

# Introduction to Structural & Practical Identifiability

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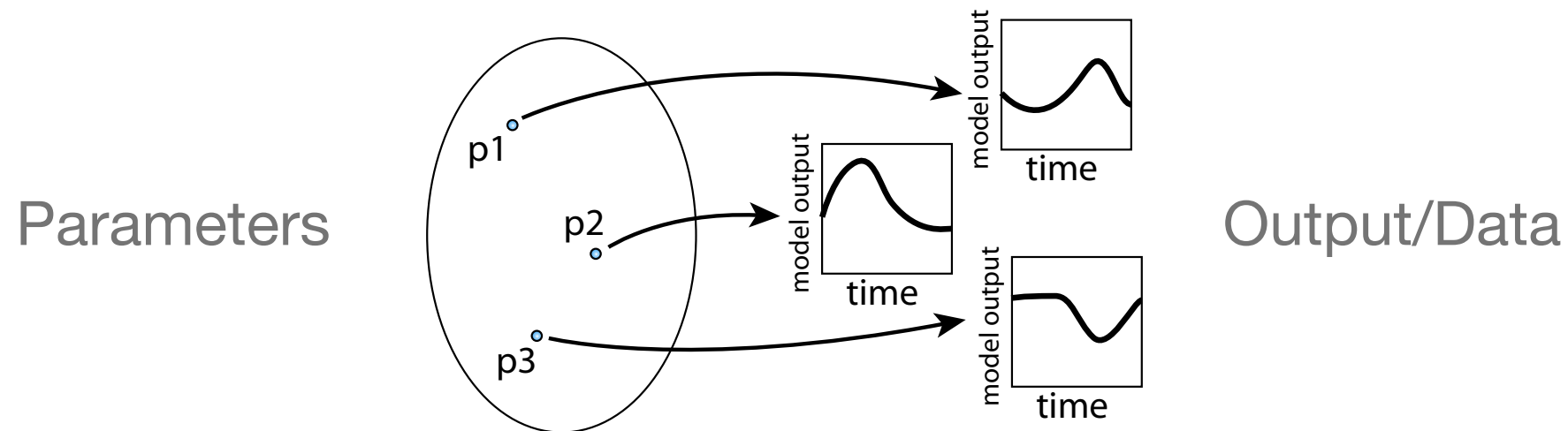
Marisa Eisenberg

Epid 814

# Identifiability

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

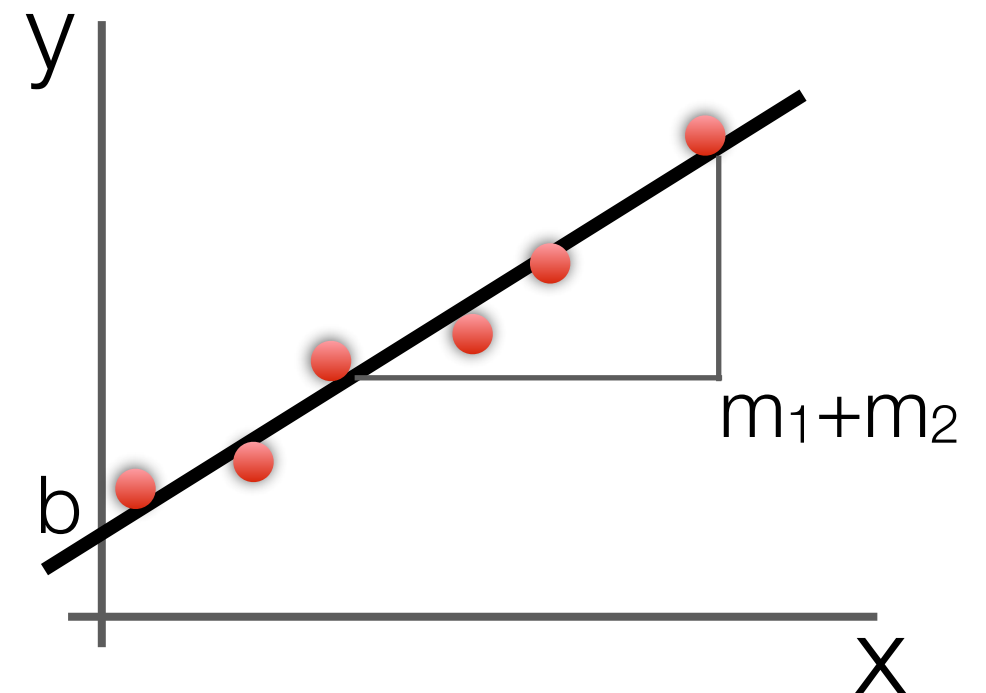


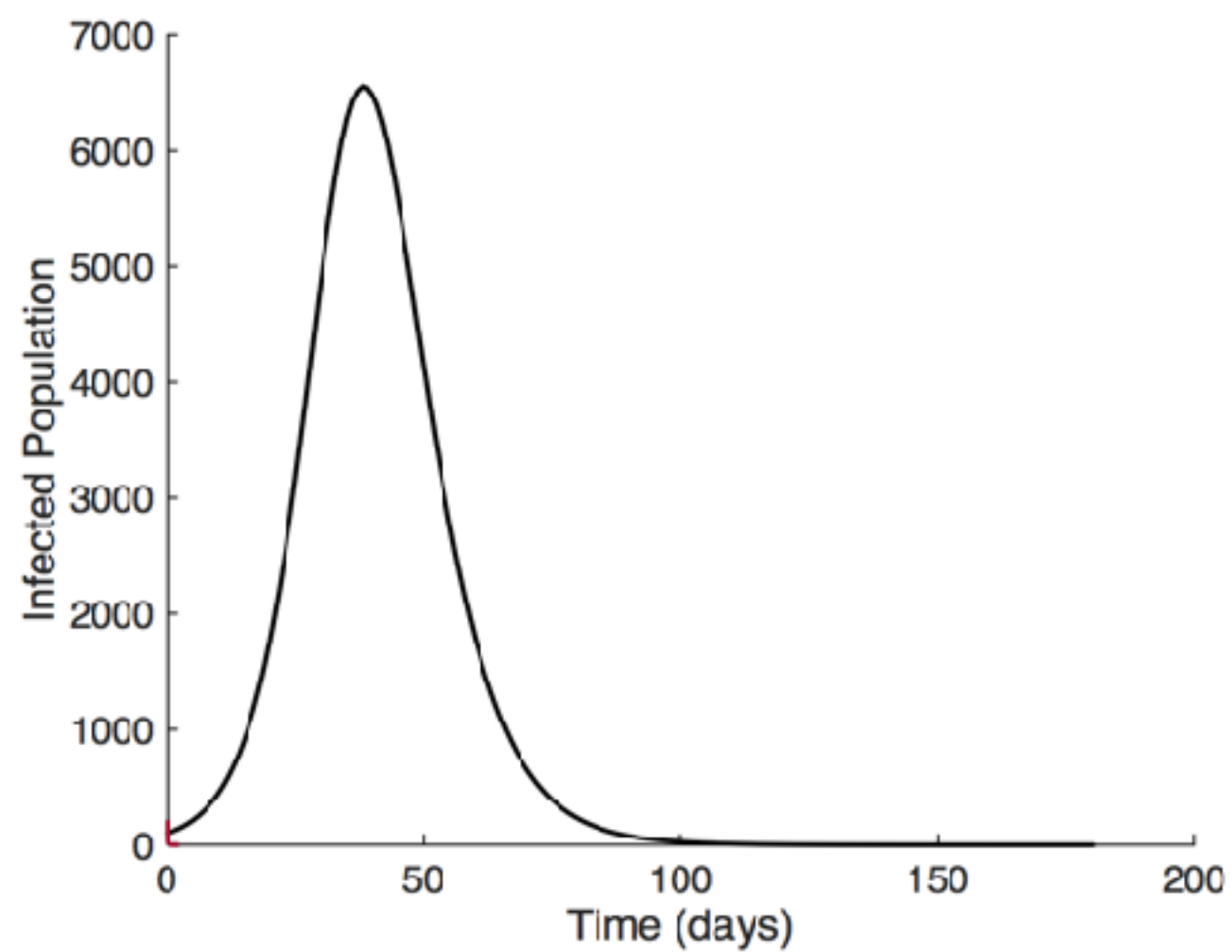
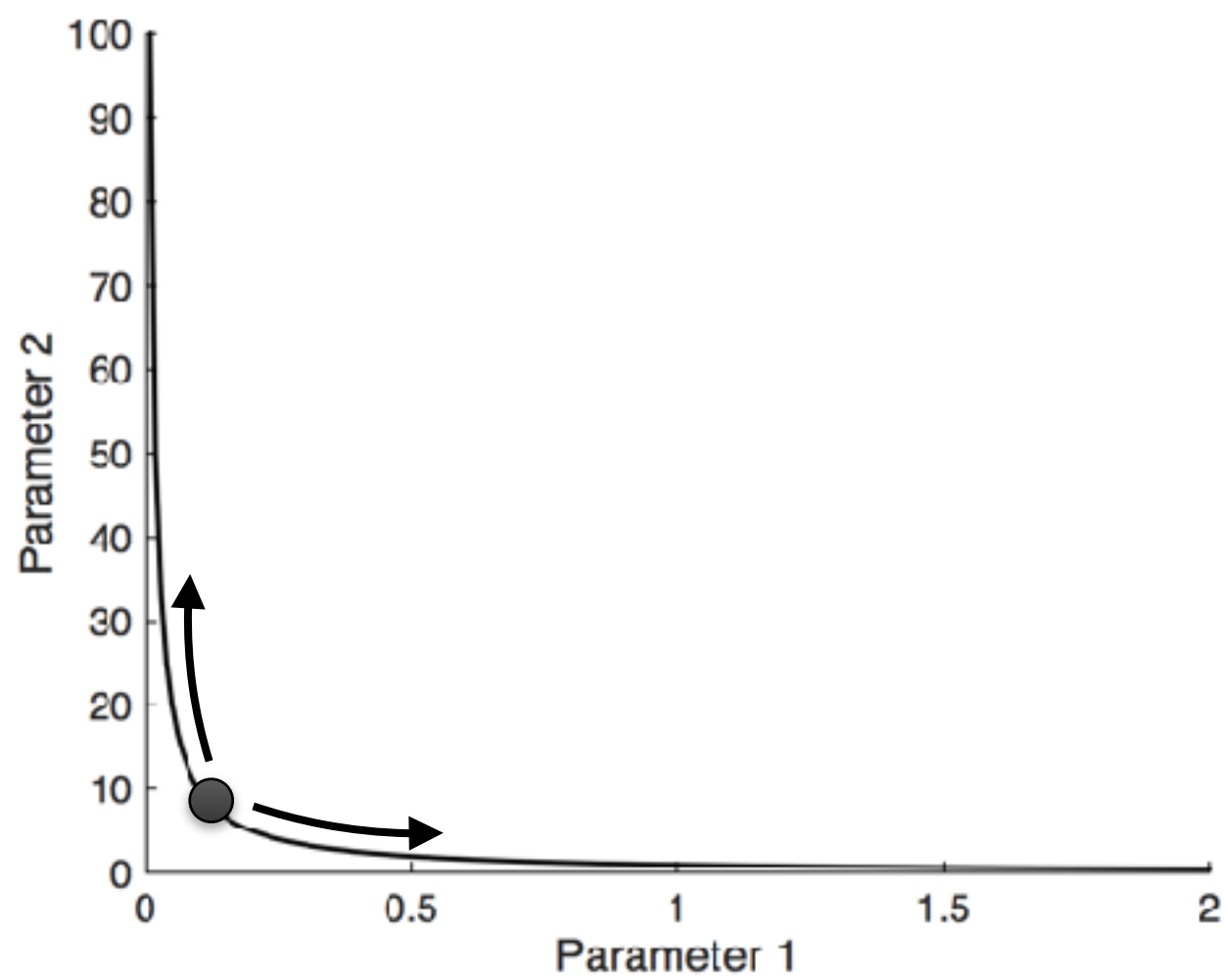
- Important problem in parameter estimation
- Many different approaches - statistics, applied math, engineering/systems theory

