

# OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

## Case Study

### Reverse dosimetry and PBPK prediction [RevK]

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## SUMMARY

This case-study demonstrates and document the use of a web interface to physiologically-based pharmacokinetic models for forward and reverse dosimetry calculations. Forward calculations compute internal concentrations from given exposure doses. Reverse calculations compute exposure doses from internal concentrations or measured biomarker levels (*e.g.*, urine concentration data). The result of those calculations can be used in risk assessments to help with *in vitro* to *in vivo* extrapolations or interspecies extrapolations.

The tools used for this case-study will be developed at NTUA and accessible as user-friendly web services for simulations with the *httk* PBPK model (*httk* is a R package) or with the *PKSim* model, or with a user-defined model.

For each of these three models, forward and reverse simulations will be performed for a referenced chemical: Imazalil for the *httk* model, Theophylline for the *PKSim* model, and Diazepam for the user-defined model. The exposure scenarios chosen will be in the range of corresponding environmental or therapeutic levels.

The conduct of the simulations and their results will be documented in the format of a User's Manual which will be accessible to future users.

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# DESCRIPTION

## Implementation team

CS leader: INERIS; Other team members: NTUA

- The code and web implementation will be developed by NTUA
- The case-studies' simulations will be run by INERIS
- Code and technical service documentation will be provided by NTUA. INERIS will document the users' operations and results of the case-study demonstrations.

## Case Study objective

The objective of this case study is to demonstrate and document the capabilities of the OpenRiskNet-developed web-services for PBPK modeling. Both forward and reverse dosimetry predictions will be illustrated.

## Risk assessment framework

The application frameworks are, for example: REACH risk assessments; SEVESO II directive on safety around industrial plants; Internal chemical, cosmetic, or pharmaceutical company assessments of workers' safety, or consumer's safety. All those require integration and extrapolation of *in vitro* and/or *in vivo* data on animals to assess human risks.

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# DEVELOPMENT

## Use Cases Associated

In the future, web-services for QSAR predictions of partition coefficients for chemicals or other PBPK parameters could be used for input in the service's PBPK models.

## Databases and tools

We will use open source software able to implement PBPK models: *R* (with package *httk*), *PKSim*, *GNU MCSim*. The *Jaqpot* biokinetic services will be used to publish the PBPK models as web services. Service clients will be developed in *Python* or as *Jupyter* notebooks.

Databases of parameter values will be provided by the *httk R* package, and the *PKSim* model.

## Technical implementation

### Implementation of the chosen PBPK model as web services:

PBPK models for a specific class of chemicals and animal species will be selected by the user from a particular PBPK modelling environment (*e.g.*, *httk* in *R*, *PKSim*, *GNU MCSim*).

The chosen PBPK model will be exposed as a web service using the *Jaqpot* modelling platform. This is possible through the *Jaqpot* Protocol of Data Interchange (JPDI) which allows to dynamically and seamlessly incorporate practically any algorithmic implementation into *Jaqpot*. The protocol specifies the form of data exchange between *Jaqpot* services and third party algorithm web service implementations. The *Jaqpot* framework already provides wrappers for the *R* language and the *Python* language. Integration with *R* is made possible through the *OpenCPU* system, which defines an HTTP API for embedded scientific computing based on *R*, although this approach could easily be generalized to other computational back-ends (Ooms, 2014). *OpenCPU* acts as a wrapper to *R* that is readily able to expose *R* functions as RESTful HTTP resources. The *OpenCPU* server takes advantage of multi-processing in the *Apache2* web server to handle concurrency. This implementation uses forks of the *R* process to serve concurrent requests immediately with little performance overhead. By doing so it enables access to those functions on simple HTTP calls converting *R* from a standalone application to a web service.

User-friendly clients will be developed in *Python* or as *Jupyter* notebooks.

### Demonstration of PBPK models that have been exposed as web services:

The three models (*httk*, *PKSim* and user-specified) will be exercised with Imazalil, Theophylline, and Diazepam, respectively.

For each chemical, we will start by identifying relevant human exposures (*e.g.* from *ExpoCast*, or published literature) to be used in forward dosimetry. For reverse dosimetry,

we will identify (*e.g.* from the US NHANES database, or the scientific literature) typical blood or urine concentrations found in humans to be used as input to the exposure dose reconstruction.

The model will be parameterized using user-specified or pre-programmed tabulated physiological data.

