Structural identifiability: An Introduction

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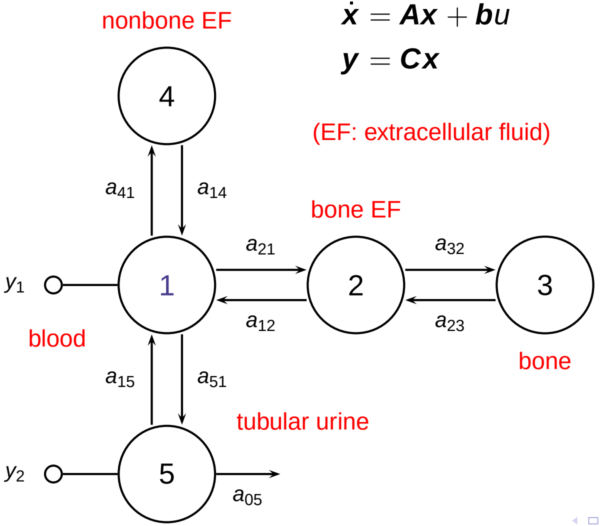
Outline

Skeletal tracer kinetics model



$$\dot{\boldsymbol{x}} = \boldsymbol{A}\boldsymbol{x} + \boldsymbol{b}u$$
$$\boldsymbol{y} = \boldsymbol{C}\boldsymbol{x}$$

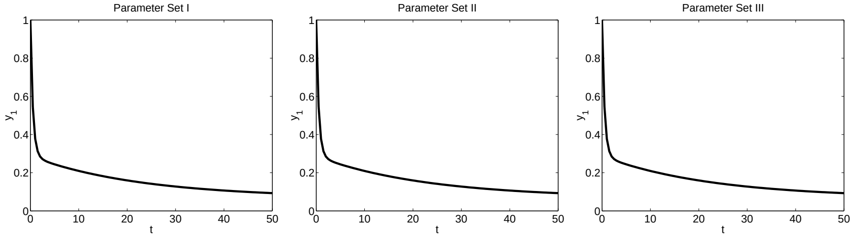
(EF: extracellular fluid)

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

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

	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



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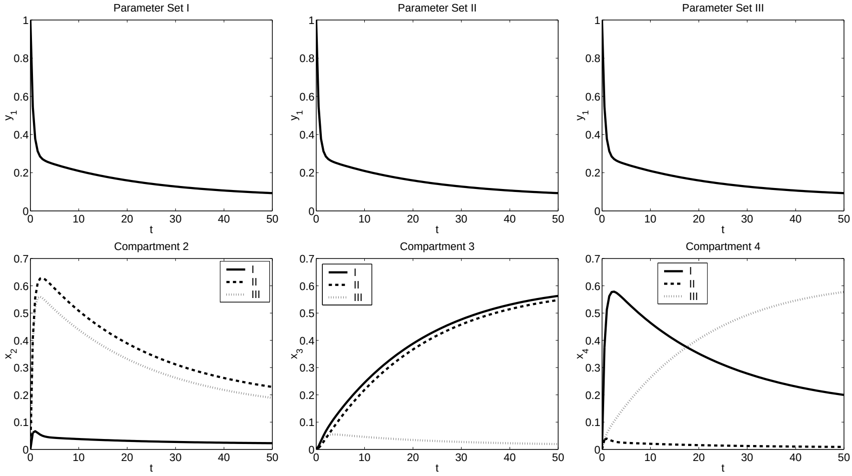
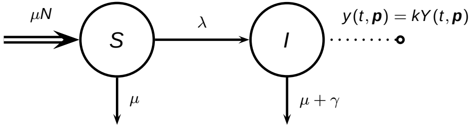


SIR Model

SIR infectious disease model:



Proportion of prevalence measured: $y(t, \boldsymbol{p}) = kY(t, \boldsymbol{p})$

Model equations:

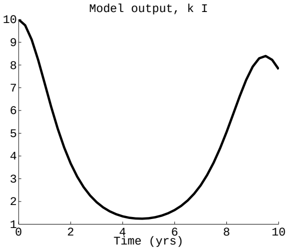
$$\dot{X} = \mu N - \mu X - \frac{\beta}{N} XY$$

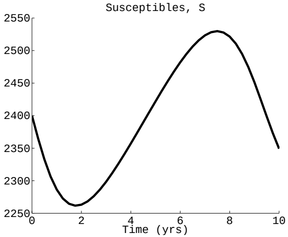
$$\dot{Y} = \frac{\beta}{N} XY - (\mu + \gamma) Y$$

$$y = kY$$

SIR model

$\mu = 0.0125, \gamma = 12$
$N = 10000$
$\beta = 50, k = 0.5$
$X(0) = 2400$
$Y(0) = 20$





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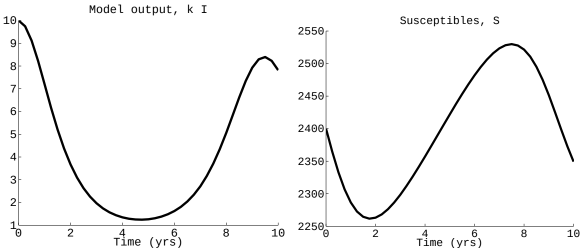

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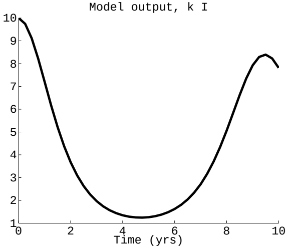

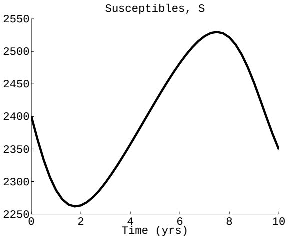

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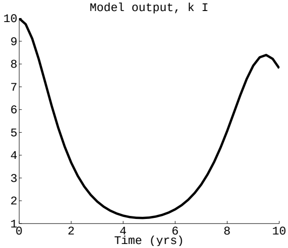

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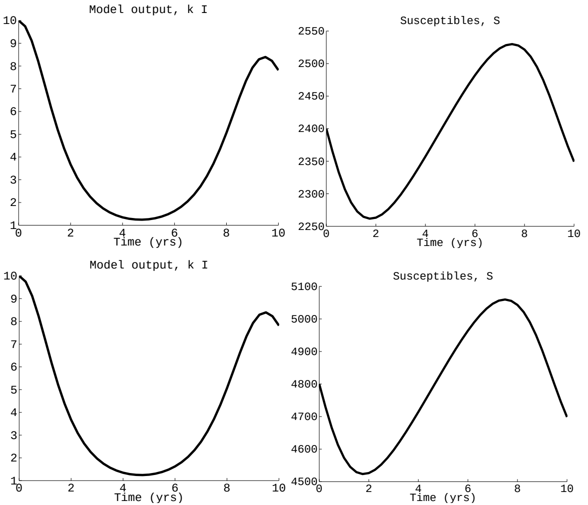
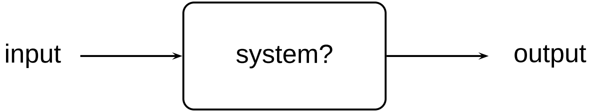


Structural identifiability

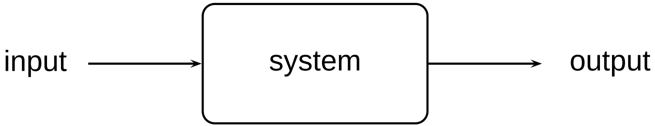


Given postulated state-space models for a given biological or biomedical process:

Structural Identifiability

Are the unknown parameters uniquely determined by the input-output behaviour?

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 general parameterised state-space model:

$$\dot{\boldsymbol{x}}(t,\boldsymbol{p}) = \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{u}(t),\boldsymbol{p}), \quad \boldsymbol{x}(0,\boldsymbol{p}) = \boldsymbol{x}_0(\boldsymbol{p}),$$
$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}),$$

where $\boldsymbol{p}$ is the r-dimensional **vector of unknown parameters**, and is assumed to lie in a set of feasible vectors: $\boldsymbol{p} \in \Omega$.

n dimensional vector $\boldsymbol{q}(t,\boldsymbol{p})$ is state vector, such that $\boldsymbol{q}_0(\boldsymbol{p})$ is the initial state (may depend on the unknown parameters)

m dimensional vector $\boldsymbol{u}(t)$ is input/control vector (our influence on system); what inputs are available depends on experiment to be performed, so $\boldsymbol{u}(\cdot) \in \mathcal{U}$, a **set of admissible inputs** (might be empty).

