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ORIGINAL PAPER

Structural identifiability and sensitivity

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Abstract

Ordinary differential equation models often contain a large number of parameters that must be determined from measurements by estimation procedure. For an estimation to be successful there must be a unique set of parameters that can have produced the measured data. This is not the case if a model is not structurally identifiable with the given set of inputs and outputs. The local identifiability of linear and nonlinear models was investigated by an approach based on the rank of the sensitivity matrix of model output with respect to parameters. Associated with multiple random drawn of parameters used as nominal values, the approach reinforces conclusions regarding the local identifiability of models. The numerical implementation for obtaining the sensitivity matrix without any approximation, the extension of the approach to multi-output context and the detection of unidentifiable parameters were also discussed. Based on elementary examples, we showed that (1°) addition of nonlinear elements switches an unidentifiable model to identifiable; (2°) in the presence of nonlinear elements in the model, structural and parametric identifiability are connected issues; and (3°) addition of outputs or/and new inputs improve identifiability conditions. Since the model is the basic tool to obtain information from a set of measurements, its identifiability must be systematically checked.

Keywords Structural identifiability · Parametric identifiability · Sensitivity functions · Rank of matrix · Ill-conditioning

Introduction

When designing models to mimic the behavior of real process and described by means of several parameters, the term identifiability refers to whether the information theoretically available from an experiment is sufficient to give a unique solution values for the parameters. The first statement of identifiability problem in the compartmental context comes from Bellman and Astrom [1] who introduced the term of "structural identifiability". The term "structural" was associated to "identifiability" because the question refers to the structure of the model representing the real process.[1]Since, several works devoted to this question were explored mainly by Jacquez [2], Cobelli [3], Walter [4] and their collaborators.

It is critical to know whether the parameters are in theory uniquely defined by the observations before going into the parameter estimation phase. This is a purely mathematical question of existence of a unique solution and it can be separated from the effect of observation error. According to the definitions related to identifiability [5], a parameter is unidentifiable, if an infinite number of solutions exist. Conversely, it is locally identifiable if there are only a finite number of solutions and globally identifiable if they exists only one solution. Similarly, the model is unidentifiable if at least one of its parameters is unidentifiable and, locally or globally identifiable if all parameters are locally or globally identifiable, respectively.

Models in biology are usually described by a set of linear or nonlinear ordinary differential equations and accordingly, they are called linear or nonlinear, respectively. For all these models, outputs/predictions are nonlinear functions with respect to their parameters. To check for global identifiability, the transfer function, the similarity transformation, the Markov parameter matrix, and

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[1] In the following, the term "identifiability" alone refers for structural identifiability.

the modal matrix approaches were proposed for linear models [2, 4]. The Taylor series, the generating series, the similarity transformation, the differential algebra and the implicit function theorem approaches were proposed for nonlinear models [6]. However, checking global identifiability can be very difficult to carry out because of the complexity of the resulting algebraic parametric relationships. The problem becomes particularly hard in the case of large and highly nonlinear models. In such cases, global approaches allow only for local identifiability results, as for instance the implicit function theorem approach.

Alternatively, in many applications in biological sciences there is prior information that constrains parameter values to certain regions in parameter space. In such cases much can be learned about identifiability by numerical methods using parameter values from the constrained region. By way, by knowing the domain of definition of the parameters, local identifiability could be transformed to global identifiability [6]. Local identifiability analyses are based on the computation of local sensitivities, the Fisher Information Matrix, the covariance matrix, or the Hessian of the minimization criterion [2, 6].

The problem seemed to be solved by all these approaches for several kinds of models and experimental situations, but there is no identifiability approach clearly appropriate to every model. Moreover, with the recent development of modeling softwares allowing fast conception of large models described by ordinary differential equations with several dozen of parameters, checking efficiently and rapidly the identifiability for a large spectrum of designed models remains a challenging task.

We propose a simple to implement and convenient to use tool for checking local identifiability. This approach is based on this Fisher Information Matrix (FIM) [7]. Our investigations have focused on the role of the FIM because its condition number plays a fundamental role in a range of useful ideas such as model comparison (Akaike Information Criteria), experimental design, as well as computation of standard errors and confidence intervals [8].

Theoretical

The maximum likelihood principle is largely used to estimate p unknown model parameters $\underline{x}$ from m noisy disturbed observations $\underline{y}$ gathered on the real process with $m > p$. If $L(\underline{x}/\underline{y})$ is the likelihood of the model to $\underline{y}$, the Information Matrix $\mathrm{I}(\underline{t}, \underline{x})$ introduced by Fisher [7] is

$$\mathrm{I}(\underline{t},\underline{x}) \triangleq \mathrm{E}\left[\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial \underline{x}}\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial \underline{x}^{\mathrm{T}}}\right] = -\mathrm{E}\left[\frac{\partial^2 \ln L(\underline{x}/\underline{y})}{\partial \underline{x}\partial \underline{x}^{\mathrm{T}}}\right] \tag{1}$$

