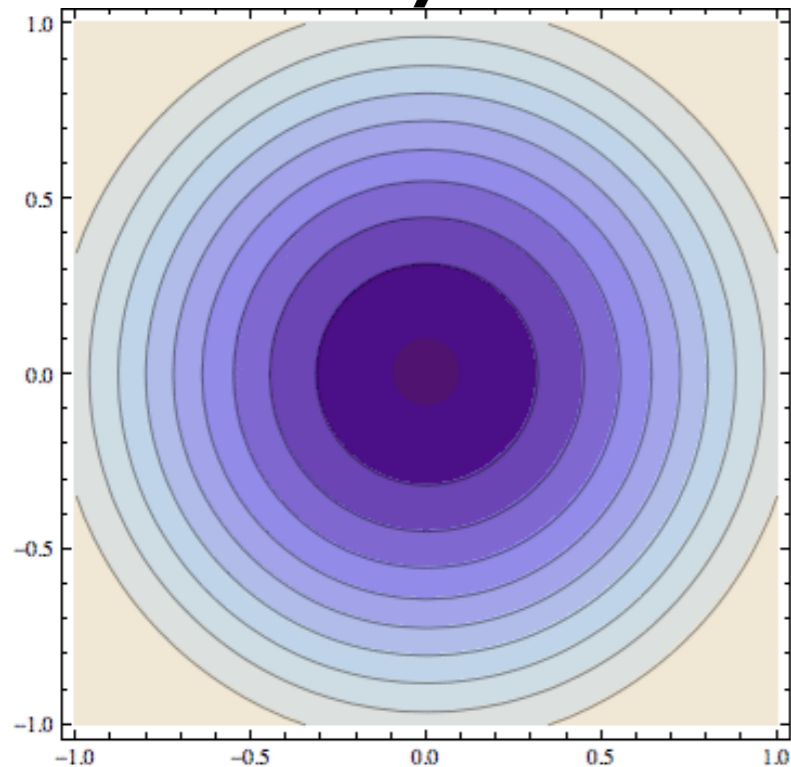
- Labs progress
- Presentations - online/in person
- Guest lecture next Tuesday—class will be all remote!
- Out of town Tuesday the 19th, next Thursday will be the last official class
  - Office hours during finals time

# Parameter Estimation

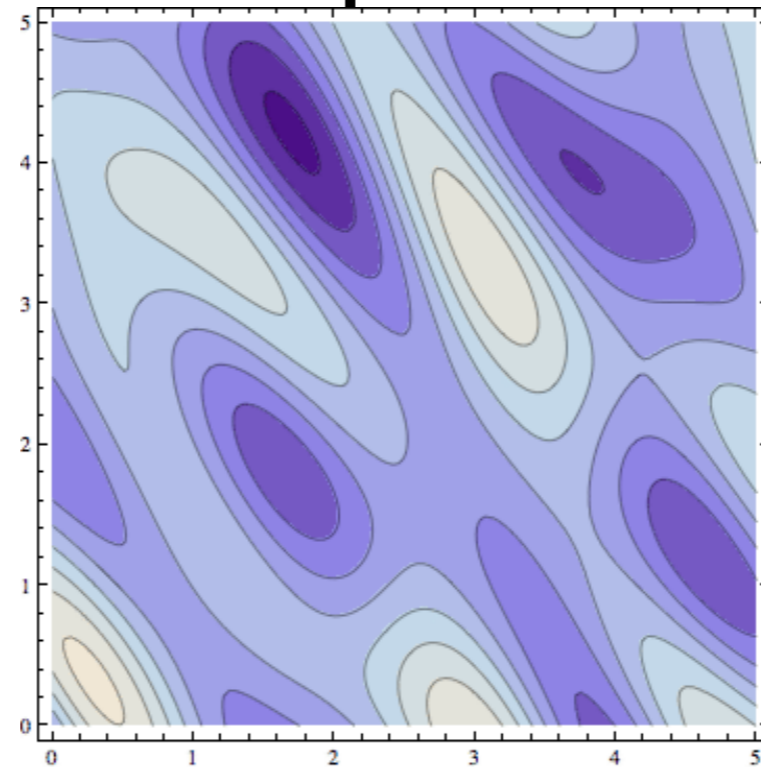
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- In general—search parameter space to find optimal fit to data
- Or to characterize distribution of parameters that matches data

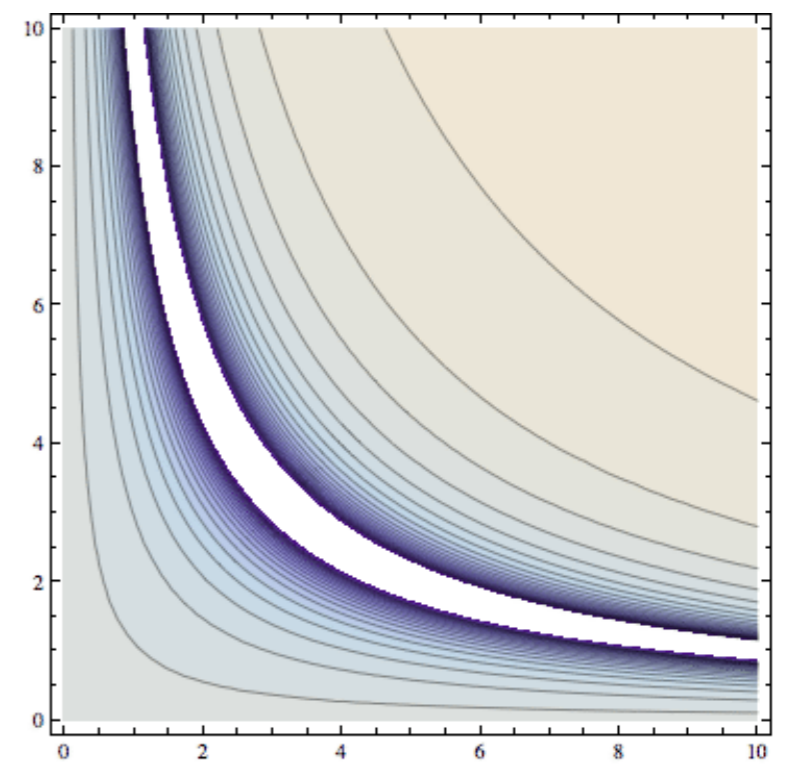
**Yay!**



**Multiple Mins**



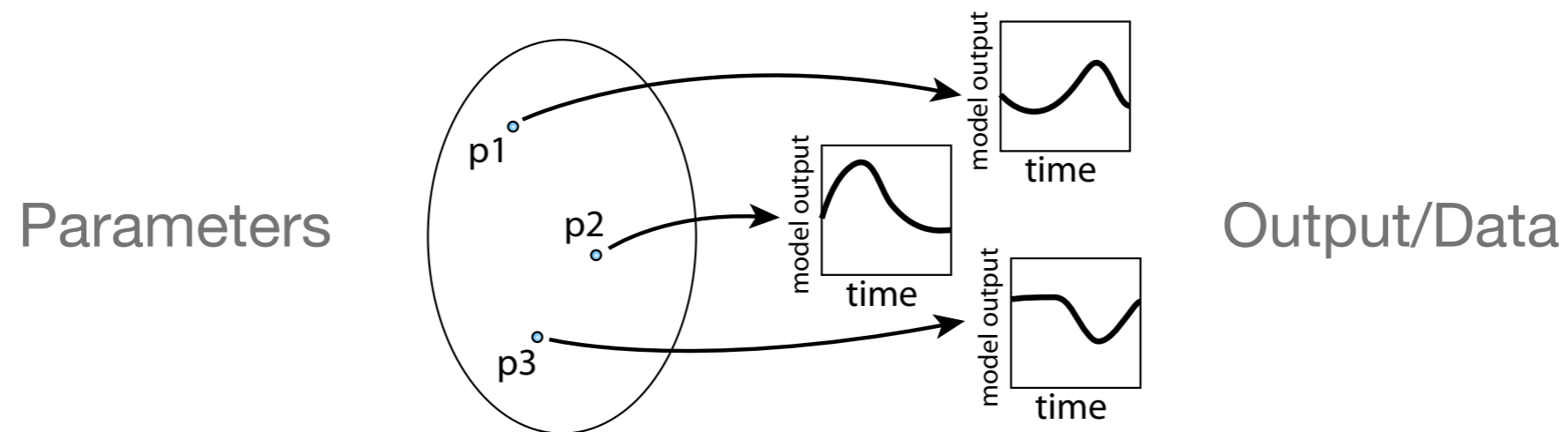
**Struct. UnID**



# Identifiability

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

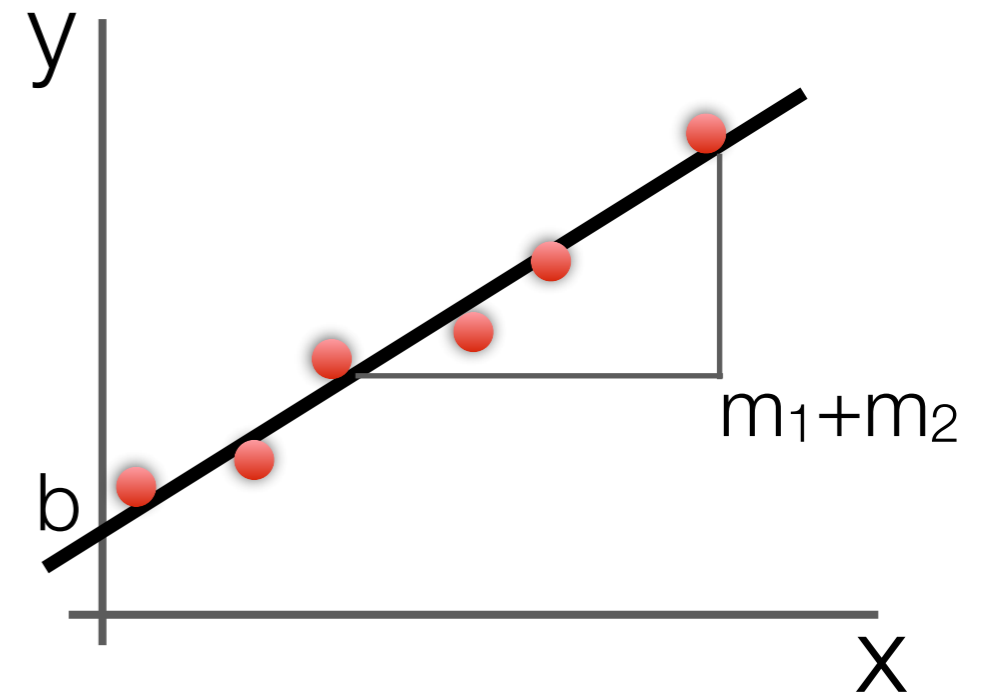


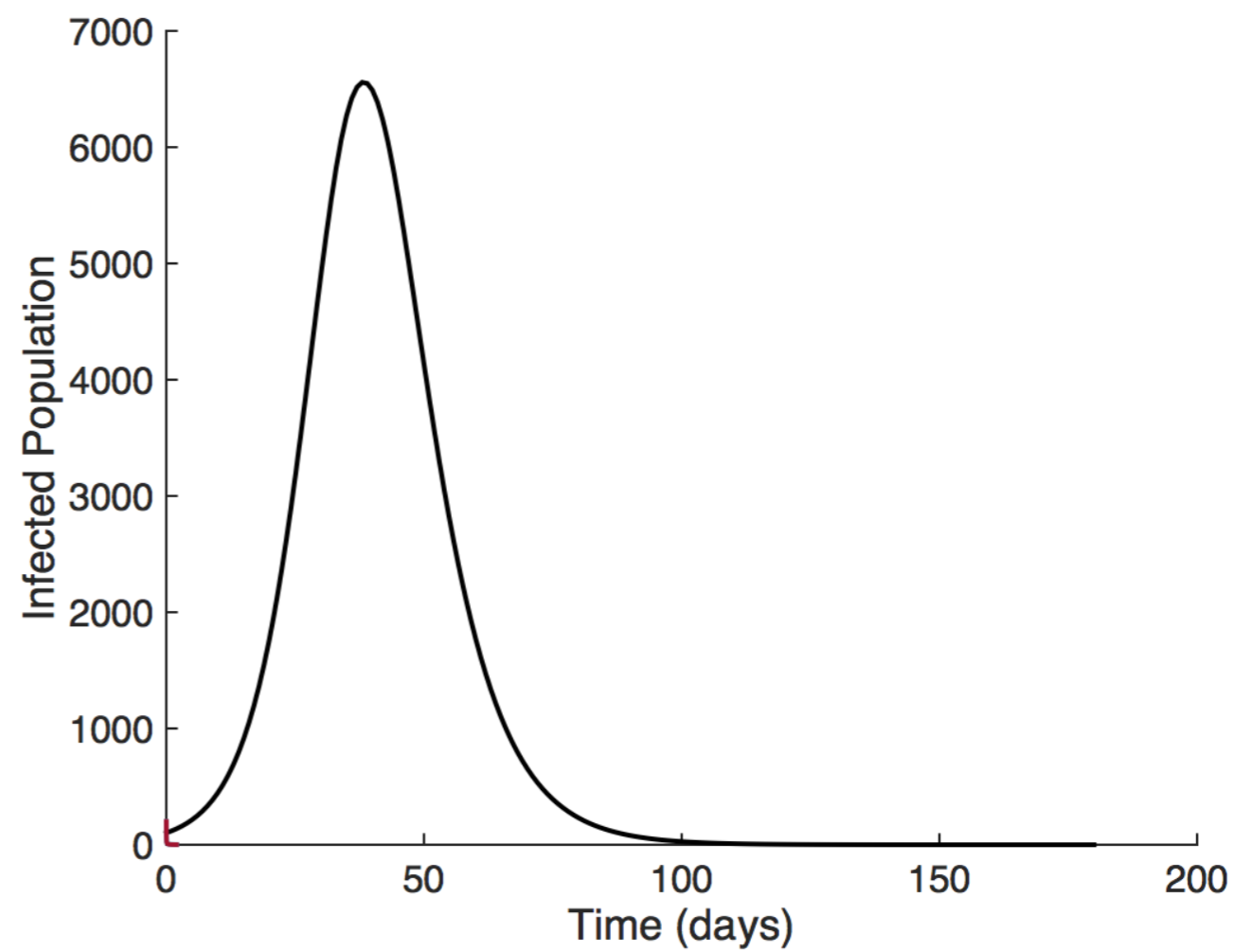
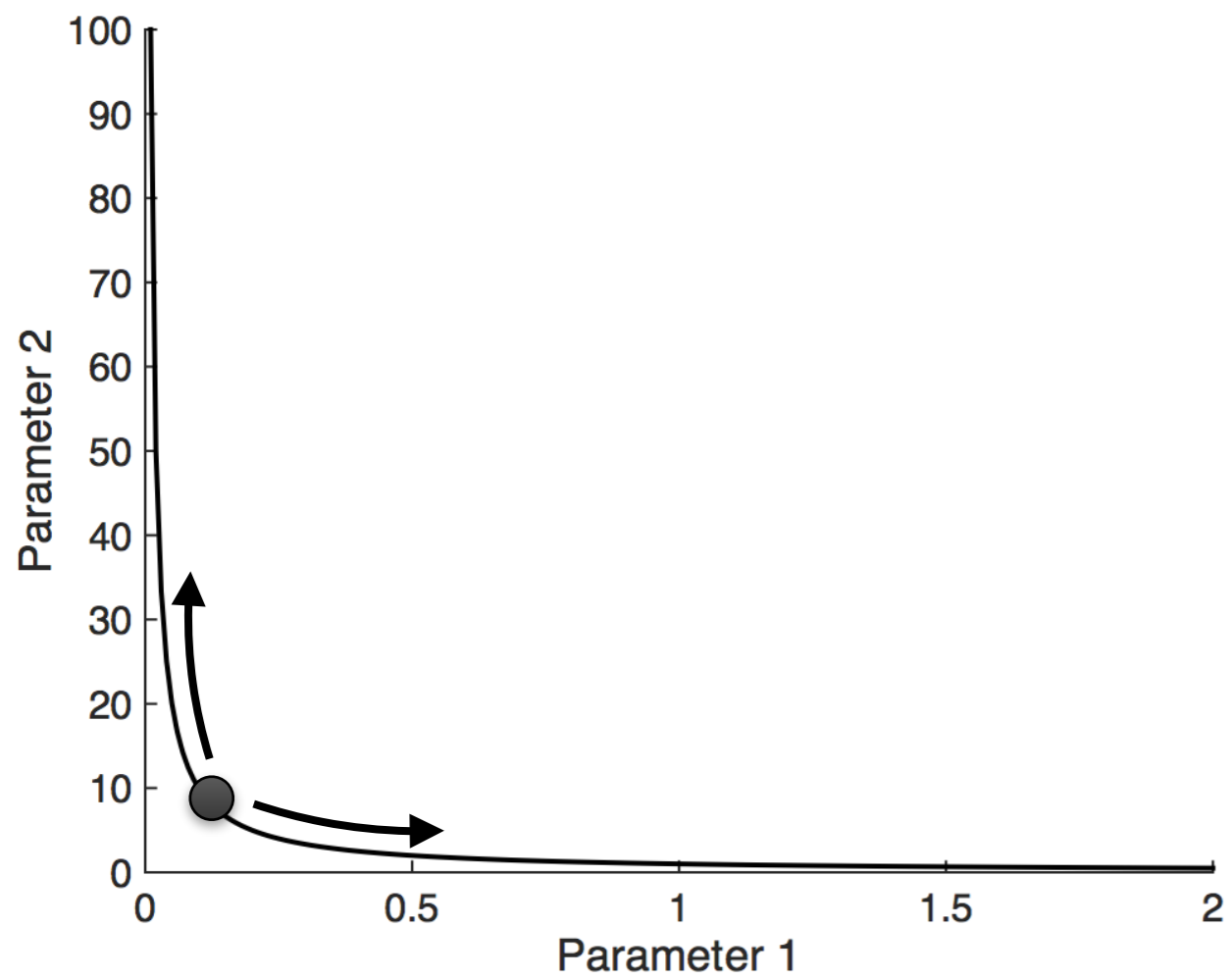
- Important problem in parameter estimation
- Many different approaches - statistics, applied math, engineering/systems theory

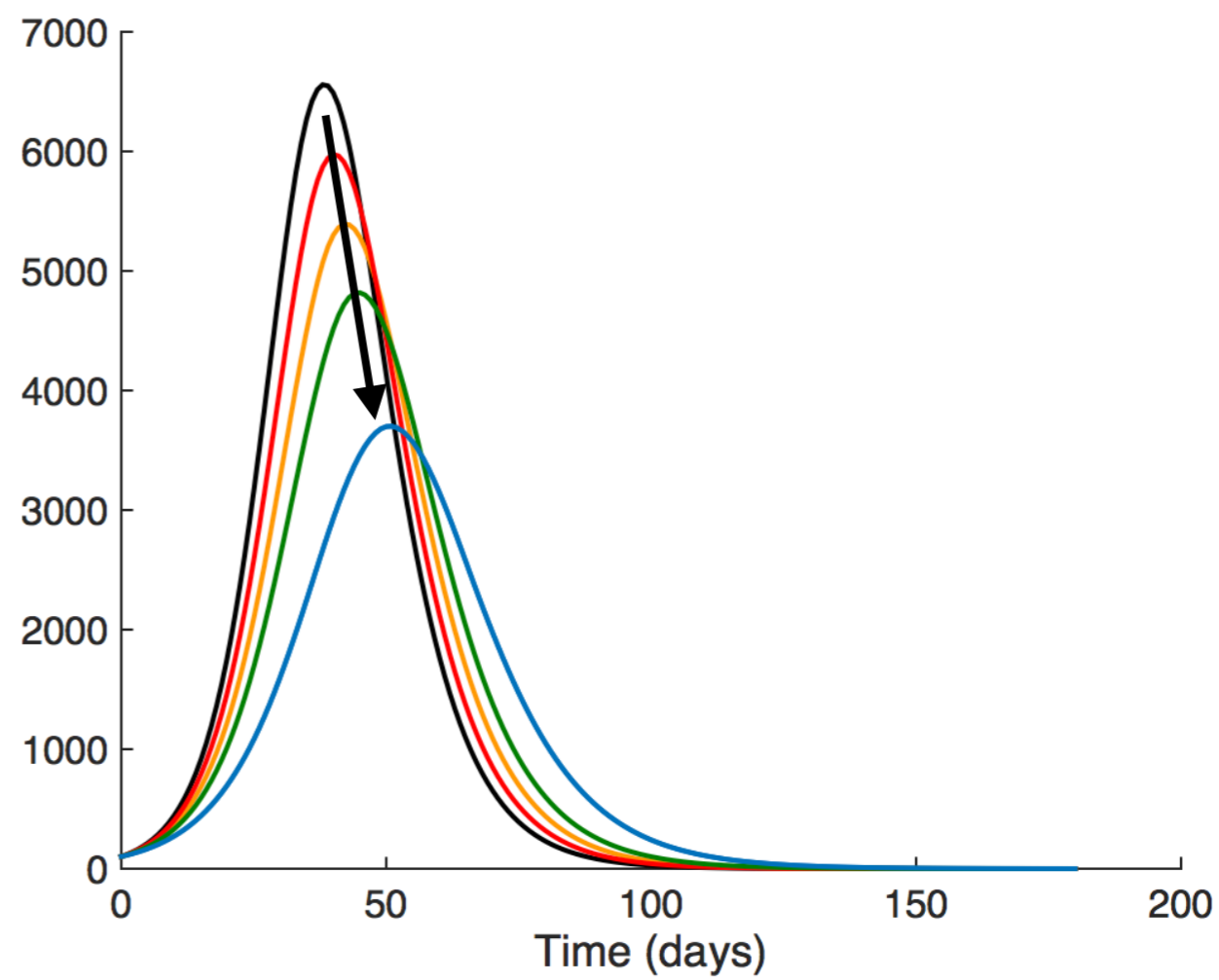
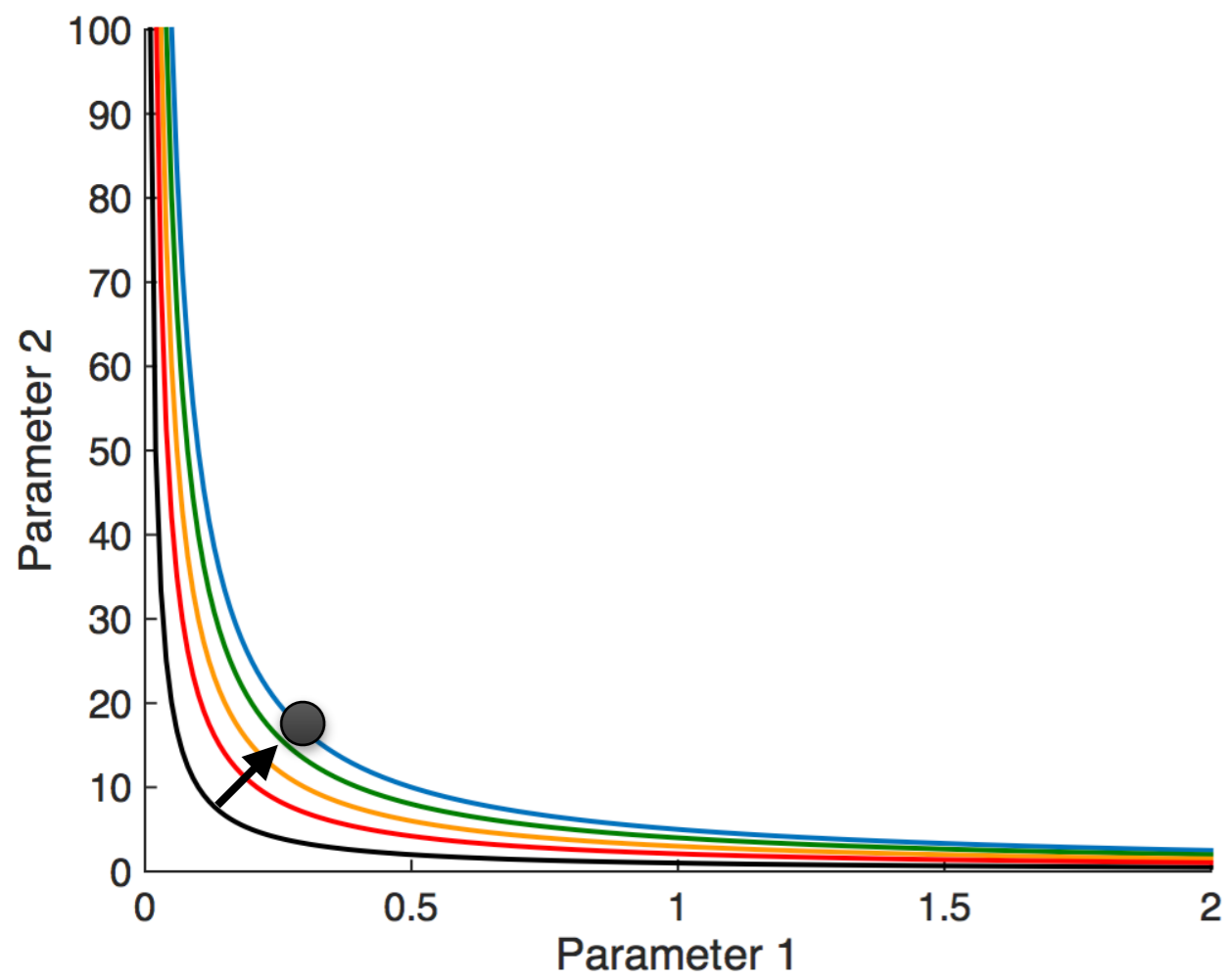
# Identifiability

