AMGET

User Manual

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AMGET is a free software and
comes with ABSOLUTELY NO WARRANTY.

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Introduction

ADAPT5 is a powerful modeling software for population pharmacokinetic *(PK)* and pharmacodynamics *(PD)* systems analysis, but provides limited built-in functionality for creating pre- and post-analysis diagnostic plots. ADAPT5 Model Evaluation Graphical Toolkit *(AMGET),* an external package written in the open-source R programming language, was developed specifically to support efficient post-processing of ADAPT5 runs, as well as output from NONMEM and S-ADAPT runs. Using interactive navigational menus, users of AMGET are able to rapidly create informative diagnostic plots enriched by the display of numerical and graphical elements with a high degree of customization through the use of a simple settings spreadsheet.

This user manual contains details about the set-up, settings and use of AMGET; for more information, comments or suggestions on AMGET feel free to contact us at guiastennec@gmail.com.

Installation

AMGET in version 1.0 is available online for free download on the Comprehensive R Archive Network *(CRAN)* website at http://cran.r-project.org. The installation of the package can be performed through any of the two following methods.

1. Download and installation in R

This is the simplest way to install the package and the method we recommend. To do so, simply enter the following command in the R console

```
install.packages('AMGET')
```

A message should confirm that the installation was performed successfully.

2. Download from CRAN

The second method consists of accessing the CRAN website, saving the package archive *(*.zip for Windows and *.tar.gz for Macs)* on your drive of choice, and then installing the package within R through the package management menu.

3. Updates

Updates will be regularly released in a constant effort of improvement to make new features, improvements to existing functions, and bug fixes available to the community. Whenever available, updates can be installed following either one of the two methods previously described. Some R graphical user interface *(GUI)* tools, such as RStudio *(http://www.rstudio.com)* also have menu options to update packages.

First Run

1. Start AMGET

To start AMGET, the package needs to have been successfully downloaded and installed in R. To load and start the package you need to enter the following commands:

```
require(AMGET)
AMGET()
```

AMGET requires the use of a settings sheet to allow the user to define the settings the graphics' options. The first time you will run AMGET, the settings file will thus be created. You will be asked where to save the *AMGET_Settings.csv* file as shown below *(e.g. C:/MyDirectory)*:

```
It appears to be the first time you are running AMGET.
The settings spreadsheet will be created, please
indicate the destination folder below:
```

If the folder specified is found, the following message will be printed:

```
The settings spreadsheet and the user manual were
successfully created in:
C:/MyDirectory/
```

The user will then be asked to define the directory where all the graphics will be saved *(e.g. C:/…/Desktop/AMGET_Plots)* as shown below. *Note: it can be the same folder where the settings file was just copied.*

```
Define the folder where all the graphics will be saved
(this can be redefined in the settings file under
output directory later on for enhanced organization of
additional projects/runs):
```

This step will update the 'Plots Output directory' information of the *AMGET_Settings.csv* that was just created. Then the following message should be printed telling you that you can now start using AMGET:

```
** The set up was successfully completed you can now
start using AMGET **
```

If later on you wish to change the output directory, simply open the settings file and modify the path associated with 'Plots Output directory' under the #DIR key, this feature can be used to when working on different projects. *Note: The different keys (#) will be described later in this manual.* This set up is a one-time occurrence, the next time AMGET is started, it will directly show you the following message:

```
Welcome to AMGET

Please indicate the path to the folder containing the
model(s) files you want to evaluate:
```

Once the working directory *(WD)* or folder containing the ADAPT 5 outputs to be evaluated has been defined, the main menu will appear, showing the different functions as displayed below:

```
  AMGET Main Menu

  WD:…/DrugX_Run001/

  Select one of the following options:
  1: Indiv. DV vs. IV profiles
  2: Goodness of fit plots
  3: Posthoc fit plots
  4: Parameter distribution profiles
  5: Visual Predictive Check
  6: Change WD
  7: Quit

  Selection:
```

The working directory can be changed at any time by selecting option no. 6 "Change WD" in the main menu. A note specifying the working directory in use is also displayed on the top of the menu.

2. The settings sheet

This file *AMGET_Settings.csv* is organized in six categories defined by the pound sign '#':

1- In #DIR you indicate the output directory where all graphics will be saved, and a toggle switch to enable/disable the file browser option when setting the WD *(Note: the toggle switch to enable/disable the file browser option is not compatible with MacOS and must remain disabled in this case)*.

2- In #IDV a multitude of options are defined for the 'Individual time versus dependent variable profiles' *(Option no. 1 in the Main menu),* such as colors used in the plot, the type of marker, axis titles and their associated units.

3- In #GOF are the options for the 'Goodness of fit plots' *(Option no. 2 in the Main menu)*

4- In #PHF are the options for the 'Posthoc fit plots' *(Option no. 3 in the Main menu)*

5- In #PRM are the options for the 'Parameters distribution profiles' *(Option no. 4 in the Main menu)*

6- In #VPC are the options for the 'Visual Predictive Check' *(Option no. 5 in the Main menu)*

The detail of these options will be described later. Do not forget to save the settings sheet every time you make a modification. If you are new to programming with R you can find more information online. The following list only serves to recommend some resources which we find extremely helpful, several other resources exist on the internet which an end user may find more useful.

R colors:

http://www.stat.columbia.edu/~tzheng/files/Rcolor.pdf

Marker *(pch)* and the lines *(lty)* types:

http://www.statmethods.net/advgraphs/parameters.html

3. Additional notes

You can make modifications in the settings while AMGET is open. The settings parameters will be refreshed at each analysis, thus you are able to quickly check out the results of a change in color of your marker in the settings file, save it

and rerun the plotting on AMGET making its use interactive and allows the user to quickly modify and customize plots to their specifications.

If for any reason AMGET cannot find the settings file while starting up, you will have to redefine where a new settings file will be copied, and redefine the output directory as described previously in ‘Start AMGET’.

