Brief paper

Structural indistinguishability between uncontrolled (autonomous) nonlinear analytic systems\textsuperscript{☆}

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Abstract

In this paper, an approach for analysing the structural indistinguishability between two uncontrolled (or autonomous) analytic systems is presented. The approach involves constructing, if possible, a smooth mapping between the trajectories of two candidate models. If either of the models satisfies an observability criterion, then such a transformation always exists when the models are indistinguishable from their outputs. The approach is illustrated by examples from epidemiology and chemical reaction kinetics. One important outcome is that the susceptible, infectious, recovered (SIR) and SIR with temporary immunity (SIRS) models are shown to be indistinguishable when a proportion of the number of infectives is measured.

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1. Introduction

An important question that needs to be addressed in parametric state space modelling is the structural identifiability problem of whether the unknown parameters of a postulated model are uniquely determined by the input–output structure (Bellman & Åström, 1970; Walter, 1982). Structural indistinguishability generalises this problem to one of determining the uniqueness of the parameterisation, or model structure, from the input–output behaviour (see, for example, Godfrey, Chapman, & Vajda, 1994; Chapman & Godfrey, 1996). In this paper, the approach developed in Evans, Chapman, Chappell and Godfrey (2002) for testing the structural identifiability of uncontrolled systems is generalised to one for testing the indistinguishability between two different competing model structures for a given process with a given output measure. This is of practical importance in situations where there is some uncertainty in the structure of the underlying process. Although, in general, the approach may not provide conclusive results, three practical examples are given in this paper where successful outcomes are achieved.

In this paper, pairs of uncontrolled (also referred to as free or autonomous) nonlinear systems of the following forms are considered:

\begin{align}
\Sigma(p) & \quad \begin{cases} 
\dot{x}(t,p) = f(x(t,p),p), & x(0,p) = x_0(p), \\
y(t,p) = h(x(t,p),p),
\end{cases} \\
\hat{\Sigma}(\tilde{p}) & \quad \begin{cases} 
\dot{\tilde{x}}(t,\tilde{p}) = \tilde{f}(\tilde{x}(t,\tilde{p}),\tilde{p}), & \tilde{x}(0,\tilde{p}) = \tilde{x}_0(\tilde{p}), \\
\dot{\tilde{y}}(t,\tilde{p}) = \tilde{h}(\tilde{x}(t,\tilde{p}),\tilde{p}),
\end{cases}
\end{align}

where \( p \in \Omega \), an open subset of \( \mathbb{R}^q \), and \( \tilde{p} \in \tilde{\Omega} \), an open subset of \( \mathbb{R}^p \), are constant parameter vectors. The sets \( \Omega \) and \( \tilde{\Omega} \) denote the sets of admissible parameter vectors for the two models (1) and (2), respectively. It is assumed that, given a \( p \in \Omega \), there exists a connected open subset of \( \mathbb{R}^q \), denoted by \( M(p) \), such that \( f(\cdot,p) \) and \( h(\cdot,p) \) are analytic functions on \( M(p) \) and \( x(t,p) \in M(p) \) for all \( t \geq 0 \). For a given \( x \) it is assumed that \( f(x,\cdot) \) and \( h(x,\cdot) \) are analytic functions on \( \Omega \). Analogous conditions are assumed for \( \hat{\Sigma}(\tilde{p}) \).

The outputs \( y(t,p) \) and \( \dot{\tilde{y}}(t,\tilde{p}) \) both take values in \( \mathbb{R}^r \), and

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it is assumed that the initial conditions $x_0(\cdot)$ and $\dot{x}_0(\cdot)$ are analytic functions in $p$ and $\dot{p}$, respectively.

**Definition 1.** The systems $\Sigma(p)$ and $\tilde{\Sigma}(\dot{p})$, where $p \in \Omega$ and $\dot{p} \in \tilde{\Omega}$, are said to be **output indistinguishable**, written $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$, if there exists a $\tau > 0$ such that $y(t,p) = \tilde{y}(t,\dot{p})$ for all $t \in [0, \tau)$.

Since the outputs $y(\cdot, p)$ and $\tilde{y}(\cdot, \dot{p})$ are analytic for all $p \in \Omega$ and $\dot{p} \in \tilde{\Omega}$, if there exists a $\tau > 0$ such that $y(t,p) = \tilde{y}(t,\dot{p})$ for all $t \in [0, \tau)$, then this is true for all $\tau > 0$.

**Definition 2.** The models $\Sigma$ and $\tilde{\Sigma}$ are said to be **structurally indistinguishable**, written $\Sigma \sim \tilde{\Sigma}$, if for generic $p \in \Omega$, i.e., for all $p \in \Omega$ except possibly for some vectors lying in a subset of a closed set of (Lebesgue) measure zero, there exists a $\dot{p} \in \tilde{\Omega}$ such that $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$; and for generic $\dot{p} \in \tilde{\Omega}$ there exists a $p \in \Omega$ such that $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$.

