OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

RevK

Reverse dosimetry and PBPK prediction

NTUA, INERIS

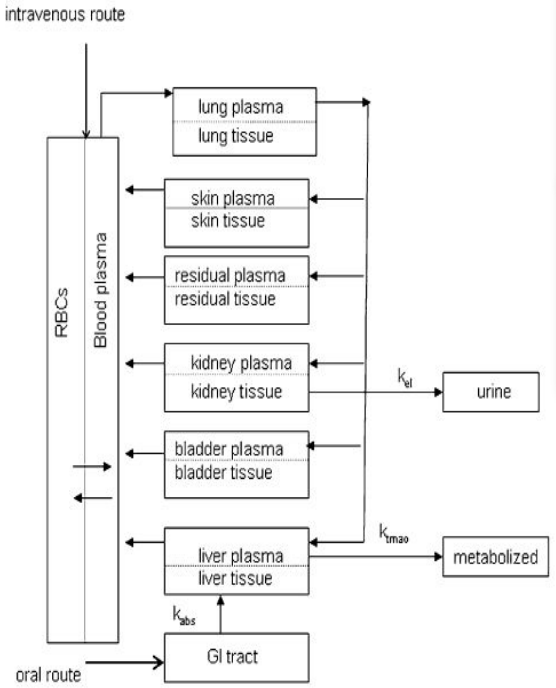
OpenRiskNet: Open e-Infrastructure to Support Data Sharing, Knowledge Integration and *in silico* Analysis and Modelling in Risk Assessment
Project Number 731075

PBPK modelling in REVK

PBPK modelling is offered through the integration of 2 modelling environments:

- ***PKSIM*** (over API): extensive, industry strength, open-source software, fixed model type
- ***httk*** (over API and Jaqpot 5 UI): R package from US EPA, more capabilities and greater modelling freedom
- ***JaqpotforR***: deploy PBPK model directly from R

PBPK model: Multi-compartment model (System of Ordinary Differential Equations, ODEs)



Non-metabolizing compartments:

$$V_{bl}^{i}\frac{dC_{v}^{i}(t)}{dt}=Q_{i}(C_{art}(t)-C_{v}^{i}(t))-\pi_{i}\left(C_{v}^{i}(t)-\frac{C^{i}(t)}{P_{i}}\right)$$

$$V^{i}\frac{dC^{i}(t)}{dt}=\pi_{i}\left(C_{v}^{i}(t)-\frac{C^{i}(t)}{P_{i}}\right)$$

Metabolizing or excretion compartments:

$$V_{bl}^{i}\frac{dC_{v}^{i}(t)}{dt}=Q_{i}(C_{art}(t)-C_{v}^{i}(t))-\pi_{i}\left(C_{v}^{i}(t)-\frac{C^{i}(t)}{P_{i}}\right)-r_{ex}^{i}\left(C_{v}^{i}(t)\right)V_{bl}^{i}$$

$$V^{i}\frac{dC^{i}(t)}{dt}=\pi_{i}\left(C_{v}^{i}(t)-\frac{C^{i}(t)}{P_{i}}\right)-r_{met}^{i}\left(C^{i}(t)\right)V^{i}$$

Blood:

$$V^{pl}\frac{dC^{pl}(t)}{dt}=u(t)+\sum_{i\in I_0\cup I_1}Q_{i}C_{v}^{i}(t)+\pi_{rbc}C^{rbc}(t)-\pi_{pl}C^{pl}(t)-Q_{pl}C^{pl}(t)$$