Individual ID vs. DV profiles

1. Description

The Individual independent variable versus dependent variable profiles is slightly different of the other AMGET features in that it actually creates graphics from the entire available input dataset used to conduct the modeling analysis with ADAPT 5. The purpose here is to provide further support non-compartmental analysis, by getting an insight into the PK and/or PD profiles shape *(linear and log scale graphs are created),* the density of sampling *(number of total individual observations)*, the influence of dosing history on PK/PD profiles *(dose events are all printed on graph, bolus doses as vertical lines, infusion as horizontal arrows whose width represent the infusion duration)*, potential non-linearity *(scatter and spaghetti plots are generated for each dose level)*, the C_{min}/T_{min} and C_{max}/T_{max} observed, the potential inter-subject variability and the number of points below the quantification limit *(this limit is defined in the settings file).*

Selecting the option Individual ID vs. DV profiles from the main menu will bring up the following sub menu:

```
Individual DV vs. IV

Select one of the following options:
1: NONMEM-shaped dataset
2: ADAPT population dataset
3: ADAPT individualized datasets
4: Main Menu
5: Quit

Selection:
```

Three different options are proposed. Indeed, while the output data generated by software such as ADAPT 5 are fairly consistent, raw datasets on the other hand can be shaped in many different formats; AMGET was designed to either use:

1- A NONMEM *(S-ADAPT)* shaped dataset
2- An ADAPT 5 population dataset *(containing subject identifier)*
3- A folder containing ADAPT 5 individual subjects datasets *(without subject identifier)*

Each of these three functions will now be described in further details.

a. NONMEM shaped dataset

Many ADAPT users also work on S-ADAPT and/or NONMEM, for this reason the Individual ID vs. DV profiles function of AMGET was made compatible with such shaped datasets as long as they are in the **.csv (comma-separated values)* format and have column header as the first row.

- ***Import the dataset***

If more than one **.csv* files are present in the folder, they will be listed on the screen and you will be asked to make a selection:

```
Select the NONMEM-shaped dataset you want to evaluate:
 1: PK_Single_Doses.dat
 2: PK_Multiple_Doses.dat
 3: PD.dat
…

Selection:
```

If only one *.csv file is found in the file it will directly be imported and processed.

Once the data imported, AMGET will then read the table header and look for the names: **ID** *(Subject Identifier)*, **DV** *(Dependent Variable)*, **AMT** *(Dose Amount)*, **CMT** *(Compartment Number)* and the **Independent variable column name** that is defined by the user in the settings sheet. *(e.g. TIME, TSLD)*. All of the variables listed except **CMT** are required. If AMGET cannot find one of the listed names a message will appear and ask you to manually define the column as illustrated in the following example:

```
The name DV could not be found in the column names,
select a substitution column:
1: ID
2: TIME
3: AMT
4: CONC
5: MDV

Selection: 4
```

If **CMT** is missing the program will continue normally and use the denomination 'Default cmt.' instead of the compartment names defined in the setting sheet. **MDV** *(Missing Dependent Variable)* is assumed to be present, if not the program will be unable to run.

- ***Plots***

When the data are imported, the settings will be loaded and the plotting will start. If everything worked correctly AMGET will print a message indicating that the run was successful and show where the files were saved. A menu prompt will then allow for additional drawing of plots, going back to the main menu, returning to the ID vs. DV menu or to quit AMGET:

```
The individuals Drug concentration vs. Time plots have
successfully been created in the folder:
C:/MyData/Plots/PK_Single_Doses_PLOTS

To continue select one of the following options:
1: Generate more individual profiles
2: Go back to the individual DV vs. IV Menu
3: Go back to the Main Menu
4: Quit

Selection:
```

A **.pdf* file named after the dataset used will be created for the plots in linear scale and one for the plots in logarithmic scale, and this for each compartment *(CMT)* defined in the dataset. Note that in logarithmic scale the DV values ≤ 0 are discarded. Each file will contain the following graphics:

1- A **spaghetti plot** and/or a **scatter plot** *(defined in settings),* for each dose level *(Figure 1)*,

2- The **individual profiles**, for each of them will be indicated the subject ID, the quantification limit *(defined in settings),* the number of observations and data point below the quantification limit *(BQL)*, the C_{min}/T_{min} and C_{max}/T_{max} for this specific subject and the dosing information *(vertical lines for bolus and arrows for infusions) (Figure 2)*.

A horizontal line marks the **quantification limit value** *(defined in settings);* AMGET will then calculate the number of points BQL to inform the user on the role of the quantitation limit in regards to the study design and sampling.

Important: *Note that the dose stratification for the spaghetti and scatter plots will be based either on* ***the first bolus dose amount*** *or* ***the first infusion amount*** *of each subject. In the case where both infusion and bolus dose are present the stratification will be based on the* ***bolus doses****.*

