

Structural identifiability and indistinguishability analysis for nonlinear systems

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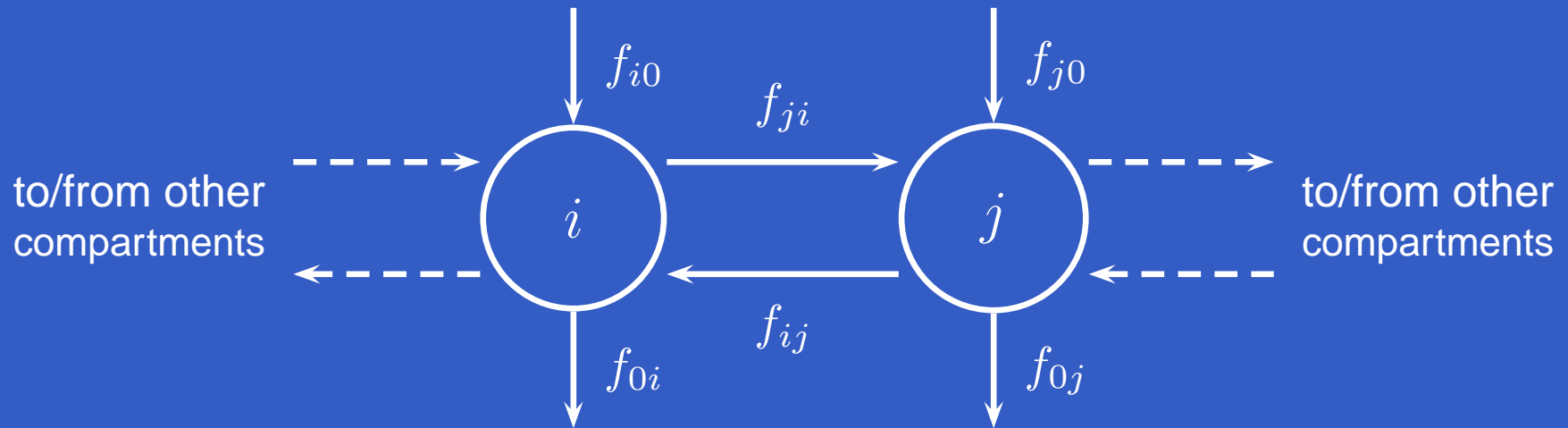
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Outline of talk

- Structural identifiability analysis
- Application to modelling of drug (topotecan) kinetics
- Structural indistinguishability analysis
- Application to infectious disease modelling
- Conclusions

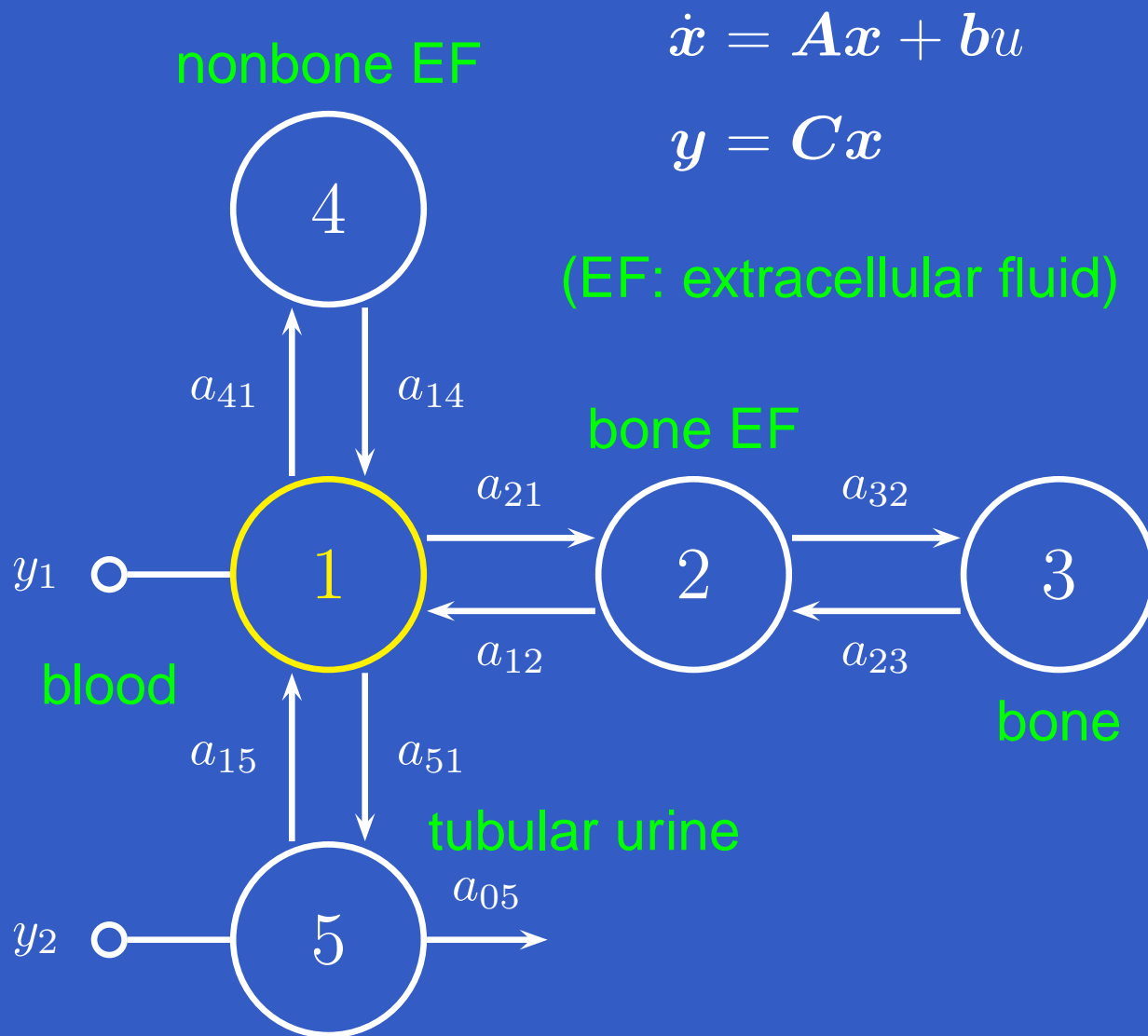
Compartmental modelling



$$\frac{dx_i}{dt} = f_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^n f_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n f_{ji} - f_{0i}, \quad i = 1, \dots, n$$

Compartmental systems consist of finite number of homogeneous, well-mixed, lumped subsystems (compartments) which exchange with each other and with the environment so that quantity/concentration in each compartment can be described by first order ODE.

Skeletal tracer kinetics model



$$\dot{x} = Ax + bu$$

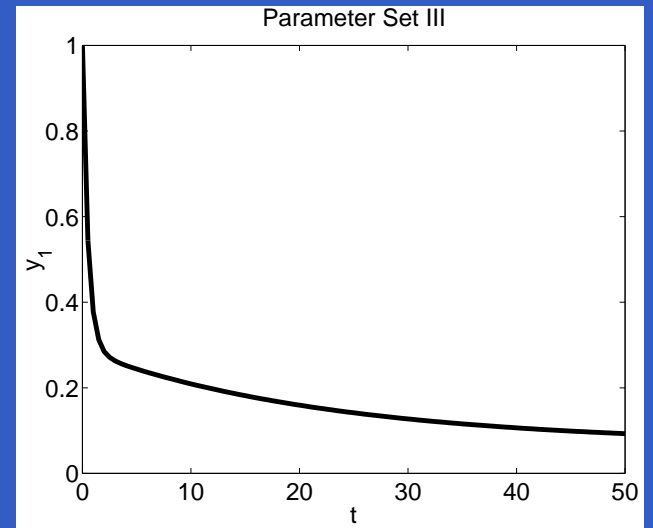
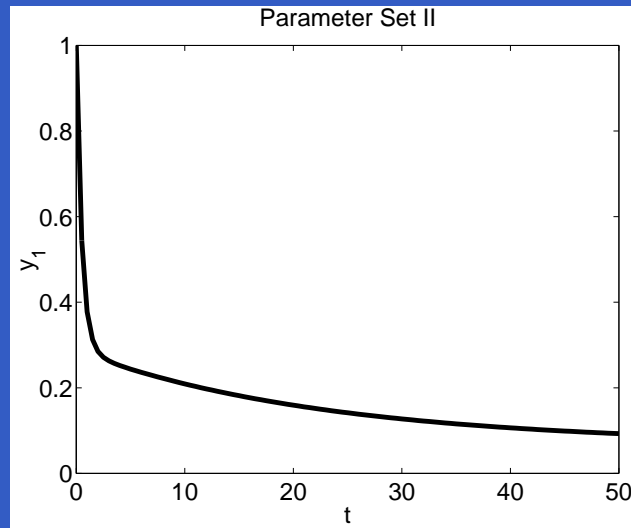
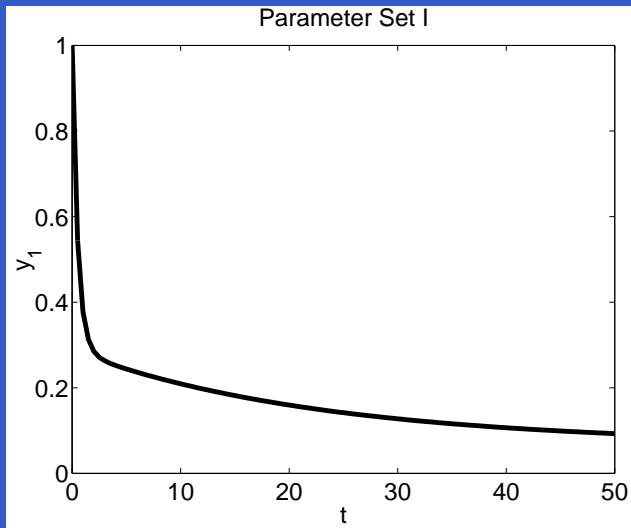
$$y = Cx$$

$$A = \begin{pmatrix} a_{11} & a_{12} & 0 & a_{14} & a_{15} \\ a_{21} & a_{22} & a_{23} & 0 & 0 \\ 0 & a_{32} & -a_{23} & 0 & 0 \\ a_{41} & 0 & 0 & -a_{14} & 0 \\ a_{51} & 0 & 0 & 0 & a_{55} \end{pmatrix}$$

