PBPK versus PK modeling of Tacrolimus drug in patients with renal transplant as knowledge engines for personalized posology software: PhysPK® development and preliminary results

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PhysPK

EMPRESARIOS AGRUPADOS

Objectives and introduction

There are hardly customized posology programs that can be used in clinical scenarios to optimize and monitor doses and administration times of drugs for patients with special requirements. However, PK / PD models have shown success in monitoring and description of distribution and elimination of drugs in clinical trials during drug development, as well as to quantify therapeutic effects. More recently, the addition of physiological knowledge by means of PBPK models is showing the ability to detect drug-drug interactions (DDI) and the influence of different pathologies in the therapeutic and adverse effect of drugs, thanks to their better predictive capability.

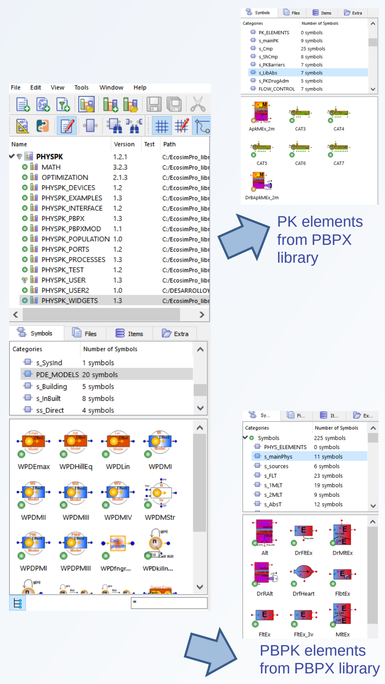
The success of pharmacokinetic and physiological modelling and simulation in drug discovery is pushing the definition of updated guidelines and recommendations to use this methodology for improving drug security and efficacy in this area.

However, there are not widely accepted software systems that facilitate the translation of the knowledge implicit in PK/ PBPK / PD models to clinical praxis.

This work is a preliminary study that addresses this lack with a proof of concept. We have developed a personalized posology software for Tacrolimus immunosuppresor drug, using a new M&S advanced software, PhysPK®. The study shows briefly a seamless process, that starts from the building of the PK and PBPK models, performs the fitting and validation following usual methods, focused on our target population, and finalizes with the use of the validated models as knowledge engines into a personalized posology software that can be run standalone in any personal computer.

The software will be tested in a next stage in a University Hospital, to validate and optimize both posology recommendations and interfaces.

Methods: PK and PBPK models building on PhysPK



- PhysPK provides pre-built validated models with sets of parameters, which can be extended by the user
- Models can be modified using PBPX (PBPK/PK/PD) extended elements (library), based on unlimited levels of aggregation (from systemic to cells, including trafficking and biochemical networks)
- Optional and extensible modules will be available to extract standard parameters from available data
- Animal and human models can be link with devices models
- New mechanisms can be easily added to facilitate evolution of knowledge
- Advanced non-PBPK physiological elements are also available (pressure dynamics, etc.)

Gérard C, Stocco J, Hulin A, Blanchet B, Verstuyft C, Durand F, et al. Determination of the most influential sources of variability in tacrolimus trough blood concentrations in adult liver transplant recipients: a bottom-up approach. The AAPS journal. 2014;16:379-91

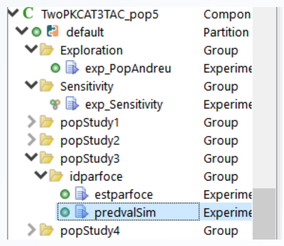
Andreu F, Colom H, Grinyó JM, Torras J, Cruzado JM, Lloberas N. Development of a Population PK Model of Tacrolimus for Adaptive Dosage Control in Stable Kidney Transplant Patients. Therapeutic Drug Monitoring. 2015;37:246-55.

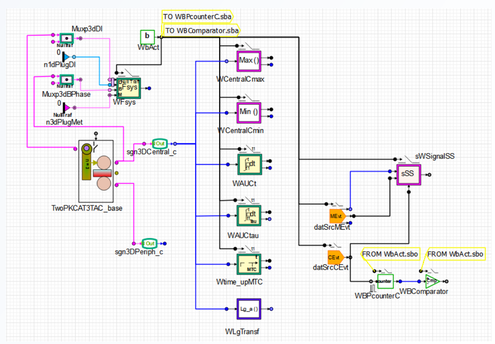
Population study and selection of the best model at each category PK / PBPK to be used as knowledge engines

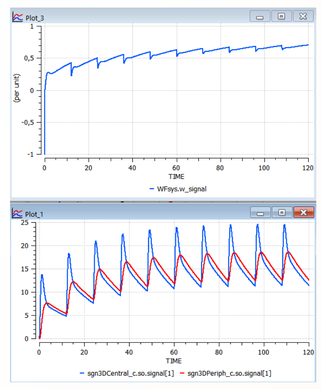
Models are studied following standard (and flexible) procedures. They are organized in the following group of simulation and optimization experiments:

- **Exploration**: folder with experiments where the model is analysed previously to the population fitting.
  - Parametric simulations: non-stochastic
  - Monte Carlo simulations: with selection of random variables or virtual patients
  - Covariate exploration
- **Sensitivity**: folder with dynamics sensitivity analysis of plausible covariates or other model variables.
- **Population Study**: group of folders.
  - DataVirtual Set studies folder for the analysis of model and population estimation methods.
    - IdPar study folders on generated DVirtualSet
  - idPar studie folders with estimation and validation analysis based on experimental Data Set values and a particular method
    - Population estimation with selected method
    - GoF analysis
    - Monte-Carlo analysis
    - Covariable selection folder (stepwise forward and backward …)

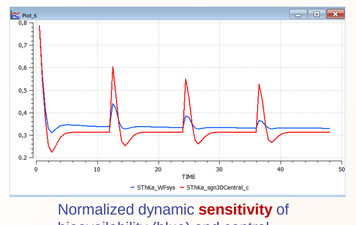
(Example) Experiment organization for Tacrolimus PK model







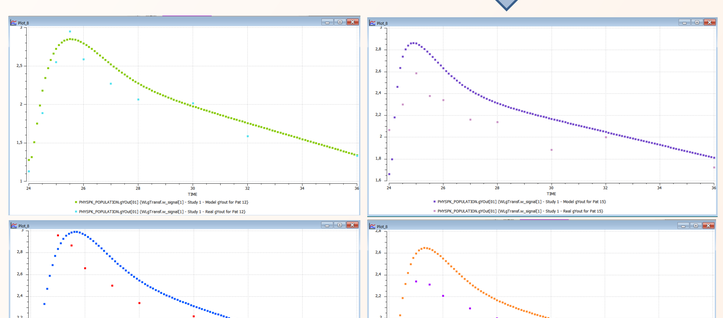
Exploration of steady-state and values of bioavailability (top) and concentrations (bottom) in PK model during 5 days for typical values of parameters (with 2 mg TAC dose each 12 h).



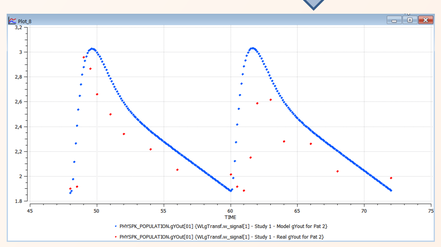
Normalized dynamic **sensitivity** of bioavailability (blue) and central Tacrolimus concentration (red) to absorption constant (Ka) in PK model

Th_CL[Cmp1] = 7.87723	VarOm1 = 0.180794
Th_Ka[Cmp1] = 0.404735	VarOm2 = 1.19711
Th_MT[Cmp1] = 1.52611	VarOm3 = 0.476767
Th_Vc = 54.8249	VarRes = 0.0187221
Th_Vp = 97.9493	
Th_Cld[Cmp1] = 41.1626	

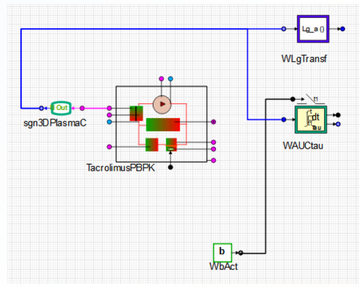
FOCE estimation of PK model for 21 stable adolescent patients with renal transplant, submitted to TAC drug oral therapy.

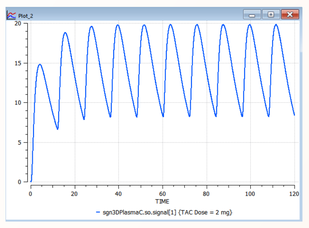


Plasma concentrations of four randomly selected patients during 12 hours with tacrolimus intake (Prograf) each 12 hours, compared to experimental values in PK model, after FOCE estimation and post-analsysis Bayes fitting.



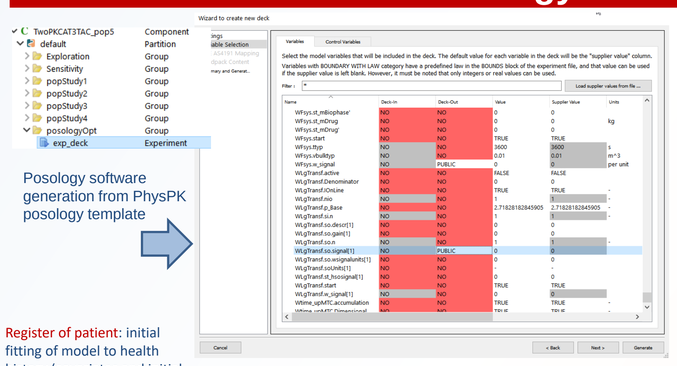
Plasma concentrations of a randomly selected patient during 12 hours used for fitting, together with the following 12 hours non-used for fitting, to evaluate the PK model predictive ability.



