ModViz POP: R Shiny-Based PK/PD Interface for Empowering Teams to Perform Real-Time Simulations

Pavan Vaddady; Bhargava Kandala

Merck & Co., Inc., Kenilworth, NJ, USA

Abstract

Objective: Demonstrate an interactive and dynamic visualization tool, ModViz POP, for simulating ordinary differential equation-based PK/PD models with variability.

Methods: ModViz POP has a built-in PK/PD ODE library of models based on the compartmental nomenclature for simulating standard IV bolus, infusion, and first-order absorption scenarios. It also gives the user the ability to plug in a model from a local directory to quickly simulate a model of interest. Users can also simulate from a project library, which serves as a repository of final PK/PD models developed by individual project teams. Beyond the PK/PD models, it can handle complex QSP models and PBPK models equally well.

Enhanced R packages, HTML/CSS, and LaTeX, in combination with Shiny, were used and provided an elegant and powerful programming framework for turning models into a web application with dynamic visualization and automated report writing. The user interface consists of several key inputs for performing the simulations.

A tabbed navigation allows the user to visualize the plots, input parameters, derived values, and equations. It provides the ability to download the underlying model, plots, simulated data, or a comprehensive report consisting of all of the key inputs and outputs of the simulations. The Help button provides a link to documentation with detailed instructions on different components of the interface.

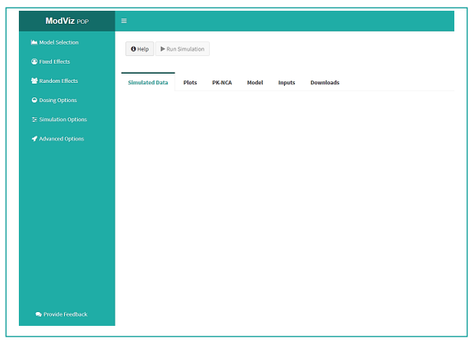
The interface also includes advanced features through which users can overlay external data over simulated data, set a certain simulation scenario as a reference, or carry out sensitivity analysis based simulations.

Conclusions: This easy-to-use interface can serve as a valuable tool for teams to explore and evaluate potential scenarios and thus facilitate collaborative decision making in the drug discovery and development paradigm.

WHAT IS MODVIZ POP?

ModViz POP is an interactive and dynamic visualization tool developed for simulating ordinary differential equation-based pharmacokinetic and pharmacodynamic (PK/PD) models with variability. Availability of a wide array of library PK/PD models, flexibility to simulate from any ODE-based user-defined model, customizable plotting features, advanced features to overlay external data, the ability to set a simulation as a reference, conduct parameter sensitivity analysis, and robust reporting features make ModViz POP an attractive platform to be leveraged by PK/PD scientists and modelers in their day-to-day activities. It is primarily programmed in R and uses key R packages such as tidyverse, mrgsolve, PKNCA, and xtable. It utilizes R Shiny for the web application framework, LaTeX for PDF report generation, and HTML and CSS for styling the graphical interface.

The user interface consists of a sidebar with several key inputs for performing the simulations. A tabbed navigation allows the user to visualize the simulated data, plots, PK NCA, model equations, and input parameters. It also provides users the ability to download the underlying model, plots, simulated data, a comprehensive report consisting of all the key inputs and outputs of the simulations, and a complete simulation session the user works on.



