Bridging the gap between open and specialized modelling tools in PBPK/PK/PD with PhysPK/EcosimPro modelling system

PBPK model of methotrexate and 6-mercaptopurine in humans with focus in reusability and multilevel modelling features

PhysPK

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Introduction

The M&S arena in biomedicine has experimented huge advances in last decades, in such a way that specialized M&S software systems are now necessary in the pharma and biomedical engineering industry.

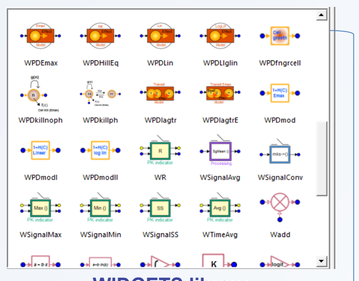
The success of Pharmacokinetics (PK) in the analysis and description of drug kinetics pushed the Physiologically based Pharmacokinetics (PBPK) as a powerful methodology to model and simulate physiological human and animals systems, solving the predictive lack of the first one. The ability of PBPK to partly use of PK results by means of semi-physiological models simplifies the integration of PBPK M&S software systems in the workflow of organization, but current software tools present important shortages:

- Specialized systems: they difficult the generation of new models from pre-built components, and the true reuse of them.
- Open and non-specialized systems: these tools requires a great effort to build a model that can be integrated in the value chain.
- Other common deficiencies:
  - **True model reusability** is limited due to the algorithmic nature of repositories in commercial software
  - **Multiscale modelling** is limited because this feature requires a technology that combines multilevel aggregation of models with the encapsulation of behaviour
  - **Custom requirements**: even specialized tools present limitations to extend the scope of models, including pressures, control, system biology approaches, and custom strategies.

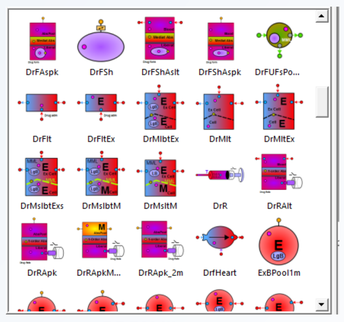
PhysPK, a new M&S software tool that solve many of these lacks, is presented by means of a study case based on a PBPK model for Methotrexate and 6-mercaptopurine. This work presents preliminary results focused on validating some PhysPK capabilities.

PhysPK overview

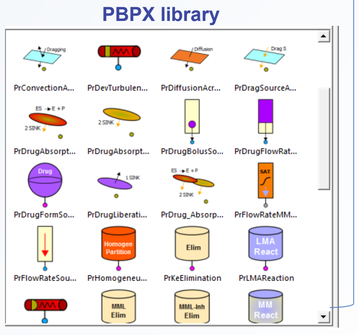
PhysPK is a multi-library M&S software tool for complex physiological systems, compliant with PBPK/ PK/PD methodologies.