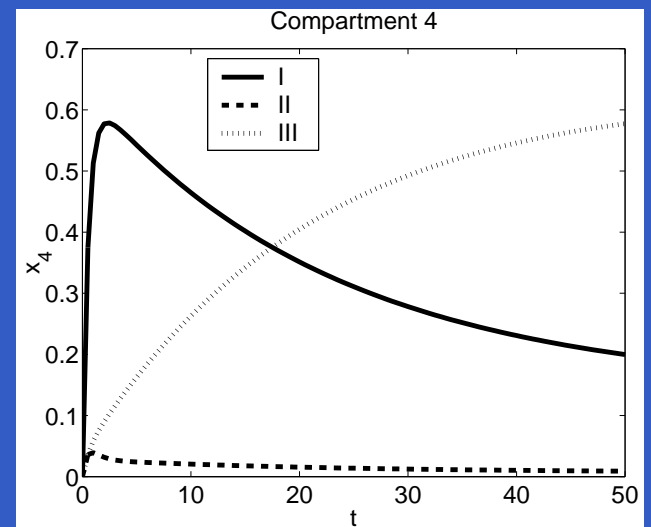
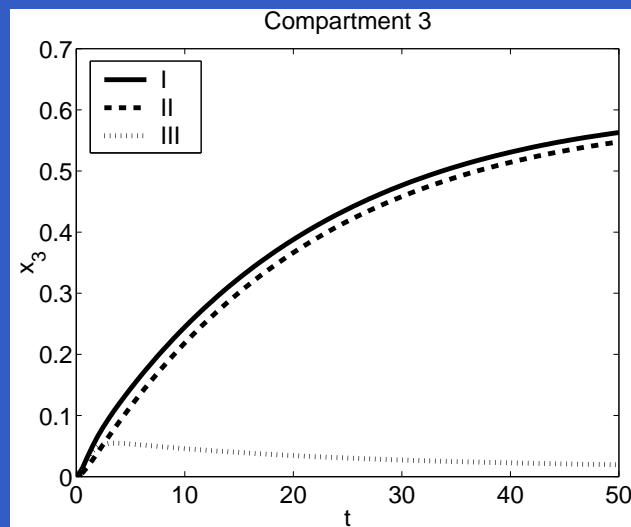
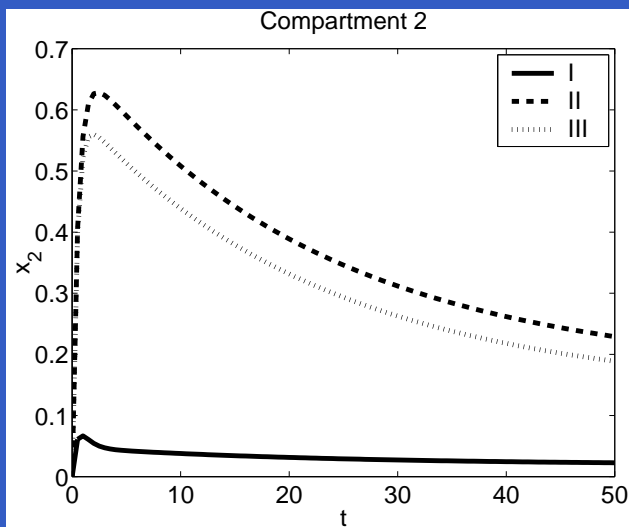
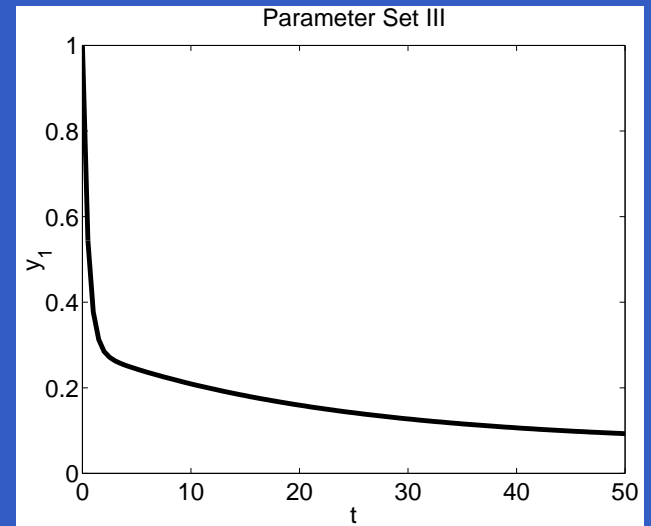
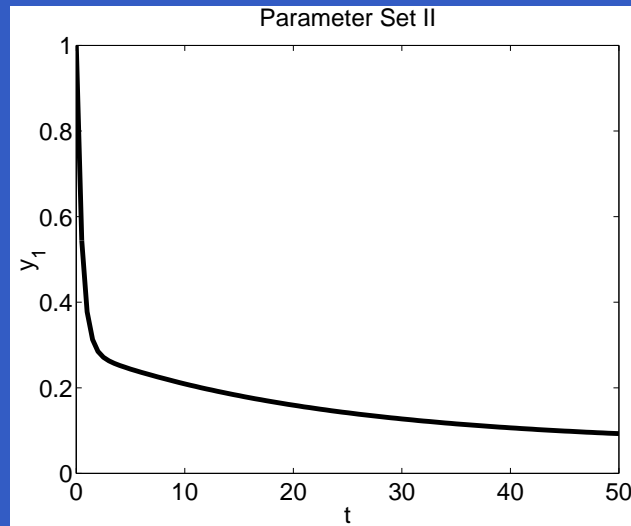
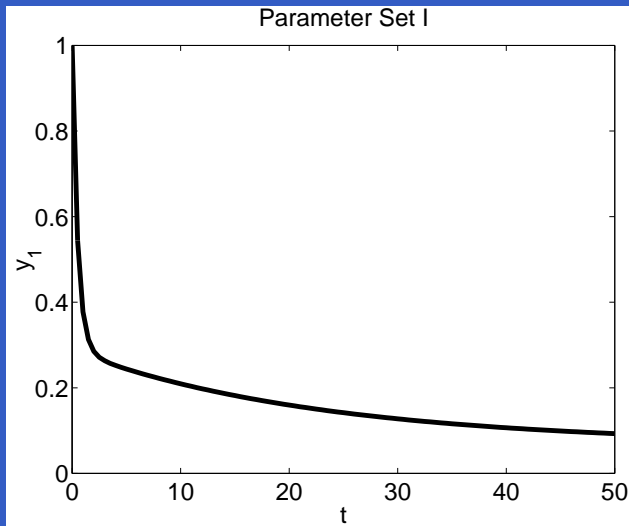
$$a_{ii} = - \sum_{j=0, i \neq j}^5 a_{ji}$$

	I	II	III
a_{05}	0.612	0.612	0.612
a_{12}	0.908	0.524	0.671
a_{14}	0.567	1.518	0.012
a_{15}	0.388	0.388	0.388
a_{21}	0.246	1.291	1.337
a_{23}	0.020	0.013	1.283
a_{32}	0.602	0.042	0.131
a_{41}	1.191	0.146	0.100
a_{51}	0.024	0.024	0.024

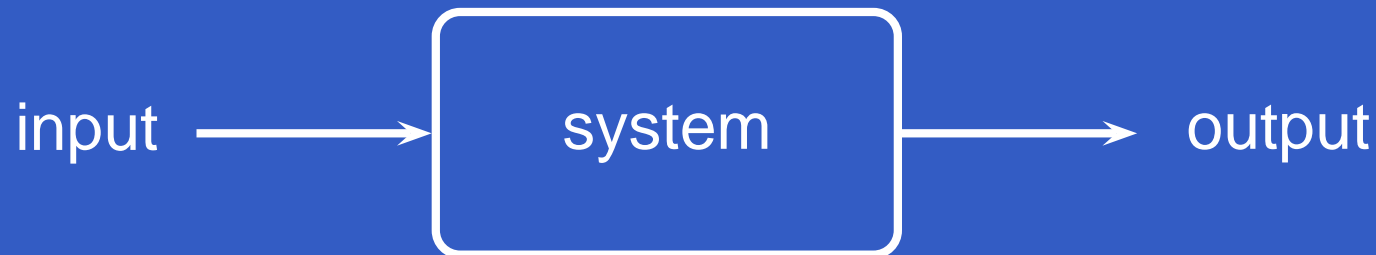
Model simulations



Model simulations



Structural identifiability



Given postulated state-space model, are the unknown parameters uniquely determined by the output (ie, perfect, continuous, noise-free data)?