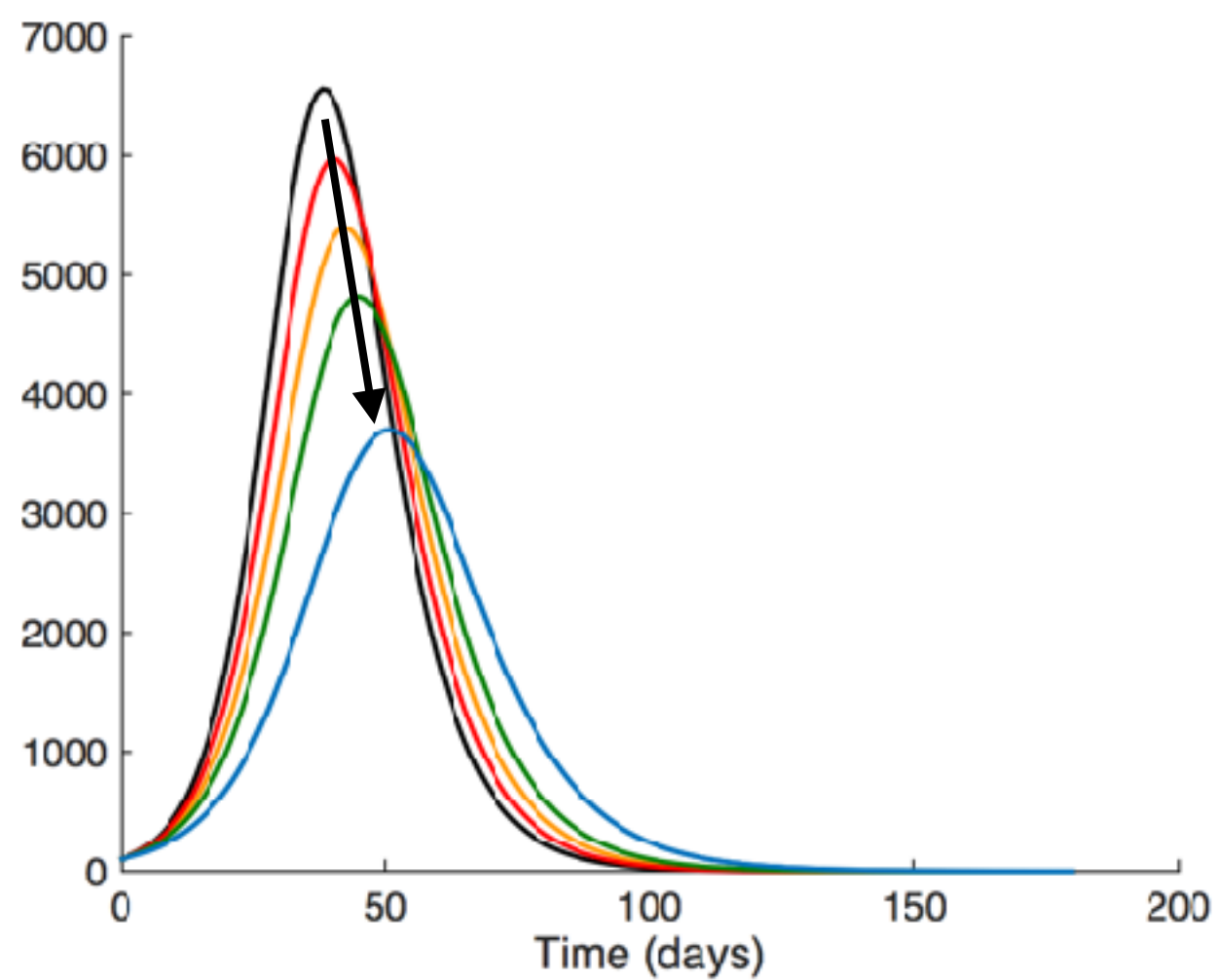
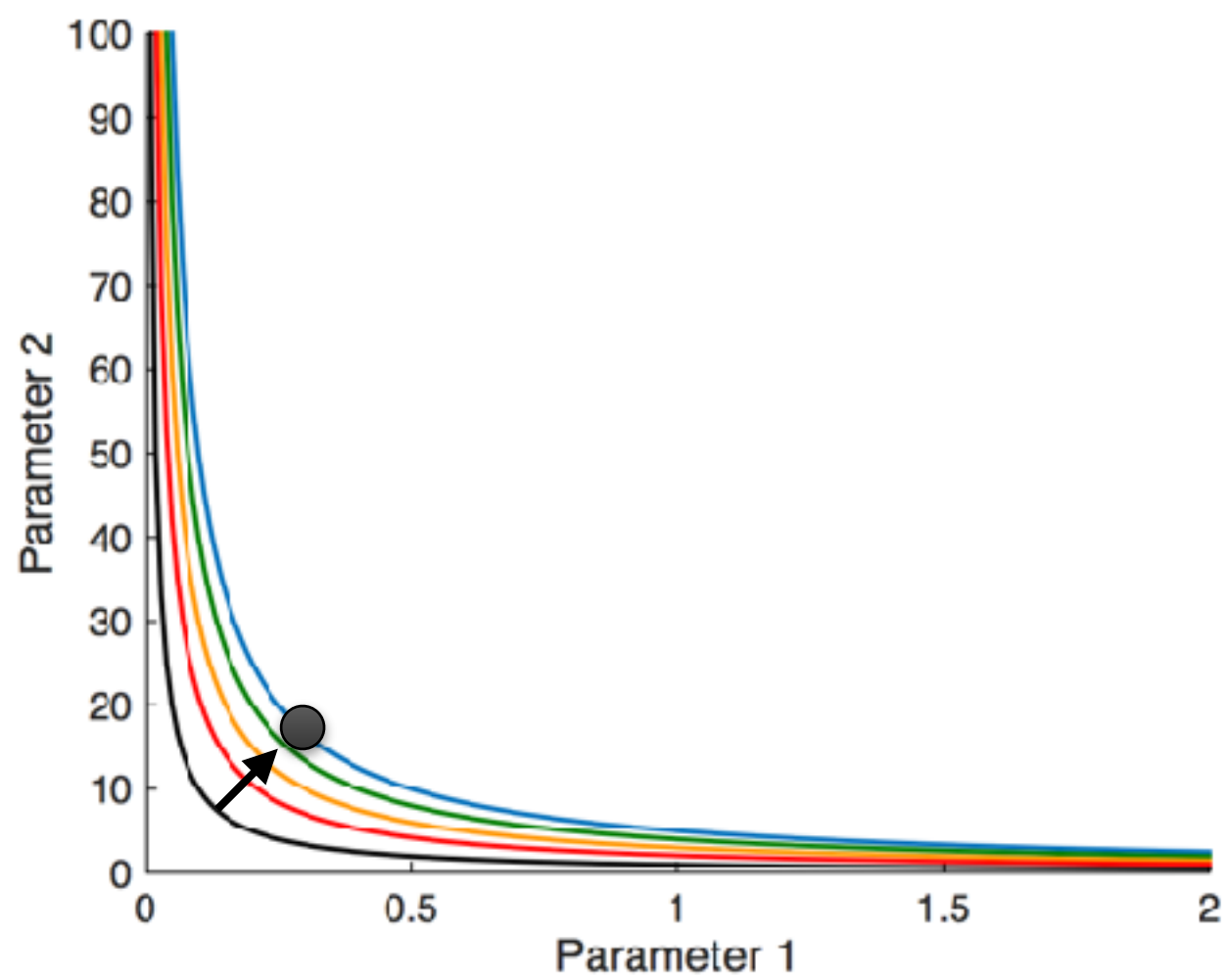
# Identifiability

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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

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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

# 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

# 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)

# 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
- **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
- **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

# 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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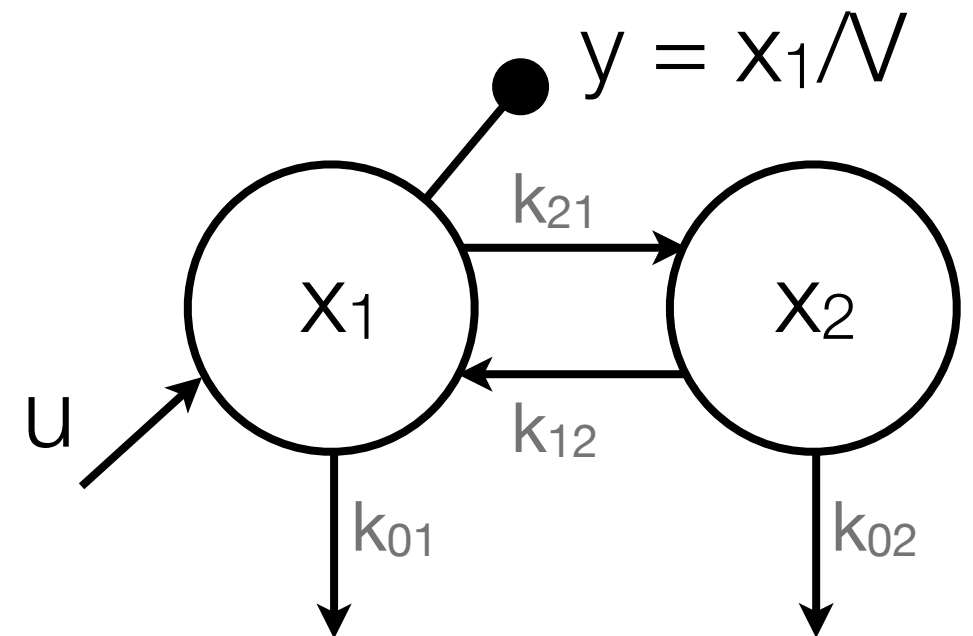
- Linear 2-Comp Model

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

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

$$y = x_1 / V$$

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



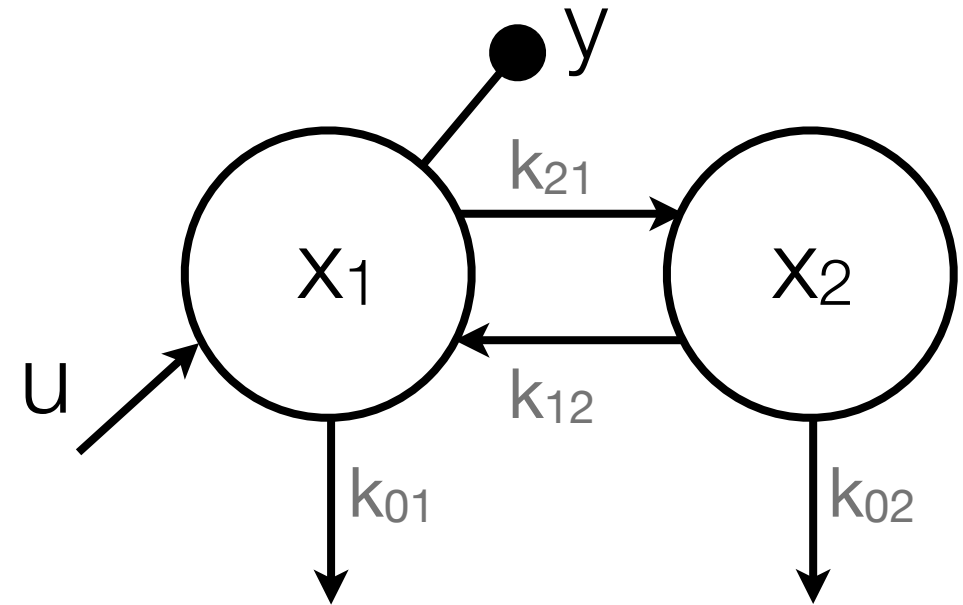
## 2-Compartment Example

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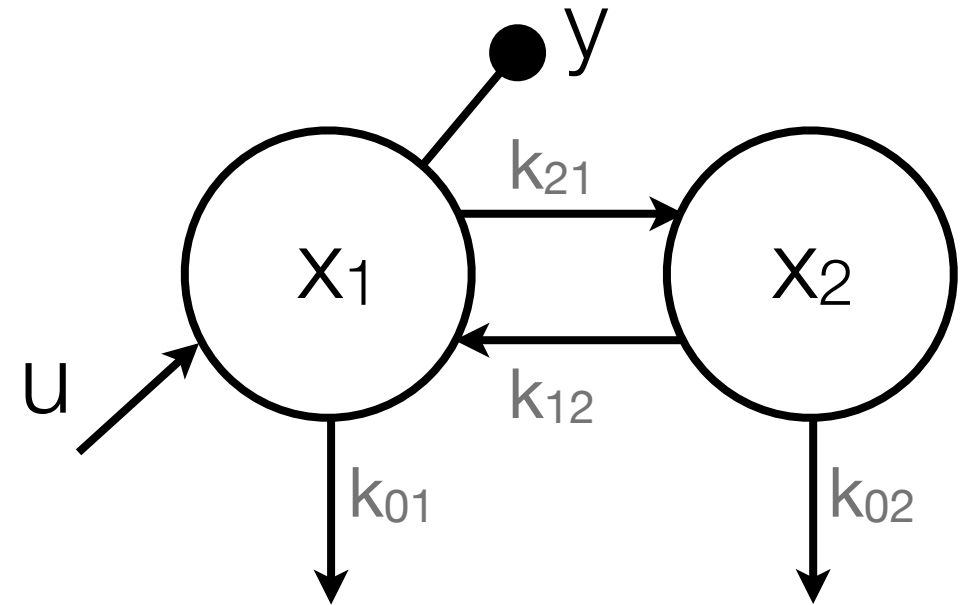


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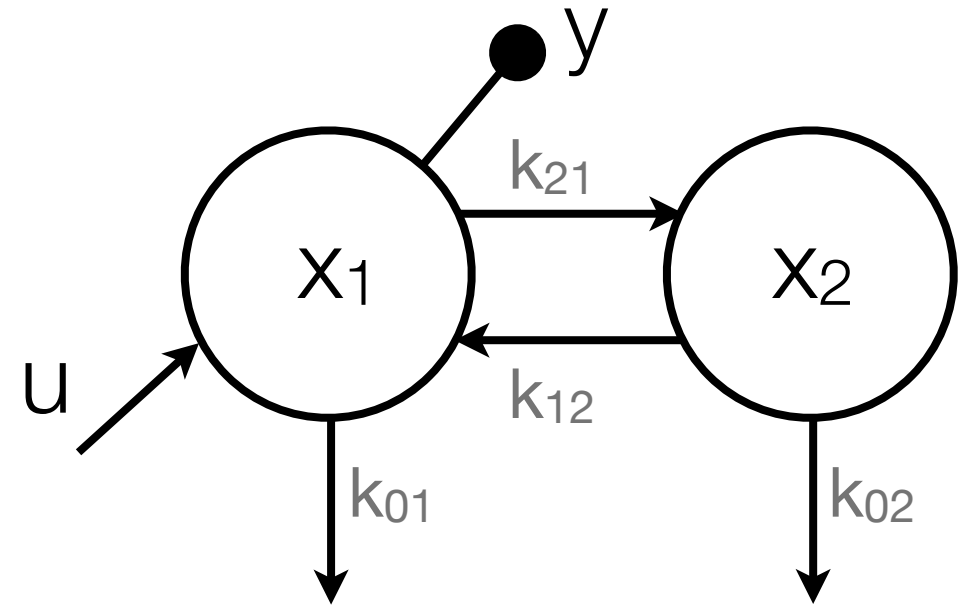


## 2-Compartment Example

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

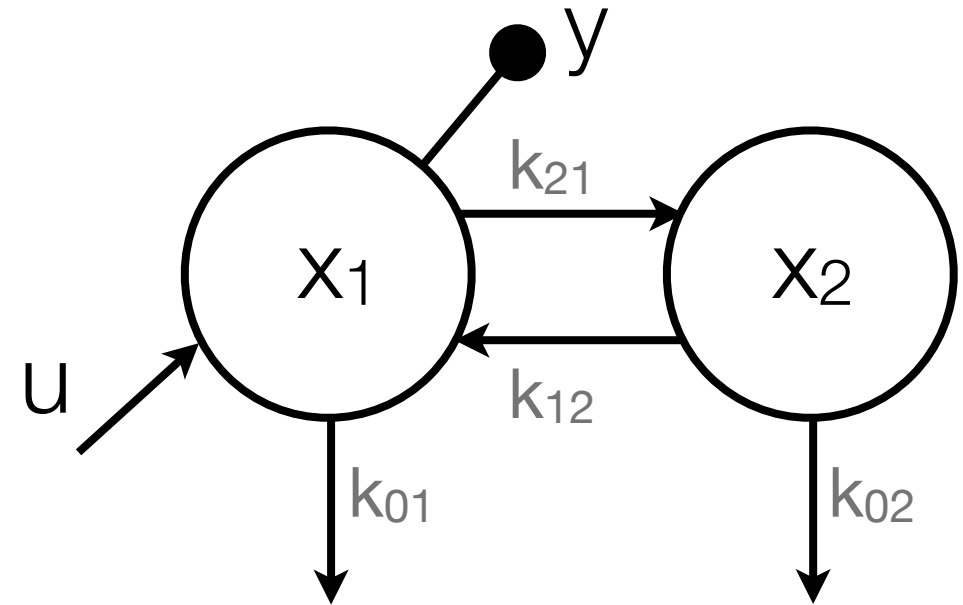
$$\dot{x}_2 = k_{21}x_1 - (k_{02} + k_{12})x_2$$