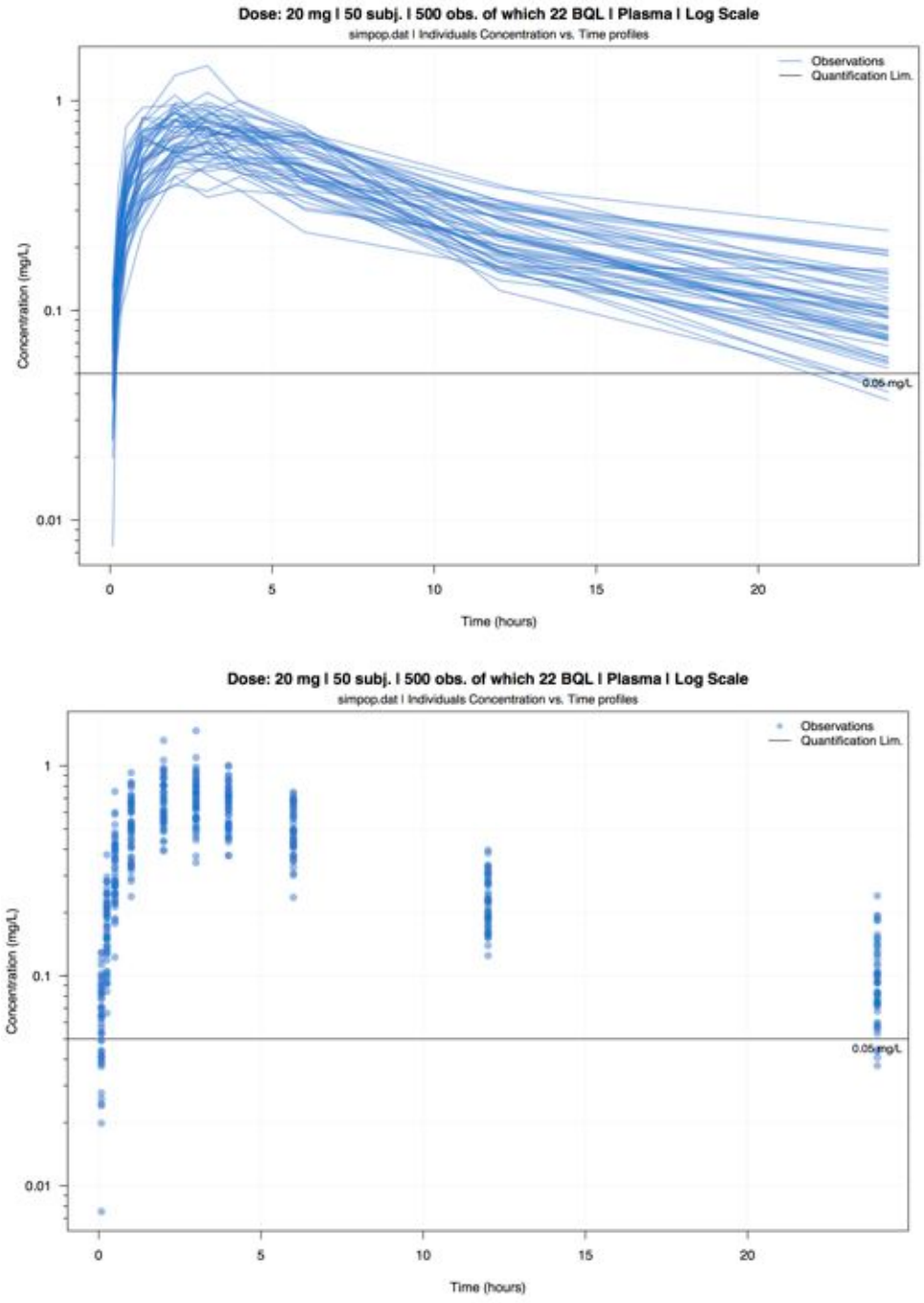

Figure 1: Example of Spaghetti (top) and scatter plots (bottom) in logarithmic scale

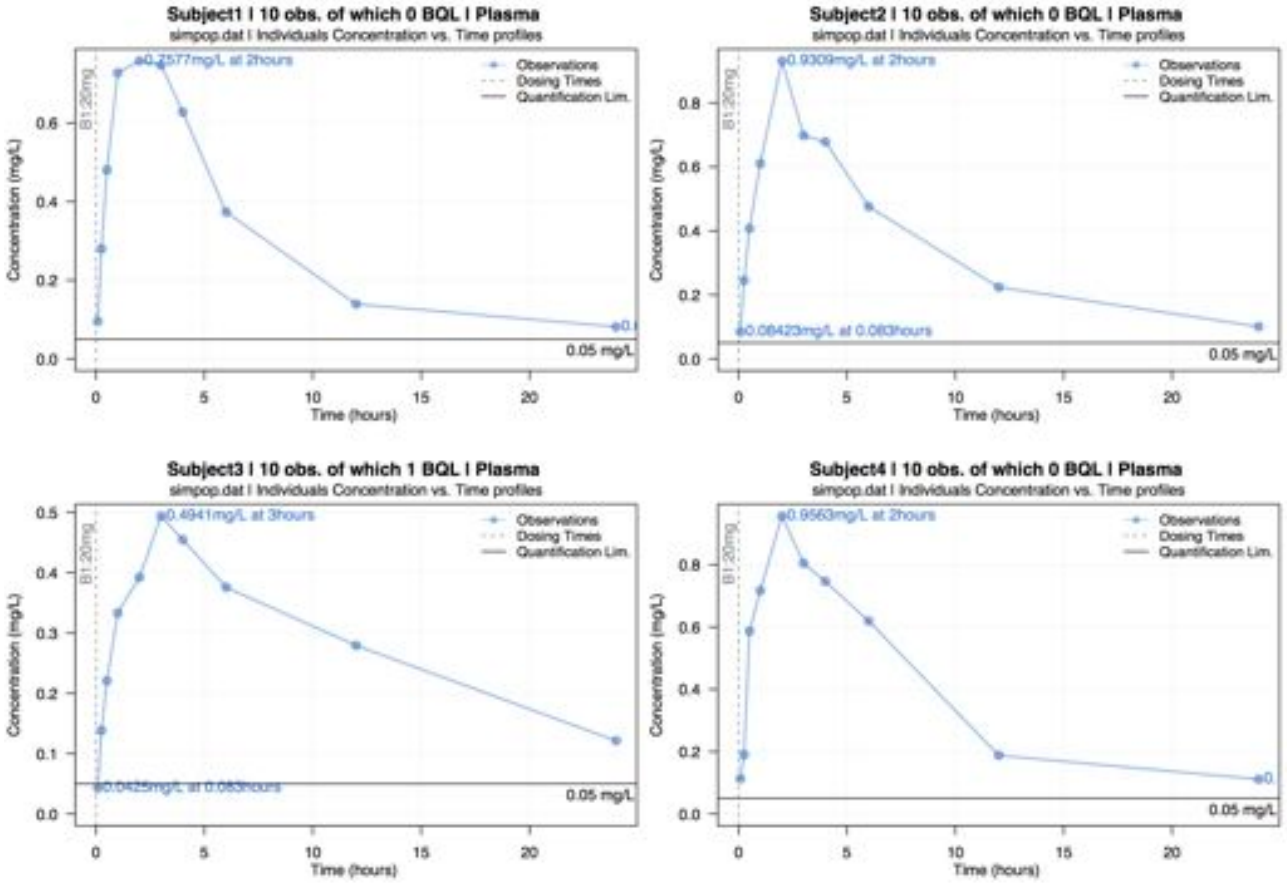

Figure 2: Example of Individual profiles illustrated using linear scale and a Layout=2

b. ADAPT 5 population dataset

AMGET allows can also make use of ADAPT 5 **.dat* population datasets *(i.e. contains subject identifier).* The same graphics that were shown in figure 1 and 2 will be generated.

- ***Import the dataset***

If more than one **.dat* dataset is found a list will be printed and you will be asked to make a selection:

```
Select the ADAPT population dataset you want to evaluate:
1: PK_Single_Doses.dat
2: PK_Multiple_Doses.dat
3: PD.dat
…

Selection:
```

In the case where only one *.*dat* file is found it will directly imported and processed.