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- 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







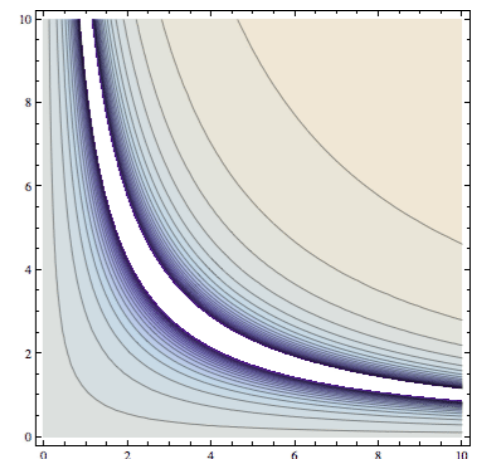
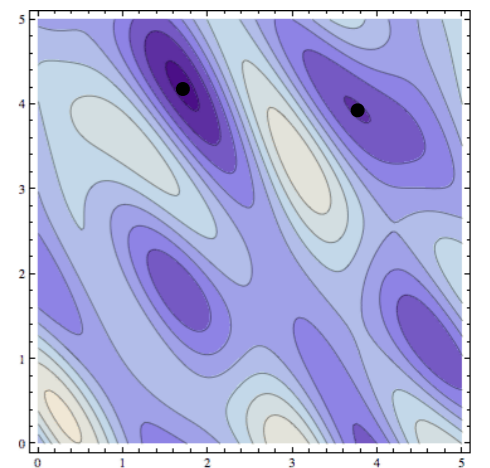
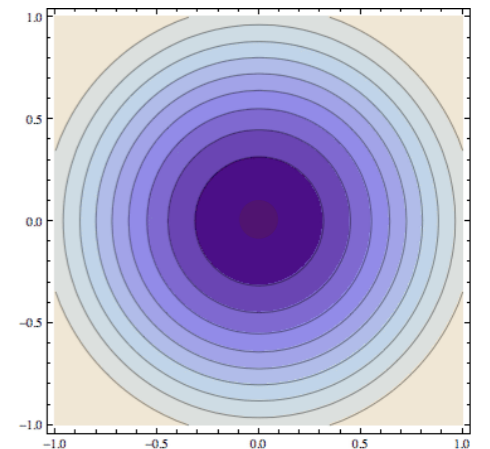
# Structural Identifiability

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- 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

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- 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

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- 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

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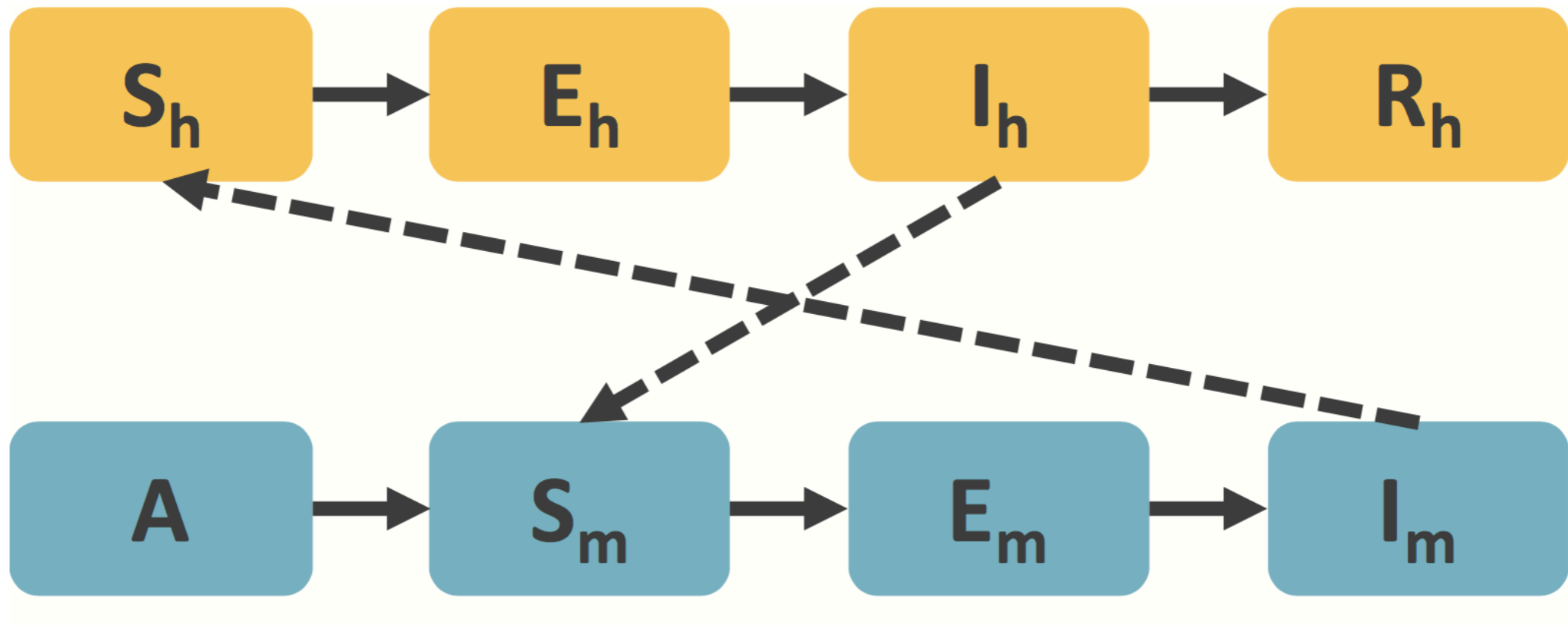
- Structural vs. practical identifiability
- Analytical vs. numerical methods
- Global vs. local results (in parameter space)

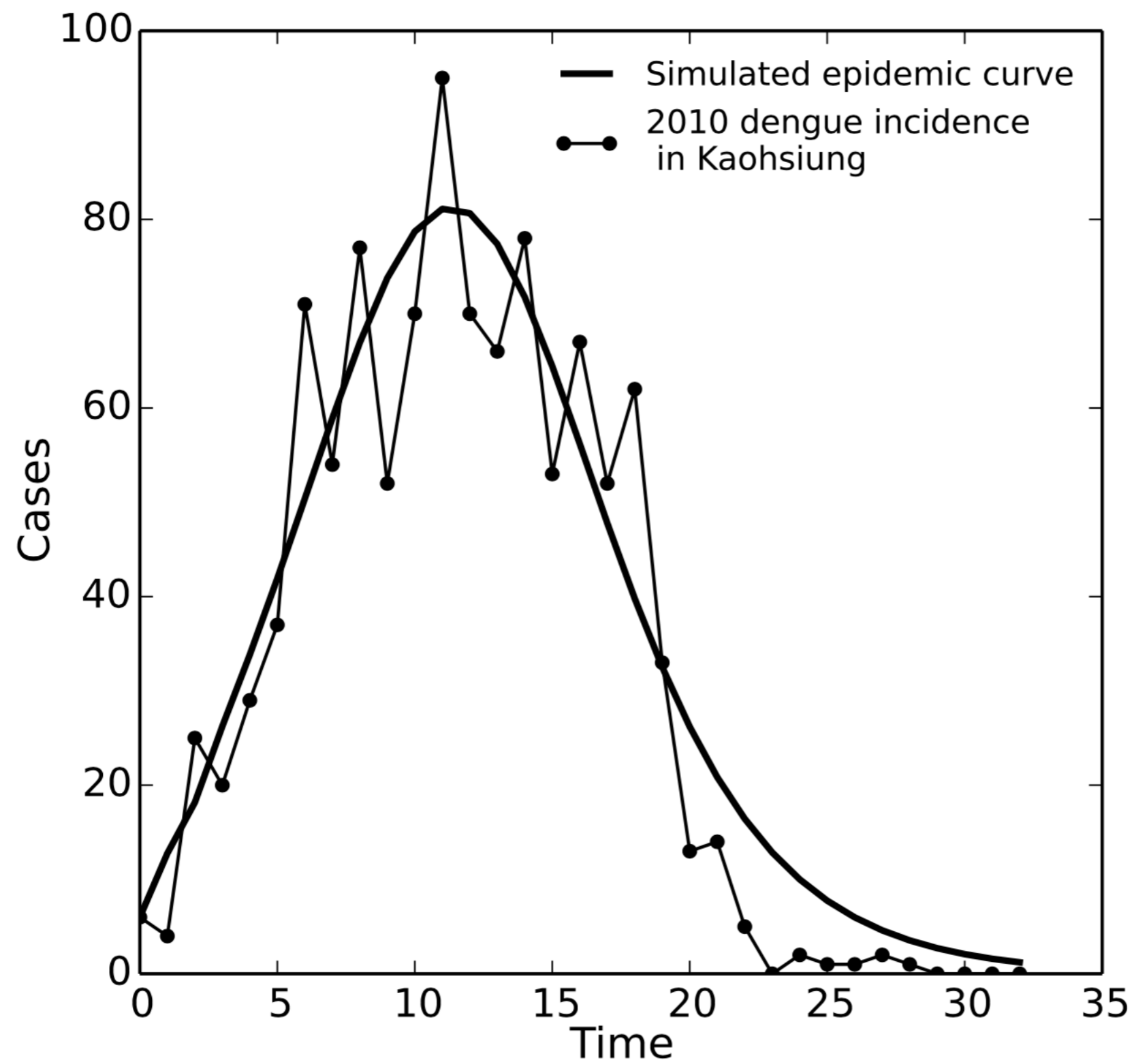
# Key Concepts

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- 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

# Dengue Model Example





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

# Intervention predictions

Fit1:

$$\beta_{mh} = 14.15$$

$$\xi = 2.03$$

$$\beta_{hm} = 0.03$$

$$\mu_a = 4.18$$

$$\mu_m = 0.32$$

$$\kappa_h =$$

$$1546.74$$

Fit2:

$$\beta_{mh} = 38.10$$

$$\xi = 0.13$$

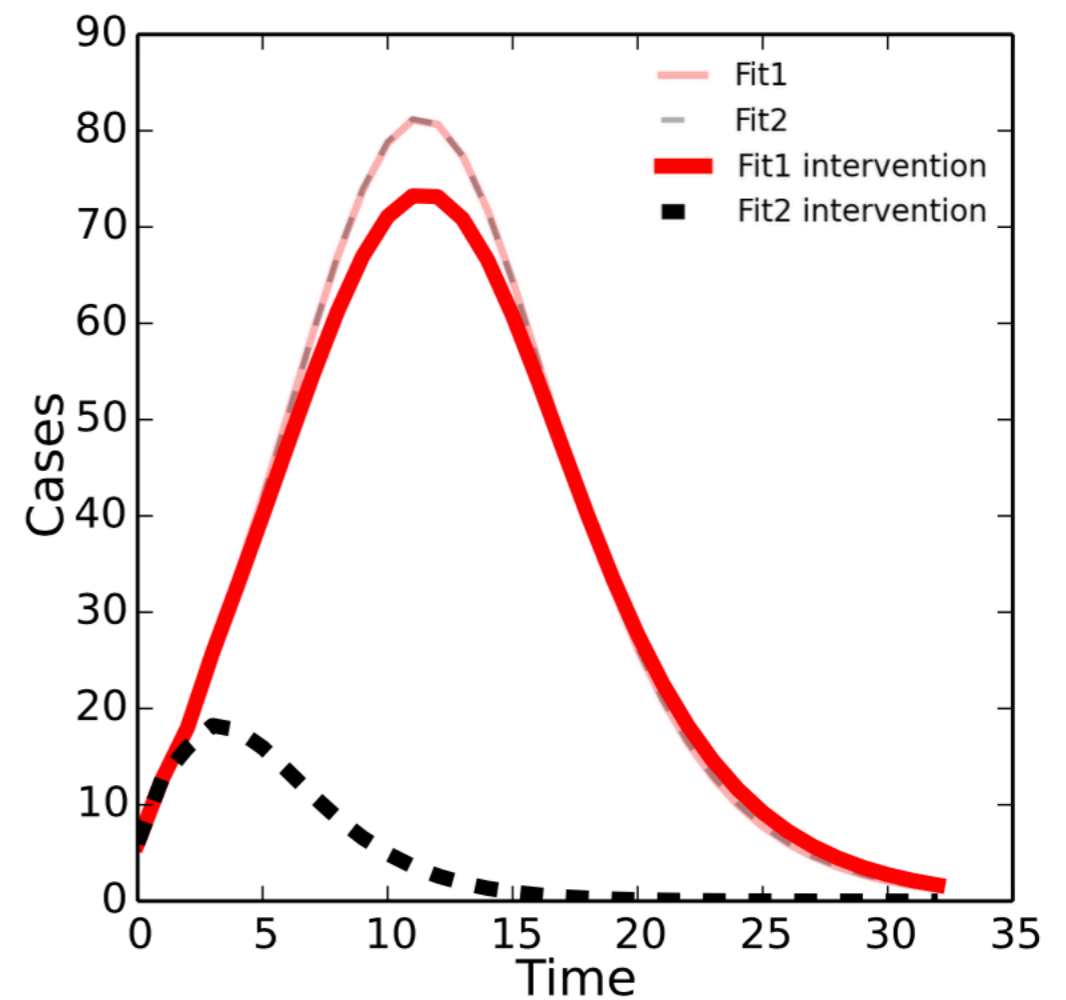
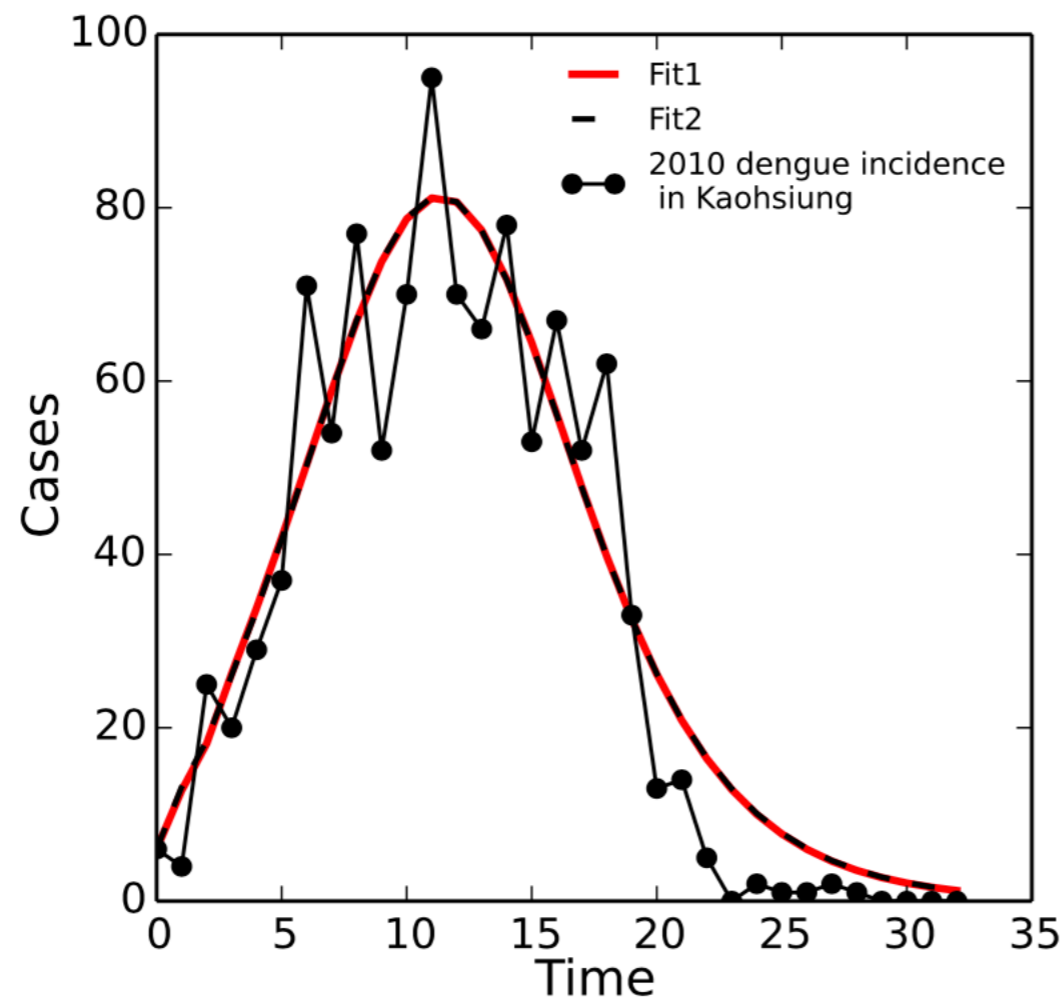
$$\beta_{hm} = 0.02$$

$$\mu_a = 0.15$$

$$\mu_m = 0.42$$

$$\kappa_h =$$

$$1625.42$$



# Methods we'll talk about today

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- 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

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- 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

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- 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

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# Methods for Structural Identifiability

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- **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

# Methods for Structural Identifiability

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- **Laplace transform** - linear models only
- **Taylor series approach** - more broad application, but only local info & may not terminate
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- **Differential algebra approach** - rational function ODE models, global info

# Differential Algebra Approach

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- 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

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- 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

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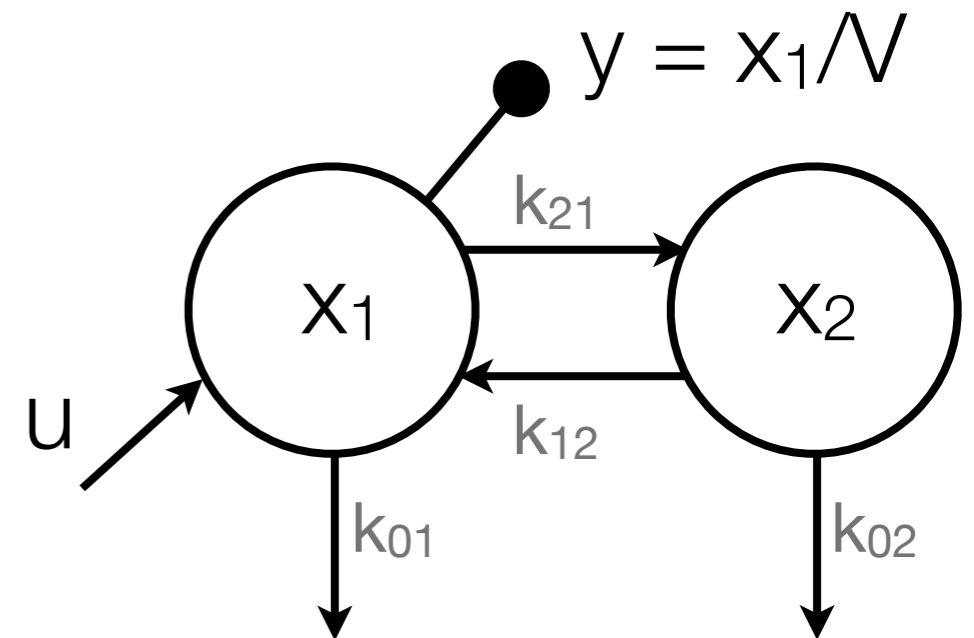
- Linear 2-Comp Model

