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1 Introduction

The ggPMX package generates standard diagnostic plots and tables for mixed effect models used in Pharmacometric (PMX) activities. The tool is built upon the ggplot2 package and supports models developed either with Monolix, NONMEM or nlmixr software. The current release (1.2) supports models fitted with Monolix versions 2016 and later, NONMEM version 7.2 and later and nlmixr.

The package aims to provide a workflow that is consistent, efficient and which results in high quality graphics ready to use in official documents and reports. The package allows a high degree of flexibility and customization, yet providing an acceptable default setting. The package also allows to fully automate plots and report generation.

The general context is the analysis of mixed effect models fitted to data. ggPMX was developed in the framework of Pharmacometric activities, in which case the model is a population pharmacokinetic (PK) and/or pharmacodynamic (PD) model and the data is clinical or pre-clinical PK and/or PD data.

In the context of model building, evaluation and qualification, it is good practice to assess the goodness-of-fit of models by inspecting (qualitatively and quantitatively) a set of graphs that indicate how well the model describes the data. Several types of diagnostic plots allow to evaluate a mixed effects model fit, the most common being:

a. residual-based plots
b. prediction-based plots
c. empirical Bayes estimates (EBE)-based plots
d. simulation-based plots.

The following figures are examples of diagnostic plots using data from Monolix.

This document introduces the ggPMX functionalities and syntax.

1.1 Architecture

The high level architecture is represented in the figure below. The key components of the package are the following:
- **Reader** - reads model outputs from different sources (i.e. text files containing population parameters, model predictions, individual random effects, simulations and data-related inputs like covariates) and restructures these outputs into standard formats for internal processing.

- **Generator** processes outputs from Reader. It contains R language code to produce the plots and is factorized into a small set of flexible key functions. A set of default plots is defined in a configuration file. The configuration file can be adapted, e.g., to have different configurations for different types of modeling activities.

- **Controller** - serves as user interface. The user will call Generator functions via wrapper functions in the Controller to produce either all the default plots or selected plots of interest. In addition to editing the configuration, the user has different options to adapt aspects of the plots to specific requirements. Plots may be adapted by setting parameters of the wrapper functions that generate the plots; there exist additional wrapper functions to change aspects of the existing default plots. The plots are, in general, returned as ggplot objects that can be further customized using ggplot functionalities.

- **Reporter** - generates sets of graphs and tables and integrates them into an output file (Word or PDF) with annotations.

The package is coded using object-oriented programming meaning that information is encoded in objects. The user can change or print the content of objects via functions. Such an implementation allows to have code that is modular and easily customizable.

### 1.2 Workflow overview

The typical workflow of ggPMX is as follows:

1. The user creates the Controller using pre-defined configurations (yaml templates) for plot settings.
2. The Controller implicitly calls the Reader that reads and stores modelling outputs into a standard format. As a result, the Controller contains all available plots with their default values according to the configuration used.

3. The Generator allows to print the available plots by calling the corresponding functions. Plots can be modified by using optional arguments.

4. A call to the Reporter allows to create a pdf or docx report. The report Rmarkdown template can also be personalized.

The most important task for the user is the Controller creation. This step requires careful consideration because it involves different options according to the type of model (PK or PKPD) and software (Monolix, NONMEM or nlmixr) used for model fitting. The next section describes the Controller creation for the different possible cases.

Once the Controller is created, it implicitly calls the Reader and creates the diagnostic plots. The user can then generate the graphs by calling pre-defined functions. The same syntax is used independent of the model structure (PK or PKPD model) and of the fitting software (Monolix, NONMEM or nlmixr).

The Reporter creates one report per endpoint, i.e., one report for PK and one for each PD endpoint.

1.3 Modeling datasets

For the sake of this document, three types of datasets are defined.

- The input modeling dataset is the one used for model fitting (the actual data). There are no particular requirements regarding this dataset. (Only in Monolix)
- The output modeling datasets are those output from the fitting tool (Monolix, NONMEM or nlmixr). See the appendix for more details on software requirements.
- The ggPMX datasets are the ones created within (internal to) ggPMX.

2 Controller

A diagnostic session starts with the creation of a Controller. The Controller is the “user interface” of the package and allows to control all possible options. It is a container that stores configuration fields (model- and input data-related information), datasets and plots. It can be used as a reference object in which the user can see the names of the existing plots, the names of the ggPMX datasets, etc. The syntax of the Controller creation differs depending on the software used for model fitting and on the number of model endpoints (or outputs). This section presents different cases of Controller creation. For simplicity, the case of models with one single output is presented first, then generalized to several outputs. Other Controller creation functions can be used with the different fitting softwares. Note that all these functions can also be used with models with several outputs.

2.1 Single-endpoint models

In general, models with only one endpoint (or output) are mostly PK models, but these could also be k-PD models.

To illustrate ggPMX functionalities, the single-endpoint built-in model called theophylline is used hereafter. The theophylline population PK example has the following characteristics:

- The input modeling data contains PK samples of 2 studies, each with 25 individuals who received a unique dose of 2000 mg theophylline.
• The model is a simple one-compartmental PK model with first-order absorption.
• The following covariates are used: weight (WT0) on volume (V) and clearance (Cl), age (AGE0), sex (SEX) and study (STUD) on clearance.
• Random effects on all three parameters (ka, Cl, V) are included.
• The residual error is proportional.

