

Jaqpot5 tutorials

Jaqpot 5: How to simulate biodistribution scenarios using custom PBPK models

USE:	How to simulate biodistribution scenarios using custom PBPK models
VERSION:	V.1.0
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INTRODUCTION

Jaqpot 5 is a user-friendly web-based e-infrastructure that allows model developers to deploy their predictive models and share them through the web. The Jaqpot 5 GUI directs the model developers to further document their models in a way that can be easily understood and used by end-users with little or no experience on machine learning and statistical analysis. The GUI also allows the end-users to apply the models on their own data for validation and/or prediction purposes and the results are collected and visualised in automatically generated tables, graphs and reports. All major machine learning and statistical data-driven algorithms are supported in Jaqpot 5, by integrating popular libraries such as the Python Scikit-learn and the R Caret libraries. Jaqpot 5 has been designed as a generic modelling and machine learning web platform, but particular emphasis is given on serving the needs of the chemo/bio/nano/pharma/ communities by integrating QSAR, biokinetics, dose-response and read-across models. Jaqpot 5 has been developed by the <u>Unit of Process Control and Informatics</u> in the School of Chemical Engineering at the National Technical University of Athens.

This document provides a tutorial for simulating biodistribution scenarios using custom PBPK models that have been deployed on Jaqpot5. The resource has been made available at https://app.jaqpot.org/.

HOW TO ACCESS A CUSTOM PBPK MODEL

An important module introduced in Jaqpot 5 is custom PBPK models that have been deployed through a developed R client. A Jaqpot user can run simulations using these models, e.g. generate forward and reverse dosimetry scenarios, provided that he has access to a model through the organization she/he is part of.

After logging into Jaqpot, the user is directed to Jaqpot's Home page, from where he can go to the models section by clicking the 'Models' tab on the left banner of the screen (Figure 1).

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		Model title: Diazepam Model Oct 16, 2019		
		* Model title: PAA-PEG PBPK model Apr 8, 2019		
		Model title: Test Periklis Mar 14, 2019		

Figure 1. 'Models' Tab

The initial screen includes models deployed by the user, private and shared ones. In order to access models that have been shared to the user via organisations, the user should click on the arrow right next to the 'Mine' tab on the top of the screen and then click the 'Shared' button (Figure 2).

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Figure 2. Selecting Share models

Following that, the user can access a specific model by clicking on the 'View' button, which is located on the far right end of the model's row (Figure 3).

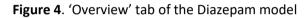
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		Model title: Shin et al. Cytotoxicity classification Model May 10, 2019	
		Model title: Linear Model for Predicting Solubility of C60 Fullerenes in Various Solvents Apr 19, 2019	
		Model title: Neural network model predicting DILI Mar 14, 2019	

Figure 3. Clicking on the 'View' tab

MODEL ENVIRONMENT

The model environment comprises 4 tabs: 'Overview', 'Features', 'Predict/Validate' and 'Discussion'. The 'Overview' tab provides a coarse description of the PBPK model, as well as specific directions which refer to the model, e.g. how to fill in the input section (Figure 4).

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WINDEL DIAZEPAN DIAZEPAN WINT: PRIKISS CONTROL	Diazepam PBP The detailed description the following figure. It co (K), brain (BA), intestine compartment to model it are divided into drug-dep partition coefficients (Kp.	of the PBPK model used can be f nnsists of 11 compartments descr (<i>IN</i>), stomach (ST), muscle (<i>MU</i>), he rest of the body (<i>RE</i>) as well a pendent and physiological (drug-	bing the concentration of adipose (AD), skin (SK), g two blood pools; venous ndependent) parameters. blood-to-plasma ratio (R	Archive	liver (LI), kidney U), one neters of the model n tissue-to-plasma		



The 'Features' tab informs the users about the dependent and independent features; each feature comes with description and units (Figure 5).