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

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

$$y = x_1 / V$$

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



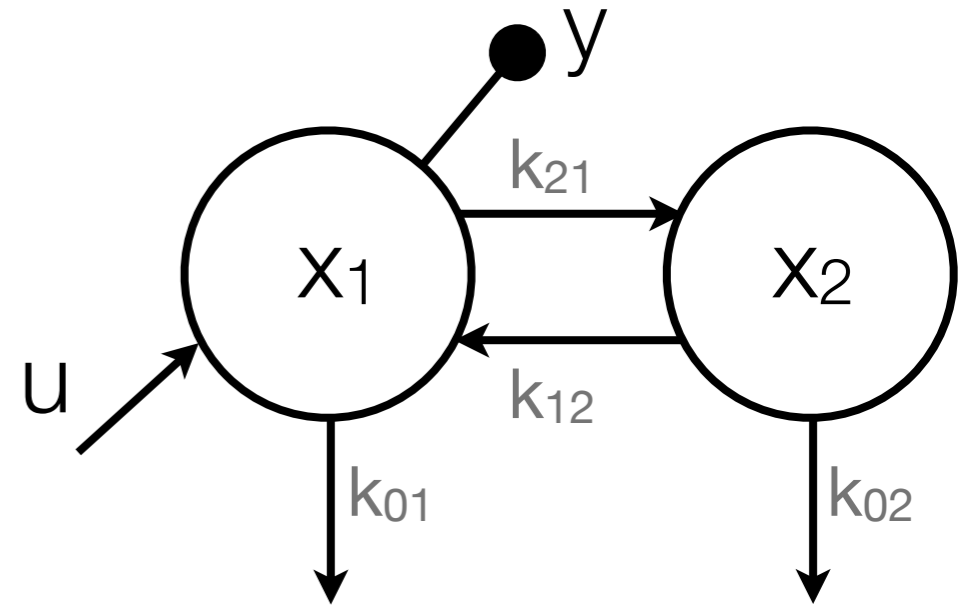
## 2-Compartment Example

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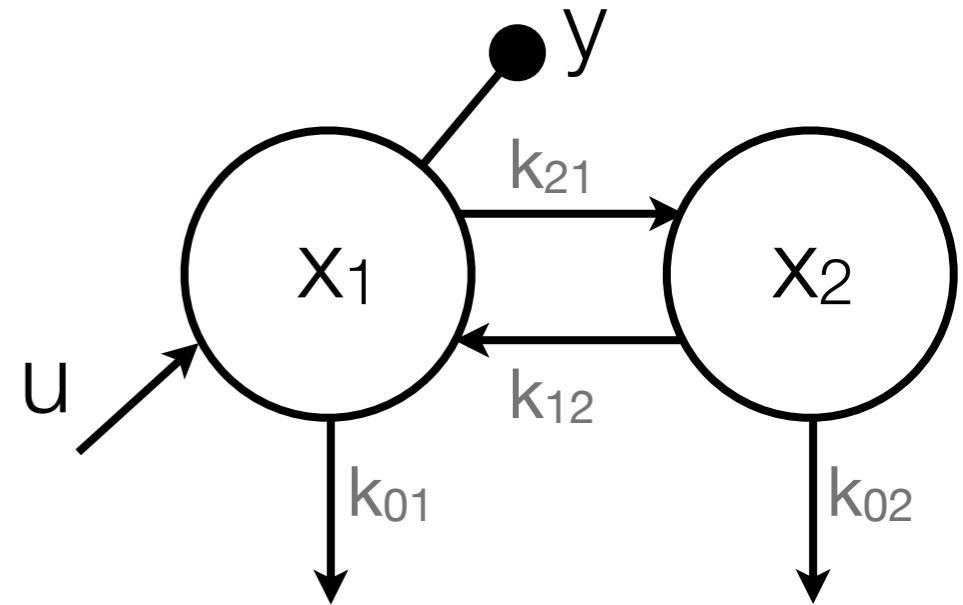


## 2-Compartment Example

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

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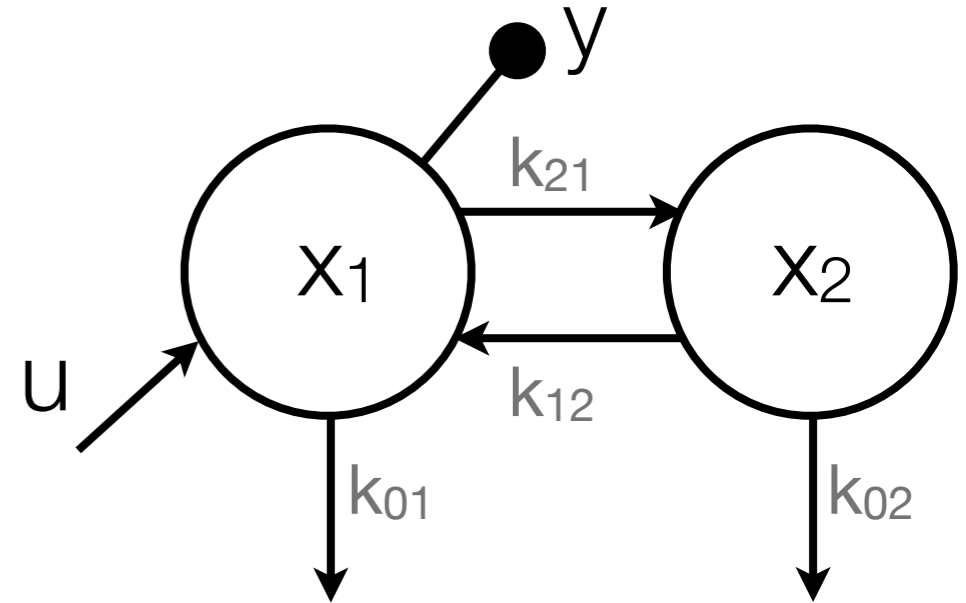


## 2-Compartment Example

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

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

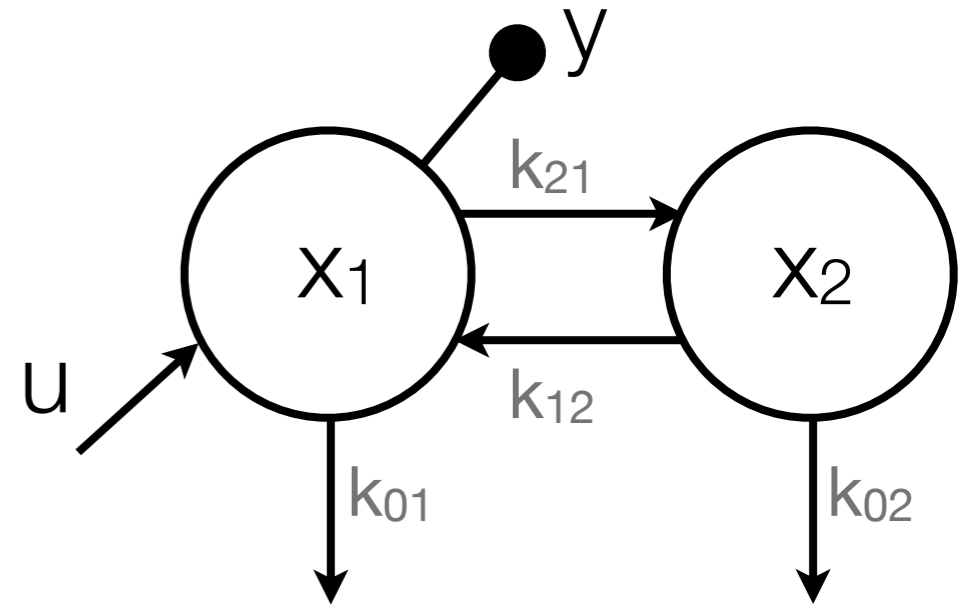


## 2-Compartment Example

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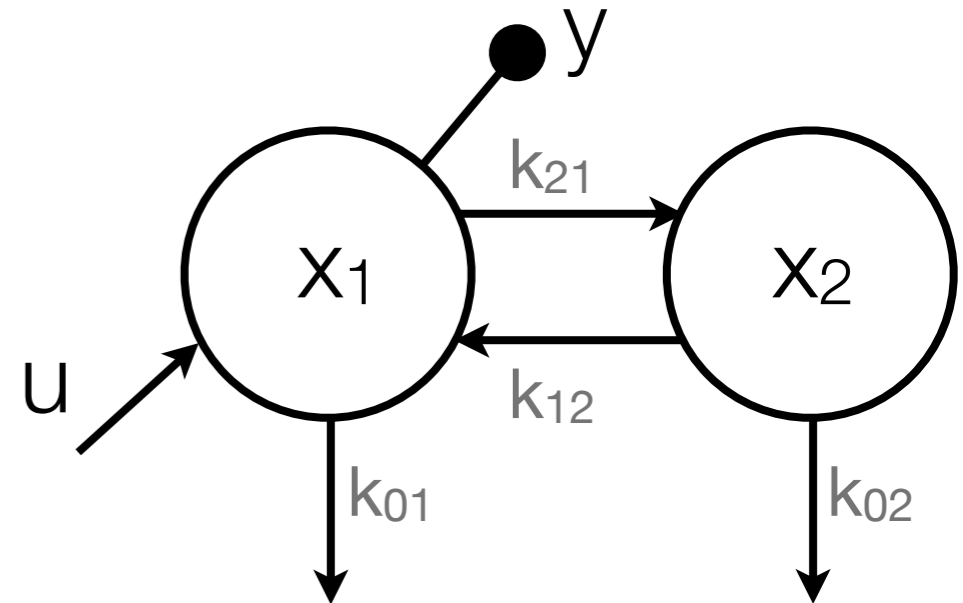
$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}u, \quad y = \mathbf{C}\mathbf{x}$$

$$\mathbf{A} = \begin{bmatrix} -k_{12} - k_{01} & k_{21} \\ k_{12} & -k_{21} - k_{02} \end{bmatrix}, \quad \mathbf{B} = \begin{bmatrix} k_{01} \\ 0 \end{bmatrix}, \quad \mathbf{C} = \begin{bmatrix} 1 & 0 \end{bmatrix}$$



## 2-Compartment Example

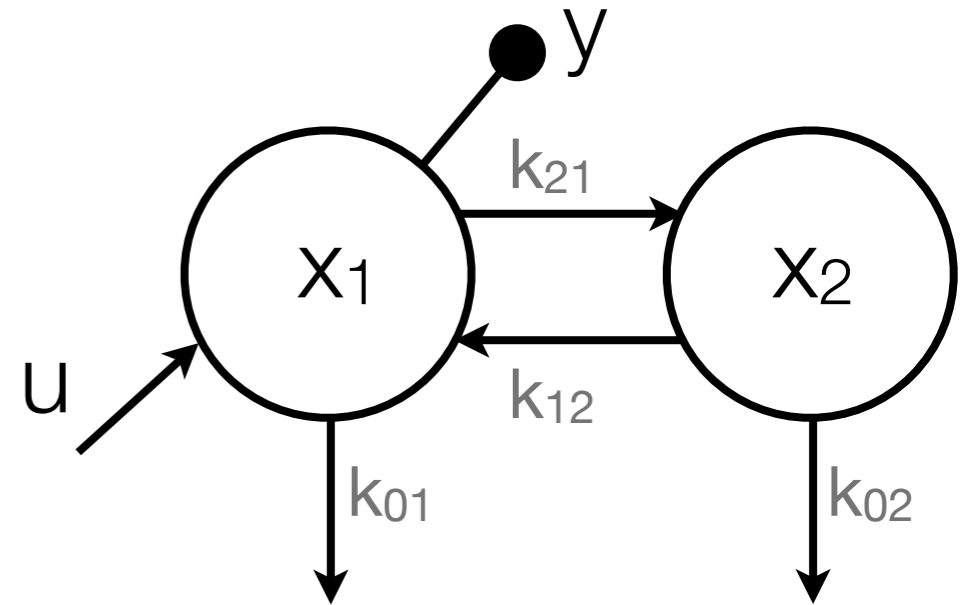
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$$\ddot{y} + (k_{01} + k_{21} + k_{12} + k_{02})\dot{y} -$$
$$(k_{12}k_{21} - (k_{02} + k_{12})(k_{01} + k_{21}))y - u(k_{12} + k_{02})/V - \dot{u}/V = 0$$

## 2-Compartment Example

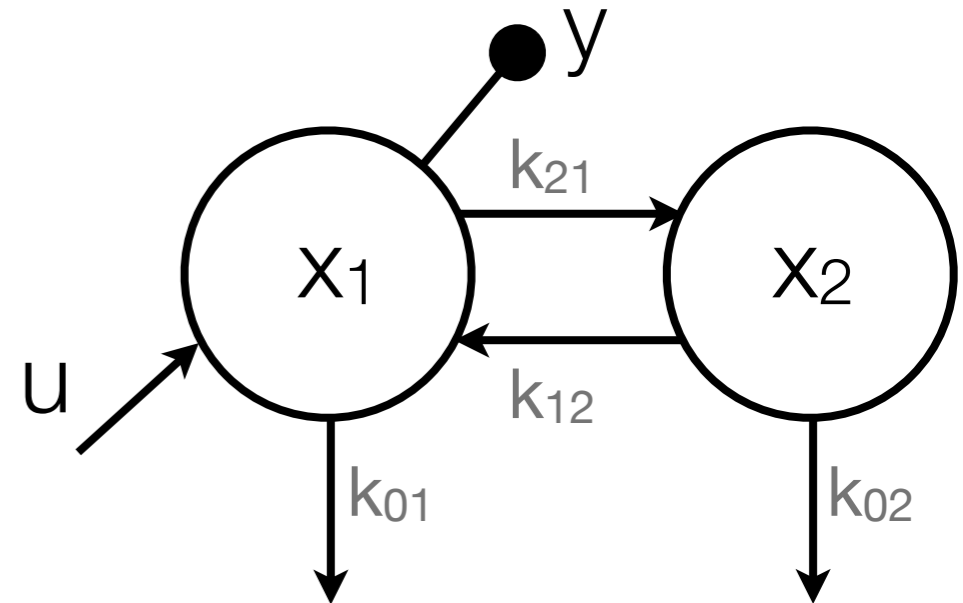
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# 2-Compartment Example

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

$$(k_{01} + k_{21} + k_{12} + k_{02})$$

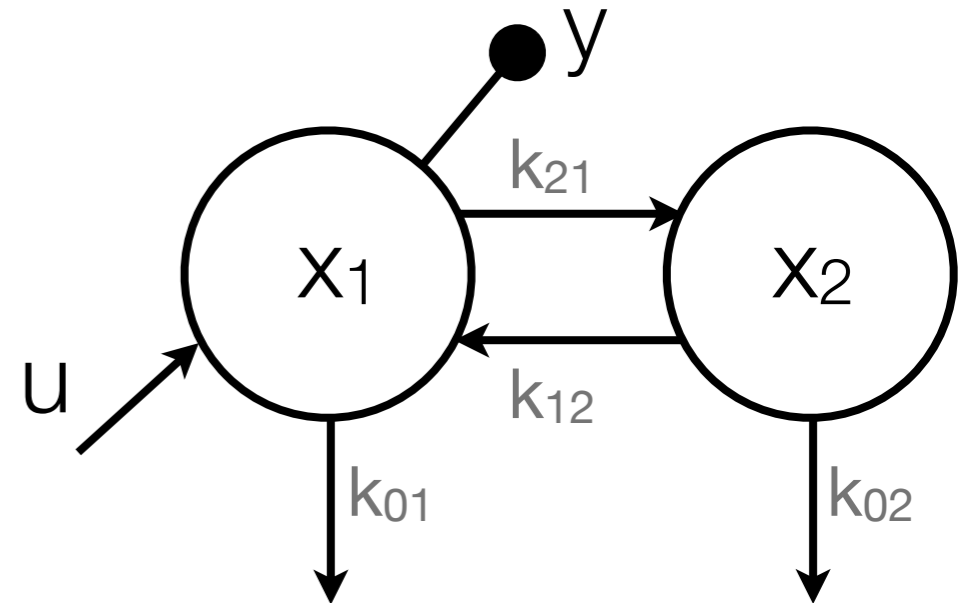
$$(k_{12} + k_{02})/V$$

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

$$1/V$$

# 2-Compartment Example

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$$(k_{01} + k_{21} + k_{12} + k_{02})$$

$$(k_{12} + k_{02}) / V$$

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

$$1 / V$$

# 2-Compartment Example

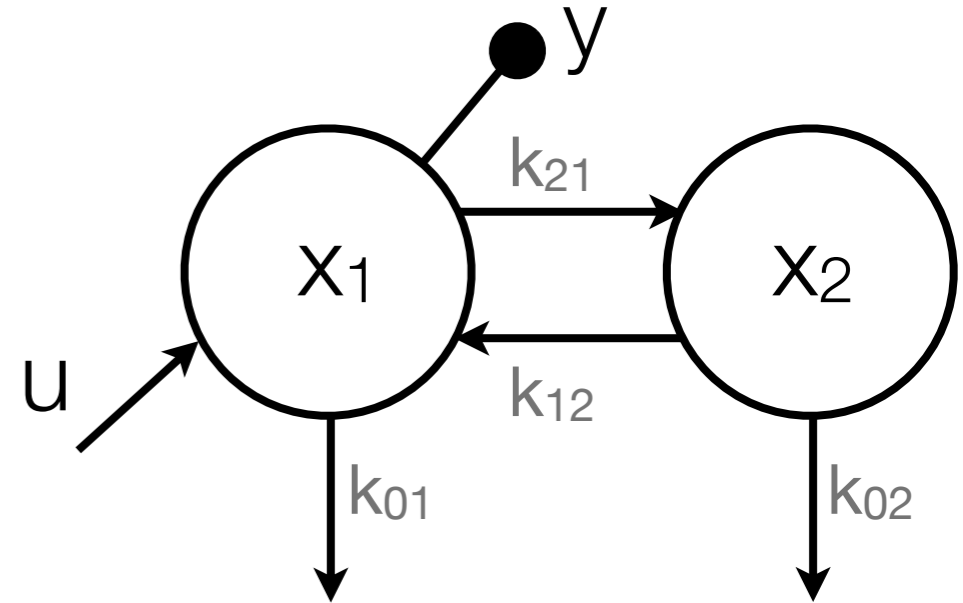
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$$1 / V$$

$$(k_{12} + k_{02}) / V$$

$$(k_{01} + k_{21} + k_{12} + k_{02})$$

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



# 2-Compartment Example

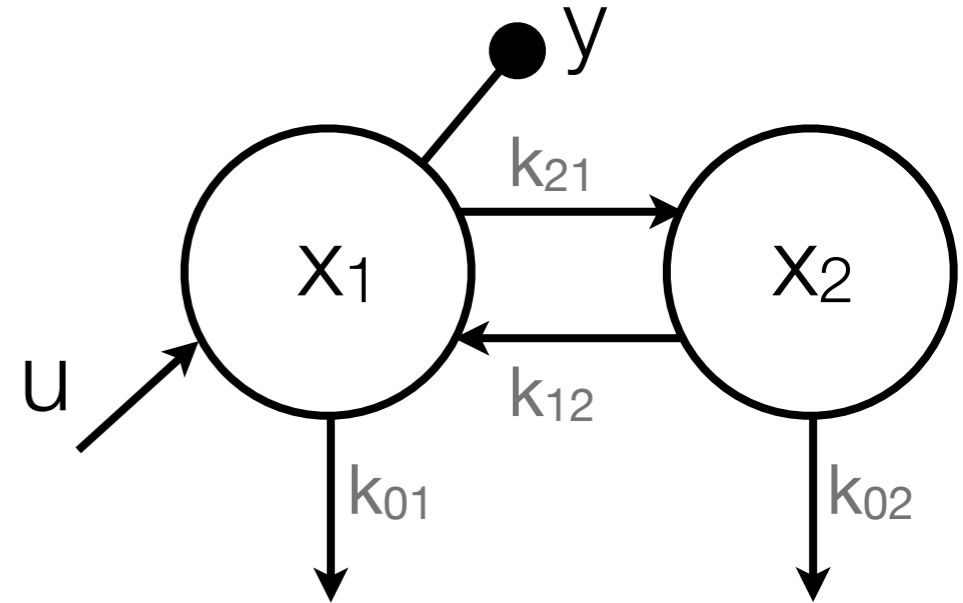
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$$1 / V = a_1$$

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

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

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



# 2-Compartment Example

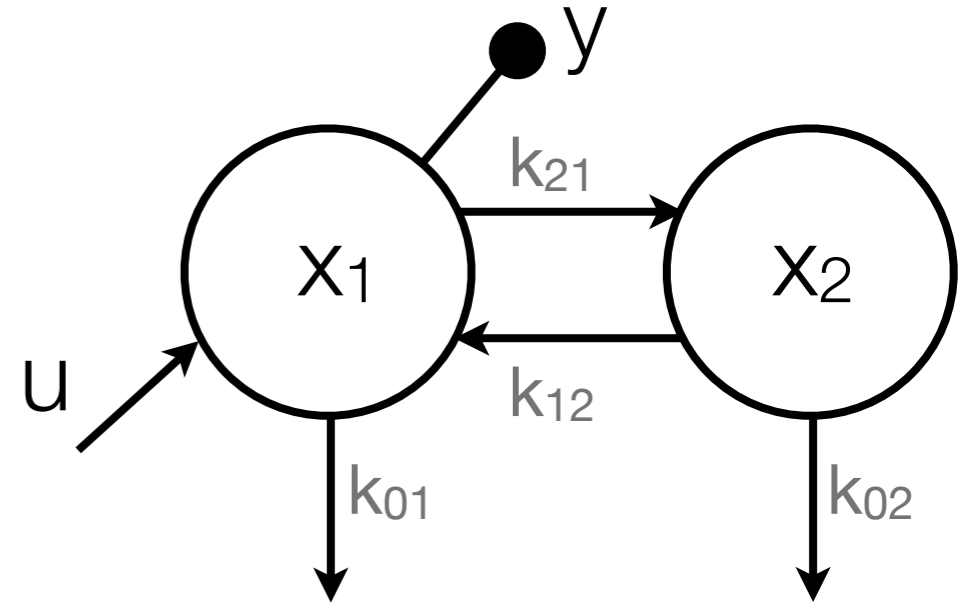
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$$1/V = a_1 \Rightarrow V = 1/a_1$$

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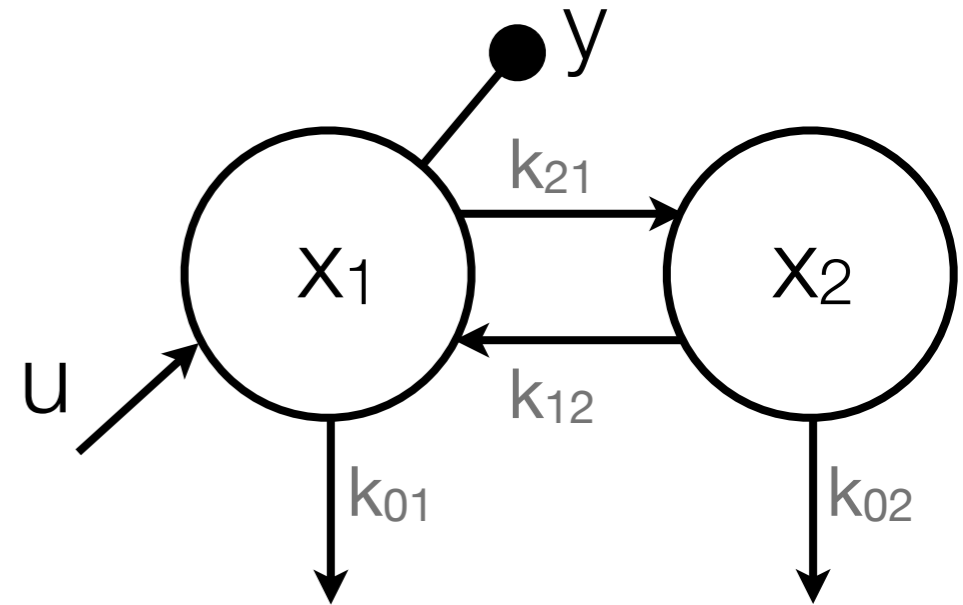
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Unidentifiable