### 2. Constructing a smooth mapping

The Lie derivative of a smooth $h$ along a vector field $f$ is the smooth function given by

$$L_f h(x) = \frac{\partial h}{\partial x}(x)f(x).$$

Let $f^\mu$ and $\tilde{f}^\mu$ denote the vector fields $f(\cdot, p)$ and $\tilde{f}(\cdot, \dot{p})$, respectively. Similarly, for $1 \leq l \leq r$, let $h^\mu_l$ and $\tilde{h}^\mu_l$ denote the coordinate functions $h_l(\cdot, p)$ and $\tilde{h}_l(\cdot, \dot{p})$, respectively. A model of the form (1) satisfies the **observability rank condition** (ORC) at $x_0(p)$ if there exist smooth functions $\mu_1, \ldots, \mu_n$ such that: For each $\tilde{p} \in \tilde{\Omega}$, $\mu_l(\cdot, \tilde{p})$ (defined on $M(\tilde{p})$) is of the form $L^m_{\tilde{p}_l}h^\mu_l(x)$, for $m \geq 0$ and $1 \leq l \leq r$ (both $m$ and $l$ depend on $i$), and the Jacobian matrix with respect to $x$, evaluated at $(x_0(p), p)$, of the function defined by

$$H : (x, p) \mapsto (\mu_1(x, p), \ldots, \mu_n(x, p))^\top$$

is nonsingular. Denote by $H_p$ the vector field $H(\cdot, p)$.

Suppose that, for some $p \in \Omega$, $\Sigma(p)$ satisfies the ORC at $x_0(p)$ with the function $H$ defined in (3). It is possible to define a corresponding function $\tilde{H}$ for $\tilde{\Sigma}(\dot{p})$ as follows: For each $i \in \{1, \ldots, n\}$, define the smooth function $\tilde{\mu}_i(\tilde{x}, \dot{p}) = L^m_{\dot{p}_l}h^\mu_l(x)$, where $\mu_l(x, p) = L^m_{\tilde{p}_l}h^\mu_l(x)$, and then define

$$\tilde{H} : (\tilde{x}, \dot{p}) \mapsto (\tilde{\mu}_1(\tilde{x}, \dot{p}), \ldots, \tilde{\mu}_n(\tilde{x}, \dot{p}))^\top.$$

If, in addition, there exists a $\tilde{p} \in \tilde{\Omega}$ such that $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$ then proceeding as in (Evans et al., 2002, Theorem 4) it is seen that

$$H(x(t, p), p) = \tilde{H}(\tilde{x}(t, \dot{p}), \dot{p})$$

for all $t \geq 0$, where $x(t, p)$ and $\tilde{x}(t, \dot{p})$ denote the state trajectories of systems $\Sigma(p)$ and $\tilde{\Sigma}(\dot{p})$, respectively. Since the ORC is satisfied, there exists an open neighbourhood $W$ of $x_0(p)$ such that $H_p : W \to H_p(W)$ is a $C^\infty$-diffeomorphism. Let $\tilde{V}_\tilde{p}$ be any open neighbourhood of $\tilde{x}_0(\dot{p})$ such that $H_p(\tilde{V}_\tilde{p}) \subset H_p(W)$. Then it is possible to define the smooth function $\lambda(\cdot, \Sigma(p), \tilde{\Sigma}(\dot{p})) : \tilde{V}_\tilde{p} \to M(p)$ by

$$\lambda(\tilde{x}, \Sigma(p), \tilde{\Sigma}(\dot{p})) = H_p^{-1}(\tilde{H}(\tilde{x}, \dot{p})).$$

When $\Sigma(p)$ and $\tilde{\Sigma}(\dot{p})$ are clear the more concise notation $\lambda(\cdot)$ will be used.

### 3. Structural indistinguishability analysis

In this section, an approach for testing the output indistinguishability of two systems $\Sigma(p)$ and $\tilde{\Sigma}(\dot{p})$ is proposed that utilises the construction of the smooth map $\lambda(\cdot, \Sigma(p), \tilde{\Sigma}(\dot{p}))$ described in the previous section. This is then used as a basis for performing a structural indistinguishability analysis between two models $\Sigma$ and $\tilde{\Sigma}$.

**Theorem 3.** Let $p \in \Omega$ and $H$ denote a function, defined via (3), for which the system $\Sigma(p)$ satisfies the ORC at $x_0(p)$. Let $\tilde{H}$ denote the corresponding function for $\tilde{\Sigma}$, as defined in (4). For any $\tilde{p} \in \tilde{\Omega}$, $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$ if and only if there exist a neighbourhood $\tilde{V}_\tilde{p}$ of $x_0(\dot{p})$, a $\tau > 0$ and a smooth map $\lambda : \tilde{V}_\tilde{p} \to M(p)$ such that

$$H(\lambda(\tilde{x}, p), p) = \tilde{H}(\tilde{x}(\tilde{p}), \dot{p}),$$

for all $\tilde{x} \in \tilde{V}_\tilde{p}$, and

$$\lambda(x_0(p)) = x_0(p),$$

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

for all $t \in [0, \tau)$.