In this definition, E[.] denotes expectation of the random variable $\underline{y}$. The developments reported in Appendix 1 show that without any approximation in the model and even for nonlinear models, $\mathrm{I}(\underline{t}, \underline{x})$ may have the following consistent form

$$\mathrm{I}(\underline{t},\underline{x}) = \Phi^{\mathrm{T}}(\underline{t},\underline{x}) D(\underline{t},\underline{x})\, \Phi(\underline{t},\underline{x}) \tag{2}$$

where $\Phi(\underline{t}, \underline{x})$ is the $m \times p$ dimensional sensitivity matrix (referred also as Jacobian) and $\underline{t}$ is the collection of non-replicated sampling times t_i with $i = 1{:}m$ and $m > p$. Rothenberg [9] reported first that "under weak regularity conditions local identifiability of $\underline{x}$ is equivalent to non-singularity of $\mathrm{I}(\underline{t}, \underline{x})$". Since $D(\underline{t}, \underline{x})$ in relationship (2) is a positive definite matrix, non-singularity of $\mathrm{I}(\underline{t}, \underline{x})$ is ensured by a full rank of $\Phi(\underline{t}, \underline{x})$, i.e., when $\mathrm{rank}[\Phi(\underline{t}, \underline{x})] = p$.

A. From a statistical point of view, maximum likelihood was proven asymptotically normal [7], i.e., $\hat{\underline{x}}$ estimates follows a multivariate normal distribution $\hat{\underline{x}} \sim \mathrm{N}_p(\underline{x}_0, C)$ where $\underline{x}_0$ is the true value of parameters of the real process and C is the covariance/precision matrix. The Cramér-Rao inequality $C(\underline{t}, \underline{x}) \geq \mathrm{I}^{-1}(\underline{t}, \underline{x})$ establishes the link between $\mathrm{I}(\underline{t}, \underline{x})$ and $C(\underline{t}, \underline{x})$. Also, from an information point of view [10], the information amount contained in the multivariate normal distribution of the maximum likelihood estimates is

$$\begin{aligned} I_N &= -\frac{p}{2}(1+\ln 2\pi) - \frac{1}{2}\ln\det[C(\underline{t},\underline{x})] \\ &= -\frac{p}{2}(1+\ln 2\pi) + \frac{1}{2}\ln\det[\mathrm{I}(\underline{t},\underline{x})] \end{aligned} \tag{3}$$

B. From a numerical point of view, $L(\underline{x}/\underline{y})$ maximization is converted to a nonlinear criterion $J(\underline{x})$ minimization by setting $J(\underline{x}) \triangleq -\ln L(\underline{x}/\underline{y})$. It follows that

$$\frac{\partial J(\underline{x})}{\partial \underline{x}} \triangleq \frac{\partial \ln L(\underline{x}/\underline{y})}{\partial \underline{x}} \text{ and } \frac{\partial^2 J(\underline{x})}{\partial \underline{x}\partial \underline{x}^{\mathrm{T}}} \triangleq \frac{\partial^2 \ln L(\underline{x}/\underline{y})}{\partial \underline{x}\partial \underline{x}^{\mathrm{T}}}$$

These elements are known in the optimization field as the gradient, $\underline{g}(\underline{x})$, and the Hessian matrix, $H(\underline{x})$, of the criterion $J(\underline{x})$, respectively [11]. They are largely used in numerical analysis optimization algorithms. Thus, relationship (1) could be also written as

$$\mathrm{I}(\underline{t},\underline{x}) = \mathrm{E}\left[\underline{g}(\underline{x})\underline{g}^{\mathrm{T}}(\underline{x})\right] = -\mathrm{E}[H(\underline{x})].$$

The above A and B illustrate the connection between statistic ($\mathrm{I}(\underline{t}, \underline{x})$ and normality of maximum likelihood) and numeric ($\underline{g}(\underline{x})$ and $H(\underline{x})$ geometric characteristics of parameter space) aspects within the estimation problem. In a geometric interpretation, (1°) $C(\underline{t}, \underline{x})$ defines the confidence areas of $\hat{\underline{x}}$, which are p-dimensional ellipsoids described by $(\underline{x} - \underline{x}_0)^T C(\underline{t}, \underline{x}_0)^{-1}(\underline{x} - \underline{x}_0) = \xi^2$ with $\xi^2 = -2 \ln(1 - \alpha)$ and $\alpha = \Pr[\hat{\underline{x}} \in \text{ellipsoid}]$; and (2°) $\underline{g}(\underline{x})$ and $H(\underline{x})$ control the shape of contour plots, they are the 1st and 2nd order coefficients in the Taylor expansion of $J(\underline{x})$. In the neighborhood of $\underline{x}_0$, contour plots and ellipsoids overlap and restrain a region in parameter space with volume V given by

$$V = \pi^{p/2}\xi^p\Gamma^{-1}(p/2+1)\det{}^{1/2}[C(\underline{t},\underline{x})] \quad (4)$$

This indicates that the highest det $[C(\underline{t}, \underline{x})]$ (or the lowest det $[\mathrm{I}(\underline{t}, \underline{x})]$), the less precise $\hat{\underline{x}}$ is. Therefore, the non identifiability associated with singularity of $\mathrm{I}(\underline{t}, \underline{x})$ corresponds to infinite V and to open confidence areas.

The check of $\Phi(\underline{t}, \underline{x})$ rank could be heuristically extended for multi-output processes, e.g., when parent drug and metabolite concentrations in the plasma and urines are measured. Since $m > p$ is the only constraint for m and rows of $\Phi(\underline{t}, \underline{x})$ require no ordering according to the t_i values (even rows could be referred to the same sampling times for different outputs), sensitivity matrices $\Phi_s(\underline{t}, \underline{x})$ for each s-th output from the q available outputs could be stacked as

$$\Phi(\underline{t},\underline{x}) = [\Phi_1(\underline{t},\underline{x}) \cdots \Phi_q(\underline{t},\underline{x})]^T$$

with $s = 1{:}q$, to obtain a large $\Phi(\underline{t}, \underline{x})$ on which the check of full rank is to be applied.