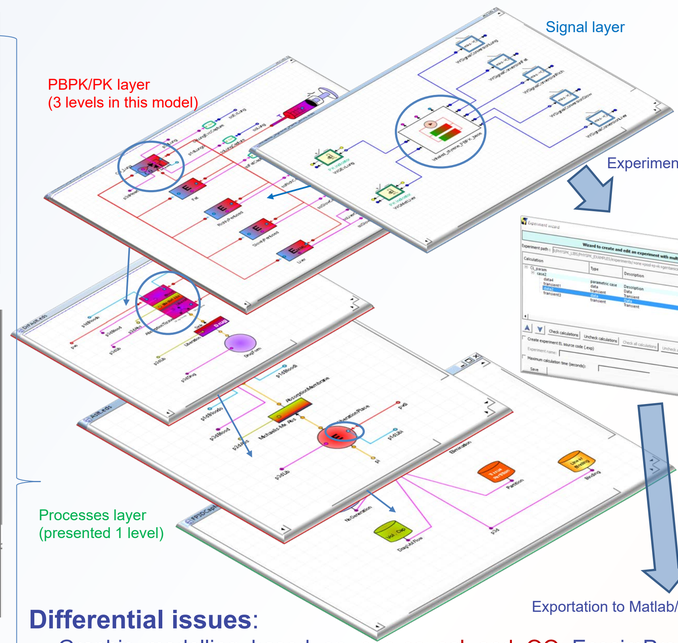
WIDGETS library

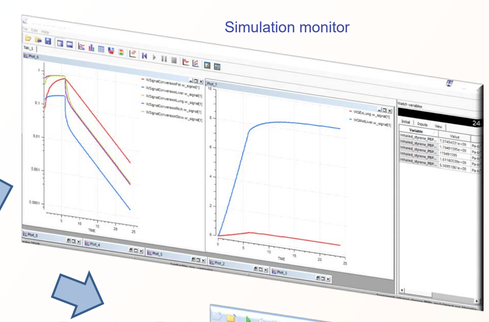


PBPX library



PROCESSES library

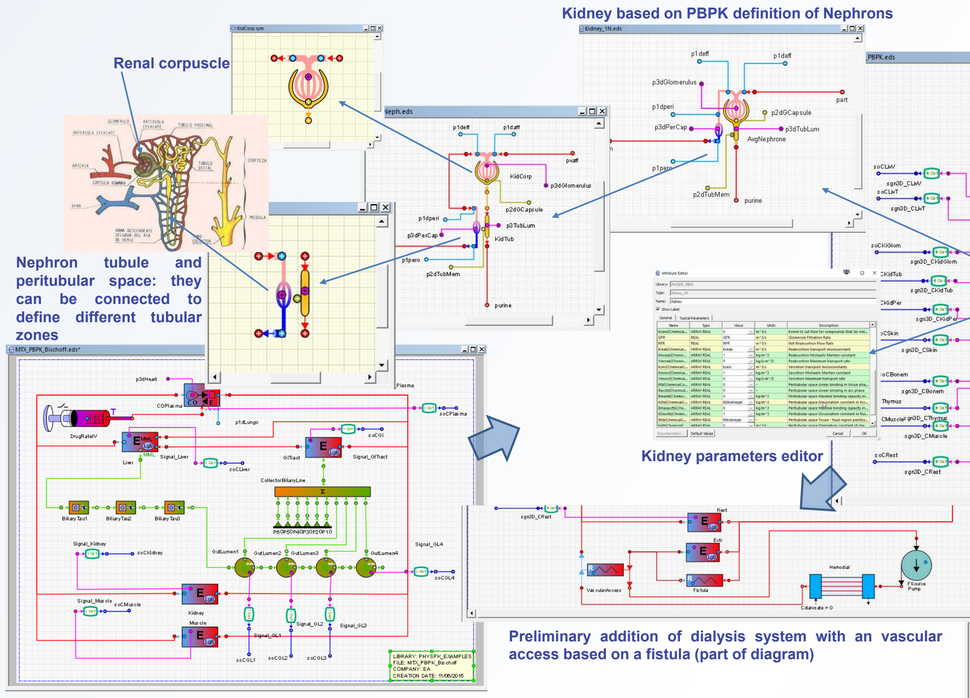


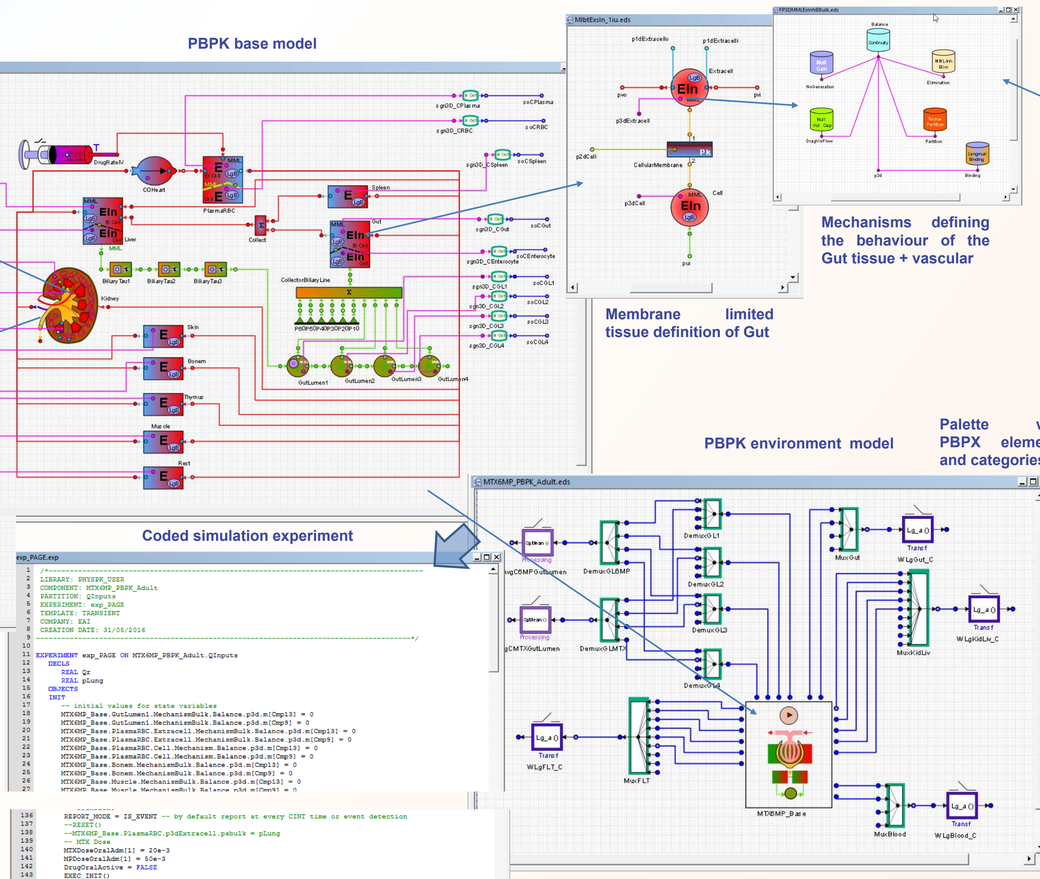


Differential issues:

- Graphic modelling based on non-causal and OO EcosimPro language, based on DAE's approach and a cutting edge modelling and simulation technology
- Open modelling based on three layer architecture: processes (dynamics), PK and Physiological elements, and signal layer (PD, control, indices, …)
- Multi-library design, including Optimization toolkit and Population toolkit.
- Simulation scenarios guided through Wizard-based experiments: steady, transient, parametric types of studies
- True model reusability based on pre-built simulation and user components (sub-models)
- True multilevel modelling based on non-limited levels of aggregated components
- Powerful objects devoted to allometric scaling, parameters conversion algorithms, IVIVE.
- Experiments and models exportation to DLLs and DECKs (autonomous modules), DLL link to Matlab/Simulink, exportation to MS Excel, input/output to different formats files, and management of COM and OPC protocols to demanding industry and academic environments
- Advanced modelling capabilities: physiology-machines (devices), pressure – flow mechanisms, capability to substitute mechanisms associated to new biological knowledge, EL code.