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	Overview	Features	Predict / Validate	Discussion	Archive				
	Dependent fea	ture / Predicted	feature						
MODEL Title: Diazepam Model Owner: periklists Description:	Mu Description: Conce Units: ng/mL	ntration in the muse	le compartment						
This is an updated PBPK model for describing the biodistribution of diazepan in humans post intravenous injection.	Ad Description: Conce Units: ng/mL	ntration in the adipo	ise compartment						
	Ht Description: Conce Units: ng/mL	intration in the heart	: compartment						

Figure 5. 'Features' tab of the Diazepam model

The 'Predict/Validate' tab is the core of the model environment. Here, the user can provide an instance of the independent features and acquire the model predictions, which, in the case of PBPK models consist mainly or concentration or mass- time profiles. The user can provide the input in two ways: the first one is through uploading a csv file containing the respective information and the second one is through filling in the input directly in Jaqpot's Graphical User Interface (GUI). In case the input consists of many features, it is strongly recommended that the user follows the first method, i.e. download the csv template (Figure 6), fill in the values (Figure 7), upload the complete csv (Figure 8), select 'None' in the pop up window asking for a dataset ID (Figure 9) and then start the prediction process (Figure 10).

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	Overview	Features Pre-	dict / Validate	Discussion	Archive					
	Choose method									
MODEL	Predict						*			
Title: Diazepam Model										
Owner: periklists Description:	Upload dataset wit	th the required indep	pendent feature	s and values						
This is an updated PBPK model for describing the biodistribution of diazepam in humans post intravenous injection.	ad template dataset (csv)									
	Input values for th	e independent featu	ires							
	dose	dosing.times	gende	r	sim.end	sim.step				
	mg	hours	0: male	1: female	hours	hours				
	weight	sim.start								
	kg	hours								

Figure 6. How to download a dataset template in csv format

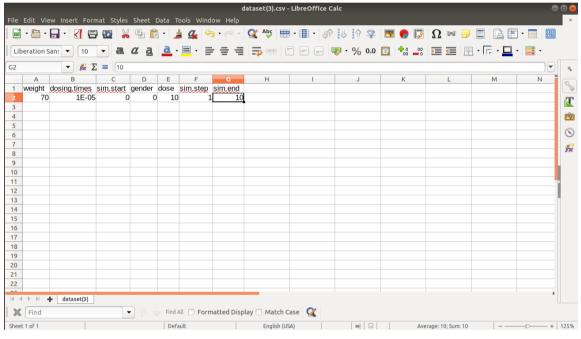
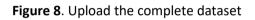


Figure 7. Complete the csv with appropriate values

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	Overview	Features	Predict / Validate	Discussion	Archive					
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of diazepam in humans post intravenous injection.	dataset (should at least contain dent features)									
	Input values for th	e independen	t features							
	dosing.times	weight	d	ose	gender	sim.end				
	hours	kg	m	g	0: male 1: female	hours				
	sim.start	sim.step	0							
	hours	hours								



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	Overview	Features Predict / V	alidate Discussion	Archive				
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	dose	dosing.times	gender	sim.end	sim.step			
	mg	hours	0: male 1: female	hours	hours			
	weight	sim.start						
	kg	hours						
								0

Figure 9. Select 'None' in the dataset id and then click on 'continue'

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	Overview	Features	Predict / Validate	Discussion	Archive						
	Choose method										
MODEL	Predict							-			
Title: Diazepam Model								_			
Owner: periklists Description:	Upload dataset	with the required	Independent featur	es and values							
This is an updated PBPK model for describing the biodistribution of diazepam in humans post	↓ ↑										
intravenous injection.	Dataset formed										
	ld dose	dosing.times	gender	sim.end	sim.step	weight	sim.start				
	0 10	0.00001	0	10	1	70	0				
	Erase dataset						Start procedu]		
	Input values for	the independent	features				Start prediction with input	t dataset		•	

Figure 10. The upload process unlocks the 'start procedure' button

As it is clear in Figure 10, once the csv is uploaded the user can review the filled values and then press the 'start procedure' button to initiate the prediction, or click on 'Erase dataset' if a mistake is spotted.

It has to be noted that if a model supports vectorized input (e.g. a vector of multiple doses), the user can only provide this kind of input only through the GUI in the following format: [value1, value2, ...] (Figure 11). In this case, the 'Start' button on the bottom right end of the screen appears only after all values have been filled in, so NULL values are not feasible.