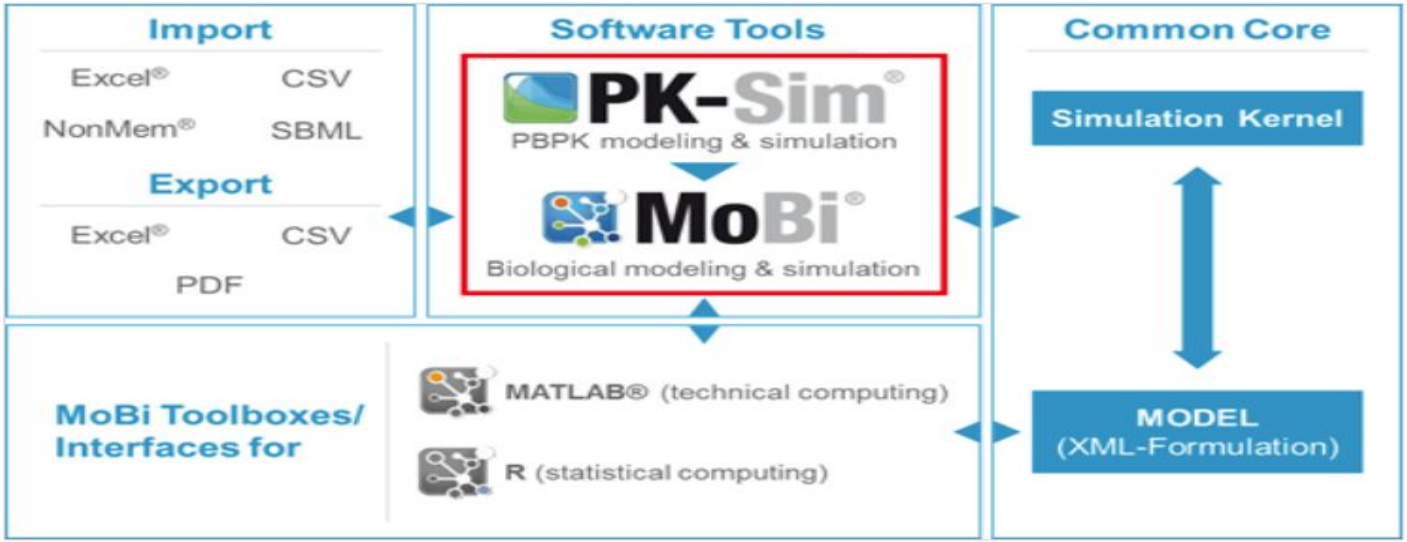
$$V^{rbc}\frac{dC^{rbc}(t)}{dt}=\pi_{pl}C^{pl}(t)-\pi_{rbc}C^{rbc}(t)$$

Lung:

$$V_{bl}^{lu}\frac{dC^{art}(t)}{dt}=Q_{lu}(C^{pl}(t)-C^{art}(t))-\pi_{lu}\left(C^{art}(t)-\frac{C^{lu}(t)}{P_{lu}}\right)$$

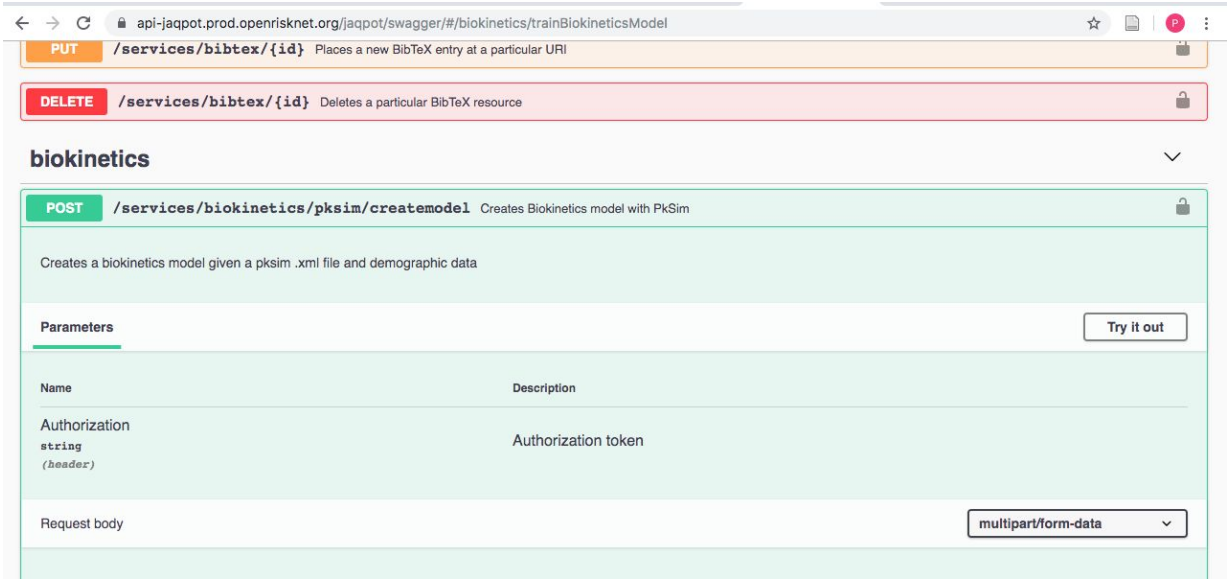
$$V^{lu}\frac{dC^{lu}(t)}{dt}=\pi_{lu}\left(C^{art}(t)-\frac{C^{lu}(t)}{P_{lu}}\right)$$

