

# STRUCTURAL IDENTIFIABILITY ANALYSIS OF SOME SEMI-PHYSIOLOGICALLY BASED AND WHOLE BODY PHYSIOLOGICAL BASED (WBPBPK) PHARMACOKINETIC MODELS

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## Introduction

- § Structural identifiability analysis (SIA) [1] is a prerequisite for population PK/PD experimental design and modelling.
- § SIA should be performed prior to the planned experiment to identify whether the internal structure (assumed unknown pathways and parameter values) can be uniquely determined by the input-output experiment.
- § **A uniquely globally identifiable model** means a unique set of parameter values can be determined by the experiment.
- § **A locally identifiable model:** there exists a finite set of distinct parameter values, which produce the same output.
- § **An unidentifiable model:** there exists an infinite set of parameter values, which produce the same observed behaviour.
- § SIA was applied to the two linear PK models.

## Methods

- § The similarity transformation approach [2] was used for the structural identifiability analysis.
- § Any linear compartmental models may be written in the form:
 
$$\dot{x} = Ax + Bu$$

$$y = Cx$$
 where  $A$  is the compartmental matrix;  $B$  is the input matrix and  $C$  is the observation matrix.
- § Provided the models are both controllable and observable [2], the similarity transformation approach can be applied.
- § The aim of the STA is to generate another model ( $\tilde{A}$ ,  $\tilde{B}$ ,  $\tilde{C}$ ) which gives the same dose-response relationship through a non-singular matrix  $T$ .

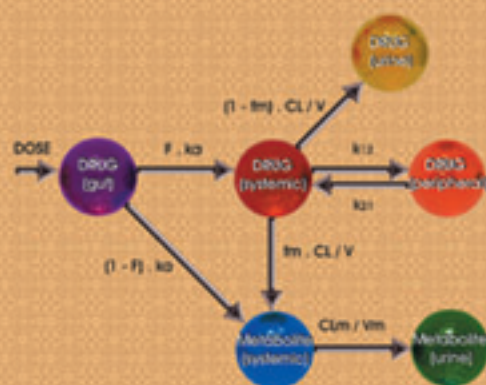
$$A = T^{-1} \tilde{A} T$$

$$B = T^{-1} \tilde{B}$$

$$C = \tilde{C} T$$

- § Only if  $T=I_n$ , the model is globally identifiable.
- § The analysis was performed using the symbolic computation software, Mathematica (WOLFRAM Research) [3].

## Semi-PBPK Drug-Metabolite Model of Dextromethorphan (DEX) & Dextrophan (DOR)



## Model Description

- § Describes the pharmacokinetics of dextromethorphan (DEX) [4] and its major metabolite dextrophan (DOR) following an oral dose administration.
- § Two compartment kinetics assumed for DEX and one compartment for DOR.
- § Elimination occurs by both metabolic and non-metabolic routes.
- § First pass kinetics incorporated by connecting the dose compartment to the metabolite systemic compartment and  $F$  as well as the parent drug systemic compartment.
- § Observations of renal elimination considered.

## Identifiability results

- § The model with no extra renal compartments added is unidentifiable.
- § Model with urine compartment added for the parent drug systemic compartment is globally uniquely identifiable. This model has 1 input and 3 observations of the parent drug systemic, metabolite systemic and drug urine compartments.
- § The model is also found to be globally uniquely identifiable when a urine compartment was added to the metabolite systemic compartment. This model also has 1 input and 3 observations.

## Whole Body-PBPK Model of Diazepam



## Model Description

- § Describes the diazepam kinetics [5] in blood and tissues, following i.v. infusion administration to rats. There are 12 tissue compartments and 2 blood compartments.
- § Incorporates prior knowledge such as tissue volumes and blood flow rates from physiological data.
- § Represents parallel closed loop circulation of blood around the body.
- § The tissue-to-blood partition coefficients ( $K_p$ s) and intrinsic clearance ( $CL_{int}$ ) are estimated through rat's WBPBPK.
- § Drug concentration level observed in 12 compartments: LI, KI, BR, SPL, ST, MU, AD, SK, TE, HT, LU and ART.

## Identifiability results

Both models, with  $K_p$ s only as free parameters and  $K_p$ s and  $CL_{int}$  as free parameters, were found to be globally uniquely identifiable. These two models have one input to the blood compartment, one blood and 11 tissues from which observations are made.

## Conclusions

The prior consideration of the structural identifiability is an important part of PK/PD experiment design that leads to an understanding of the relationship between the observed drug concentration profiles and the internal structure of the proposed model. This allows examination of the proposed model and assumptions before any actual experiment is carried out.

## Reference

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## Acknowledgement

We acknowledge Professor Keith Godfrey, Dr Neil Evans and Dr Mike Chappell from the Simulation and Modelling Group, University of Warwick for their invaluable opinions and Amin Rostami from the University of Sheffield for discussions of the drug-metabolite model.