Review: To be or not to be an identifiable model. Is this a relevant question in animal science modelling?

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**Supplementary material S1**

**Three methods for performing structural identifiability analysis of dynamic models**

This section describes briefly three methods for testing structural identifiability in dynamic models. Consider the model described by the following ordinary differential equations

$$\frac{dx(t)}{dt}=f\left(x,u,p, t\right), x\left(0\right)=x\_{0} $$

$y\_{m}(t)=g(x,u,p,t)$ (1)

where $t$ is the time, $x$ is the vector of state variables, $y\_{m}$is the vector of model observables, and $u$isthe vector of external stimuli (input vector). The equations contain a set of parameters defined by the vector$ p$, and **f,** **g** are vector functions.

*Laplace Transform*

If the model in Eq. (1) is linear, a classical approach for testing its structural identifiability is via the analysis of the transfer function of the model resulting from the Laplace transformation ([Bellman and Astrom, 1970](#_ENREF_1)). The transfer function matrix $H\left(s,p\right)$ is defined by

$H\left(s,p\right)=\frac{Y\left(s,p\right)}{U\left(s,p\right)}$ (2)

where $s$ is the argument of the Laplace domain, $Y\left(s,p\right)$ and $U\left(s,p\right) $are the Laplace transforms of the observables ($y\_{m}$) and inputs ($u$).

Once $H\left(s,p\right)$ is written in canonical form, we can proceed to write the transfer function matrix for two parameters sets $p,p^{\*}$. Further, by establishing the relation $H\left(s,p\right)≡ H\left(s,p^{\*}\right)$ we can derive a set of equations translating the identities of the coefficients of $H\left(s,p\right)$ and $H\left(s,p^{\*}\right)$.

If the solution for the set of equations is unique for $p$, that is $p=p^{\*}$, the model is structurally identifiable.

For illustration, let us consider the following single-input and single-output (SISO) model

$$\frac{dx(t)}{dt}=\left(a+b\right)∙x+c∙u, x\_{0}=0 $$

 $y(t)=x(t)$ (3)

with parameters $a,b,c$ and the input $u$. The observable $y(t)$ is the state variable $x(t)$. By applying the Laplace transform, we obtain

 $sX\left(s\right)=\left(a+b\right) ∙X\left(s\right)+c ∙U\left(s\right) $ (4)

where $X\left(s\right), U\left(s\right)$ correspond respectively to the state variable and the input variable in the Laplace domain. The model observable in the Laplace domain is $Y\left(s\right)=X\left(s\right)$. The transfer function is given by

$$H\left(s\right)=\frac{Y\left(s\right)}{U\left(s\right)}=\frac{c}{s-\left(a+b\right)} $$

 (5)

The identity equations are

 $c=c^{\*}$ (6)

 $a+b=a^{\*}+b^{\*}$ (7)

From Eq. (6) and Eq. (7), we can conclude that the parameter $c$ is uniquely identifiable while the parameters $a,b$ are nonidentifiable since Eq. (7) have infinite solutions.

Many examples of identifiability analysis for linear compartmental models are presented in [Carson *et al.*, 1983](#_ENREF_2).

*Taylor series expansion*

This approach was developed by [Pohjanpalo, 1978](#_ENREF_5). It assumes that the vector functions **f,** **g** in Eq. (1) are continuously differentiable in their arguments, implying that the state and the observable vectors can have infinitely many time derivatives. The development of the Taylor series of the observable $y\_{m}(t)$ in the model described by Eq. (1) results

$y\_{m}\left(t\right)=y\_{m}\left(0\right)+t\frac{dy\_{m}}{dt}\left(0\right)+\frac{t^{2}}{2!}\frac{d^{2}y\_{m}}{dt^{2}}\left(0\right)+\cdots +\frac{t^{k}}{k!}\frac{d^{k}y\_{m}}{dt^{k}}\left(0\right), k=0,1, 2, \cdots ,\infty $ (8)

Let us denote

 $a\_{k}=\frac{d^{k}y\_{m}}{dt^{k}}\left(0\right)$ (9)

Since the observable vector is a unique function of time, all its derivatives ($a\_{k}$) are unique and known. The structural identifiability of the model is determined from the analysis of the equations of the successive derivatives $a\_{k}$ evaluated at two parameters sets $pp^{\*}$. The model is structurally identifiable if

$a\_{k}\left(p\right)=a\_{k}\left(p^{\*}\right), k=0,1,2,\cdots ,k\_{max}⇒ p=p^{\*}$ (10)

where $k\_{max}$ is at least the number of unknown parameters.

