PBPK modelling on the Jaqpot web platform - a PAA-peg nanoparticles case study

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Overview

- Physiologically- based pharmacokinetic (PBPK) modelling is used for predicting the biokinetics (absorption, distribution, metabolism and excretion) of a substance in an organism. Recently, PBPK modelling has been extended and successfully applied for describing the biokinetics of Nanomaterials (NMs).
- Jaqpot is an open computational web-platform that enables the systematic production, collection, organization, validation, storage and sharing of predictive models, with emphasis on predictive toxicology.
- A web service route has been established for hosting PBPK models in the Jaqpot environment, bridging the gap between PBPK developers and end-users.

Introduction

PBPK models offer a methodology for predicting the internal distribution and exposure of a chemical in an organism and, as such, they are useful in predictive toxicology and in risk assessment. PBPK models fuse physiological and drug- related information and describe known physiological relationships through compartmental modeling, where each compartment represents an existing tissue. The main outcome of this type of models is the production of concentration-time profiles in each tissue following the external exposure of the organism to the substance. PBPK modelling of NMs is more challenging due to their complicated in vivo disposition properties compared to conventional chemicals. Several PBPK models have been developed for NMs, but most efforts lack the capacity to accurately describe the complex bioprocesses related to NMs. One of the earliest publications which consider the process of NMs uptake by phagocytizing cells (PCs) for improving the description of the biodistribution process is the one of Li et al. (https://doi.org/10.3109/17435390.2013.863406). The model introduced a subcompartment in each tissue for describing the activity of PCs and managed to adequately describe the biodistribution of pegylated polyacrylamide (PAA- peg) nanoparticles in rats. The success of the Li model made it an ideal candidate for showcasing the functionality of the Jaqpot web services.

Workflow

Jaqpot (app.jaqpot.org) is a computational platform developed by NTUA, that facilitates in silico modeling and enables the systematic production, collection, organization, validation, storage and sharing of predictive models. Special infrastructure has been developed in Jaqpot, to allow and support the development, implementation and deployment of PBPK models as ready-to-use web services. The necessary elements for uploading a PBPK model to Jaqpot are:

- A list of independent variables, which are the inputs to the model
- A list of dependent variables, which are the model outputs
- A function containing the ODE system

Following the deployment of the model on Jaqpot, the model developer can further process and enrich the model metadata on the Jaqpot Graphical User Interface (GUI). Specifically:

- In the "*Overview*" tab, he can include a detailed verbal and schematic description of the model, in Markdown language (Figure 1).
- In the "*Data*" tab, he can add a short description, units and ontological class for each of the features of the model, dependent or independent. The information of the "Data" tab is inherited by the "Predict" tab (Figure 2).

Results

The Li et al. (2014) PBPK model was deployed on Jaqpot as part of the transnational access (TA) activities of the NanoCommons EU Horizon 2020 project, aiming to increase the visibility of the model and allow simulation and testing of different biodistribution scenarios by users.

