

TUTORIAL

ModVizPop: A shiny interface for empowering teams to perform interactive pharmacokinetic/pharmacodynamic simulations

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Abstract

ModVizPop is an interactive and dynamic visualization tool developed for simulating differential equation-based population pharmacokinetic (PK) and pharmacodynamic (PD) models with variability. It has a built-in PK/PD ordinary differential equations library of models to choose from alongside the ability to plug in a user-defined model from a local or project directory. The user interface consists of several key inputs for performing the simulations as well as options to visualize the plots, perform simple noncompartmental analysis, and review inputs and model code. It also provides the ability to download the underlying model, plots, simulated data, or a comprehensive report consisting of all the key inputs and outputs of the simulations. The interface includes advanced features where users can overlay external data on a simulation, set a certain simulation scenario as a reference, or carry out sensitivity analysis-based simulations. This easy-to-use interface can serve as a valuable tool to project teams to evaluate potential scenarios facilitating collaborative decision making in the drug discovery and development paradigm.

INTRODUCTION

ModVizPop is an interactive and dynamic visualization tool developed for simulating ordinary differential equation-based pharmacokinetic (PK) and pharmacodynamic (PD) models with variability (Figure 1). The following features make ModVizPop an attractive platform to be leveraged by PK/PD scientists and modelers in their day-to-day activities: availability of a wide array of library PK/PD models; flexibility to simulate from any ordinary differential equations (ODE)-based, user-defined model; customizable plotting features; advanced features to

overlay external data; abilities to set a simulation as a reference; conduct parameter sensitivity analysis; and robust reporting. It is primarily programmed in R and uses key R packages such as tidyverse,¹ mrgsolve,² PKNCA,³ and xtable.⁴ It uses Shiny⁵ for the web application framework, LaTeX for PDF report generation, and HTML and CSS for styling 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 and plots; perform PK noncompartmental analysis (NCA); and review model equations, code, and input parameters.

Pavan Vaddady and Bhargava Kandala contributed equally towards the development of this tutorial.

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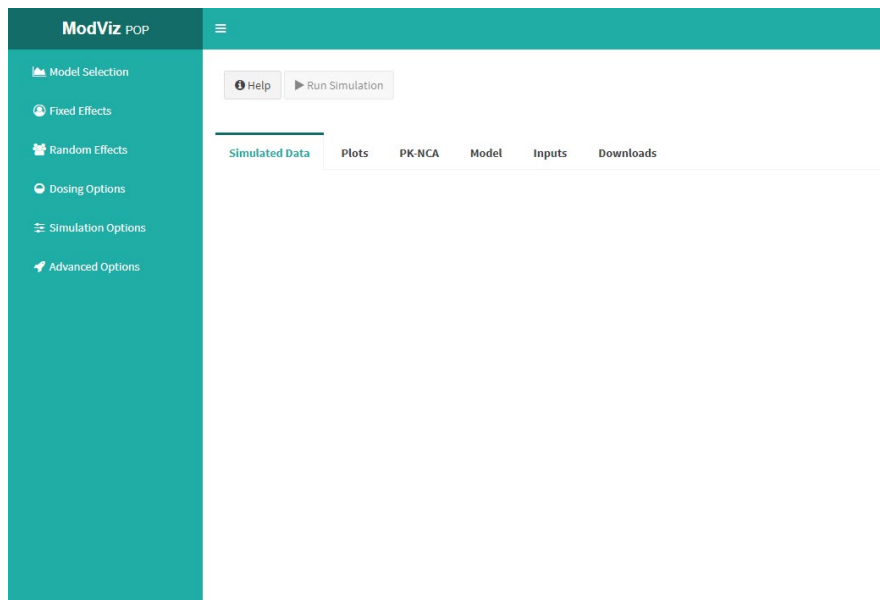


FIGURE 1 ModVizPop interface showing the different navigation options

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. The Help button is a link to ModVizPop documentation with detailed instructions on different components of the interface for running custom simulations.

APPLICATION DEVELOPMENT AND MAINTENANCE

As more drug development teams embrace model-informed drug development approaches to streamline and accelerate the development of novel therapies, there is a need for tools that enable drug developers to test ideas and simulate relevant clinical trial scenarios before actual trials are run. This was the motivation behind ModVizPop—an application that can be used to run model-based simulations by changing key inputs in a live team setting. The development of this application started almost 4 years ago with an initial version where mean PK/PD profiles could be simulated. Encouraged by the utility of the application by colleagues within the discovery and development groups, the ability to simulate random effects was incorporated to cater to the needs of the quantitative clinical pharmacologists within the clinical development groups.

The current set of features in ModVizPop⁶ are thoughtfully incorporated based on the user feedback over time while ensuring ease of navigation. Also, as a part of qualification, we compared the outputs of ModVizPop simulations from different PK/PD models with NONMEM-based simulations and found them to be comparable.⁷

In the spirit of making this an open-source application, the code is released under the terms of GNU General Public License Version 3⁸, which is a strong copyleft license, conditioned on making available complete source code of licensed works and modifications. The underlying code is accessible on GitHub and the instructions to install and access the application are provided in the Accessing the Application section.