As example, consider the following model

$$\frac{dx\_{1}\left(t\right)}{dt}=p\_{1}∙x\_{1}∙x\_{2}, x\_{10}=1.0 $$

$$\frac{dx\_{2}(t)}{dt}=p\_{2}∙u, x\_{20}=2.0 $$

 $y\_{1}(t)= x\_{1}(t)$ (11)

With parameters $p\_{1},p\_{2}$ and the input $u$. The model has two state variables$ x\_{1}\left(t\right), x\_{2}(t)$ and one observable $y\_{1}(t)$ that corresponds to the state variable $x\_{1}(t)$. By developing the successive derivatives of $y\_{1}(t)$, we obtain

 $a\_{0}=x\_{10}=1.0$ (12)

 $a\_{1}=p\_{1}∙x\_{10}∙x\_{20}=2.0∙p\_{1}$ (13)

$a\_{2}=p\_{1}^{2}∙x\_{10}∙x\_{20}^{2}+ p\_{1}∙p\_{2}∙x\_{10}∙u=4.0∙p\_{1}^{2}+p\_{1}∙p\_{2}∙u$ (14)

The model is globally identifiable. The parameter $p\_{1} $can be uniquely obtained from the coefficient $a\_{1}$, and subsequently $p\_{2}$ can be uniquely recovered from $a\_{2}$.

*Generating series*

This method was developed by [Walter and Lecourtier, 1982](#_ENREF_7) and it is conceptually similar to the Taylor series approach. Consider the model described by the following ordinary differential equations

$$\frac{dx(t)}{dt}=f\_{0}\left(x,u,p, t\right)+\sum\_{i=1}^{m}f\_{i}\left(x,p, t\right)u\_{i} , x\left(0\right)=x\_{0} $$

$y\_{m}(t)=g(x,p,t)$ (15)

where $f\_{i}$($i=0,1,\cdots ,m$) and **g** are analytic, implying that the model observables can be expanded in series with respect to time and the model inputs. The coefficients of the series are $g(x(t),p,t)$ and the successive Lie derivatives evaluated at $t=0$

 $L\_{f\_{j\_{0}}}\cdots \left.L\_{f\_{j\_{k}}} g(x,p,t)\right|\_{0}$ (16)

where $L\_{f}g(x,p,t)$ is the Lie derivative of **g** along **f**, defined by

$L\_{f}g(x,p,t)=\sum\_{i=1}^{n\_{x}}f\_{i}\left(x,p, t\right)\frac{∂g(x,p,t)}{∂x\_{j}} $ (17)

with $n\_{x}$ the number of state variables.

Analogous to the Taylor series, let $s(p)$ the vector of the series coefficients. The model is structurally identifiable if ([Walter and Pronzato, 1996](#_ENREF_8)).

$s\left(\hat{p}\right)=s\left(p^{\*}\right) ⇒\hat{p}=p^{\*}$ (18)

As example, consider again the model in Eq. (11), which can be written as

$$\frac{dx(t)}{dt}=\left[\begin{matrix}p\_{1}∙x\_{1}∙x\_{2}\\0\end{matrix}\right] +\left[\begin{matrix}0\\p\_{2}\end{matrix}\right]u , x\left(0\right)= \left[\begin{matrix}1.0&2.0\end{matrix}\right]^{T}$$

$y\_{m}(t)=x\_{1} $ (19)

where $f\_{0}\left(x,u,p, t\right)=\left[\begin{matrix}p\_{1}∙x\_{1}∙x\_{2}\\0\end{matrix}\right]$ , $f\_{1}\left(x,u,p, t\right)=\left[\begin{matrix}0\\p\_{2}\end{matrix}\right]$ , $g\left(x,p,t\right)=x\_{1}$

The first Lie derivative operators are

$L\_{f\_{0}}=\left[p\_{1}∙x\_{1}∙x\_{2}\right]\frac{∂}{∂x\_{1}}$ (20)

$L\_{f\_{1}}=p\_{2}\frac{∂}{∂x\_{2}}$ (21)

The coefficients of the series are the following Lie derivatives

$L\_{f\_{0}}\left.g\right|\_{0}= $ $\left.\left[p\_{1}∙x\_{1}∙x\_{2}\right]\frac{∂x\_{1}}{∂x\_{1}}\right|\_{0}$

$= $ $\left.p\_{1}∙x\_{1}∙x\_{2}\right|\_{0}=2∙p\_{1}$ (22)

$L\_{f\_{1}}L\_{f\_{0}}\left.g\right|\_{0}= $ $p\_{2}\frac{∂}{∂x\_{2}}\left.\left\{L\_{f\_{0}}g\right\}\right|\_{0}$

$= $ $p\_{2}\frac{∂}{∂x\_{2}}\left.\left\{p\_{1}∙x\_{1}∙x\_{2}\right\}\right|\_{0}$

$= $ $\left.p\_{1}∙p\_{2}∙x\_{1}\right|\_{0}=p\_{1}∙p\_{2}$ (23)

From the coefficient in Eq. (22), it is deduced that $p\_{1}$ is identifiable. From Eq. (23), we obtain that $p\_{2}$ is identifiable.

Finally, the interested reader is referred to recent literature on structural identifiability methods and their comparison ([Chis *et al.*, 2011](#_ENREF_3); [Miao *et al.*, 2011](#_ENREF_4); [Raue *et al.*, 2014](#_ENREF_6)).

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