$\boldsymbol{y}(t,\boldsymbol{p})$ is the l-dimensional output/observation vector (what we can measure in the system). In the following we make explicit that output $\boldsymbol{y}$ depends on $\boldsymbol{p} \in \Omega$ and $\boldsymbol{u} \in \mathcal{U}$ by writing $\boldsymbol{y}(t,\boldsymbol{p};\boldsymbol{u})$.

Parameter identifiability

For generic $\boldsymbol{p} \in \Omega$, the parameter p_i is said to be locally identifiable if there exists a neighbourhood of vectors around $\boldsymbol{p}$, $\mathcal{N}(\boldsymbol{p})$, such that if $\overline{\boldsymbol{p}} \in \mathcal{N}(\boldsymbol{p}) \subseteq \Omega$ and:

$$\text{for every input } \boldsymbol{u} \in \mathcal{U} \text{ and } t \geq 0, \quad \boldsymbol{y}(t,\boldsymbol{p};\boldsymbol{u}) = \boldsymbol{y}(t,\overline{\boldsymbol{p}};\boldsymbol{u})$$

then $\overline{p}_i = p_i$.

In particular, if the neighbourhood $\mathcal{N}(\boldsymbol{p}) = \Omega$ can be used in the previous definition, then the parameter p_i is globally/uniquely identifiable.

If the parameter p_i is **not locally identifiable**, i.e., there is no suitable neighbourhood $\mathcal{N}(\boldsymbol{p})$, then it is said to be unidentifiable.

Structural identifiability

Structurally globally/uniquely identifiable

A parameterised state space model is structurally globally/uniquely identifiable (**SGI**) if all of the unknown parameters p_i are globally/uniquely identifiable.

Structurally locally identifiable

A state space model is structurally locally identifiable (**SLI**) if all of the unknown parameters p_i are locally identifiable and at least one of these parameters is **not** globally identifiable.

Unidentifiable

A state space model is unidentifiable if at least one of the unknown parameters p_i is unidentifiable.

Remarks

- Necessary condition for parameter estimation
  - Essential for parameters with practical significance
  - Prerequisite to experiment design
- 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)
- 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
- Differential algebra
  - Rational systems with differentiable inputs/outputs
  - Heavily dependent on symbolic computation

Laplace Transform Approach

General linear system

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

where

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

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

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

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

$$\begin{aligned} s\boldsymbol{Q}(s) &= \boldsymbol{A}(\boldsymbol{p})\boldsymbol{Q}(s) + \boldsymbol{B}(\boldsymbol{p})\boldsymbol{U}(s) \\ \boldsymbol{Y}(s) &= \boldsymbol{C}(\boldsymbol{p})\boldsymbol{Q}(s) \\ &= \boldsymbol{C}(\boldsymbol{p})\left(s\boldsymbol{I}_n - \boldsymbol{A}(\boldsymbol{p})\right)^{-1}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{U}(s) \end{aligned}$$

Laplace Transform Approach

This gives relationship between LTs of input & output:

$$\boldsymbol{Y}(s) = \boldsymbol{G}(s)\boldsymbol{U}(s),$$

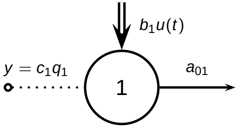
where the matrix

$$\boldsymbol{G}(s) = \boldsymbol{C}(\boldsymbol{p})\left(s\boldsymbol{I}_n - \boldsymbol{A}(\boldsymbol{p})\right)^{-1}\boldsymbol{B}(\boldsymbol{p})$$

is the transfer (function) matrix

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

Example: 1 Compartment



Input: impulse: $b_1u(t) = b_1n_0\delta(t)$; b_1 unknown, n_0 known

Output: $y = c_1q_1$, where c_1 unknown.

System equations:

Transfer function: $\boldsymbol{G}(s) =$

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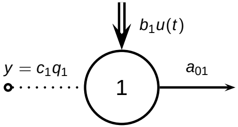

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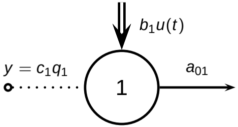

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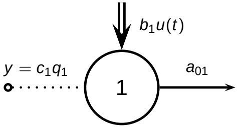

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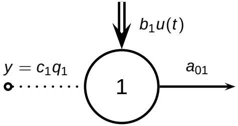

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- So b_1c_1 and a_{01} globally identifiable

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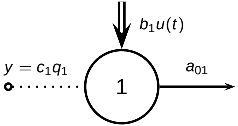

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- So $b_1 c_1$ and a_{01} globally identifiable
- But b_1 and c_1 unidentifiable

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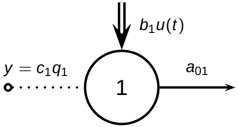

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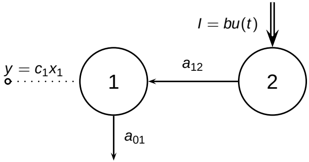
- So b_1c_1 and a_{01} globally identifiable
- But b_1 and c_1 unidentifiable
- So model is unidentifiable unless b_1 or c_1 known (then **SGI**)

Example: 2 Compartments



Model is:

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

$$y = \begin{bmatrix} c & 0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

Transfer function:

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

Locally identifiable example

Transfer function:

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

and so the following are unique:

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

- 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

Taylor series approach

Generally applied when there is a single input (eg, 0 or impulse)

Outputs $y_i(t, \boldsymbol{p})$ expanded as Taylor series about $t = 0$:

$$y_i(t,\boldsymbol{p}) = y_i(0,\boldsymbol{p}) + \dot{y}_i(0,\boldsymbol{p})t + \ddot{y}_i(0,\boldsymbol{p})\frac{t^2}{2!} + \cdots + y_i^{(k)}(0,\boldsymbol{p})\frac{t^k}{k!} + \ldots$$

where

$$y_i^{(k)}(0,\boldsymbol{p}) = \left.\frac{\mathrm{d}^k y_i}{\mathrm{d}t^k}\right|_{t=0} \qquad (k = 1, 2, \ldots).$$

Taylor series coefficients $y_i^{(k)}(0,\boldsymbol{p})$ unique for particular output

Approach reduces to determining solutions for $\boldsymbol{p}$ that give:

$$y_i(0,\boldsymbol{p}), \quad y_i^{(k)}(0,\boldsymbol{p}) \qquad (1 \le i \le l, k \ge 1).$$

Notice that we have a possibly infinite list of coefficients:

$$y_1(0,\boldsymbol{p}), \ldots, y_l(0,\boldsymbol{p}), \dot{y}_1(0,\boldsymbol{p}), \ldots, \dot{y}_l(0,\boldsymbol{p}), \ddot{y}_1(0,\boldsymbol{p}), \ldots, \ddot{y}_l(0,\boldsymbol{p}), \ldots$$

For linear systems: at most $2n - 1$ independent equations needed

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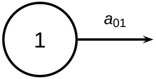

Input: impulse in I.C.s: $q_1(0) = b_1 n_0$; b_1 unknown, n_0 known.

Output: $y = c_1 q_1$, where c_1 unknown.

System equations:

First coefficient: $y(0, \boldsymbol{p}) =$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) =$

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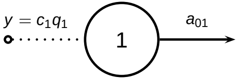

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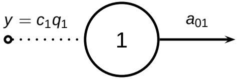

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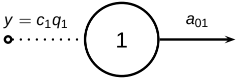

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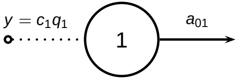

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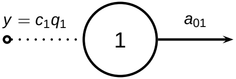

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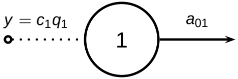
Second coefficient: $\dot{y}(0, \boldsymbol{p}) = \; - a_{01} b_1 c_1 n_0$

- So $b_1 c_1$ & $b_1 c_1 a_{01}$ unique

Example: 1 Compartment



Input: impulse in I.C.s: $q_1(0) = b_1 n_0$; b_1 unknown, n_0 known.

Output: $y = c_1 q_1$, where c_1 unknown.

