Structural identifiability: An Introduction

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1 Motivation
   - Skeletal tracer kinetics
   - Infectious disease modelling

2 Structural identifiability
   - Laplace transform approach
   - Taylor series approach
   - Similarity transformation/exhaustive modelling approach

3 Techniques for nonlinear models
   - Taylor series approach
   - Observable normal form
\[ \dot{x} = Ax + bu \]
\[ y = Cx \]

(SEF: extracellular fluid)
Model simulations

Parameter Set I

Parameter Set II

Parameter Set III

Motivation
Structural identifiability
Techniques for nonlinear models
Skeletal tracer kinetics
Infectious disease modelling
Model simulations

Parameter Set I

Parameter Set II

Parameter Set III

Compartment 2

Compartment 3

Compartment 4
**SIR Model**

SIR infectious disease model:

\[ S(t, p) = \mu N - \mu S - \frac{\beta}{N} SY \]

\[ Y(t, p) = \beta S Y - (\mu + \gamma) Y \]

Proportion of prevalence measured: \( y(t, p) = k Y(t, p) \)

Model equations:

\[ X(t) = \mu N - \mu X - \frac{\beta}{N} XY \]

\[ Y(t) = \frac{\beta}{N} XY - (\mu + \gamma) Y \]

\[ y(t) = k Y(t) \]
\[
\mu = 0.0125, \quad \gamma = 12 \\
N = 10000 \\
\beta = 50, \quad k = 0.5 \\
X(0) = 2400 \\
Y(0) = 20
\]
$\mu = 0.0125, \gamma = 12$
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$\beta = 50, k = 0.5$
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$\mu = 0.0125, \gamma = 12$
$N = 20000$
$\beta = 50, k = 0.25$
$X(0) = 4800$
$Y(0) = 40$
SIR model

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$X(0) = 4800$
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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?
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:

\[
\begin{align*}
\dot{x}(t, p) &= f(x(t, p), u(t), p), \\
x(0, p) &= x_0(p), \\
y(t, p) &= h(x(t, p), p),
\end{align*}
\]

where \(p\) is the \(r\)-dimensional vector of unknown parameters, and is assumed to lie in a set of feasible vectors: \(p \in \Omega\).

\(n\) dimensional vector \(q(t, p)\) is state vector, such that \(q_0(p)\) is the initial state (may depend on the unknown parameters).

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

\(y(t, p)\) is the \(l\)-dimensional output/observation vector (what we can measure in the system). In the following we make explicit that output \(y\) depends on \(p \in \Omega\) and \(u \in \mathcal{U}\) by writing \(y(t, p; u)\).
For generic $\bm{p} \in \Omega$, the parameter $p_i$ is said to be **locally identifiable** if there exists a neighbourhood of vectors around $\bm{p}$, $\mathcal{N}(\bm{p})$, such that if $\bar{\bm{p}} \in \mathcal{N}(\bm{p}) \subseteq \Omega$ and:

$$y(t, \bm{p}; \bm{u}) = y(t, \bar{\bm{p}}; \bm{u})$$

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

In particular, if the neighbourhood $\mathcal{N}(\bm{p}) = \Omega$ 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 $\mathcal{N}(\bm{p})$, 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

\[
\dot{x}(t, p) = A(p)x(t, p) + B(p)u(t), \quad x(0, p) = x_0(p), \\
y(t, p) = C(p)x(t, p),
\]

where

- \(A(p)\) is an \(n \times n\) matrix of rate constants
- \(B(p)\) is an \(n \times m\) input matrix
- \(C(p)\) is an \(l \times n\) output matrix

Assume that \(x_0 = 0\) (not essential) & take Laplace transforms:

\[
sQ(s) = A(p)Q(s) + B(p)U(s) \\
Y(s) = C(p)Q(s) \\
= C(p)(sl_n - A(p))^{-1}B(p)U(s)
\]
Laplace Transform Approach

This gives relationship between LTs of input & output:

\[ Y(s) = G(s)U(s), \]

where the matrix

\[ G(s) = C(p)(sl_n - A(p))^{-1}B(p) \]

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

Input: impulse: \( b_1 u(t) = b_1 n_0 \delta(t) \); \( b_1 \) unknown, \( n_0 \) known

Output: \( y = c_1 q_1 \), where \( c_1 \) unknown.

System equations:

Transfer function: \( G(s) = \)
Example: 1 Compartment

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

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

**System equations:**

$$\dot{q}_1 = -a_{01} q_1 + b_1 u(t), \quad q_1(0) = 0,$$

$$y = c_1 q_1$$

**Transfer function:** $G(s) = \ldots$
Example: 1 Compartment

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

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

**System equations:**

$$\dot{q}_1 = -a_{01} q_1 + b_1 u(t), \quad q_1(0) = 0,$$

$$y = c_1 q_1$$

**Transfer function:**

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

Input: impulse: $b_1 u(t) = b_1 n_0 \delta(t)$; $b_1$ unknown, $n_0$ known
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System equations:
$$\dot{q}_1 = -a_{01} q_1 + b_1 u(t), \quad q_1(0) = 0,$$
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Transfer function: $G(s) = C(p)(sl_n - A(p))^{-1} B(p) = \frac{b_1 c_1}{s + a_{01}}$
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$$y = c_1 q_1$$

Transfer function: $G(s) = C(p) (s I_n - A(p))^{-1} B(p) = \frac{b_1 c_1}{s + a_{01}}$

So $b_1 c_1$ and $a_{01}$ globally identifiable.
Example: 1 Compartment

Input: impulse: \( b_1 u(t) = b_1 n_0 \delta(t); \) \( b_1 \) unknown, \( n_0 \) known

Output: \( y = c_1 q_1, \) where \( c_1 \) unknown.

System equations:
\[
\dot{q}_1 = -a_{01} q_1 + b_1 u(t), \quad q_1(0) = 0,
\]
\[
y = c_1 q_1
\]

Transfer function: \( G(s) = C(p) (sI_n - A(p))^{-1} B(p) = \frac{b_1 c_1}{s + a_{01}} \)

- So \( b_1 c_1 \) and \( a_{01} \) globally identifiable
- But \( b_1 \) and \( c_1 \) unidentifiable
**Example: 1 Compartment**

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

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**System equations:**

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\dot{q}_1 = -a_{01} q_1 + b_1 u(t), \quad q_1(0) = 0,
$$

$$
y = c_1 q_1
$$

**Transfer function:**

$$
G(s) = C(p) (sl_n - A(p))^{-1} B(p) = \frac{b_1 c_1}{s + a_{01}}
$$

- So $b_1 c_1$ 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:

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

- 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
Taylor series approach
Generally applied when there is a single input (eg, 0 or impulse)

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

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

where

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

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

Approach reduces to determining solutions for $p$ that give:

$$y_i(0, p), \quad y_i^{(k)}(0, p) \quad (1 \leq i \leq l, k \geq 1).$$

Notice that we have a possibly infinite list of coefficients:

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

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

First coefficient: $y(0, p) =$
Second coefficient: $\dot{y}(0, p) =$
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System equations:

\[
\dot{q}_1 = -a_{01} q_1, \quad q_1(0) = b_1 n_0,
\]

\[
y = c_1 q_1
\]

First coefficient: $y(0, p) =$

Second coefficient: $\dot{y}(0, p) =$
Example: 1 Compartment

\[ y = c_1 q_1 \]

\[ \begin{array}{c}
\text{Input:} \quad \text{impulse in I.C.s:} \quad q_1(0) = b_1 n_0; \quad b_1 \text{ unknown,} \quad n_0 \text{ known.} \\
\text{Output:} \quad y = c_1 q_1, \quad \text{where} \quad c_1 \text{ unknown.}
\end{array} \]

System equations:

\[ \dot{q}_1 = -a_{01} q_1, \quad q_1(0) = b_1 n_0, \]

\[ y = c_1 q_1 \]

First coefficient: \[ y(0, p) = b_1 c_1 n_0 \]

Second coefficient: \[ \dot{y}(0, p) = \]
Example: 1 Compartment

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

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First coefficient: \( y(0, p) = b_1 c_1 n_0 \)

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

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

So \( b_1 c_1 \) & \( b_1 c_1 a_{01} \) unique
**Example: 1 Compartment**

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**System equations:**
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\dot{q}_1 = -a_{01} q_1, \quad q_1(0) = b_1 n_0, \\
y = c_1 q_1
\]

First coefficient: \( y(0, p) = b_1 c_1 n_0 \)

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

- So \( b_1 c_1 \) & \( b_1 c_1 a_{01} \) unique (ie \( b_1 c_1 \) & \( a_{01} \) globally identifiable)
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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
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**System equations:**

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First coefficient: \( y(0, p) = b_1 c_1 n_0 \)

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

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

\[
\dot{q}_1(t, p) = \\
\dot{q}_2(t, p) = \\
y(t, p) =
\]
Example: 2 Compartments

Input: bolus intravenous injection of drug (unknown amount)

Output: concentration of drug in the plasma

System equations:

\[
\begin{align*}
\dot{q}_1(t, p) &= -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) &= \\
y(t, p) &=
\end{align*}
\]
Example: 2 Compartments

Input: bolus intravenous injection of drug (unknown amount)

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\dot{q}_1(t, p) = -(a_01 + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) = a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \\
y(t, p) = c_1 q_1
\]
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y(t, p) &= c_1q_1(t, p)
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\[ y(t, p) = c_1 q_1(t, p) \]

First coefficient:

Second coefficient:

Third coefficient:

Fourth coefficient:
Motivation
Structural identifiability
Techniques for nonlinear models

Laplace transform approach
Taylor series approach
Similarity transformation/exhaustive modelling approach

\[
\dot{q}_1(t, p) = - (a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) = a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \\
y(t, p) = c_1 q_1(t, p)
\]

First coefficient: \( y_1(0, p) = c_1 b_1 \)

Second coefficient:

Third coefficient:

Fourth coefficient:
\begin{align*}
\dot{q}_1(t, p) &= -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
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\end{align*}

First coefficient: \( y_1(0, p) = c_1 b_1 \)

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

Third coefficient: 

Fourth coefficient:
\begin{align*}
\dot{q}_1(t, p) &= -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) &= a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \\
y(t, p) &= c_1 q_1(t, p)
\end{align*}

First coefficient: \( y_1(0, p) = c_1 b_1 \)

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

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

Fourth coefficient:
\[ \dot{q}_1(t, p) = -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \]
\[ \dot{q}_2(t, p) = a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \]
\[ y(t, p) = c_1 q_1(t, p) \]

First coefficient: \( y_1(0, p) = c_1 b_1 \)

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

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

Fourth coefficient:
\[ \begin{align*}
\dot{q}_1(t, p) &= -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) &= a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \\
y(t, p) &= c_1 q_1(t, p)
\end{align*} \]

First coefficient: \( y_1(0, p) = c_1 b_1 \)

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

Third coefficient:
\[ y^{(2)}_1(t, p) = c_1 (-(a_{01} + a_{21}) \dot{q}_1(t, p) + a_{12} \dot{q}_2(t, p)) \]
\[ \implies y^{(2)}_1(0, p) = c_1 \left( (a_{01} + a_{21})^2 b_1 + a_{12} a_{21} b_1 \right) \]

Fourth coefficient: \( y^{(3)}_1(t, p) = \)
\[ c_1 \left( (a_{01} + a_{21})^2 \dot{q}_1 - a_{12} (a_{01} + a_{21}) \dot{q}_2 + a_{12} a_{21} \dot{q}_1 - a_{12}^2 \dot{q}_2 \right) \]
\[
\begin{align*}
\dot{q}_1(t, p) &= -(a_{01} + a_{21}) q_1(t, p) + a_{12} q_2(t, p), \quad q_1(0, p) = b_1 \\
\dot{q}_2(t, p) &= a_{21} q_1(t, p) - a_{12} q_2(t, p), \quad q_2(0, p) = 0 \\
y(t, p) &= c_1 q_1(t, p)
\end{align*}
\]

First coefficient: \( y_1(0, p) = c_1 b_1 \)

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

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

Fourth coefficient: \( y_1^{(3)}(t, p) = \)
\[
c_1 \left( (a_{01} + a_{21})^2 \dot{q}_1 - a_{12} (a_{01} + a_{21}) \dot{q}_2 + a_{12} a_{21} \dot{q}_1 - a_{12}^2 \dot{q}_2 \right)
\]
\[
\implies y_1^{(3)}(0, p) = b_1 c_1 \left[ (a_{01} + a_{21}) \left[ - (a_{01} + a_{21})^2 - 2 a_{12} a_{21} \right] - a_{12}^2 a_{21} \right]
\]
$y_1(0, p) = c_1 b_1$

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

$y_1^{(2)}(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right)$

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

- First coefficient:
- Second coefficient:
- Third coefficient:
- Fourth coefficient:
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y_1(0, p) = c_1 b_1
\dot{y}_1(0, p) = -b_1 c_1 (a_{01} + a_{21})
y_1^{(2)}(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right)
y_1^{(3)}(0, 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:
- Third coefficient:
- Fourth coefficient:
$y_1(0, p) = c_1 b_1$

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

$y_1^{(2)}(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right)$

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

- First coefficient: $b_1 c_1$ unique
- Second coefficient: $a_{01} + a_{21}$ unique
- Third coefficient:
- Fourth coefficient:
\[ y_1(0, p) = c_1 b_1 \]
\[ \dot{y}_1(0, p) = -b_1 c_1 (a_{01} + a_{21}) \]
\[ y_1^{(2)}(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right) \]
\[ y_1^{(3)}(0, p) = b_1 c_1 \left( (a_{01} + a_{21}) \left( - (a_{01} + a_{21})^2 - 2 a_{12} a_{21} \right) - a_{12}^2 a_{21} \right) \]

