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Structural Identifiability of Parallel Pharmacokinetic Experiments as Constrained Systems

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Introduction

Pharmacokinetics (PK) is the study of the absorption, distribution, metabolism and elimination of a therapeutic agent in the body. There are a number of 'classical' compartmental models used for such purposes, however the complexity of its structure can result in problems for parameter estimation. Results obtained from parallel experiments show improvement of parameter estimation, and hence we propose a new methodology to construct such parallel experiments in the context of structural identifiably analysis to validate these parameter estimation phenomena.

Structural Identifiability Analysis

For a parameter vector p that parameterises a linear compartmental system:

$$\begin{aligned} \dot{x}(t,p) &= A(p)\cdot x(t,p) + B(p)\cdot u(t,p) \;; \quad \text{for} \quad (t \geq 0), \\ x(0,p) &= x_0(p) \;; \\ y(t,p) &= C(p)\cdot x(t,p) \;; \quad \text{for} \quad (p = p_1,\ldots,p_q), \end{aligned} \qquad (1)$$

x : amount of drug; y : observed drug concentration; u(t): input to the system; A, B, and C : matrices that are dependent on the parameter vector p.

As a structural property, a model is structurally globally(locally) identifiable if all parameter vectors *p* are uniquely (locally) identifiable.

Similarity transformation approach: for two linear system (A,B,C) and $(\tilde{A},\tilde{B},\tilde{C})$. If the following conditions are satisfied then the systems have equivalent input-output behaviour.

1. The two systems are structurally observable.
2. The two systems are structurally controllable.
3. There exists a non-singular matrix *T* such that the systems are similar:

$$A = T^{-1}\tilde{A}T, \quad B = T^{-1}\tilde{B}, \quad C = \tilde{C}T \qquad (2)$$

Constrained Structures

The concept of a parallel experiment is formulated with the assumption that some of its rate constants change between experiments. For a single PK model of the form (1) represented by the triple $(A(p),B(p),C(p))$, the parallel experiment structure representing *n* experiments and parameterised by P' may be represented by the triple , $(A'(p'),B'(p'),C'(p'))$

where:

$$A'(p') = \begin{bmatrix} A(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & A(E^n(p')) \end{bmatrix} \quad B'(p') = \begin{bmatrix} B(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & B(E^n(p')) \end{bmatrix} \quad C'(p') = \begin{bmatrix} C(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & C(E^n(p')) \end{bmatrix}$$

Here $E^i : P' \to P$ for $i = 1\ldots n$ is a map between the constrained parallel experiment parameters and the individual model parameters.

Notice that $dimension(P') < n \cdot dimension(P)$ which is as a result of the constraints.

The function *E* represents the ***a priori*** assumptions of common and changing parameter values. Notice that if (A,B,C) is controllable and observable then $(A'(p'),B'(p'),C'(p'))$ is controllable and observable. The parallel experiment structure is now of the form (1) and may be analysed using criteria (2)

Three Case Studies and Results

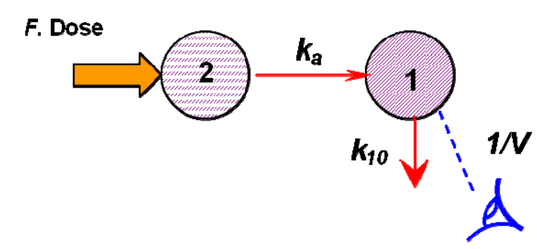
Single experiment identifiability analysis

One-compartment model with 1st order absorption. This model represents the one compartment distribution of a compound after absorption from the gut.

- For a given $p = (F, V, k_a, k_{10})$ an infinite number of possible matries *T* of the form

$$T = F/\tilde{F}\begin{bmatrix} k_a/k_{10} & 0 \\ k_{10} - k_a/k_{10} & 1 \end{bmatrix}$$

- The model is thus locally identifiable with two solutions: $(V/F, k_a, k_{10})$ and $(Vk_{10}/Fk_a, k_{10}, k_a)$

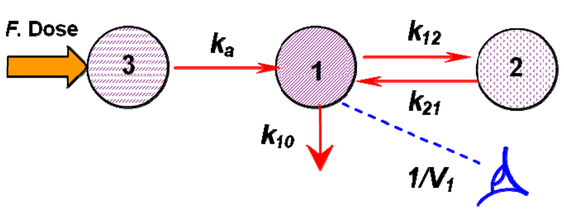


'Classical' two compartments PK model with a third compartment representing the absorption of an orally administrated dose.