# 2-Compartment Example

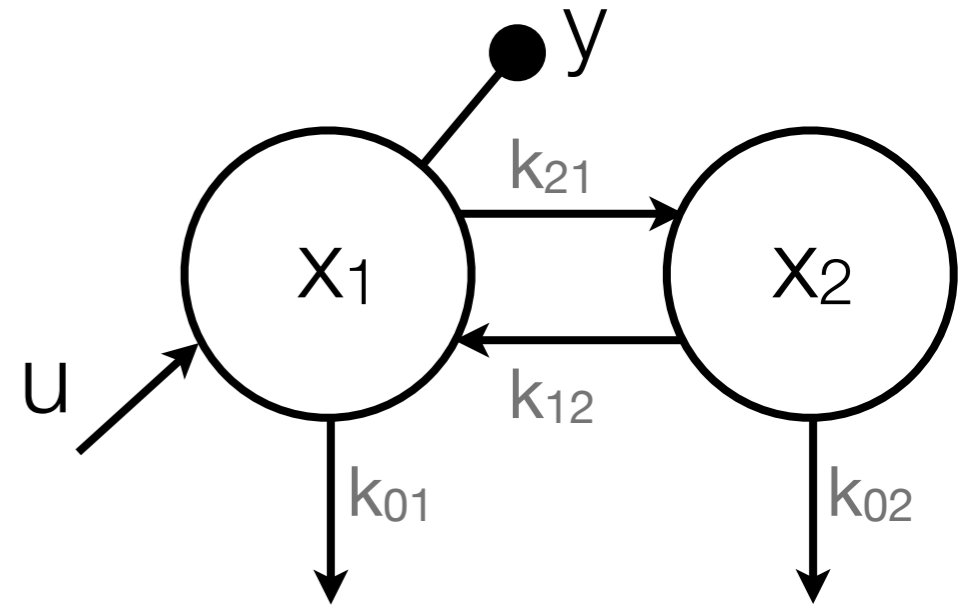
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Unidentifiable

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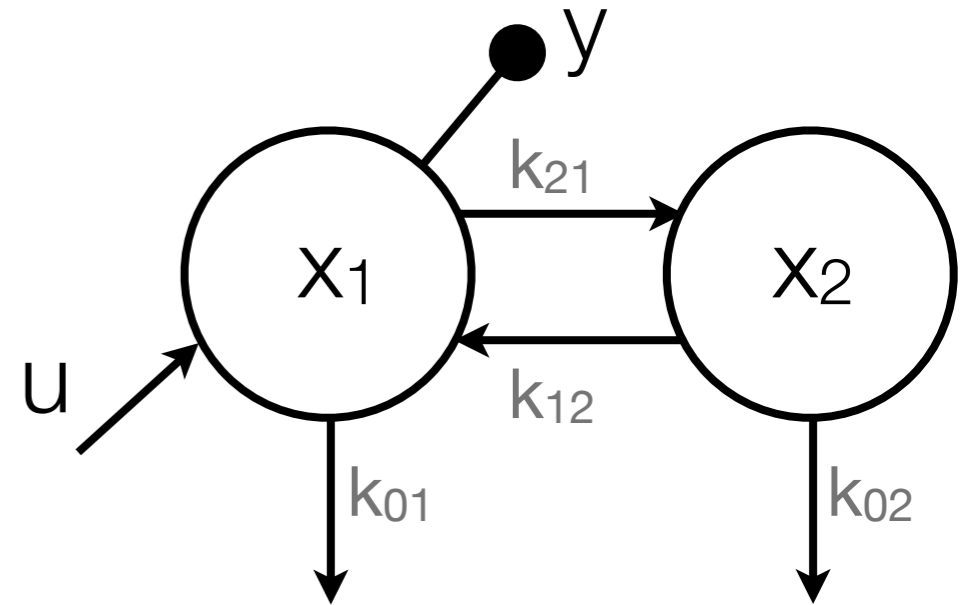
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Unidentifiable

# 2-Compartment Example

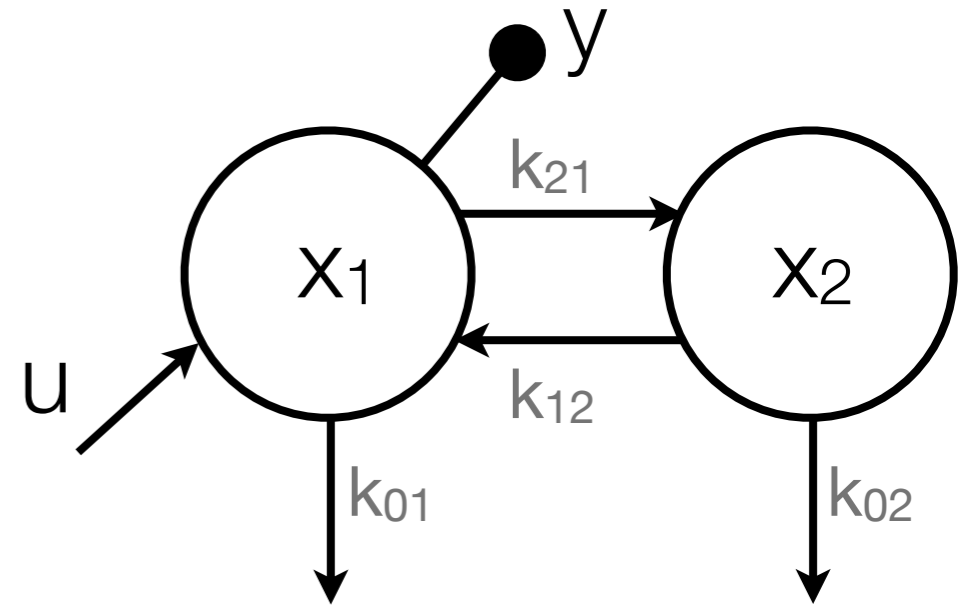
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Unidentifiable

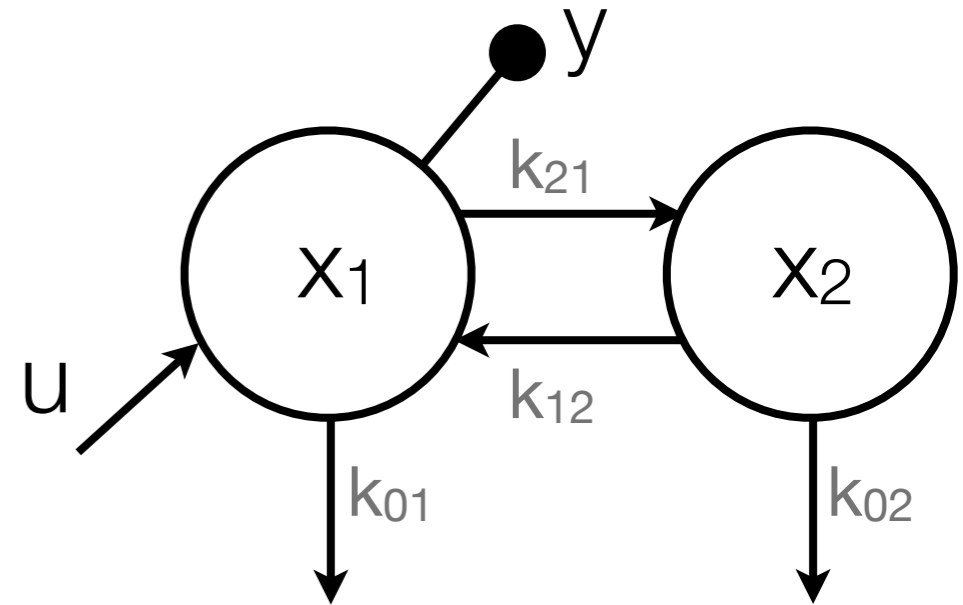
## 2-Compartment Example

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

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

$$y = x_1 / V$$



## 2-Compartment Example

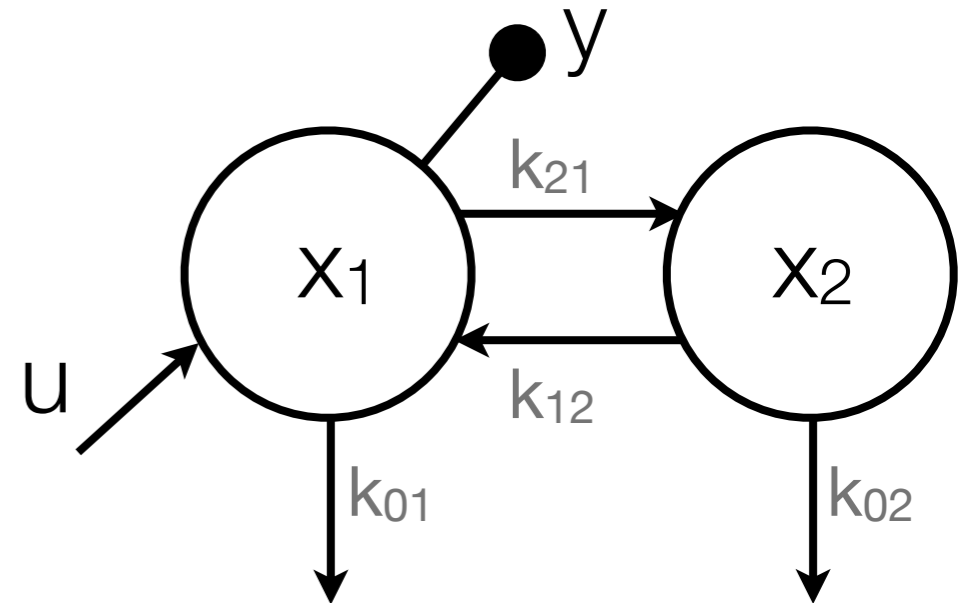
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$$\dot{x}_1 = u + \underline{k_{12}}x_2 - (\underline{k_{01}} + k_{21})x_1$$

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

$$y = x_1 / \underline{V}$$

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



## 2-Compartment Example

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

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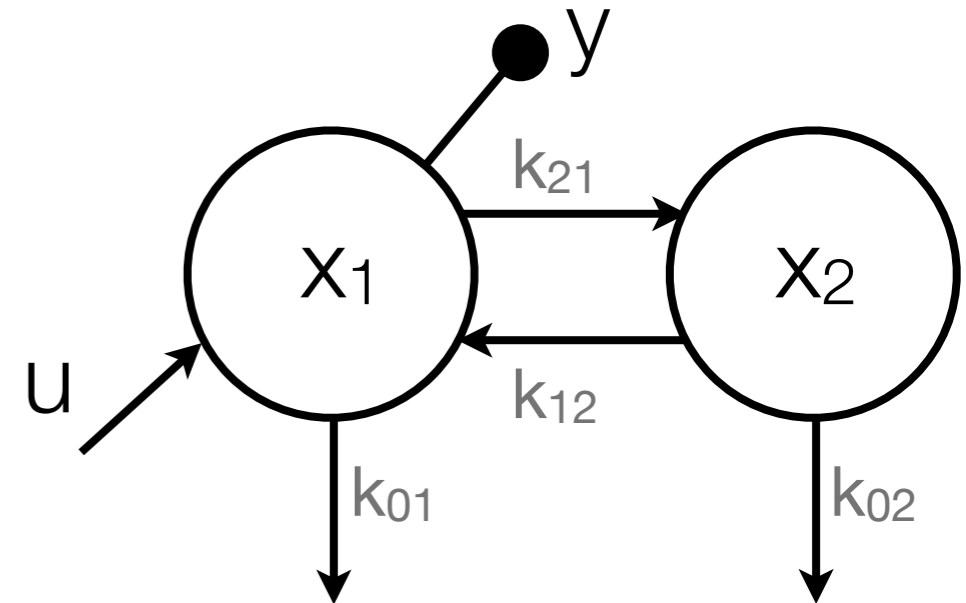
$$y = x_1 / \underline{V}$$

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

$$\dot{x}_1 = u + \underline{x}_2 - (\underline{k_{01}} + k_{21})x_1$$

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

$$y = x_1 / \underline{V}$$



Or add information  
about one of  
the parameters

# Reparameterization

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- 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

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- 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

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- 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

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- 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)
- Particularly useful as a way to prove identifiability results for broad classes of models

# Numerical Methods for Identifiability Analysis

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# Numerical Approaches to Identifiability

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- 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

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

# Simple Simulation Approach

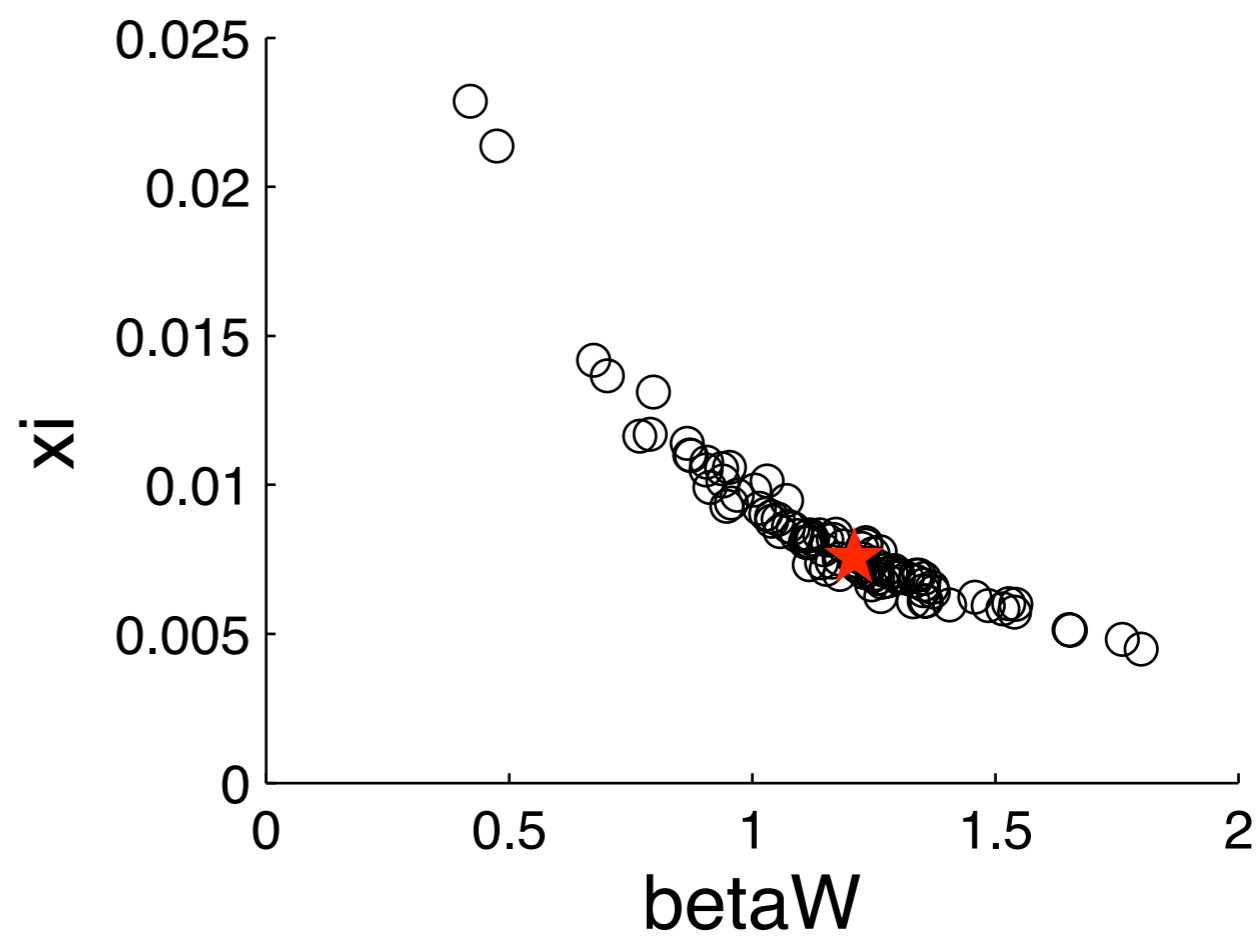
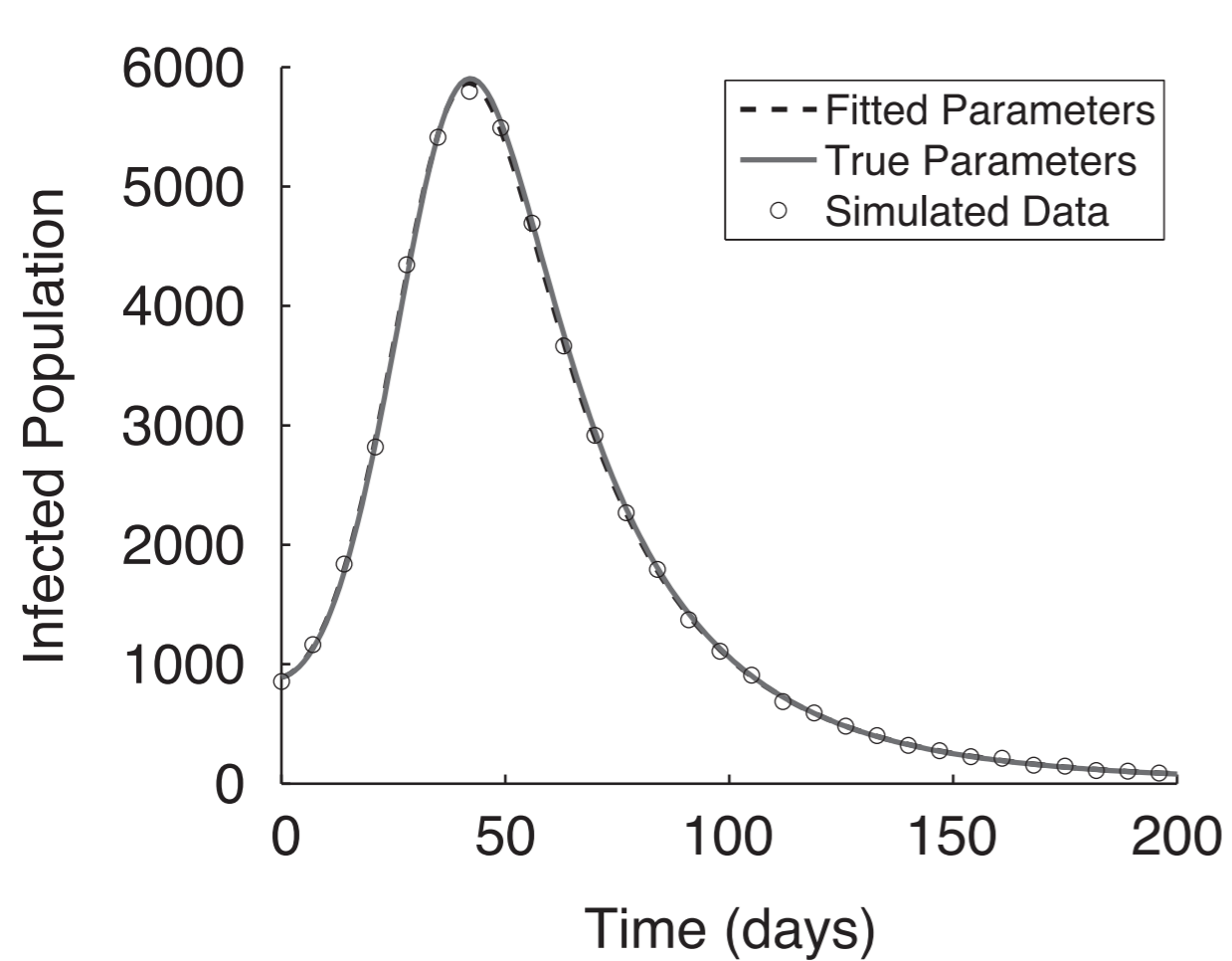
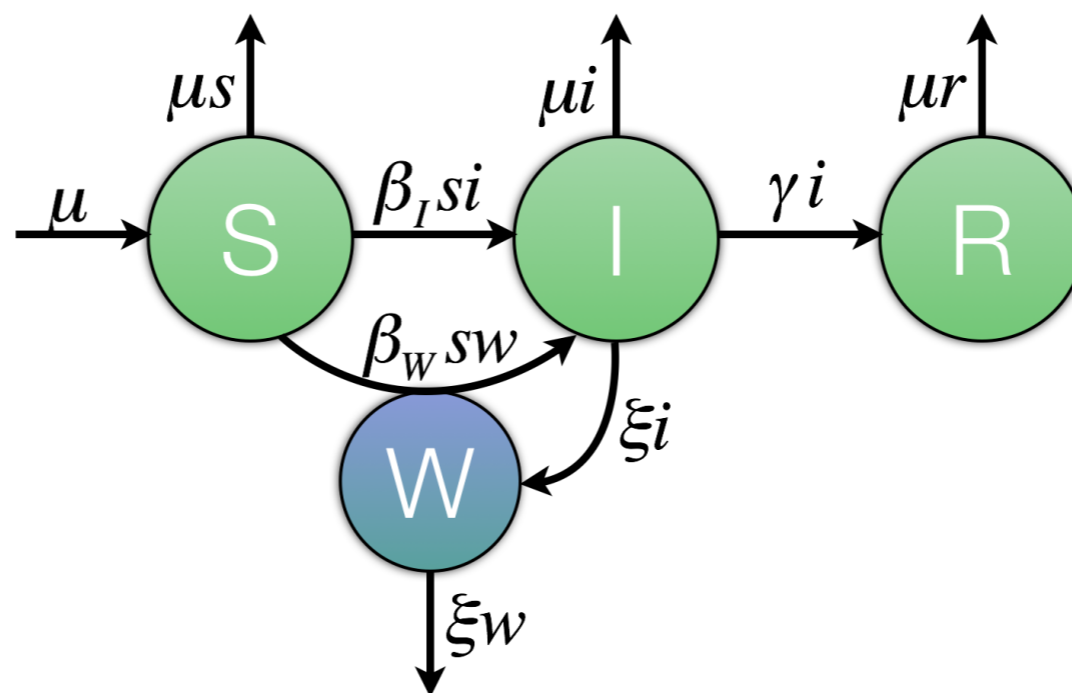
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- Simulate data using a single set of 'true' parameter values
- Without noise for structural identifiability
- With noise for practical identifiability (in this case generate multiple realizations of the data)

# Simple Simulation Approach

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- 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



# Parameter Sensitivities

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

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

# Fisher Information Matrix

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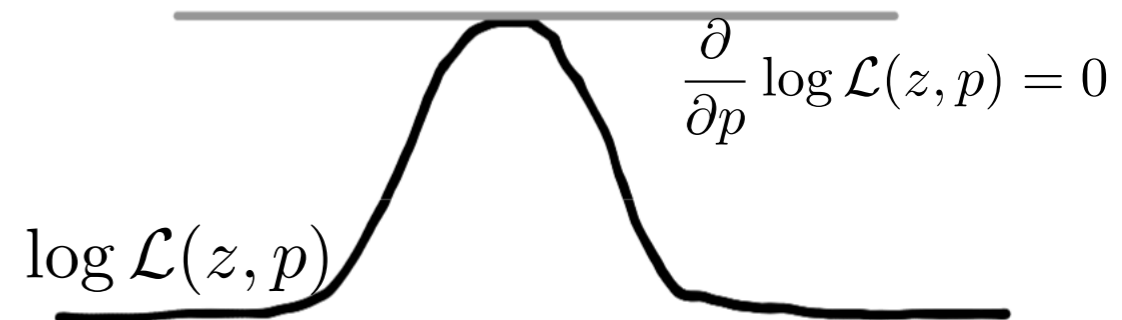
- Useful in testing practical & structural ID - represents amount of information that the output  $y$  contains about parameters  $p$
- Relates to sensitivities via the score:  $\frac{\partial}{\partial p} \log \mathcal{L}(z, p)$ 
  - Sensitivity of the log likelihood
  - Gives us a sense of how the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

# Fisher Information Matrix

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

- The variance of the score is the Fisher information:



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

- Why the variance?

