A PRIORI IDENTIFIABILITY ANALYSIS IN PHARMACOKINETIC EXPERIMENT DESIGN

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ABSTRACT

Mathematical modelling and dynamic identification experiments are increasingly employed in quantitative pharmacokinetic studies. This paper addresses the so-called identifiability problem which has to be faced \textit{a priori}, \textit{i.e.}, once a certain pharmacokinetic model structure has been postulated and the input-output experiment planned, but prior to its performing. More precisely, identifiability analysis addresses the question of whether it is possible to obtain solutions for the unknown parameters of the chosen model structure from data collected \textit{via} those input-output tests which can be carried out. The prerequisite value of identifiability analysis for the design of a well-posed pharmacokinetic experiment is emphasized. A precise set of identifiability definitions are given with reference to a general pharmacokinetic experiment design model. Three classes of pharmacokinetic models are discussed in some detail, namely the nonlinear saturable models, the linear or linearizable models and the linear compartmental models. Available methods for testing in practice identifiability for these three classes of experiment design models are reviewed, compared and exemplified. Connections between the identifiability property of a given model and the possibility of reconstructing/predicting system variables of interest not directly accessible to measurement, which is one of the purposes for which pharmacokinetic models are often built, are stressed.

1. INTRODUCTION

Mathematical models are increasingly employed in pharmacokinetic studies both at the organ and whole-organism level with the
purpose of evaluating parameters not directly accessible to measure-
ments relating to the uptake, distribution and elimination of a drug, and of predicting its time courses and levels in non-accessible
sites (1,2). For this kind of models, in contrast to the so-called
dose-response models, usually one or more physiologically isomorphic
structures are, at least tentatively, postulated which try to re-
flect through the incorporation of all available a priori knowledge
of the system, consistent with purpose and level of the study, the
various biochemical processes explicitly, i.e., in a parametric
form. In this context, lumped-parameter dynamic models, that is
models described by ordinary linear and nonlinear differential equa-
tions, are widely employed in pharmacokinetic studies and will be
considered in this paper.

However, it is worth noting that under certain circumstances,
a lumped-parameter model may not be adequate, for instance, if the
assumptions of homogeneous distribution or perfect mixing are not
valid. In these cases, therefore, distributed models should be
considered [see (3) for recent examples of lumped vs. distributed
pharmacokinetic modelling approaches].

The type of models we shall deal with may be easily grasped
by looking at Figure 1 where some hypothetical pharmacokinetic model
structures are diagrammed. Once, for a given system, one or more
well-posed model structures have been, at least tentatively, postu-
lated on the basis of validated a priori knowledge, and thus the
set of unknown parameters of the interest has been clearly deline-
ated (e.g., \( V_1, k_{12}, k_{21}, k_{o1}, k_{o2} \) in the example of Figure 1a;
\( V_1, k_{12}, k_{o1}, V_m, K_m \) in the system of Figure 1b), the input-output
identification experiment has to be designed. The following prob-
lems/questions are relevant for obtaining accurate estimates for
parameters of interest:

1. Which are the accessible input ports into which test-input
signals can be introduced, and which are the accessible output ports
from which output signals can be measured? For example, if the
three models of Figure 1 refer to an intact organism study, it could
happen that in cases a, b and c, only 1 is accessible for the input-
output experiment (e.g., an intravenous injection of a drug dose and
the measurement of the plasma concentration), and that in case d,
whilst pools 1 and 3 are both accessible for a test input (e.g.,
oral and intravenous doses, respectively), only pool 3 is accessible
for output measurement.

2. Which inputs ports must be probed and what types of test-input
signals should be employed (e.g., pulse dose or an infusion)?

3. Which output ports must be measured, how long and at which times
should the samples be collected and with what error?