Whenever the model is proved to be unidentifiable, it is interesting to know which parameters are responsible to this drawback. The check of rank may be used for a new model obtained after fixing the value of a parameter in the original model. The new model will have a $m \times (p - 1)$ dimensional sensitivity matrix $\tilde{\Phi}(\underline{t},\underline{x})$ obtained from $\Phi(\underline{t}, \underline{x})$ after removing the column corresponding to the fixed parameter. If $\mathrm{rank}[\tilde{\Phi}(\underline{t},\underline{x})] = p-1$, the fixed parameter is unidentifiable, otherwise the unidentifiable parameters lie among the others. By fixing one parameter after another, this procedure allows detection of unidentifiable parameters. However, it is important to note that fixing a parameter value to zero is somewhat risky because the functionality of the model is modified and may be not compatible with the functionality of the real process.

In a computational aspect, when the model output is given by a closed form, the sensitivity functions can be obtained by applying elementary derivation rules. When the model is given by a set of n differential equations

$$\frac{d\underline{y}(t,\underline{x})}{dt} = \underline{f}\left[t,\underline{x},\underline{y}(t,\underline{x}),u(t)\right] \quad \underline{y}(0,\underline{x}) = \underline{y}_0(\underline{x}),$$

the sensitivity functions with respect to parameters x_j with $j = 1{:}p$ can be implemented as additional differential equations

$$\frac{d}{dt}\left[\frac{\partial \underline{y}(t,\underline{x})}{\partial x_j}\right] = \frac{\partial}{\partial x_j}\left[\underline{f}\left(t,\underline{x},\underline{y}(t,\underline{x}),u(t)\right)\right]$$
$$\frac{\partial \underline{y}(0,\underline{x})}{\partial x_j} = \frac{\partial \underline{y}_0(\underline{x})}{\partial x_j}$$

to the original ones. Thus, outputs and sensitivities of the model can be obtained by integrating numerically the set of $n(p + 1)$ differential equations. The above formulation shows that even identifiability of parameters involved within the initial conditions can be investigated. To compute the rank of $\Phi(\underline{t}, \underline{x})$, nominal values, $\underline{x}_N$, for $\underline{x}$ are needed. They can be selected from available similar studies or be drawn randomly from the domain of definition of the parameters. The rank is computed with the MATLAB [12] function "rank" (number of singular values greater than machine tolerance). Alternatively, computed sensitivities can be used to obtain the gradient $\underline{g}(\underline{x})$ of the criterion $J(\underline{x})$ and therefore to employ 1st derivative methods, e.g., quasi-Newton, for criterion minimization [11].

Results

A series of examples is presented. For the two-compartment configurations in the first three examples, V_1 and V_2 are volumes of distribution and, k_1 and k_2 are elimination rates associated with compartments 1 and 2, respectively. The parameter values were considered ranging between 1 and 500 L for volumes of distributions and, 10^{-3} and 10 h^{-1} for rates. For each example, 200 $\underline{x}_N$ were randomly drawn from uniform log-scaled distributions of the parameter values.

For the two-compartment model in Fig. 1, the administration compartment is the 1st one and the sampled compartments can be compartment 1, compartment 2, or both compartments. Accordingly, the number of parameters in the model is 1, 1 or 2 volumes of distribution (V_1 or V_2), respectively, plus 4 linear rates $(k_1 \quad k_2 \quad k_{12} \quad k_{21})$.

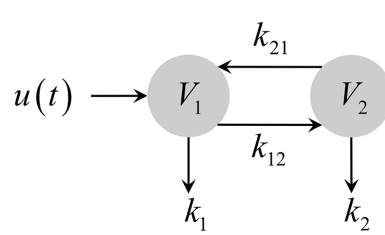

Fig. 1 Two-compartment configuration; the administration site is the 1st compartment and both compartments can be sampled. V_1 and V_2 are volumes of distribution of compartments 1 and 2, respectively; k_1 and k_2 are elimination rates from compartments 1 and 2, respectively; k_{12} and k_{21} are transfer rates between compartments; and $u(t)$ is known function describing the administration protocol

A. When compartment 1 is sampled (parameters $V_1 \quad k_1 \quad k_2 \quad k_{12} \quad k_{21}$), the model is unidentifiable since rank[$\Phi(\underline{t}, \underline{x}_N)$] = 4 and $p = 5$. If one of V_1, k_{12} and k_{21} is fixed, rank[$\Phi(\underline{t}, \underline{x}_N)$] = 3 and $p = 4$. Consequently, the unidentifiable parameters are those remaining free in the model, i.e., k_1 or k_2. If one of k_1 and k_2 is fixed, the model becomes identifiable since rank[$\Phi(\underline{t}, \underline{x}_N)$] = 4 and $p = 4$.
B. When compartment 2 is sampled (parameters $V_2 \quad k_1 \quad k_2 \quad k_{12} \quad k_{21}$), the model is unidentifiable since rank[$\Phi(\underline{t}, \underline{x}_N)$] = 3 and $p = 5$. This indicates 2 unidentifiable parameters in the model; one of them is V_2 and the other one is either k_1 or k_2.
C. Volumes V_1 and V_2 are identifiable only when compartments 1 and 2 are sampled (parameters $V_1 \quad V_2 \quad k_1 \quad k_2 \quad k_{12} \quad k_{21}$); again one of k_1 and k_2 needs to be fixed. This illustrates the importance of the relative position of sampling and administration sites for identifiability.