- ***Plots***

If the run was successful, AMGET will print a message indicating that the files were successfully created and show where they have been saved, as illustrated in the following example:

```
The individuals Drug Concentration vs. Time plots have
successfully been created in the folder:
C:/MyData/Plots/PK_Single_Doses_PLOTS

To continue select one of the following options:
1: Generate more individual profiles
2: Go back to the individual DV vs. IV Menu
3: Go back to the Main Menu
4: Quit

Selection:
```

The *.pdf files will be created following the same principle as previously described in the NONMEM shaped dataset.

c. ADAPT 5 individuals dataset

The third option available is to use a multitude individuals ADAPT 5 datasets. Those datasets will be compiled within AMGET and used as a population dataset.

- ***Import the datasets***

All the *.*dat* datasets will be listed prior to compiling. You can then either confirm the importation, go back to the different menus or exit, as illustrated in the following example:

```
The 4 following datasets have been found and will be
imported:
ID_01.dat
ID_02.dat
ID_03.dat
ID_04.dat

Do you wish to continue?
1: Yes
2: Go back to the individual DV vs. IV Menu
3: Go back to the Main Menu
4: Quit

Selection:
```

If you decide to continue ALL the datasets of the list will be imported. It is important to note that AMGET will not reorder the dataset; they will be imported and compiled as ordered in the list. It is recommended if you use a numeric subject identifier like it is the case in the example shown above to use the format 01 and or even 001 for analysis of datasets containing more than one hundred subjects.

- ***Plots***

Similarly to what was described previously, a successful run will be confirmed by a message from AMGET indicating that the files were successfully created and where they were saved as illustrated below:

```
The individuals Drug Concentration vs. Time plots have
successfully been created in the folder:
C:/MyData/Plots/4_pooled_datasets_PLOTS

To continue select one of the following options:
1: Generate more individual profiles
2: Go back to the individual DV vs. IV Menu
3: Go back to the Main Menu
4: Quit

Selection:
```

The graphics created are similar to what has been described previously, however in this case in addition to the *.pdf files, a population *.*dat* file will also be saved. This data file was created for the user to ensure that the compiling was done

correctly; in addition this population dataset can be used by ADAPT 5 for modeling purposes.

2. IDV Settings

The #IDV settings can be used for the NONMEM-shaped, ADAPT population and ADAPT individual datasets. The settings allows you to modify:

Name	Description	Accepted values
Dependent Var. Name	Label for the Y axis	Any character name
Dependent Var. Units	Units for the Y axis	Any character name
Independent Var. Name	Label for the X axis	Any character name
Independent Var. Units	Units for the X axis	Any character name
Dose Units	Units of the doses	Any character name
Points Color	Color of the points for scatter plots and individual profiles	R colors
Points Shape	Shape of the points for scatter plots and individual profiles	0 to 25
Transparency	Transparency factor for all points and lines	0 *(transparent)* to 1 *(opaque)*
Line Type	Line type for spaghetti and individual profiles	1 to 6
Line Weight	Line width for spaghetti and individual profiles	>0
Dose Event Color	Color for dose lines and/or arrows	R colors
QL value	Value to be used for the Quantification Limit	Numeric
QL Line Color	Line color for the Quantification Limit	R colors
QL Line type	Line type to mark the Quantification Limit	1 to 6
Layout	Layout for the individual profiles *(number of rows and columns per page)*	1, 2 or 3
Spaghetti/Scatter plots	Allow to plot either spaghetti or scatter plot or both	Spaghetti, Scatter, Both or None
Legend Position	Position of the legend on the graphics	top, bottom, left, right, center, topleft, topright, bottomleft,…
Titles (Y/N)	Enable/disable titles on the plots	Y to enable or N to disable
Log Plots (Y/N)	Generate plots in log scale	Y for yes or N for no
CMT Names	Names for each of the compartments in the dataset	Any character name

Goodness of fit plots

1. Description

ADAPT 5 provides some built-in options for goodness of fit plot, however the format post script makes them inconvenient. AMGET offers advanced goodness of fit plots. Additional features make those plots informative with additional information embedded directly onto the plot such as: AIC *(Akaike information criterion)*, BIC *(Bayesian information criterion)*, OFV *(objective function value)*, R^2 *(coefficient of determination)*, number of observation, subjects, iterations, the algorithm used, the model description *(defined in the ADAPT model file *.for)* and local regression curves *(loess)*.

2. Using the GOF function

To obtain and plot this information AMGET uses the table **RSD.csv* and the **.run* files generated by ADAPT 5 after a given run. In order to use this function you have to ensure that for each model to be analyzed, these two files are available in the working directory.

- ***Import the dataset***

If more than one of **RSD.csv* file is present in the folder a list will be printed and you will be asked to make a selection:

```
Select the model you want to evaluate:
1: Model_1
2: Model_2
3: Model_3
…

Selection:
```

In the case where only one file is found it will be imported and processed automatically. Once the data are imported, AMGET will look for the associated **.run*

file to get all the additional information. If the associated *.*run* file cannot be found, a message will tell you that the file could not be found and will send you back to the main menu.

Notes:

- OFV is the -2log likelihood. Some of the ADAPT 5 algorithm report the –log likelihood, in this case AMGET will transform it into a -2 log likelihood. Iterative Two Stage Analysis *(ITS)* will instead report the Maximum A Posteriori Objective Function *(MAP OFV).*
- R^2 is calculated on both linear and logarithmic scale,
- The loess curve uses a local regression method; the degree of smoothing *(α)* can be changed in the settings sheet.

- ***Plots***

If the run worked correctly, AMGET will indicate that the files were successfully created and indicate the directory where they were saved, as illustrated below:

```
The Goodness of fit plots have successfully been created
in the folder:
C:/MyData/Plots/Model_1_PLOTS

To continue select one of the following options:
1: Generate more Goodness of fit plots
2: Posthoc fit plots
3: Parameter distribution profiles
4: Go back to the Main Menu
5: Quit

Selection:
```

One *.pdf file will be created for each compartment Y(x) of the data *(e.g. Plasma, Urine)*. Within each file, seven plots are generated: Dependent variable vs. Individual Model Predictions (linear and log scale), Dependent variable vs. Population Model Predictions (linear and log scale), Standardized Residuals vs. Independent Variable, Standardized Residuals vs. Individual Model Predictions and Standardized Residuals vs. Model Predictions.

Note: If the data (observations and/or model predictions) contains values equal to or less than zero this data will be discarded on the log scale plots.