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	Choose method								
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Title: Diazepam Model Owner: periklists Description:	Upload dataset with	the required indepe	endent features and val	ues					
This is an updated PBPK model for describing the biodistribution of diazepam in humans post intravenous injection.	↓ ↑ Input values for the	independent featur	es	ļ					
	gender O	weight 70	sim.start O	dose [10,15,10]	dosing.times [0.001,3,15]				
	0: male 1: female	kg	hours	mg	hours				
	sim.step 1	sim.end							
	hours	hours							
						Start			

Figure 11. Example of a vector input on the GUI

When the prediction process is initiated, a small log is generated on the screen and, if no error occurs, the user can proceed to the results by clicking on the double arrow icon on the bottom of the screen (Figure 12).

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E Jaqpot **	Predict Task started Predicted dataset or value will be returned PREDKTOM Task is now running. Prediction Task is now running. Model retrieved successfully. Searching dataset Dataset has been retrieved. Starting Prediction Prediction completed successfully. Dataset was built successfully. Now saving to database Task Completed Successfully.	Search jacpot				B
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Figure 12. Click on the 'View prediction' icon to obtain the predictions

The results are given on a tabular format on the GUI and can be downloaded for further processing by clicking on the download button (Figure 13).

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	2	0	0.00001	L O	0	0	0	0	0	0	0	0	0	0	0	0			
	3	21.2368	1	231.3758	36.8978	8 14.1672	2 20.8904	15.8869	513.4203	230.2104	19.617	12.8609	20.2755	14.7328	23.9359	8.895			
	4	14.4062	2	157.8264	25.085	4 9.4955	14.2105	10.6367	538.4165	157.7192	13.438	8.7202	13.8262	10.0394	16.293	6.0615			
	5	13.5834	3	148.9061	23.658	7 8.9409	13.4031	10.0142	528.0355	148.8783	12.684	8.2217	13.0443	9.4708	15.3685	5.7182			
	6	13.2159	4	144.8846	5 23.019	1 8.698	13.0408	9.7421	515.3186	144.8632	12.3424	7.9992	12.692	9.215	14.9532	5.5638			
	7	12.8898	5	141.31	22.451	1 8.4833	12.7191	9.5016	502.7203	141.2895	12.0379	7.8018	12.3789	8.9876	14.5842	5.4265			
												Item	s per page:	30 1	- 12 of 12	<	>		
	Downlo	bad	Plots																
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Figure 13. The 'Download' button allows downloading the results in a csv format

The 'Plots' button which is positioned right next to the 'Download' button allows the user to produce plots by selecting the desired dependent features using the drag-and-drop technique (Figure 14). The desired plot then appears under the predictions (Figure 15).

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Id	Id	time	ц		Ht Br	
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2	Art				0 0	
3	Re	-			328 23.9359 8.895	
4	Mu				1394 16.293 6.0615 108 15.3685 5.7182	
6	Ad	0			.5 14.9532 5.5638	
7	Ven				76 14.5842 5.4265	
	Lu				1 - 12 of 12 < >	
	cı.					
Downlo						
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Figure 14. A plot can be generated by dragging and dropping the desired dependent features on the x and y-axis respectively

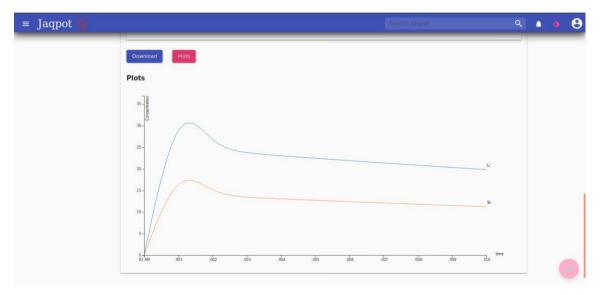


Figure 15. Plot that shows the concentration of diazepam in the liver and stomach compartment

Finally, the user can add comments and remarks or ask a question regarding the model under the 'Discussion' tab (Figure 16).

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	Overview	Features	Predict / Validate	Discussion	Archive				
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Figure 16. 'Discussion' tab of the Diazepam model

Support