System equations:

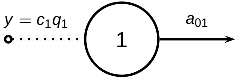
$$\dot{q}_1 = -a_{01} q_1, \qquad q_1(0) = b_1 n_0,$$
$$y = c_1 q_1$$

First coefficient: $y(0, \boldsymbol{p}) = b_1 c_1 n_0$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) = \; - a_{01} b_1 c_1 n_0$

- So $b_1 c_1$ & $b_1 c_1 a_{01}$ unique (ie $b_1 c_1$ & a_{01} globally identifiable)

Example: 1 Compartment



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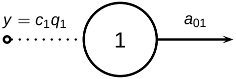
- But b_1 and c_1 unidentifiable

Example: 1 Compartment



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System equations:

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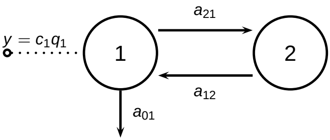
- So $b_1 c_1$ & $b_1 c_1 a_{01}$ unique (ie $b_1 c_1$ & a_{01} globally identifiable)
- But b_1 and c_1 unidentifiable
- So model unidentifiable unless b_1 &/or c_1 known (then **SGI**)

Example: 2 Compartments



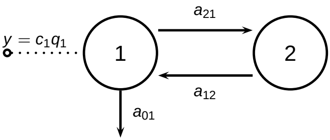
Input: bolus intravenous injection of drug (unknown amount)

Output: concentration of drug in the plasma

System equations:

$$\dot{q}_1(t, \boldsymbol{p}) =$$
$$\dot{q}_2(t, \boldsymbol{p}) =$$
$$y(t, \boldsymbol{p}) =$$

Example: 2 Compartments



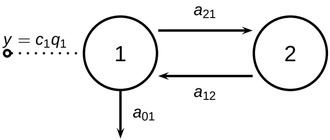
Input: bolus intravenous injection of drug (unknown amount)

Output: concentration of drug in the plasma

System equations:

$$\begin{aligned}
\dot{q}_1(t,\mathbf{p}) &= -(a_{01}+a_{21})\,q_1(t,\mathbf{p}) + a_{12}q_2(t,\mathbf{p}), \qquad q_1(0,\mathbf{p}) = b_1 \\
\dot{q}_2(t,\mathbf{p}) &= \\
y(t,\mathbf{p}) &=
\end{aligned}$$

Example: 2 Compartments



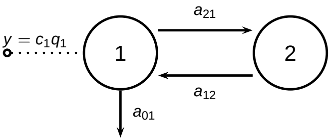
Input: bolus intravenous injection of drug (unknown amount)

Output: concentration of drug in the plasma

System equations:

$$\dot{q}_1(t,\boldsymbol{p}) = -(a_{01} + a_{21})\,q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
$$\dot{q}_2(t,\boldsymbol{p}) = a_{21}q_1(t,\boldsymbol{p}) - a_{12}q_2(t,\boldsymbol{p}), \qquad q_2(0,\boldsymbol{p}) = 0$$
$$y(t,\boldsymbol{p}) =$$

Example: 2 Compartments



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y(t,\boldsymbol{p}) &= c_1q_1(t,\boldsymbol{p})
\end{aligned}$$

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$$y(t,\boldsymbol{p}) = c_1q_1(t,\boldsymbol{p})$$

First coefficient:

Second coefficient:

Third coefficient:

Fourth coefficient:

$$\dot{q}_1(t,\boldsymbol{p}) = -(a_{01}+a_{21})\,q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
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$$y(t,\boldsymbol{p}) = c_1q_1(t,\boldsymbol{p})$$

First coefficient: $y_1(0,\boldsymbol{p}) = c_1b_1$

Second coefficient:

Third coefficient:

Fourth coefficient:

$$\dot{q}_1(t,\boldsymbol{p}) = -\left(a_{01}+a_{21}\right)q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
$$\dot{q}_2(t,\boldsymbol{p}) = a_{21}q_1(t,\boldsymbol{p}) - a_{12}q_2(t,\boldsymbol{p}), \qquad q_2(0,\boldsymbol{p}) = 0$$
$$y(t,\boldsymbol{p}) = c_1q_1(t,\boldsymbol{p})$$

First coefficient: $y_1(0,\boldsymbol{p}) = c_1b_1$

Second coefficient: $\dot{y}_1(0,\boldsymbol{p}) = -c_1\left(a_{01}+a_{21}\right)b_1$

Third coefficient:

Fourth coefficient:

$$\dot{q}_1(t,\boldsymbol{p}) = -\left(a_{01}+a_{21}\right)q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
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Second coefficient: $\dot{y}_1(0,\boldsymbol{p}) = -c_1\left(a_{01}+a_{21}\right)b_1$

Third coefficient:
$$y_1^{(2)}(t,\boldsymbol{p}) = c_1\left(-\left(a_{01}+a_{21}\right)\dot{q}_1(t,\boldsymbol{p}) + a_{12}\dot{q}_2(t,\boldsymbol{p})\right)$$

Fourth coefficient:

$$\dot{q}_1(t,\boldsymbol{p}) = -\left(a_{01}+a_{21}\right)q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
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Third coefficient:

$$y_1^{(2)}(t,\boldsymbol{p}) = c_1\left(-\left(a_{01}+a_{21}\right)\dot{q}_1(t,\boldsymbol{p}) + a_{12}\dot{q}_2(t,\boldsymbol{p})\right)$$
$$\implies \qquad y_1^{(2)}(0,\boldsymbol{p}) = c_1\left(\left(a_{01}+a_{21}\right)^2 b_1 + a_{12}a_{21}b_1\right)$$

Fourth coefficient:

$$\dot{q}_1(t,\boldsymbol{p}) = -(a_{01}+a_{21})\,q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
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First coefficient: $y_1(0,\boldsymbol{p}) = c_1b_1$

Second coefficient: $\dot{y}_1(0,\boldsymbol{p}) = -c_1\,(a_{01}+a_{21})\,b_1$

Third coefficient:
$$y_1^{(2)}(t,\boldsymbol{p}) = c_1\,(-(a_{01}+a_{21})\,\dot{q}_1(t,\boldsymbol{p}) + a_{12}\dot{q}_2(t,\boldsymbol{p}))$$
$$\Longrightarrow \qquad y_1^{(2)}(0,\boldsymbol{p}) = c_1\left((a_{01}+a_{21})^2\,b_1 + a_{12}a_{21}b_1\right)$$

Fourth coefficient: $y_1^{(3)}(t,\boldsymbol{p}) =$
$$c_1\left((a_{01}+a_{21})^2\,\dot{q}_1 - a_{12}\,(a_{01}+a_{21})\,\dot{q}_2 + a_{12}a_{21}\dot{q}_1 - a_{12}^2\dot{q}_2\right)$$

$$\dot{q}_1(t,\boldsymbol{p}) = -\left(a_{01}+a_{21}\right)q_1(t,\boldsymbol{p}) + a_{12}q_2(t,\boldsymbol{p}), \qquad q_1(0,\boldsymbol{p}) = b_1$$
$$\dot{q}_2(t,\boldsymbol{p}) = a_{21}q_1(t,\boldsymbol{p}) - a_{12}q_2(t,\boldsymbol{p}), \qquad q_2(0,\boldsymbol{p}) = 0$$
$$y(t,\boldsymbol{p}) = c_1 q_1(t,\boldsymbol{p})$$

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Third coefficient:

$$y_1^{(2)}(t,\boldsymbol{p}) = c_1\left(-\left(a_{01}+a_{21}\right)\dot{q}_1(t,\boldsymbol{p}) + a_{12}\dot{q}_2(t,\boldsymbol{p})\right)$$
$$\implies \qquad y_1^{(2)}(0,\boldsymbol{p}) = c_1\left(\left(a_{01}+a_{21}\right)^2 b_1 + a_{12}a_{21}b_1\right)$$

Fourth coefficient: $y_1^{(3)}(t,\boldsymbol{p}) =$

$$c_1\left(\left(a_{01}+a_{21}\right)^2\dot{q}_1 - a_{12}\left(a_{01}+a_{21}\right)\dot{q}_2 + a_{12}a_{21}\dot{q}_1 - a_{12}^2\dot{q}_2\right)$$

$$\Rightarrow y_1^{(3)}(0,\boldsymbol{p}) = b_1c_1\left[\left(a_{01}+a_{21}\right)\left[-\left(a_{01}+a_{21}\right)^2 - 2a_{12}a_{21}\right] - a_{12}^2a_{21}\right]$$

$$
\begin{aligned}
y_1(0,\boldsymbol{p}) &= c_1 b_1\\
\dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1\left(a_{01}+a_{21}\right)\\
y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1\left(\left(a_{01}+a_{21}\right)^2 + a_{12}a_{21}\right)\\
y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1\left(\left(a_{01}+a_{21}\right)\left(-\left(a_{01}+a_{21}\right)^2 - 2a_{12}a_{21}\right) - a_{12}^2 a_{21}\right)
\end{aligned}
$$