-For a given $p = (F, V_1, k_a, k_{12}, k_{21}, k_{10})$, such models have tri-exponential impulse (bolus dose) response.

-A structural identifiability analysis [6] demonstrates that there are 3 equivalent solutions and thus the model is locally identifiable.

-This is by again considering *V/F* as a parameter.



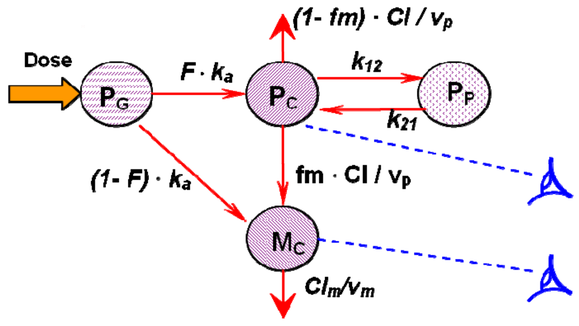
This is a 4 compartments parent-metabolite model used to model the PK of dextromethorphan and dextrophan.

- The parameterisation of the model is

$$p = (V_m, V_p, Cl_m, k_{12}, k_{21}, k_a, f_m, Cl, F)$$

- The model is found to be unidentifiable.
- The identifiable parameter combinations are:

$$p_{new} = \left(\frac{V_m}{1-F}, \frac{V_p}{F}, \frac{Cl_m}{V_m}, \frac{Cl}{V_p}, \frac{Ff_m}{1-F}, k_{12}, k_{21}, k_a\right)$$



Parallel experiments (different formulation) identifiability analysis

The same drug is dosed orally using two different formulations. It can be assumed that the body pharmacokinetic parameters *V* and k10 are constant between the two experiments, but that the bioavailability *F* and absorption rate *ka* will vary: $p' = (V, k_{10}, k_a^1, k_a^2, F^1, F^2)$

- The new structure yields the matrix *T* of the form $T = F/\tilde{F}\cdot I_4$
- This means that the parameterisation p' is unidentifiable. However the uniquely identifiable parameter combinations are $(V/F^1, V/F^2, k_a^1, k_a^2, k_{10})$
- Thus the local identifiable indeterminacy between the absorption rate constant and the rate of elimination has been eliminated.

The same compound is dosed orally on two separate occasions where the formulation is different.

- A new parameterisation will be formed: $p' = (V_1, k_{12}, k_{21}, k_{10}, k_a^1, k_a^2, F^1, F^2)$
- An analysis of this proposed parallel experiment shows that the disposition parameters k_{12} , k_{21} and k_{10} are globally identifiable, as are the two absorption rate k_a^1 and k_a^2 .
- The two combination parameters V_1/F^1 and V_1/F^2 are also shown to be globally identifiable.

The oral dose administration regimen was divided into two parts

1. DEX (30mg), quinidine placebo administrated at 1 hour.
2. DEX (30mg), quinidine sulphate 50mg anteceded at 1 hour.

- Constraint placed is that the parameters will remain constant for the 2 experiments except for those influenced by quinidine.
- This parallel structure with such parameterisation is then globally structurally identifiable.

Placebo		Quinidine
E_H	→	E_H`
$Cl = (Q_H \cdot E_H)$	→	Cl`
$F = (1 - E_H)$	→	F`
$f_m = (Cl_m/(Cl_m + Cl_R))$	→	f_m`

$$p' = (V_m, V_p, Cl_m, k_{12}, k_{21}, k_a, f_m^1, f_m^2, Cl^1, Cl^2, F^1, F^2)$$

Conclusion

A preliminary formulation has been presented that places the concept of a parallel experiment in the context of a single constrained model structure. Three case studies have been examined in order to illustrate the constrained model concept. The parallel experimental design has been shown to be beneficial with regards to structural identifiability. Multiple experiments will also be beneficial from a system identification point of view. Incorporation of prior knowledge into parallel experiment model structures with constrained parameterisation allows sufficient information to be present in the input-output behaviour to give unique parameter estimates. The results show that the parallel experiment strategies can be very powerful in providing globally structurally identifiable PK models.

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