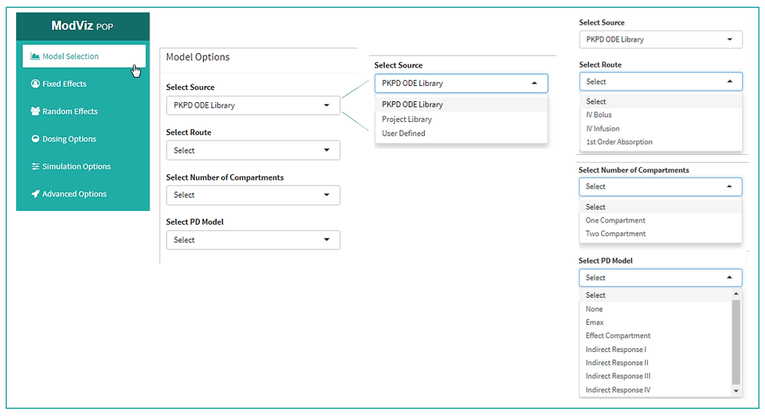
MODEL SELECTION SOURCES

1. PK/PD ODE Library: This is a library of PK/PD models based on the compartmental nomenclature (eg, V1, CL, KA, etc) for simulating standard IV bolus, infusion, and first-order absorption simulations.
2. Project Library: This is a repository of PK/PD models for project teams developed specifically for a project-based application to impact decision making.
3. User Defined: This gives the ability to plug in a user-defined model from a local directory to quickly simulate a model.

In addition, a custom event input option provides the ability to input complex dosing scenarios by browsing for a file and uploading it.

PK/PD LIBRARY AND MODEL SELECTION

If a PK/PD library is selected in the Source selection (also the default selection), the Model selection provides options for selection of route, number of compartments, and PD model. Route of Administration selection includes IV bolus, IV infusion, and first-order absorption. Number of Compartments selection includes one-compartment and two-compartment models as options. PD Model selection includes none (meant for PK-only simulations), Emax, effect compartment, and indirect response I to IV models (meant for stimulation/inhibition of factors controlling production/loss of drug response).

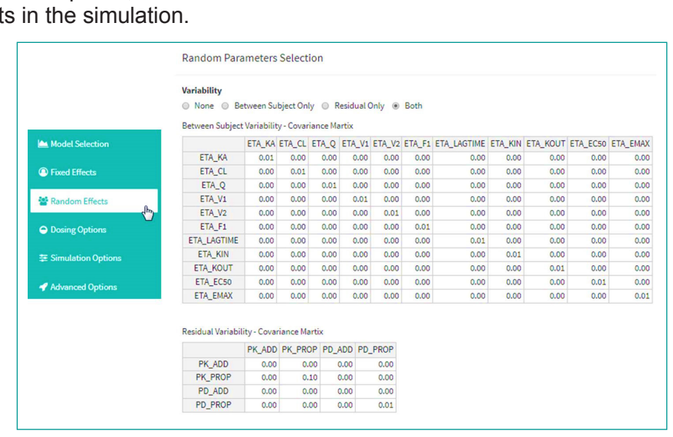


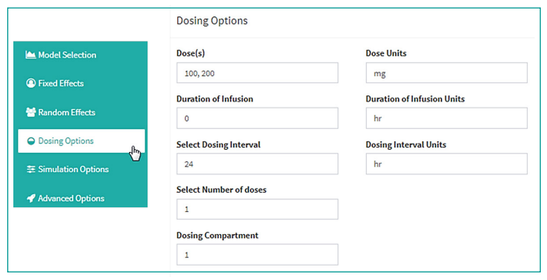
INPUTS FOR SIMULATION

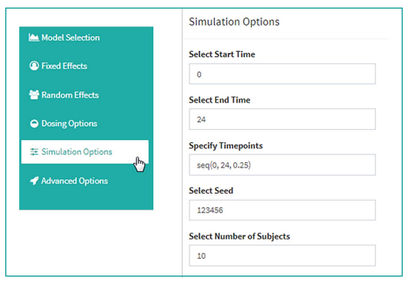
Fixed- and Random-Effects options include ability to edit fixed-effects parameters and random-effects parameters.

Dosing Options include dose(s), duration of infusion, number of doses, dosing interval, and dosing compartment as inputs.

Simulation Options include start time and end time of the simulation, along with the step size, which indicates the smallest time interval between two time points in the simulation.