- First coefficient:
- Second coefficient:
- Third coefficient:
- Fourth coefficient:

$$
\begin{aligned}
y_1(0,\boldsymbol{p}) &= c_1 b_1 \\
\dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1 \left(a_{01} + a_{21}\right) \\
y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01} + a_{21}\right)^2 + a_{12} a_{21}\right) \\
y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01} + a_{21}\right)\left(-\left(a_{01} + a_{21}\right)^2 - 2a_{12} a_{21}\right) - a_{12}^2 a_{21}\right)
\end{aligned}
$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient:
- Third coefficient:
- Fourth coefficient:

$$
\begin{aligned}
y_1(0,\boldsymbol{p}) &= c_1 b_1 \\
\dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1 \left(a_{01} + a_{21}\right) \\
y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1 \left((a_{01} + a_{21})^2 + a_{12} a_{21} \right) \\
y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1 \left((a_{01} + a_{21}) \left(-(a_{01} + a_{21})^2 - 2a_{12} a_{21} \right) - a_{12}^2 a_{21} \right)
\end{aligned}
$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01} + a_{21}$ unique
- Third coefficient:
- Fourth coefficient:

$$y_1(0,\boldsymbol{p}) = c_1 b_1$$
$$\dot{y}_1(0,\boldsymbol{p}) = -b_1 c_1 (a_{01} + a_{21})$$
$$y_1^{(2)}(0,\boldsymbol{p}) = b_1 c_1 \left((a_{01} + a_{21})^2 + a_{12} a_{21} \right)$$
$$y_1^{(3)}(0,\boldsymbol{p}) = b_1 c_1 \left((a_{01} + a_{21}) \left(-(a_{01} + a_{21})^2 - 2a_{12} a_{21} \right) - a_{12}^2 a_{21} \right)$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01} + a_{21}$ unique
- Third coefficient: $a_{12} a_{21}$ unique
- Fourth coefficient:

$$
\begin{aligned}
y_1(0,\boldsymbol{p}) &= c_1 b_1 \\
\dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1 \left(a_{01} + a_{21}\right) \\
y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01} + a_{21}\right)^2 + a_{12} a_{21}\right) \\
y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01} + a_{21}\right)\left(-\left(a_{01} + a_{21}\right)^2 - 2a_{12}a_{21}\right) - a_{12}^2 a_{21}\right)
\end{aligned}
$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01} + a_{21}$ unique
- Third coefficient: $a_{12} a_{21}$ unique
- Fourth coefficient: a_{12} unique

$$\begin{aligned} y_1(0,\boldsymbol{p}) &= c_1 b_1 \\ \dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1 \left(a_{01}+a_{21}\right) \\ y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01}+a_{21}\right)^2 + a_{12}a_{21}\right) \\ y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01}+a_{21}\right)\left(-\left(a_{01}+a_{21}\right)^2 - 2a_{12}a_{21}\right) - a_{12}^2 a_{21}\right) \end{aligned}$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01}+a_{21}$ unique
- Third coefficient: $a_{12}a_{21}$ unique
- Fourth coefficient: a_{12} unique
- So a_{21} and then a_{01} unique

$$
\begin{aligned}
y_1(0,\boldsymbol{p}) &= c_1 b_1 \\
\dot{y}_1(0,\boldsymbol{p}) &= -b_1 c_1 \left(a_{01}+a_{21}\right) \\
y_1^{(2)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01}+a_{21}\right)^2 + a_{12}a_{21}\right) \\
y_1^{(3)}(0,\boldsymbol{p}) &= b_1 c_1 \left(\left(a_{01}+a_{21}\right)\left(-\left(a_{01}+a_{21}\right)^2 - 2a_{12}a_{21}\right) - a_{12}^2 a_{21}\right)
\end{aligned}
$$

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01}+a_{21}$ unique
- Third coefficient: $a_{12}a_{21}$ unique
- Fourth coefficient: a_{12} unique
- So a_{21} and then a_{01} unique
- Same result as before

Similarity transformation/exhaustive modelling approach

Generates set of all possible linear models: $(\boldsymbol{A}(\overline{\boldsymbol{p}}), \boldsymbol{B}(\overline{\boldsymbol{p}}), \boldsymbol{C}(\overline{\boldsymbol{p}}))$

with same I/O behaviour as given one: $(\boldsymbol{A}(\boldsymbol{p}), \boldsymbol{B}(\boldsymbol{p}), \boldsymbol{C}(\boldsymbol{p}))$

Consider the model given by

$$\begin{aligned} \dot{\boldsymbol{q}}(t,\boldsymbol{p}) &= \boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\boldsymbol{p}) = \boldsymbol{q}_0(\boldsymbol{p}), \\ \boldsymbol{y}(t,\boldsymbol{p}) &= \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}), \end{aligned} \tag{1}$$

and suppose that following are satisfied:

Controllability rank condition:

$$\text{rank}\begin{pmatrix}\boldsymbol{B}(\boldsymbol{p}) & \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) & \ldots & \boldsymbol{A}(\boldsymbol{p})^{n-1}\boldsymbol{B}(\boldsymbol{p})\end{pmatrix} = n$$

Observability rank condition: $\text{rank}\begin{pmatrix}\boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \\ \vdots \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p})^{n-1}\end{pmatrix} = n$

If both are satisfied model is minimal.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

$$\dot{\boldsymbol{z}}(t) = \boldsymbol{T}\dot{\boldsymbol{q}}(t, \boldsymbol{p}) =$$

$$= \qquad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}),$$

$$\boldsymbol{y}(t, \boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t, \boldsymbol{p}) =$$

has identical input-output behaviour.

Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\dot{\boldsymbol{q}}(t, \overline{\boldsymbol{p}}) = \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t, \overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0, \overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}),$$
$$\boldsymbol{y}(t, \overline{\boldsymbol{p}}) = \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t, \overline{\boldsymbol{p}}),$$

with identical input-output behaviour as the initial one (1), then

$$\boldsymbol{A}(\overline{\boldsymbol{p}}) =$$
$$\boldsymbol{B}(\overline{\boldsymbol{p}}) =$$
$$\boldsymbol{C}(\overline{\boldsymbol{p}}) =$$

for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

$$\dot{\boldsymbol{z}}(t) = \boldsymbol{T}\dot{\boldsymbol{q}}(t,\boldsymbol{p}) = \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t)$$

$$= \qquad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}),$$

$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) =$$

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Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\dot{\boldsymbol{q}}(t,\overline{\boldsymbol{p}}) = \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}),$$
$$\boldsymbol{y}(t,\overline{\boldsymbol{p}}) = \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}),$$

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for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

$$\dot{\boldsymbol{z}}(t) = \boldsymbol{T}\dot{\boldsymbol{q}}(t,\boldsymbol{p}) = \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t)$$

$$= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t), \quad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}),$$

$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) =$$

has identical input-output behaviour.

Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\dot{\boldsymbol{q}}(t,\overline{\boldsymbol{p}}) = \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}),$$

$$\boldsymbol{y}(t,\overline{\boldsymbol{p}}) = \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}),$$

with identical input-output behaviour as the initial one (1), then

$$\boldsymbol{A}(\overline{\boldsymbol{p}}) =$$

$$\boldsymbol{B}(\overline{\boldsymbol{p}}) =$$

$$\boldsymbol{C}(\overline{\boldsymbol{p}}) =$$

for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

$$\dot{\boldsymbol{z}}(t) = \boldsymbol{T}\dot{\boldsymbol{q}}(t,\boldsymbol{p}) = \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t)$$
$$= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t), \quad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}),$$
$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t).$$

has identical input-output behaviour.

Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\dot{\boldsymbol{q}}(t,\overline{\boldsymbol{p}}) = \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}),$$
$$\boldsymbol{y}(t,\overline{\boldsymbol{p}}) = \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}),$$

with identical input-output behaviour as the initial one (1), then

$$\boldsymbol{A}(\overline{\boldsymbol{p}}) =$$
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for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

$$\begin{aligned}\dot{\boldsymbol{z}}(t) &= \boldsymbol{T}\dot{\boldsymbol{q}}(t,\boldsymbol{p}) = \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t) \\ &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t), \quad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}), \\ \boldsymbol{y}(t,\boldsymbol{p}) &= \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t).\end{aligned}$$

has identical input-output behaviour.

Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\begin{aligned}\dot{\boldsymbol{q}}(t,\overline{\boldsymbol{p}}) &= \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}), \\ \boldsymbol{y}(t,\overline{\boldsymbol{p}}) &= \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}),\end{aligned}$$

with identical input-output behaviour as the initial one (1), then

$$\begin{aligned}\boldsymbol{A}(\overline{\boldsymbol{p}}) &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}, \\ \boldsymbol{B}(\overline{\boldsymbol{p}}) &= \\ \boldsymbol{C}(\overline{\boldsymbol{p}}) &= \end{aligned}$$

for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Then there exists invertible $n \times n$ matrix $\boldsymbol{T}$ such that, if $\boldsymbol{z} = \boldsymbol{T}\boldsymbol{q}$:

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with identical input-output behaviour as the initial one (1), then

$$\begin{aligned}\boldsymbol{A}(\overline{\boldsymbol{p}}) &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}, \\ \boldsymbol{B}(\overline{\boldsymbol{p}}) &= \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p}), \\ \boldsymbol{C}(\overline{\boldsymbol{p}}) &= \end{aligned}$$

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$$\begin{aligned}\dot{\boldsymbol{z}}(t) = \boldsymbol{T}\dot{\boldsymbol{q}}(t,\boldsymbol{p}) &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t)\\ &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t) + \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})\boldsymbol{u}(t), \quad \boldsymbol{z}(0) = \boldsymbol{T}\boldsymbol{q}_0(\boldsymbol{p}),\\ \boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p}) &= \boldsymbol{C}(\boldsymbol{p})\boldsymbol{T}^{-1}\boldsymbol{z}(t).\end{aligned}$$

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Therefore, if $\overline{\boldsymbol{p}} \in \Omega$ gives rise to a model:

$$\begin{aligned}\dot{\boldsymbol{q}}(t,\overline{\boldsymbol{p}}) &= \boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}) + \boldsymbol{B}(\overline{\boldsymbol{p}})\boldsymbol{u}(t), \quad \boldsymbol{q}(0,\overline{\boldsymbol{p}}) = \boldsymbol{q}_0(\overline{\boldsymbol{p}}),\\ \boldsymbol{y}(t,\overline{\boldsymbol{p}}) &= \boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{q}(t,\overline{\boldsymbol{p}}),\end{aligned}$$

with identical input-output behaviour as the initial one (1), then

$$\begin{aligned}\boldsymbol{A}(\overline{\boldsymbol{p}}) &= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p})\boldsymbol{T}^{-1},\\ \boldsymbol{B}(\overline{\boldsymbol{p}}) &= \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p}),\\ \boldsymbol{C}(\overline{\boldsymbol{p}}) &= \boldsymbol{C}(\boldsymbol{p})\boldsymbol{T}^{-1},\end{aligned}$$

for some invertible $n \times n$ matrix $\boldsymbol{T}$.

Sometimes easier to deal with:

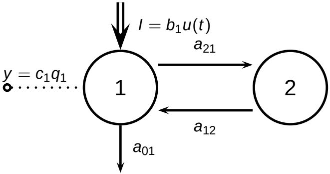
$$\boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{T} = \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p}), \quad (2)$$

$$\boldsymbol{B}(\overline{\boldsymbol{p}}) = \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p}), \quad (3)$$

$$\boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{T} = \boldsymbol{C}(\boldsymbol{p}). \quad (4)$$

- If only solution is $\boldsymbol{T} = \boldsymbol{I}_n$ then $\overline{\boldsymbol{p}} = \boldsymbol{p}$ and the system is **SGI**
- If $\boldsymbol{T}$ can take any of a finite set (with more than 1 element) of possibilities, then the system is **SLI**
- Otherwise, ($\boldsymbol{T}$ can take any of a infinite set of possibilities) then the system is unidentifiable

Example: Two-compartment model.



System equations:

$$\dot{\boldsymbol{q}}(t, \boldsymbol{p}) = \boldsymbol{A}(\boldsymbol{p})\boldsymbol{q}(t, \boldsymbol{p}) + \boldsymbol{B}(\boldsymbol{p})u(t), \qquad \boldsymbol{q}(0, \boldsymbol{p}) = \boldsymbol{0}$$
$$y(t, \boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t, \boldsymbol{p})$$

where

$$\boldsymbol{A}(\boldsymbol{p}) = \qquad , \ \boldsymbol{B}(\boldsymbol{p}) = \qquad , \ \boldsymbol{C}(\boldsymbol{p}) =$$

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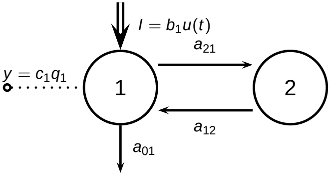

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$$y(t,\boldsymbol{p}) = \boldsymbol{C}(\boldsymbol{p})\boldsymbol{q}(t,\boldsymbol{p})$$

where

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \ \boldsymbol{B}(\boldsymbol{p}) = \qquad , \ \boldsymbol{C}(\boldsymbol{p}) =$$

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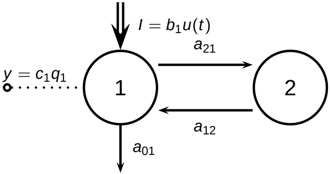

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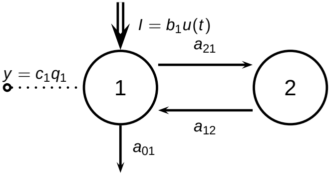

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Controllability:

$$\left[\boldsymbol{B}(\boldsymbol{p}) \; \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p})\right] = \left[\qquad \right]$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \left[\qquad \right]$$

Equation (3):

$$\boldsymbol{B}(\overline{\boldsymbol{p}}) = \qquad \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})$$

and so

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

$$\begin{bmatrix} \boldsymbol{B}(\boldsymbol{p}) & \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} b_1 & \\ 0 & \end{bmatrix}$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} \quad \end{bmatrix}$$

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Controllability:

$$\begin{bmatrix} \boldsymbol{B}(\boldsymbol{p}) \ \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix}$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} \quad \end{bmatrix}$$

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Controllability:

$$\left[\boldsymbol{B}(\boldsymbol{p}) \; \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p})\right] = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \qquad \text{rank } 2$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} \quad \end{bmatrix}$$

Equation (3):

$$\boldsymbol{B}(\overline{\boldsymbol{p}}) = \qquad \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p})$$

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$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

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Observability:

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Observability:

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Observability:

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Controllability:

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So model is minimal

Equation (3):

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$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

$$\begin{bmatrix} \boldsymbol{B}(\boldsymbol{p}) & \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \qquad \text{rank 2}$$

Observability:

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Equation (3):

$$\boldsymbol{B}(\overline{\boldsymbol{p}}) = \begin{pmatrix} \overline{b}_1 \\ 0 \end{pmatrix} = \boldsymbol{T}\boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} t_{11} & t_{12} \\ t_{21} & t_{22} \end{pmatrix} \begin{pmatrix} b_1 \\ 0 \end{pmatrix}$$

and so

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

$$\left[\boldsymbol{B}(\boldsymbol{p}) \ \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p})\right] = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \qquad \text{rank 2}$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1(a_{01}+a_{21}) & c_1 a_{12} \end{bmatrix} \qquad \text{rank 2}$$

So model is minimal

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and so

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

$$\begin{bmatrix} \boldsymbol{B}(\boldsymbol{p}) & \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \qquad \text{rank } 2$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1(a_{01}+a_{21}) & c_1 a_{12} \end{bmatrix} \qquad \text{rank } 2$$

So model is minimal

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and so $t_{21} = 0$ and

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \ \boldsymbol{B}(\boldsymbol{p}) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{pmatrix} c_1 & 0 \end{pmatrix}$$

Controllability:

$$\begin{bmatrix} \boldsymbol{B}(\boldsymbol{p}) & \boldsymbol{A}(\boldsymbol{p})\boldsymbol{B}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1(a_{01}+a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \qquad \text{rank } 2$$

Observability:

$$\begin{bmatrix} \boldsymbol{C}(\boldsymbol{p}) \\ \boldsymbol{C}(\boldsymbol{p})\boldsymbol{A}(\boldsymbol{p}) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1(a_{01}+a_{21}) & c_1 a_{12} \end{bmatrix} \qquad \text{rank } 2$$

So model is minimal

Equation (3):

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and so $t_{21} = 0$ and $t_{11} = \overline{b}_1 / b_1$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \ 0 \end{bmatrix}, \ \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

Equation (4):

$$\boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{T} = \begin{pmatrix} \overline{c}_1 & 0 \end{pmatrix} \begin{pmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{pmatrix} = \begin{pmatrix} c_1 & 0 \end{pmatrix} = \boldsymbol{C}(\boldsymbol{p})$$

and so

Equation (2):

$$\boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{T} =$$

$$= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p}) =$$

$$=$$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \ 0 \end{bmatrix}, \ \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