We welcome fellow pharmacometricians from academia, industry, regulatory agencies, and nonprofit organizations to further enhance this application by directly contributing to the code or by submitting relevant PK/PD models for the benefit of the pharmacometrics community. This would help organically add useful features based on the feedback and contributions from the userbase.

MODEL SELECTION

Model Selection option (Figure 2) provides a pop-up menu for selecting the source for the models (default: PKPD ODE Library) along with a custom event input or individual data set as input option.

The source selection, via a drop-down menu, provides the following sources to choose the model file from:

1. PKPD ODE Library: a library of PK/PD models based on the compartmental nomenclature (e.g., V1, CL, KA) for simulating standard intravenous (i.v.) bolus, i.v. infusion, or first-order absorption routes of administration.
2. Project Library: a repository of PK/PD models for project teams developed specifically for a project-based application to impact decision making.

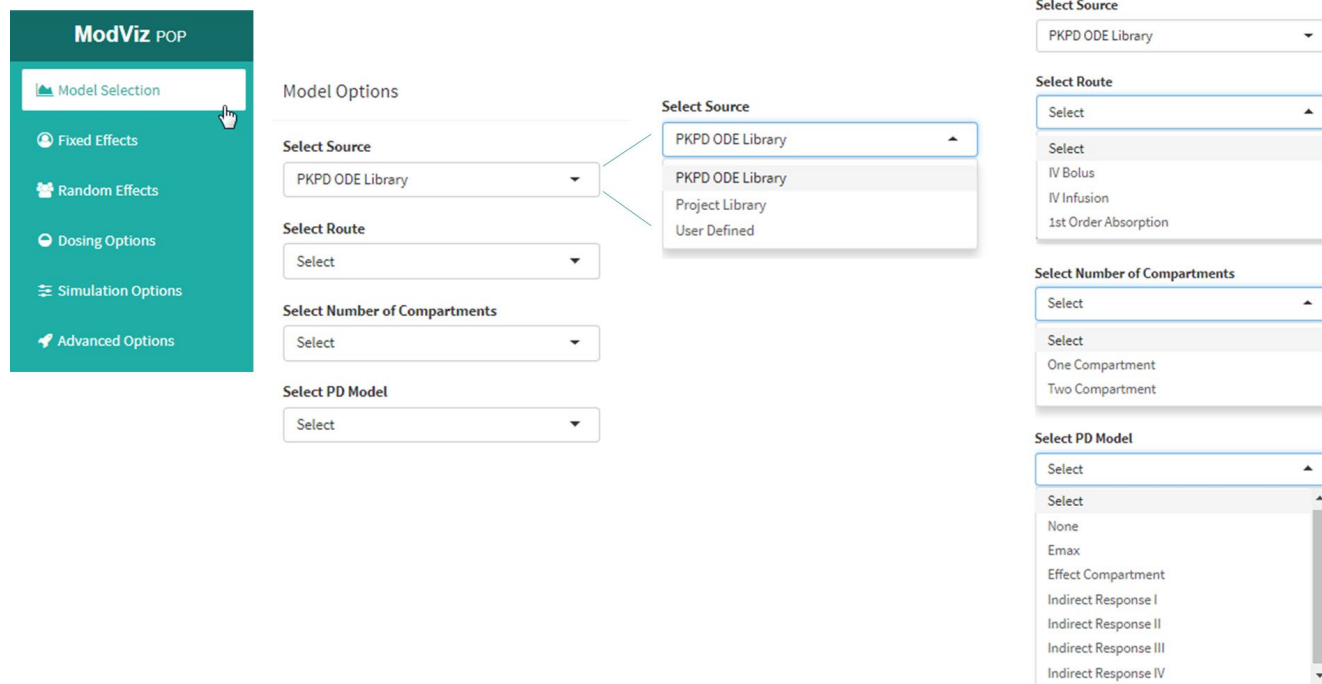


FIGURE 2 Different model selection options available in the interface to customize the model input

3. User Defined: provides the user an option to input a custom model from local directory to simulate from. An example of a user-defined model is shown in the Model S1. Model files have to follow mrgsolve nomenclature.²

A custom event input option provides the ability to input complex dosing scenarios by uploading a custom dosing file from the user's local directory. In instances where the user wants to define the complete input data set, that can also be provided as an input with this option. Examples of custom event input files are illustrated in the (Data S1-S3). Please note that the number of compartments in the event input should be at maximum the number of compartments defined in the model. For example, a one-compartment i.v. bolus model cannot accept events that are dosed into the second compartment. That will require a model that defines at least two compartments.

If a PKPD ODE 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 1st Order Absorption. Number of Compartments selection includes one-compartment and two-compartment models as options. PD Model selection includes options None (for PK-only simulations); E_{max} , Effect Compartment, Indirect Response I to IV models (for PK/PD simulations) (Figure 2). Once all of the options are chosen in the Model Selection, by clicking Load Model, ModVizPop loads and compiles the model. A progress bar on the bottom right-hand corner indicates

when the process is complete. Also, the loaded model is shown under the Load Model button to provide the user clarity on which model is currently loaded for simulation.