Necessary theoretical prerequisite to:

- experiment design
- system identification
- parameter estimation

Formal definition

Consider following parameterised system:

$$\begin{aligned}\dot{\mathbf{x}}(t, \mathbf{p}) &= \mathbf{f}(\mathbf{x}(t, \mathbf{p}), \mathbf{p}), & \mathbf{x}(0, \mathbf{p}) &= \mathbf{x}_0(\mathbf{p}), \\ \mathbf{y}(t, \mathbf{p}) &= \mathbf{h}(\mathbf{x}(t, \mathbf{p}), \mathbf{p}).\end{aligned}$$

- For generic $\mathbf{p} \in \Omega$:
 - ★ p_i *locally identifiable* if, $\bar{\mathbf{p}} \in N$, neighbourhood of \mathbf{p} , and $\mathbf{y}(\cdot, \mathbf{p}) \equiv \mathbf{y}(\cdot, \bar{\mathbf{p}})$ implies $\bar{p}_i = p_i$
 - ★ p_i *globally identifiable* if $N = \Omega$
 - ★ p_i *unidentifiable* if not locally identifiable
- Model is *structurally globally/locally identifiable* if each p_i globally/locally identifiable
- Otherwise model is *unidentifiable* (ie, if any p_i is)

Structural identifiability

- Necessary condition for parameter estimation
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- Identifiability does *not* guarantee
 - ★ Good fit to experimental data
 - ★ Good fit *only* with unique vector of parameters
- Unidentifiable implies infinite number of parameter vectors will give same fit (even for perfect data)

Techniques

- Many techniques for linear systems
 - ★ Laplace transform or transfer function
 - ★ Taylor series of output
 - ★ Similarity transformation (exhaustive modelling)
- Taylor series and similarity transformation approaches are applicable for nonlinear systems
- Generalisation of similarity transformation method for uncontrolled nonlinear systems
- Differential algebra
 - ★ Polynomial systems with differentiable inputs/outputs
 - ★ Heavily dependent on symbolic computation
- Identifiability problem reduces to determining the number of solutions in a set of nonlinear algebraic equations

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General linear system

$$\dot{\mathbf{x}}(t, \mathbf{p}) = \mathbf{A}(\mathbf{p})\mathbf{x}(t, \mathbf{p}) + \mathbf{B}(\mathbf{p})\mathbf{u}(t), \quad \mathbf{x}(0, \mathbf{p}) = \mathbf{x}_0(\mathbf{p}),$$

$$\mathbf{y}(t, \mathbf{p}) = \mathbf{C}(\mathbf{p})\mathbf{x}(t, \mathbf{p}),$$

where

$\mathbf{A}(\mathbf{p})$ is an $n \times n$ matrix of rate constants

$\mathbf{B}(\mathbf{p})$ is an $n \times m$ input matrix

$\mathbf{C}(\mathbf{p})$ is an $l \times n$ output matrix

Assume that $\mathbf{x}_0 = 0$ (not essential) & take Laplace transforms:

$$s\mathbf{Q}(s) = \mathbf{A}(\mathbf{p})\mathbf{Q}(s) + \mathbf{B}(\mathbf{p})\mathbf{U}(s)$$

$$\mathbf{Y}(s) = \mathbf{C}(\mathbf{p})\mathbf{Q}(s)$$

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$$= \mathbf{C}(\mathbf{p}) (s\mathbf{I}_n - \mathbf{A}(\mathbf{p}))^{-1} \mathbf{B}(\mathbf{p})\mathbf{U}(s)$$

Laplace Transform Approach

This gives relationship between LTs of input & output:

$$Y(s) = G(s)U(s),$$

where the matrix

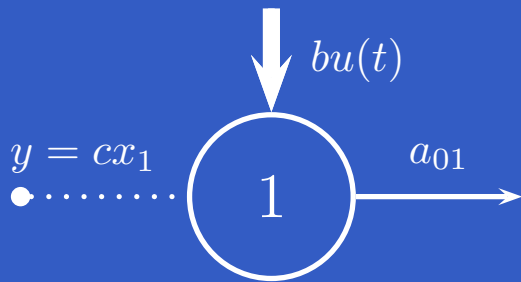
$$G(s) = C(p) (sI_n - A(p))^{-1} B(p)$$

is the transfer (function) matrix

- Measurements for $G(s)$ assumed known
- Coefficients of powers of s in numerators & denominators uniquely determined by input-output relationship

Example: 1 Compartment

Model:



$$\dot{x} = -a_{01}x + bu$$

$$y = cx$$

where $u(t) = n_0\delta(t)$ (n_0 known)

Transfer function:

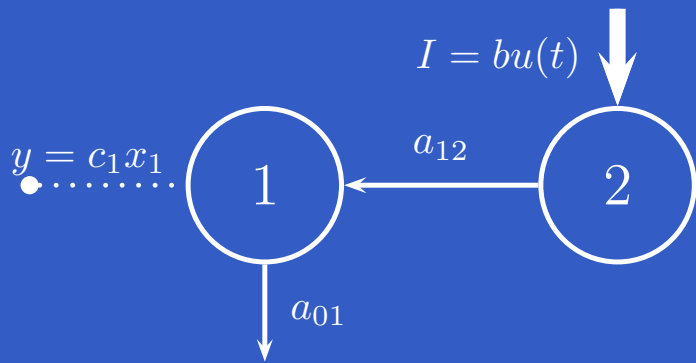
$$G(s) = \frac{cb}{s + a_{01}}$$

so cb and a_{01} unique (globally identifiable)

But c and b unidentifiable

Unless c or b known and then all globally identifiable

Example: 2 Compartments



Model is:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -a_{01} & a_{12} \\ 0 & -a_{12} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} 0 \\ b \end{bmatrix} u(t)$$

$$y = [c \quad 0] \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

Transfer function:

$$G(s) = [c \quad 0] \begin{bmatrix} s + a_{01} & -a_{12} \\ 0 & s + a_{12} \end{bmatrix}^{-1} \begin{bmatrix} 0 \\ b \end{bmatrix}$$

$$= \frac{bca_{12}}{(s + a_{01})(s + a_{12})}$$

A cautionary tale

Transfer function:

$$G(s) = \frac{bca_{12}}{(s + a_{01})(s + a_{12})}$$

and so the following are unique:

$$bca_{12}, \quad a_{01} + a_{12} \quad \text{and} \quad a_{01}a_{12}$$

- Yields two possible solutions for a_{01} and a_{21}
- If b (or c) known then two possible solutions for c (or b) hence locally identifiable
- If neither b nor c known then unidentifiable
- If both b and c known then globally identifiable

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- Determine $\mathcal{S}(p)$ set of all parameters \bar{p} s.t.

$$\lambda(\mathbf{x}_0(\bar{\mathbf{p}})) = \mathbf{x}_0(\mathbf{p}),$$

$$\mathbf{f}(\lambda(\mathbf{x}(t, \bar{\mathbf{p}})), \mathbf{p}) = \frac{\partial \lambda}{\partial \mathbf{x}}(\mathbf{x}(t, \bar{\mathbf{p}})) \mathbf{f}(\mathbf{x}(t, \bar{\mathbf{p}}), \bar{\mathbf{p}}),$$

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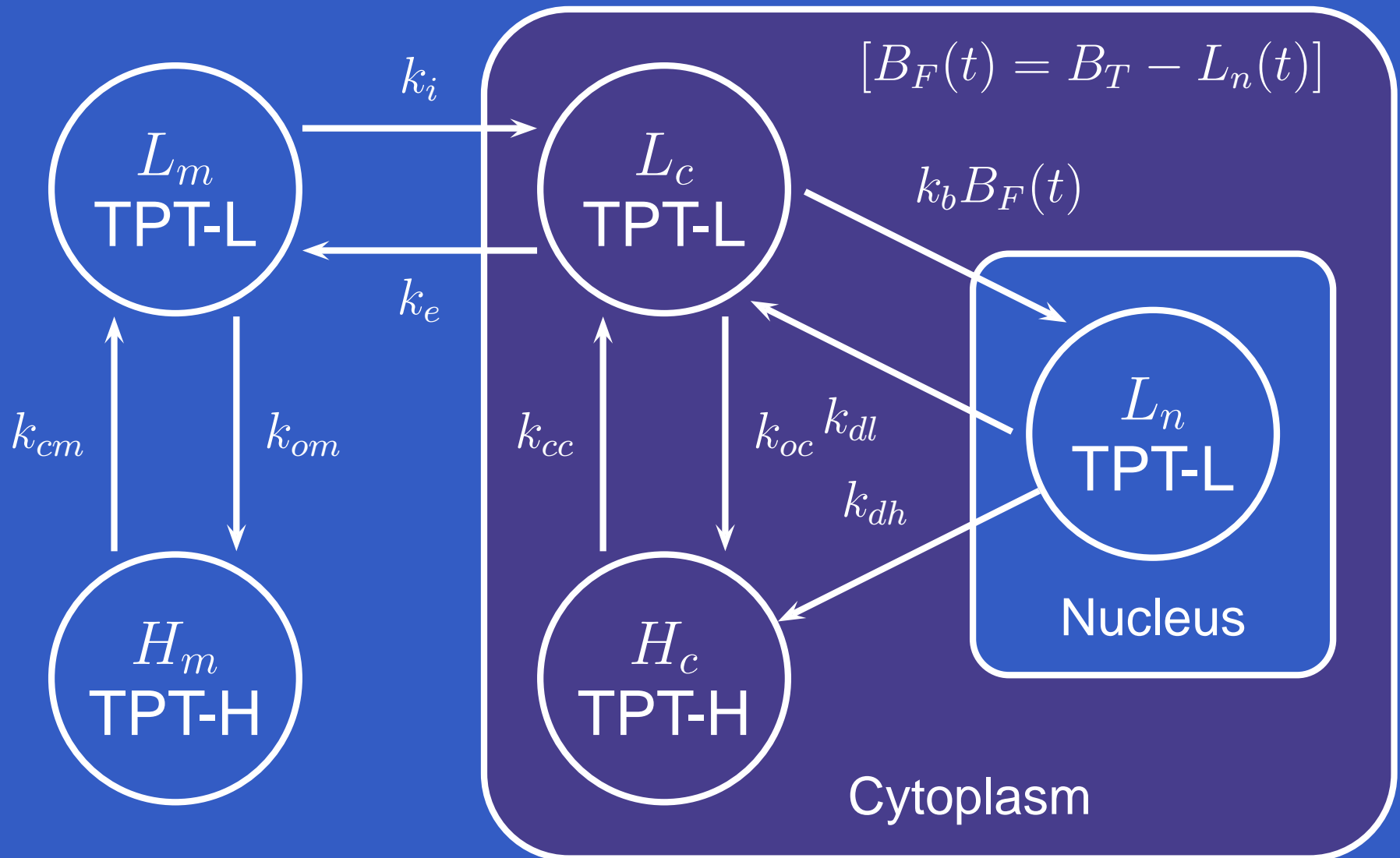
$$\mathbf{h}(\lambda(\mathbf{x}(t, \bar{\mathbf{p}})), \mathbf{p}) = \mathbf{h}(\mathbf{x}(t, \bar{\mathbf{p}}), \bar{\mathbf{p}})$$