## 2-Compartment Example

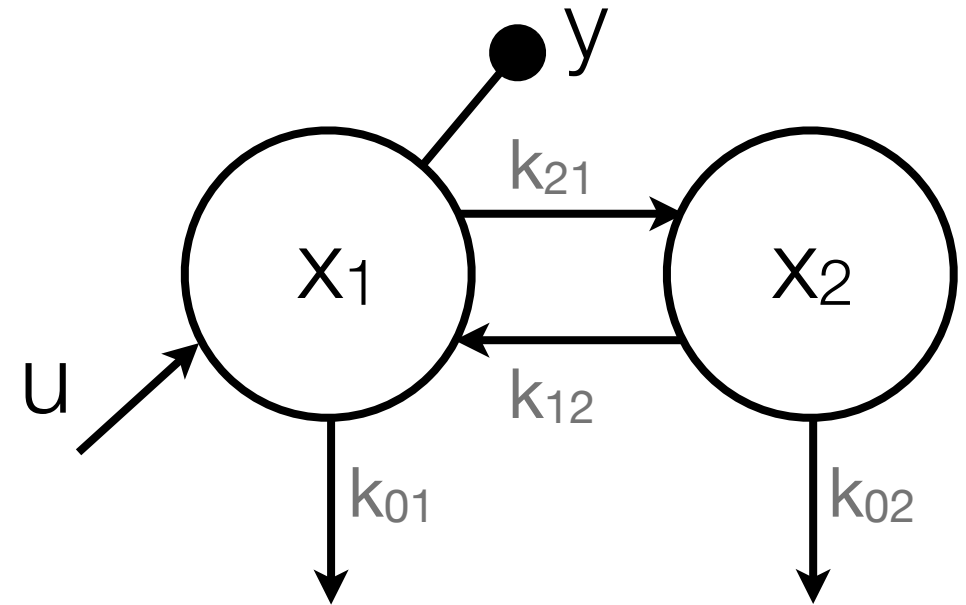
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$$\dot{\mathbf{x}} = \begin{bmatrix} -k_{12} - k_{01} & k_{21} \\ k_{12} & -k_{21} - k_{02} \end{bmatrix} \mathbf{x} + \begin{bmatrix} k_{01} \\ 0 \end{bmatrix} u + \begin{bmatrix} k_{21} \\ k_{02} \end{bmatrix} y$$



## 2-Compartment Example

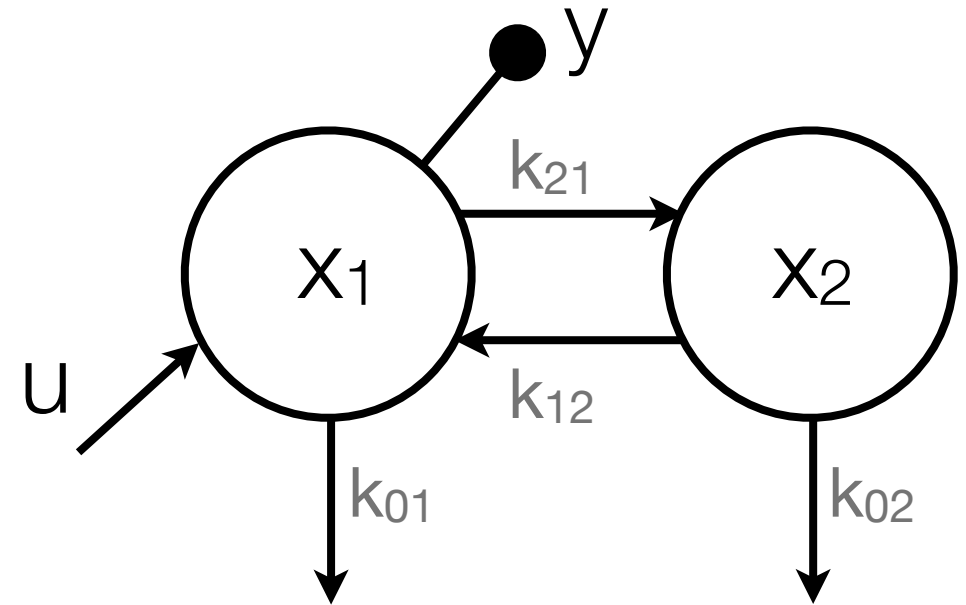
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$$\ddot{y} + (k_{01} + k_{21} + k_{12} + k_{02})\dot{y} -$$
$$(k_{12}k_{21} - (k_{02} + k_{12})(k_{01} + k_{21}))y - u(k_{12} + k_{02})/V - \dot{u}/V = 0$$

## 2-Compartment Example

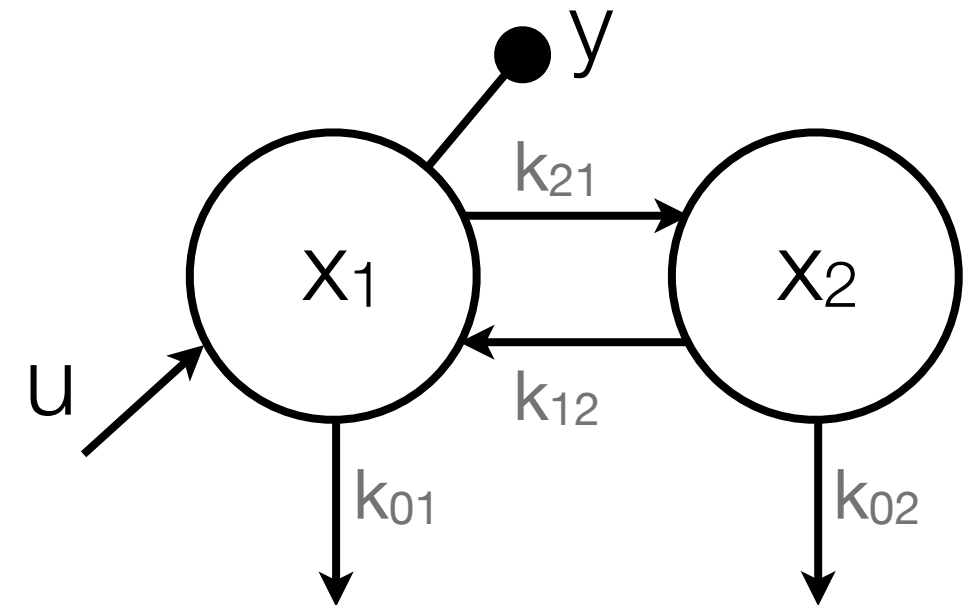
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$$\ddot{y} + (k_{01} + k_{21} + k_{12} + k_{02})\dot{y} - \left(k_{12}k_{21} - (k_{02} + k_{12})(k_{01} + k_{21})\right)y - u(k_{12} + k_{02})/V - \dot{u}/V = 0$$

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

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

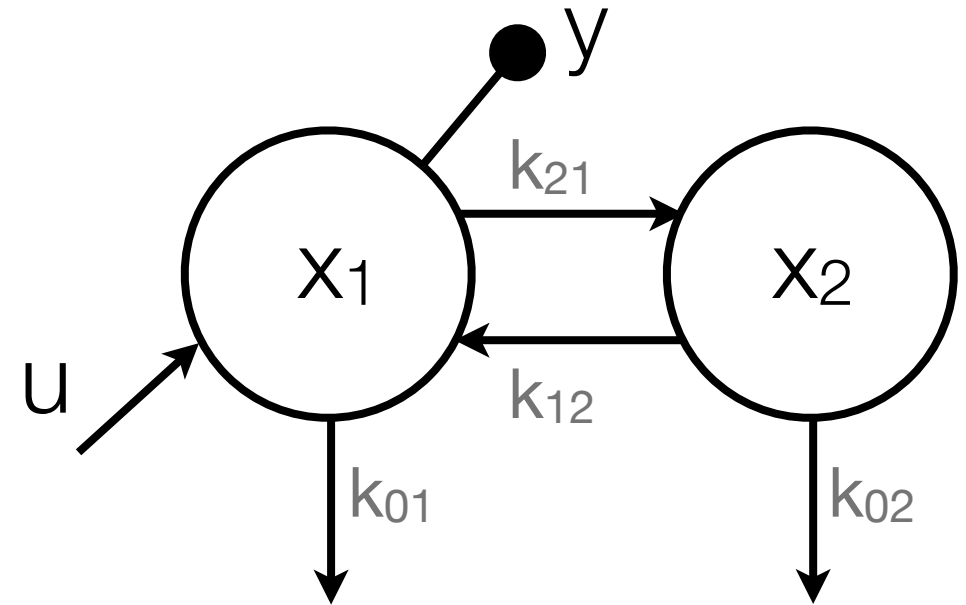
$$\left(k_{12}k_{21} - (k_{02} + k_{12})(k_{01} + k_{21})\right)$$

$$1/V$$



# 2-Compartment Example

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

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

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

$$1 / V$$

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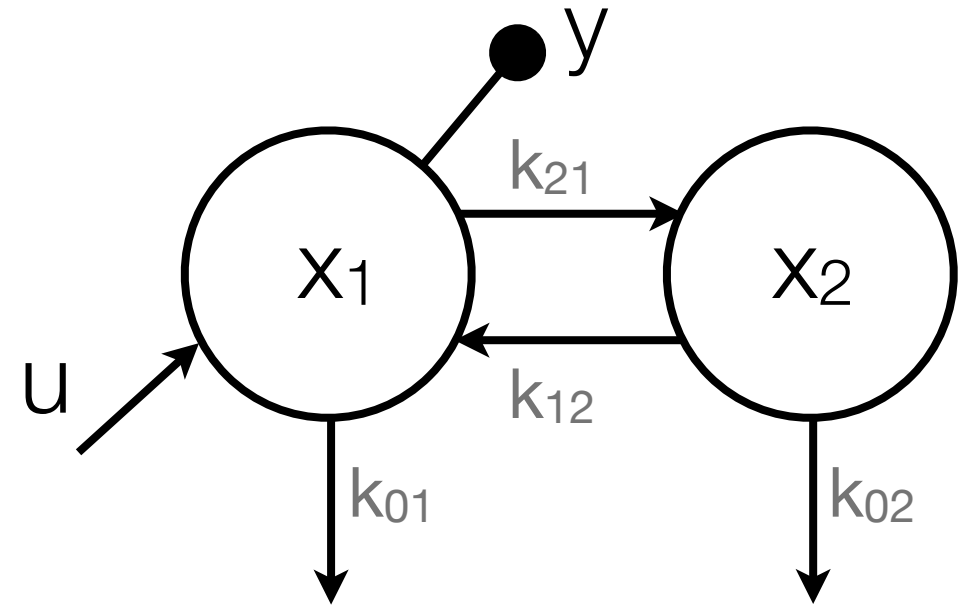
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$$1 / V$$

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

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

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



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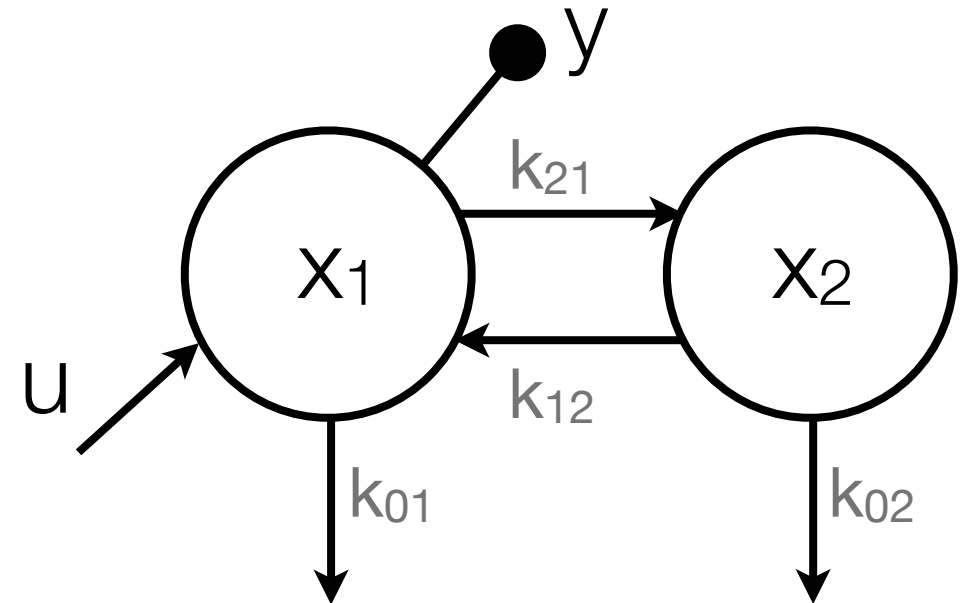
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$$1 / V = a_1$$

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

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

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



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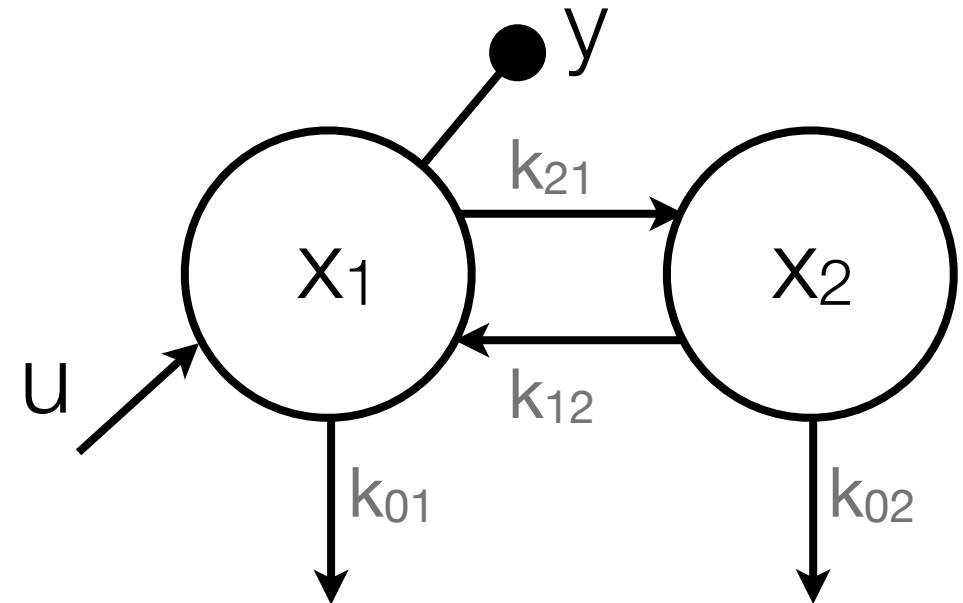
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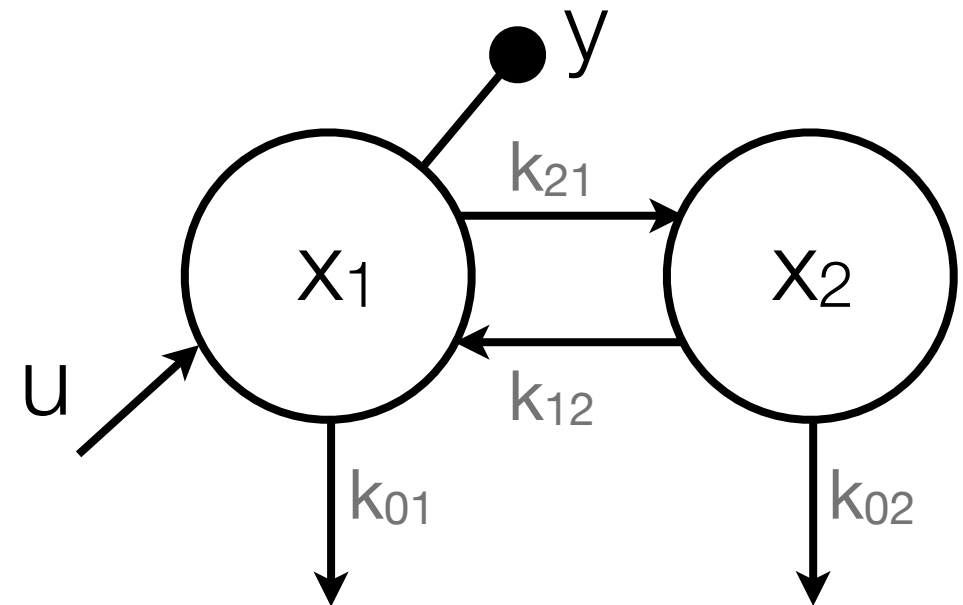
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Unidentifiable