Equation (4):

$$\boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{T} = \begin{pmatrix} \overline{b}_1\overline{c}_1/b_1 & \overline{c}_1 t_{12} \end{pmatrix} = \begin{pmatrix} c_1 & 0 \end{pmatrix} = \boldsymbol{C}(\boldsymbol{p})$$

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$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \; 0 \end{bmatrix}, \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

Equation (4):

$$\boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{T} = \begin{pmatrix} \overline{b}_1\overline{c}_1/b_1 & \overline{c}_1 t_{12} \end{pmatrix} = \begin{pmatrix} c_1 & 0 \end{pmatrix} = \boldsymbol{C}(\boldsymbol{p})$$

and so $t_{12} = 0$ and

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$$=$$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \; 0 \end{bmatrix}, \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

Equation (4):

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and so $t_{12} = 0$ and $\overline{b}_1\overline{c}_1 = b_1 c_1$

Equation (2):

$$\boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{T} =$$

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$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \ 0 \end{bmatrix}, \ \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

Equation (4):

$$\boldsymbol{C}(\overline{\boldsymbol{p}})\boldsymbol{T} = \begin{pmatrix} \overline{b}_1\overline{c}_1/b_1 & \overline{c}_1 t_{12} \end{pmatrix} = \begin{pmatrix} c_1 & 0 \end{pmatrix} = \boldsymbol{C}(\boldsymbol{p})$$

and so $t_{12} = 0$ and $\overline{b}_1\overline{c}_1 = b_1 c_1$

Equation (2):

$$\boldsymbol{A}(\overline{\boldsymbol{p}})\boldsymbol{T} = \begin{pmatrix} -(\overline{a}_{01}+\overline{a}_{21}) & \overline{a}_{12} \\ \overline{a}_{21} & -\overline{a}_{12} \end{pmatrix} \begin{pmatrix} \overline{b}_1/b_1 & 0 \\ 0 & t_{22} \end{pmatrix}$$

$$= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p}) =$$

$$=$$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \ 0 \end{bmatrix}, \ \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

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$$= \boldsymbol{T}\boldsymbol{A}(\boldsymbol{p}) = \begin{pmatrix} \overline{b}_1/b_1 & 0 \\ 0 & t_{22} \end{pmatrix} \begin{pmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}$$

$$=$$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \ \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \ 0 \end{bmatrix}, \ \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

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$$= \begin{bmatrix} -\frac{\overline{b}_1}{b_1}(\overline{a}_{01}+\overline{a}_{21}) & t_{22}\overline{a}_{12} \\ \frac{\overline{b}_1}{b_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{bmatrix} =$$

$$\boldsymbol{A}(\boldsymbol{p}) = \begin{bmatrix} -(a_{01}+a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \; \boldsymbol{C}(\boldsymbol{p}) = \begin{bmatrix} c_1 \; 0 \end{bmatrix}, \; \boldsymbol{T} = \begin{bmatrix} \overline{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}$$

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$$= \begin{bmatrix} -\frac{\overline{b}_1}{b_1}(\overline{a}_{01}+\overline{a}_{21}) & t_{22}\overline{a}_{12} \\ \frac{\overline{b}_1}{b_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{bmatrix} = \begin{bmatrix} -\frac{\overline{b}_1}{b_1}(a_{01}+a_{21}) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{bmatrix}$$

$$\begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(\overline{a}_{01}+\overline{a}_{21}\right) & t_{22}\overline{a}_{12} \\ \frac{\overline{b}_1}{b_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

so (1,2) component:

(2,1) component:

(1,1) component:

So:

$$\begin{pmatrix} -\frac{\bar{b}_1}{b_1}\left(\bar{a}_{01}+\bar{a}_{21}\right) & t_{22}\bar{a}_{12} \\ \frac{b_1}{\bar{b}_1}\bar{a}_{21} & -\bar{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\bar{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\bar{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

$$\bar{a}_{12} = a_{12}$$

so (1,2) component:

(2,1) component:

(1,1) component:

So:

$$\begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(\overline{a}_{01}+\overline{a}_{21}\right) & t_{22}\overline{a}_{12} \\ \frac{b_1}{\overline{b}_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

$$\overline{a}_{12} = a_{12}$$

so (1,2) component:

$$t_{22} = \overline{b}_1/b_1$$

(2,1) component:

(1,1) component:

So:

$$\begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(\overline{a}_{01}+\overline{a}_{21}\right) & t_{22}\overline{a}_{12} \\ \frac{b_1}{\overline{b}_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

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So:

$$\begin{pmatrix} -\frac{\overline{b}_1}{b_1}(\overline{a}_{01}+\overline{a}_{21}) & t_{22}\overline{a}_{12} \\ \frac{\overline{b}_1}{b_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\overline{b}_1}{b_1}(a_{01}+a_{21}) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

$$\overline{a}_{12} = a_{12}$$

so (1,2) component:

$$t_{22} = \overline{b}_1/b_1$$

(2,1) component:

$$\overline{a}_{21} = a_{21}$$

(1,1) component:

$$\overline{a}_{01} = a_{01}$$

So:

$$\begin{pmatrix} -\frac{\bar{b}_1}{b_1}\left(\bar{a}_{01}+\bar{a}_{21}\right) & t_{22}\bar{a}_{12} \\ \frac{b_1}{\bar{b}_1}\bar{a}_{21} & -\bar{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\bar{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\bar{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

$$\bar{a}_{12} = a_{12}$$

so (1,2) component:

$$t_{22} = \bar{b}_1/b_1$$

(2,1) component:

$$\bar{a}_{21} = a_{21}$$

(1,1) component:

$$\bar{a}_{01} = a_{01}$$

So:

- a_{01}, a_{12} and a_{21} all globally identifiable

$$\begin{pmatrix} -\frac{\bar{b}_1}{b_1}(\bar{a}_{01}+\bar{a}_{21}) & t_{22}\bar{a}_{12} \\ \frac{\bar{b}_1}{b_1}\bar{a}_{21} & -\bar{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\bar{b}_1}{b_1}(a_{01}+a_{21}) & \frac{\bar{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

(2,2) component:

$$\bar{a}_{12} = a_{12}$$

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(2,1) component:

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(1,1) component:

$$\bar{a}_{01} = a_{01}$$

So:

- a_{01}, a_{12} and a_{21} all globally identifiable
- combination b_1c_1 globally identifiable

$$\begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(\overline{a}_{01}+\overline{a}_{21}\right) & t_{22}\overline{a}_{12} \\ \frac{\overline{b}_1}{b_1}\overline{a}_{21} & -\overline{a}_{12}t_{22} \end{pmatrix} = \begin{pmatrix} -\frac{\overline{b}_1}{b_1}\left(a_{01}+a_{21}\right) & \frac{\overline{b}_1}{b_1}a_{12} \\ a_{21}t_{22} & -a_{12}t_{22} \end{pmatrix}$$

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(2,1) component:

$$\overline{a}_{21} = a_{21}$$

(1,1) component:

$$\overline{a}_{01} = a_{01}$$

So:

- a_{01}, a_{12} and a_{21} all globally identifiable
- combination b_1c_1 globally identifiable
- individual b_1 and c_1 unidentifiable

Techniques for nonlinear models

Techniques for nonlinear models:

- generally more difficult to apply
- can be less systematic
- do not always yield full information concerning identifiability
- must be careful about what inputs there are to the system

Dealing with state space models of form:

$$\begin{aligned} \dot{\boldsymbol{x}}(t,\boldsymbol{p}) &= \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p},\boldsymbol{u}(t)), \quad \boldsymbol{x}(0,\boldsymbol{p}) = \boldsymbol{x}_0(\boldsymbol{p}), \\ \boldsymbol{y}(t,\boldsymbol{p}) &= \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}), \end{aligned} \tag{5}$$

where

- $\boldsymbol{p} \in \Omega$ is an r dimensional (parameter) vector
- $\boldsymbol{x}(t,\boldsymbol{p})$ is an n dimensional (state) vector
- $\boldsymbol{u}(t)$ is an m dimensional (input) vector
- $\boldsymbol{y}(t,\boldsymbol{p})$ is an l dimensional (output) vector