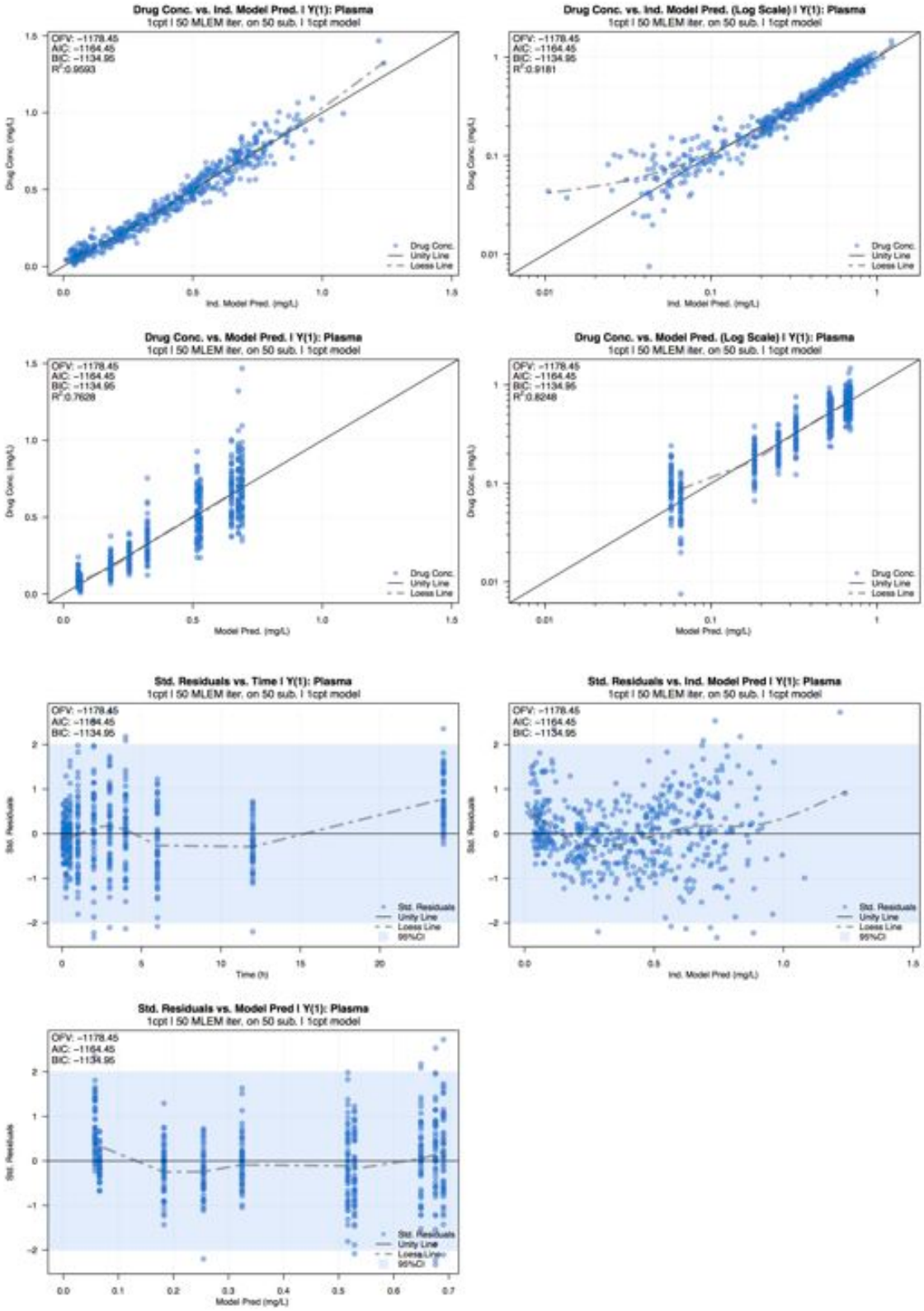

Figure 3: Example of Goodness of fit plots using Layout=2

3. GOF Settings

The #GOF settings allows you to modify:

Name	Description	Accepted values
Dependent Var. Name	Label for DV	Any character name
Dependent Var. Units	Units for DV	Any character name
Independent Var. Name	Label for IV	Any character name
Independent Var. Units	Units for IV	Any character name
Points Color	Color of the points for the scatter plots	R colors
Points Shape	Shape of the points for the scatter plots	0 to 25
Transparency	Transparency factor for all points and loess lines	0 *(transparent)* to 1 *(opaque)*
Loess Line Smooth	Smoothing factor for the loess line	Numeric *(around 1)* higher the smoother
Loess Line Color	Color of the loess lines	R colors
Loess Line Type	Line type for the loess lines	1 to 6
Loess Line Weight	Line width for the loess lines	>0
Shade Color	Color for the -2 to 2 area or lines in residuals plots	R colors
Shade Density	-1 for colored area, 0 for lines at -2 and 2, >0 for variable density of shaded area	Numeric *(-1, 0 or >0)*
Layout	Layout for each page *(number of rows and columns per page)*	1 or 2
Legend Position	Position of the legend on the residuals graphics	top, bottom, left, right, center, topleft, topright, bottomleft,...
Titles (Y/N)	Enable/disable titles on the plots	Y to enable or N to disable
CMT Names	Names for each of the compartments in the dataset	Any character name

Posthoc Fits

1. Description

ADAPT 5 outputs a plot table after any model parameter estimation run (**PLT.csv)*. This file contains by default a thousand model prediction points per subject evenly distributed on the given time interval. Thus a detailed model prediction profile for each subjects can be drawn and not only predictions at the measurement times as is the case in other modeling tools. AMGET takes advantage of this feature to create informative posthoc fits plots. On these profiles, the observed data, population profile, number of observations, R^2, OFV, parameters values are added for each subject, offering another way to evaluate the goodness of fit of the model predictions.

2. Using the PHF function

To create these plots AMGET requires the **PLT.csv*, **IND.csv, *RSD.csv* and **.run* files generated by ADAPT, in order to use this function to ensure that for each model your are going to analyze you have those four files in the working directory.

- ***Import the dataset***

The program starts by looking for the **PLT.csv* file, if more than one of those file are present in the folder a list will be printed and you will be asked to make a selection as illustrated below:

```
Select the model you want to evaluate:
1: Model_1
2: Model_2
3: Model_3
…

Selection:
```

In the case where only one file is found it will be imported and processed automatically. The **PLT.csv* will be read to get the individual model predictions, the

IND.csv to get the individual parameter values *(if the *IND.csv cannot be found the program will still run but the parameter value will not be reported)*, the **RSD.csv* for the model population profile and the **.run* file to get some additional information.