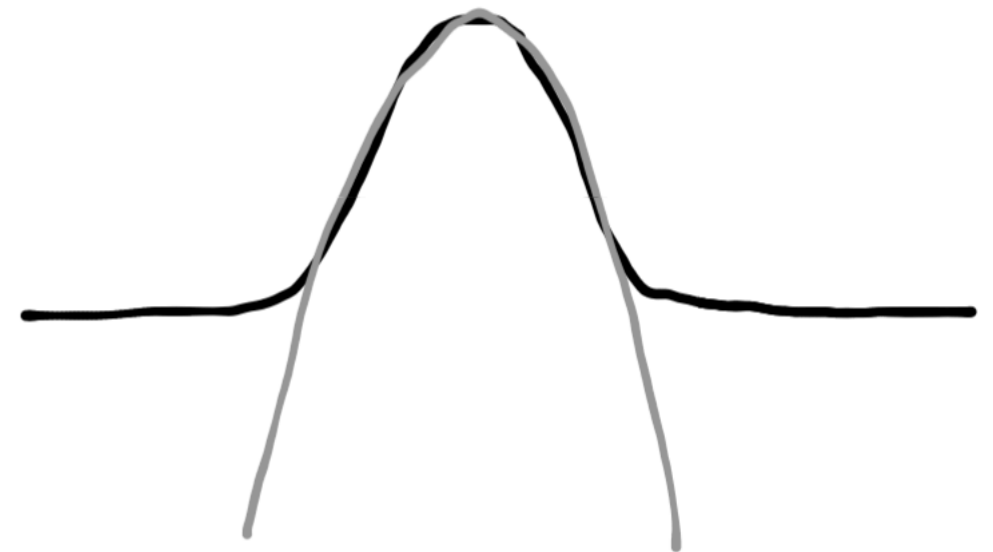
# Fisher information matrix

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- In matrix form:

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

- FIM -  $N_P \times N_P$  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

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

# Fisher Information Matrix

---

- For looking at structural ID, often just use

$$F = X^T X$$

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

# Fisher information matrix

---

- **Cramer-Rao Bound:**  $\text{FIM}^{-1} \leq \text{Cov}(p)$
- Diagonal of the covariance matrix gives variances for the parameters (use to calculate confidence intervals)
- $\text{Rank}(\text{FIM}) = \text{number of identifiable parameters/ combinations}$

# Identifiability & the FIM

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- Covariance matrix/confidence interval estimates from Cramér-Rao bound:  $\text{Cov} \geq \text{FIM}^{-1}$
- e.g. large confidence interval  $\Rightarrow$  probably at least practically unID
- Often can detect structural unID as ‘near-infinite’ (gigantic) variances in  $\text{Cov} \sim \text{FIM}^{-1}$

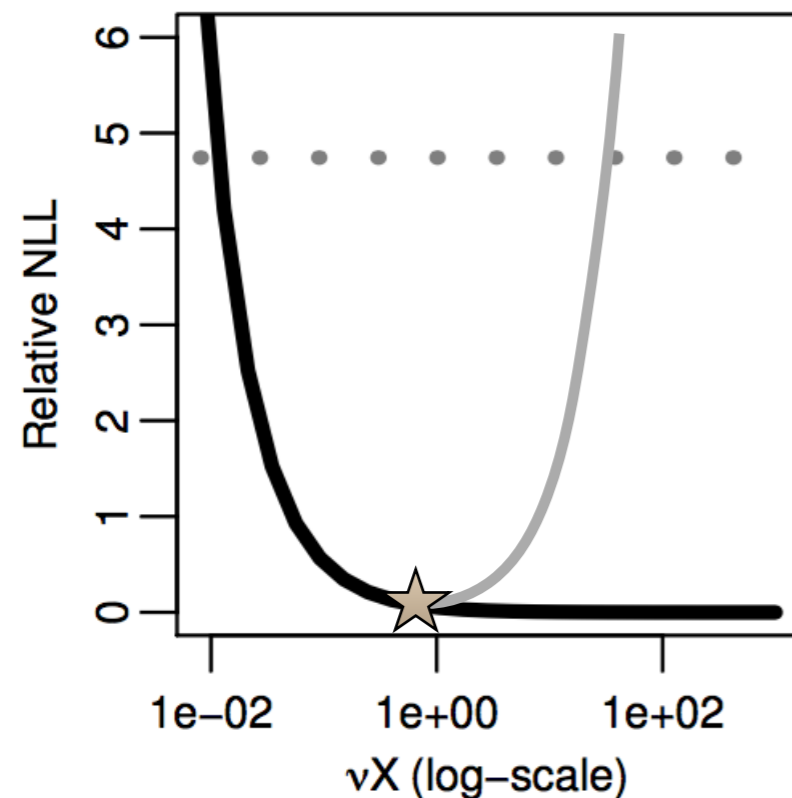
# Identifiability & the FIM

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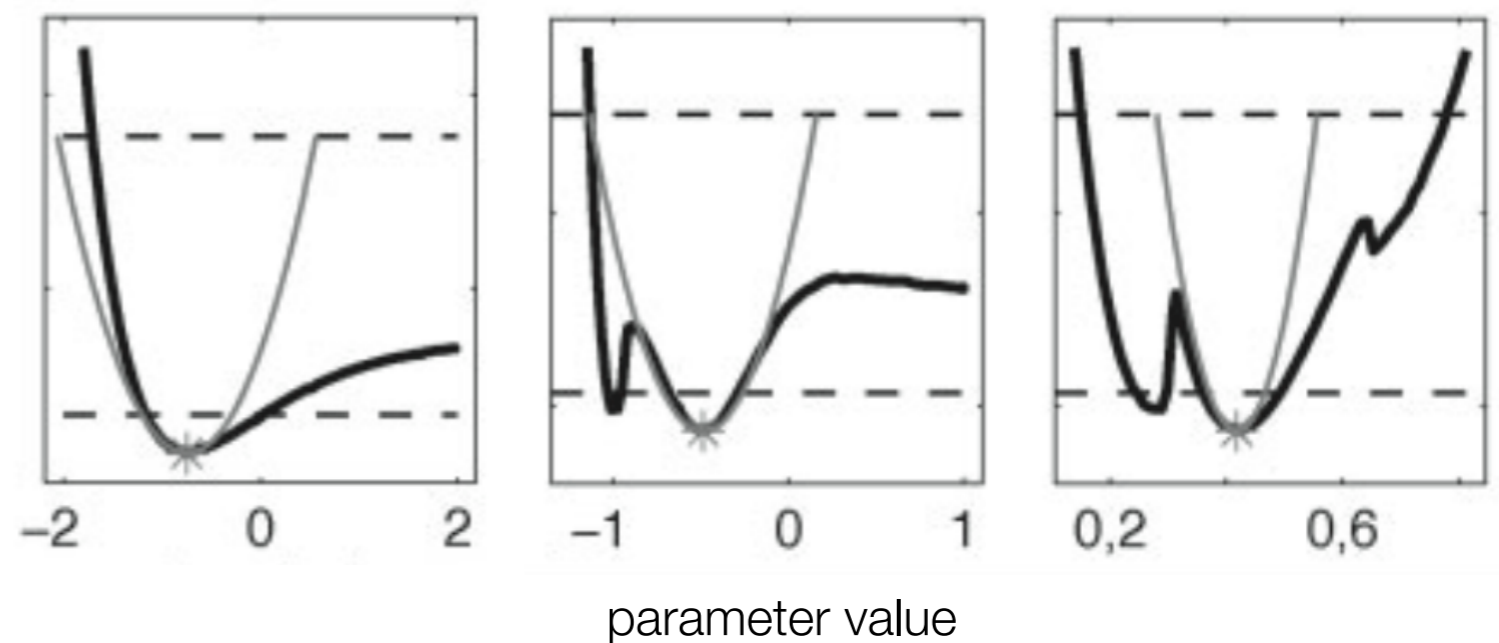
- **Rank of the FIM or the sensitivity matrix** is number of identifiable combinations/parameters - can do a lot by testing sub-FIMs and versions of the FIM
- Use FIM to find blocks of related parameters & how many to fix (not estimate)
- Identifiable combinations - can often see what parameters are 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)

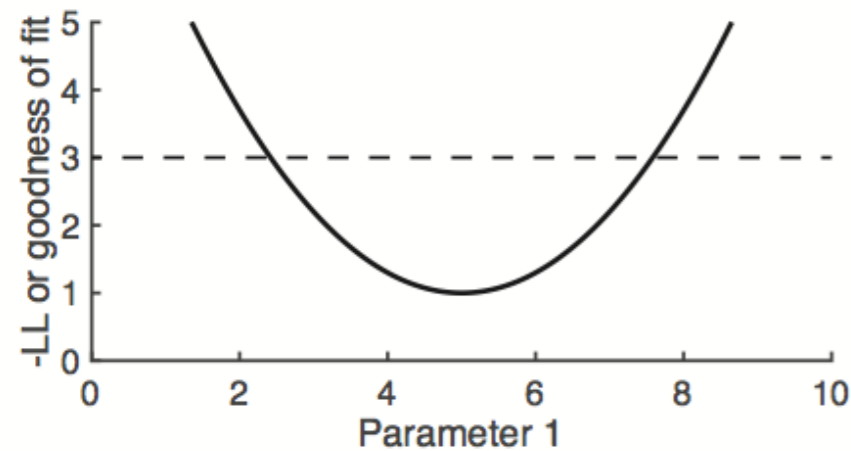
# Profile Likelihood

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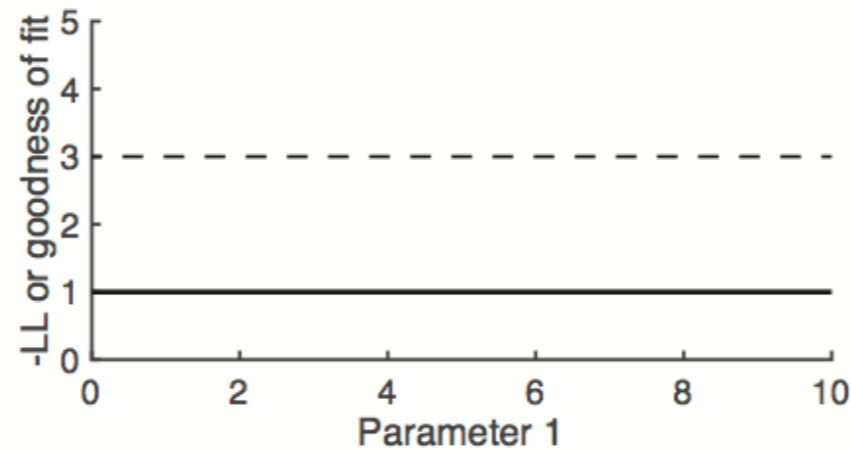
- Choose a range of values for parameter  $p_i$
- For each value, fix  $p_i$  to that value, and fit the rest of the parameters
- Report the best likelihood/RSS/cost function value for that  $p_i$  value
- Plot the best likelihood values for each value of  $p_i$ —this is the profile likelihood

# Profile Likelihoods

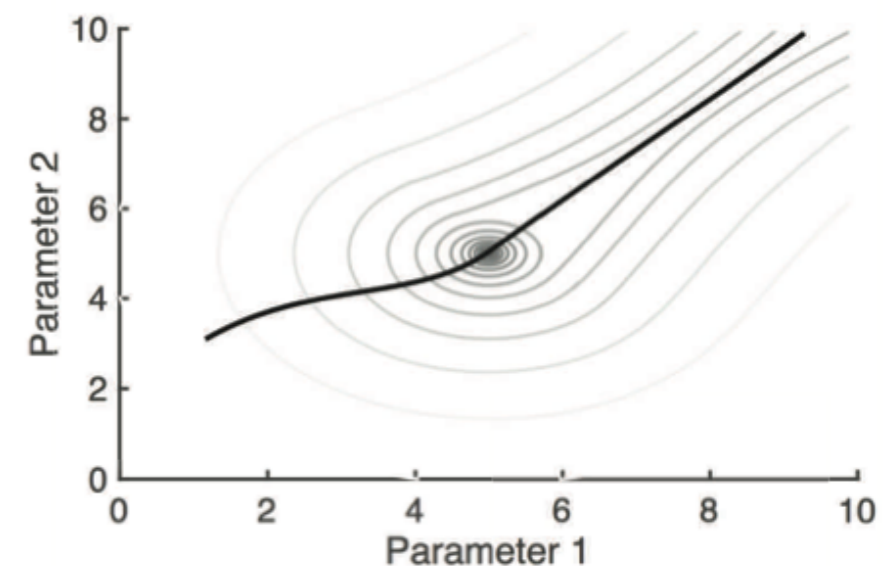
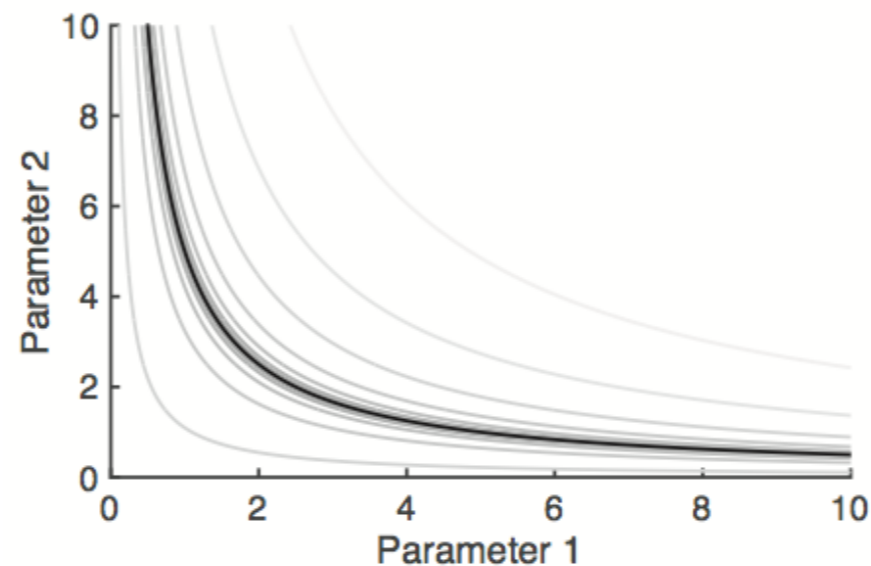
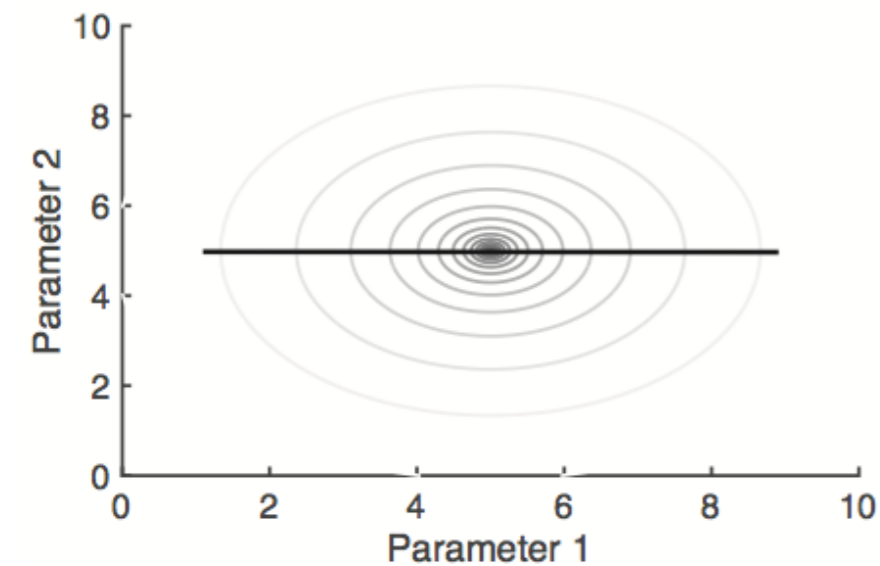
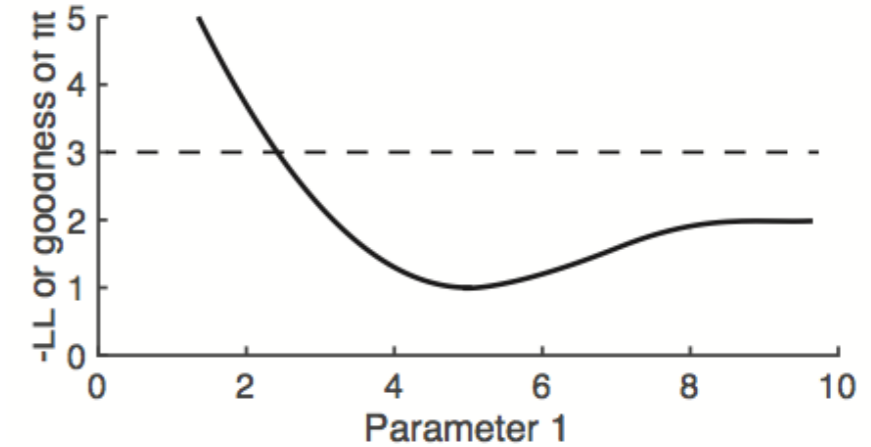
identifiable



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

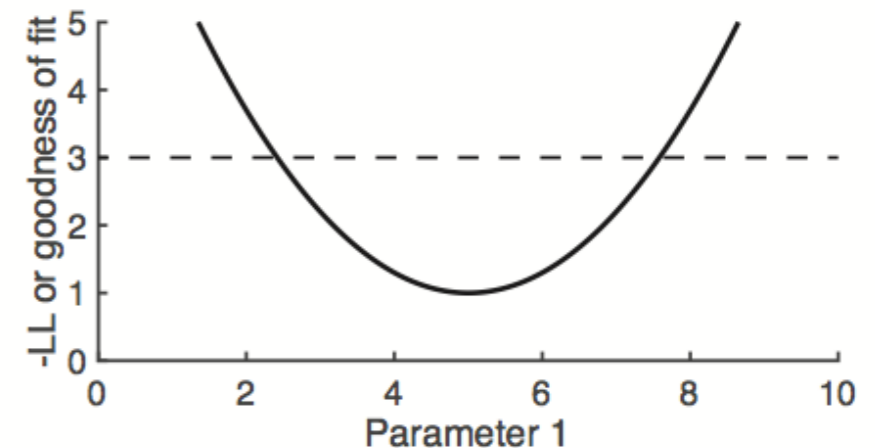
# Profile-based Confidence Intervals

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

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

is approximately  $\chi^2$ -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  $\chi^2$

# Profile Likelihood

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- 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)

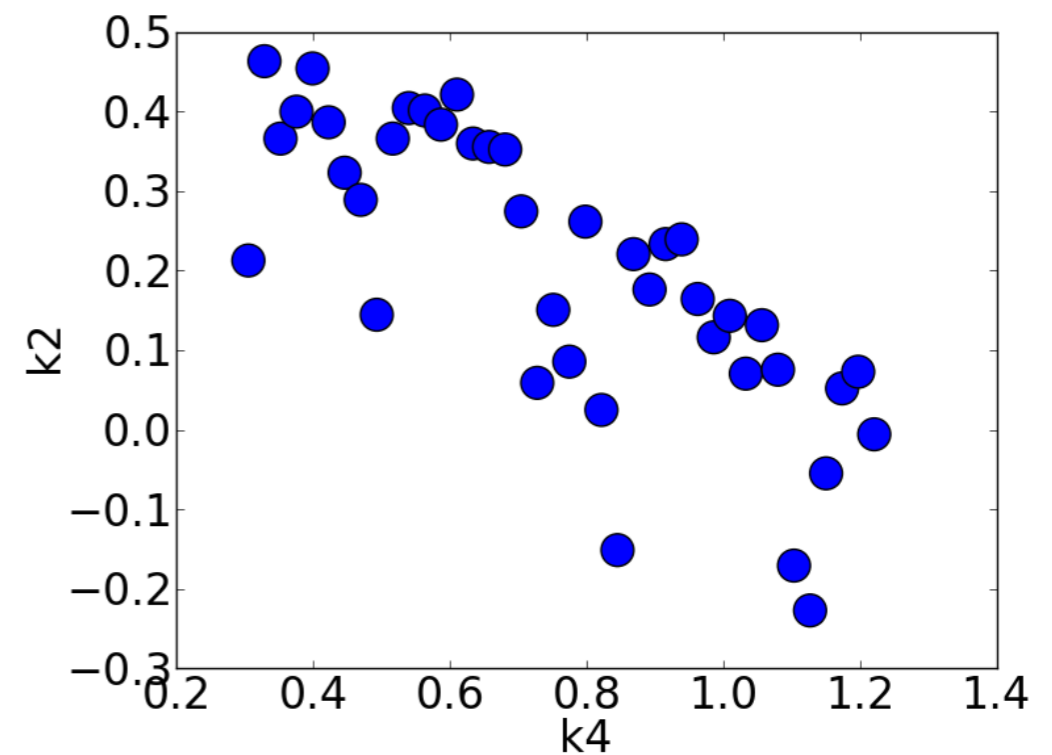
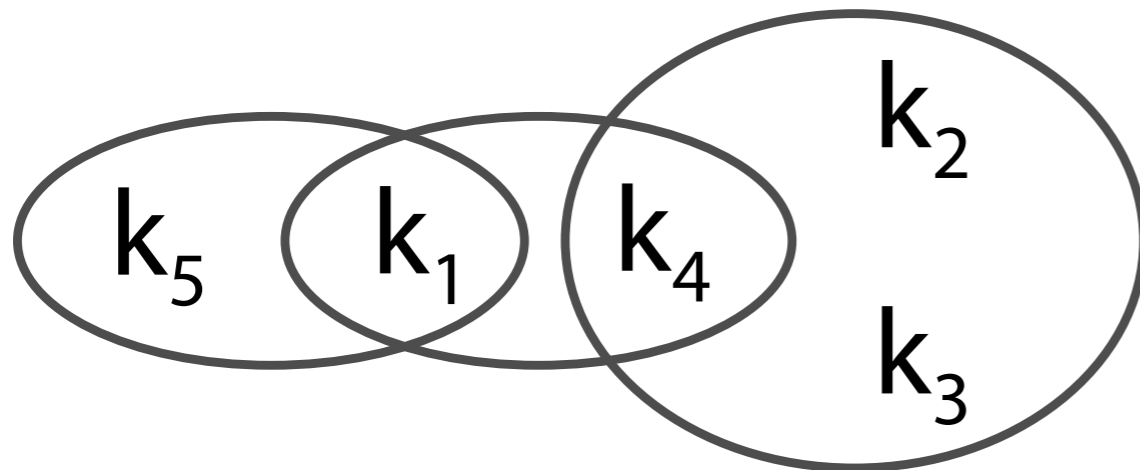
# Some potential issues