**Proof.** Given $\tilde{p} \in \tilde{\Omega}$, suppose that $\Sigma(p) \sim \tilde{\Sigma}(\dot{p})$, and let $\lambda(\cdot, \Sigma(p), \tilde{\Sigma}(\dot{p}))$ denote the smooth mapping constructed in (5), as outlined in the previous section. If $\tilde{V}_\tilde{p}$ denotes a corresponding neighbourhood of $x_0(\dot{p})$ on which $\lambda$ is defined, then let $\tau > 0$ be such that $\tilde{x}(t, \tilde{p}) \in \tilde{V}_\tilde{p}$ for all $t \in [0, \tau)$.

Eqs. (6), (7), and (9) are satisfied automatically as a result of the construction of $\lambda$. For Eq. (8) note that

$$f(\lambda(\tilde{x}(\tilde{t}, \tilde{p})), p) = \tilde{f}(\tilde{x}(\tilde{t}, \dot{p})),$$

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

for all $t \in [0, \tau)$.

Conversely, let $\tilde{p} \in \tilde{\Omega}$ and $\tilde{V}_\tilde{p}$ be an open neighbourhood of $\tilde{x}_0(\dot{p})$. Choose $\tau > 0$ such that $\tilde{x}(t, \tilde{p}) \in \tilde{V}_\tilde{p}$ for all $t \in [0, \tau)$. Suppose that $\lambda : \tilde{V}_\tilde{p} \to M(p)$ is a smooth mapping that satisfies (7)–(9) for all $t \in [0, \tau)$. Defining $z(t) = \lambda(\tilde{x}(\tilde{t}, \dot{p}))$, for $t \in [0, \tau)$, it is seen that $z(\cdot)$ is the solution of the following system:

$$\dot{z}(t) = \frac{\partial \lambda}{\partial x}(\tilde{x}(\tilde{t}, \dot{p}))\tilde{f}(\tilde{x}(\tilde{t}, \dot{p}), \dot{p}) = f(z(t), p) \text{ (by (8))},$$

$$z(0) = \lambda(x_0(p)) = x_0(p) \text{ (by (7))}.$$
By the uniqueness of solutions to (1) it is seen that \( z(t) = x(t, p) \) on \([0, \tau]\). Moreover, Eq. (9) implies that
\[
\hat{j}(t, \hat{p}) = \hat{h}(\hat{x}(t, \hat{p}), \hat{p}) = h(\lambda_\hat{x}(t, \hat{p}), p)
\]
for all \( t \in [0, \tau] \) and so \( \Sigma(p) \sim \hat{\Sigma}(\hat{p}) \). \( \square \)

Let \( \mathcal{U}(\Sigma(p); \hat{\Sigma}) \) denote the set of all \( \hat{p} \in \hat{\Omega} \) such that \( \Sigma(p) \sim \hat{\Sigma}(\hat{p}) \). For \( p \in \Omega \) such that \( \Sigma(p) \) satisfies the ORC at \( x_0(p) \), Theorem 3 provides a means for determining the set \( \mathcal{U}(\Sigma(p); \hat{\Sigma}) \). This set forms the basis for performing a structural indistinguishability analysis between models \( \Sigma \) and \( \hat{\Sigma} \). The models \( \Sigma \) and \( \hat{\Sigma} \) are structurally indistinguishable if and only if the following two conditions are satisfied:

1. For generic \( p \in \Omega \) the set \( \mathcal{U}(\Sigma(p); \hat{\Sigma}) \neq \emptyset \).
2. For generic \( \hat{p} \in \hat{\Omega} \) there exists a \( p \in \Omega \) such that \( \hat{p} \in \mathcal{U}(\Sigma(p); \hat{\Sigma}) \).

When applying Theorem 3 Eqs. (8) and (9) may prove computationally intensive. However, an easier test for indistinguishability is provided by noting that the ORC is only used in the proof of Theorem 3 to construct the smooth mapping \( \lambda(\cdot; \Sigma(p); \hat{\Sigma}(\hat{p})) \) between output indistinguishable systems.

**Corollary 4.** Let \( p \in \Omega \) and \( \hat{p} \in \hat{\Omega} \). If there exist a neighbourhood \( \bar{V}_p \) of \( x_0(p) \) and a smooth map \( \lambda: \bar{V}_p \rightarrow M(p) \) such that
\[
\dot{\lambda}(x_0(\hat{p})) = x_0(p), \quad (10)
\]
\[
f(\lambda(\hat{x}), p) = \frac{\partial \lambda}{\partial \hat{x}}(\hat{x}) \hat{f}(\hat{x}, \hat{p}), \quad (11)
\]
\[
h(\lambda(\hat{x}), p) = \hat{h}(\hat{x}, \hat{p}), \quad (12)
\]
for all \( \hat{x} \in \bar{V}_p \) then \( \Sigma(p) \sim \hat{\Sigma}(\hat{p}) \).