The Project Library option in the Source Selection (within Model Selection tab) lets the user select a model from a repository of PK/PD models. These models are developed by individuals, groups, or project teams to aid model-informed drug discovery and development decisions across relevant programs. Users who would like to have a model that needs to be uploaded to the repository, please create a pull request on the ModVizPop github repository (<https://github.com/PavanVaddady/modvizpop>). For User Defined Source Selection, select the *.cpp model file from the local path and select Load Model. It will load the model onto ModVizPop.

FIXED AND RANDOM EFFECTS

Once the model selection is complete, ModVizPop provides an interface to input fixed and random effects. The Fixed Effects option brings up the fixed effect parameters window, and the Random Effects option opens the random effect parameters. ModVizPop automatically populates the fixed and random effects parameters and their default values from the model file that was loaded. For the PKPD ODE Library models, the parameter values need to be updated to the set of PK/PD parameters for compounds of interest. The unit options of the parameters are placeholders for users to note the correct units. They are not

programmed to adjust for the specified doses or concentrations automatically. Users must carefully provide the units as ModVizPop is agnostic to these units.

Random Effects (Figure 3) provides the following options for random effect parameters for different simulations:

- None: simulate with only fixed effects and no variability.
- Between Subject Only: simulate using only between subject variability and no residual variability.
- Residual Only: simulate using only residual variability and no between subject variability.
- Both: simulate using both between subject variability and residual variability.

Additional details around the random effects options are illustrated in the examples provided in the (Text S1). Interoccasion variability can also be included if it is coded using the ETA nomenclature (by using either the Between Subject Only or Both option). All of the input matrices must be block matrices. The covariances need to be properly set to zero in instances where there are only diagonal elements. When there are two separate matrices such as for PK and PD parameters, they need to be pooled into a single block matrix. In instances where the input matrix gets very large, such as for a given user-defined model, the recommendation is that the matrix

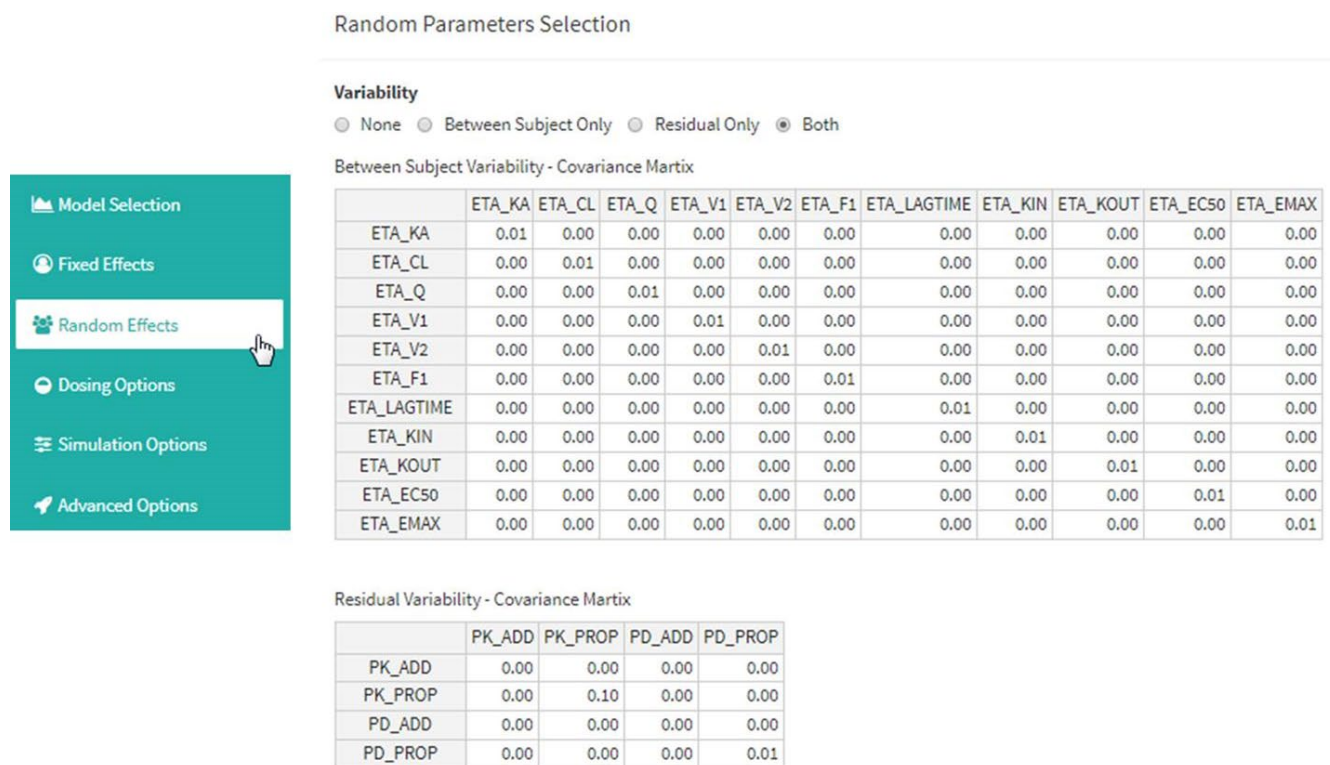
be filled out in the actual model file with ideally minimal edits needed in the interface.