If one of k_1, k_2, k_{12} and k_{21} rates is nonlinear, e.g., $k_2 = \frac{\mu}{\kappa + y_2(t)}$, the model is structurally globally identifiable [4]. But when $\kappa \gg y_2(t)$, the globally identifiable model switches to unidentifiable. In a more elaborated investigation relative to case A (parameters $V_1 \quad k_1 \quad \mu \quad \kappa \quad k_{12} \quad k_{21}$), Fig. 2 illustrates the percentage of $\underline{x}_N$ leading to full rank of $\Phi(\underline{t}, \underline{x})$ as a function of the intensity of input signal $u(t)$. For low input levels, $u(t) < 10^{-4}$mg, $y_2(t)$ remains low and the peripheral elimination $k_p \approx \mu/\kappa$ becomes an unidentifiable parameter. When the input increases, k_2 becomes "more identifiable" (percentage increases) and for $u(t) > 10^4$ mg, the full rank is reached for almost all randomly selected $\underline{x}_N$.

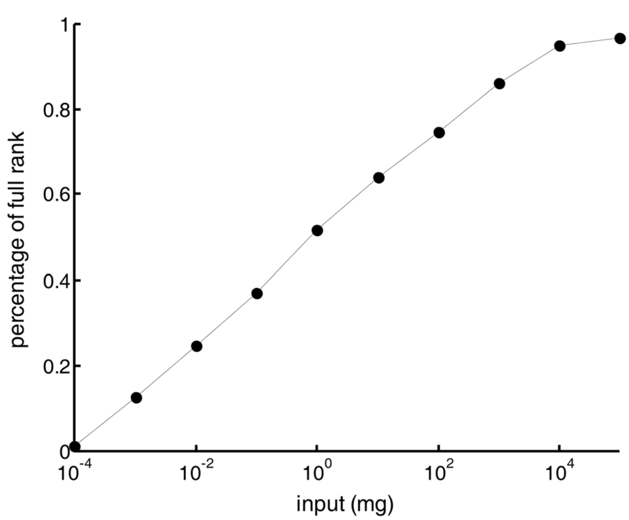

Fig. 2 Percentage of nominal values leading to full rank of sensitivity matrix as a function of the intensity of input signal

Figure 3 presents the elementary example of multi-output systems. Two differential equations describe the parent drug $y_1(t)$ and the metabolite $y_2(t)$ concentrations that are observed in compartments 1 and 2, respectively

$$\frac{dy_1(t)}{dt} = -(k_1 + k_M)y_1(t) + \frac{u(t)}{V_1} \qquad y_1(0) = 0$$
$$\frac{dy_2(t)}{dt} = k_M \frac{V_1}{V_2} y_1(t) - k_2 y_2(t) \qquad y_2(0) = 0$$

Five parameters are involved in the model, $V_1 \quad V_2 \quad k_1 \quad k_2$ and the metabolism rate k_M. Since rank[$\Phi(\underline{t}, \underline{x}_N)$] = 4 and $p = 5$, the model is unidentifiable. If one of V_2, k_1 and k_M is fixed, the derived model becomes identifiable since rank[$\Phi(\underline{t}, \underline{x}_N)$] = 4 and $p = 4$. To switch the original unidentifiable model to identifiable, either

- introduce a nonlinear metabolism rate, e.g., $k_M = \frac{\mu}{\kappa + y_1(t)}$, but with experimental conditions preventing weakness of $\kappa \gg y_1(t)$ type, or
- re-parameterize the model by introducing the fraction of drug metabolized $f_M = k_M/(k_1 + k_M)$ to obtain

$$\frac{dy_1(t)}{dt} = -k_1^* y_1(t) + \frac{u(t)}{V_1} \qquad y_1(0) = 0$$
$$\frac{dy_2(t)}{dt} = k_1^* \frac{V_1}{V_2^*} y_1(t) - k_2 y_2(t) \qquad y_2(0) = 0$$

with four parameters $V_1 \quad V_2^* = \dfrac{V_2}{f_M} \quad k_2$ and $k_1^* = \frac{k_1}{1 - f_M}$, the total elimination rate from compartment 1. In the estimation step V_2^* will be overestimated with respect to the real values.

Figure 4 illustrates the basic compartmental configuration relative to oral administration associated with bioavailability issues. Compartments 1 and 2 correspond to depot and blood compartments, respectively. It is also assumed enabling to administer and sample in both compartments. Five parameters are involved in the model: V_1, V_2 (considered when compartments 1 and 2 are sampled, respectively), k_2, the bioavailability F_a, and the absorption

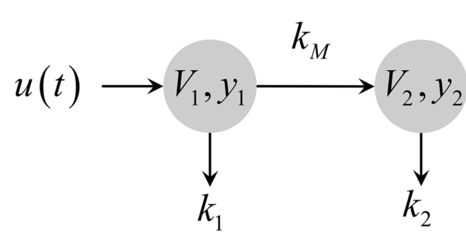

Fig. 3 Elementary example of multi-output system; compartments 1 and 2 are associated with parent drug $y_1(t)$ and metabolite $y_2(t)$ concentrations, respectively; V_1 and V_2 are volumes of distribution and, k_1 and k_2 are elimination rates associated with compartments 1 and 2, respectively; k_M is the metabolism rate; and $u(t)$ is known function describing the administration protocol