- Globally identifiable at p if $\mathcal{S}(p) = \{p\}$

Topotecan

- Topotecan (TPT) is a water-soluble derivative of camptothecin (an extract from the Chinese tree *Camptotheca acuminata*)
- An active form of TPT is a topoisomerase I inhibitor
 - ★ Topo-I enzyme necessary for alleviating torsional stress during DNA replication (synthesis phase)
 - ★ TPT acts to trap topo-I in reversible complex with DNA preventing re-ligation of strand of DNA
 - ★ Leads to double-stranded DNA breaks and cell death
- Approved for clinical use against ovarian and small cell lung carcinomas (*Hycamtin*[®])

Modelling of TPT kinetics



Model equations

$$\dot{L}_m = -(k_{om} + k_i) L_m + k_{cm} H_m + \left(\frac{k_e}{v_1} \right) L_c,$$

$$\dot{H}_m = k_{om} L_m - (k_o + k_{cm}) H_m,$$

$$\dot{L}_c = (k_i v_1) L_m - (k_e + k_{oc} + k_b B_F) L_c + k_{cc} H_c + v_2 k_{dl} L_n,$$

$$\dot{H}_c = k_{oc} L_c - k_{cc} H_c + v_2 k_{dh} L_n,$$

$$\dot{L}_n = \left(\frac{k_b}{v_2} \right) B_F L_c - (k_{dl} + k_{dh}) L_n.$$

where $B_F = (B_T - L_n)$, $v_1 = V_m/V_c$ and $v_2 = V_n/V_c$

(Volumes: V_m medium, V_c cytoplasm, V_n nucleus)

Identifiability analysis

- Using HPLC able to quantify:
 - ★ extracellular TPT-L & TPT-H (L_m & H_m , resp.)
 - ★ intracellular TPT-L & TPT-H (L_i & H_i , resp.) where

$$H_i = H_c / (1 + v_2) \quad \& \quad L_i = (L_c + v_2 L_n) / (1 + v_2)$$

- So model output is $\mathbf{y} = (L_m, H_m, L_i, H_i)^T$

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- Model is unidentifiable since the following are:
 - ★ k_b, B_T, v_1 and v_2
 - ★ However, $(k_b v_1) / v_2, (B_T v_2) / v_1$ & $(1 + v_2) / v_1$ unique

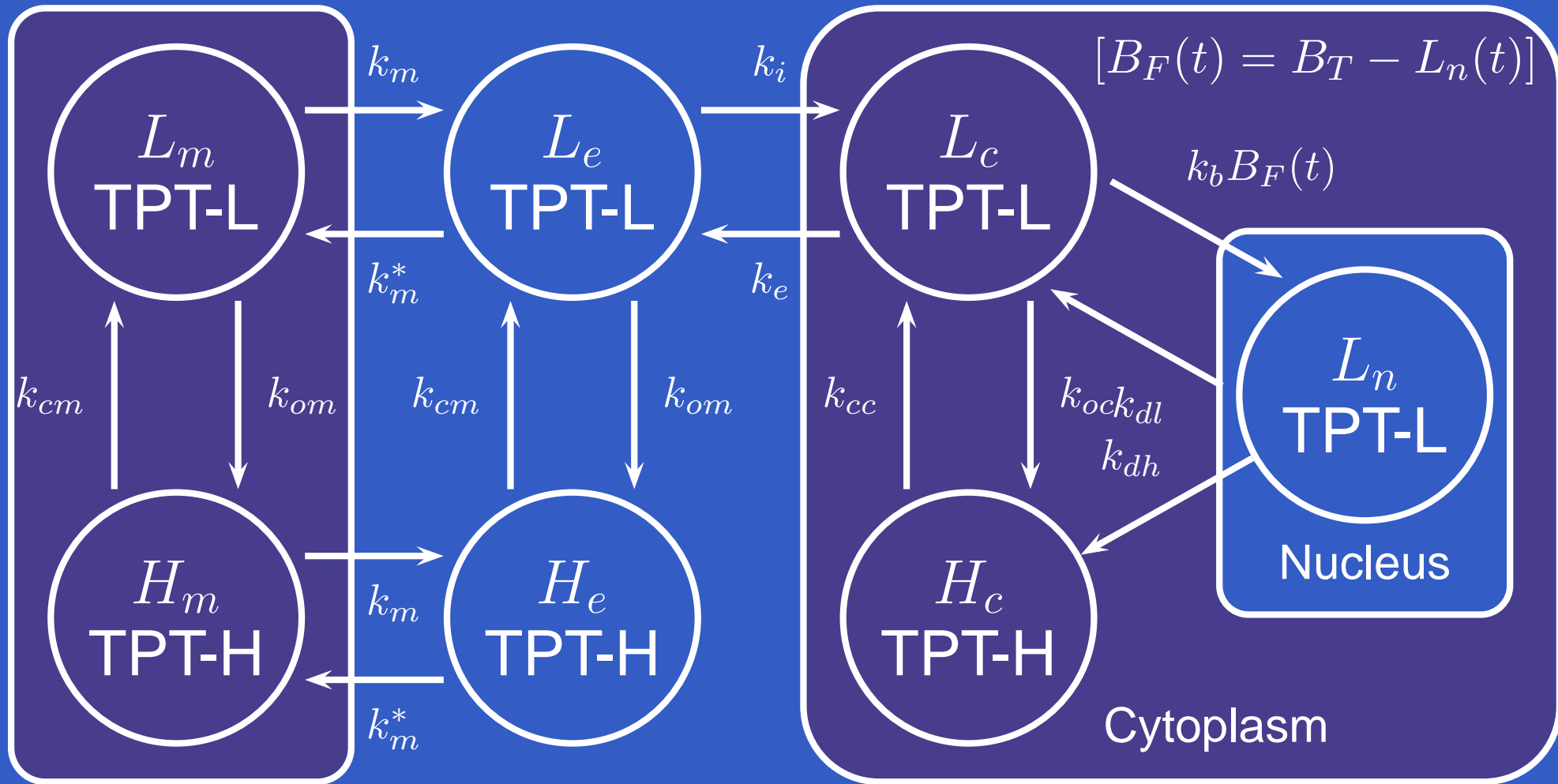
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 - ★ However, $(k_b v_1) / v_2, (B_T v_2) / v_1$ & $(1 + v_2) / v_1$ unique
- If either v_1 or v_2 known then model is structurally globally identifiable

Full (microscopy) model



Model equations

$$\dot{L}_m = -(k_m + k_{om}) L_m + k_{cm} H_m + v_0 k_m^* L_e$$

$$\dot{H}_m = k_{om} L_m - (k_m + k_{cm}) H_m + v_0 k_m^* H_e$$

$$\dot{L}_e = \left(\frac{k_m}{v_0} \right) L_m - (k_m^* + k_{om} + k_i) L_e + k_{cm} H_e + \left(\frac{k_e}{v_1} \right) L_c,$$

$$\dot{H}_e = \left(\frac{k_m}{v_0} \right) H_m + k_{om} L_e - (k_m^* + k_{cm}) H_e,$$

$$\dot{L}_c = (k_i v_1) L_e - (k_e + k_{oc}) L_c - k_b (B_T - L_n) L_c + k_{cc} H_c + v_2 k_{dl} L_n,$$

$$\dot{H}_c = k_{oc} L_c - k_{cc} H_c + v_2 k_{dh} L_n,$$

$$\dot{L}_n = \left(\frac{k_b}{v_2} \right) (B_T - L_n) L_c - (k_{dl} + k_{dh}) L_n.$$

Volume ratios: $v_0 = V_e/V_m$, $v_1 = V_e/V_c$, $v_2 = V_n/V_c$
(V_m medium, V_e extracellular compartment, V_c cytoplasm, V_n nucleus)