For forward dosimetry predictions, each model will be run with the given exposure scenario to predict internal concentrations after 24 hours. Plots of the concentration time-courses will be generated and compared to reference simulations (generated with the stand-alone versions of the same packages).

For reverse dosimetry the model will be run forward iteratively with user set exposures so as to match the input biomarkers (that is: manually invert the model). The external exposure level leading to data-matching biomarker level will be recorded as final estimate.

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## OUTCOMES

In the Appendix, two tutorials provide descriptions of preliminary implementations of this case study: the first tutorial uses *PKSim* with theophylline as the chemical of interest. The second tutorial uses *httk* and Imazalil. Those were demonstrated and received positive feedback during the biokinetics workshop of the OpenTox Euro conference in Basel, 2017, where we had the opportunity to interact with potential users.

The preliminary results of this case-study demonstrates that the OpenRiskNet framework can be used as a central e-platform for the biokinetics community, where the users can publish, share, search and use PBPK models. Additional biokinetic models will be integrated in the future and will be tested in terms of producing successful results (time-concentration profiles). The case study will deliver a User's Manual including a tutorial for this service.

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## REFERENCES

1. Ooms, J. The OpenCPU System : Towards a Universal Interface for Scientific Computing through Separation of Concerns. *arXiv* **2014**, 1–23.
2. C. Chomenidis, G. Drakakis, G. Tsiliki, E. Anagnostopoulou, A. Valsamis, P. Doganis, P. Sopasakis, H. Sarimveis, Jaqpot Quattro: A Novel Computational Web Platform for Modeling and Analysis in Nanoinformatics (*Journal of Chemical Information and Modeling*, 57, 2161-2172, 2017).

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# APPENDIX

## Integration of PKsim in OpenRiskNet Infrastructure through the Jaqpot modelling platform

(Presented in OpenRiskNet/OpenTox Euro 2017 Biokinetics Workshop)

The goal of this hands-on workshop is to show how to create a PBPK model using PKSim [1] and expose it as a web service through the Jaqpot modelling platform.

Software requirements: The attendees should download and install in their PCs the Open Systems Pharmacology Suite: <https://github.com/Open-Systems-Pharmacology/Suite/releases/tag/v7.1.0>

And the gene expression database

[https://github.com/Open-Systems-Pharmacology/Suite/releases/download/v7.1.0/GENEDB\\_human.mdb](https://github.com/Open-Systems-Pharmacology/Suite/releases/download/v7.1.0/GENEDB_human.mdb)

In PKSim select Utilities, then Options, then “Application” and for Human you give the path where the database is stored.

All other necessary files that should be downloaded are available in the google drive:

[https://drive.google.com/drive/folders/1wGmqNYI8GnDL\\_orrE2JqPQAMauHStbPi](https://drive.google.com/drive/folders/1wGmqNYI8GnDL_orrE2JqPQAMauHStbPi)

Assuming that the PBPK model has been saved in xml format (as explained in Powerpoint presentation), the following steps should be followed in Swagger JaqPot API documentation <http://test.jaqpot.org:8080/jaqpot/swagger/> :

- 1) Create a JaqPot dataset containing the physiological parameters of the individual on which the PBPK model was developed. We assume that these parameters (age, height, weight) are included in a csv file testPK.csv
  - a. Use the **POST /dataset/createDummyDataset** method: Choose the testPK.csv file and give any title and description to the produced dataset. In the end of the response body a dataset id is generated.
  - b. Use the **GET /dataset/{id}** method: Copy the dataset id in the relevant field and press Try it out!. In the Request URL the full dataset URI of the produced dataset is shown. Store the URI of the dataset.  
Example: <http://test.jaqpot.org:8080/jaqpot/services/dataset/SDea5BEhgvPRTx>
- 2) Produce a JaqPot resource that implements the PBPK model as a web service
  - a. Use the **POST /biokinetics/train** method. Insert the following information in the parameter fields:  
File: Choose the PBPK xml file sim\_individual\_1\_XML.xml



Dataset-uri: Copy the full dataset URI

Title and description: Any title and description is fine

Algorithm-uri: <http://test.jaqpot.org:8080/jaqpot/services/algorithm/pk-sim>

Parameters: {"ageUnit":["years"], "individual":[1], "heightUnit":["m"], "weightUnit":["kg"], "drug":["Theophylline"]}

After pressing the Try it out! button, a task ID is generated In the end of the response body