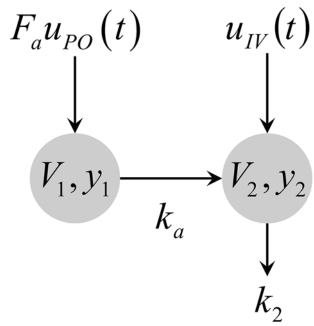

Fig. 4 Two-compartment configuration associated with the analysis of bioavailability. Compartments 1 and 2 are depot and blood compartment, respectively, with associated drug concentrations $y_1(t)$ and $y_2(t)$, and volumes of distribution V_1 and V_2. Both oral $u_{PO}(t)$ and intravenous $u_{IV}(t)$ administration routes are possible and both compartments can be sampled. F_a is the bioavailability and, k_a and k_2 are the absorption and elimination rates, respectively

rate k_a. The model is described by the following differential equations

$$\frac{dy_1(t)}{dt} = -k_a y_1(t) + \frac{F_a}{V_1} u_{PO}(t) \qquad y_1(0) = 0$$
$$\frac{dy_2(t)}{dt} = k_a \frac{V_1}{V_2} y_1(t) - k_2 y_2(t) + \frac{1}{V_2} u_{IV}(t) \qquad y_2(0) = 0$$

where $u_{PO}(t)$ and $u_{IV}(t)$ are the oral and intravenous inputs, respectively. Table 1 summarizes the analysis focused on F_a identifiability. Cases 8 and 9 involve both intravenous and oral administrations. For cases 1, 2, 3 and 9, absorption compartment is not sampled and V_1 is not involved in the model. One can note successively:

- models of cases 1 and 4 are unidentifiable because F_a, V_1 and V_2 parameters are unidentifiable.
- models of cases 2, 3, 5, 6 and 7 are identifiable. However, these cases are not interesting because F_a, V_1 and V_2 should be fixed at values not prior known.
- models of cases 8 and 9 correspond to identifiable models. Case 9 is more relevant than case 8 because it requires samples only in the blood compartment.

Therefore, the well known statement "to obtain bioavailability, sample in the blood after oral and intravenous administrations" is confirmed by checking the $\Phi(\underline{t}, \underline{x})$ rank. Therefore, it is advisable to add observables or inputs to improve identifiability.

Finally, the model presented in Appendix 2 was reported in [6] as a benchmark pharmacokinetic model and it was analyzed by the proposed tool.

Discussion

Calculating the rank of a matrix was already involved in investigations relative to identifiability. The check of $\Phi(\underline{t}, \underline{x})$ rank was first reported by Rothenberg [9], it was clearly formulated by Dotsch et al. [13] for engineering applications, it was proposed in a probabilistic semi-numerical approach by Karlsson et al. [14] for testing local identifiability. Alternatively, checking the structural identifiability by means of the FIM determinant was also employed [2, 15–17]. However, the approaches are not equivalent from a numerical analysis point of view. In fact, calculating the rank is more reliable than checking the closeness of the determinant to zero [18]. Therefore, checking structural identifiability by means of $\Phi(\underline{t}, \underline{x})$ rank should be favoured over the FIM determinant calculation.

Table 1 Identifiability analysis of bioavailability

No.	Admin IV	Sample 1	p	rank[$\Phi(\underline{t}, \underline{x})$]	Rank after removing one of				
					F_a	V_1	V_2	k_a	k_2
1	×	×	4	3	3	×	3	2	2
2	×	×	3	3	2	×	•	2	2
3	×	×	3	3	•	×	2	2	2
4	×	✔	5	4	4	4	4	3	3
5	×	✔	4	4	•	3	3	3	3
6	×	✔	4	4	3	•	3	3	3
7	×	✔	4	4	3	3	•	3	3
8	✔	✔	5	5	4	4	4	4	4
9	✔	×	4	4	3	×	3	3	3

Successive columns indicate the experimental conditions, the number of parameters in the model, the rank of sensitivity matrix of the model, and the rank of sensitivity matrix of models obtained after fixing one parameter in the initial model

×: absence of the feature in experimental conditions and absence of parameter in the model; ✔: presence of the feature in experimental conditions; •: fixed parameter in the model

In an integrated approach, the subset selection algorithm proposed by Cintron-Arias et al. [8] first selects parameters according to the $\Phi(\underline{t}, \underline{x})$ rank to ensure non-singularity of FIM, and second computes its inverse for the calculation of the standard errors and confidence intervals. Finally, by analyzing the $\Phi(\underline{t}, \underline{x})$ rank deficiency in nonlinear models, Chappell et al. [19] proposed adequate re-parameterizations to obtain locally identifiable models.

Our motivation was to remind the appropriate, reliable and simple use of $\Phi(\underline{t}, \underline{x})$, as a tool for checking local identifiability for a large spectrum of designed pharmacokinetic models with the extension to multi-output context and the detection of unidentifiable parameters.