Note: As described previously OFV represents the -2 log likelihood. Some of the ADAPT 5 algorithms report the –log likelihood, in this case AMGET will transform it into a –2 log likelihood for each individuals. ITS report instead the MAP OFV.

- ***Plots***

The option to use a logarithmic scale on the Y-axis is offered and can be activated in the settings sheet under #PHF. If the run worked correctly, AMGET will indicate that the files were successfully created and where they were saved, as illustrated below:

```
The Posthoc fit plots have successfully been created
in the folder:
C:/MyData/Plots/Model_1_PLOTS

To continue select one of the following options:
1: Generate more Posthoc fit plots
2: Goodness of fit plots
3: Parameter distribution profiles
4: Go back to the main menu
5: Quit

Selection:
```

Note that one *.pdf file will be created for each compartment.

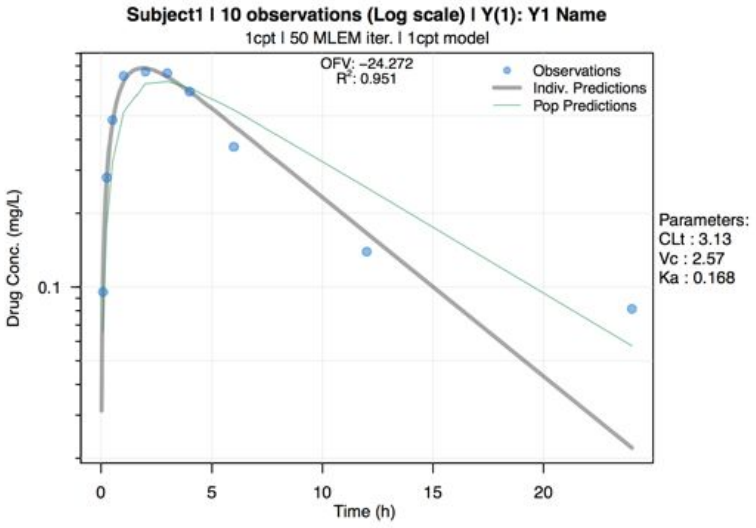

Figure 4: Example of Posthoc fit for a given individual on log scale

3. PHF Settings

The #PHF settings allows you to modify:

Name	Description	Accepted values
Dependent Var. Name	Label for the Y axis	Any character name
Dependent Var. Units	Units for the Y axis	Any character name
Independent Var. Name	Label for the X axis	Any character name
Independent Var. Units	Units for the X axis	Any character name
Points Color	Color of the observations points	R colors
Points Shape	Shape of the observations points	0 to 25
Transparency	Transparency factor for all points and lines	0 *(transparent)* to 1 *(opaque)*
Obs. Line Color	Color of the line connecting the observations points	R colors
Obs. Line Type	Line type for the line connecting the observations points	1 to 6 *(0 to disable)*
Obs. Line Weight	Line width for the line connecting the observations points	>0
Pred. Line Color	Color of the individual model prediction line	R colors
Pred. Line Type	Line type for the individual model prediction line	1 to 6
Pred. Line Weight	Line width for the individual model prediction line	>0
Pop. Line draw (Y/N)	Enable/disable the population model pred. line drawing	Y to enable or N to disable
Pop. Line Color	Color of the population model pred. line	R colors
Pop. Line Type	Line type for the population model pred. line	1 to 6
Pop. Line Weight	Line width for the population model pred. line	>0
Layout	Layout for each page *(number of rows and columns per page)*	1, 2 or 3
Legend Position	Position of the legend on the residuals graphics	top, bottom, left, right, center, topleft, topright, bottomleft,…
Log Y-axis (Y/N)	Use logarithmic scale on Y axis	Y for Log or N for linear
Parameters Value (Y/N)	Print the individual parameter value next to the plots	Y for yes or N for no
Titles (Y/N)	Enable/disable titles on the plots.	Y to enable or N to disable
CMT Names	Names for each of the compartments in the dataset	Any character name

Parameter distribution profiles

1. Description

Looking at models parameter distribution is an important part of model evaluation. Such graphics can help make an informed choice on the most appropriate distribution to be used.

AMGET creates two different kinds of distribution plots *(figure 5):* the first one is based on the density of the distribution, the second is a histogram of the frequencies. In addition, a second set of graphics are generated to plot the objective function value as well as for all the model parameter the variation of their value in regards to the iteration number during the minimization *(figure 6)*.

2. Using the PRM function

To create these plots AMGET requires the **IND.csv,* and **.run* files generated by ADAPT for the parameter distribution and **IT.csv* for the parameter value vs. iteration, in order to use this function you have to ensure that for each model your are going to analyze these three files are available in the working directory.

- ***Import the dataset***

The program starts by looking for the **IND.csv* file, if more than one of those **IND.csv* file are present in the folder a list will be printed and you will be asked to make a selection:

```
Select the model you want to evaluate:
1: Model_1
2: Model_2
3: Model_3
…

Selection:
```

In the case where only one file is found it will be imported and processed directly.

- ***Plots***

If the run worked correctly, AMGET will indicate that the files were successfully created and where they were saved, as illustrated below:

```
The parameters distribution profiles have successfully
been created in the folder:
C:/MyData/Plots/Model_1_PLOTS

To continue select one of the following options:
1: Generate more parameters distribution profiles
2: Goodness of fit plots
3: Posthoc fits
4: Go back to the main menu
5: Quit

Selection:
```