Taylor series approach

This approach for linear models also works for nonlinear ones:

$$y_i(t,\boldsymbol{p}) = y_i(0,\boldsymbol{p}) + \dot{y}_i(0,\boldsymbol{p})t + \ddot{y}_i(0,\boldsymbol{p})\frac{t^2}{2!} + \cdots + y_i^{(k)}(0,\boldsymbol{p})\frac{t^k}{k!} + \ldots$$

where $y_i^{(k)}(0,\boldsymbol{p}) = \left.\dfrac{\mathrm{d}^k y_i}{\mathrm{d}t^k}\right|_{t=0} \qquad (k = 1, 2, \ldots).$

Taylor series coefficients $y_i^{(k)}(0,\boldsymbol{p})$ unique for particular output

Notice that we have a possibly infinite list of coefficients:

$$y_i(0,\boldsymbol{p}), \dot{y}_i(0,\boldsymbol{p}), \ddot{y}_i(0,\boldsymbol{p}), \ldots \qquad i = 1, \ldots, l$$

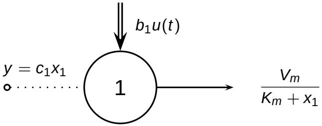
& upper bound on number of coefficients needed more difficult

If model is autonomous, single output ($m = 1$), upper bound is:

- Transfer coefficients all polynomial: $n + r$
- If any coefficient rational: $n + r + 1$

Quite difficult to use TSA to prove model is unidentifiable

Example: 1 compartment



Model equations:

$$\dot{x}_1 = -\frac{V_m x_1}{K_m + x_1}, \qquad x_1(0) = b_1$$

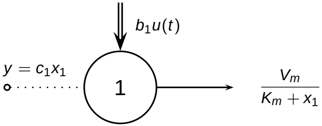
$$y = c_1 x_1$$

First coefficient: $y(0, \boldsymbol{p}) = b_1 c_1$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) = -\frac{c_1 V_m b_1}{K_m + b_1}$

Third coefficient: $y^{(2)}(t, \boldsymbol{p}) = \frac{\mathrm{d}}{\mathrm{d}t}\left(-\frac{c_1 V_m x_1}{K_m + x_1}\right)$

Example: 1 compartment



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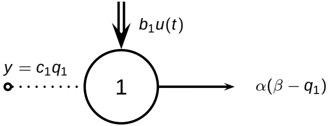
Use symbolic tools such as MATHEMATICA, MAPLE

Example: One compartment with Langmuir elimination:



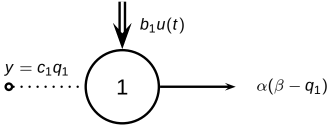
Model equations:

First coefficient: $y(0, \boldsymbol{p}) =$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) =$

Third coefficient: $y^{(2)}(t, \boldsymbol{p}) =$

Example: One compartment with Langmuir elimination:



Model equations:

$$\dot{q}_1 = -\alpha q_1(\beta - q_1), \qquad q_1(0) = 1$$
$$y = c_1 q_1$$

First coefficient: $y(0, \boldsymbol{p}) =$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) =$

Third coefficient: $y^{(2)}(t, \boldsymbol{p}) =$

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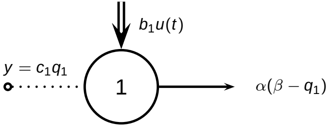

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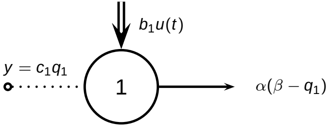

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First coefficient: $y(0, \boldsymbol{p}) = c_1$

Second coefficient: $\dot{y}(0, \boldsymbol{p}) = \; -c_1\alpha(\beta - 1)$

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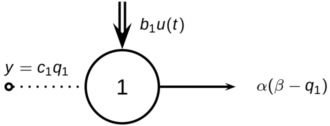

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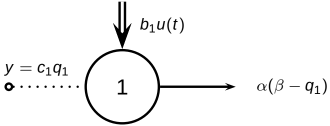
Example: One compartment with Langmuir elimination:



Model equations:

$$\dot{q}_1 = -\alpha q_1(\beta - q_1), \qquad q_1(0) = 1$$
$$y = c_1 q_1$$

First coefficient: $y(0, \mathbf{p}) = c_1$

Second coefficient: $\dot{y}(0, \mathbf{p}) = -c_1\alpha(\beta - 1)$

Third coefficient: $y^{(2)}(t, \mathbf{p}) = -c_1\alpha\left(\beta\dot{q}_1 - 2q_1\dot{q}_1\right)$

$$\Longrightarrow y^{(2)}(0, \mathbf{p}) = c_1\alpha^2(\beta - 1)(\beta - 2)$$

$$
\begin{aligned}
y(0,\boldsymbol{p}) &= c_1 \\
\dot{y}(0,\boldsymbol{p}) &= -c_1\alpha(\beta-1) \\
y^{(2)}(0,\boldsymbol{p}) &= c_1\alpha^2(\beta-1)(\beta-2)
\end{aligned}
$$

- First coefficient:
- Second coefficient:
- Third coefficient:

$$y(0,\boldsymbol{p}) = c_1$$
$$\dot{y}(0,\boldsymbol{p}) = -c_1\alpha(\beta-1)$$
$$y^{(2)}(0,\boldsymbol{p}) = c_1\alpha^2(\beta-1)(\beta-2)$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient:
- Third coefficient:

$$
\begin{aligned}
y(0,\boldsymbol{p}) &= c_1 \\
\dot{y}(0,\boldsymbol{p}) &= -c_1\alpha(\beta-1) \\
y^{(2)}(0,\boldsymbol{p}) &= c_1\alpha^2(\beta-1)(\beta-2)
\end{aligned}
$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient: $\alpha(\beta-1)$ unique
- Third coefficient:

$$
\begin{aligned}
y(0,\boldsymbol{p}) &= c_1 \\
\dot{y}(0,\boldsymbol{p}) &= -c_1\alpha(\beta-1) \\
y^{(2)}(0,\boldsymbol{p}) &= c_1\alpha^2(\beta-1)(\beta-2)
\end{aligned}
$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient: $\alpha(\beta-1)$ unique
- Third coefficient: $\alpha^2(\beta-1)(\beta-2)$ unique

$$
\begin{aligned}
y(0,\boldsymbol{p}) &= c_1 \\
\dot{y}(0,\boldsymbol{p}) &= -c_1\alpha(\beta-1) \\
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\end{aligned}
$$

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- Second coefficient: $\alpha(\beta-1)$ unique
- Third coefficient: $\alpha(\beta-2)$ unique

$$
\begin{aligned}
y(0,\boldsymbol{p}) &= c_1 \\
\dot{y}(0,\boldsymbol{p}) &= -c_1\alpha(\beta-1) \\
y^{(2)}(0,\boldsymbol{p}) &= c_1\alpha^2(\beta-1)(\beta-2)
\end{aligned}
$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient: $\alpha(\beta-1)$ unique
- Third coefficient: $\alpha(\beta-1)-\alpha$ unique

$$y(0, \boldsymbol{p}) = c_1$$
$$\dot{y}(0, \boldsymbol{p}) = -c_1\alpha(\beta - 1)$$
$$y^{(2)}(0, \boldsymbol{p}) = c_1\alpha^2(\beta - 1)(\beta - 2)$$

- First coefficient: c_1 unique (globally identifiable)
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- Third coefficient: α unique (globally identifiable)

$$y(0, \boldsymbol{p}) = c_1$$
$$\dot{y}(0, \boldsymbol{p}) = -c_1 \alpha(\beta - 1)$$
$$y^{(2)}(0, \boldsymbol{p}) = c_1 \alpha^2 (\beta - 1)(\beta - 2)$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient: $\alpha(\beta - 1)$ unique
- Third coefficient: α unique (globally identifiable)
- And so β globally identifiable

$$
\begin{aligned}
y(0, \boldsymbol{p}) &= c_1 \\
\dot{y}(0, \boldsymbol{p}) &= -c_1 \alpha(\beta - 1) \\
y^{(2)}(0, \boldsymbol{p}) &= c_1 \alpha^2 (\beta - 1)(\beta - 2)
\end{aligned}
$$

- First coefficient: c_1 unique (globally identifiable)
- Second coefficient: $\alpha(\beta - 1)$ unique
- Third coefficient: α unique (globally identifiable)
- And so β globally identifiable
- All parameters globally identifiable so model is **SGI**

Now for something a little more advanced . . .