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

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

$$y = x_1 / V$$

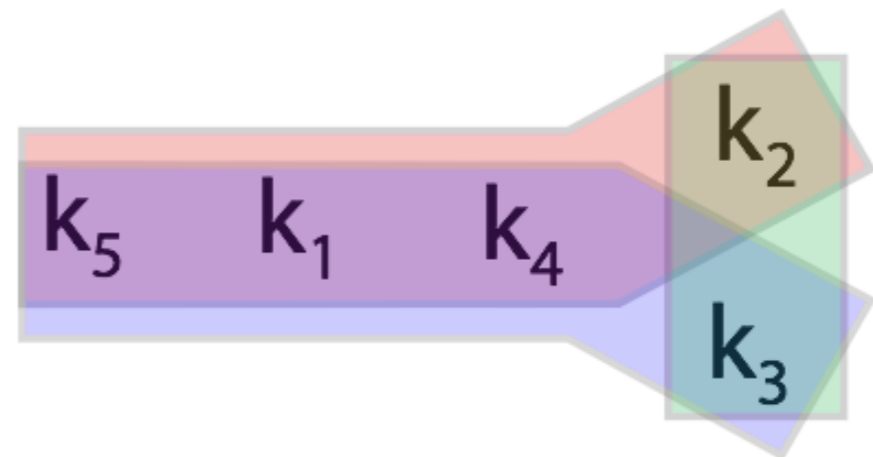
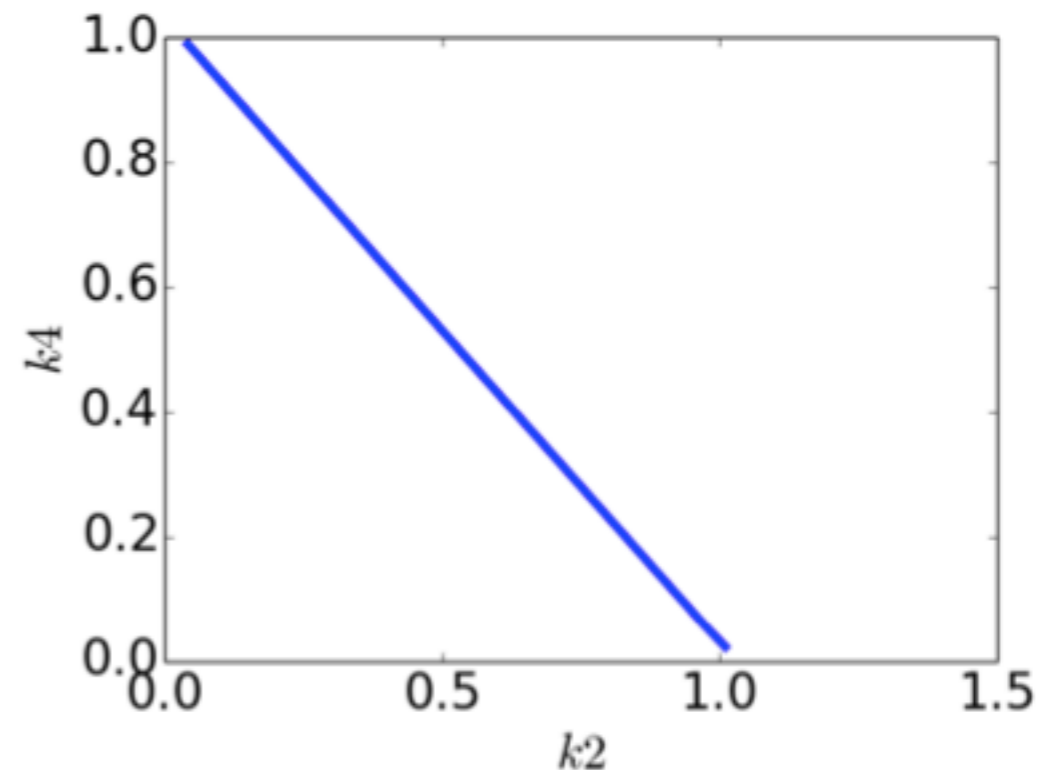
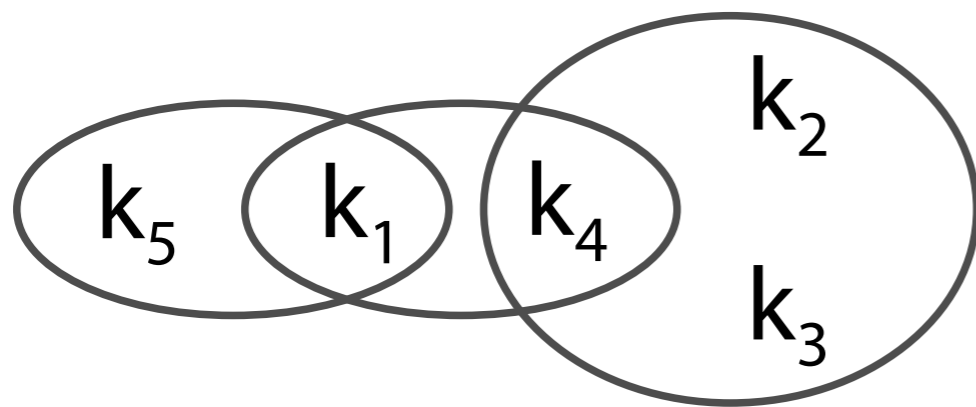


# Example Model

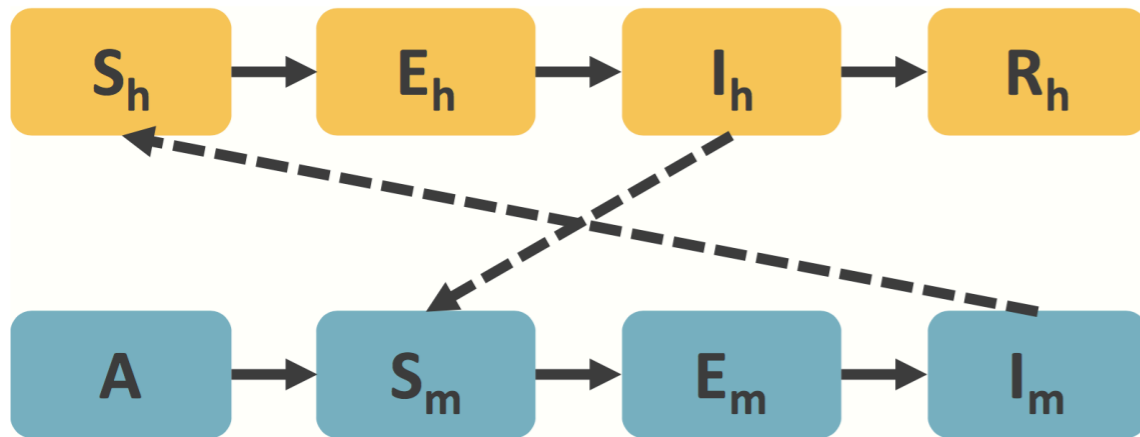
$$\dot{x}_1 = k_1 x_2 - (k_2 + k_3 + k_4) x_1$$

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

$$y = x_1 / V$$



# Dengue Model Example



$$\frac{dS_h}{dt} = \mu(1 - S_h) - \beta_{mh}^* S_h I_m$$

$$\frac{dE_h}{dt} = \beta_{mh}^* S_h I_m - \alpha E_h - \mu E_h$$

$$\frac{dI_h}{dt} = \alpha E_h - \eta I_h - \mu I_h$$

$$\frac{dR_h}{dt} = \eta I_h - \mu R_h$$

$$\frac{dA}{dt} = \xi^* (S_m + E_m + I_m) (1 - A) - \mu_a^* A$$

$$\frac{dS_m}{dt} = A - \beta_{hm} S_m I_h - \mu_m S_m$$

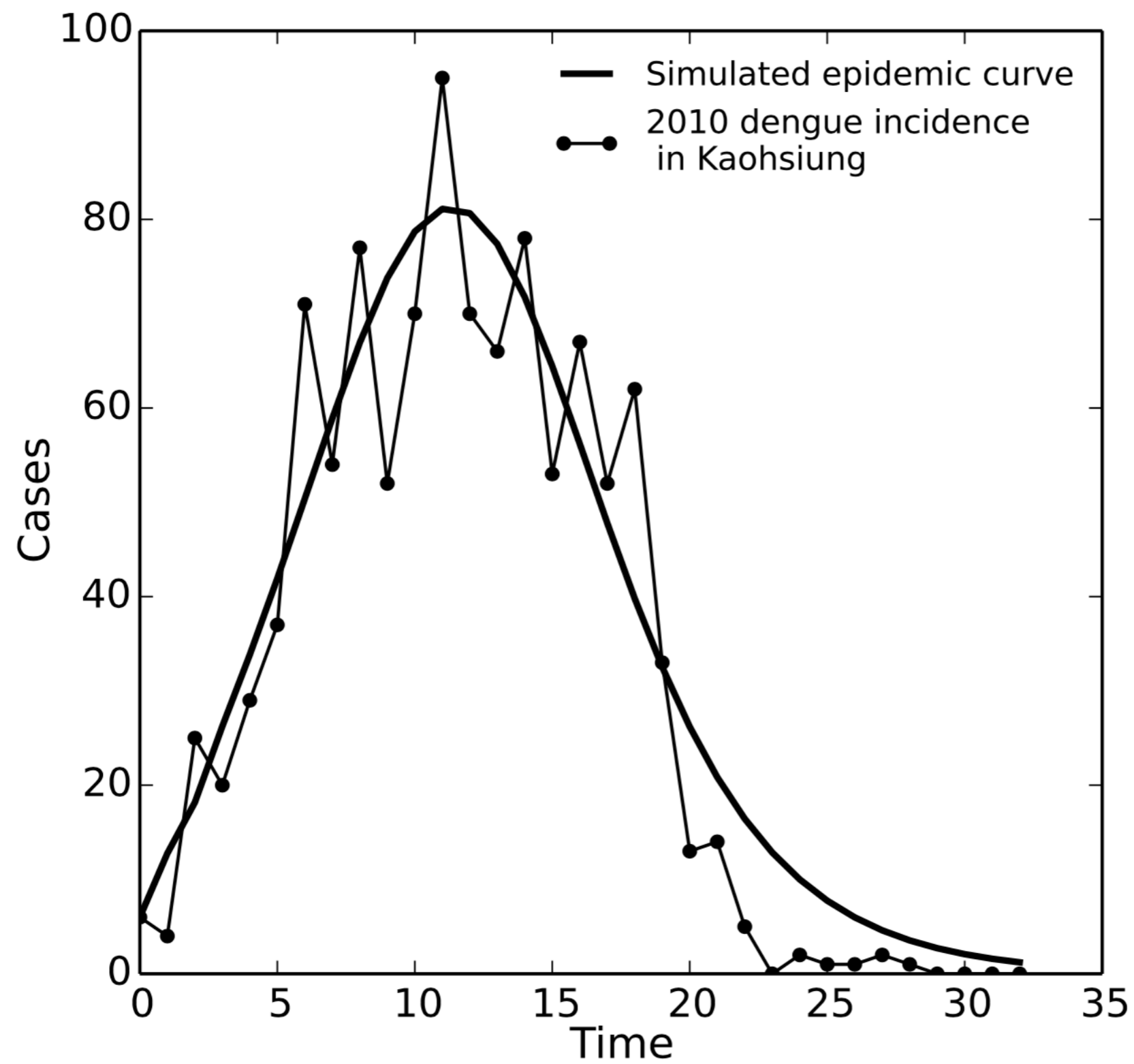
$$\frac{dE_m}{dt} = \beta_{hm} S_m I_h - \gamma E_m - \mu_m E_m$$

$$\frac{dI_m}{dt} = \gamma E_m - \mu_m I_m$$

# Measurement Model & Structural Identifiability

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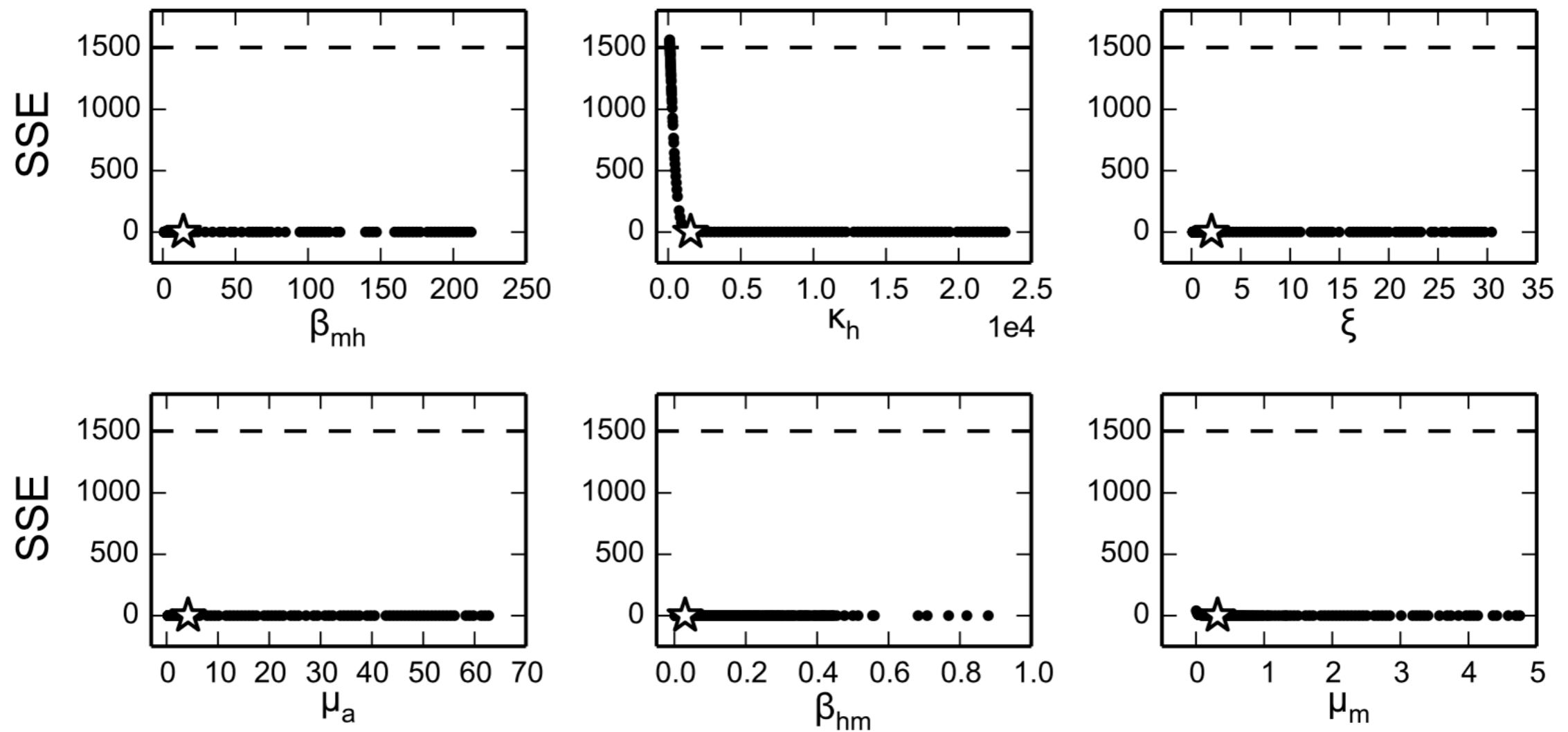
- Measure human incidence data,  $y = \kappa_h \alpha E_h$  , integrated to weekly incidence
- Differential algebra approach and FIM-based approaches show structural identifiability



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

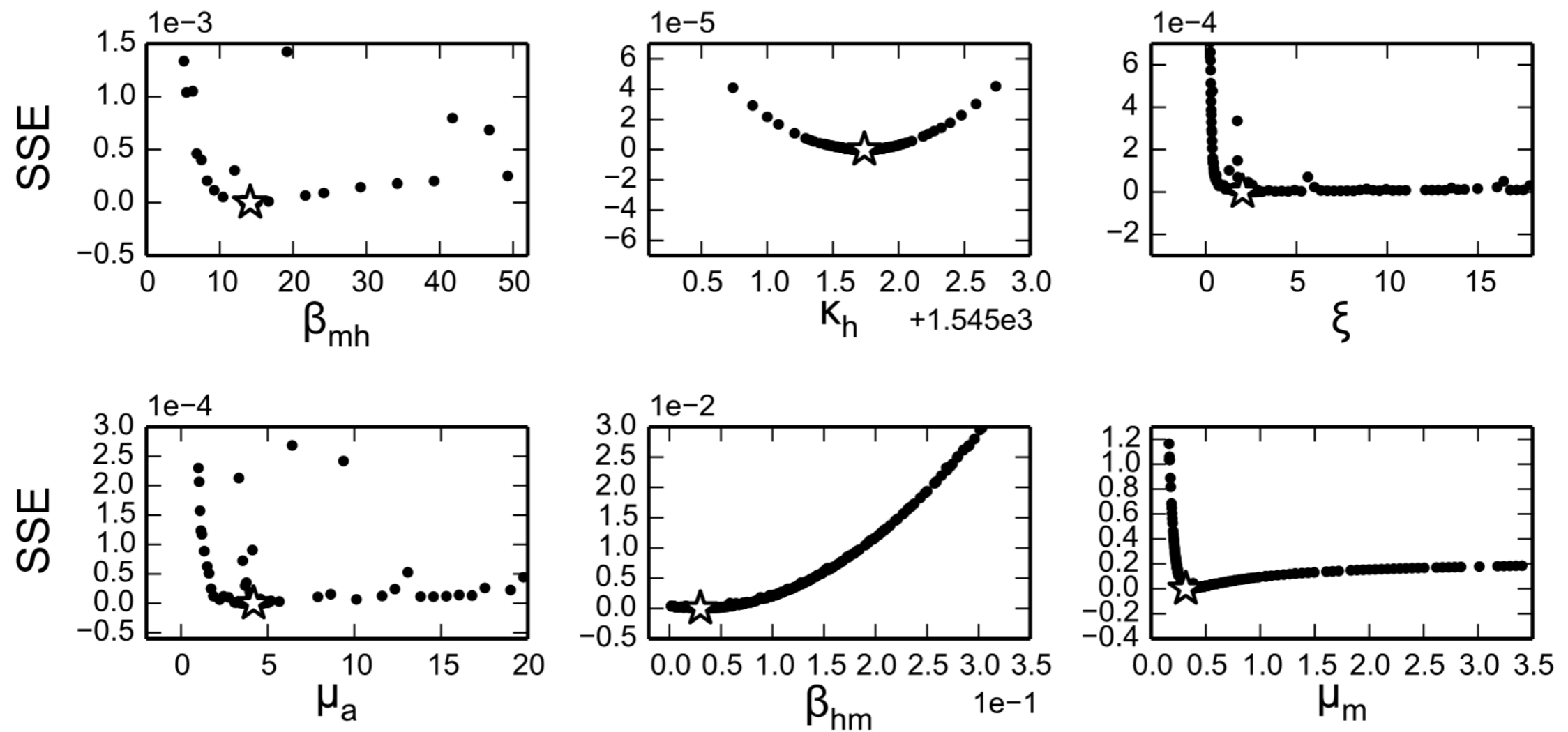
# What about practical identifiability?

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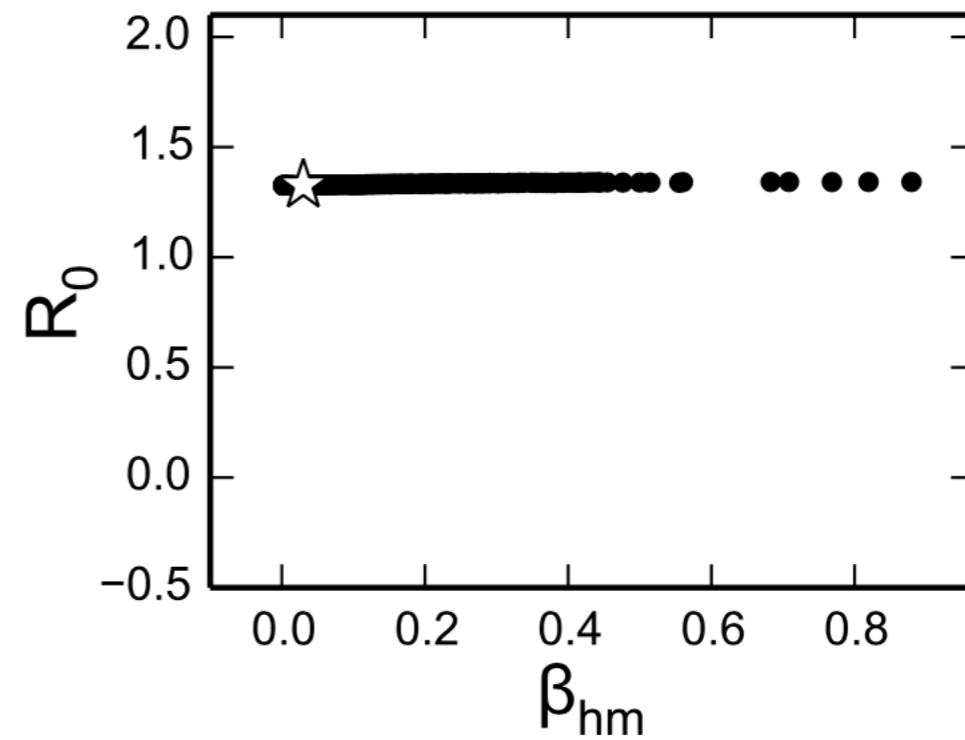
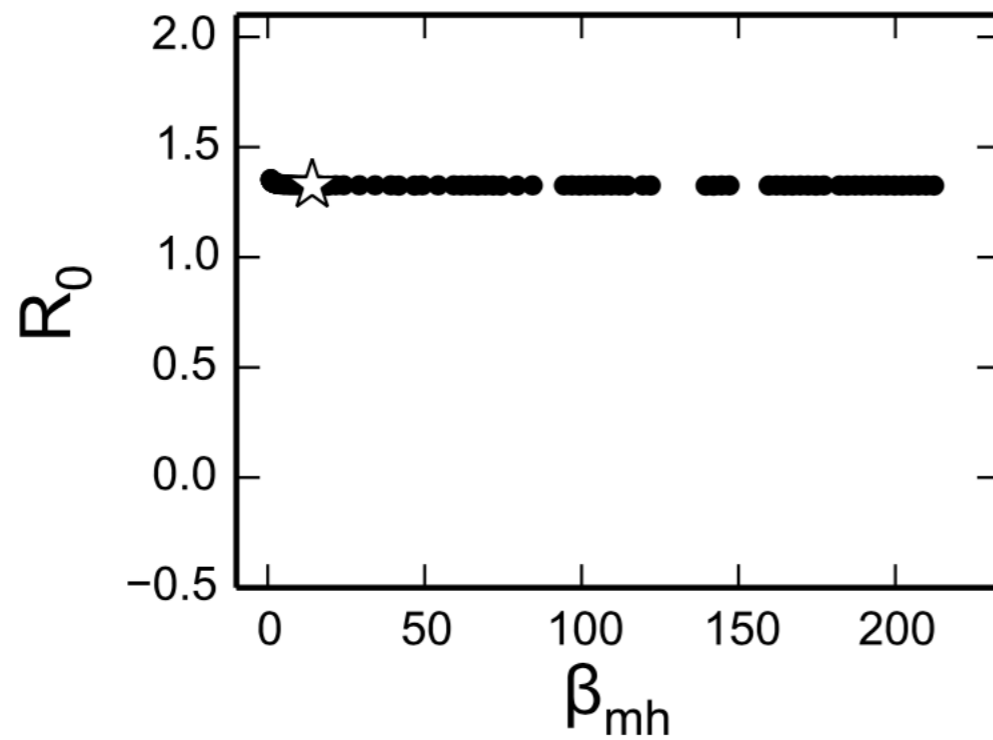
# What about practical identifiability?