DOSING INPUTS

Dosing options include Dose(s), Duration of Infusion, Number of Doses, Dosing Interval, and Dosing Compartment as inputs. Dose(s) input lets the user simulate more than one dose at a time by using comma-separated values for the doses. Number of Doses input can be used to simulate a multiple-dose scenario. Dosing interval can be customized using the Dosing Interval input. Duration of Infusion option is available when an i.v. infusion option is chosen in the Model Selection from the Library of PK/PD models. Duration of Infusion and Dosing Compartment options are both available when a User Defined or Project Library model is chosen. Dosing compartment defaults to one but can be modified as per the model requirements. Note that in instances where a custom event option is used, Dosing Options cannot be selected.

SIMULATION OPTIONS

Simulation options include selection of start time, end time, and in between timepoints that can be given as an input to



Random Parameters Selection

Variability

None
 Between Subject Only
 Residual Only
 Both

Between Subject Variability - Covariance Matrix

	ETA_KA	ETA_CL	ETA_Q	ETA_V1	ETA_V2	ETA_F1	ETA_LAGTIME	ETA_KIN	ETA_KOUT	ETA_EC50	ETA_EMAX
ETA_KA	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ETA_CL	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ETA_Q	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ETA_V1	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ETA_V2	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00
ETA_F1	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
ETA_LAGTIME	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00
ETA_KIN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
ETA_KOUT	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00
ETA_EC50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
ETA_EMAX	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01

Residual Variability - Covariance Matrix

	PK_ADD	PK_PROP	PD_ADD	PD_PROP
PK_ADD	0.00	0.00	0.00	0.00
PK_PROP	0.00	0.10	0.00	0.00
PD_ADD	0.00	0.00	0.00	0.00
PD_PROP	0.00	0.00	0.00	0.01

FIGURE 3 Random Parameters Selection window to customize the inputs for between subject and residual variability

simulation, an optional seed and the number of subjects to simulate. These options are filled out by default and can be left as such or they can be further modified as per the user requirements. For example, End Time can be extended to simulate the elimination of the drug beyond the default end time of the last dosing interval. The default timepoints include a sequence of timepoints with a step size of 0.25. This step size indicates the smallest time interval between two timepoints in the simulation and can be modified as necessary. The user can also define new comma-separated values or sequences or a combination of these as timepoints for simulation. Some examples are the following:

```
seq(0,                24,                1)
c(0,1,  2,  4,  6,  8,  12,  16,  24)
c(0, 1, 2, seq(4, 24, 2), 48)
```

When random effects are turned off using the None option, Select Seed will not be available, and Select Number of Subjects will default to one. Once all of the options are selected, clicking Run Simulation will run the simulation. A progress bar indicates the simulation completion.

SIMULATION OPTIONS

There are multiple outputs generated once the simulation is carried out. The tabs on the right side include these outputs. These include Simulated Data, Plots, PK-NCA, Model, Inputs, and Downloads tabs.

The first of these tabs is the simulated data. The Column Visibility option lets users choose columns that will be visible in the table. A Search option can let one search for the existence of any content within the table. Through the column headers, the users can sort the order of the column contents. Searchable text boxes are available in the footer of each column to subset the data in the columns. Also, a paged navigation is available on the right-hand bottom corner to switch through multiple pages of data.

Under the Plots tab, two additional options are provided. Plot Options is used to customize the plots generated, and the Plot Simulation button plots the data per the options chosen. Various plot options are available to customize the plots (Figure 4).