Open Systems Pharmacology Suite with PK-Sim and MoBi



http://www.systems-biology.com/products/pk-sim.html

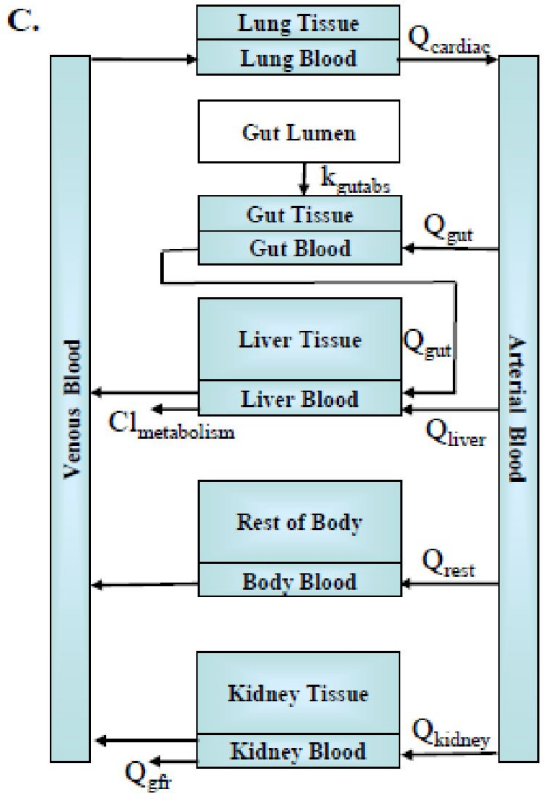
PKSIM modelling in Jaqpot API



https://api-jaqpot.prod.openrisknet.org/jaqpot/swagger/#/biokinetics

The httk R package

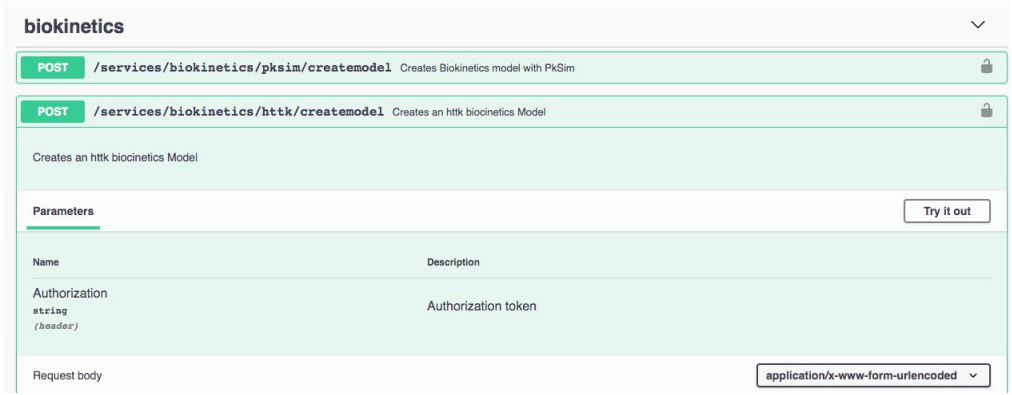
- Four toxicokinetic models have been created in this package, ranging from single-compartmental models to full PBTK models.
- Structure-derived physicochemical properties and species-specific physiological data.
- The package can currently use human *in vitro* data to make predictions for 553 chemicals in humans, rats, mice, dogs, and rabbits, including 94 pharmaceuticals and 415 ToxCast chemicals.
- The package contains tools for Monte Carlo sampling and reverse dosimetry along with functions for the analysis of concentration vs. time simulations.
- httk support oral or iv dosing.