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# How does this affect $R_0$ ?

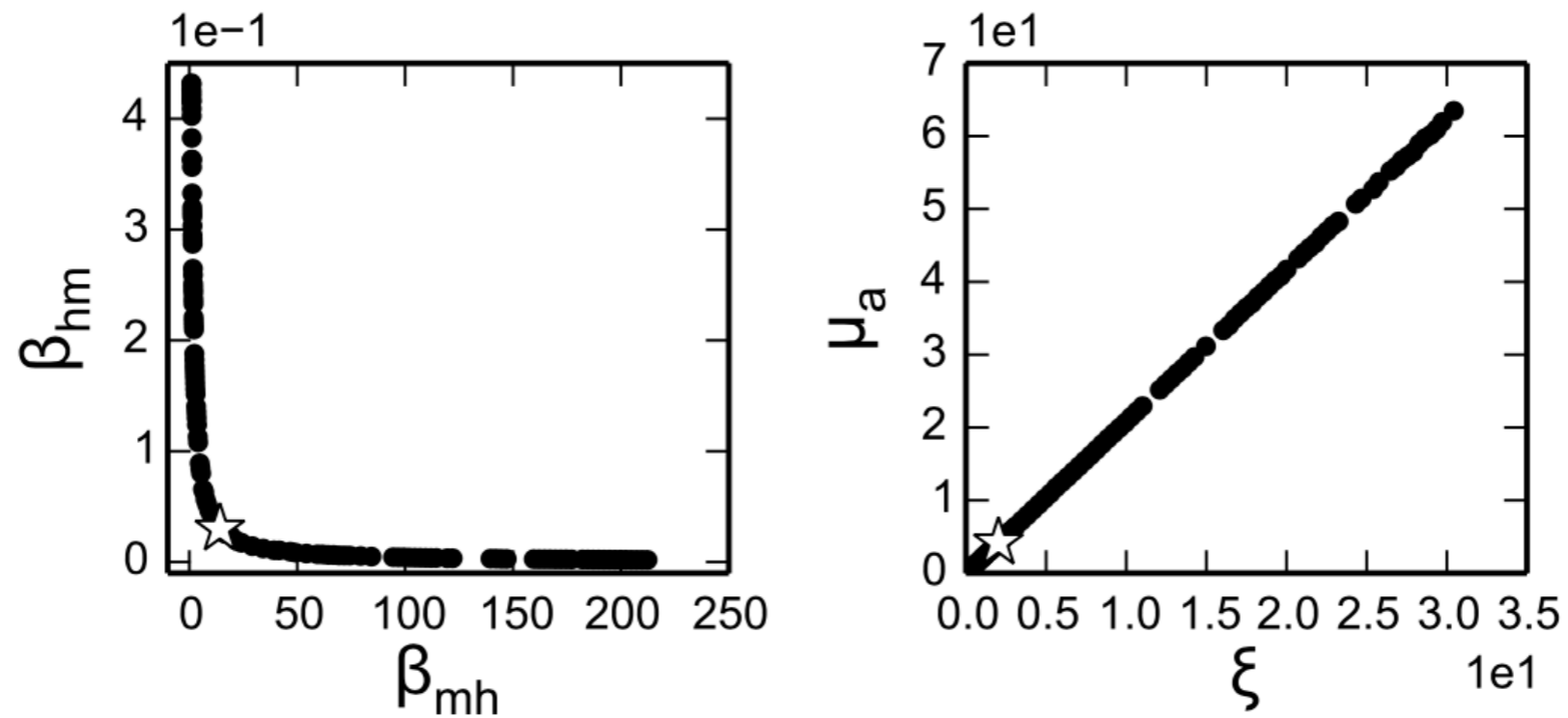
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$$\mathcal{R}_0 = \sqrt{\frac{S_m \alpha \beta_{hm} \beta_{mh} \gamma}{(\alpha + \mu)(\eta + \mu)(\gamma + \mu_m) \mu_m}}.$$

# 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:

$$\beta_{mh} = 14.15$$

$$\xi = 2.03$$

$$\beta_{hm} = 0.03$$

$$\mu_a = 4.18$$

$$\mu_m = 0.32$$

$$\kappa_h =$$

$$1546.74$$

Fit2:

$$\beta_{mh} = 38.10$$

$$\xi = 0.13$$

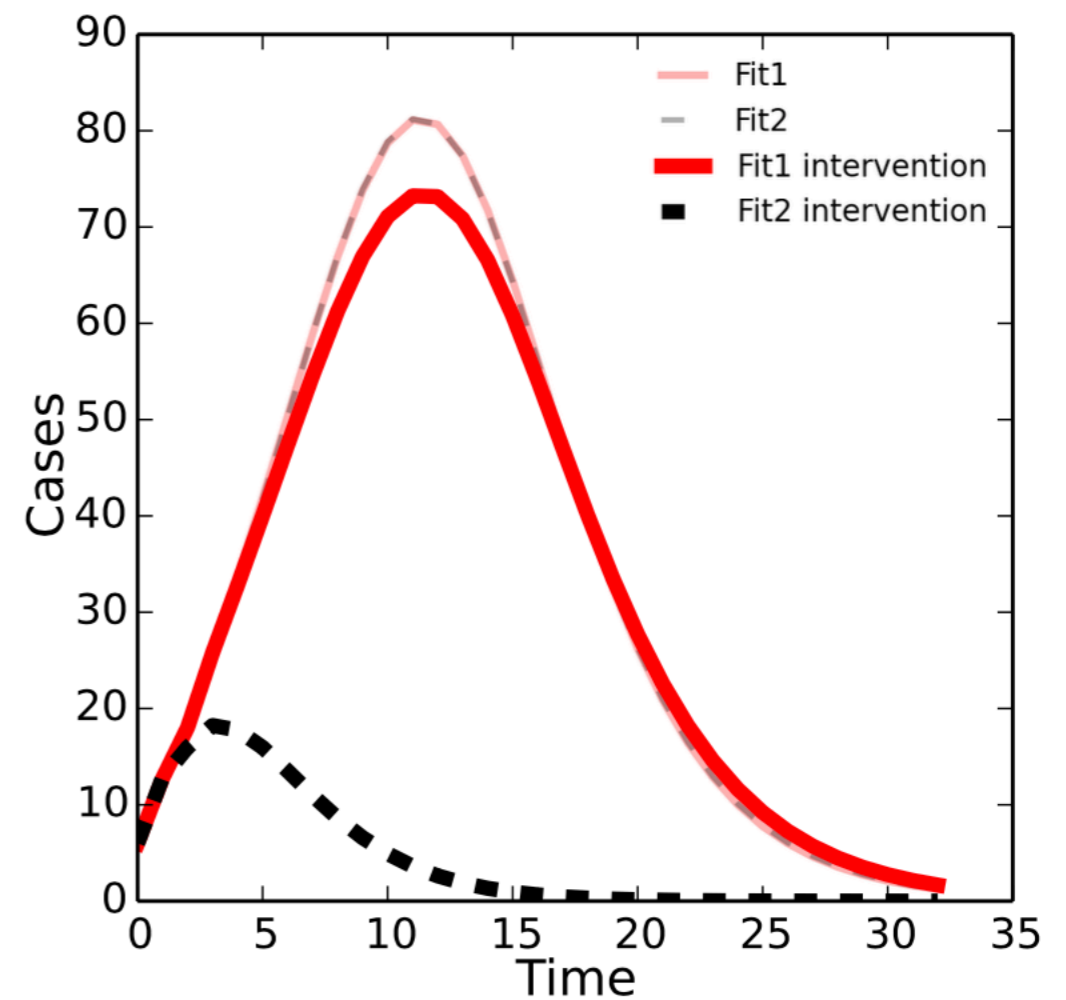
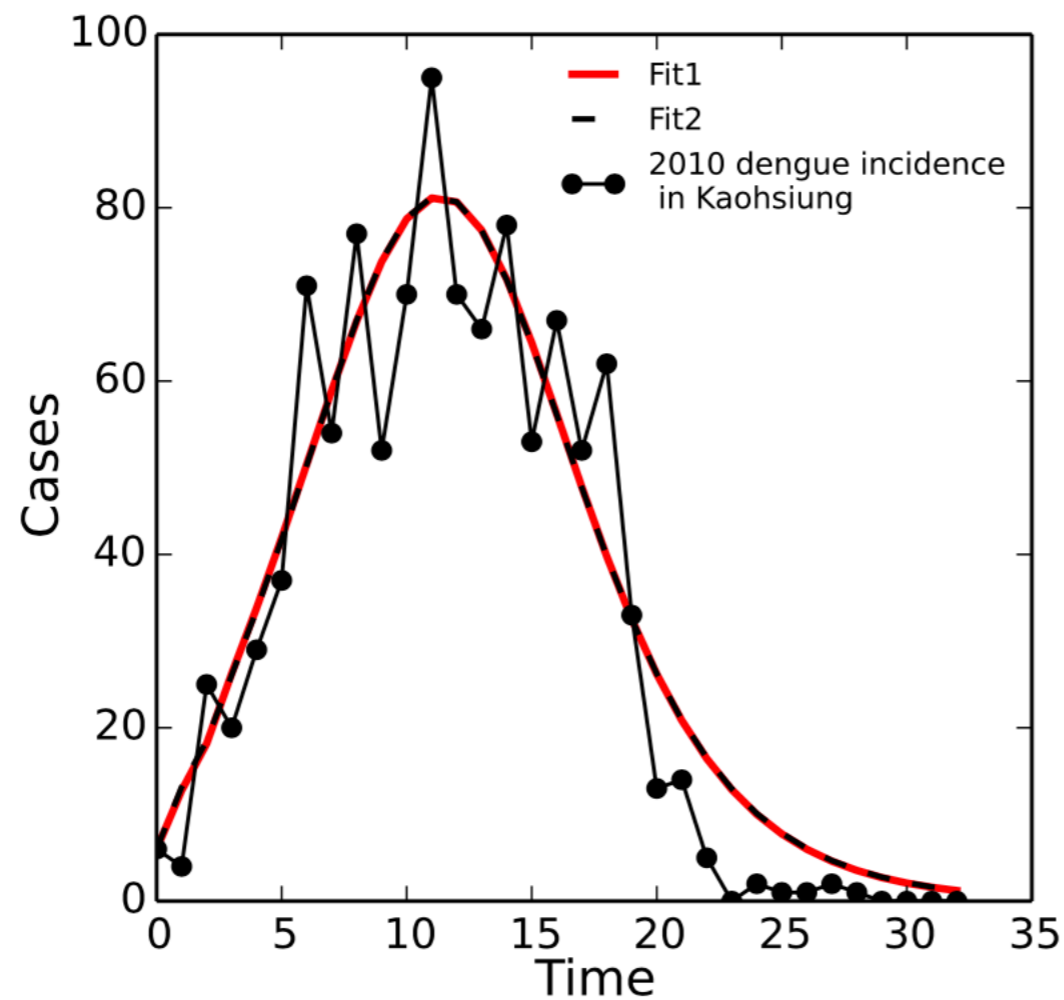
$$\beta_{hm} = 0.02$$

$$\mu_a = 0.15$$

$$\mu_m = 0.42$$

$$\kappa_h =$$

$$1625.42$$



# Sidenote: Identifiability in a Bayesian Context

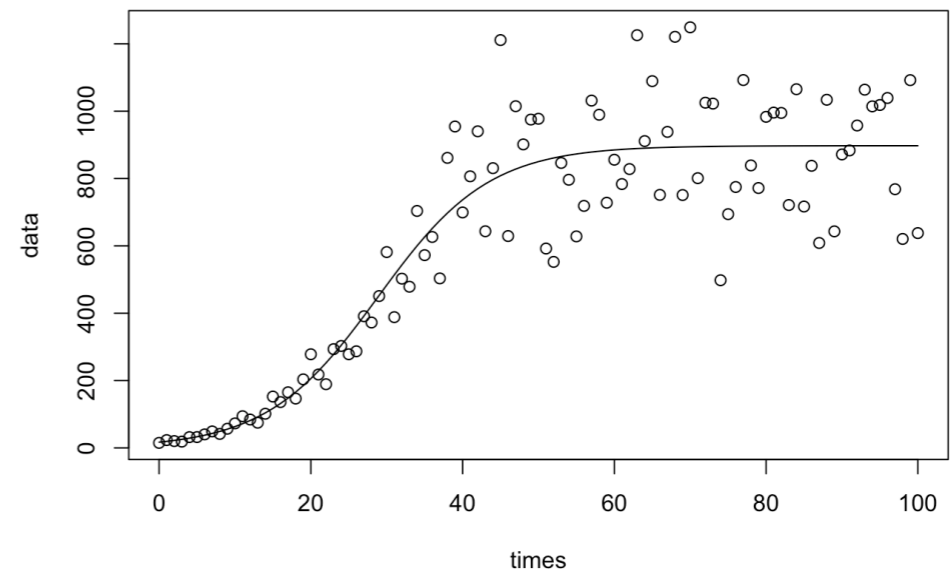
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- Unidentifiability can affect the performance of MCMC and other sampling methods, and can lead to broad, flat posteriors or heavy reliance on the prior
- Simple unidentifiable model example:

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

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

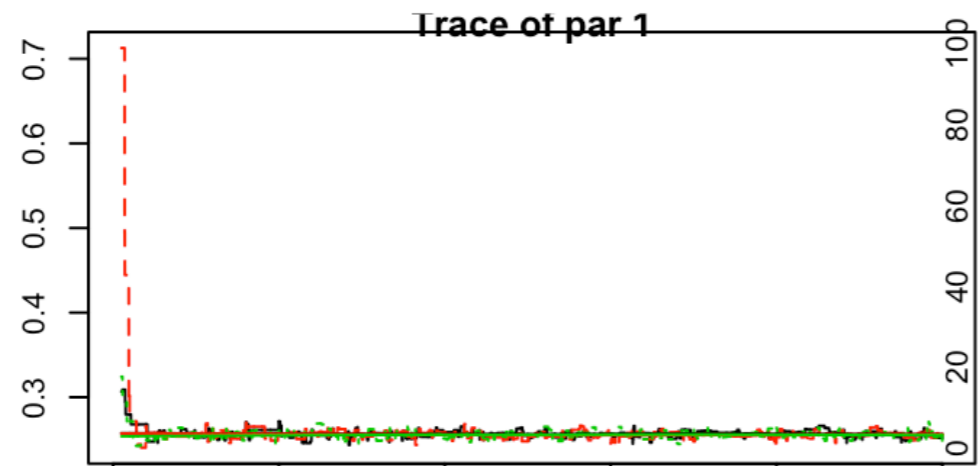
$$y = kNI$$



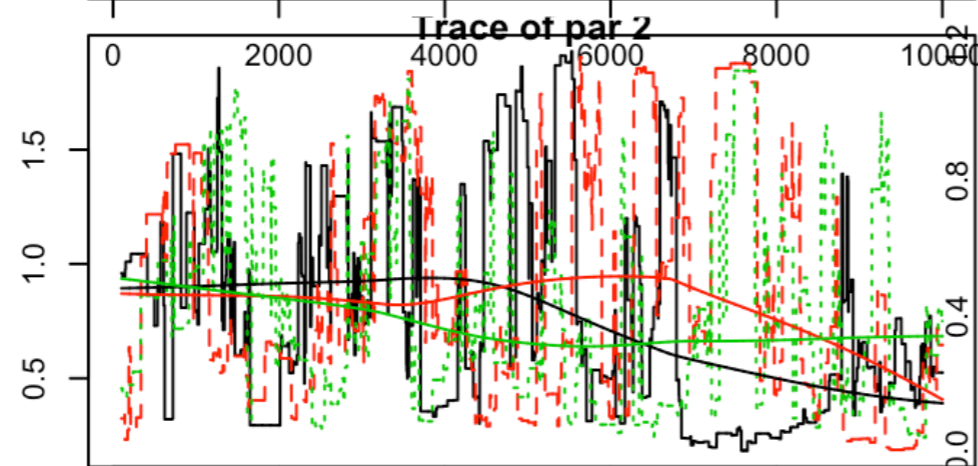
- Try MCMC (e.g. with Metropolis-Hastings or variants of)

# Unidentifiable model

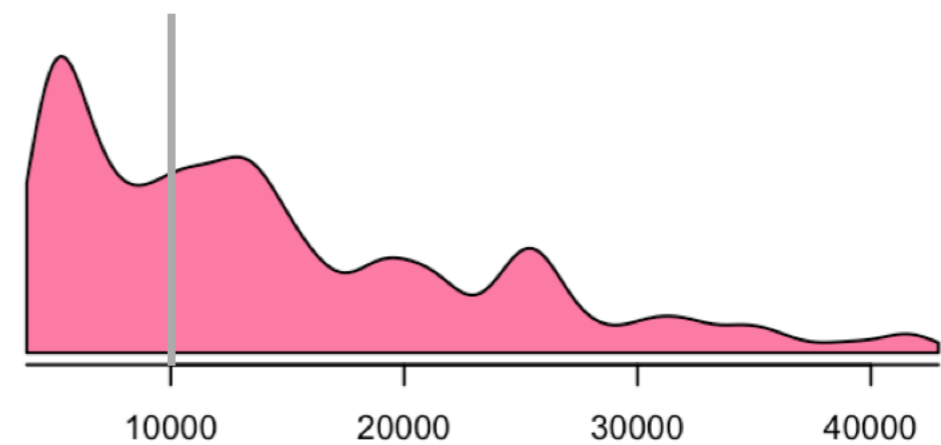
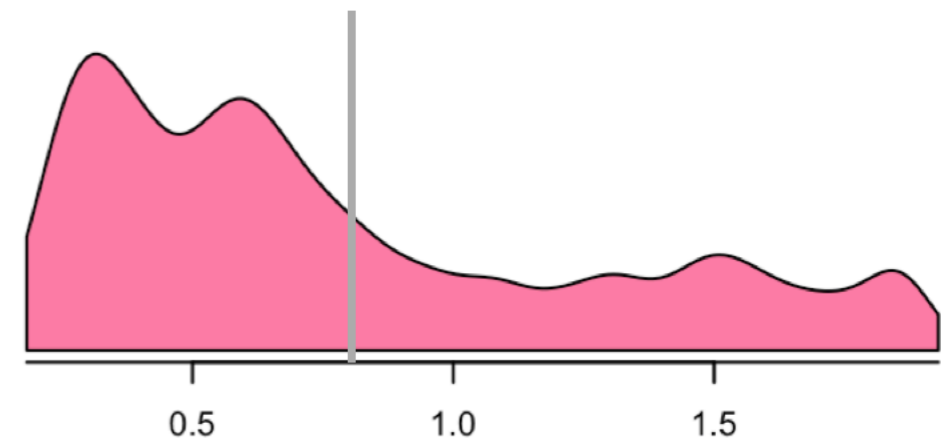
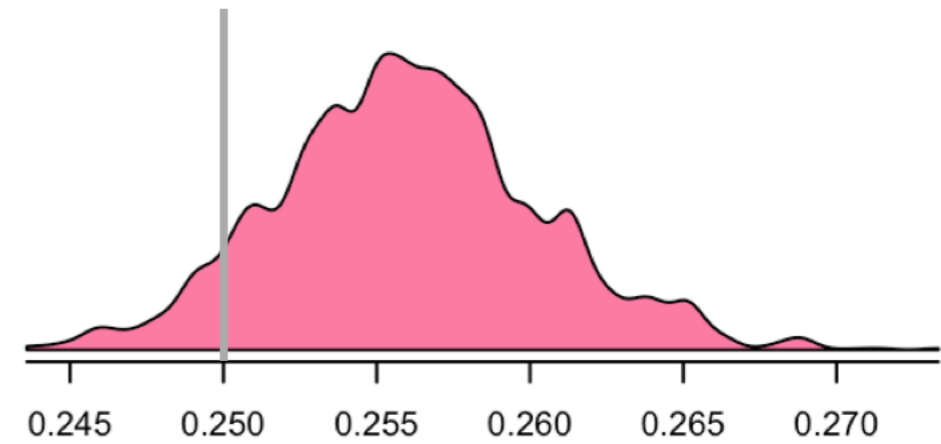
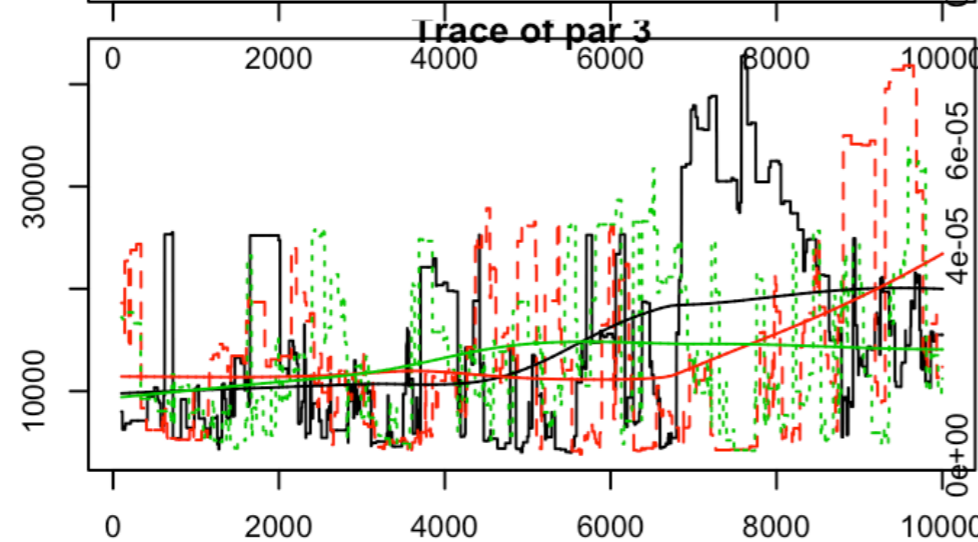
$\beta$