Identifiability

Taylor series approach: ($i = 1, \dots, r$)

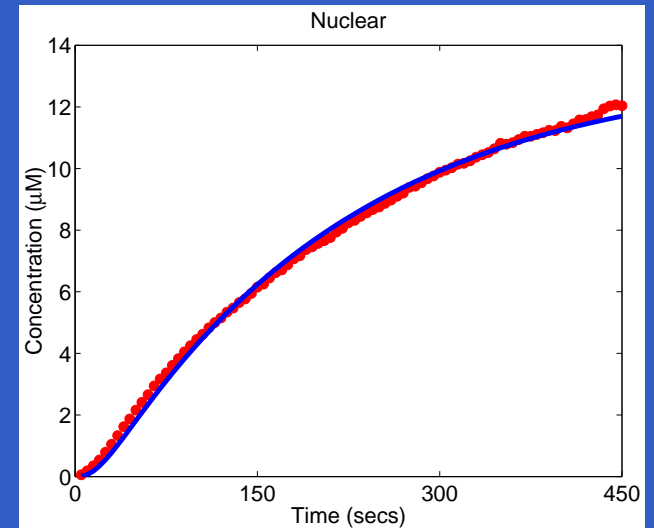
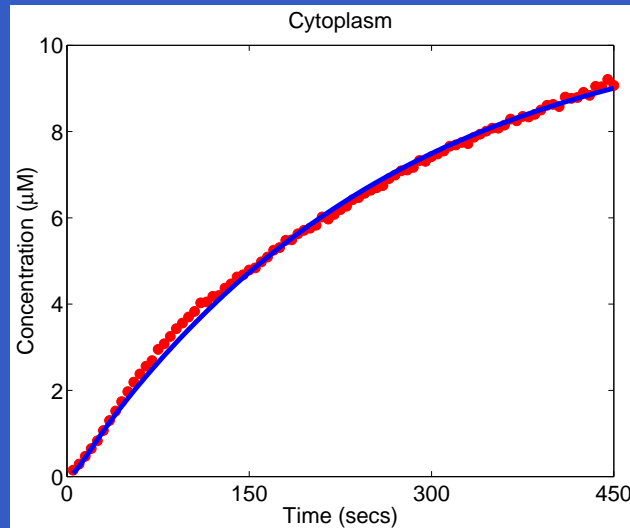
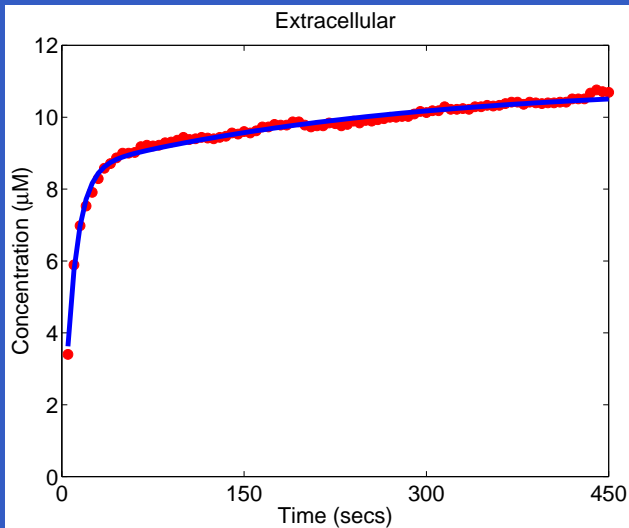
$$y_i(t, \mathbf{p}) = y_i(0, \mathbf{p}) + \dots + \frac{t^k}{k!} \lim_{\tau \rightarrow 0^+} \frac{d^k y_i}{dt^k}(\tau, \mathbf{p}) + \dots$$

Uniqueness of the coefficients implies

$$y_i^{(k)}(0, \mathbf{p}) = y_i^{(k)}(0, \bar{\mathbf{p}}) \quad k = 0, 1, 2, 3, \dots$$

- Microscopy (TPSLM) experiments: Measure total concentration of TPT in **extracellular region** ($L_e + H_e$), **cytoplasm** ($L_c + H_c$), **nucleus** (L_n)
- All parameters globally (uniquely) identifiable

Model fits



Fixed Value

k_{om}	1.56e-4
k_{cm}	2.96e-4
k_{cc}	1.56e-4
k_{oc}	2.96e-4
v_2	0.39

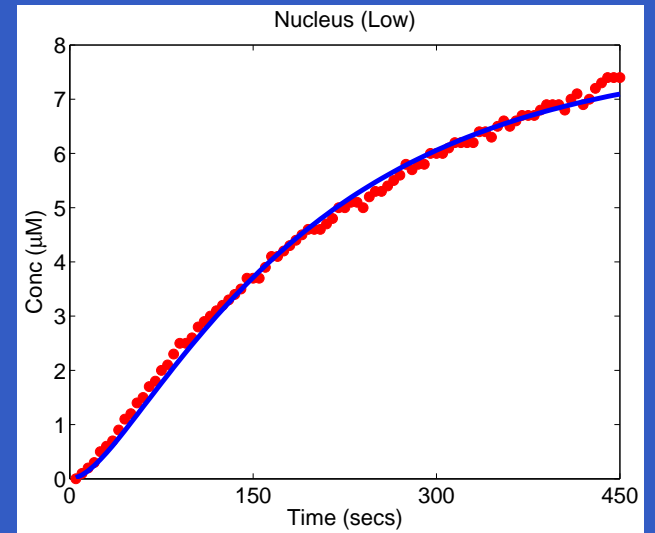
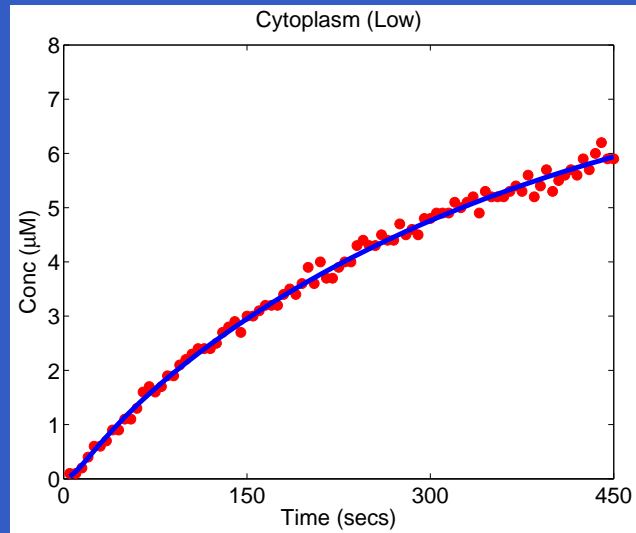
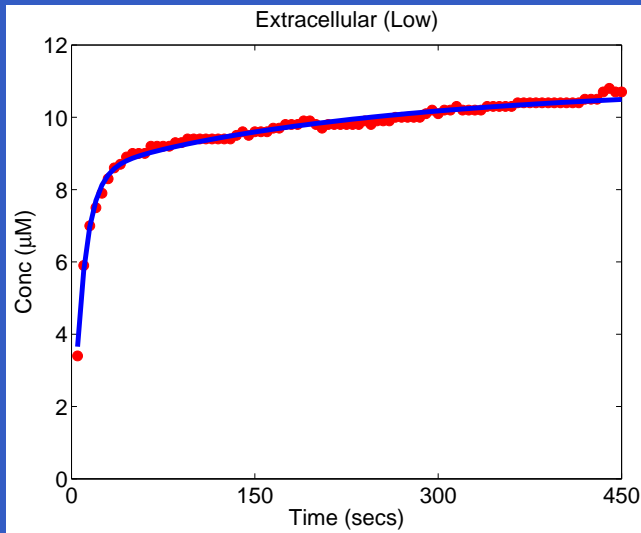
Value SDLN

k_m	1.44e-9	0.03
k_m^*	8.66e-2	0.02
k_i	2.26e-2	0.04
k_e	7.92e-3	0.01
v_0	1.53e-8	0.04