- b. Use the **GET /task/{id}** method. Copy the task ID in the relevant field and press the Try it out! Button. If the status in the end of the response body is not COMPLETED wait for a few seconds and try again. The model has been created and its complete URI is shown in the response body. You can now share the model with the rest of the world. For the next step store the model id. This is the id after model/ in “result” in the response body
- 3) Use the model for obtaining drug concentration-time profiles
- a. Use the **POST /model/{id}** method. In the dataset\_uri you can use the same dataset URI that was used in the first step. Alternatively, you can create an alternative dataset for a different individual. In the id field copy the id of the produced model. After pressing the Try it out! button a task ID is created.
  - b. Use the **GET /task/{id}** method. Copy the task ID in the relevant field and press the Try it out! Button. The dataset with drug concentration –time data has been created. For the next step store the dataset id. This is the id after dataset/ in “result” in the response body
  - c. Use the **GET /dataset/{id}** method: Copy the dataset id in the relevant field and press Try it out!. In the Response Body, drug concentration values are shown along with corresponding time points.

## Integration of httk in OpenRiskNet Infrastructure through the Jaqpot modelling platform

High-Throughput toxicokinetics (httk) is an R package for simulation and analysis of chemical toxicokinetics [2]. httk has been integrated in the Jaqpot platform and will be accessible from the OpenRiskNet infrastructure. The goal of this tutorial is to demonstrate how to obtain toxicokinetics predictions from the httk package using Jaqpot services and functionalities.

Currently the following httk parameters are supported:

1. "chem.name", which is the chemical name of the compound under study
2. "species", which is the species of interest (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human")
3. "days", the length of the simulation in days,
4. "dose", the amount of the single dose specified (mg/kg/day) with the default value being NULL.

We will use the example of administering Imazalil administered to a human (BW=70kgr) also initializing other basic parameters based on the multiple compartment model introduced in [3]. The compartments used in this model are the gutlumen, gut, liver, kidneys, veins, arteries, lungs, and the rest of the body. The extra compartments include the amounts or concentrations metabolized by the liver and excreted by the kidneys through the tubules.

The following steps should be followed using the Swagger JaqPot API UI at <http://jaqpot.org:8080/jaqpot/swagger/>:

- 1) Produce a JaqPot resource that implements the httk model as a web service
  - a. Use the **POST/biokinetics/httk/createmodel** method.

Insert the following information in the parameter fields:

Title and description: Any title and description is fine

Parameter string:

```
{"chem.name":["imazalil"],"species":["Human"],"days":[10],"dose":[10]}
```

Press 'Try it out!' In the field response body a json string will appear. There the user can find the task ID.

- b. Use the **GET /task/{id}** method. Copy the task ID in the relevant field and press the 'Try it out!' button. If the status at the end of the response body is not COMPLETED wait for a few seconds and try again. The model has been created and its complete URI is shown in the

response body. For the next step store the model id. This is the id appearing after model/ in “result” in the response body.

The raw model together with the initial parameters of the multiple compartment model, are returned.

- 2) Use the model for obtaining drug concentration-time profiles
  - a. Use the **POST biokinetics/httpk/model/{id}** method in the biokinetics section. Submit model id obtained before and then press the button ‘Try it out!’. A task ID is created.
  - b. Use the **GET /task/{id}** method. Copy the task ID in the relevant field and press the Try it out! Button. The dataset with drug concentration –time data has been created. For the next step store the dataset id. This is the id found after dataset/ in the “result” in the response body.
  - c. Use the **GET /dataset/{id}** method: Copy the dataset id in the relevant field and press ‘Try it out!’. In the Response Body, drug concentration values are shown along with corresponding time points (in days), and AUC (area under the curve) of the plasma concentration values.

These are the first lines of the result giving concentrations in uM:

```
"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", "0"
"2", "1365.8025", "0.1105", "13.1333", "9.2261", "59.1467", "2.8637", "277.1605", "25
8.6781", "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", "1
56.002", "0", "15.5963", "0.0312", "15.2265", "0.4629"
"5", "266.2664", "1.7291", "20.5252", "15.0134", "111.6516", "25.5365", "259.9901", "
120.0944", "0", "14.9834", "0.0417", "14.6313", "0.6817"
"6", "154.3925", "2.2885", "19.4394", "14.2189", "105.7722", "29.7367", "210.7735", "
96.3627", "0", "14.1908", "0.0521", "13.8573", "0.8898"
"7", "89.5232", "2.8195", "18.5569", "13.5674", "100.7951", "32.4253", "175.7869", "8
1.3744", "0", "13.5466", "0.0625", "13.2273", "1.0874"
"8", "51.9093", "3.3285", "17.938", "13.1087", "97.2449", "34.0891", "152.7805", "72.
164", "0", "13.0947", "0.0729", "12.7851", "1.2773"
"9", "30.0992", "3.8225", "17.5331", "12.8081", "94.9023", "35.0962", "138.2902", "66
.602", "0", "12.7992", "0.0833", "12.4959", "1.4619"
"10", "17.4528", "4.3068", "17.2782", "12.6186", "93.42", "35.6962", "129.3984", "63.
2808", "0", "12.6131", "0.0938", "12.3137", "1.6431"
```