- First coefficient: \( b_1 c_1 \) unique
- Second coefficient: \( a_{01} + a_{21} \) unique
- Third coefficient: \( a_{12} a_{21} \) unique
- Fourth coefficient:
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\[ y_1(0, p) = c_1 b_1 \]
\[ \dot{y}_1(0, p) = -b_1 c_1 (a_{01} + a_{21}) \]
\[ y^{(2)}_1(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right) \]
\[ y^{(3)}_1(0, p) = b_1 c_1 \left( (a_{01} + a_{21}) \left( - (a_{01} + a_{21})^2 - 2a_{12} a_{21} \right) - a_{12}^2 a_{21} \right) \]

- First coefficient: \[ b_1 c_1 \] unique
- Second coefficient: \[ a_{01} + a_{21} \] unique
- Third coefficient: \[ a_{12} a_{21} \] unique
- Fourth coefficient: \[ a_{12} \] unique
\[ y_1(0, p) = c_1 b_1 \]
\[ \dot{y}_1(0, p) = -b_1 c_1 (a_{01} + a_{21}) \]
\[ y^{(2)}_1(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right) \]
\[ y^{(3)}_1(0, p) = b_1 c_1 \left( (a_{01} + a_{21}) \left(- (a_{01} + a_{21})^2 - 2a_{12} a_{21} \right) - a_{12}^2 a_{21} \right) \]

- First coefficient: \( b_1 c_1 \) unique
- Second coefficient: \( a_{01} + a_{21} \) unique
- Third coefficient: \( a_{12} a_{21} \) unique
- Fourth coefficient: \( a_{12} \) unique
- So \( a_{21} \) and then \( a_{01} \) unique
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\[ y_1(0, p) = c_1 b_1 \]

\[ \dot{y}_1(0, p) = -b_1 c_1 (a_{01} + a_{21}) \]

\[ y^{(2)}_1(0, p) = b_1 c_1 \left( (a_{01} + a_{21})^2 + a_{12} a_{21} \right) \]

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

- First coefficient: \( b_1 c_1 \) unique
- Second coefficient: \( a_{01} + a_{21} \) unique
- Third coefficient: \( a_{12} a_{21} \) unique
- Fourth coefficient: \( a_{12} \) 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: \((A(p), B(p), C(p))\) with same I/O behaviour as given one: \((A(p), B(p), C(p))\)

Consider the model given by

\[
\begin{align*}
\dot{q}(t, p) &= A(p)q(t, p) + B(p)u(t), \quad q(0, p) = q_0(p), \\
y(t, p) &= C(p)q(t, p),
\end{align*}
\]

and suppose that following are satisfied:

**Controllability rank condition:**

\[
\text{rank} \left( B(p) \quad A(p)B(p) \quad \ldots \quad A(p)^{n-1}B(p) \right) = n
\]

**Observability rank condition:**

\[
\text{rank} \begin{pmatrix} C(p) \\ C(p)A(p) \\ \vdots \\ C(p)A(p)^{n-1} \end{pmatrix} = n
\]

If both are satisfied model is **minimal**.
Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:

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

$$
= z(0) = Tq_0(p),
$$

has identical input-output behaviour.

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

$$
\dot{q}(t, \overline{p}) = A(\overline{p})q(t, \overline{p}) + B(\overline{p})u(t), \quad q(0, \overline{p}) = q_0(\overline{p}),
$$

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

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

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

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

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

for some invertible $n \times n$ matrix $T$. 
Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:
\[
\dot{z}(t) = T\dot{q}(t, p) = TA(p)q(t, p) + TB(p)u(t)
\]
\[
= z(0) = Tq_0(p),
\]
\[
y(t, p) = C(p)q(t, p) = \]
has identical input-output behaviour.

Therefore, if $\bar{p} \in \Omega$ gives rise to a model:
\[
\dot{q}(t, \bar{p}) = A(\bar{p})q(t, \bar{p}) + B(\bar{p})u(t), \quad q(0, \bar{p}) = q_0(\bar{p}),
\]
\[
y(t, \bar{p}) = C(\bar{p})q(t, \bar{p}),
\]
with identical input-output behaviour as the initial one (1), then
\[
A(\bar{p}) =
\]
\[
B(\bar{p}) =
\]
\[
C(\bar{p}) =
\]
for some invertible $n \times n$ matrix $T$.  

MJ Chappell University of Warwick July 2016
Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:

$$
\dot{z}(t) = T\dot{q}(t, p) = TA(p)q(t, p) + TB(p)u(t) = TA(p)T^{-1}z(t) + TB(p)u(t), \quad z(0) = Tq_0(p),
$$

$$
y(t, p) = C(p)q(t, p) = \quad
$$

has identical input-output behaviour.

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

$$
\dot{q}(t, \vec{p}) = A(\vec{p})q(t, \vec{p}) + B(\vec{p})u(t), \quad q(0, \vec{p}) = q_0(\vec{p}),
$$

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

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

$$
A(\vec{p}) = \quad
$$

$$
B(\vec{p}) = \quad
$$

$$
C(\vec{p}) = \quad
$$

for some invertible $n \times n$ matrix $T$. 

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Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:

\[
\begin{align*}
\dot{z}(t) &= T\dot{q}(t, p) = TA(p)q(t, p) + TB(p)u(t) \\
&= TA(p)T^{-1}z(t) + TB(p)u(t), \quad z(0) = Tq_0(p), \\
y(t, p) &= C(p)q(t, p) = C(p)T^{-1}z(t).
\end{align*}
\]

has identical input-output behaviour.

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

\[
\begin{align*}
\dot{q}(t, \overline{p}) &= A(\overline{p})q(t, \overline{p}) + B(\overline{p})u(t), \quad q(0, \overline{p}) = q_0(\overline{p}), \\
y(t, \overline{p}) &= C(\overline{p})q(t, \overline{p}),
\end{align*}
\]

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

\[
\begin{align*}
A(\overline{p}) &= \\
B(\overline{p}) &= \\
C(\overline{p}) &=
\end{align*}
\]

for some invertible $n \times n$ matrix $T$. 
Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:

$$\begin{align*}
\dot{z}(t) &= T\dot{q}(t, p) = TA(p)q(t, p) + TB(p)u(t) \\
&= TA(p)T^{-1}z(t) + TB(p)u(t), \quad z(0) = Tq_0(p), \\
y(t, p) &= C(p)q(t, p) = C(p)T^{-1}z(t).
\end{align*}$$

has identical input-output behaviour.