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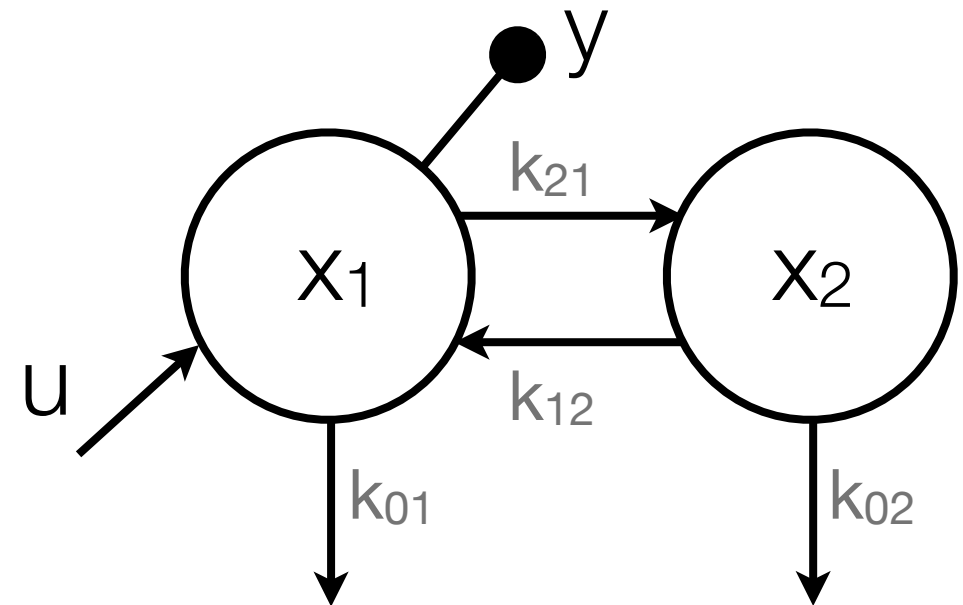
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Unidentifiable

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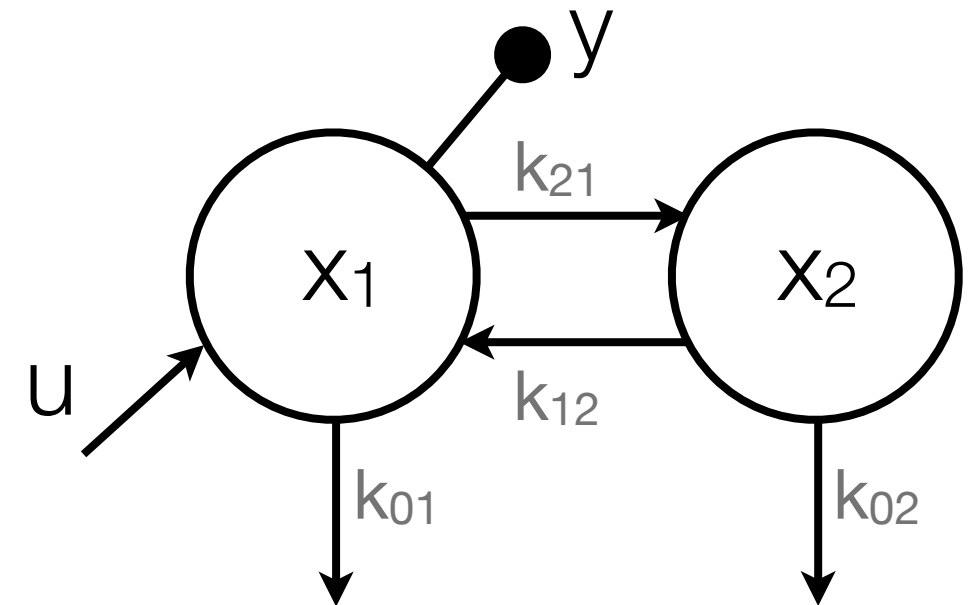
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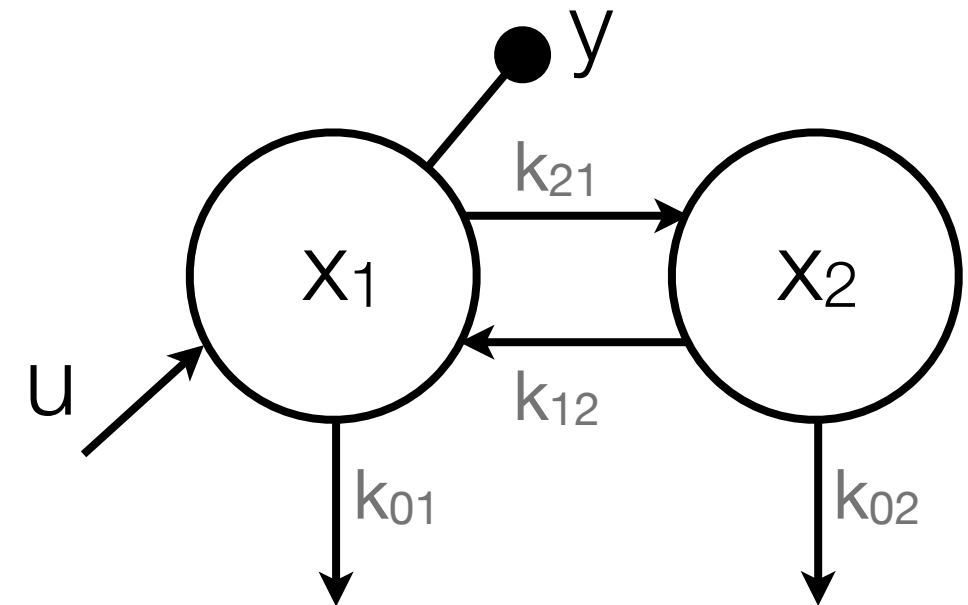
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Unidentifiable



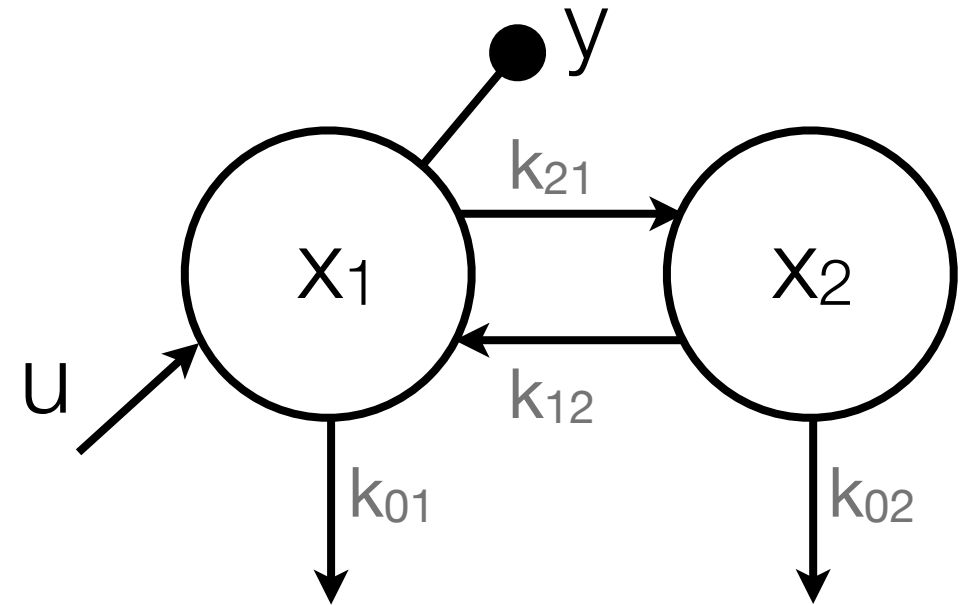
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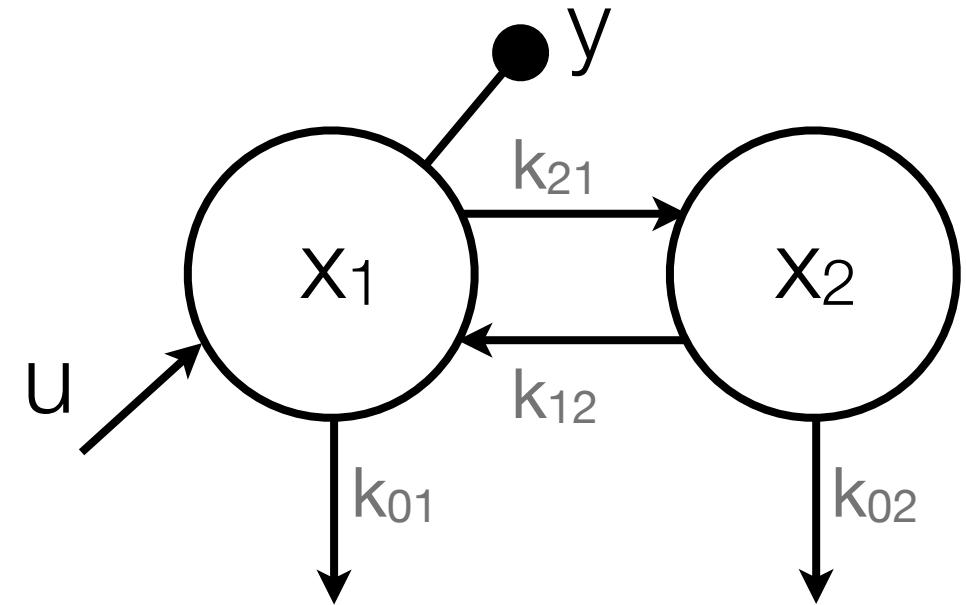
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$$y = x_1 / \underline{V}$$

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



## 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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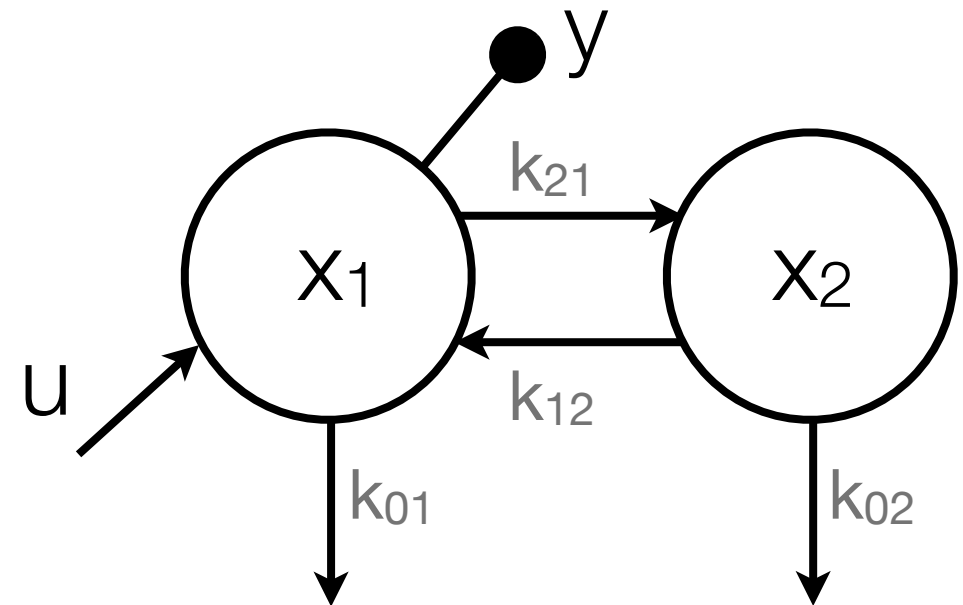
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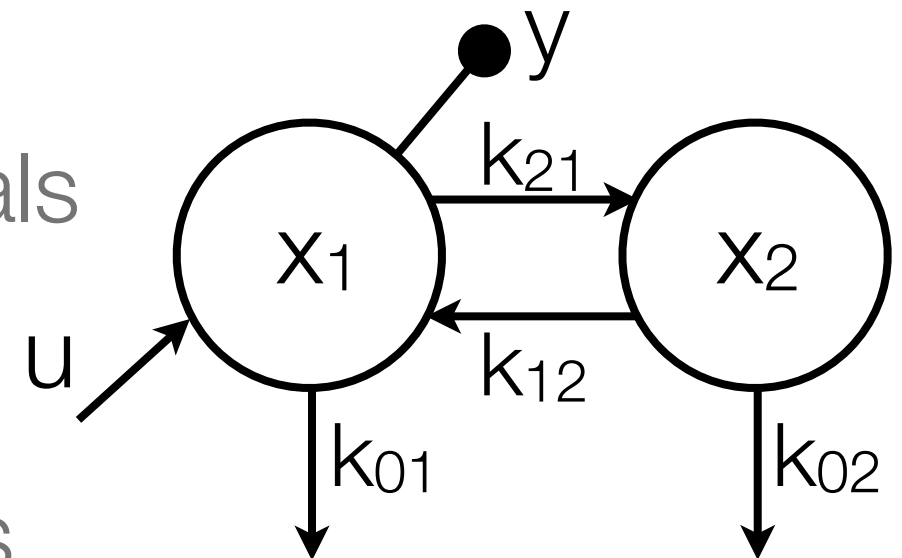


Or add information  
about one of  
the parameters

# Differential Algebra Approach

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- 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



# 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)

# Differential Algebra Approach

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- 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

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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