SIMULATION OUTPUTS

There are multiple outputs generated once the simulation is carried out. They are:

Simulated Data tab includes a table of viewable data.

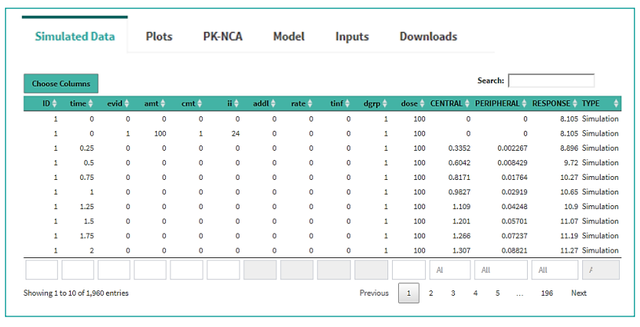
Plots containing plotting options tab give the ability to customize the output plots.

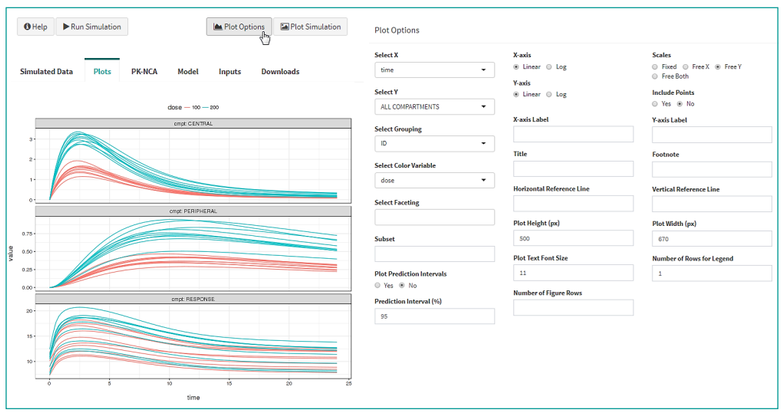
PK-NCA tab summarizes the non-compartmental analysis for the simulated PK data.

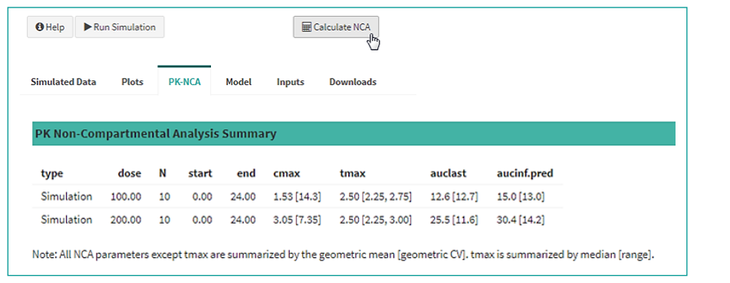
Model tab lists the initial conditions for the parameters along with the differential equations and any associated equations describing the underlying model.

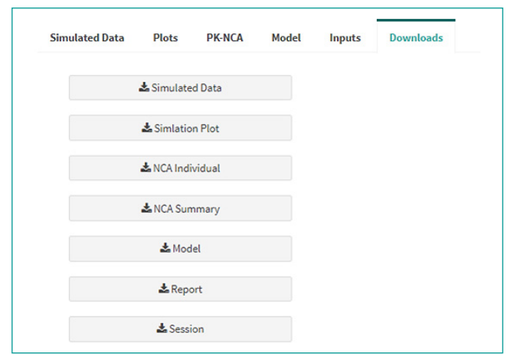
Inputs tab lists the values of the dosing events, fixed- and random-effects parameters of the model, and the simulation options for the currently run simulation scenario.

Downloads tab has several download options, including downloading Simulated Data (.csv), Simulation Plot (.png), Individual NCA Results (.csv), NCA Summary (.tab), Model File (.cpp), and Report (.pdf), which summarizes all of the components and results of the simulation in a comprehensive report.