While structural identifiability is a theoretical property of the postulated model structure given a set of inputs and outputs, parametric identifiability is intrinsically related to experimental data, experimental design and errors. Structural identifiability is checked by means of the $\Phi(\underline{t}, \underline{x})$ rank and parametric identifiability depends on $I(\underline{t}, \underline{x})$ involving $\Phi(\underline{t}, \underline{x})$ and $D(\underline{t}, \underline{x})$ elements in the relationship (2). $\Phi(\underline{t}, \underline{x})$ expresses the sensitivity of model outputs and $D(\underline{t}, \underline{x})$ expresses the observation error variance model and its sensitivity. This sharing was expected because structural identifiability is relative to model structural characteristics by means of $\Phi(\underline{t}, \underline{x})$ and does not depend on the experimental process involved in $D(\underline{t}, \underline{x})$. Relationship (10) in Appendix 1 is the definition of $D(\underline{t}, \underline{x})$ for a variance model of power-law type given by the relationship (9). From these relationships, heteroscedastic, homoscedastic and other type of errors can be derived according to the values given in the exponent α.

While $D(\underline{t}, \underline{x})$ does not impact structural identifiability, it plays an important role in designing optimal experiments by enhancing performances related to parametric identifiability [20–23]. According to a geometric interpretation, optimization of experiments should lead to closed ellipsoid contours (FIM non-singular), ellipsoids with the smaller possible volume (the most precise estimates) and condition number close to unit (equally distributed reliability in all parameters). These conditions could be met by selecting adequate observation time interval, adequate position of administration and sampling sites, adequate position of sampling times, the quality of observation error, etc. For instance, to minimize the volume of ellipsoids given by the relationship (4), det $[I(\underline{t}, \underline{x})]$ should be maximized; according to the relationship (3), this leads to maximum available amount of information for estimation purposes of $\underline{x}$.

From the presented examples, it is clear that identifiability strongly depends on the relative position of administration and sampling sites for compartmental configurations or generally, on the relative position of inputs and outputs in differential equations describing the model. Thus to check identifiability, much attention was initially focused on linear system and control theory with investigation of observability and controllability conditions [2, 15, 24].

One might conjecture that the presence of nonlinear elements forces an unidentifiable structure to become identifiable. Nevertheless, nonlinear elements may cause ill-conditioned issues affecting the calculation of the matrix rank by singular value decomposition. Accordingly, conclusions relative to identifiability may depend on the input signal as illustrated in Fig. 2. When inputs are not exciting enough ($u(t) < 10^{-4}$ mg), nonlinearities are smoothed, the model becomes quasi-linear, and it has more chances to switch to unidentifiable. When inputs are exciting enough ($u(t) > 10^{4}$mg), the local identifiability check confirms the global identifiability of the model. Between the above limits, ill-conditioned issues occur, strong and weak at the low and high exciting inputs, respectively. For the parameter estimation step, the question turns in a parametric identifiability problem: determining the more informative inputs.

The benchmark pharmacokinetic model is identifiable as also reported by Chis et al. [6]. Nevertheless, parameters k_a and k_c involved in the nonlinear sigmoid terms induce ill-conditioned issues. As discussed above, the initial conditions (here playing the role of inputs) should be exciting enough to prevent situations of $k_c k_a \gg k_c y_3(t) + k_a y_1(t)$ type. However, the problem is hard to solve because of the simultaneous presence of $y_1(t)$ and $y_3(t)$ in the denominator of the nonlinear term.

From an identifiability analysis, more general conclusions can be drawn since in such as analyses, unidentifiable parameters could be revealed allowing for suggestions of re-parameterization or/and of the addition of observables or/and new inputs to improve identifiability.

Along the estimation process, sensitivity functions are the only tool allowing the link between the state space (where the system outputs evolve) and the parameter space (where the estimation–minimization process seeks for a representative point of the real system). A comprehensive review was presented by Hamby of more than a dozen sensitivity analysis methods [25]. Already, the linear independence of sensitivity matrix columns was reported in the optimization context as the key element impacting the algorithm convergence [26].

In pharmacokinetics, elementary considerations for identifiability were presented by Bonate [27]. Yates et al. [28] analyzed the identifiability of linear physiologically based pharmacokinetic models by using the transfer matrix approach. The same author presented the general context of model identifiability and distinguishability for compartmental configurations [29]. In target mediated drug disposition models, the receptor binding model is usually approximated by a quasi- or pseudo-steady state approximation [30]. However, when using such an approximation, it has been shown that the on and off rates of drug binding to the receptor are unidentifiable [31]. Janzen et al. [32] commented identifiability of pharmacodynamic models by using the input–output approach [33], a variant of implicit function theorem, and expanded identifiability analysis even in population pharmacokinetic–pharmacodynamic pharmaco-statistical models. Shivva et al. [16, 17] investigated graphically the determinant of FIM to analyze structural identifiability issues for nonlinear fixed and mixed effects models. The basic idea is to smooth within FIM the contribution of the residual error variance, so that the shape of the obtained graphics informs about properties of the remaining Jacobian–sensitivity matrix. Therefore, the graphics criterion of Shivva et al. (Eq. 5) is conceptually equivalent but numerically different to the check of $\Phi(\underline{t}, \underline{x})$ rank here presented.