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

$$\begin{align*}
\dot{q}(t, \bar{p}) &= A(\bar{p})q(t, \bar{p}) + B(\bar{p})u(t), \quad q(0, \bar{p}) = q_0(\bar{p}), \\
y(t, \bar{p}) &= C(\bar{p})q(t, \bar{p}),
\end{align*}$$

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

$$\begin{align*}
A(\bar{p}) &= TA(p)T^{-1}, \\
B(\bar{p}) &= \\
C(\bar{p}) &=
\end{align*}$$

for some invertible $n \times n$ matrix $T$.  

Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:

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

\[
= T A(p) T^{-1} z(t) + T B(p) u(t), \quad z(0) = T q_0(p),
\]

\[
y(t, p) = C(p) q(t, p) = C(p) T^{-1} z(t).
\]

has identical input-output behaviour.

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

\[
\dot{q}(t, \bar{p}) = A(\bar{p}) q(t, \bar{p}) + B(\bar{p}) u(t), \quad q(0, \bar{p}) = q_0(\bar{p}),
\]

\[
y(t, \bar{p}) = C(\bar{p}) q(t, \bar{p}),
\]

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

\[
A(\bar{p}) = T A(p) T^{-1},
\]

\[
B(\bar{p}) = T B(p),
\]

\[
C(\bar{p}) =
\]

for some invertible $n \times n$ matrix $T$. 
Then there exists invertible $n \times n$ matrix $T$ such that, if $z = Tq$:
\[
\dot{z}(t) = T \dot{q}(t, p) = T A(p) q(t, p) + T B(p) u(t) \\
= T A(p) T^{-1} z(t) + T B(p) u(t), \quad z(0) = T q_0(p),
\]
\[
y(t, p) = C(p) q(t, p) = C(p) T^{-1} z(t).
\]

has identical input-output behaviour.

Therefore, if $\bar{p} \in \Omega$ gives rise to a model:
\[
\dot{q}(t, \bar{p}) = A(\bar{p}) q(t, \bar{p}) + B(\bar{p}) u(t), \quad q(0, \bar{p}) = q_0(\bar{p}),
\]
\[
y(t, \bar{p}) = C(\bar{p}) q(t, \bar{p}),
\]

with identical input-output behaviour as the initial one (1), then
\[
A(\bar{p}) = T A(p) T^{-1},
\]
\[
B(\bar{p}) = T B(p),
\]
\[
C(\bar{p}) = C(p) T^{-1},
\]

for some invertible $n \times n$ matrix $T$. 

Sometimes easier to deal with:

\[ A(\bar{p}) T = TA(p), \]  
\[ B(\bar{p}) = TB(p), \]  
\[ C(\bar{p}) T = C(p). \]  

- If only solution is \( T = I_n \) then \( \bar{p} = p \) and the system is \textbf{SGI}
- If \( T \) can take any of a finite set (with more than 1 element) of possibilities, then the system is \textbf{SLI}
- Otherwise, (\( T \) can take any of a infinite set of possibilities) then the system is unidentifiable
Example: Two-compartment model.

\begin{align*}
\dot{q}(t, p) &= A(p)q(t, p) + B(p)u(t), \quad q(0, p) = 0 \\
y(t, p) &= C(p)q(t, p)
\end{align*}

where

\begin{align*}
A(p) &= \\
B(p) &= \\
C(p) &=
\end{align*}
Example: Two-compartment model.

System equations:

\[
\dot{q}(t, p) = A(p)q(t, p) + B(p)u(t), \quad q(0, p) = 0
\]
\[
y(t, p) = C(p)q(t, p)
\]

where

\[
A(p) = \begin{pmatrix}
-a_{01} - a_{21} & a_{12} \\
a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \\
C(p) =
\]
**Example:** Two-compartment model.

System equations:

\[
\dot{q}(t, p) = A(p)q(t, p) + B(p)u(t), \quad q(0, p) = 0 \\
y(t, p) = C(p)q(t, p)
\]

where

\[
A(p) = \begin{pmatrix}
-(a_{01} + a_{21}) & a_{12} \\
a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix}
b_1 \\
0
\end{pmatrix}, \quad C(p) = \ldots
\]
**Example:** Two-compartment model.

![Diagram of a two-compartment model](image)

System equations:

\[
\begin{align*}
\dot{q}(t, p) &= A(p)q(t, p) + B(p)u(t), \quad q(0, p) = 0 \\
y(t, p) &= C(p)q(t, p)
\end{align*}
\]

where

\[
A(p) = \begin{pmatrix}
-(a_{01} + a_{21}) & a_{12} \\
a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix}
b_1 \\
0
\end{pmatrix}, \quad C(p) = \begin{pmatrix}
c_1 & 0
\end{pmatrix}
\]
\[
A(p) = \begin{pmatrix}
-a_01 - a_{21} & a_{12} \\
a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix}
\]

Controllability:

\[
\begin{bmatrix}
B(p) & A(p)B(p)
\end{bmatrix} = \begin{bmatrix}
\end{bmatrix}
\]

Observability:

\[
\begin{bmatrix}
C(p) \\
C(p)A(p)
\end{bmatrix} = \begin{bmatrix}
\end{bmatrix}
\]

Equation (3):

\[
B(\bar{p}) = TB(p)
\]

and so
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\[ A(p) = \begin{pmatrix} - (a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix} \]

Controllability:
\[
\begin{bmatrix} B(p) & A(p) & B(p) \end{bmatrix} = \begin{bmatrix} b_1 \\ 0 \end{bmatrix}
\]

Observability:
\[
\begin{bmatrix} C(p) \\ C(p)A(p) \end{bmatrix} = \begin{bmatrix} \text{?} \\ \text{?} \end{bmatrix}
\]

Equation (3):
\[ B(\bar{p}) = TB(p) \]

and so
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\[
A(p) = \begin{pmatrix}
- (a_{01} + a_{21}) & a_{12} \\
 a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix}
\]

Controllability:
\[
\begin{bmatrix}
B(p) & A(p)B(p)
\end{bmatrix} = \begin{bmatrix}
b_1 & -b_1 (a_{01} + a_{21}) \\
0 & b_1 a_{21}
\end{bmatrix}
\]

Observability:
\[
\begin{bmatrix}
C(p) \\
C(p)A(p)
\end{bmatrix} = \begin{bmatrix}
\end{bmatrix}
\]

Equation (3):
\[
B(\bar{p}) = TB(p)
\]

and so
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\[ A(p) = \begin{pmatrix} - (a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix} \]

Controllability:
\[ \begin{bmatrix} B(p) & A(p) & B(p) \end{bmatrix} = \begin{bmatrix} b_1 & - b_1 (a_{01} + a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \quad \text{rank 2} \]

Observability:
\[ \begin{bmatrix} C(p) \\ C(p) A(p) \end{bmatrix} = \begin{bmatrix} \end{bmatrix} \]

Equation (3):
\[ B(\bar{p}) = T B(p) \]

and so
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\[
A(p) = \begin{pmatrix}
-(a_{01} + a_{21}) & a_{12} \\
 a_{21} & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix}
\]