**Proof.** This follows from Theorem 3 by noting that the ORC is not used in the appropriate part of the proof. \( \square \)

For a given model \( \Sigma \) and parameter vector \( p \in \Omega \), let \( \mathcal{U}_\infty(\Sigma(p); \hat{\Sigma}) \) denote the set of all \( \hat{p} \in \hat{\Omega} \) such that there exists a smooth \( \lambda \) and a neighbourhood \( \bar{V}_p \) (of \( x_0(p) \)) that satisfy Corollary 4, then it follows that \( \mathcal{U}_\infty(\Sigma(p); \hat{\Sigma}) \subseteq \mathcal{U}(\Sigma(p); \hat{\Sigma}) \).

To further reduce computational complexity, the following subsets of \( \mathcal{U}_\infty(\Sigma(p); \hat{\Sigma}) \) can be considered:

1. \( \mathcal{U}_0(\Sigma(p); \hat{\Sigma}) \) for those \( \hat{p} \in \hat{\Omega} \) such that \( \lambda \) is an invertible diagonal linear map;
2. \( \mathcal{U}_1(\Sigma(p); \hat{\Sigma}) \) for those \( \hat{p} \in \hat{\Omega} \) such that \( \lambda \) is an invertible linear map;
3. \( \mathcal{U}_2(\Sigma(p); \hat{\Sigma}) \) for those \( \hat{p} \in \hat{\Omega} \) such that \( \lambda \) is a smooth diffeomorphism.

These give rise to the following nested sequence of sets:
\[
\mathcal{U}_\infty(\Sigma(p); \hat{\Sigma}) \subseteq \mathcal{U}_1(\Sigma(p); \hat{\Sigma}) \subseteq \mathcal{U}_2(\Sigma(p); \hat{\Sigma}) \\
\subseteq \mathcal{U}_0(\Sigma(p); \hat{\Sigma}) \subseteq \mathcal{U}(\Sigma(p); \hat{\Sigma}).
\]
Therefore, Corollary 4 can be used to show structural indistinguishability between models by considering each of the special cases above, in order of increasing computational complexity. If, at the last stage, it is found that \( \mathcal{U}_\infty(\Sigma(p); \hat{\Sigma}) = \emptyset \) the full test provided by Theorem 3 should be attempted to determine \( \mathcal{U}(\Sigma(p); \hat{\Sigma}) \). From this, it may be possible to establish whether two models are structurally indistinguishable.

**4. Examples**

**Example 5.** Consider the following two models for the spread of an infectious disease in a population of constant size:
\[
\Sigma(p) \left\{ \begin{array}{ll}
\dot{S} = \mu N - \mu S - \beta SI, & S(0) = S_0, \\
\dot{I} = \beta SI - (\mu + \sigma)I, & I(0) = I_0,
\end{array} \right.
\]
\[
\hat{\Sigma}(\hat{p}) \left\{ \begin{array}{ll}
\dot{\hat{S}} = (\hat{\mu} + \hat{\sigma})\hat{N} - (\hat{\mu} + \hat{\sigma})\hat{S} - \hat{\beta}\hat{S}\hat{I} - \hat{\hat{\sigma}}\hat{I}, & \hat{S}(0) = \hat{S}_0, \\
\dot{\hat{I}} = \hat{\beta}\hat{S}\hat{I} - (\hat{\mu} + \hat{\sigma})\hat{I}, & \hat{I}(0) = \hat{I}_0.
\end{array} \right.
\]

Model \( \Sigma(p) \) is the general Susceptible, Infectious, Recovered (SIR) model structure (Kermack & McKendrick, 1927; Bailey, 1975; Capasso, 1993), and \( \hat{\Sigma}(\hat{p}) \) is the general Susceptible, Infectious, Recovered with temporary immunity (SIRS) model structure (Hethcote, 1976; Capasso, 1993). Suppose that it is possible to measure an unknown proportion of the number of infectious individuals, i.e., the prevalence, so that the output structures for the systems are
\[
y(t, p) = kl \quad \text{and} \quad \hat{y}(t, \hat{p}) = \hat{k}\hat{l},
\]
respectively. An output of this form is appropriate when the ratio of the number of cases to the number of infectious individuals in the population can be assumed to be constant, and the data consist of the reported number of cases (e.g., this was assumed by Weber, Weber, and Milligan (2001) for respiratory syncytial virus). The unknown parameter vectors, \( p \) and \( \hat{p} \) are given by \( p = (\mu, N, \beta, \sigma, k, S_0, I_0)^T \) and \( \hat{p} = (\hat{\mu}, \hat{\sigma}, \hat{N}, \hat{\beta}, \hat{\hat{\sigma}}, \hat{\hat{\mu}}, \hat{k}, \hat{I}_0, \hat{S}_0) \). It is assumed that all parameters in both models are positive and \( \Theta = \mathbb{R}_{>0}^7 \) and \( \hat{\Theta} = \mathbb{R}_{>0}^8 \). In particular, it should be noted that it is not possible to have \( \hat{\sigma} = 0 \) in \( \hat{\Sigma} \).