$k$

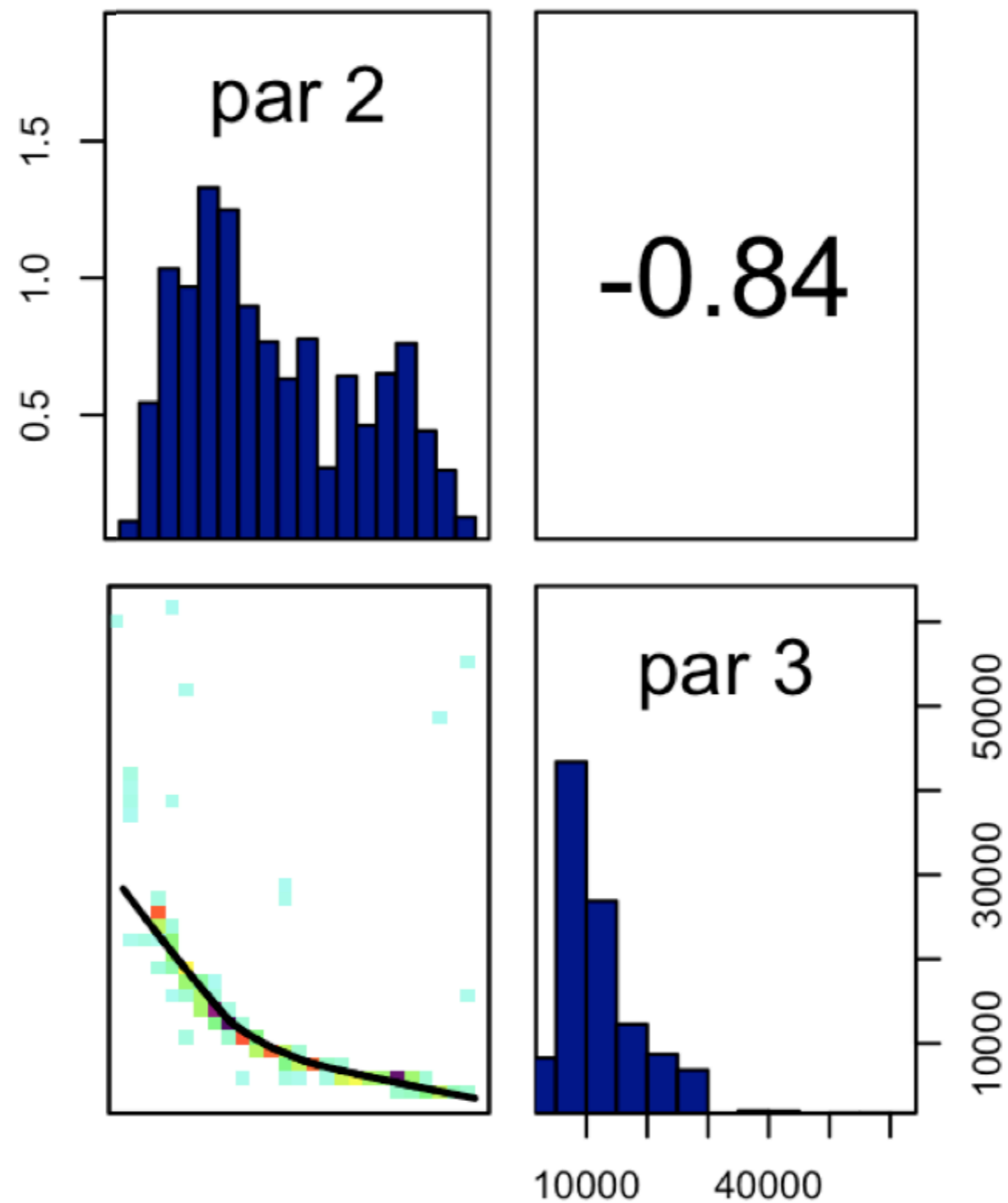


$N$

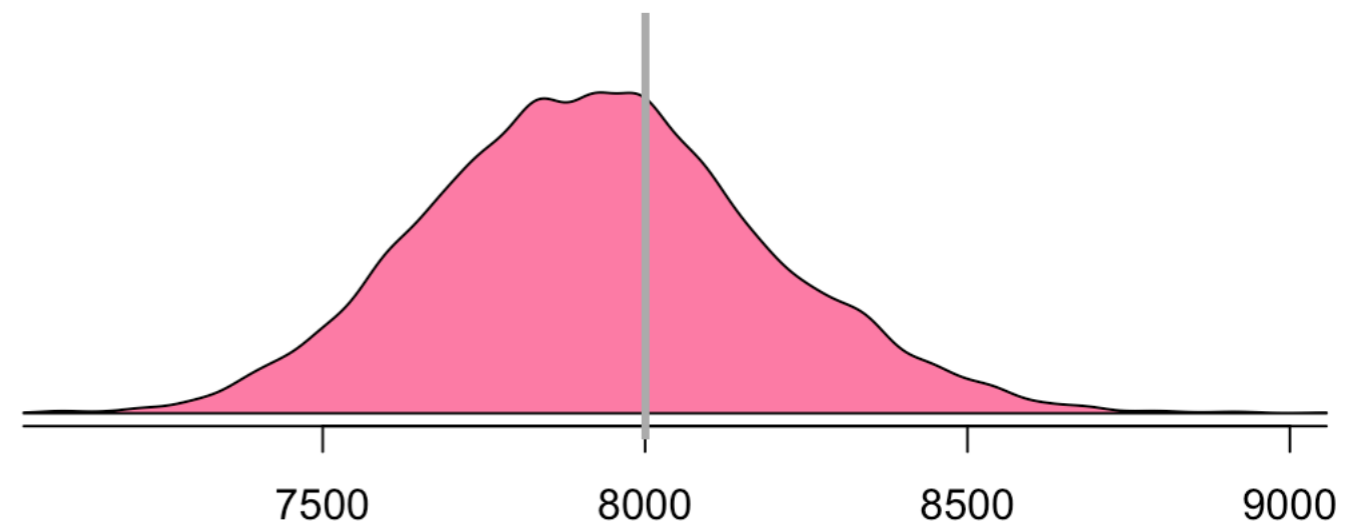
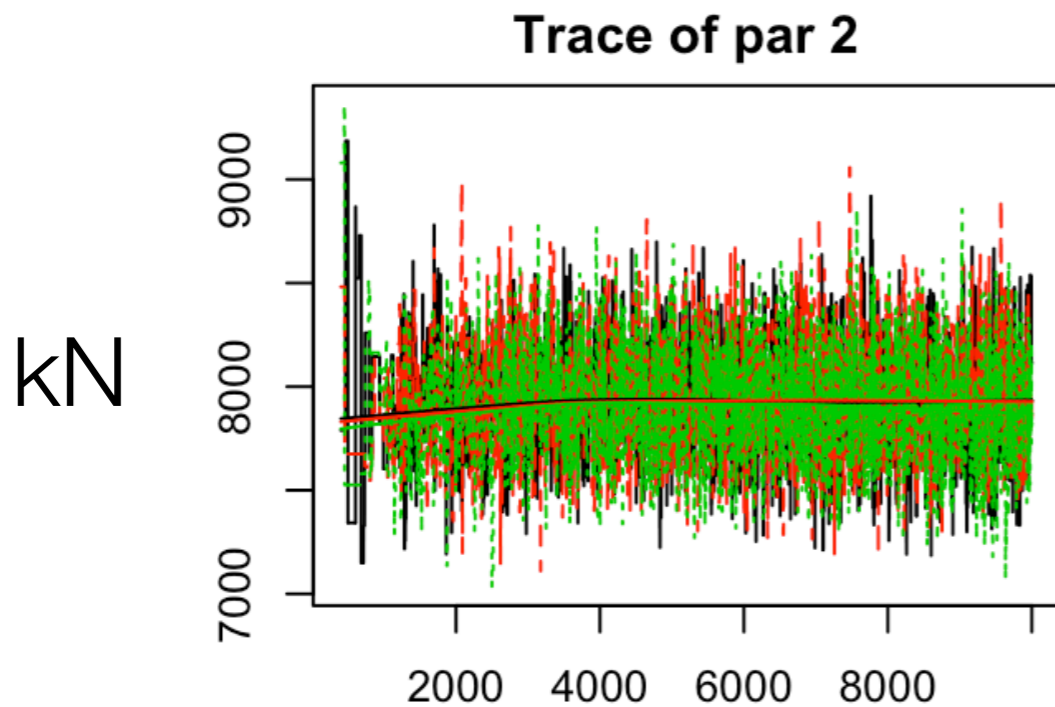
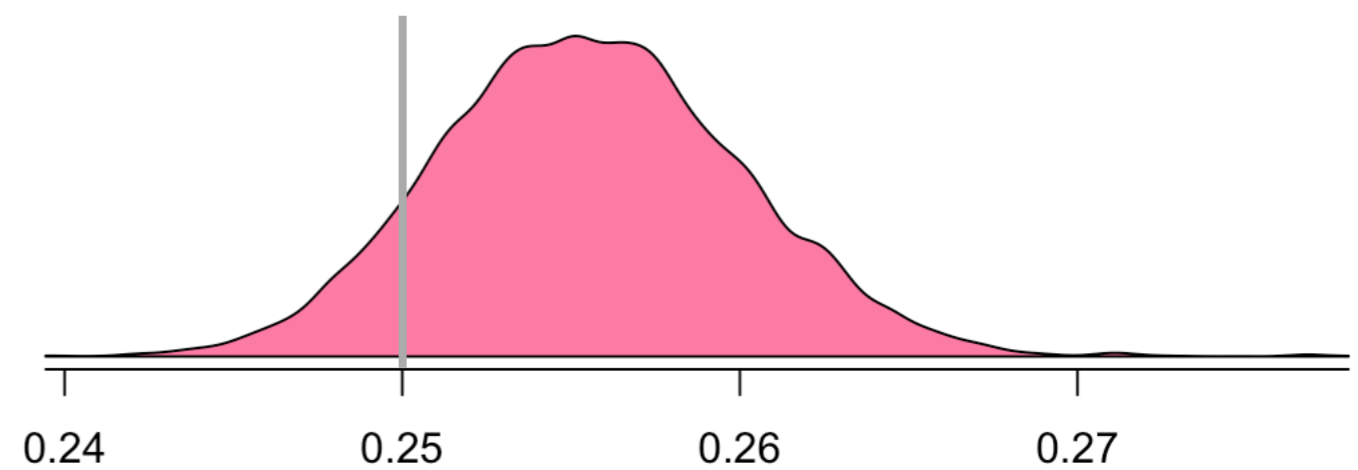
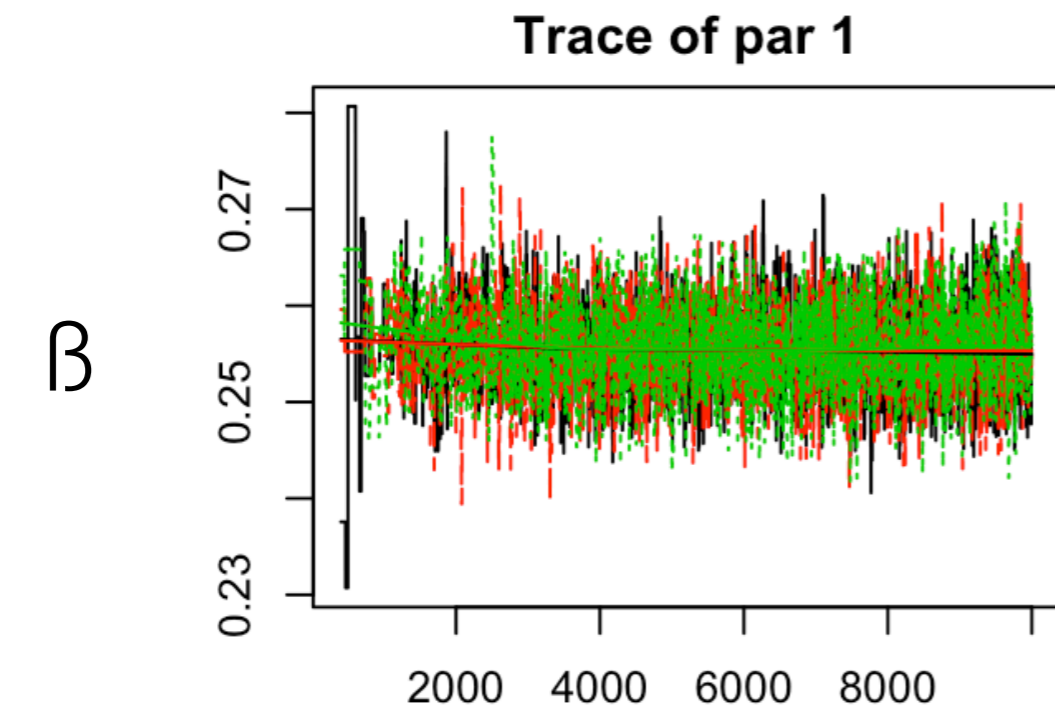


# Correlation between k and N

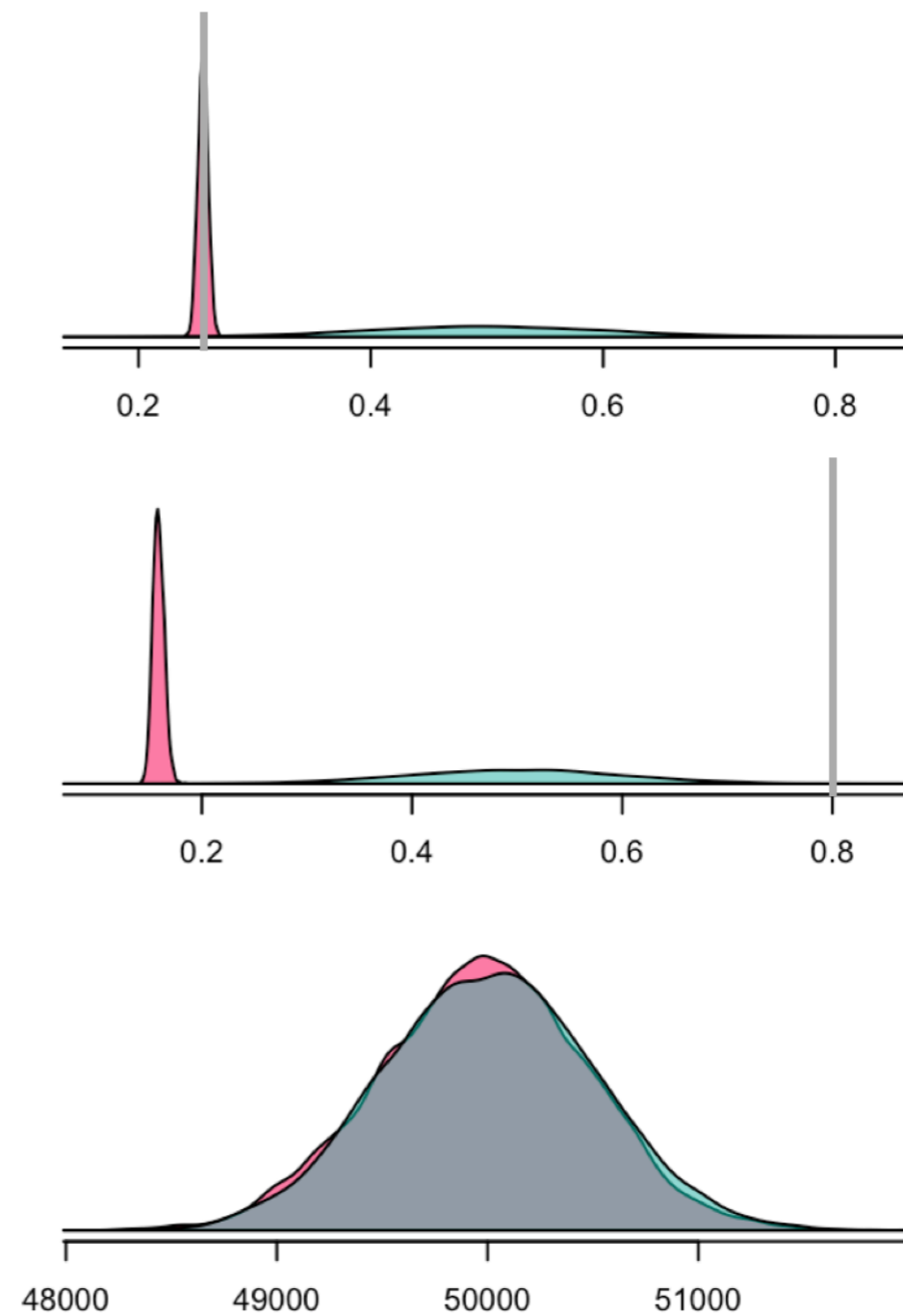
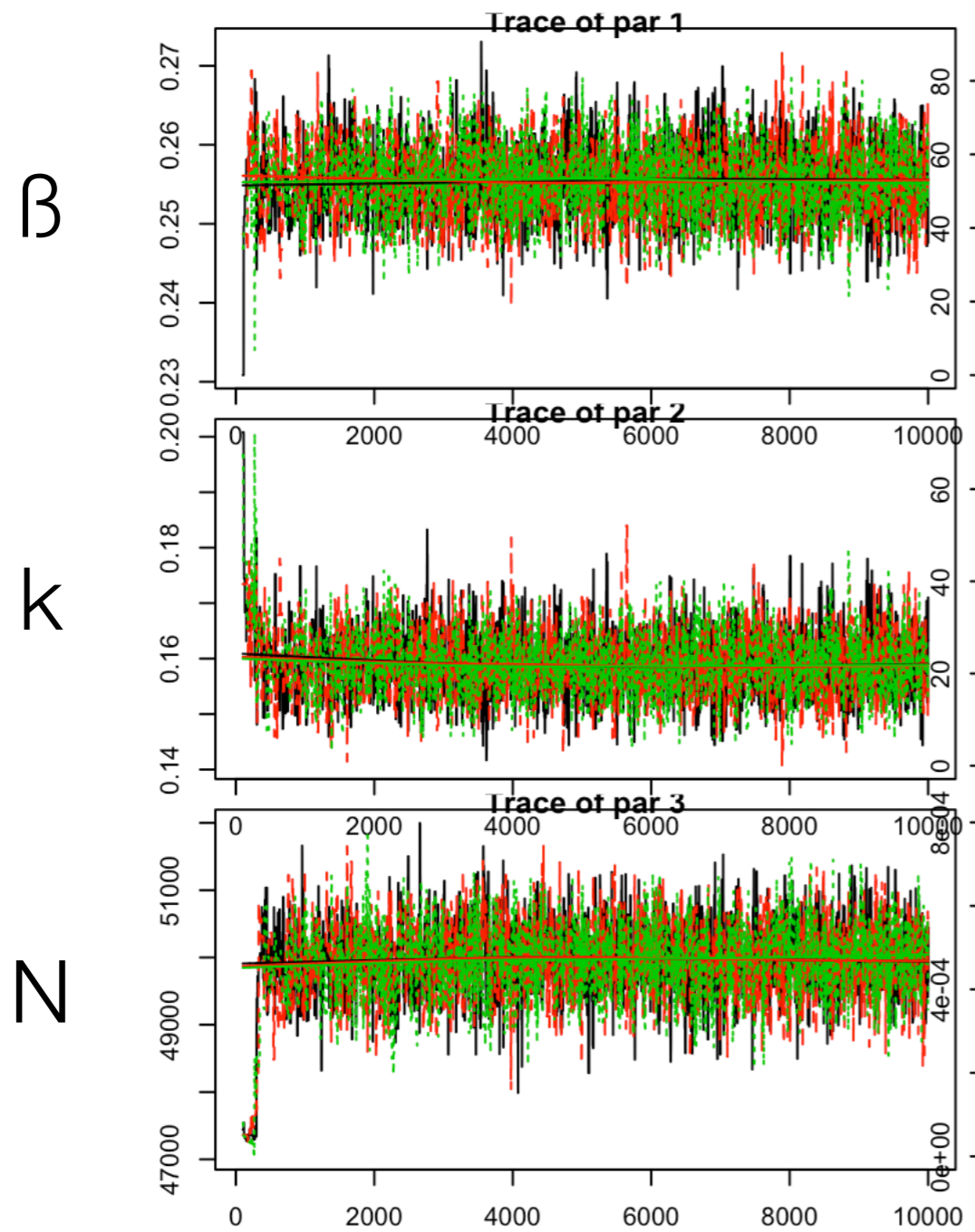
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# Reparameterize to make the model identifiable



# Adding a strong prior



■ posterior ■ prior

# Conclusions

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- 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

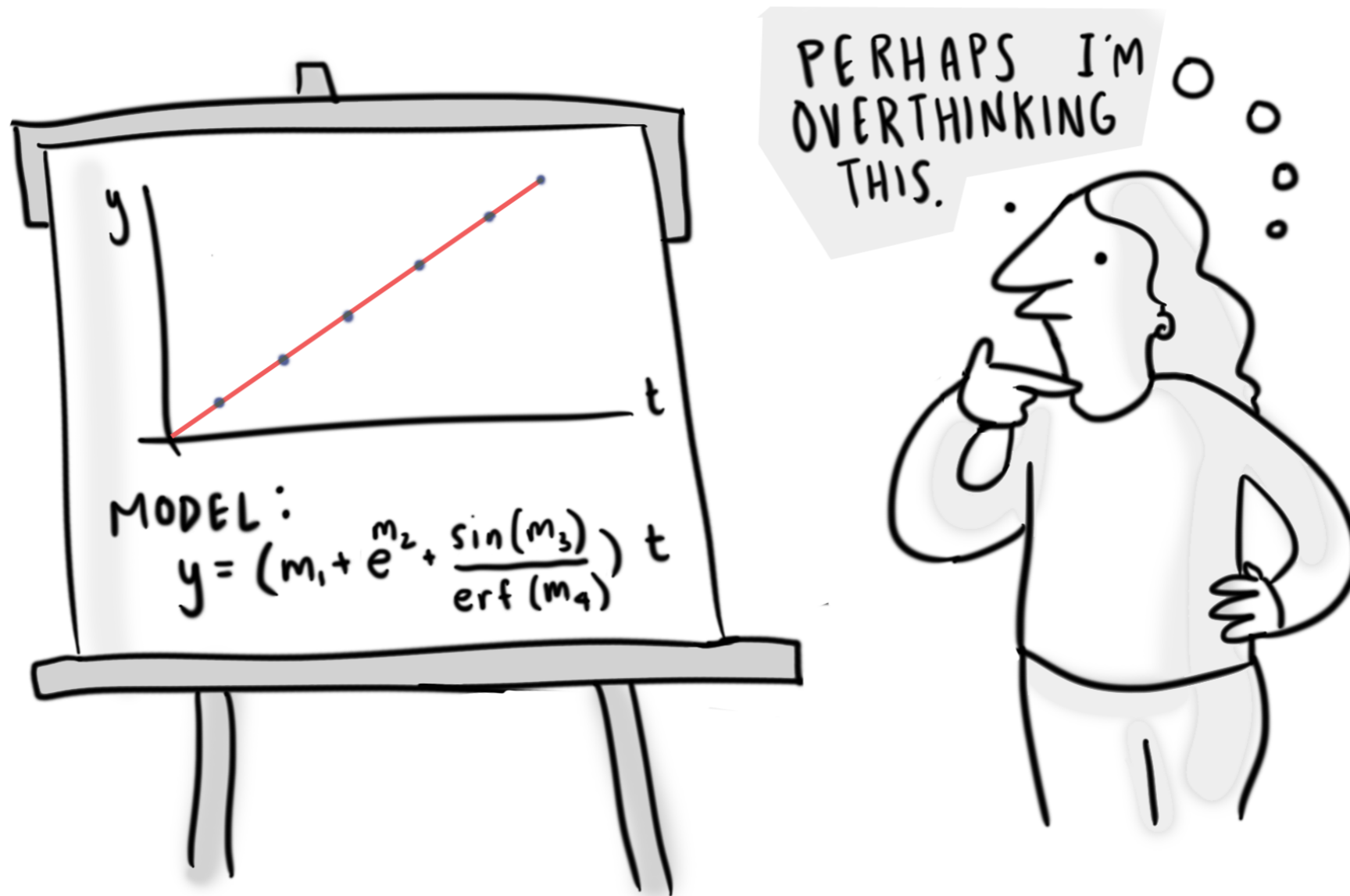
# Conclusions

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- 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?

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