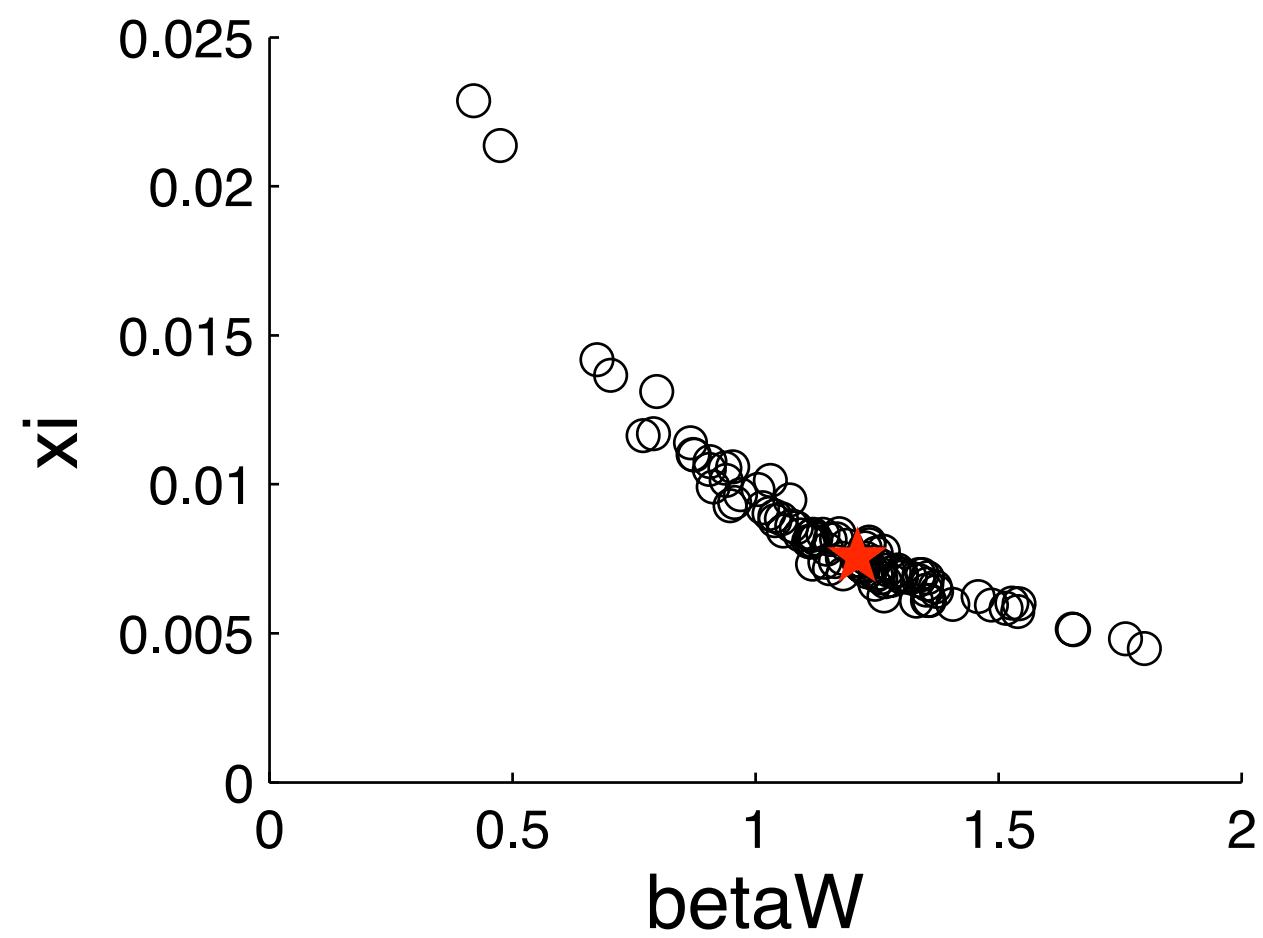
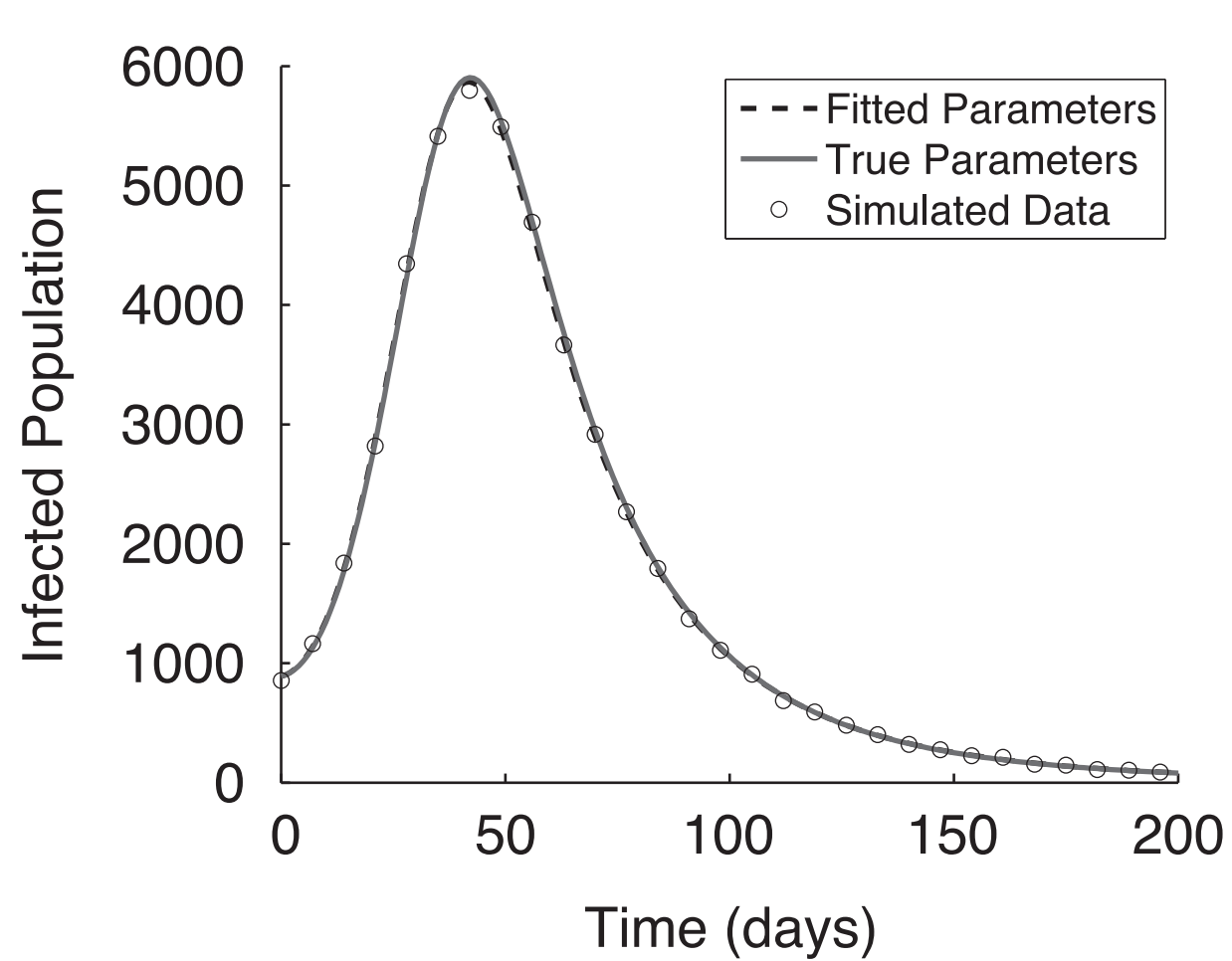
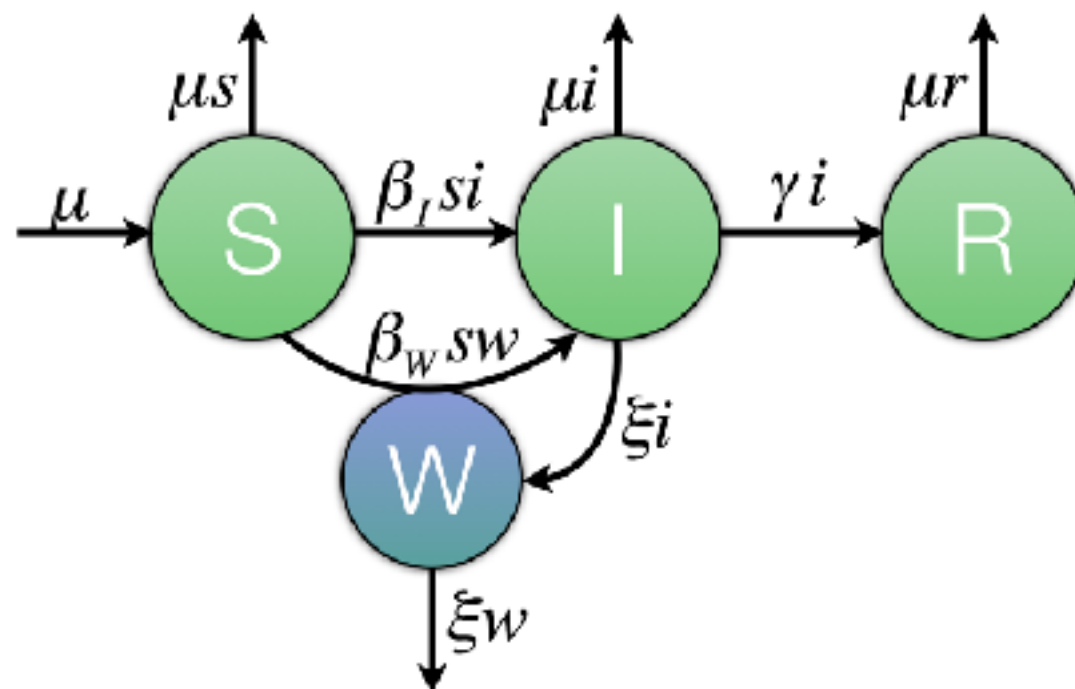
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- Simulate data using a single set of 'true' parameter values
- Without noise for structural identifiability
- With noise for practical identifiability (in this case generate multiple realizations of the data)

# 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
- 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

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- FIM -  $N_P \times N_P$  matrix

$$[\mathcal{I}(\theta)]_{i,j} = \mathbb{E} \left[ \left( \frac{\partial}{\partial \theta_i} \log f(X; \theta) \right) \left( \frac{\partial}{\partial \theta_j} \log f(X; \theta) \right) \middle| \theta \right]$$

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

# Fisher Information Matrix

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- Special case when errors are normally distributed

$$F = X^T W X$$

$W$  = weighting matrix

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

# Fisher Information Matrix

---

- For looking at structural ID, often just use

$$F = X^T X$$

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



# 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  $\text{Cov} \sim \text{FIM}^{-1}$

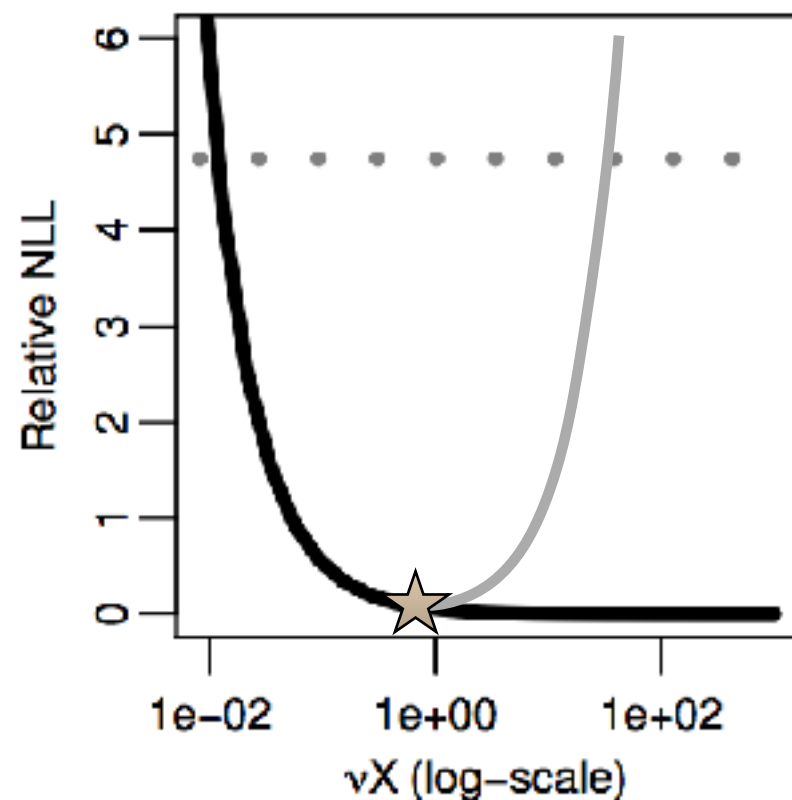
# Identifiability & the FIM

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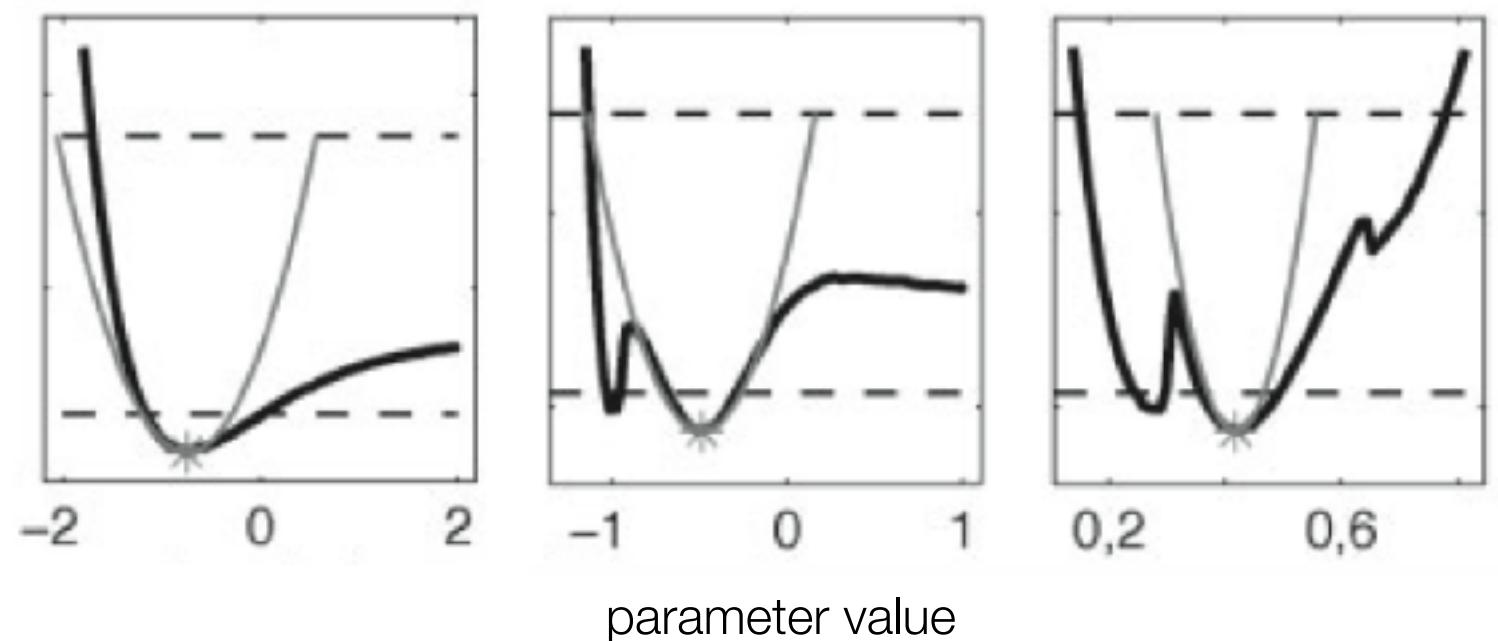
- **Rank of the FIM** is number of identifiable combinations/parameters - can do a lot by testing sub-FIMs and versions of the FIM
- Use FIM to find blocks of related parameters & how many to fix (not estimate)
- Identifiable combinations - can often see what parameters are related, but don't know form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