Developing a PBPK model with oral administration of MTX and 6-MP under PhysPK





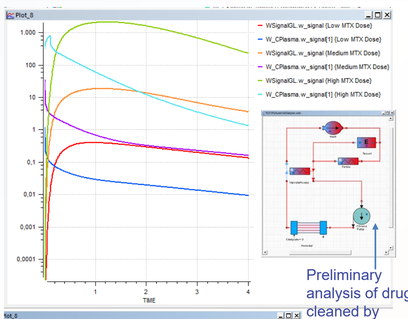
PBPK model for the prediction of 6-MP and MTX kinetics and interactions in patients with acute lymphoblastic leukaemia (ALL), taken the earlier work of Ogungbenro et al (2014) as a reference. A previous PBPK model for MTX was the starting point. Simplified building process:

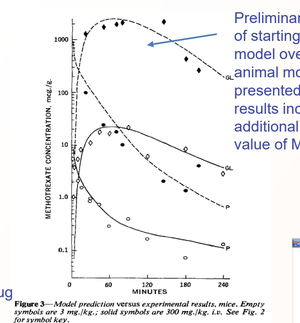
- **Building of a PBPK base** model with stomach, gut lumen, enterocyte, gut tissue, spleen, liver vascular, liver tissue, kidney vascular, kidney tissue, skin, bone marrow, thymus, muscle, rest of body and RBC. Strong quasi-static MTX binding is considered in near all tissues. Gut enterocyte and liver includes metabolism of 6-MP through Xanthine oxidase (XO), which is reversibly inhibited by MTX. RBC includes polymerization of MTX. Kidney is described through the nephron dynamics.
- **Environment and population (application) models** are built using the PBPK based model. The parameters used by this application model are processed by allometric or other types of algorithms, to customize the model to requirements.
- **The PBPK application model is executed through the associated experiments**, making population-optimization fitting, parametric analysis, transient studies, etc. Results are obtained in a rich monitor environment and in different format output files.