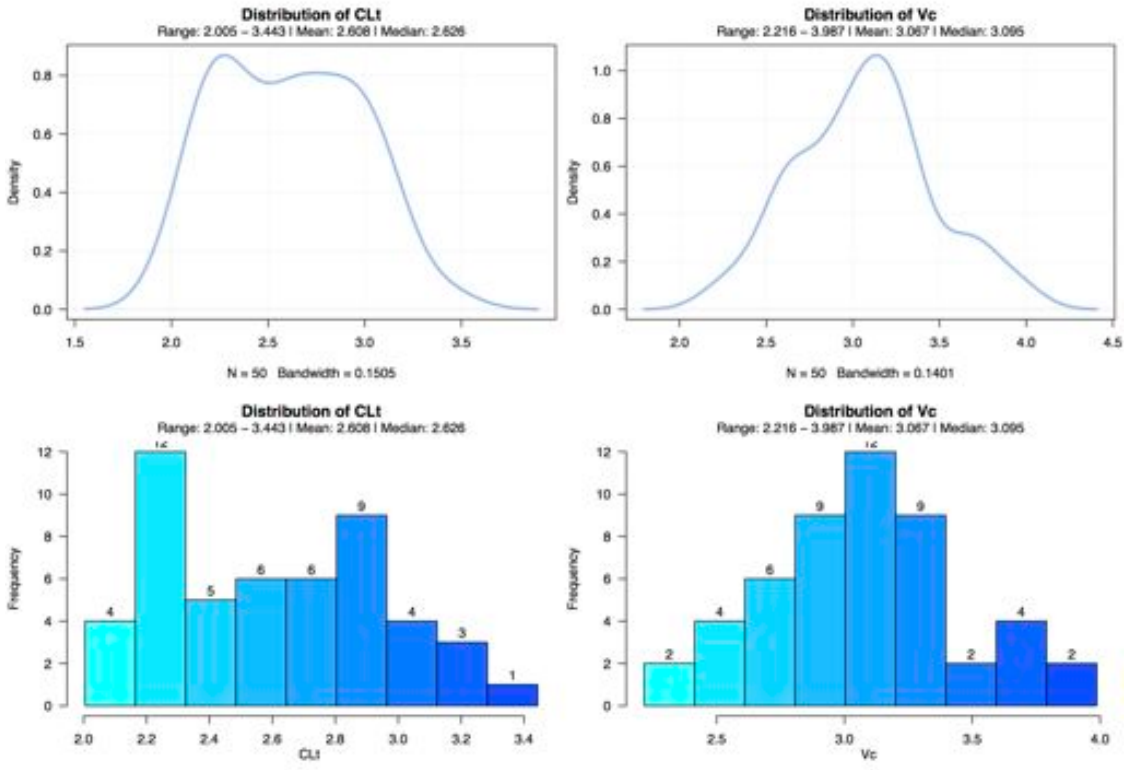

Figure 5: Example of Parameter distribution plots for total clearance (CLt) and Volume of central compartment (Vc) using Layout=2

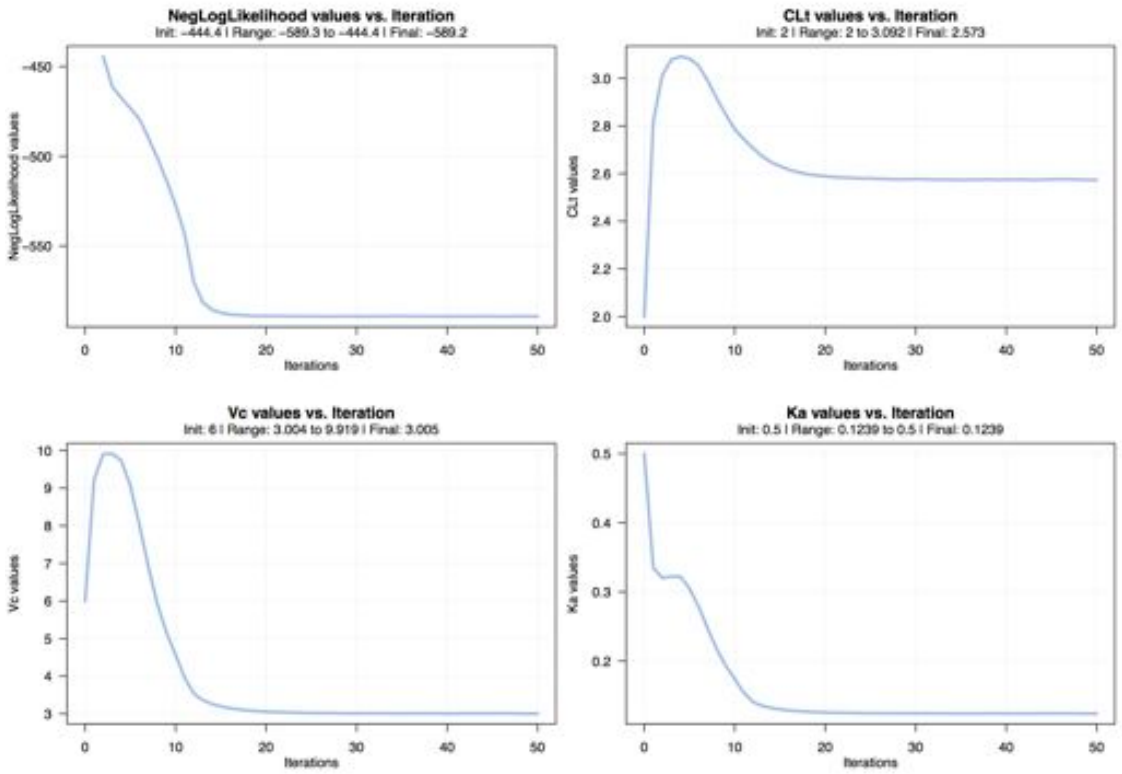

Figure 6: Example OFV and Parameter values in regards to the iteration number using Layout=2

3. PRM Settings

The #PRM settings allows you to modify:

Name	Description	Accepted values
Layout	Layout for each page	1 or 2
Number of Breaks	Number of breaks for the histogram	Integer
Histograms (Y/N)	Enable/disable histogram graphs	Y to draw or N to disable
Line Color	Color of lines for density and iteration plots	R colors
Line Type	Line type for density and iteration plots	1 to 6
Line Weight	Line width for density and iteration plots	>0
Transparency	Transparency factor for all lines	0 *(transparent)* to 1 *(opaque)*
Titles (Y/N)	Enable/disable titles on the plots	Y to enable or N to disable

Visual Predictive Check

1. Description

Observing Visual Predictive Checks is a very useful way to assess that the model correctly describes the observations, however the procedure to run the simulations, calculate the percentiles and create the graphics can be time consuming. A VPC function was therefore added to AMGET.

AMGET will not run the simulations, but will calculate the percentile envelope *(defined in the settings sheet)* for the simulated and the observed data, as well as the simulated and observed medians and create the graphics in a fraction of second.

2. Using the VPC function

- ***Requirements***

To create the VPC, AMGET requires the initial dataset **.dat* used for the parameter estimation, to collect the observed data and **POP.csv* of the simulation to collect the simulated data generated by ADAPT. In order to use this function you have to ensure that for each model to be analyzed, these two files are both available in the working directory.