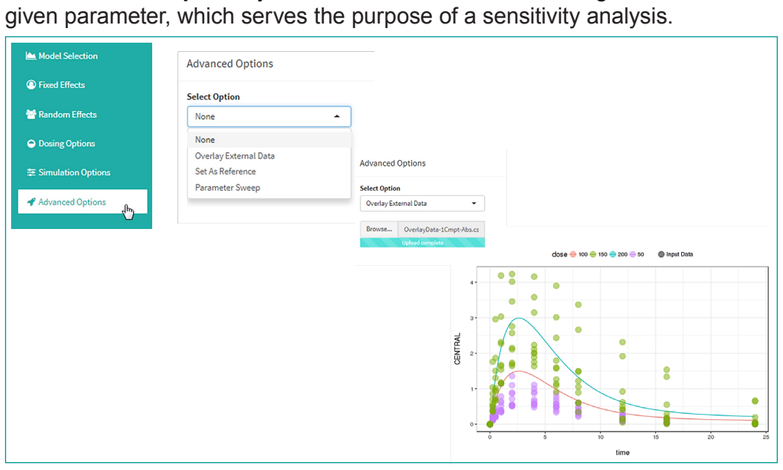
ADVANCED OPTIONS

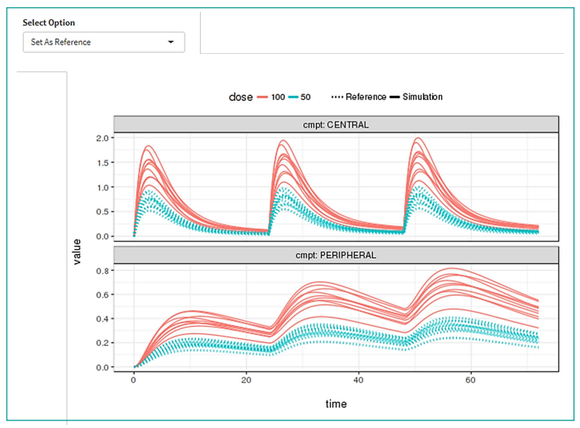
The Advanced Options tab enables users to:

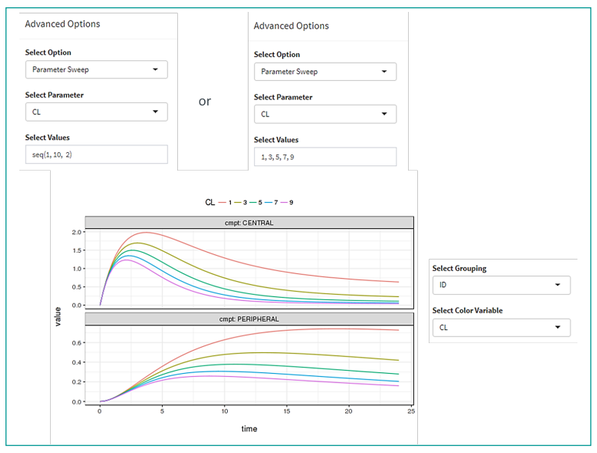
Overlay External Data: Upload external data and overlay that on top of a simulation.

Set as Reference: Set a certain simulation scenario as a reference and perform a second simulation and compare the two results.

Parameter Sweep: Carry out simulations with a wide range of values for a given parameter, which serves the purpose of a sensitivity analysis.







CONCLUSION

This easy-to-use interface can serve as a valuable tool for teams to explore and evaluate potential scenarios and thus facilitate collaborative decision making in the drug discovery and development paradigm.

References

Chang W, et al. shiny: Web application framework for R. R package version 0.13.2. https://CRAN.R-project.org/package=shiny. 2016.

Baron KT, et al. mrgsolve: Simulate from ODE-based population PK/PD and systems pharmacology models. 2017.

Presented at ACoP; San Diego, CA, USA; October 7-10, 2018.