Let \( \lambda \) be a smooth mapping that satisfies the conditions of Corollary 4. It is seen from Eq. (12) that
\[
\lambda(\hat{x}) = \frac{\hat{l}}{k} \hat{I}
\]
for all \( \hat{x} = (\hat{S}, \hat{I})^T \) in a neighbourhood \( \bar{V}_p \) of \( (\hat{S}_0, \hat{I}_0)^T \). Equating the second components of both sides of Eq. (11) it is seen that
\[
\beta \lambda_1(\hat{x}) \frac{\hat{l}}{k} - (\mu + \sigma)\frac{\hat{l}}{k} = \frac{\hat{l}}{k} (\hat{\beta}\hat{S}\hat{I} - (\hat{\mu} + \hat{\sigma})\hat{I})
\]
for all \( \hat{x} \in \bar{V}_p \), and so
\[
\lambda_1(\hat{x}) = \frac{\hat{l}}{\beta} S + \frac{(\mu + \sigma) - (\mu + \hat{\sigma})}{\beta}.
\]
Now equating the first components of both sides of Eq. (11) it is seen that
\[
\mu \mathcal{N} - \left( \mu + \frac{\beta k I}{k} \right) \left( \frac{\hat{\beta}}{\beta} S + \frac{(\mu + \sigma) - (\mu + \sigma)}{\beta} \right) = \frac{\hat{\beta}}{\beta} (\tilde{\mu} + \tilde{\sigma}) \hat{N} - (\tilde{\mu} + \tilde{\sigma}) \hat{S} - \hat{\beta} \hat{S} \hat{I} - \hat{\sigma} \hat{I}.
\]
Equating coefficients on both sides of this equation shows that
\[
[\text{const}] \quad \mu \left( N - \frac{(\mu + \sigma) - (\mu + \sigma)}{\beta} \right) = \frac{\hat{\beta}(\tilde{\mu} + \tilde{\sigma})}{\beta},
\]
\[
[S] \quad \frac{\mu \hat{\beta}}{\beta} = \frac{\hat{\beta}(\tilde{\mu} + \tilde{\sigma})}{\beta}, \quad [S \hat{I}] = \frac{\hat{\beta}^2}{\beta},
\]
\[
[I] \quad \frac{k((\mu + \sigma) - (\mu + \sigma))}{\beta} = \frac{\hat{\beta} \hat{z}}{\beta}.
\]
From these equations it is seen that
\[
\tilde{\mu} + \tilde{\sigma} = \mu, \quad \hat{k}/\hat{\beta} = k/\beta, \quad \tilde{\sigma} = \sigma, \quad \hat{\beta} \hat{N} + \hat{\sigma} = \beta N.
\]
Finally, for Eq. (10) to be satisfied it must be the case that
\[
\left( \frac{\hat{\beta} \hat{S}_0 + \hat{\sigma}}{\beta} \right) = \left( \frac{S_0}{I_0} \right)
\]
and so
\[
\hat{\beta} \hat{S}_0 + \hat{\sigma} = \beta S_0 \quad \text{and} \quad \hat{\beta} I_0 = \beta I_0.
\]
In summary, it is seen that for generic \( p \in \Omega = \mathbb{R}^7, \)
\[
\mathcal{U}_\infty(\Sigma(p); \tilde{\Sigma}) = \{ \tilde{p} \in \tilde{\Omega} : \tilde{\mu} + \tilde{\sigma} = \beta N, \hat{k} \hat{I}_0 = \beta I_0 \}
\]
where \( \tilde{\Omega} = \mathbb{R}^5, \) Note that, given a \( p \in \Omega, \) then for any \( N > 0 \)
and \( 0 < \tilde{\sigma} \leq \min \{ \mu, \beta S_0 \}, \) it follows that \( \tilde{\mu} = \mu - \tilde{\sigma} > 0, \quad \tilde{\sigma} = \sigma, \quad \hat{\beta} \hat{N} + \hat{\sigma} = \beta N, \hat{\beta} \hat{S}_0 + \hat{\sigma} = \beta S_0, \hat{\beta} \hat{I}_0 = \beta I_0 \}
\]
so that \( \mathcal{U}(\Sigma(p); \tilde{\Sigma}) \neq \emptyset. \) Conversely, for a generic \( \tilde{p} \in \tilde{\Omega}, \)
\[
\mathcal{U}_\infty(\Sigma(p); \tilde{\Sigma}) \neq \emptyset.
\]
Simply set \( \beta > 0 \) arbitrarily and then the remaining parameters in \( p \) are uniquely determined, and positive, by the equations constituting the set \( \mathcal{U}_\infty(\Sigma(p); \tilde{\Sigma}). \) It follows that \( \Sigma \sim \tilde{\Sigma}, \) i.e., the two models are structurally indistinguishable for this observation.

Even though \( \tilde{\Sigma}(\tilde{p}) \) has an extra parameter, the fact that it may match the output of \( \Sigma(p) \) generically is surprising since the obvious mechanism of setting \( \tilde{\sigma} = 0 \) is not permitted. Also, it is natural to expect this extra parameter to give rise to a wider variety of possible output measurements which proves not to be the case. This is caused by the particular measurement in place and the implication of this is that it is not possible from prevalence data to determine whether the SIR model structure is more appropriate than the SIRS one.