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- 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)

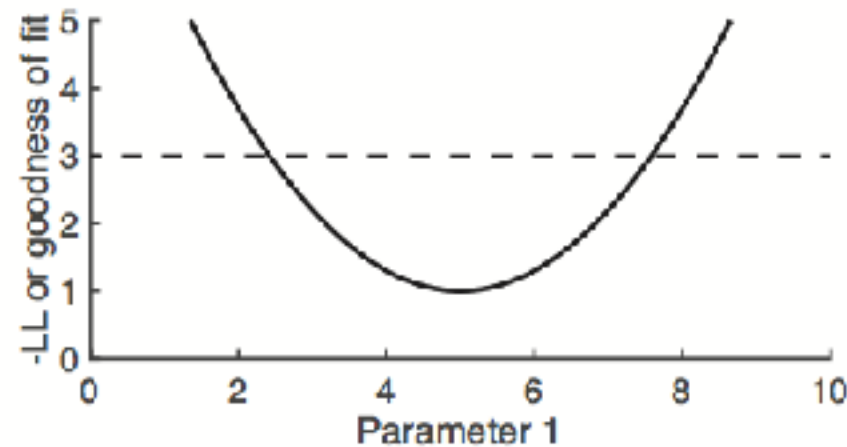
# Profile Likelihood

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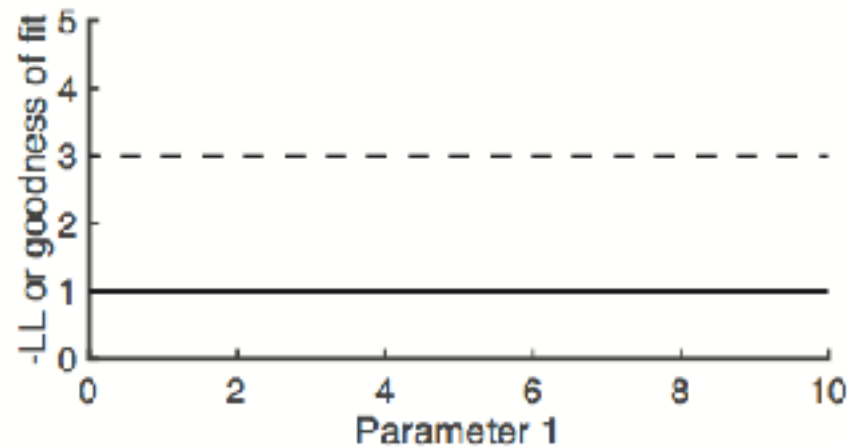
- Choose a range of values for parameter  $p_i$
- For each value, fix  $p_i$  to that value, and fit the rest of the parameters
- Report the best likelihood/RSS/cost function value for that  $p_i$  value
- Plot the best likelihood values for each value of  $p_i$ —this is the profile likelihood

# Profile Likelihoods

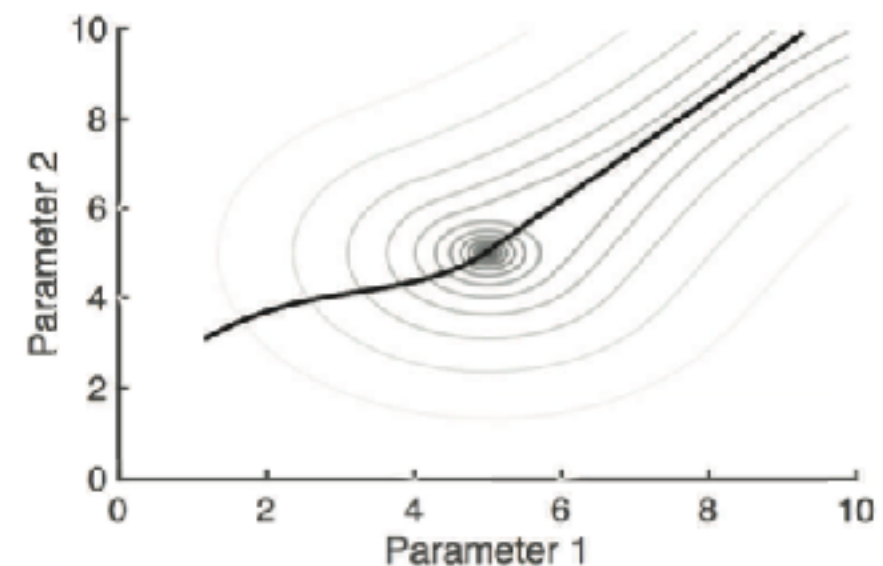
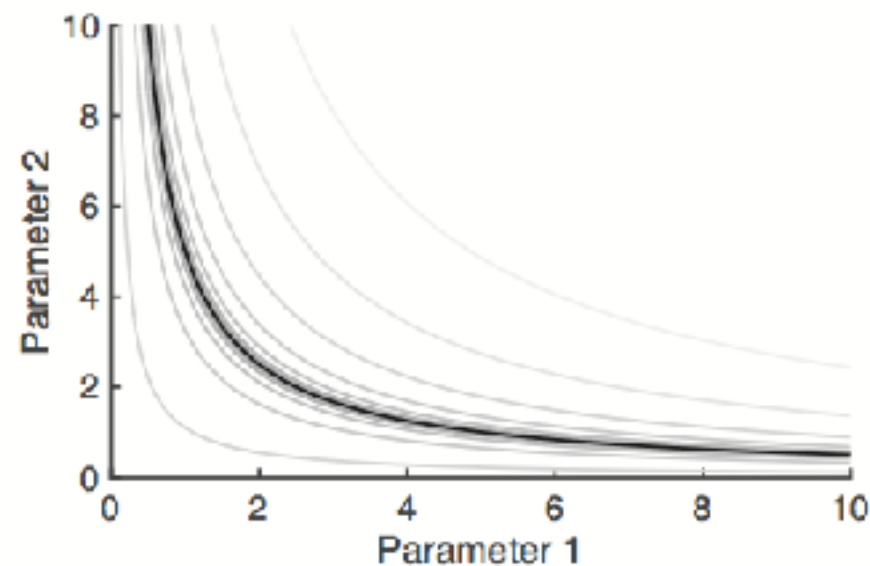
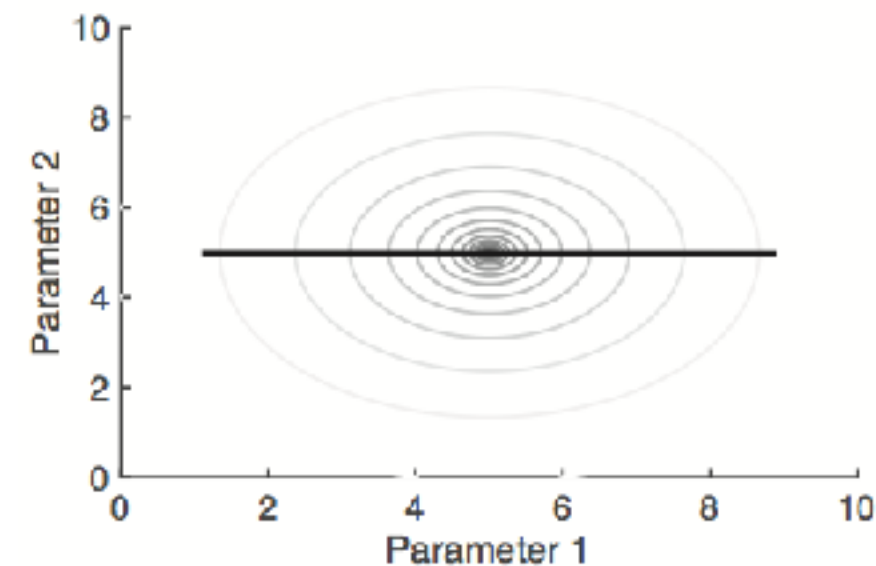
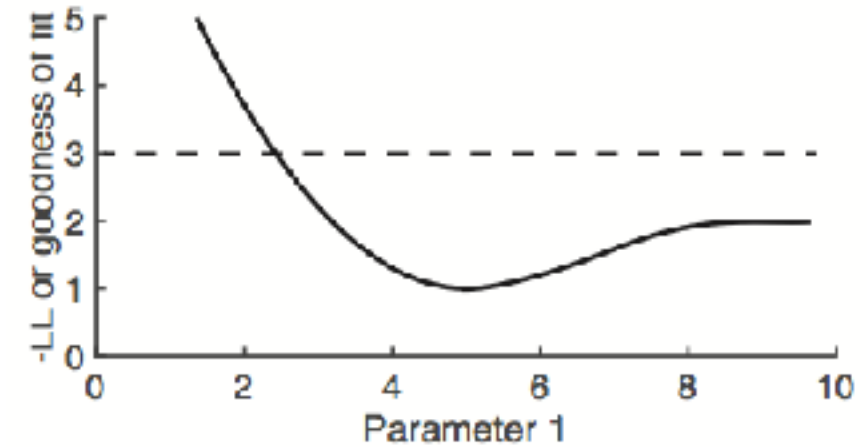
identifiable



structurally  
unidentifiable



practically  
unidentifiable



# Profile Likelihood & ID

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- 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 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)



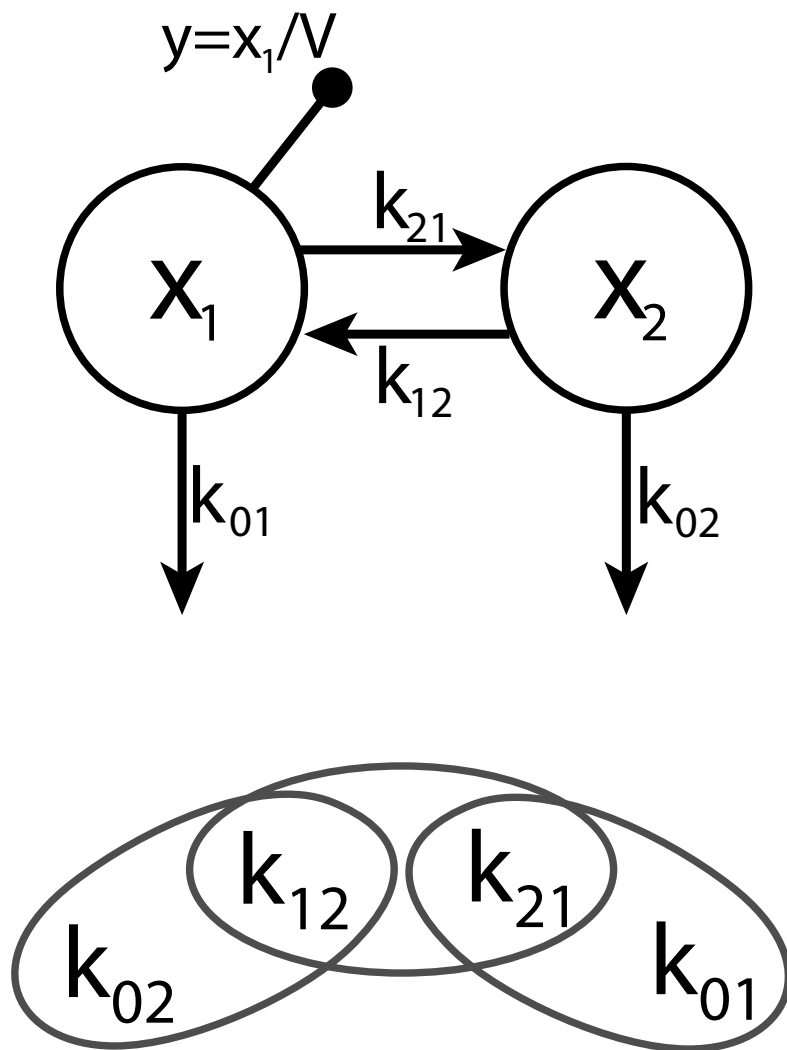
## 2-Compartment Example

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

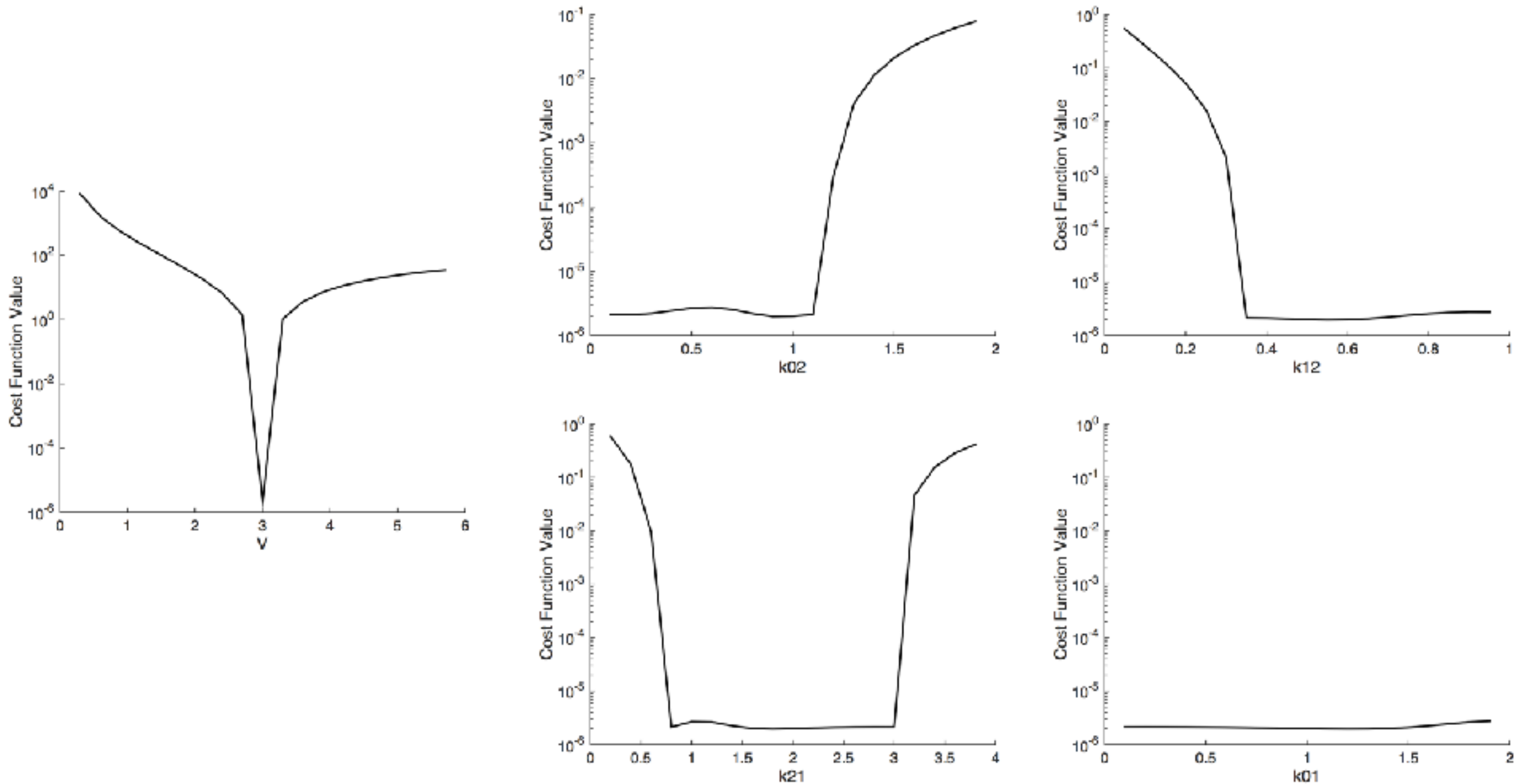
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$$(k_{01} + k_{21} - k_{12} + k_{02}) = a_3$$