- **Select X, Select Y:** you can select the variables to be plotted on the X-axis and the Y-axis. ALL COMPARTMENTS defaults to all the compartments present in the model.
- **Select Grouping:** one can select a grouping variable to group the lines by (e.g., ID).
- **Select Color Variable:** similarly, a color variable option is available to color the groups specified in this option.
- **Select Faceting:** selecting one or more faceting variables (e.g., ID, Dose) allows you to visualize a matrix of simulations based on the levels of the faceting variables.
- **Subset:** Subset is an option to create a subset for plotting. For example, if one is interested in looking only at a particular dose, say 100 mg, despite simulating many dose levels, they can use subset option and have “dose==100,” which will subset the simulated data set to this dose and will only plot these new data. Note that the simulated data will not change.
- **Plot Prediction Interval, Prediction Interval (%):** when simulating with variability, the Prediction Interval provides an option to look at the bands as shaded areas rather than spaghetti plots (e.g., a visual predictive check or VPC-like set up). One can also specify the level of the prediction intervals. An illustration of a VPC-type simulation is provided in the (Text S1).
- **X-axis,Y-axis:** linear, log-linear, log-log plotting are possible by changing the x and y axes to either a linear scale or a log scale.
- **Scales:** Scales provides a means to have a uniform scale between different facets to easily compare profiles across them. One can choose either a Fixed, Free X, Free Y, or Free Both scale to tailor the plots.
- **Include Points:** this option provides the user an option to plot points on top of the existing plot.
- **X-axisLabel, Y-axis Label, Title, Footnote:** one can also customize the labels for X-axis, Y-axis, title, and footnote.
- **Horizontal and Vertical Reference Line:** a reference horizontal or vertical line can be added to the plots by specifying values at which these reference lines should occur.
- **Plot Height, Plot Width:** plot height and width can be adjusted (in pixels) to customize the size of the plot.
- **Plot Text Font Size:** font size of the text in the figure can be adjusted to make it readable.
- **Number of Figure Rows:** this provides an option to customize the layout of the facets. For example, if there are eight facets, and one wants to have a 4-row \times 2-column layout, they can provide 4 rows as an option and the figure automatically chooses 2 columns, making it a 4 \times 2 layout.
- **Number of Rows for Legend:** if there are many parts in the legend, one can choose the number of rows for the legend for ease of reading the legend.

The PK NCA tab summarizes the NCA for the simulated PK data. The interface provides Calculate NCA button to perform NCA calculations. Depending on whether it is a single dose or multiple dose, NCA-calculated parameters differ. For example, with a single dose, AUC0-inf will be provided. For multiple doses, the first and last dose NCA parameters will be provided. Instead of AUC0-inf, AUC0-tau and Cavg will be estimated. For documentation on how these NCA parameters are calculated, refer

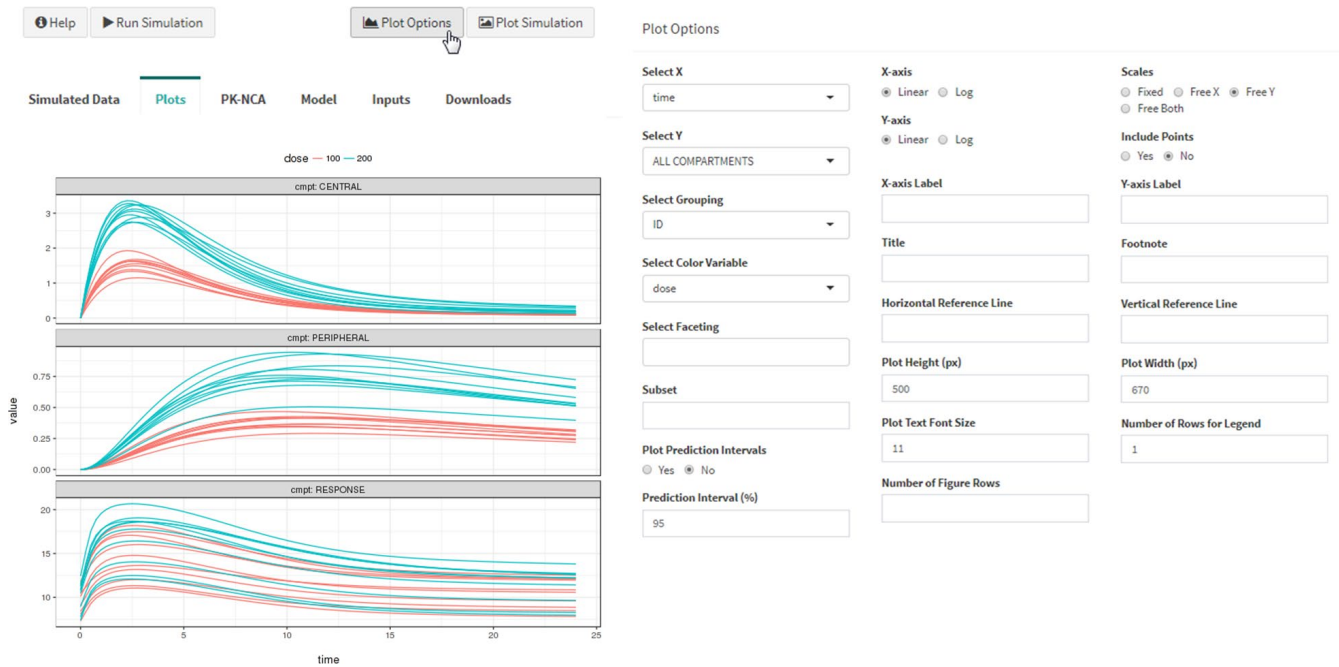


FIGURE 4 Different plotting options that can be used to customize the plot generated

