Sujet de stage – M2

Extending saemixPBPK to multiple responses to estimate CYP3A4-related PBPK parameters

Mots-clés : Pharmacométrie, Pharmacocinétique, Modélisation, Modèles non-linéaires à effets mixtes, Parameter estimation, R programming, Physiologically Based Pharmacokinetics Modeling, SAEM algorithm

Durée du stage : 6 mois

Début du stage souhaité : Mars 2025

Diplôme préparé : Master – Diplôme d'ingénieur

Formation recommandée : Bac+4, expertise en biostatistiques ou biomathématiques, pharmacologie (Ecole d'ingénieur, M1)

Possibilité de poursuivre en thèse : Oui

Localisation du stage : Sanofi (Vitry-sur-Seine) & INSERM (Faculté de Médecine Bichat-Claude Bernard, Paris)

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Background :

Physiologically Based Pharmacokinetic (PBPK) modelling is a powerful tool in drug development since it allows the integration of drug specific information as well as physiological relevant parameters to predict drug concentrations [Kuepfer et al. 2016]. One of the major limitations of this approach is to rely on average concentrations; when individual data are available, they are usually treated as naïve pooled approach without any consideration of individual information. As consequence, when these models are used for simulation, usually only the a priori known variability (e.g. physiological variability) is considered, while for unknown variability (e.g. intrinsic clearance, dissolution, and transit times) an arbitrarily chosen variability is often integrated in the simulation. Open System Pharmacology (OSP) Suite [Lippert et al. 2016] is a fully developed open source PBPK platform that integrate a whole-body PBPK model allowing full flexibility to modify and manipulate such model via scripting languages in R . The R package saemixPBPK [Teutonico et al. 2024] is an R package that allows the connection between the PBPK models developed with the OSP Suite and the R package saemix [Comets et al. 2017] allowing the estimation of population parameter values and variability coupling nonlinear mixed-effects modeling with a whole-body PBPK model.

Objectives :

The objective of this project is to expand the functionalities of the package saemixPBPK as well as to explore the application of this methodology in classical PBPK modeling applications.

Internship :

We will use the data from the case-study presented in [Teutonico et al. 2024], where a PBPK model for a drug with good oral absorption (capsule formulation) and a clearance partly attributed to CYP3A4, a cytochrome involved in the metabolism of many drugs, was developed using Phase 1 data after single and repeated dosing. Data from a drug-drug interaction study using itraconazole (8 subjects) were used to estimate in vivo CYP3A4 Fm (metabolisation fraction) based on the new proposed hybrid approach coupling the PBPK model with a population approach. In that work, itraconazole clearance and variability as well as a population estimate of the capsule dissolution time for itraconazole were estimated, comparing two mechanistic hypotheses on the source of the observed variability. In this project, we will integrate the data for hydroxy-itraconazole (also metabolized via CYP3A4) collected in the study in order to identify the two processes. As final results three parameters will be estimated: CYP3A4 abundance, Itraconazole intrinsic clearance and hydroxy-itraconazole intrinsic clearance. The data used will be the plasma concentrations of itraconazole and its metabolite and the model used will be the itraconazole model available in the library of PK-Sim, which already integrates the two molecules.

Required skills

- An interest for modelling in biology or healthy science
- Competency with statistical software R
- Autonomy, creativity
- Ability to write and communicate in English

Bibliography

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Kuepfer L., et al. (2016). Applied concepts in PBPK modeling: how to Build a PBPK/PD Model. *CPT Pharmacometrics Syst Pharmacol.*

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