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

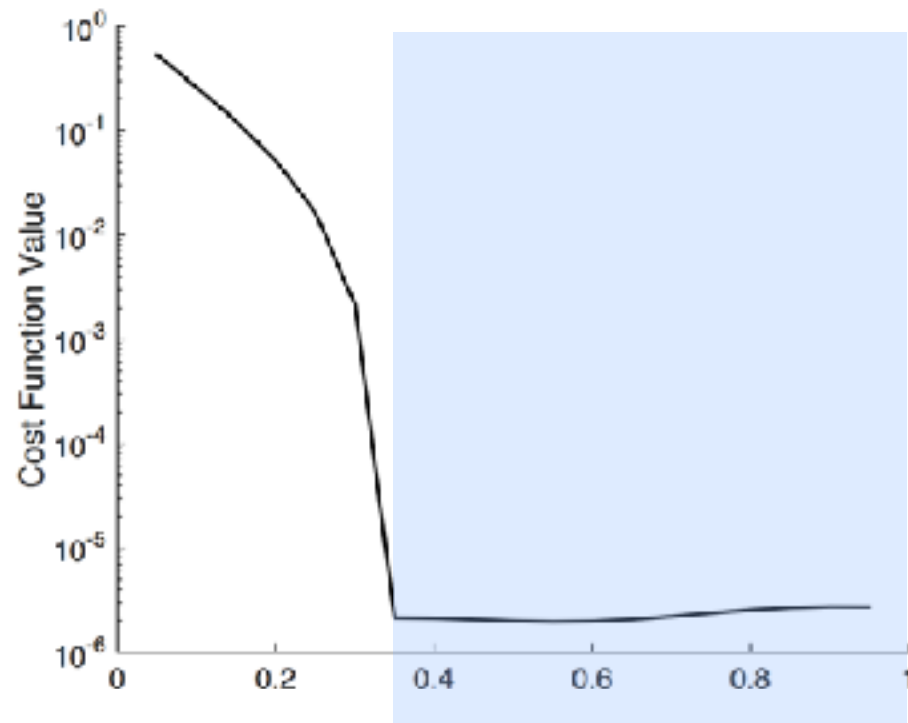


# Profile Likelihoods

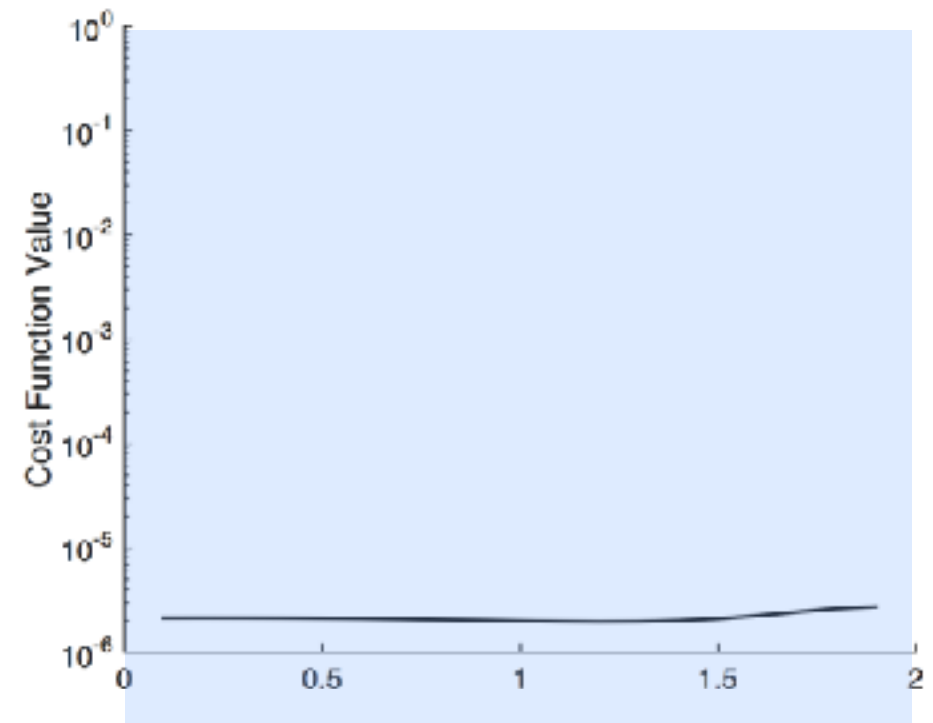


# Parameter Relationships

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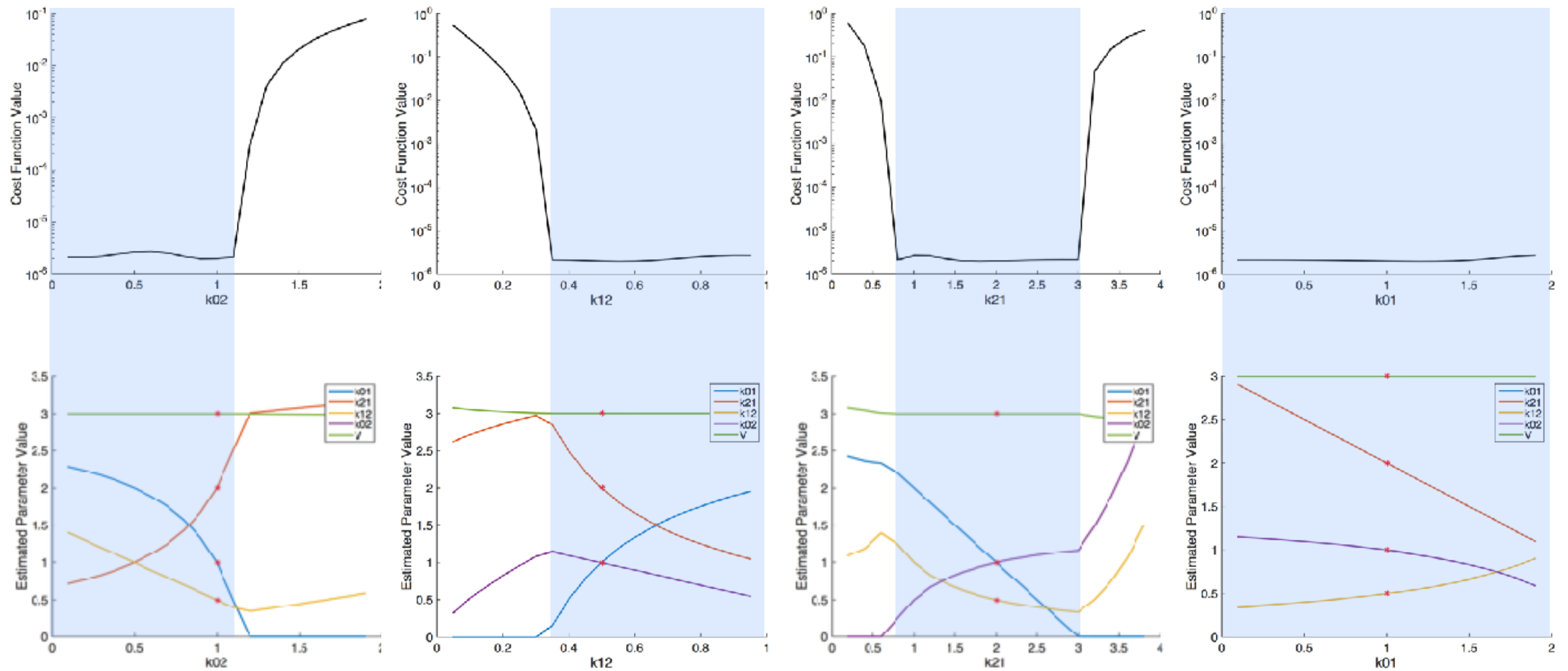


k12



k01

# Parameter Relationships



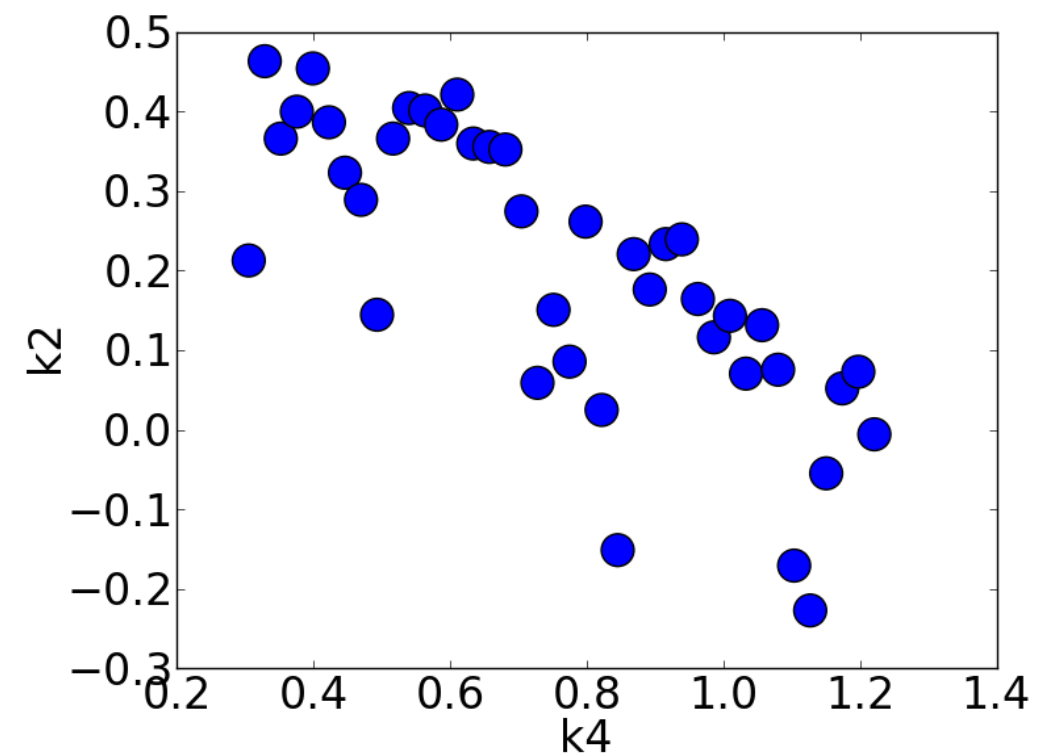
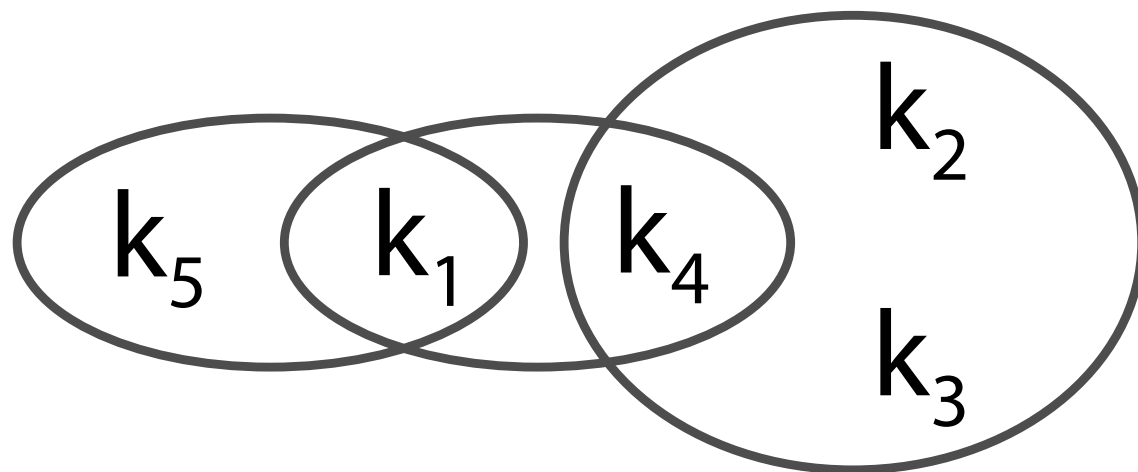
# Some potential issues

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

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

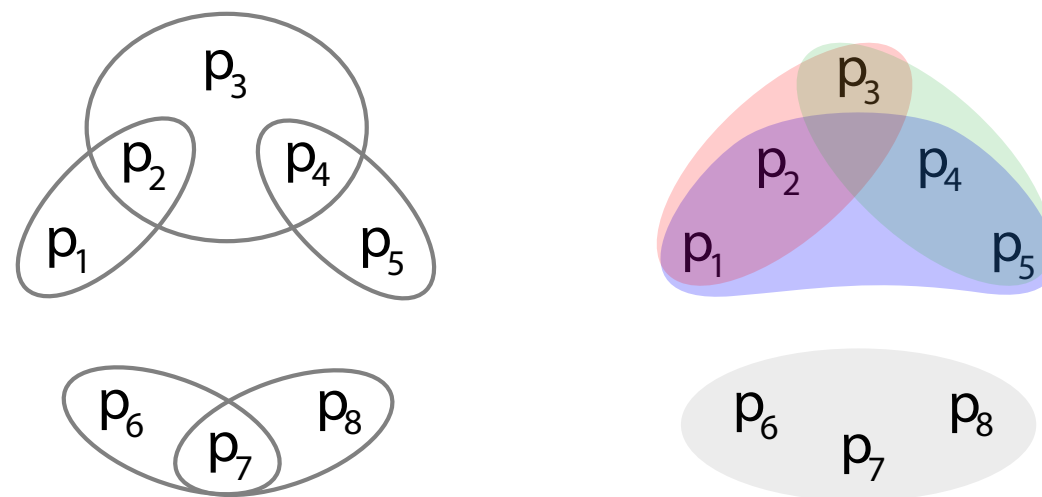
$$y = x_1 / V$$



# FIM Subset Approach

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- 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

