

TablerPMX is an open-source Shiny[1] application, soon available on GitHub [2], for the simulation of pharmacokinetic (PK) models. It implements a user-friendly interface to input model parameters, dosing regimen, and settings for simulations from a library of models. The application utilizes mrgsolve [3], an R package for simulation from hierarchical, ordinary differential equation (ODE) based models typically employed in drug development, for model description and simulation, providing a convenient and popular method for expressing models and rapid calculation over the large numbers of subjects in population simulations. TablerPMX presents results on screen, with plots of the typical subject and population simulations and summary of key PK parameters, and in a downloadable report.

Objectives

- Provide an easy to use, GUI-based tool for simulating from PK models
- Demonstrate TablerPMX by simulating a dupilumab model from literature

Methods

TablerPMX was developed primarily based on the R Shiny and mrgsolve packages. The GUI consists of 5 main tabs: Model Selection; Simulation Details; Simulation Output; Report Generation; and Documentation.

A literature model for dupilumab[4] was selected to demonstrate the simulation workflow. On the Model Selection tab, a two-compartment model with linear and non-linear elimination and first order absorption was selected. The model parameters were entered in the dialog windows that appear when clicking on the Fixed Effects and Random Effects buttons (figures 1 and 2).

Figure 1. Fixed effects editing window (partial view)

Fixed Parameters Selection

TVKE Value

TVKE Units

ALBV2 Value

ALBV2 Units

0.0418

L/day

-0.484

unitless

TVV2 Value

TVV2 Units

WTVMAX Value

WTVMAX Units

2.76

L

0.224

unitless

TVK23 Value

TVK23 Units

DOSE Value

DOSE Units

0.0952

L/day

0

mg

TVK32 Value

TVK32 Units

REGNUM Value

REGNUM Units

0.163

L

0

unitless

Figure 2. Random effects editing window

Select Simulated Random Effects

Variability Options

None

Interindividual Variability

Residual Variability

Both

Interindividual Variability - Correlation Matrix

	ETA_KE	ETA_V2	ETA_VMAX	ETA_KA	ETA_FSC
ETA_KE	0.039				
ETA_V2	0.000	0.008			
ETA_VMAX	0.000	0.000	0.059		
ETA_KA	0.000	0.000	0.000	0.243	
ETA_FSC	0.000	0.000	0.000	0.000	0.132

Residual Variability - Correlation Matrix

	PROP	ADD
PROP	0.039	
ADD	0.000	2.980

Check Matrices

TablerPMX: an open-source Shiny application for PK simulation

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TablerPMX is under active development, with the following key features currently implemented:

- Selection of a PK model from a library that includes variations of linear and non-linear elimination, multiple compartments, target mediated drug disposition, and absorption compartment,
- The ability to load a custom user-defined model in the form of an mrgsolve model file,
- A graphical user interface (GUI) for entering fixed and random effect parameters, dosing regimen (using mrgsolve “doseRx” syntax), and simulation settings,
- Review of plots and tables on-screen and in a downloadable report, and
- The ability to download dosing and simulation tables for further analysis.

Figure 3. Simulation Details tab with specified regimen and preview of the dosing profile

REGENERON

Loaded Model: popPK_2cmt_linearnm_jvnc

Simulation Steps:

- Expand Rx Dataset
- Run Simulation

Dashboard

Model Selection

Simulation Details

Simulation Output

Start simulation

Report Generation

Feedback

Documentation

Rx Specification of Dosing Regimens

Define Dosing Regimen

600 then 300 q14x12 in 1

Submit dosing regimen

Rx Label Syntax Documentation

Add dosing regimen

Dosing Regimen Label

REG02

Dosing Regimen ID

2

Save data as .csv

dosing_regimen.csv

Download Rx Dosing Event Dataset (.csv)

Rx Dosing Event Dataset

ID	TIME	AMT	RATE	EVID	CMT	ADOL	S	SS
1	0.00	300.00	0.00	1	1	9	5.00	0

Simulation Options

Time Grid

Simulation Settings

Solver Settings

Expand Rx Dataset

Rx Dosing Profile

Table 1. Simulated exposure parameters for the two regimens [mean (SD) median (5th %-ile, 95th %-ile)]

Parameter	200 Q2W	300 Q2W
AUC	639.9 (238.6) 613.8 (289.3, 1065)	1177 (368.1) 1134 (636.1, 1834)
Cmax	63.35 (23.02) 60.65 (31.6, 103.7)	114.1 (35.93) 109.5 (63.45, 177.4)
Cmin	34.9 (17.28) 32.32 (11.78, 66.89)	67.35 (27.82) 62.94 (29.55, 117.9)
Tmax	5.07 (2.532) 5 (2, 10)	5.196 (2.696) 5 (2, 10)

Figure 4. Dupilumab simulated PK profiles (median and 90% prediction interval)

REGENERON

Loaded Model: Zhang_dupi_2022

Dashboard

Model Selection

Simulation Details

Simulation Output

Start simulation

Report Generation

Pharmacokinetic profiles

DV

Time after dose (days)

150

100

50

0

DV

Time after dose (days)

150

100

50

0

Show prediction interval:

10%-90%

Concentration units:

mg/L

Dependent Variable

DV

Download the simulated dataset (.csv)

A2PG

The dosing for two regimens -- s.c.: 300 mg q2w (with a 600 mg loading dose) and 200 mg q2w (with a 400 mg loading dose) – was entered on the Simulation Details tab (Figure 3). The Simulation Settings were changed to simulate 1000 random subjects. The simulation was completed, and a report was generated.

Results

The simulated profiles (median and 95% prediction interval, Figure 4) were consistent with the published phase 3 results in the publication[4]. The mean (SD) Cmax, Tmax, Cmin, and AUC were: 63 (23) mg/L , 5 (2.5) days, 35 (17) mg/L and 640 (239) mg/L*day for the 200 Q2W regimen; and 114 (36) mg/L , 5.2 (2.7) days, 67 (28), and 1180 (368) mg/L*day for the 300 Q2W regimen. The 300 mg Q2W simulated exposures were similar to the post hoc Cmin and AUC in the phase 3 trial (64.5 mg/L and 1064 mg/L*day, respectively).

Conclusion

TablerPMX provides an easy-to-use interface for simulating many common PK models. The application was able to reproduce results from a published PK model. TablerPMX may prove useful to modelers and non-modeler colleagues who wish to quickly evaluate new dosing regimens and or covariate effects in existing models without having to implement the simulation code and model translations (e.g. from NONMEM) themselves.

References

[1] Winston Chang, Joe Cheng, JJ Allaire, Carson Sievert, Barret Schloerke, Yihui Xie, Jeff Allen, Jonathan McPherson, Alan Dipert and Barbara Borges (2021). shiny: Web Application Framework for R. R package version 1.7.1. <https://CRAN.R-project.org/package=shiny>

[2] <https://github.com/>

[3] Kyle T Baron (2022). mrgsolve: Simulate from ODE-Based Models. R package version 1.0.3. <https://CRAN.R-project.org/package=mrgsolve>

[4] Zhang L, Gao Y, Li M, Xu C, Davis JD, Kanamaluru V, Lu Q. Population pharmacokinetic analysis of dupilumab in adult and adolescent patients with asthma. CPT Pharmacometrics Syst Pharmacol. 2021 Aug;10(8):941-952.

Acknowledgements

TablerPMX has been based on PMX Sim from PMX Solutions, under the AGPL-3.0 license:
<https://app.axiaal.com/PKSim/>
<https://www.pmxsolutions.com>
<https://github.com/michielve/>