Observable normal form approach

Single output, no (or single) input

For generic parameter vector $\boldsymbol{p}$:

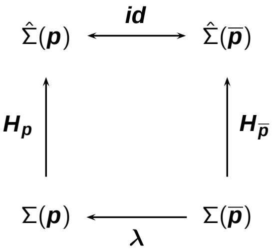
- Check an observability criterion
  - Define $\mu_1(\boldsymbol{x},\boldsymbol{p}) = h(\boldsymbol{x},\boldsymbol{p})$ and

$$\mu_{i+1}(\boldsymbol{x},\boldsymbol{p}) = \frac{\partial \mu_i}{\partial \boldsymbol{x}}(\boldsymbol{x},\boldsymbol{p})\boldsymbol{f}(\boldsymbol{x},\boldsymbol{p}) \qquad i = 1,\ldots,n-1$$

  - Define $\boldsymbol{H}_{\boldsymbol{p}}(\boldsymbol{x}) = (\mu_1(\boldsymbol{x},\boldsymbol{p}),\ldots,\mu_n(\boldsymbol{x},\boldsymbol{p}))^T$
  - Rank of $\dfrac{\partial \boldsymbol{H}_{\boldsymbol{p}}}{\partial \boldsymbol{x}}(\boldsymbol{x}_0(\boldsymbol{p}))$ is n
- So $\boldsymbol{H}_{\boldsymbol{p}}(\cdot)$ diffeomorphism on neighbourhood of $\boldsymbol{x}_0(\boldsymbol{p})$
  - Hence is a coordinate transformation ...

Previous approach

- Coordinate transformation between models that are indistinguishable via available output
  - $\boldsymbol{H_p}(\boldsymbol{\lambda}(\boldsymbol{x})) = \boldsymbol{H_{\overline{p}}}(\boldsymbol{x})$



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

$$\boldsymbol{\lambda}(\boldsymbol{x}_0(\overline{\boldsymbol{p}})) = \boldsymbol{x}_0(\boldsymbol{p})$$

$$\boldsymbol{f}(\boldsymbol{\lambda}(\boldsymbol{x}(t)), \boldsymbol{p}) = \frac{\partial \boldsymbol{\lambda}}{\partial \boldsymbol{x}}(\boldsymbol{x}(t))\boldsymbol{f}(\boldsymbol{x}(t), \overline{\boldsymbol{p}})$$

$$\boldsymbol{h}(\boldsymbol{\lambda}(\boldsymbol{x}(t)), \boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t), \overline{\boldsymbol{p}})$$

$$(\boldsymbol{x}(t) = \boldsymbol{x}(t, \overline{\boldsymbol{p}}))$$

Observability normal form

System $\hat{\Sigma}$ is the observability normal form, $\boldsymbol{z} = \boldsymbol{H_p}(\boldsymbol{x})$:

$$\begin{aligned}\dot{z}_1 &= z_2 \\ &\vdots \\ \dot{z}_{n-1} &= z_n \\ \dot{z}_n &= \mu_{n+1}(\boldsymbol{H}_{\boldsymbol{p}}^{-1}(\boldsymbol{z}), \boldsymbol{p}) \\ y &= z_1\end{aligned}$$

Last equation gives input-output equation for system and so, for all $\overline{\boldsymbol{p}} \in \mathcal{S}(\boldsymbol{p})$, have

$$\mu_{n+1}(\boldsymbol{H}_{\boldsymbol{p}}^{-1}(\boldsymbol{z}(t)), \boldsymbol{p}) = \mu_{n+1}(\boldsymbol{H}_{\overline{\boldsymbol{p}}}^{-1}(\boldsymbol{z}(t)), \overline{\boldsymbol{p}}) \qquad \forall t \geq 0$$

Using output equation

Now rewrite output equation in form:

$$\phi_0(\boldsymbol{z}(t), \dot{z}_n(t)) + \sum_{i=1}^{m} \sigma_i(\boldsymbol{p})\phi_i(\boldsymbol{z}(t), \dot{z}_n(t)) = 0$$

where $\phi_i(\boldsymbol{z}(t), \dot{z}_n(t))$ are linearly independent

Then if $\overline{\boldsymbol{p}} \in \mathcal{S}(\boldsymbol{p})$

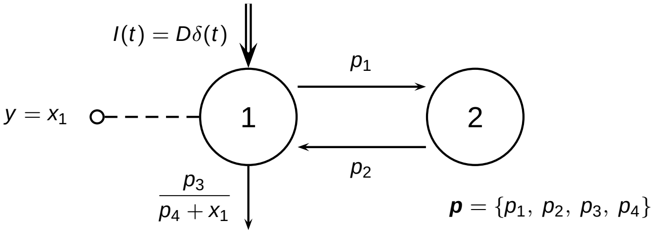
$$\sum_{i=1}^{m} (\sigma_i(\boldsymbol{p}) - \sigma_i(\overline{\boldsymbol{p}}))\, \phi_i(\boldsymbol{z}(t), \dot{z}_n(t)) = 0$$

and so

$$\sigma_i(\boldsymbol{p}) = \sigma_i(\overline{\boldsymbol{p}}) \qquad i = 1, \ldots, m$$

Example

Consider two-compartment model:



$$\mu_1(\boldsymbol{x}, \boldsymbol{p}) = x_1$$

$$\mu_2(\boldsymbol{x}, \boldsymbol{p}) = -p_1 x_1 + p_2 x_2 - \frac{p_3 x_1}{p_4 + x_1}$$

Example: Observability normal form

Observability condition met provided $p_2 \neq 0$ (ie, for all $\boldsymbol{p}$) so can transform into:

$$\dot{z}_1(t, \boldsymbol{p}) = z_2(t, \boldsymbol{p})$$

$$\dot{z}_2(t, \boldsymbol{p}) = -(p_1 + p_2) z_2(t, \boldsymbol{p}) - \frac{p_2 p_3 z_1(t, \boldsymbol{p})}{p_4 + z_1(t, \boldsymbol{p})} - \frac{p_3 p_4 z_2(t, \boldsymbol{p})}{(p_4 + z_1(t, \boldsymbol{p}))^2}$$

where

$$z_1(0, \boldsymbol{p}) = D \quad \text{and} \quad z_2(0, \boldsymbol{p}) = -p_2 D - \frac{p_3 D}{p_4 + D}$$

Example: Output equation

Output equation:

$$z_1^2\dot{z}_2 + p_4^2\dot{z}_2 + 2p_4z_1\dot{z}_2 + p_2p_3p_4z_1 + p_2p_3z_1^2 + \left(p_3p_4 + p_4^2(p_1+p_2)\right)z_2 + 2p_4(p_1+p_2)z_1z_2 + (p_1+p_2)z_1^2z_2 = \phi_0(\mathbf{z},\dot{z}_n) + \sum_{i=1}^{7}\sigma_i(\mathbf{p})\phi_i(\mathbf{z},\dot{z}_n) = 0$$

Linear independence of terms guaranteed by checking the Wronskian, or can use constructive algebra methods (in MAPLE):

```
F := Vector([-p[1]*x[1]+p[2]*x[2]-p[3]*x[1]/(p[4]+x[1]),
p[1]*x[1]-p[2]*x[2]]);
H := x[1];
io := iorel(F,H)
```

Code modified from Evans et al *Automatica* **49**:48-57, 2013, which was based on PhD by Forsman (1991) *Constructive Commutative Algebra in Nonlinear Control Theory*

Example: Identifiability

$$\sigma_i(\boldsymbol{p}) = \sigma_i(\overline{\boldsymbol{p}}) \qquad i = 1, \ldots, 7$$

for any $\overline{\boldsymbol{p}} \in \mathcal{S}(\boldsymbol{p})$.

$$\begin{aligned}
\sigma_2(\boldsymbol{p}) &= p_4 & \Longrightarrow && \overline{p}_4 &= p_4 \\
\sigma_4(\boldsymbol{p}) &= p_2 p_3 & \Longrightarrow && \overline{p}_2\overline{p}_3 &= p_2 p_3 \\
\sigma_7(\boldsymbol{p}) &= p_1 + p_2 & \Longrightarrow && \overline{p}_1 + \overline{p}_2 &= p_1 + p_2 \\
\sigma_5(\boldsymbol{p}) &= p_3 p_4 + p_4^2(p_1 + p_2) & \Longrightarrow && \overline{p}_3 &= p_3
\end{aligned}$$

Solving these shows that $\overline{\boldsymbol{p}} = \boldsymbol{p}$, ie $\mathcal{S}(\boldsymbol{p}) = \{\boldsymbol{p}\}$

Therefore model is *structurally globally identifiable*

Summary

- 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
- Observability normal form highly appropriate for both analyses
  - Previously unsolved example (for identifiability) now solved!
  - Some computational difficulties remain
  - Generates input-output relations
- Structural indistinguishability similarly important
  - More general framework *but* exact
  - Generally pairwise comparison of schemes