Controllability:

\[
\begin{bmatrix}
B(p) & A(p)B(p)
\end{bmatrix} = \begin{bmatrix} b_1 & -b_1(a_{01} + a_{21}) \\
0 & b_1a_{21}
\end{bmatrix}
\]

rank 2

Observability:

\[
\begin{bmatrix}
C(p) \\
C(p)A(p)
\end{bmatrix} = \begin{bmatrix} c_1 & 0 \end{bmatrix}
\]

Equation (3):

\[
B(\overline{p}) = TB(p)
\]

and so
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\[ A(p) = \begin{pmatrix} -(a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix} \]

Controllability:
\[
\begin{bmatrix} B(p) \ A(p) \ B(p) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1 (a_{01} + a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix} \quad \text{rank 2}
\]

Observability:
\[
\begin{bmatrix} C(p) \\ C(p) \ A(p) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1 (a_{01} + a_{21}) & c_1 a_{12} \end{bmatrix}
\]

Equation (3):
\[ B(\overline{p}) = TB(p) \]

and so
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\[ A(p) = \begin{pmatrix} - (a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix} \]

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

Observability:
\[
\begin{bmatrix} C(p) & C(p) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1 \left( a_{01} + a_{21} \right) & c_1 a_{12} \end{bmatrix} \quad \text{rank 2}
\]

Equation (3):
\[ B(\bar{p}) = T B(p) \]

and so
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Taylor series approach
Similarity transformation/exhaustive modelling approach

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

Controllability:
\[
\begin{bmatrix} \mathbf{B}(p) \mathbf{A}(p) \mathbf{B}(p) \end{bmatrix} = \begin{bmatrix} b_1 & -b_1 (a_{01} + a_{21}) \\ 0 & b_1 a_{21} \end{bmatrix}
\]
rank 2

Observability:
\[
\begin{bmatrix} \mathbf{C}(p) \\ \mathbf{C}(p) \mathbf{A}(p) \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ -c_1 (a_{01} + a_{21}) & c_1 a_{12} \end{bmatrix}
\]
rank 2

So model is minimal

Equation (3):
\[ \mathbf{B}(\mathbf{p}) = T \mathbf{B}(p) \]

and so
\[
A(p) = \begin{pmatrix}
-a_01 + a_{21} & a_{12} \\
21 & -a_{12}
\end{pmatrix}, \quad B(p) = \begin{pmatrix} b_1 \\ 0 \end{pmatrix}, \quad C(p) = \begin{pmatrix} c_1 & 0 \end{pmatrix}
\]

Controllability:
\[
\begin{bmatrix}
B(p) & A(p)B(p)
\end{bmatrix} = \begin{bmatrix}
b_1 & -b_1(a_{01} + a_{21}) \\
0 & b_1a_{21}
\end{bmatrix}
\]
rank 2

Observability:
\[
\begin{bmatrix}
C(p) \\
C(p)A(p)
\end{bmatrix} = \begin{bmatrix}
c_1 & 0 \\
-c_1(a_{01} + a_{21}) & c_1a_{12}
\end{bmatrix}
\]
rank 2

So model is minimal

Equation (3):
\[
B(\bar{p}) = \begin{pmatrix} \bar{b}_1 \\ 0 \end{pmatrix} = TB(p) = \begin{pmatrix} t_{11} & t_{12} \\
t_{21} & t_{22}\end{pmatrix}\begin{pmatrix} b_1 \\ 0 \end{pmatrix}
\]
and so
Motivation

Structural identifiability

Techniques for nonlinear models

Laplace transform approach

Taylor series approach

Similarity transformation/exhaustive modelling approach

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

Controllability:

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

Observability:

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

So model is minimal

Equation (3):

\[ B(\bar{p}) = \begin{pmatrix} \bar{b}_1 \\ 0 \end{pmatrix} = TB(p) = \begin{pmatrix} t_{11} & t_{12} \\ t_{21} & t_{22} \end{pmatrix} \begin{pmatrix} b_1 \\ 0 \end{pmatrix} = \begin{pmatrix} t_{11} b_1 \\ t_{21} b_1 \end{pmatrix} \]

and so
Motivation

Structural identifiability

Techniques for nonlinear models

- Laplace transform approach
- Taylor series approach
- Similarity transformation/exhaustive modelling approach

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

**Controllability:**

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

**Observability:**

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

So model is **minimal**

**Equation (3):**

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

and so $t_{21} = 0$ and
Motivation
Structural identifiability
Techniques for nonlinear models

Laplace transform approach
Taylor series approach
Similarity transformation/exhaustive modelling approach

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

Controllability:
\[
\begin{bmatrix}
B(p) \quad A(p) \quad B(p)
\end{bmatrix}
= \begin{bmatrix}
b_1 & -b_1 (a_{01} + a_{21}) \\
0 & b_1 a_{21}
\end{bmatrix}
\text{ rank 2}
\]

Observability:
\[
\begin{bmatrix}
C(p) \\
C(p) \quad A(p)
\end{bmatrix}
= \begin{bmatrix}
c_1 & 0 \\
-c_1 (a_{01} + a_{21}) & c_1 a_{12}
\end{bmatrix}
\text{ rank 2}
\]

So model is minimal

Equation (3):
\[
B(\bar{p}) = \begin{pmatrix} \bar{b}_1 \\ 0 \end{pmatrix} = TB(p) = \begin{pmatrix} t_{11} & t_{12} \\
t_{21} & t_{22} \end{pmatrix} \begin{pmatrix} b_1 \\ 0 \end{pmatrix} = \begin{pmatrix} t_{11} b_1 \\ t_{21} b_1 \end{pmatrix}
\]

and so $t_{21} = 0$ and $t_{11} = \bar{b}_1 / b_1$
\[
A(p) = \begin{bmatrix}
-(a_{01} + a_{21}) & a_{12} \\
a_{21} & -a_{12}
\end{bmatrix},
\quad C(p) = [c_1 \ 0],
\quad T = \begin{bmatrix}
\bar{b}_1/b_1 & t_{12} \\
0 & t_{22}
\end{bmatrix}
\]

Equation (4):
\[
C(p) T = \begin{pmatrix}
\bar{c}_1 & 0
\end{pmatrix}
\begin{pmatrix}
\bar{b}_1/b_1 & t_{12} \\
0 & t_{22}
\end{pmatrix} = \begin{pmatrix}
c_1 & 0
\end{pmatrix} = C(p)
\]

and so

Equation (2):
\[
A(p) T =
\]

\[
= T A(p) =
\]

\[
= T A(p) =
\]
\[ A(\mathbf{p}) = \begin{bmatrix} - (a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \quad C(\mathbf{p}) = \begin{bmatrix} c_1 & 0 \end{bmatrix}, \quad T = \begin{bmatrix} \bar{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix} \]