Conclusion

Since the model is the kernel tool to obtain information from a set of measurements, its identifiability must be systematically checked for individual and population pharmacokinetic–pharmacodynamic analyses. The tool presented here applies indistinguishably for linear or nonlinear models with time-invariant or -varying parameters and even parameters involved in initial conditions of differential equations. It explores the rank of sensitivity matrix obtained without any approximation (i.e., series expansion, finite difference approximation, computing high order derivatives of the output, rewriting the model in polynomial form, etc.). Associated with multiple random drawn of parameters used as nominal values, the approach reinforces conclusions regarding the local identifiability of models. Conversely, the only weakness of the tool is its disability to discern between global identifiability (i.e., one solution) and local identifiability (i.e., finite number of solutions). Since identifiability is disconnected from experimental process, much of the material presented here is extensible to other error variance models and other estimation criteria than the maximum likelihood. The approach can be applied not only in pharmacokinetics and pharmacodynamics but also for all models aiming at describing the behavior of a real process.

Local and global identifiability of model structures are strongly connected properties. Actually, global identifiability implies local identifiability and local identifiability is a necessary condition for global identifiability. Structural local identifiability bridges theoretical structural global identifiability and practical parametric identifiability in the sense that it alerts for possible ill-conditioning before the estimation step. Structural identifiability, parameter identifiability and optimal sampling design should go together as linked steps in the parameter estimation inverse problem.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Appendix 1

Hypotheses

Observations on the system consist in measurements y_i from m samples drawn at t_i times, $i = 1{:}m$. Vectors $\underline{y}$ and $\underline{t}$ compile the above y_i, and t_i, respectively. The ultimate goal is to fit these data by a model involving p parameters x_j, $j = 1{:}p$, by maximizing the likelihood function $L(\underline{x}/\underline{y})$, where $\underline{x}$ is the vector collection of x_j. The fundamental assumption is $m > p$.

Three working hypotheses are commonly introduced:

1. Measurements y_i are considered random, obtained by adding the observation error e_i to the model output $y(t_i, \underline{x})$, i.e., $y_i = y(t_i, \underline{x}) + e_i$.
2. The error e_i follows the normal distribution $e_i \sim N(0, \sigma_i^2)$ with zero mean and variance σ_i^2. Then, the random y_i is distributed according to $y_i \sim N[y(t_i, \underline{x}), \sigma_i^2]$. Also, the reduced observation error
$$\varepsilon_i(t_i, \underline{x}) = \frac{y_i - y(t_i, \underline{x})}{\sigma_i}$$
follows the standard normal distribution, i.e., $\varepsilon_i(t_i, \underline{x}) \sim N(0, 1)$.
3. Observation errors are independent for different samples, i.e., $E[\varepsilon_i \varepsilon_j] = 0$ for $i \neq j$ (whereas $E[\varepsilon_i^2] = 1$).

Likelihood and sensitivity

Under the above conditions, the negative log likelihood to be minimized is

$$-\ln L\left(\underline{x}/\underline{y}\right) = \frac{1}{2}\sum_{i=1}^{m} \ln\left(2\pi\sigma_i^2\right) + \frac{1}{2}\sum_{i=1}^{m} \varepsilon_i^2$$

with derivative with respect to a given model parameter x_j

$$-\frac{\partial \ln L\left(\underline{x}/\underline{y}\right)}{\partial x_j} = \sum_{i=1}^{m} \frac{1}{\sigma_i}\frac{\partial \sigma_i}{\partial x_j} + \sum_{i=1}^{m} \frac{1}{\varepsilon_i}\frac{\partial \varepsilon_i}{\partial x_j} = \sum_{i=1}^{m} \left(1 - \varepsilon_i^2\right)\frac{1}{\sigma_i}\frac{\partial \sigma_i}{\partial x_j} - \sum_{i=1}^{m} \varepsilon_i \frac{1}{\sigma_i}\frac{\partial y(t_i, \underline{x})}{\partial x_j}. \tag{5}$$

The sensitivity of the variance model σ_i is

$$\rho_{ij} = \frac{\partial \sigma_i}{\partial x_j} \quad (6)$$

and the sensitivity of the model output $y(t_i, \underline{x})$ at time t_i and with respect to the parameter x_j is

$$\varphi_{ij} = \frac{\partial y(t_i, \underline{x})}{\partial x_j}. \quad (7)$$

They are compiled in vector forms

$$\underline{\rho}_j = [\rho_{1j} \quad \cdots \quad \rho_{mj}]^{\mathrm{T}} \text{ and } \underline{\varphi}_j = [\varphi_{1j} \quad \cdots \quad \varphi_{mj}]^{\mathrm{T}}.$$

The error ε components in relationship (5) are also presented in vector form

$$\underline{w} = \begin{bmatrix} 1-\varepsilon_1^2 & \cdots & 1-\varepsilon_m^2 \end{bmatrix}^{\mathrm{T}} \text{ and } \underline{z} = \begin{bmatrix} 1-\varepsilon_1 & \cdots & 1-\varepsilon_m \end{bmatrix}^{\mathrm{T}}$$

to obtain the final form of the above derivative (5)

$$-\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_j} = \underline{w}^{\mathrm{T}} \Sigma^{-1/2} \underline{\rho}_j - \underline{z}^{\mathrm{T}} \Sigma^{-1/2} \underline{\varphi}_j,$$

where Σ is a m-order diagonal matrix with elements σ_i^2.