**Example 6.** Consider the two chemical reaction schemes shown in Fig. 1. In the first reaction scheme (Fig. 1(a)) chemical \( S \) reversibly reacts with chemical \( E \) to form a complex \( (C_1). \) This complex can then reversibly react with \( S \) to form another complex \( (C_2) \) from which the product \( (P) \) is formed.

The second reaction scheme (Fig. 1(b)) is similar, except that \( S \) does not react with the first complex, but with \( E \) to form the second complex. The first reaction scheme can therefore be regarded as a co-operative one, where the formation of the first complex enables formation of the second complex and therefore the product.

Let \( s, c_1, c_2 \) and \( p \) denote the concentrations of chemical \( S, \) first complex, second complex and product, respectively. Using the Law of Mass Action and assuming that the total concentration of chemical \( E, e(t), \) satisfies the conservation law
\[
e(t) = e(0) - c_1(t) - c_2(t),
\]
the two reaction schemes give rise to the following models. For the first reaction scheme the model, denoted by \( \Sigma(k), \) is:
\[
\dot{s} = -k_1 s_0 e_0 - c_1 - c_2 + k_{-1} c_1 - k_{-2} c_2,
\]
\[
\dot{c}_1 = k_1 s_0 (e_0 - c_1 - c_2) - k_{-1} c_1 - k_{-2} c_1 + k_{-2} c_2,
\]
\[
\dot{c}_2 = k_2 s_0 c_1 - k_{-1} c_2 - k_{-2} c_2,
\]
Fig. 1. A pair of reaction schemes involving two chemicals (\( S \) and \( E \)), two complexes (\( C_1 \) and \( C_2 \)), and a product (\( P \)). (a) Reaction scheme 1 and (b) Reaction scheme 2.
\[ \dot{p} = k_3 c_2, \]
\[ \dot{s} = s_0, \quad c_1(0) = 0, \quad c_2(0) = 0, \quad p(0) = 0, \]
where \( e_0 = e(0) \) and \( k = (k_1, k_{-1}, k_2, k_{-2}, k_3, s_0, e_0)^T \) denotes the vector of unknown parameters. For the second reaction scheme the model, denoted by \( \Sigma(k) \), is:
\[ \dot{\tilde{s}} = -\tilde{s}(\tilde{e}_0 - \tilde{c}_1 - \tilde{c}_2)(\tilde{k}_1 + \tilde{k}_2 \tilde{s}) + \tilde{k}_{-1} \tilde{c}_1 + \tilde{k}_{-2} \tilde{c}_2, \]
\[ \dot{\tilde{c}}_1 = \tilde{k}_3 \tilde{s}(\tilde{e}_0 - \tilde{c}_1 - \tilde{c}_2) - \tilde{k}_{-1} \tilde{c}_1, \]
\[ \dot{\tilde{c}}_2 = \tilde{k}_3 \tilde{s}^2(\tilde{e}_0 - \tilde{c}_1 - \tilde{c}_2) - \tilde{k}_{-2} \tilde{c}_2 - \tilde{k}_3 \tilde{c}_2, \]
\[ \dot{\tilde{p}} = \tilde{k}_3 \tilde{c}_2, \]
\[ \tilde{s}(0) = \tilde{s}_0, \quad \tilde{c}_1(0) = 0, \quad \tilde{c}_2(0) = 0, \quad \tilde{p}(0) = 0, \]
with \( \tilde{k} = (\tilde{k}_1, \tilde{k}_{-1}, \tilde{k}_2, \tilde{k}_{-2}, \tilde{k}_3, \tilde{s}_0, \tilde{e}_0)^T \). Indistinguishability between \( \Sigma(k) \) and \( \tilde{\Sigma}(\tilde{k}) \) is analysed for the situation where the rate of change of the concentration of product (i.e., \( \dot{p} \) and \( \dot{\tilde{p}} \)) is measured. Therefore, the last equation in each model is regarded as the output, so that the states are given by \( x = (s, c_1, c_2)^T \) and \( \tilde{x} = (\tilde{s}, \tilde{c}_1, \tilde{c}_2)^T \), respectively.