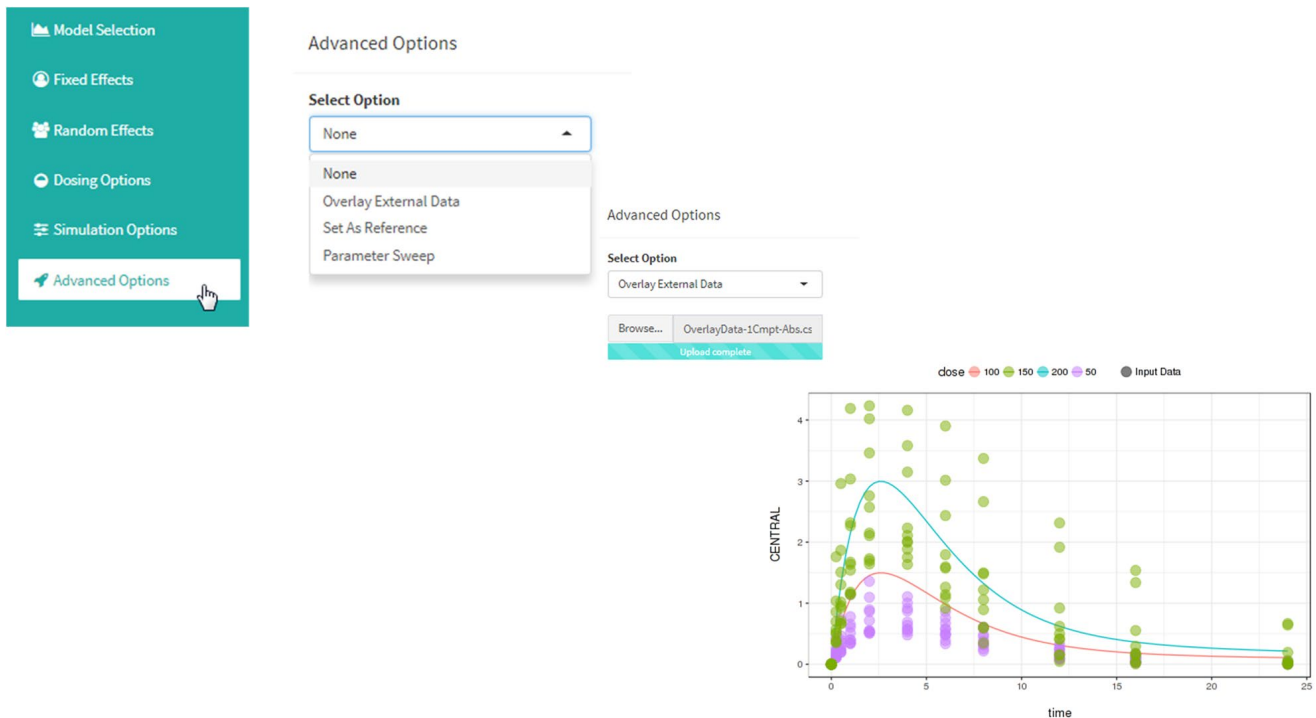


FIGURE 5 The available Advanced Options as well as an example illustrating overlaying external data

to the PKNCA R library documentation. Note that PKNCA will not be calculated in the following situations:

- When a custom event input data set is provided.
- For any external overlaid data.
- When compartment CENTRAL is labeled differently or is not present in the model.
- When clearance and central volume of distribution parameters are not explicitly labelled as CL and V1 in the model.
- When total observations exceed 100,000.