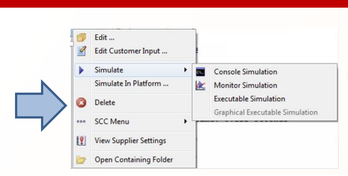


Exploration of steady-state and values of plasma concentrations in PBPK model during 5 days for typical values of parameters (with 2 mg TAC dose each 12 h and 60 Kg of Body Weight).

Customized Posology Software based on PK/PD/PBPK models

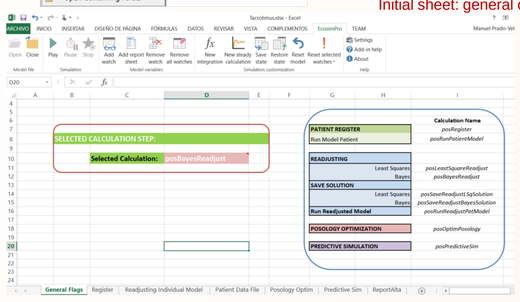


Posology software generation from PhysPK posology template

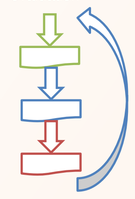


Selection for this case study: standalone run on Excel program

Initial sheet: general options

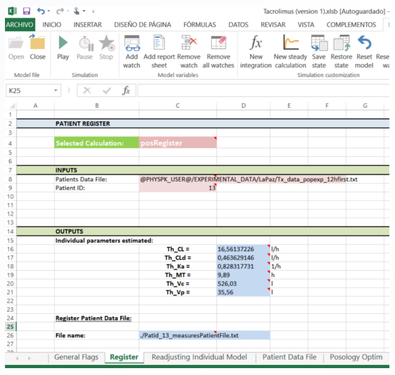


Patient visit / evaluation

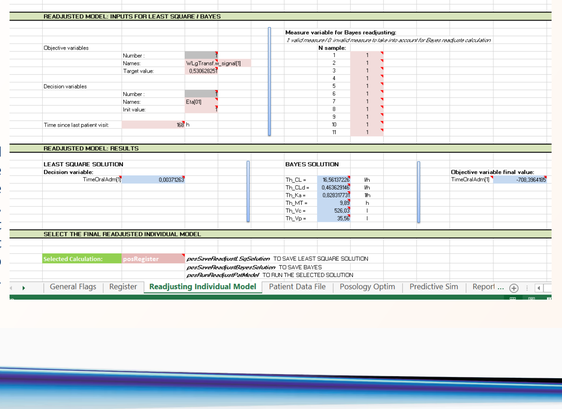


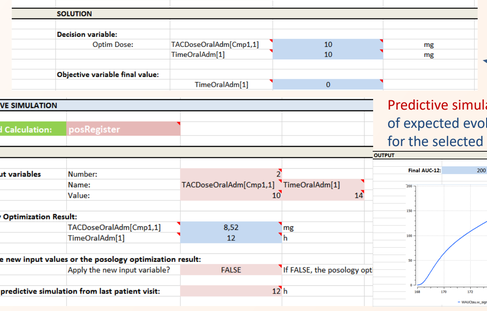
Posology optimization: objective variables (targets) and control variables (decision) are selected during the phase of Posology Software building (using PhysPK template).

Register of patient: initial fitting of model to health history (covariates and initial data, according to population study structure)



Readjust of individual model: after initial fitting of model (and perhaps a first computation of TAC posology) the model is readjusted each time of posology needs to be recalculated, if new relevant health history (covariates, therapy outcomes, and sample data) is acquired. Readjust can be perform by two techniques (Bayesian and Least Squares) and the best readjust is saved, according to physician choice.





Predictive simulation: simulation of expected evolution of AUC12 for the selected posology

We do not present final results of model population fitting for the two models, and particularly with PBPK model, including covariates (influence of HCT, CYP3A4, CYP3A5, RBC binding, …), and other relevant features of these ones, because they exceed the scope of the present study. Notwithstanding preliminary results show that PBPK model provide better predictive capability than PK model, fitted with RBC strong binding and liver clearance of TAC.

Summary

- PK and PBPK models for Tacrolimus drug have been built using a new advanced multilevel physiological modelling and simulation software, PhysPK®
- The building process was guided by a graphic user interface with unlimited aggregation levels and without the necessity of mathematical skills.
- Models have been analysed, explored, fitted and validated using standard and flexible modules inside PhysPK, focused to our target population, and finally adjusted to individual patients.
- Preliminary outcomes show a better predictive capability in PBPK model, as expected, but there are not procedural differences in their use as knowledge engines for the posology program.
- We have shown the reliability of PhysPK to generate a customized posology software based on any PK/PD/PBPK model as knowledge engine, using the DECK technology and the Posology optimization module of PhysPK.
- The developed customized posology software runs on Excel, and includes a graphic interface with plots and standards Windows controls. However, textual console is also a valid alternative when no graphic details are required by the physician or clinical pharmacologist.
- The posology software integrates a workflow of the pharmacological treatment, from the patient register up to the posology computation to fulfil with the desired target (e.g. AUC 12 h) and other requirements (toxicity levels, ..). It also includes what-if scenarios.