To see that the ORC is satisfied at \( x_0(k) = (s_0, 0, 0)^T \) for \( \Sigma(k) \)
\[ H(x, k) = (\mu_1(x, k), \mu_2(x, k), \mu_3(x, k))^T \]
where \( x = (s, c_1, c_2)^T \), \( k = (k_1, k_{-1}, k_2, k_{-2}, k_3, s_0, e_0)^T \) and \( \mu_1(x, k) = k_5 s_2 \)
\[ \mu_2(x, k) = d_1 \mu_1(x, k)f(x, k), \]
\[ \mu_3(x, k) = d_2 \mu_2(x, k)f(x, k). \]
The Jacobian matrix of \( H(\cdot, k) \), evaluated at \( x_0(k) \), is given by
\[ \frac{\partial H}{\partial x}(x_0(k), k) = \begin{pmatrix} 0 & 0 & k_3 \\ 0 & k_2 k_3 s_0 & -k_3 (k_3 + k_{-2}) \\ 2e_0 k_1 k_2 k_3 & -k_2 k_3 s_0 x_1 & k_5 x_2 \end{pmatrix}, \]
where \( x_1 = e_0 k_1 + k_3 + k_{-1} + k_{-2} + (k_1 + k_2) s_0 \) and \( x_2 = (k_3 + k_{-2})^2 + k_2 s_0 (k_{-2} - k_1) s_0 \). With \( k \in \Omega = \mathbb{R}_{>0}^7 \) it is seen that this matrix has full rank and so \( \Sigma(k) \) satisfies the ORC at \( x_0(k) \).

Define the corresponding function
\[ \hat{H}(\hat{x}, \hat{k}) = (\hat{\mu}_1(\hat{x}, \hat{k}), \hat{\mu}_2(\hat{x}, \hat{k}), \hat{\mu}_3(\hat{x}, \hat{k}))^T \]
for \( \hat{\Sigma}(\hat{p}) \), where
\[ \hat{\mu}_1(\hat{x}, \hat{k}) = \hat{k}_3 \hat{c}_2, \]
\[ \hat{\mu}_2(\hat{x}, \hat{k}) = d_1 \hat{\mu}_1(\hat{x}, \hat{k})f(\hat{x}, \hat{k}), \]
\[ \hat{\mu}_3(\hat{x}, \hat{k}) = d_2 \hat{\mu}_2(\hat{x}, \hat{k})f(\hat{x}, \hat{k}). \]
and consider a smooth mapping \( \lambda \) that satisfies (6). If \( \lambda \) also satisfies (7) then it is seen that
\[ H(\lambda(\tilde{x}_0(\tilde{k})), k) = \begin{pmatrix} 0 \\ 0 \\ k_1 k_2 k_3 \tilde{s}_0 \end{pmatrix} = \tilde{H}(\tilde{x}_0(\tilde{k}), \tilde{k}) \]
\[ = \begin{pmatrix} 0 \\ \tilde{k}_3 \tilde{s}_0 \tilde{c}_0 \\ \tilde{k}_3 \tilde{s}_0 \tilde{c}_0 (\tilde{k}_1 + \tilde{k}_2 \tilde{s}_0) (\tilde{s}_0 - 2 \tilde{e}_0) \end{pmatrix}, \]
and so \( \tilde{k} \not\in \hat{\Omega} = \mathbb{R}_{>0}^7 \). This means that \( \mathcal{W}(\Sigma(p); \hat{\Sigma}) = \emptyset \) and the two models are distinguishable.

**Example 7.** For the two reaction schemes shown in Fig. 1, suppose that the complexes \( C_1 \) and \( C_2 \) formed are instantaneously at equilibrium, and remain so throughout the time-course of interest. Performing a pseudo-steady state approximation \( \dot{c}_1 = \dot{c}_2 = 0 \) yields
\[ c_1 = e_0 k_1 (k_3 + k_{-2}) s \beta(s), \]
\[ c_2 = e_0 k_1 k_2 s^2 / \beta(s), \]
\[ (\beta(s) = (k_{-1} + s k_1) (k_3 + k_{-2}) + k_2 s (k_3 + k_1 s) ) \]
for the first reaction scheme and
\[ \dot{c}_1 = \tilde{e}_0 \tilde{k}_1 \tilde{s} (\tilde{k}_3 + \tilde{k}_{-2}) / \tilde{\beta}(\tilde{s}), \]
\[ \dot{c}_2 = \tilde{e}_0 \tilde{k}_3 \tilde{s} / \tilde{\beta}(\tilde{s}), \]
\[ (\tilde{\beta}(\tilde{s}) = (\tilde{k}_{-1} + \tilde{k}_1 \tilde{s}) (\tilde{k}_3 + \tilde{k}_{-2}) + \tilde{k}_2 \tilde{k}_{-1} \tilde{s}^2), \]
for the second. The models for the two reaction schemes, after making a pseudo-steady state approximation, are therefore given by
\[ \begin{cases} \dot{s} = -2 e_0 k_1 k_2 k_3 s \beta(s), \\ \Sigma(k) \end{cases} \]
\[ \begin{cases} \dot{\tilde{s}} = -\tilde{e}_0 \tilde{k}_{-1} \tilde{k}_2 \tilde{k}_3 \tilde{s}^2 \tilde{\beta}(\tilde{s}), \\ \tilde{\Sigma}(\tilde{k}) \end{cases} \]
\[ \begin{cases} \dot{p} = e_0 k_1 k_2 k_3 s^2 / \beta(s), \\ s(0) = s_0, \quad p(0) = 0, \end{cases} \]
\[ \begin{cases} \dot{\tilde{p}} = \tilde{e}_0 \tilde{k}_{-1} \tilde{k}_2 \tilde{k}_3 \tilde{s}^2 / \tilde{\beta}(\tilde{s}), \\ \tilde{s}(0) = \tilde{s}_0, \quad \tilde{p}(0) = 0. \end{cases} \]
Indistinguishability between \( \Sigma(k) \) and \( \tilde{\Sigma}(\tilde{k}) \) is again analysed for the situation where the rate of change of the concentration of product (i.e., \( \dot{p} \) and \( \dot{\tilde{p}} \)) is measured. Similarly, the last equation in each model is regarded as the output.