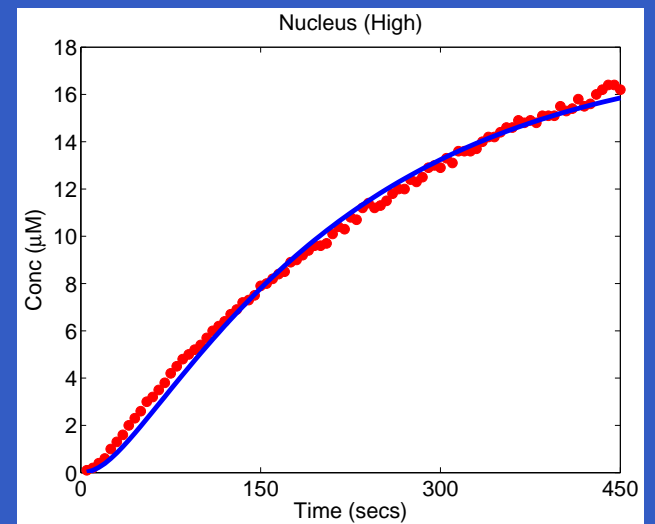
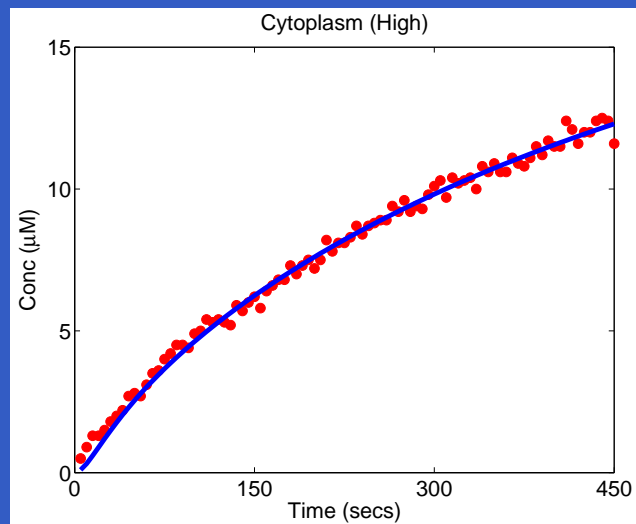
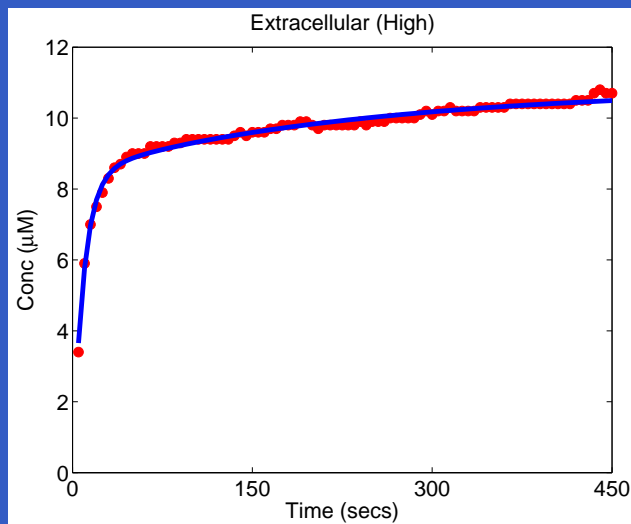
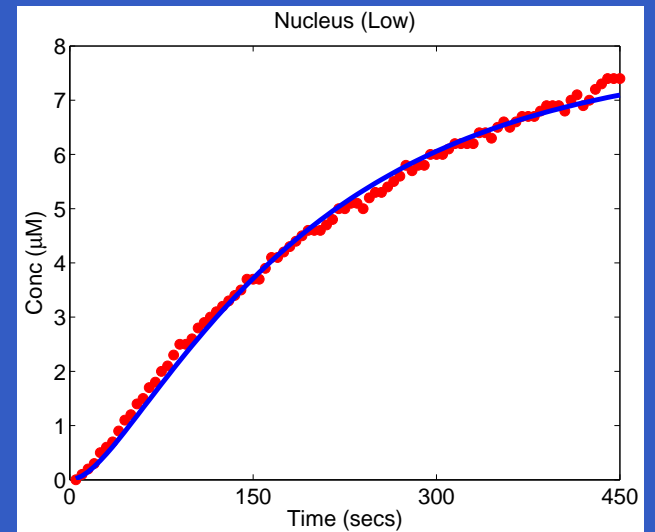
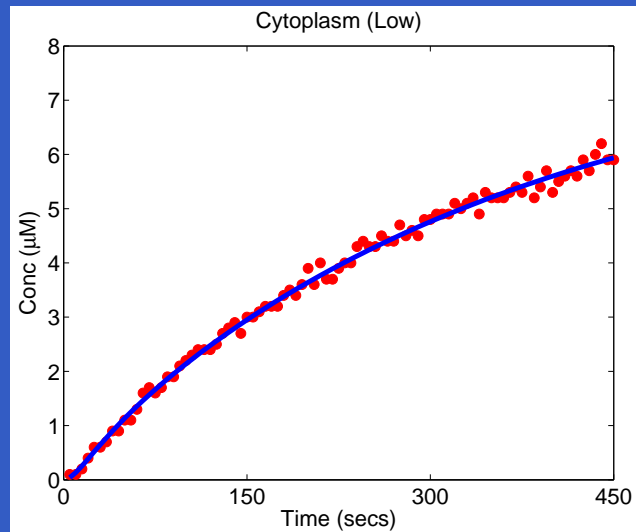
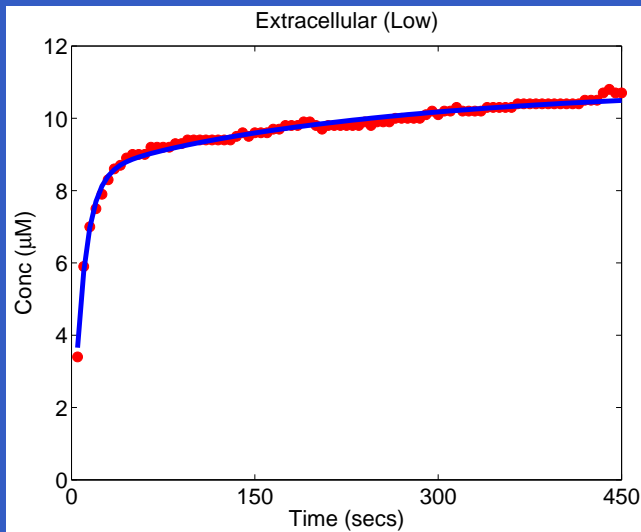
Value SDLN

k_b	3.80e-4	0.06
k_{dl}	5.52e-2	0.06
k_{dh}	4.16e-8	NWD
B_T	8.95e+1	NWD
RMS	0.1449	

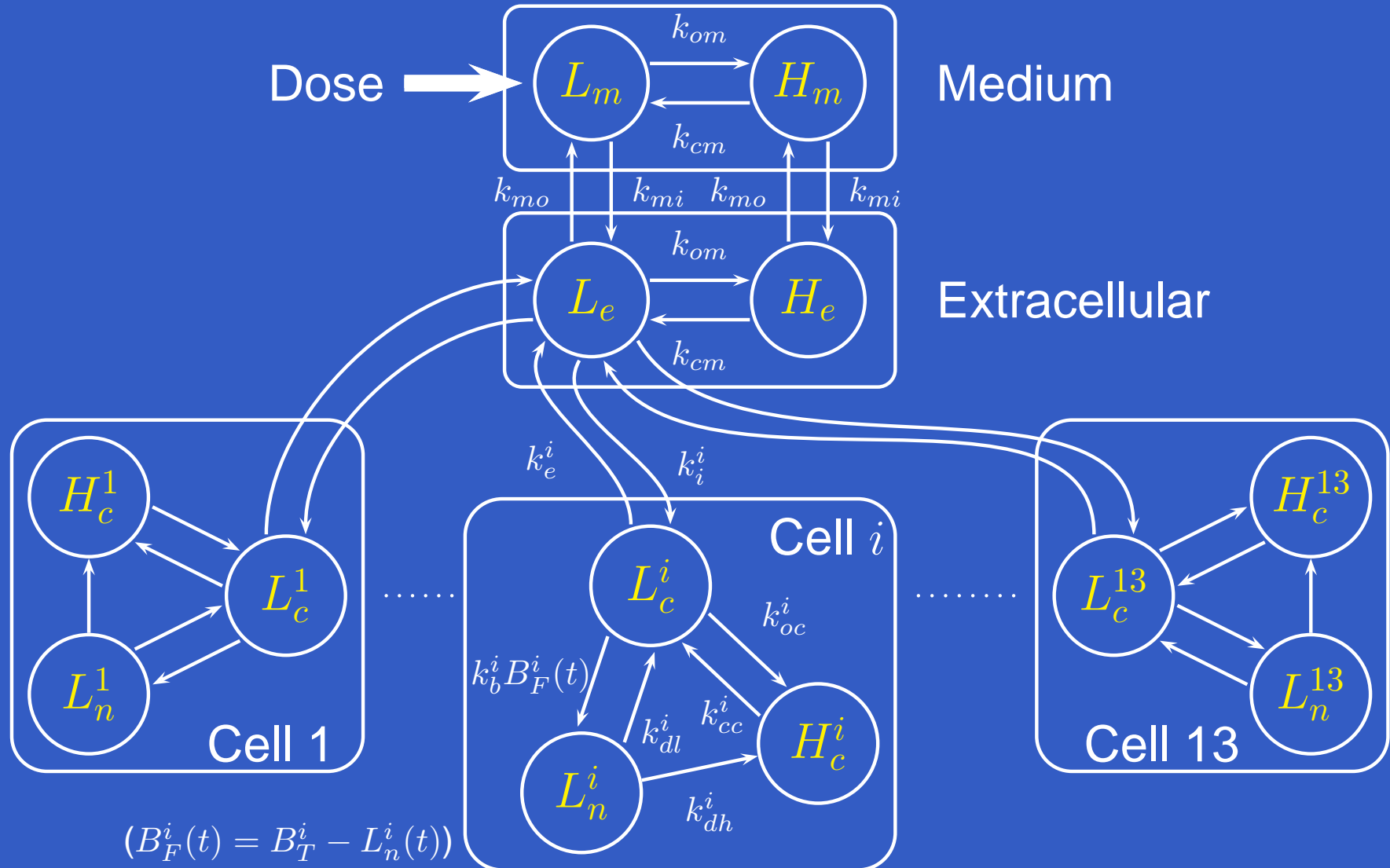
Inter-cell heterogeneity



Inter-cell heterogeneity



Exploring heterogeneity



Model equations

$$\dot{L}_m = -(k_{mi} + k_{om}) L_m + k_{cm} H_m + v_0 k_{mo} L_e$$

$$\dot{H}_m = k_{om} L_m - (k_{mi} + k_{cm}) H_m + v_0 k_{mo} H_e$$

$$\dot{L}_e = \left(\frac{k_{mi}}{v_0} \right) L_m - \left(k_{mo} + k_{om} + \sum_{j=1}^{13} k_i^{[j]} \right) L_e + k_{cm} H_e + \frac{1}{v_1} (k_e^{[j]} L_c^{[j]})$$