Select Option

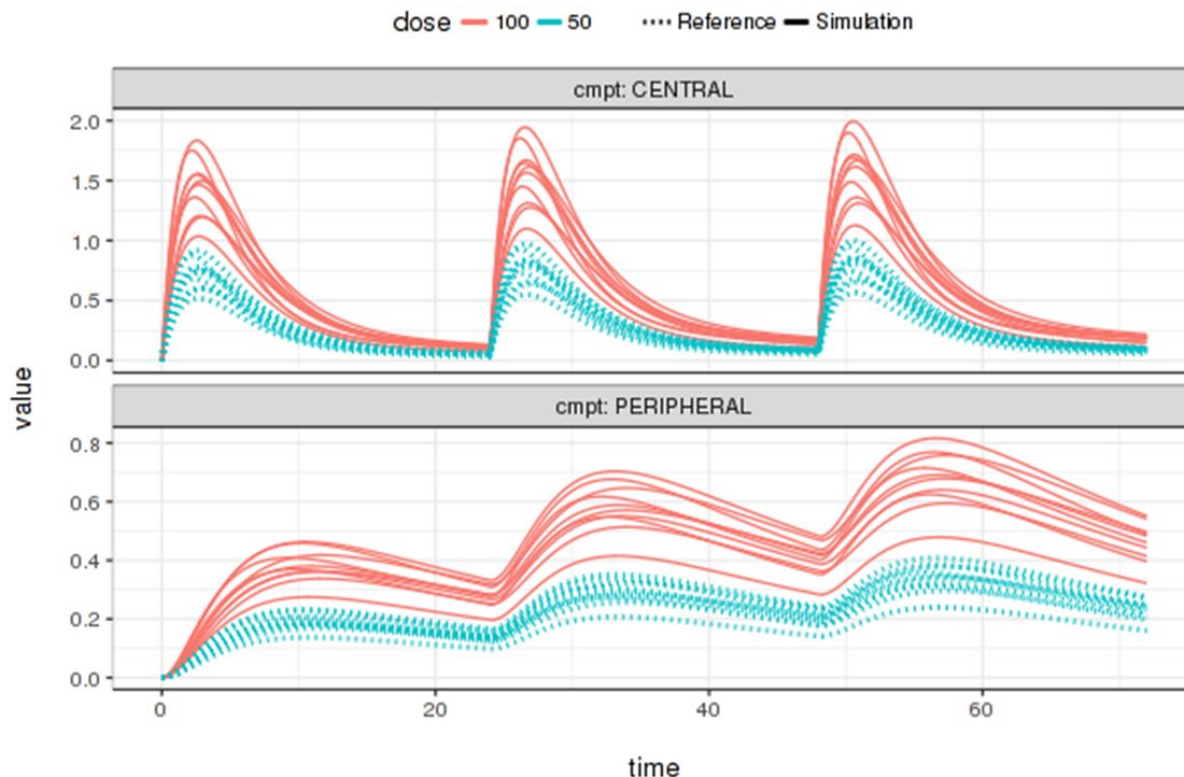


FIGURE 6 Advanced option of setting an existing simulation (dose = 50) as a reference and overlaying a new simulation (dose = 100)

The Model tab lists the initial conditions for the parameters along with the differential equations and any associated equations describing the underlying model. This tab also lists the complete model code for user reference.

The 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. When advanced features such as Set As Reference are used, ModVizPop presents the values of both the current simulation and the reference scenarios.

There are several download options once the simulation is run. They include 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. There is also a Session (.zip) download option that can be used to download the complete user session, which includes all the plots, model files, and individual and summary NCA files generated during the session.

ADVANCED OPTIONS

The advanced options tab enables users to:

- Overlay External Data: upload external data and overlay that on top of a simulation (Figure 5).
- Set As Reference: set a certain simulation scenario as a reference and perform a second simulation and compare the two results (Figure 6).
- Parameter Sweep: carry out simulations with a wide range of values for a given parameter that serves the purpose of a sensitivity analysis (Figure 7).

Note that the Model Selection option will not be accessible if Advanced Options are chosen.

After performing a simulation and obtaining an output, the user has an option to overlay external data by selecting the Overlay External Data option from the advanced options. Subsequently, users can browse and select an input data set from their local directory. Upon selection of the data set and running simulation, the uploaded data will