[1] <http://www.systems-biology.com/products/pk-sim.html>

[2] <https://cran.r-project.org/web/packages/httk/httk.pdf>

[3] Kilford, P. J., Gertz, M., Houston, J. B. and Galetin, A. (2008). Hepatocellular binding of drugs: correction for unbound fraction in hepatocyte incubations using microsomal binding or drug lipophilicity data. *Drug Metabolism and Disposition* 36(7), 1194-7, 10.1124/dmd.108.020834.

**Other examples:**

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

```
{"chem.name":["imazalil"],"species":["Rat"],"days":[10],"dose":[10]}
```

```
{"chem.name":["Acetochlor"],"species":["Rat"],"days":[10],"dose":[10]}
```

## Integration of custom made PBPK models in the Jaqpot modelling platform

Besides the integration of httk and PKSim, we offer the option to the users to create, upload and share a custom-made PBPK model through the Jaqpot infrastructure.

An example is the PBPK model described in [4], which describes the biokinetics of diazepam in humans.

The model is currently accessible through the local deployment of Jaqpot in the following URL: <https://app.jaqpot.org/model/ecTo8uVZb7AF9KXBp0sp>.

Under the Overview tab, detailed information about the model are provided:

**MODEL**  
**Title:** Diazepam PBPK  
**Owner:** partelispanka  
**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 Gueorguieva 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 ( $f_u$ ), blood-to-plasma ratio ( $R$ ), and intrinsic hepatic clearance ( $CL_{int}$ , in  $LI$ ). The physiological parameters of the model are simply the regional tissue blood flows ( $Q$ ) and tissue volumes ( $V$ ).

Under the Data tab, all independent (weight, gender, infusion time, dose and initial concentration in all compartments) and dependent variables (concentrations in all compartments: adipose, muscle, brain, skin, gonads, kidneys, heart, the rest of the body, stomach, liver, arterial blood, lungs, intestines, venous blood) are defined.

In the Predict/Validate tab the user can simulate a scenario. As an example, the model is asked to simulate the concentration-time profiles produced after administering 5mg of

diazepam to a male weighted 70Kg. The infusion time is 0.1 hours and all initial concentrations are assumed equal to 0.

The screenshot shows the Jagpot web application interface. The browser address bar displays the URL: <https://app.jagpot.org/model/ect0buVZb7AF9KEXp0p>. The application header includes the Jagpot logo and navigation tabs: Overview, Data, Predict / validate (active), and Discussion. On the left, a sidebar displays the model information:

**MODEL**  
**Title: Diazepam PBPK**  
 Owner: pantelispanka  
 Description:  
 A 14 compartment model with permeability-limited assumption of DIAZEPAM for Human

The main content area is titled 'Choose method' and contains a 'Predict' button. Below this is an 'Upload dataset with the required independent features and values' section with download and upload icons. The 'Input values for the independent features' section contains a grid of input fields:

weight 70 kg	dose 5 mg	infusion_time 0.1 hours	CO_MU 0 mg / mL	gender 0 0: male, 1: female	CO_AD 0 mg / mL
CO_GO 0 mg / mL	CO_SK 0 mg / mL	CO_HT 0 mg / mL	CO_BR 0 mg / mL	CO_KI 0 mg / mL	CO_RE 0 mg / mL
CO_ST 0 mg / mL	CO_IN 0 mg / mL	CO_LU 0 mg / mL	CO_ART 0 mg / mL	CO_LI 0 mg / mL	CO_VEN 0 mg / mL

A 'Start' button is located at the bottom right of the input grid.

[4] Gueorguieva, I., Arons, L., Rowland, M. (2006). Diazepam Pharmacokinetics from Preclinical to Phase I Using a Bayesian Population Physiologically Based Pharmacokinetic Model with Informative Prior Distributions in Winbugs. *Journal of Pharmacokinetics and Pharmacodynamics*, 33(5), 571–594.