Equation (4):

\[ C(\overline{\mathbf{p}})T = \left( \bar{b}_1 \bar{c}_1/b_1, \ \bar{c}_1 t_{12} \right) = \begin{bmatrix} c_1 & 0 \end{bmatrix} = C(\mathbf{p}) \]

and so

Equation (2):

\[ A(\overline{\mathbf{p}})T = \]

\[ = TA(\mathbf{p}) = \]
\[ A(p) = \begin{bmatrix} -(a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \quad C(p) = [c_1, 0], \quad T = \begin{bmatrix} b_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix} \]

Equation (4):
\[ C(p)T = \left( \frac{b_1 c_1}{b_1}, c_1 t_{12} \right) = \begin{bmatrix} c_1 \\ 0 \end{bmatrix} = C(p) \]
and so \( t_{12} = 0 \) and

Equation (2):
\[ A(p)T = \]
\[ = TA(p) = \]
Motivation

Structural identifiability

Techniques for nonlinear models

Laplace transform approach

Taylor series approach

Similarity transformation/exhaustive modelling approach

\[
A(p) = \begin{bmatrix}
-a_0 - a_2 & a_1 \\
-a_1 & -a_2
\end{bmatrix}, \quad C(p) = [c_1 \ 0], \quad T = \begin{bmatrix}
\overline{b}_1/\overline{b}_1 & t_{12} \\
0 & t_{22}
\end{bmatrix}
\]

Equation (4):

\[
C(p)T = \left( \overline{b}_1 \overline{c}_1/\overline{b}_1 \quad \overline{c}_1 t_{12} \right) = \begin{bmatrix}
c_1 \\
0
\end{bmatrix} = C(p)
\]

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

Equation (2):

\[
A(p)T =
\]

\[
= TA(p) =
\]

---

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University of Warwick  
July 2016  
Structural identifiability
Motivation

Structural identifiability

Techniques for nonlinear models

Laplace transform approach

Taylor series approach

Similarity transformation/exhaustive modelling approach

\[
A(p) = \begin{bmatrix}
-(a_{01} + a_{21}) & a_{12} \\
a_{21} & -a_{12}
\end{bmatrix}, \quad C(p) = [c_1 \ 0], \quad T = \begin{bmatrix}
b_1/b_1 & t_{12} \\
0 & t_{22}
\end{bmatrix}
\]

Equation (4):

\[
C(p)T = \left(\bar{b}_1\bar{c}_1/b_1 \quad \bar{c}_1 t_{12}\right) = \left(c_1 \ 0\right) = C(p)
\]

and so \(t_{12} = 0\) and \(\bar{b}_1\bar{c}_1 = b_1 c_1\)

Equation (2):

\[
A(p)T = \begin{bmatrix}
-(\bar{a}_{01} + \bar{a}_{21}) & \bar{a}_{12} \\
\bar{a}_{21} & -\bar{a}_{12}
\end{bmatrix} \begin{bmatrix}
b_1/b_1 & 0 \\
0 & t_{22}
\end{bmatrix}
= TA(p) =
\]
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Structural identifiability
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\[
A(p) = \begin{bmatrix}
-(a_{01} + a_{21}) & a_{12} \\
 a_{21} & -a_{12}
\end{bmatrix}, \quad C(p) = [c_1 \ 0], \quad T = \begin{bmatrix}
b_1/b_1 & t_{12} \\
0 & t_{22}
\end{bmatrix}
\]

Equation (4):

\[
C(p)T = \begin{pmatrix}
\bar{b}_1 \bar{c}_1/b_1 & \bar{c}_1 t_{12}
\end{pmatrix} = \begin{pmatrix}
c_1 & 0
\end{pmatrix} = C(p)
\]

and so \( t_{12} = 0 \) and \( \bar{b}_1 \bar{c}_1 = b_1 c_1 \)

Equation (2):

\[
A(p)T = \begin{pmatrix}
-(\bar{a}_{01} + \bar{a}_{21}) & \bar{a}_{12} \\
 \bar{a}_{21} & -\bar{a}_{12}
\end{pmatrix} \begin{pmatrix}
b_1/b_1 & 0 \\
0 & t_{22}
\end{pmatrix}
\]

\[
= TA(p) = \begin{pmatrix}
\bar{b}_1/b_1 & 0 \\
0 & t_{22}
\end{pmatrix} \begin{pmatrix}
-(a_{01} + a_{21}) & a_{12} \\
 a_{21} & -a_{12}
\end{pmatrix}
\]
\[ A(p) = \begin{bmatrix} -(a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \quad C(p) = \begin{bmatrix} c_1 & 0 \end{bmatrix}, \quad T = \begin{bmatrix} \frac{b_1}{b_1} & t_{12} \\ 0 & t_{22} \end{bmatrix} \]

Equation (4):
\[
C(p)T = \left( \frac{b_1 c_1}{b_1} \quad c_1 t_{12} \right) = \begin{bmatrix} c_1 & 0 \end{bmatrix} = C(p)
\]

and so \( t_{12} = 0 \) and \( \frac{b_1 c_1}{b_1} = b_1 c_1 \)

Equation (2):
\[
A(p)T = \left( -(a_{01} + a_{21}) \quad a_{12} \right) \left( \frac{b_1}{b_1} \quad 0 \right) \left( \frac{b_1}{b_1} \quad 0 \right) \\
= TA(p) = \left( \frac{b_1}{b_1} \quad 0 \right) \left( 0 \quad t_{22} \right) \left( -(a_{01} + a_{21}) \quad a_{12} \right) \\
= \left[ \begin{array}{cc}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & t_{22} a_{12} \\
\frac{b_1}{b_1} a_{21} & -a_{12} t_{22}
\end{array} \right] = \ldots
\]
\[A(p) = \begin{bmatrix} -(a_{01} + a_{21}) & a_{12} \\ a_{21} & -a_{12} \end{bmatrix}, \quad C(p) = [c_1 \ 0], \quad T = \begin{bmatrix} \bar{b}_1/b_1 & t_{12} \\ 0 & t_{22} \end{bmatrix}\]

Equation (4):
\[C(p)T = \begin{bmatrix} \bar{b}_1 \bar{c}_1/b_1 & \bar{c}_1 t_{12} \end{bmatrix} = \begin{bmatrix} c_1 & 0 \end{bmatrix} = C(p)\]

and so \(t_{12} = 0\) and \(\bar{b}_1 \bar{c}_1 = b_1 c_1\)