$$\dot{H}_e = (k_{mi}/v_0) H_m + k_{om} L_e - (k_{mo} + k_{cm}) H_e$$

$$\dot{L}_c^{[j]} = k_i^{[j]} v_1 L_e - \left(k_e^{[j]} + k_{oc}^{[j]} - k_b^{[j]} \left(B_T^{[j]} - L_n^{[j]} \right) \right) L_c^{[j]} + k_{cc}^{[j]} H_c^{[j]} + v_2 k_{dl}^{[j]} L_n^{[j]}$$

$$\dot{H}_c^{[j]} = k_{oc}^{[j]} L_c^{[j]} - k_{cc}^{[j]} H_c^{[j]} + v_2 k_{dh}^{[j]} L_n^{[j]}$$

$$\dot{L}_n^{[j]} = \left(\frac{k_b^{[j]}}{v_2} \right) \left(B_T^{[j]} - L_n^{[j]} \right) L_c^{[j]} - \left(k_{dl}^{[j]} + k_{dh}^{[j]} \right) L_n^{[j]}$$

Volume ratios: $v_0 = V_e/V_m$, $v_1 = V_e/V_c$, $v_2 = V_n/V_c$

Structural identifiability

- Coupled system of 43 ODEs giving 107 unknown parameters
- Microscopy (TPSLM) data: 27 observation functions
- Identifiability analysis via Taylor series approach
- Full model (107 parameters) has computational problems
- Reduced model (81 parameters) tractable
 - ★ Hydrolysis parameters assumed known
 - ★ All parameters globally (uniquely) identifiable
- Model response insensitive to likely variation in hydrolysis parameters

Structural indistinguishability

Consider following pair of systems:

$$\Sigma(\mathbf{p}) \begin{cases} \dot{\mathbf{x}}(t, \mathbf{p}) = \mathbf{f}(\mathbf{x}(t, \mathbf{p}), \mathbf{p}), & \mathbf{x}(0, \mathbf{p}) = \mathbf{x}_0(\mathbf{p}), \\ \mathbf{y}(t, \mathbf{p}) = \mathbf{h}(\mathbf{x}(t, \mathbf{p}), \mathbf{p}). \end{cases}$$

$$\tilde{\Sigma}(\tilde{\mathbf{p}}) \begin{cases} \dot{\tilde{\mathbf{x}}}(t, \tilde{\mathbf{p}}) = \tilde{\mathbf{f}}(\tilde{\mathbf{x}}(t, \tilde{\mathbf{p}}), \tilde{\mathbf{p}}), & \tilde{\mathbf{x}}(0, \tilde{\mathbf{p}}) = \tilde{\mathbf{x}}_0(\tilde{\mathbf{p}}), \\ \tilde{\mathbf{y}}(t, \tilde{\mathbf{p}}) = \tilde{\mathbf{h}}(\tilde{\mathbf{x}}(t, \tilde{\mathbf{p}}), \tilde{\mathbf{p}}), \end{cases}$$

- $\Sigma(\mathbf{p})$ and $\tilde{\Sigma}(\tilde{\mathbf{p}})$ ($\mathbf{p} \in \Omega$, $\tilde{\mathbf{p}} \in \tilde{\Omega}$) **output indistinguishable**, $\Sigma(\mathbf{p}) \sim \tilde{\Sigma}(\tilde{\mathbf{p}})$, if $\mathbf{y}(t, \mathbf{p}) = \tilde{\mathbf{y}}(t, \tilde{\mathbf{p}})$ for all t .
- Σ and $\tilde{\Sigma}$ **structurally indistinguishable** if
 - ★ for generic $\mathbf{p} \in \Omega$ there exists $\tilde{\mathbf{p}} \in \tilde{\Omega}$ s.t. $\Sigma(\mathbf{p}) \sim \tilde{\Sigma}(\tilde{\mathbf{p}})$;
 - ★ for generic $\tilde{\mathbf{p}} \in \tilde{\Omega}$ there exists $\mathbf{p} \in \Omega$ s.t. $\Sigma(\mathbf{p}) \sim \tilde{\Sigma}(\tilde{\mathbf{p}})$.

Outline of approach

For generic parameter vector p :

- Check an observability criterion
 - ★ Gives smooth functions $\mu_1(\mathbf{x}, \mathbf{p}), \dots, \mu_n(\mathbf{x}, \mathbf{p})$
 - ★ and smooth functions $\tilde{\mu}_1(\tilde{\mathbf{x}}, \tilde{\mathbf{p}}), \dots, \tilde{\mu}_n(\tilde{\mathbf{x}}, \tilde{\mathbf{p}})$

- Construct smooth λ from

$$\mu_i(\lambda(\tilde{\mathbf{x}}), \mathbf{p}) = \tilde{\mu}_i(\tilde{\mathbf{x}}, \tilde{\mathbf{p}}), \quad i = 1, \dots, n$$

- Determine $\mathcal{U}(\Sigma(p); \tilde{\Sigma})$ set of all parameters \tilde{p} s.t.

$$\lambda(\tilde{\mathbf{x}}_0(\tilde{p})) = \mathbf{x}_0(p),$$

$$\mathbf{f}(\lambda(\tilde{\mathbf{x}}(t, \tilde{p})), \mathbf{p}) = \frac{\partial \lambda}{\partial \tilde{\mathbf{x}}}(\tilde{\mathbf{x}}(t, \tilde{p})) \tilde{\mathbf{f}}(\tilde{\mathbf{x}}(t, \tilde{p}), \tilde{\mathbf{p}}),$$

$$\mathbf{h}(\lambda(\tilde{\mathbf{x}}(t, \tilde{p})), \mathbf{p}) = \tilde{\mathbf{h}}(\tilde{\mathbf{x}}(t, \tilde{p}), \tilde{\mathbf{p}})$$

Indistinguishability analysis

- Σ and $\tilde{\Sigma}$ structurally indistinguishable if and only if
 - ★ for generic $p \in \Omega$, $\mathcal{U}(\Sigma(p); \tilde{\Sigma}) \neq \emptyset$, and
 - ★ for generic $\tilde{p} \in \tilde{\Omega}$ there exists a $p \in \Omega$ s.t.
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- Approach can be computationally intensive

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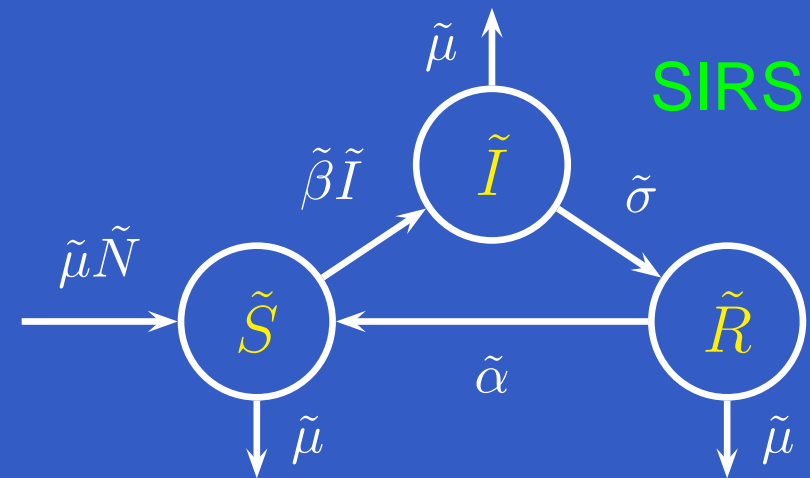
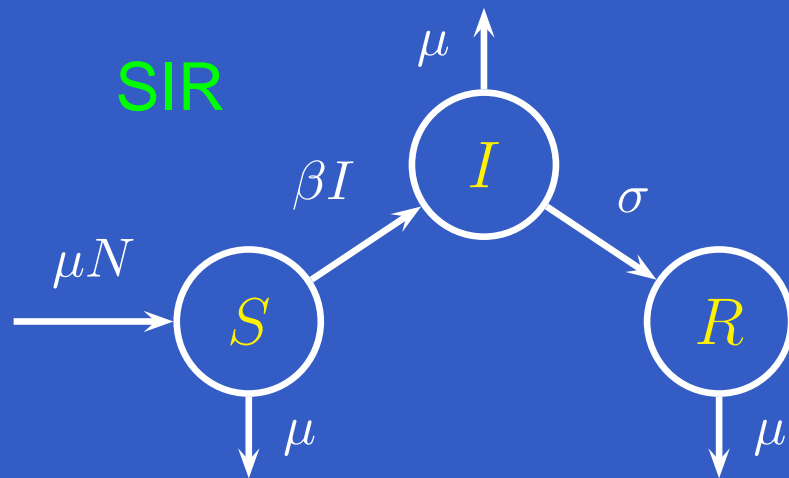
- To show structural indistinguishability (easier):

- ★ Determine $\mathcal{U}_\infty(\Sigma(p); \tilde{\Sigma})$ set of all parameters \tilde{p} s.t. there exists λ satisfying: $\lambda(\tilde{x}_0(\tilde{p})) = x_0(p)$,