It is presented a simple transient experiment which simulates the evolution of the system physiology during 20 hours, after the oral drug administration. The transient experiment structure is created by PhysPK in EL code if it is demanded by the users. There are also graphic wizards, that can manage external parameter data sets in a friendly an powerful way. The experiment can be compiled and run internally (PhysPK IDE) or exported for external execution.

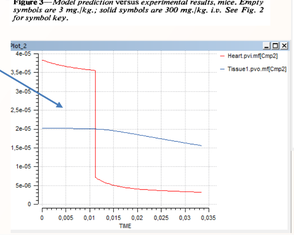
Reference works:
Ogungbenro, K., & Aarons, L. (2014). Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 1: Methotrexate. Journal of Pharmacokinetics and Pharmacodynamics, 41(2), 159–171.
Ogungbenro, K., & Aarons, L. (2014). Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 2: 6-mercaptopurine and its interaction with methotrexate. Journal of Pharmacokinetics and Pharmacodynamics, 41(2), 173–185.

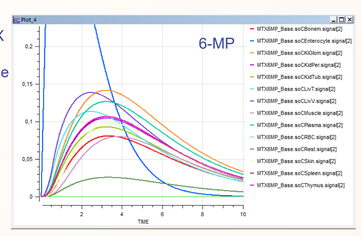
Results

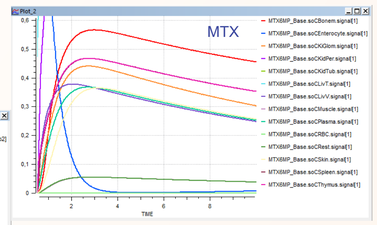




Preliminary validation of starting PBPK MTX model over different animal models (mouse presented). PhysPK results include an additional very low value of MTX.







6-MP and MTX concentrations for the indicated tissues and average adult, and the oral dosing of figure 3.

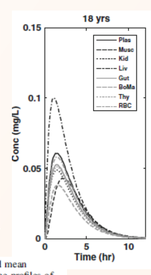


Fig. 3 Simulated mean concentration–time profiles of 6-mercaptopurine in plasma (Plas), muscle (Muse), kidney (Kid), liver (Liv), gut (Gut), bone marrow (BoMa), thymus (Thy) and red blood cells (RBC) following oral dosing of 75 mg/m^2 to 5, 10 and 18 years old subjects

6-MP and MTX plasma concentrations for the conditions of figure 9. Preliminary analysis of influence of reduction in renal clearance (GFR) in MTX.

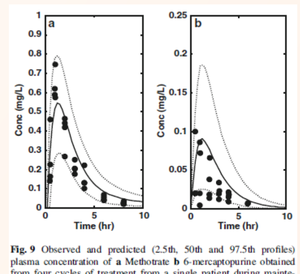
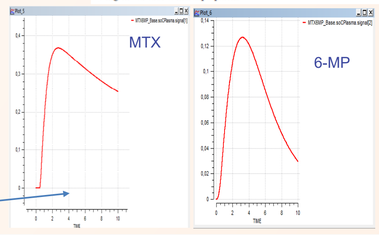
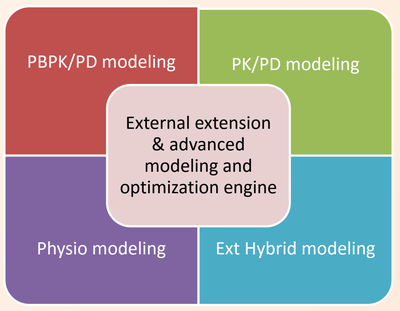


Fig. 9 Observed and predicted (2.5th, 50th and 97.5th profiles) plasma concentration of a Methotrate b 6-mercaptopurine obtained from four cycles of treatment from a single patient during maintenance treatment with stable 20 mg/m^2 of oral methotrexate and 75 mg/m^2 of oral 6-mercaptopurine



Summary and roadmap

- PhysPK combines a strong modeling flexibility with biomedical expertise
- The functional scope includes PK, PBPK, PD, and it extends toward much more rich scenarios
- PhysPK facilitates the modelling reusability
- PhysPK architecture provides support to multilevel modelling.



- A precomercial version PhysPK is being evaluated by a group of research organisms
- A commercial version of PhysPK will be delivered at the end of 2016