A similar derivative of ln $L(\underline{x}/\underline{y})$ with respect to another parameter x_k is considered and the expectation of the above derivatives product is

$$\begin{aligned} &\mathrm{E}\left[\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_j}\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_k}\right] \\ &= \underline{\rho}_j^{\mathrm{T}} \Sigma^{-1/2} \mathrm{E}[\underline{w}\underline{w}^{\mathrm{T}}] \Sigma^{-1/2} \underline{\rho}_k - \varphi_j^{\mathrm{T}} \Sigma^{-1/2} \mathrm{E}[\underline{z}\underline{w}^{\mathrm{T}}] \Sigma^{-1/2} \underline{\rho}_k \\ &- \underline{\rho}_j^{\mathrm{T}} \Sigma^{-1/2} \mathrm{E}[\underline{w}\underline{z}^{\mathrm{T}}] \Sigma^{-1/2} \underline{\varphi}_k + \varphi_j^{\mathrm{T}} \Sigma^{-1/2} \mathrm{E}[\underline{z}\underline{z}^{\mathrm{T}}] \Sigma^{-1/2} \underline{\varphi}_k. \end{aligned}$$

According to the rules of moments for a multivariate normal distribution [34]

$$\mathrm{E}[\underline{w}\underline{w}^{\mathrm{T}}] = 2I \quad \mathrm{E}[\underline{z}\underline{w}^{\mathrm{T}}] = \mathrm{E}[\underline{w}\underline{z}^{\mathrm{T}}] = 0 \quad \mathrm{E}[\underline{z}\underline{z}^{\mathrm{T}}] = I,$$

the previous expression becomes

$$\mathrm{E}\left[\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_j}\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_k}\right] = 2\underline{\rho}_j^{\mathrm{T}} \Sigma^{-1} \underline{\rho}_k + \underline{\varphi}_j^{\mathrm{T}} \Sigma^{-1} \underline{\varphi}_k. \quad (8)$$

Error variance model

To weight observations, the error variance model

$$\sigma = K y^a(t, \underline{x}) \quad (9)$$

is commonly used. Because it involves model outputs $y(t_i, \underline{x})$, σ depend on model parameters $\underline{x}$ and the presence of the sensitivities of the variance model ρ_{ij} is justified in relationship (8). Given the model (9) and definition (7), the sensitivity of the variance model (6) becomes

$$\rho_{ij} = Kay^{a-1}(t_i, \underline{x}) \frac{\partial y(t_i, \underline{x})}{\partial x_j} = a \frac{\sigma_i}{y(t_i, \underline{x})} \varphi_{ij}$$

or $\underline{\rho}_j = a\Sigma^{1/2} Y^{-1} \underline{\varphi}_j$ and alternatively $\underline{\rho}_k = a\Sigma^{1/2} Y^{-1} \underline{\varphi}_k$ with Y the diagonal m-order matrix with elements $y(t_i, \underline{x})$.

Accordingly, the final form of relationship (8) is

$$\begin{aligned} \mathrm{E}\left[\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_j}\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial x_k}\right] &= \varphi_j^{\mathrm{T}} [2a^2 Y^{-2} + \Sigma^{-1}] \underline{\varphi}_k \\ &= \varphi_j^{\mathrm{T}} D \underline{\varphi}_k \end{aligned}$$

with

$$D \triangleq 2a^2 Y^{-2} + \Sigma^{-1}. \quad (10)$$

By expanding the above relationship for j, $k = 1{:}p$,

$$\mathrm{E}\left[\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial \underline{x}}\frac{\partial \ln L(\underline{x}/\underline{y})}{\partial \underline{x}^{\mathrm{T}}}\right] = \Phi^{\mathrm{T}}(\underline{t}, \underline{x}) D(\underline{t}, \underline{x})\, \Phi(\underline{t}, \underline{x})$$

where elements φ_{ij} are compiled in the $\Phi(\underline{t}, \underline{x})$ $m \times p$ sensitivity matrix of model outputs at $\underline{t}$ with respect to the model parameters $\underline{x}$. Again, $D(\underline{t}, \underline{x})$ is a m-order positive definite matrix depending on model output matrix Y and on variance model of observation error matrix Σ.

Appendix 2

The benchmark pharmacokinetic model [35] is described by the set of ordinary differential equations

$$\begin{aligned} \frac{dy_1(t)}{dt} &= \alpha_1[y_2(t) - y_1(t)] - \frac{k_a V_m y_1(t)}{k_c k_a + k_c y_3(t) + k_a y_1(t)} & y_1(0) &= C_0 \\ \frac{dy_2(t)}{dt} &= \alpha_2[y_1(t) - y_2(t)] & y_2(0) &= 0 \\ \frac{dy_3(t)}{dt} &= \beta_1[y_4(t) - y_3(t)] - \frac{k_c V_m y_3(t)}{k_c k_a + k_c y_3(t) + k_a y_1(t)} & y_3(0) &= \gamma C_0 \\ \frac{dy_4(t)}{dt} &= \beta_2[y_3(t) - y_4(t)] & y_2(0) &= 0 \end{aligned}$$

involving nine parameters presented below with their associated domains of definition

$$\begin{aligned} 10^{-2} &\le \alpha_1 \le 10 \\ 10^{-2} &\le \alpha_2 \le 10 \\ 10^{-2} &\le \beta_1 \le 10 \\ 10^{-2} &\le \beta_2 \le 10 \\ 10^{-2} &\le k_a \le 10 \\ 10^{-2} &\le k_c \le 10 \\ 10 &\le V_m \le 10^3 \\ 100 &\le C_0 \le 10^4 \\ 0.1 &\le \gamma \le 10 \end{aligned}$$

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