Equation (2):
\[A(p)T = \begin{bmatrix} -(\bar{a}_{01} + \bar{a}_{21}) & \bar{a}_{12} \\ \bar{a}_{21} & -\bar{a}_{12} \end{bmatrix} \begin{bmatrix} \bar{b}_1/b_1 & 0 \\ 0 & t_{22} \end{bmatrix} = \begin{bmatrix} -\frac{\bar{b}_1}{b_1} (a_{01} + a_{21}) & \bar{a}_{12} \\ \frac{\bar{b}_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_{22} \end{bmatrix} = \begin{bmatrix} -\frac{\bar{b}_1}{b_1} (a_{01} + a_{21}) & \bar{b}_1/a_{12} \\ a_{21} t_{22} & -a_{12} t_{22} \end{bmatrix}\]
\[
\begin{pmatrix}
-\frac{b_1}{b_1} (\bar{a}_{01} + \bar{a}_{21}) & t_{22} \bar{a}_{12} \\
\frac{b_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_{22}
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & \frac{b_1}{b_1} a_{12} \\
 a_{21} t_{22} & -a_{12} t_{22}
\end{pmatrix}
\]

(2,2) component:

so (1,2) component:

(2,1) component:

(1,1) component:

So:
\[
\begin{pmatrix}
-\frac{b_1}{b_1} (\bar{a}_{01} + \bar{a}_{21}) & t_{22} \bar{a}_{12} \\
\frac{b_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_{22}
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & \frac{b_1}{b_1} a_{12} \\
\frac{b_1}{b_1} a_{21} t_{22} & -a_{12} t_{22}
\end{pmatrix}
\]

(2,2) component:

\[
\bar{a}_{12} = a_{12}
\]

so (1,2) component:

(2,1) component:

(1,1) component:

So:
\[
\begin{pmatrix}
-\frac{b_1}{b_1} (\bar{a}_{01} + \bar{a}_{21}) & t_{22} \bar{a}_{12} \\
\frac{b_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_{22}
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & \frac{b_1}{b_1} a_{12} \\
a_{21} t_{22} & -a_{12} t_{22}
\end{pmatrix}
\]

(2,2) component:

\[\bar{a}_{12} = a_{12}\]

so (1,2) component:

\[t_{22} = \frac{b_1}{b_1}\]

(2,1) component:

(1,1) component:

So:
Motivation

Structural identifiability

Techniques for nonlinear models

Laplace transform approach

Taylor series approach

Similarity transformation/exhaustive modelling approach

\[
\begin{pmatrix}
-\frac{b_1}{b_1} (\bar{a}_{01} + \bar{a}_{21}) & t_22 \bar{a}_{12} \\
\frac{b_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_22
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & \frac{b_1}{b_1} a_{12} \\
\frac{b_1}{b_1} & \frac{b_1}{b_1}
\end{pmatrix}
\]

(2,2) component:

\[
\bar{a}_{12} = a_{12}
\]

so (1,2) component:

\[
t_{22} = \frac{b_1}{b_1}
\]

(2,1) component:

\[
\bar{a}_{21} = a_{21}
\]

(1,1) component:

So:
\[
\begin{pmatrix}
-\frac{b_1}{b_1} \left( \bar{a}_{01} + \bar{a}_{21} \right) & t_{22} \bar{a}_{12} \\
\frac{b_1}{b_1} \bar{a}_{21} & -\bar{a}_{12} t_{22}
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} \left( a_{01} + a_{21} \right) & \frac{b_1}{b_1} a_{12} \\
\bar{a}_{21} t_{22} & -a_{12} t_{22}
\end{pmatrix}
\]

(2,2) component:
\[
\bar{a}_{12} = a_{12}
\]
so (1,2) component:
\[
t_{22} = \frac{b_1}{b_1}
\]
(2,1) component:
\[
\bar{a}_{21} = a_{21}
\]
(1,1) component:
\[
\bar{a}_{01} = a_{01}
\]
So:
Motivation

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Techniques for nonlinear models

Laplace transform approach

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Similarity transformation/exhaustive modelling approach

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

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

(2,2) component:
\[
\bar{a}_{12} = a_{12}
\]

so (1,2) component:
\[
t_{22} = \frac{b_1}{b_1}
\]

(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
- combination \(b_1 c_1\) globally identifiable
\[
\begin{pmatrix}
-\frac{b_1}{b_1} (\overline{a}_{01} + \overline{a}_{21}) & t_{22}\overline{a}_{12} \\
\frac{b_1}{b_1} \overline{a}_{21} & -\overline{a}_{12} t_{22}
\end{pmatrix}
= \begin{pmatrix}
-\frac{b_1}{b_1} (a_{01} + a_{21}) & \frac{b_1}{b_1} a_{12} \\
\overline{a}_{21} t_{22} & -a_{12} t_{22}
\end{pmatrix}
\]

(2,2) component:
\[
\overline{a}_{12} = a_{12}
\]
so (1,2) component:
\[
t_{22} = \frac{b_1}{b_1}
\]
(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 \( b_1 c_1 \) 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:

\[
\begin{align*}
\dot{x}(t, p) &= f(x(t, p), p, u(t)), \quad x(0, p) = x_0(p), \\
y(t, p) &= h(x(t, p), p),
\end{align*}
\]

where
- \(p \in \Omega\) is an \(r\) dimensional (parameter) vector
- \(x(t, p)\) is an \(n\) dimensional (state) vector
- \(u(t)\) is an \(m\) dimensional (input) vector
- \(y(t, p)\) is an \(l\) dimensional (output) vector
Taylor series approach
This approach for linear models also works for nonlinear ones:

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

where \( y_i^{(k)}(0, p) = \frac{d^k y_i}{dt^k} \bigg|_{t=0} \) \( (k = 1, 2, \ldots) \).

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

Notice that we have a possibly infinite list of coefficients:

\[ y_i(0, p), \dot{y}_i(0, p), \ddot{y}_i(0, p), \ldots \quad i = 1, \ldots, l \]

& 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:

\[ \dot{x}_1 = - \frac{V_m x_1}{K_m + x_1}, \quad x_1(0) = b_1 \]

\[ y = c_1 x_1 \]

First coefficient: \( y(0, p) = b_1 c_1 \)

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

Third coefficient: \( y^{(2)}(t, p) = \frac{d}{dt} \left( - \frac{c_1 V_m x_1}{K_m + x_1} \right) \)
Example: 1 compartment

Model equations:

\[
\frac{dx_1}{dt} = -\frac{V_m x_1}{K_m + x_1}, \quad x_1(0) = b_1
\]

\[
y = c_1 x_1
\]

First coefficient: \(y(0, p) = b_1 c_1\)

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

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

Use symbolic tools such as MATHEMATICA, MAPLE
**Example:** One compartment with Langmuir elimination:

\[
y = c_1 q_1 \alpha (\beta - q_1)
\]

Model equations:

First coefficient: \( y(0, p) = \)

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

Third coefficient: \( y^{(2)}(t, p) = \)
Example: One compartment with Langmuir elimination:

Model equations:

\[
\dot{q}_1 = -\alpha q_1 (\beta - q_1), \quad q_1(0) = 1
\]

\[
y = c_1 q_1
\]

First coefficient: \( y(0, p) = \)

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

Third coefficient: \( y^{(2)}(t, p) = \)
Example: One compartment with Langmuir elimination:

Model equations:
\[ \dot{q}_1 = -\alpha q_1 (\beta - q_1), \quad q_1(0) = 1 \]
\[ y = c_1 q_1 \]

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Example: One compartment with Langmuir elimination:

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\begin{align*}
y &= c_1 q_1, \\
\dot{q}_1 &= -\alpha q_1 (\beta - q_1), \quad q_1(0) = 1 \\
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\end{align*}
\]

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\[ \implies y^{(2)}(0, p) = c_1 \alpha^2 (\beta - 1)(\beta - 2) \]
Motivation

Structural identifiability

Techniques for nonlinear models

Taylor series approach

Observable normal form

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

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- First coefficient: \( c_1 \) unique (globally identifiable)
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\[ y(0, p) = c_1 \]
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- First coefficient: \( c_1 \) unique (globally identifiable)
- Second coefficient: \( \alpha(\beta - 1) \) unique
- Third coefficient: \( \alpha(\beta - 1) - \alpha \) unique
\[ y(0, p) = c_1 \]
\[ \dot{y}(0, p) = -c_1 \alpha (\beta - 1) \]
\[ y^{(2)}(0, p) = c_1 \alpha^2 (\beta - 1) (\beta - 2) \]

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- And so \( \beta \) globally identifiable
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- Third coefficient: \( \alpha \) unique (globally identifiable)
- And so \( \beta \) 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 \( \mathbf{p} \):

- Check an observability criterion
  - Define \( \mu_1(\mathbf{x}, \mathbf{p}) = h(\mathbf{x}, \mathbf{p}) \) and
    \[
    \mu_{i+1}(\mathbf{x}, \mathbf{p}) = \frac{\partial \mu_i}{\partial \mathbf{x}}(\mathbf{x}, \mathbf{p})f(\mathbf{x}, \mathbf{p}) \quad i = 1, \ldots, n - 1
    \]
  - Define \( H_p(\mathbf{x}) = (\mu_1(\mathbf{x}, \mathbf{p}), \ldots, \mu_n(\mathbf{x}, \mathbf{p}))^T \)
  - Rank of \( \frac{\partial H_p}{\partial \mathbf{x}}(\mathbf{x}_0(\mathbf{p})) \) is \( n \)
- So \( H_p(\cdot) \) diffeomorphism on neighbourhood of \( \mathbf{x}_0(\mathbf{p}) \)
  - Hence is a coordinate transformation \ldots
Coordinate transformation between models that are indistinguishable via available output

\[ H_p (\lambda(x)) = H_{\bar{p}}(x) \]

Determine \( S(p) \) set of all parameters \( \bar{p} \)

s.t.

\[ \lambda(x_0(\bar{p})) = x_0(p) \]

\[ f(\lambda(x(t)), p) = \frac{\partial \lambda}{\partial x}(x(t))f(x(t), \bar{p}) \]

\[ h(\lambda(x(t)), p) = h(x(t), \bar{p}) \]

\[ (x(t) = x(t, \bar{p})) \]
Observability normal form

System $\hat{\Sigma}$ is the observability normal form, $\mathbf{z} = \mathbf{H}_p(\mathbf{x})$:

\[
\begin{align*}
\dot{z}_1 &= z_2 \\
\vdots \\
\dot{z}_{n-1} &= z_n \\
\dot{z}_n &= \mu_{n+1}(\mathbf{H}_p^{-1}(\mathbf{z}), \mathbf{p}) \\
y &= z_1
\end{align*}
\]

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

\[
\mu_{n+1}(\mathbf{H}_p^{-1}(\mathbf{z}(t)), \mathbf{p}) = \mu_{n+1}(\mathbf{H}_p^{-1}(\mathbf{z}(t)), \overline{\mathbf{p}}) \quad \forall t \geq 0
\]
Now rewrite output equation in form:

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

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

Then if \( \overline{p} \in S(p) \)

\[
\sum_{i=1}^{m} \left( \sigma_i(p) - \sigma_i(\overline{p}) \right) \phi_i(z(t), \dot{z}_n(t)) = 0
\]

and so

\[ \sigma_i(p) = \sigma_i(\overline{p}) \quad i = 1, \ldots, m \]
Consider two-compartment model:

\[ l(t) = D\delta(t) \]

\[ y = x_1 \]

\[ \mu_1(x, p) = x_1 \]

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

\[ p = \{ p_1, p_2, p_3, p_4 \} \]
Example: Observability normal form

Observability condition met provided $p_2 \neq 0$ (i.e., for all $p$) so can transform into:

\[
\begin{align*}
\dot{z}_1(t, p) &= z_2(t, p) \\
\dot{z}_2(t, p) &= -(p_1 + p_2)z_2(t, p) - \frac{p_2 p_3 z_1(t, p)}{p_4 + z_1(t, p)} - \frac{p_3 p_4 z_2(t, p)}{(p_4 + z_1(t, p))^2}
\end{align*}
\]

where

\[
\begin{align*}
z_1(0, p) &= D \quad \text{and} \quad z_2(0, p) = -p_2 D - \frac{p_3 D}{p_4 + D}
\end{align*}
\]
Example: Output equation

Output equation:

\[ z_1^2 \dot{z}_2 + p_4^2 \dot{z}_2 + 2p_4 z_1 \dot{z}_2 + p_2 p_3 p_4 z_1 + p_2 p_3 z_1^2 \]
\[ + \left( p_3 p_4 + p_4^2 (p_1 + p_2) \right) z_2 + 2p_4 (p_1 + p_2) z_1 z_2 \]
\[ + (p_1 + p_2) z_1^2 z_2 = \phi_0(z, \dot{z}_n) + \sum_{i=1}^{7} \sigma_i(p) \phi_i(z, \dot{z}_n) = 0 \]

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

\[
\begin{align*}
p[1]*x[1]-p[2]*x[2]]);
H & := x[1];
io & := \text{iorel}(F,H)
\end{align*}
\]

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

\[ \sigma_i(p) = \sigma_i(\bar{p}) \quad i = 1, \ldots, 7 \]

for any \( \bar{p} \in S(p) \).

\[ \begin{align*}
\sigma_2(p) &= p_4 & \quad \Rightarrow & \quad \bar{p}_4 = p_4 \\
\sigma_4(p) &= p_2p_3 & \quad \Rightarrow & \quad \bar{p}_2\bar{p}_3 = p_2p_3 \\
\sigma_7(p) &= p_1 + p_2 & \quad \Rightarrow & \quad \bar{p}_1 + \bar{p}_2 = p_1 + p_2 \\
\sigma_5(p) &= p_3p_4 + p_4^2(p_1 + p_2) & \quad \Rightarrow & \quad \bar{p}_3 = p_3
\end{align*} \]

Solving these shows that \( \bar{p} = p \), ie \( S(p) = \{p\} \)

Therefore model is \textit{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