Consider the simplest case of Corollary 4, where the mapping \( \lambda \) is linear, say \( \lambda(s) = ts \) for some \( t \in \mathbb{R} \). It is seen from Eq. (12) that
\[ e_0 k_1 k_2 k_3 t^2 \beta(s) - \tilde{e}_0 \tilde{k}_{-1} \tilde{k}_2 \tilde{k}_3 \tilde{s}^2 \beta(t \tilde{s}) = 0 \]
for all \( s \) in a neighbourhood of \( s_0 \). Since \( \tilde{s}(0) \neq 0 \) there exists a nontrivial interval (containing \( s_0 \)) on which the polynomial left-hand side of Eq. (14) is zero. This polynomial must
therefore be the zero polynomial. The coefficients (of powers of $\theta$) are

$$[s^3] \left[ k_1 k_2 \theta^{-1} \theta^2 (e_0 k_3 - e_0 k_1), [s^3] e_0 k_1 k_2 k_3 \theta (-2 + k_1) \theta^{-1} (\theta + k_3) - e_0 k_1 k_2 k_3 (k_1 k_2 + k_3 (k_1 + k_2)), [s^3] \theta^{-1} (e_0 k_1 k_2 k_3 \theta (-2 + k_3) - e_0 k_1 k_2 k_3 (k_1 k_2 + k_3)) \right]$$

and these must be equal to 0. Solving for the parameters in $\hat{k}$ yields

$$\hat{e}_0 k_3 = e_0 k_1, \quad \hat{k}_1 = \frac{(k_2 k_3 + k_1 (k_2 + k_3))}{k_2}, \quad \hat{k}_2 = \frac{k_2}{k_1 k_2}.$$  

If $k$ and $\hat{k}$ satisfy these relations, then Eq. (11) holds if and only if

$$e_0 k_1 k_2 k_3 (t - 2) \theta^2 = 0$$

and so, since it is assumed that $\theta \in \Omega = \mathbb{R}_{>0}^3$, it must be the case that $t = 2$. The initial condition, Eq. (10) is satisfied if $\lambda \tilde{s}_0 = 2 \tilde{s}_0 = s_0$. In summary, it is seen that for generic $k \in \Omega$,  

$$\mathcal{H}_\lambda (\Sigma (k); \tilde{\Sigma}) = \left\{ \hat{k} \in \tilde{\Omega} : \frac{\theta^{-1} + \hat{k}_3}{k_2} = \frac{k_2}{k_1} (k_3 + k_2) \right\}.$$  

where $\tilde{\Omega} = \mathbb{R}_{>0}^3$. An analysis of $\mathcal{H}_\lambda (\Sigma (k); \tilde{\Sigma})$, similar to that of $\mathcal{H}_\infty (\Sigma (p); \tilde{\Sigma})$ in Example 5, shows that the models are structurally indistinguishable.

Note that, if the initial concentration of $E$ is known, then $\hat{e}_0 = e_0$, $\mathcal{H}_\lambda (\Sigma (k); \tilde{\Sigma}) \neq \emptyset$ for generic $k \in \Omega = \mathbb{R}_{>0}^3$, and the models are still structurally indistinguishable.

5. Conclusion

Structural indistinguishability generalises the problem considered by structural identifiability, from one of the uniqueness of the unknown parameters from a given output, to one of the uniqueness of the parameterisation or model structure. In this paper the approach developed in (Evans et al., 2002) for testing the structural identifiability of uncontrolled systems was extended to one for testing the indistinguishability between different models for a given process.

The approach developed utilises the existence of a smooth mapping between the states of two structurally indistinguishable models, when one of them satisfies an observability rank condition. The existence of such a mapping, even when the observability condition does not hold, ensures indistinguishability between the models. Therefore different forms for the mapping can be used in order of increasing computational complexity to test for indistinguishability. The full test provided by Theorem 3 is only necessary when this test fails to provide a result, such as when the models are not indistinguishable.

In Example 5, it was shown that the general SIR and SIRS models are structurally indistinguishable when it is only possible to measure a proportion of the prevalence.

In Examples 6 and 7, it was shown how two distinguishable models for a chemical reaction process can become structurally indistinguishable following a pseudo-steady state assumption. In a similar fashion, Chappell (1996) considered the impact a pseudo-steady state assumption has on the structural identifiability of a two-state model involving saturable binding. A comparable result was obtained in that a certain degree of structural identifiability was lost when applying a pseudo-steady state assumption.

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