Note: AMGET is not (yet) capable to stratify your data by dose or any other covariate. If your data contain more than one dose level, a simulation should be performed ***for each dose level*** *(name them accordingly), subsets of the dataset containing the observation should be generated accordingly for each dose levels. VPC can then be generated for each dose level.*

Note also that AMGET is able to differentiate the different outputs Y(x), therefore multiple output each corresponding to one dose level could potentially be used to circumvent this issue, though at this time, however this has not been tested in a specific example at this time.

- ***Import the datasets***

AMGET will start by looking for the results of the simulation which is generated in the **POP.csv* files. If more than one of **POP.csv* file is present in the folder a list will be printed and you will be asked to make a selection:

```
Select the model you want to evaluate:
1: Model_1_SIM
2: Model_2_SIM
3: Model_3_SIM
…

Selection:
```

In the case where only one file is found it will be imported and processed directly. Once the data are imported AMGET will look for the observations in the **.dat* file, similar to the previous step, if more than one dataset **.dat* is found you will be asked to make a selection.

```
Select the datafile containing the OBSERVATIONS used by
Model_1_SIM:
1: Model_1.dat
2: Model_2.dat
3: Model_3.dat
…

Selection:
```

- ***Plots***

If the run worked correctly, AMGET will indicate that the files were successfully created and where they were saved, as illustrated below:

```
The Visual Predictive Check have successfully been
created in the folder:
C:/MyData/Plots/Model_1_SIM_PLOTS

To continue select one of the following options:
1: Generate more Visual Predictive Check
2: Go back to the Main Menu
3: Quit

Selection:
```

A **.pdf* file will be created for the plots in linear scale and one for the plots in logarithmic scale, and this for each compartment defined in the dataset.

Note that in logarithmic scale the observations or simulated values < 0 are discarded from the percentile calculation and the drawing.

- ***Data binning***

For data binning, AMGET calculates and plot the low, high percentiles and the median of the observations, however in some instances, the measurement do not happen at the same time, because of this, AMGET will bin the data using time intervals *(interval defined in settings)*. Within each bin the upper and lower percentiles and the median will be used as Y coordinates and the X coordinates will be the average time of the bin to be used. If, for each time point all measurements are taken at the same time, simply set the interval to a value inferior to the smallest sample interval in your data.

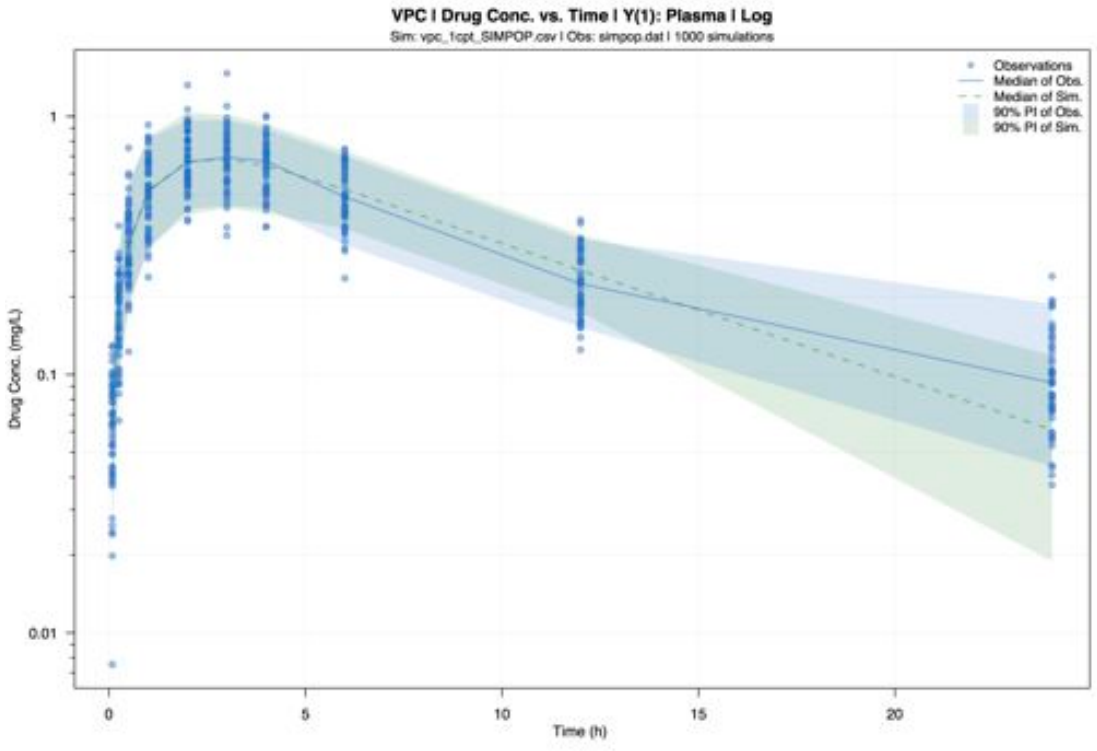

Figure 7: Example of VPC in logarithmic scale

3. VPC Settings

The #VPC settings allows you to modify:

Name	Description	Accepted values
Dependent Var. Name	Label for the Y axis	Any character name
Dependent Var. Units	Units for the Y axis	Any character name
Independent Var. Name	Label for the X axis	Any character name
Independent Var. Units	Units for the X axis	Any character name
Points Color	Color of the observations points	R colors
Points Shape	Shape of the observations points	0 to 25
Transparency	Transparency factor for all points shaded area and lines	0 *(transparent)* to 1 *(opaque)*
Obs. Line Color	Color of the observations lines	R colors
Obs. Line Type	Line type for the observations lines	1 to 6 *(0 to disable)*
Obs. Line Weight	Line width for the observations lines	>0
Sim. Color	Color of the Simulated data lines and shaded area	R colors
Sim. Shaded area Density	-1 for colored area, 0 for lines at -2 and 2, >0 for variable density of shaded area *(>0 not compatible with log scale)*	Numeric *(-1, 0 or >0)*
Sim. Line Type	Line type for the simulated data if density = 0	1 to 6
Layout	Layout for each page *(number of rows and columns per page)*	1, 2 or 3
Lower Percentile	Value for the lower percentile	0 to 1 *(<Upper percentile)*
Upper Percentile	Value for the upper percentile	0 to 1 *(>Lower percentile)*
Time interval for obs.	Time interval for data binning	Numeric
Legend Position	Position of the legend on the residuals graphics	top, bottom, left, right, center, topleft, topright,bottomleft,…
Titles (Y/N)	Enable/disable titles on the plots.	Y to enable or N to disable
CMT Names	Names for each of the compartments in the dataset	Any character name

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