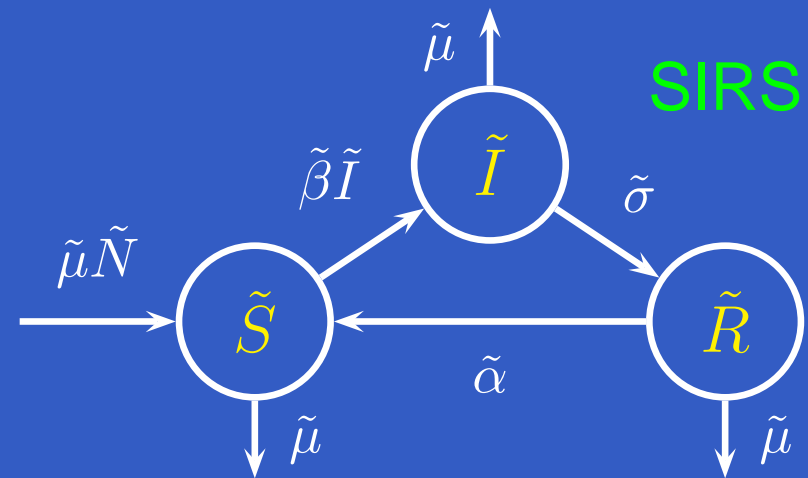
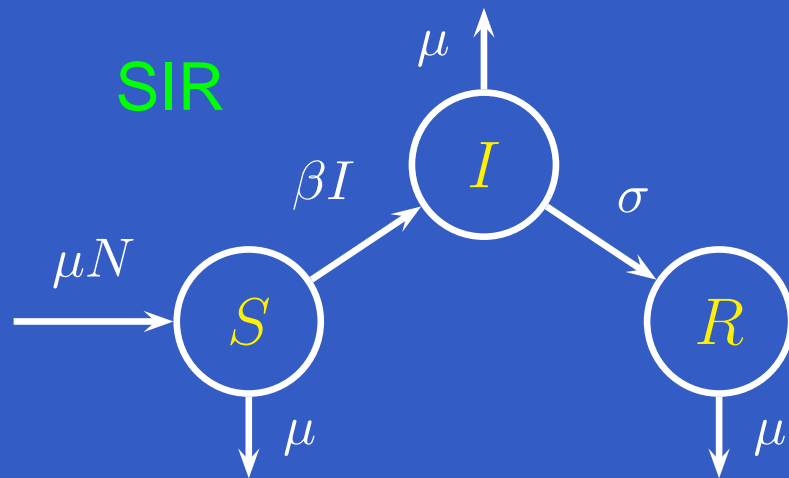
$$f(\lambda(\tilde{x}), p) = \frac{\partial \lambda}{\partial \tilde{x}}(\tilde{x}) \tilde{f}(\tilde{x}, \tilde{p}), \quad h(\lambda(\tilde{x}), p) = \tilde{h}(\tilde{x}, \tilde{p})$$

- ★ Then $\mathcal{U}_\infty(\Sigma(p); \tilde{\Sigma}) \subseteq \mathcal{U}(\Sigma(p); \tilde{\Sigma})$

Application

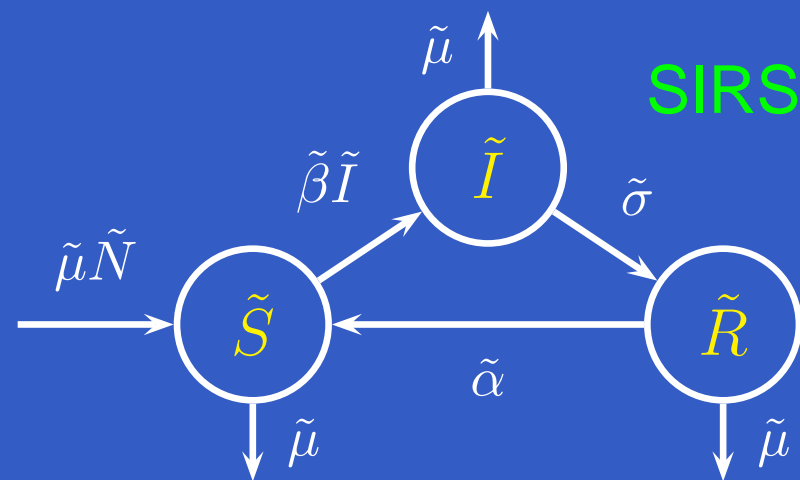
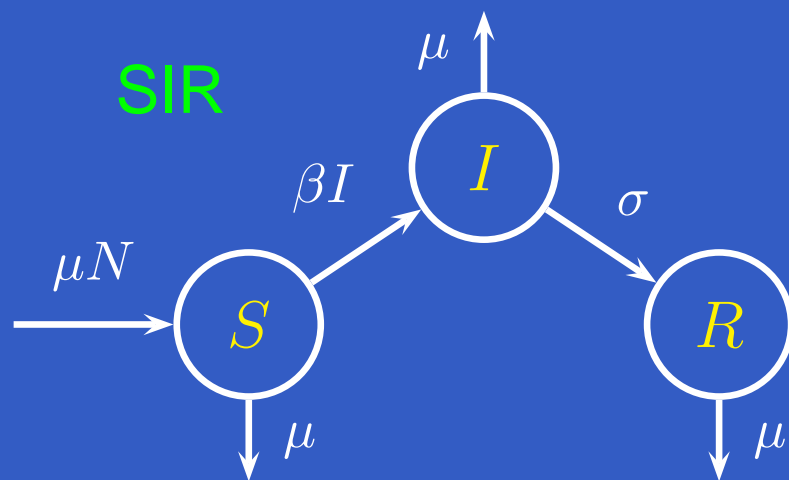


Application



- Measure kI and $\tilde{k}\tilde{I}$

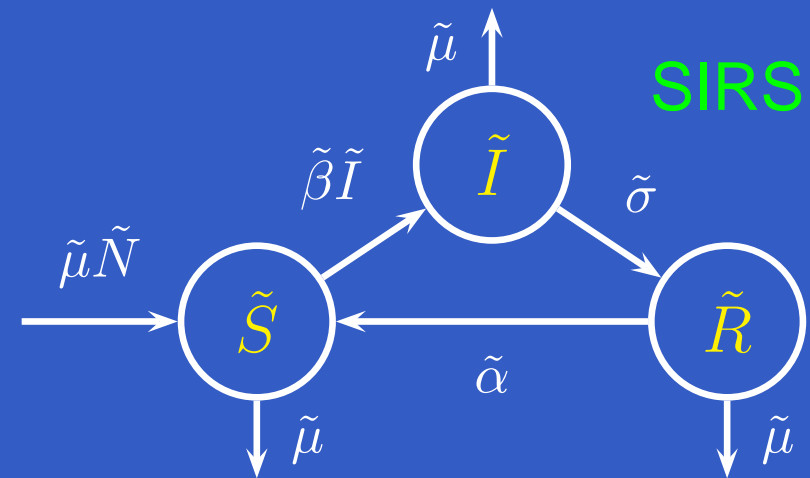
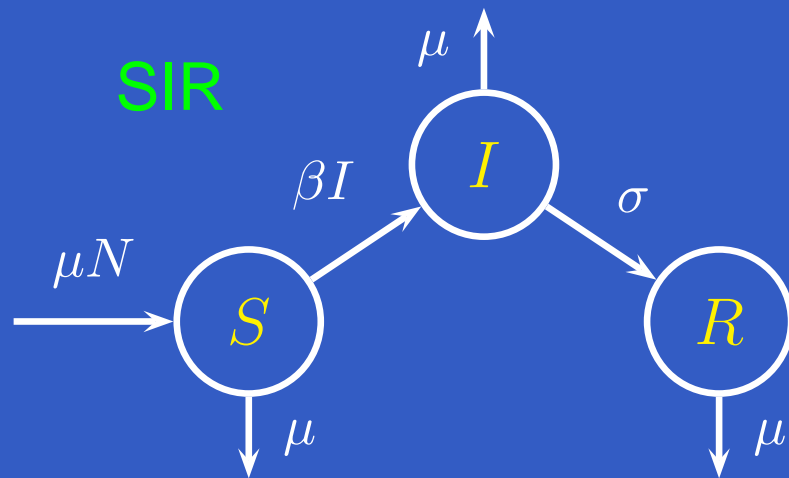
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- $\mathcal{U}_\infty(\Sigma(\mathbf{p}); \tilde{\Sigma}) = \{\tilde{\mathbf{p}} \in \tilde{\Omega} : \tilde{\mu} + \tilde{\alpha} = \mu,$

$$\tilde{k}/\tilde{\beta} = k/\beta, \tilde{\sigma} = \sigma, \tilde{\beta}\tilde{N} + \tilde{\alpha} = \beta N, \tilde{\beta}\tilde{S}_0 + \tilde{\alpha} = \beta S_0, \tilde{\beta}\tilde{I}_0 = \beta I_0\}$$

Application



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- Structurally indistinguishable

Conclusions

- Structural identifiability is an important step in modelling process
 - ★ Theoretical prerequisite to experiment design, system identification, and parameter estimation
 - ★ Techniques involve generation, manipulation & solution of nonlinear algebraic equations
 - ★ Need for more tractable techniques for nonlinear systems
- Structural indistinguishability similarly important (more general framework)
- Both are highly relevant to models in Biomedical Systems Modelling/Systems Biology