https://cran.r-project.org/web/packages/httk/index.html

httk modelling workflow in Jaqpot API (example)

This example uses the Jaqpot httk service to create a concentration-time simulation and the AUC curve for 10 days after administering a single dose of 0.1mg/Kg of bisphenolA to a human (weight 70 Kg)



Input dataset:

{"chem.name":["bisphenol A"],"species":["Human"],"days":[10],"dose":[0.1]}

Output dataset

"Substance","Agutlumen","Atubules","Cplasma","Cart","Ckidney","Crest","Cliver","Cgut","Ametabolized","Cven","time","Clung","AUC"

"1","2355.4749","0","0","0","0","0","0","0","0","0","0","0","0"

"2","1365.8025","0.1105","13.1333","9.2261","59.1467","2.8637","277.1605","258.6781","0","9.5873","0.0104","9.3056","0.0598"

"3","791.9496","0.5618","20.3668","14.7784","106.6832","11.1376","356.6631","205.9325","0","14.8678","0.0208","14.501","0.2427"

"4","459.2054","1.1426","21.3648","15.6043","115.3854","19.338","318.4675","156.002","0","15.5963","0.0312","15.2265","0.4629"

Tutorial available at: https://drive.google.com/drive/u/0/folders/1mA2xudmZXeHcav60NpDeJubzvwFHkKwI

JaqpotforR

```
> library(JaqpotforR)

> deploy.pbpk.jaqpot(dataframe = user_input, covariate_model = covariates,
  odes = odes, comp = comp_names)
  Base path of jaqpot *etc: https://api.jaqpot.org/ : https://api.jaqpot.org/

  [1] "Model created. The id is:  sjXlNK6TsOTfdfB7q4wP
```

PBPK modelling through Jaqpot GUI

Jaqpot

Overview | Data | Predict / Validate | Discussion

MODEL
Title:
Diazepam
PBPK

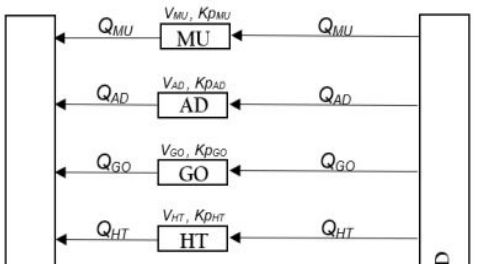
Owner: pantelispanka

Description:

A 14 compartment model with permeability-limited assumption of DIAZEPAM for Human

Diazepam PBPK model

The detailed description of the PBPK model used can be found in Gueorgueiva et al., 2006. Its schematic representation can be seen in the following figure. It consists of 11 compartments describing the concentration of the drug in various tissues, namely liver (*LI*), kidney (*KI*), brain (*BR*), intestine (*IN*), stomach (*ST*), muscle (*MU*), adipose (*AD*), skin (*SK*), gonads (*GO*), heart (*HT*) and lungs (*LU*), one compartment to model the rest of the body (*RE*) as well as two blood pools; venous (*VEN*) and arterial (*ART*). The parameters of the model are divided into drug-dependent and physiological (drug-independent) parameters. The first category comprises eleven tissue-to-plasma partition coefficients (K_p), fraction unbound in plasma (*fu*), blood-to-plasma ratio (*R*), and intrinsic hepatic clearance (CL_{int}, in *L/h*). The physiological parameters of the model are simply the regional tissue blood flows (*Q*) and tissue volumes (*V*).



PBPK modelling through Jaqpot GUI