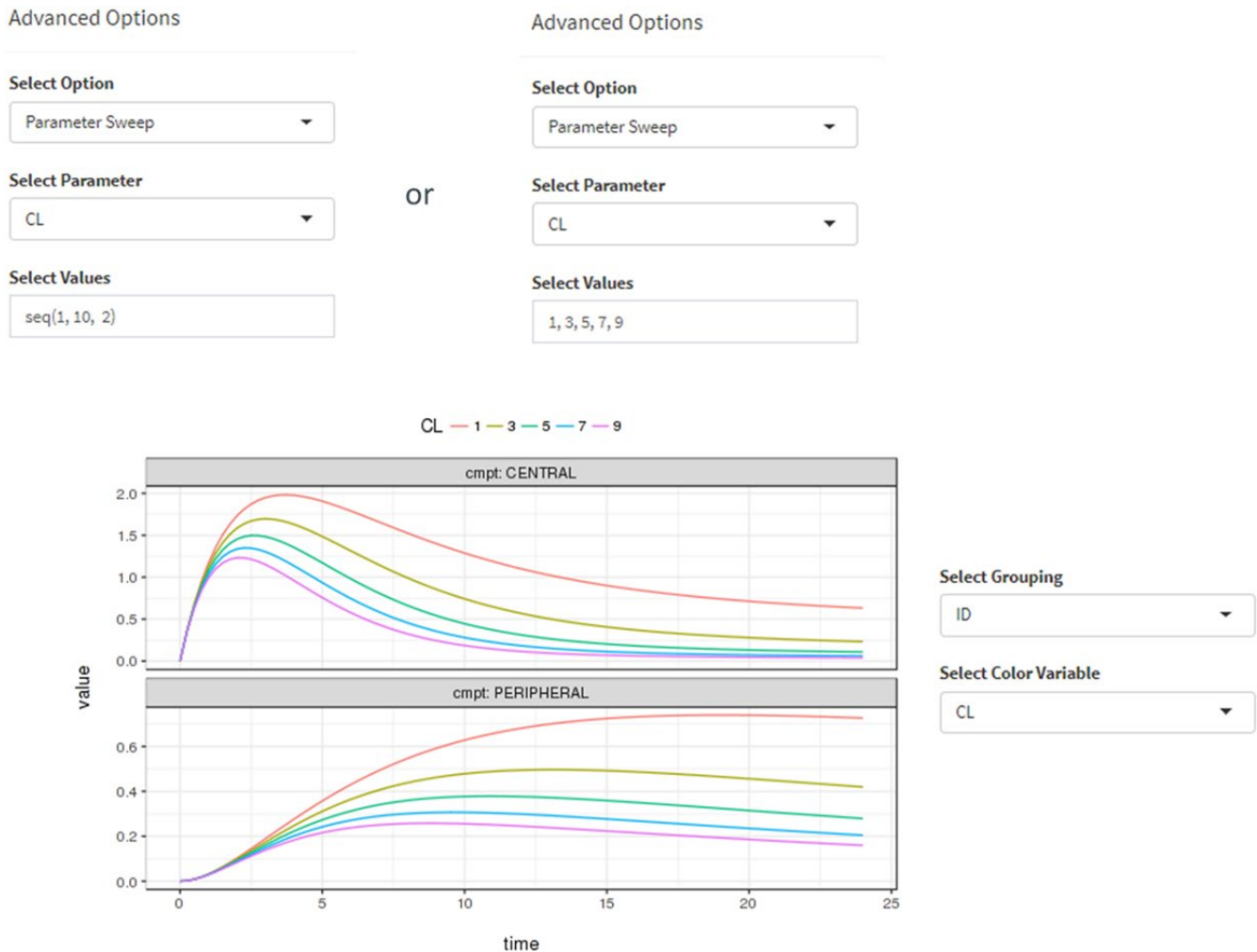


FIGURE 7 Advanced option for performing a parameter sweep. Shown are the different ways one could provide the input of varying the values of CL and the resulting plot from those different values

be added to the plot as points on top of the simulated lines in the plot. The additional plotting options Overlay Shape and Overlay Point Size are available, and they can be used to customize the shape and size of the points.

There are formatting rules for input data set. ID, time, dose, and compartment name(s) are the minimum column names needed to overlay data. Column names for compartments should match the exact names as denoted in the plot headers or in the simulated data, which can be downloaded and explored. Data classes should be all numeric in the external data set. Overlay does not work if there is a character in the data set to be overlaid. The Help section in the interface provides details on the format of the input data set.

Following a simulation, the user can set that scenario as a reference by selecting Set As Reference option from the Advanced Options. Subsequently, the user can change any of the values under Fixed Effects, Random Effects, Dosing Options, and/or Simulation Options to perform a second simulation. The output will contain both the

reference scenario (dotted line) and the latest simulation (solid line) results in all of the outputs. The additional plotting options Reference Linetype and Reference Line Size are available, and they can be used to customize the line type and size of the lines.

On some occasions, it is worthwhile performing a sensitivity analysis by varying the values of a certain parameter and studying how these changes affect the overall output. ModVizPop users can do that by selecting Parameter Sweep option from the Advanced Options. Once selected, the user is asked to select a parameter of interest from the model for which a sensitivity analysis is to be carried out. Once the parameter is selected, the user has an option of providing values of the parameter as a sequence or comma-separated values or a combination of these to evaluate the outcome at these different values as shown in Figure 7. Selecting Run Simulation and selecting a grouping variable or color variable to be the parameter of interest in the Plot Options helps better visualize the results of the sensitivity analysis.

ACCESSING THE APPLICATION

There are a couple of options available to access the application.

1. Using the github repository (<https://github.com/PavanVaddady/modvizpop>).

Users can install the application as an R package using the following command. They need to ensure that the R package dependencies and Rtools are preinstalled (see <https://github.com/PavanVaddady/modvizpop/blob/main/inst/shiny-apps/myapp/installPackages.R>).

```
devtools::install_github("PavanVaddady/modvizpop")
```

Once installed, they can access the application using the following commands:

```
library(modvizpop)
runmodvizpop()
```

2. Using shinyapps.io (<https://pavanvaddady.shinyapps.io/modvizpop/>):

The application is ready to use by clicking on the link. There is no additional installation needed.

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.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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REFERENCES

1. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Software*. 2019;4(43):1686.
2. Baron KT. mrgsolve: simulate from ODE-based models. R package version 0.10.4. <https://CRAN.R-project.org/package=mrgsolve>
3. Denney W, Duvvuri S, Buckeridge C. Simple, automatic noncompartmental analysis: the PKNCA R package. *J Pharmacokinet Pharmacodyn*. 2015;42(1):11-107, S65.
4. Dahl DB, Scott D, Roosen C, Magnusson A, Swinton J. xtable: export tables to LaTeX or HTML. R package version 1.8-4. <https://CRAN.R-project.org/package=xtable>. Published 2019.
5. Chang W, Joe Cheng JJ, Allaire CS, et al. shiny: web application framework for R. R package version 1.6.0. <https://CRAN.R-project.org/package=shiny>
6. Vaddady P, Kandala B. ModViz POP: R shiny-based PK/PD interface for empowering teams to perform real-time simulations. M-079. Abstracts for the Ninth American Conference on Pharmacometrics (ACoP9). *J Pharmacokinet Pharmacodyn*. 2018;45:3-134.
7. Ananthula HK, Kandala B & Vaddady P Comparison of PK/PD simulations using ModViz POP, an R-Shiny based PK/PD interface and NONMEM. In: Abstracts for the Tenth American Conference on Pharmacometrics (ACoP10); 2019; Orlando, FL. Abstract M-101. October 20, 2019-October 23, 2019.
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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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