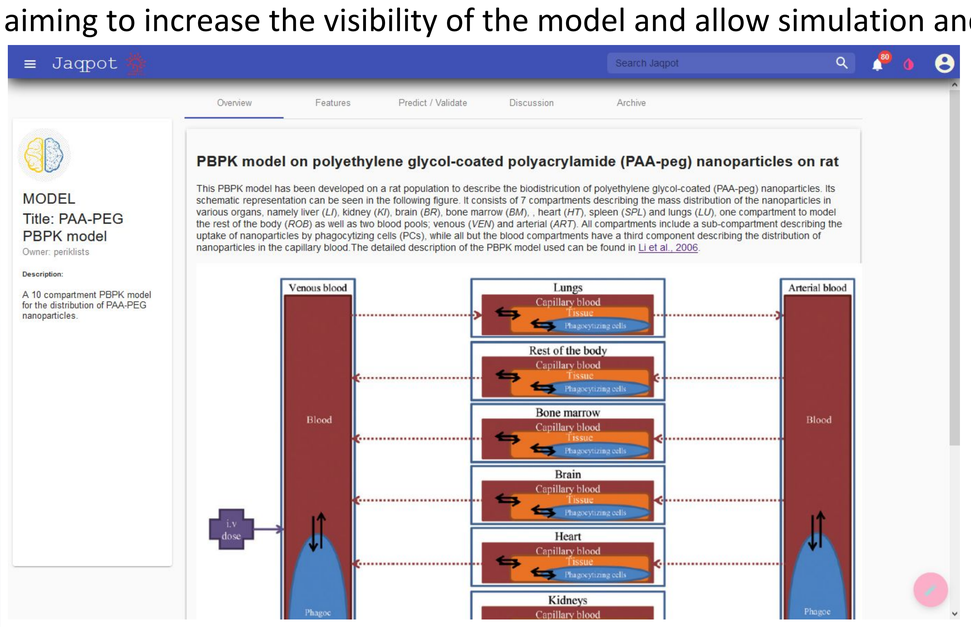

Figure 1 "Overview" tab of the Li et al. model.

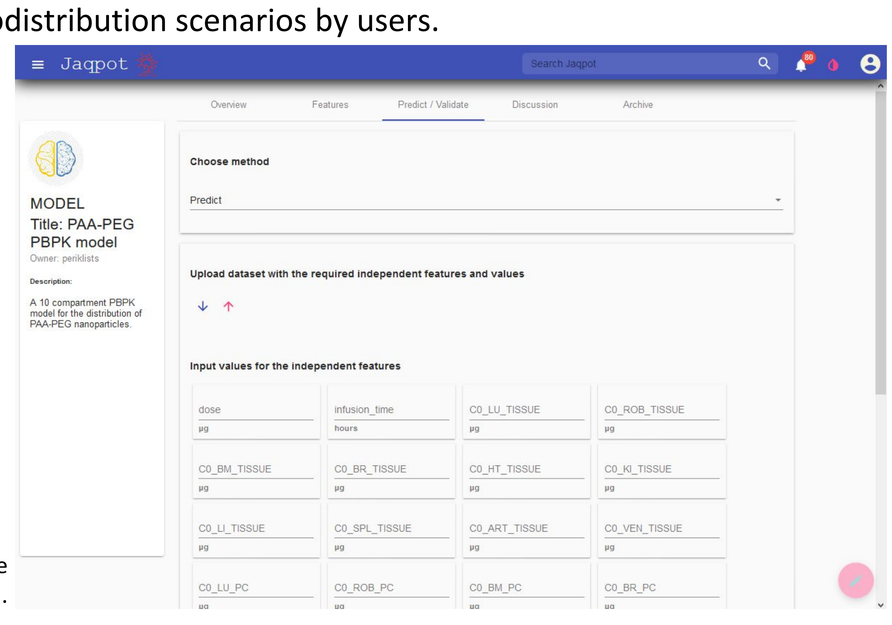

Figure 2 "*Prediction*" tab of the Li et al. model.

The end-user of the model can read all the details for the model and the variables involved in the model in the "*Overview*" and "*Data*" tabs, but most importantly he can perform simulation and generate concentration-time profiles in the "*Predict*" tab by providing values for the independent features either manually or by uploading an csv file. For the Li et al. model the user can select the infusion time, dose, initial mass of PAA-peg for each compartment, as well as the duration and time step of the simulation. When all values are completed, the user can click the start button, initialising the prediction process. Shortly after, the mass profiles of PAA-peg in each compartment are generated and presented in a Table format on the GUI. The user can then download the data in CSV format and further process them offline.