# FIM Subset Approach

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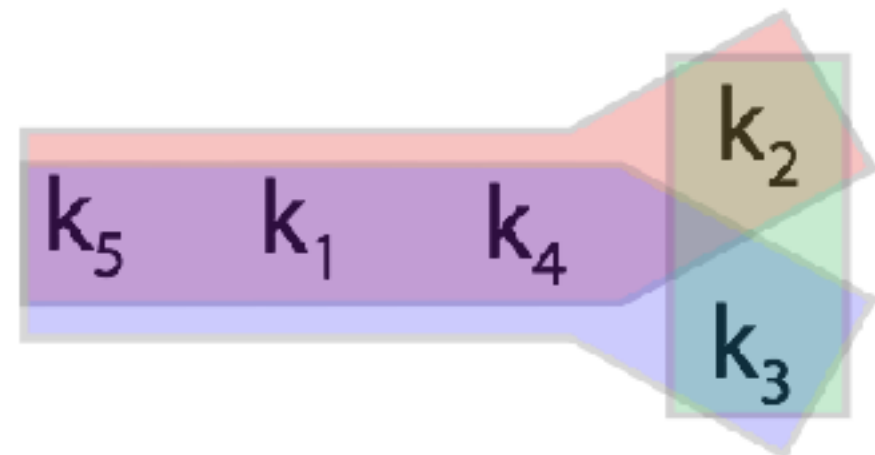
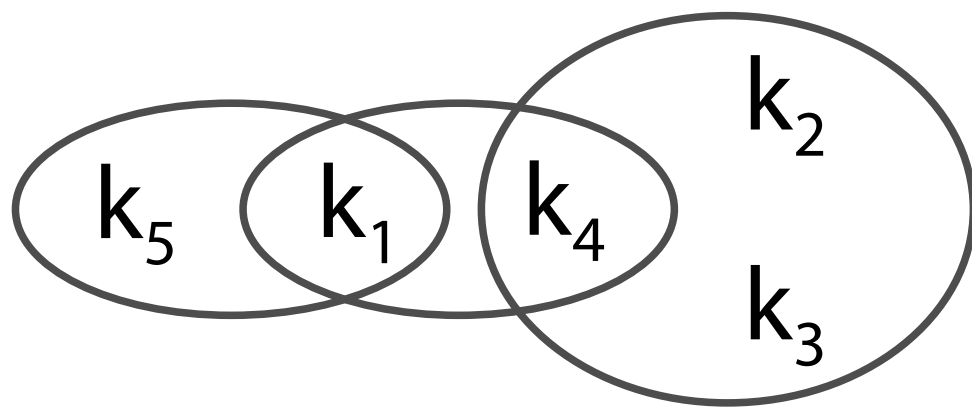
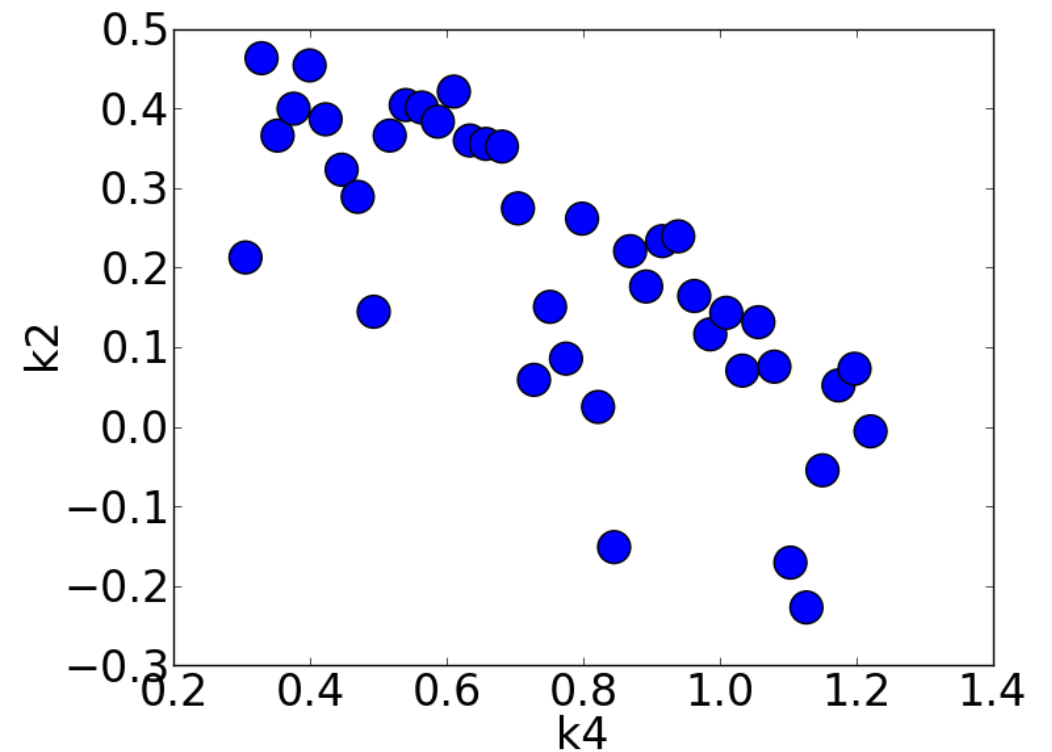
- Use the FIM rank to select subsets of parameters which are *nearly full rank* (i.e. which become full rank if any single parameter is fixed)
- Use these subsets when likelihood profiling to determine all parameter relationships
- Polynomial interpolation to recover identifiable combinations

# Example Model

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

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

$$y = x_1 / V$$



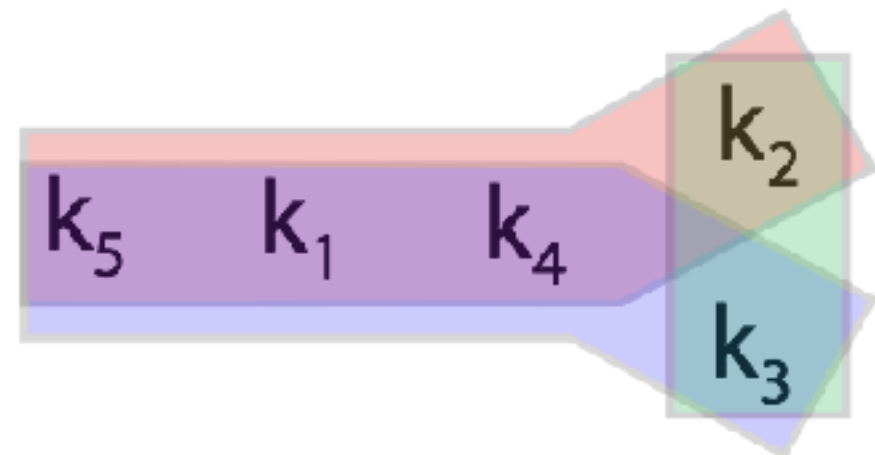
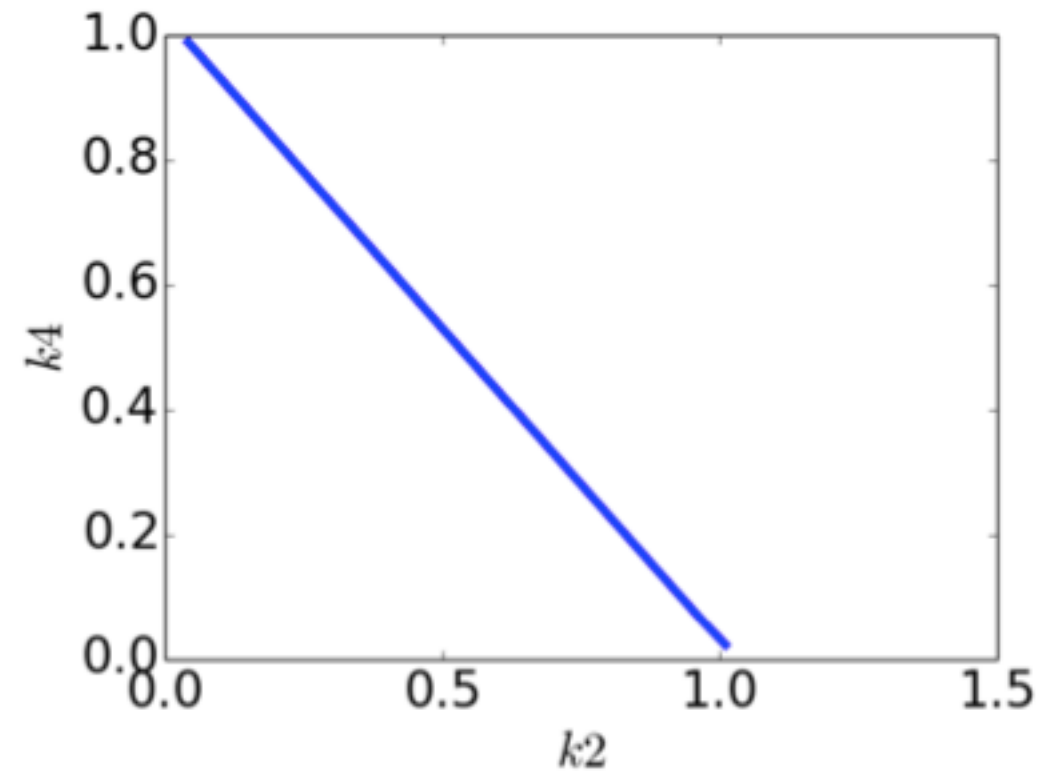
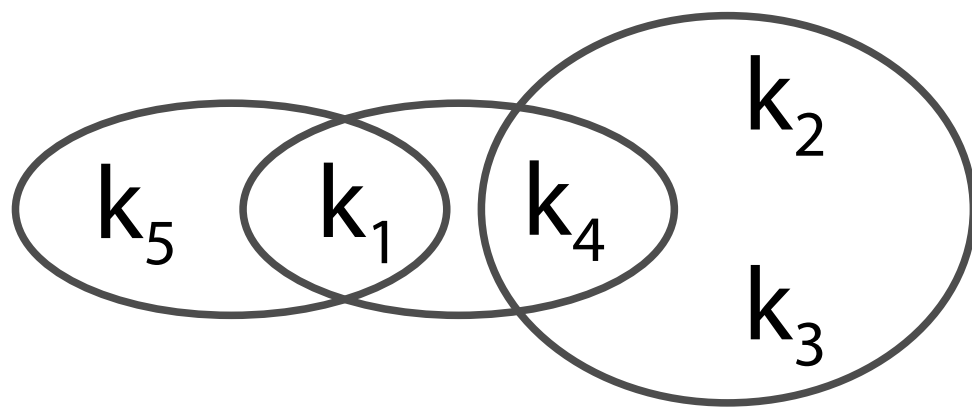


# Example Model

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

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

$$y = x_1 / V$$



# 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

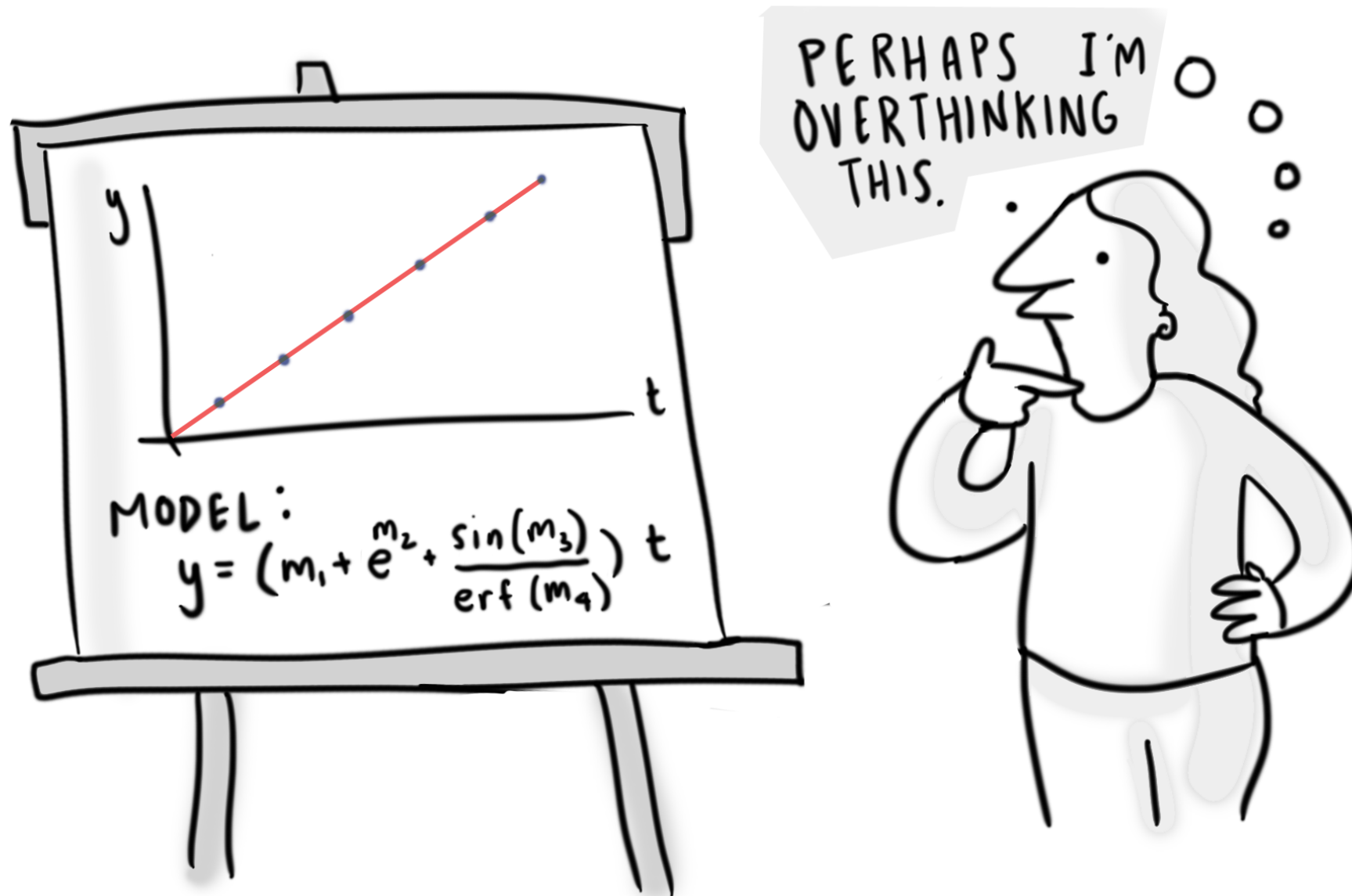
# Conclusions

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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>