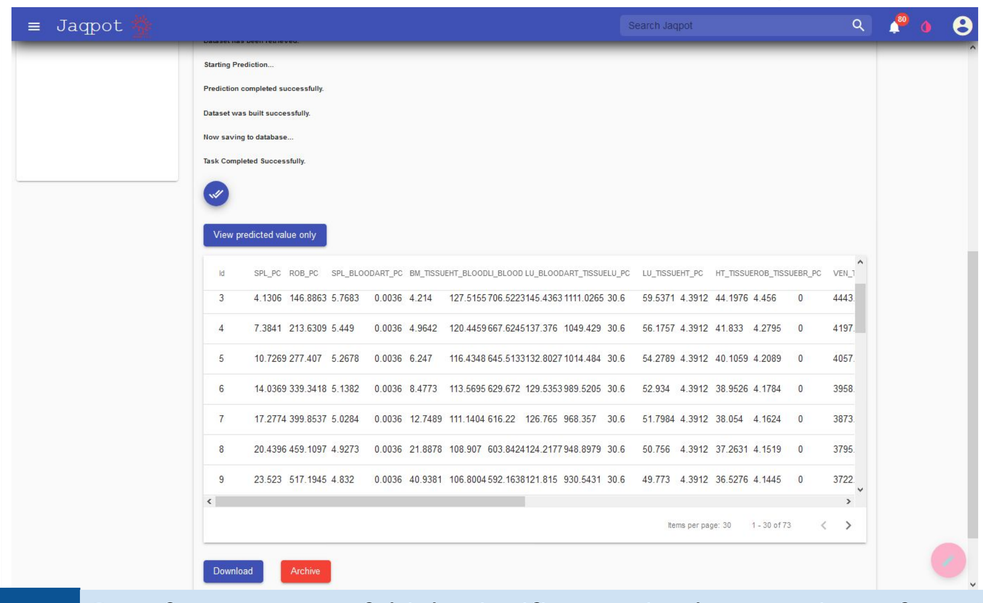

Figure 3 Results presentation format in the "*Prediction*" tab, after a simulation.

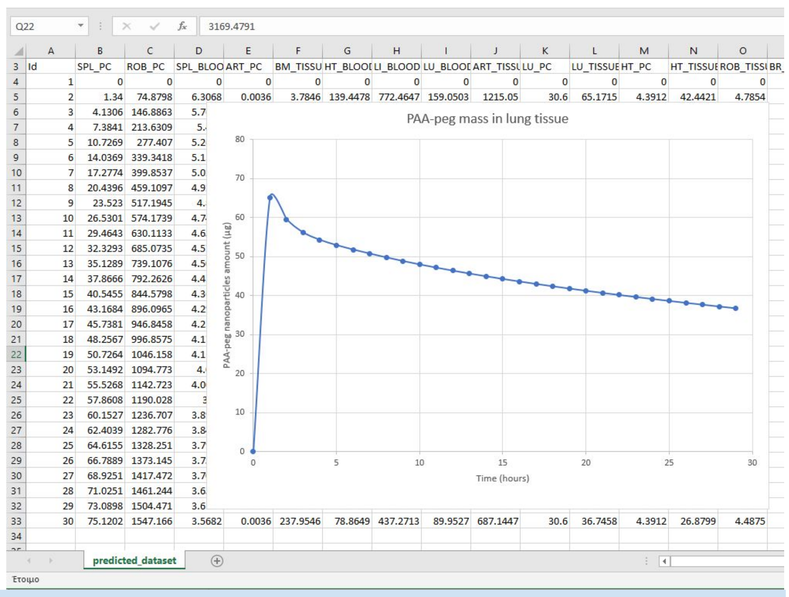

Figure 4 Example of offline data processing of a simulation of the PAA-peg PBPK model.

Future Work

One future step of high significance is the creation of an R library that will allow R users to deploy custom PBPK models on Jaqpot. Even non-experienced model developers will be able to deploy their models, rendering Jaqpot a central repository for hosting, sharing, testing and using nanoPBPK models. The GUI will be extended by providing functionalities to automatically produce concentration-time profiles within the Jaqpot environment. This improvement will enable generation of mass/concentration time profile plots on the GUI, thus minimising the need for offline post-processing.

Acknowledgements

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