The input modeling dataset has the following columns:

<table>
<thead>
<tr>
<th>ID</th>
<th>TIME</th>
<th>AMT</th>
<th>Y</th>
<th>EVID</th>
<th>WT0</th>
<th>AGE0</th>
<th>SEX</th>
<th>STUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.0</td>
<td>2000</td>
<td>0</td>
<td>1</td>
<td>87</td>
<td>73</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td>130</td>
<td>0</td>
<td>87</td>
<td>73</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.0</td>
<td>228</td>
<td>0</td>
<td>87</td>
<td>73</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2.0</td>
<td>495</td>
<td>0</td>
<td>87</td>
<td>73</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>3.0</td>
<td>484</td>
<td>0</td>
<td>87</td>
<td>73</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>5.0</td>
<td>479</td>
<td>0</td>
<td>87</td>
<td>73</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Note that the DVID (or CMT/YTYPE) column is missing, but since this is a single-endpoint model, it is not necessary in that case.

2.2 Controller creation

An example of Controller creation is wrapped in a function called “theophylline()” for quick reference:

ctr <- theophylline()

2.2.1 Models fitted with Monolix (versions 2016 and later)

### pmx_mlx()

The controller initialization using the Monolix controller pmx_mlx(), which is a wrapper function for pmx() with sys="mlx" (See Appendix A).

theophylline_path <- file.path(system.file(package = "ggPMX"), "testdata", "theophylline")
work_dir <- file.path(theophylline_path, "Monolix")
input_data_path <- file.path(theophylline_path, "data_pk.csv")

ctr <- pmx_mlx(
  directory = work_dir,
  input = input_data_path,
  dv = "Y"
)

### pmx_mlxtran()

The controller initialization can be simplified by using the Monolix controller pmx_mlxtran(). This function parses the mlxtran file of a Monolix project and assigns automatically the different fields necessary to the Controller creation. The only mandatory argument is file_name, the path to the mlxtran file.

mlxtran_path <- file.path(system.file(package = "ggPMX"),
                          "testdata", "1_popPK_model", "project.mlxtran")

ctr <- pmx_mlxtran(file_name = mlxtran_path)

The user can verify the content of the Controller and how parameters are assigned by printing it.
2.2.2 Models fitted with NONMEM (versions 7.2 and later)

```{r}
### pmx_nm()

The controller initialization using the NONMEM controller `pmx_nm()` is based on reading functions of the xpose package. It is highly recommended (but not required) to use the “sdtab, patab, cotab, catab” table naming convention followed by a run number (e.g. sdtab001,cotab001) This will enable automatic recognition of covariates. It is also recommended to name the model files accordingly (e.g. run001.lst). In order to generate a VPC a simulation dataset is required (see section about VPC)

For controller generation it is recommended to use the model file:

```{r}
nonmem_dir <- file.path(system.file(package = "ggPMX"), "testdata","extdata")
ctr <- pmx_nm(
    directory = nonmem_dir,
    file = "run001.lst"
)
```

or the run number. The standard prefix is “run”, however can be specified using `prefix`

```{r}
nonmem_dir <- file.path(system.file(package = "ggPMX"), "testdata","extdata")
ctr <- pmx_nm(
    directory = nonmem_dir,
    runno = "001" #can be a string or a number
)
```

2.2.3 Models fitted with nlmixr

```{r}
### pmx_nlmixr()

It is simple to create a ggPMX controller for a nlmixr object using `pmx_nlmixr()`. Using the theophylline example with a nlmixr model we have:

```{r}
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- 1 # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45; label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}
```
The `fit` object is a nlmixr fit; You can read it into the nlmixr controller by:

```r
ctr <- pmx_nlmixr(fit,
                   vpc = FALSE)  # VPC is turned on by default, can turn off
```

### 2.2.4 Optional arguments for controller creation

The following are some optional arguments to the controller function (for details of each option, see the corresponding section or use `?pmx_mlx`, `?pmx_nm`, `?pmx_nlmixr`):

- **cats**: character vector of categorical covariates
- **conts**: character vector of continuous covariates
- **occ**: character occasional covariate variable name (currently not available for NONMEM or nlmixr)
- **strats**: character extra stratification variables
- **settings**: global pmxSettingsClass (`pmx_settings()`) shared between all plots
- **endpoint**: pmxEndpointClass (`pmx_endpoint()`) or integer or character of the endpoint code (depends on the fitting software)
- **sim**: pmxSimClass object for VPC generation. (syntax for VPC generation is depending on the fitting software)

### 2.3 Multiple-endpoint models

Models with more than one endpoint (or output) are mostly PKPD models, but these could also be, for example, PK binding models in which there are measurements and predictions of both PK and its target.

ggPMX produces one diagnostics report per endpoint. As a consequence, the endpoint (if more than one) should be set at the time of the Controller creation in order to filter the observations dataset and to keep only the values corresponding to the endpoint of interest. There are two ways of dealing with endpoints, using `pmx_endpoint()` (only for Monolix), or a simplified syntax for endpoints which is supported by all software outputs.

#### 2.3.1 Using `pmx_endpoint()` (only for Monolix)

To handle this, the user creates an “endpoint” object using the function `pmx_endpoint()` having the following attributes:

- **code** (character): how the endpoint is coded in the input (modeling) dataset
- **label**: can be used in the title of some plots or for the report file name
- **unit**: used in the axis label for some plots
- **files** (list): `list(predictions="predictions1", finegrid ="finegrid1")`
- **trans**: whether the value must be transformed before being displayed and which transformation to use.

To illustrate the Controller creation with multiple-endpoint models, a built-in PKPD example is used. The input dataset is called `pk_pd.csv` and has the following columns.
## id time amt dv dvid wt sex age
## 1 100 0.0 100 . 3 66.7 1 50
## 2 100 0.5 . 0 3 66.7 1 50
## 3 100 1.0 . 1.9 3 66.7 1 50
## 4 100 2.0 . 3.3 3 66.7 1 50
## 5 100 3.0 . 6.6 3 66.7 1 50
## 6 100 6.0 . 9.1 3 66.7 1 50

The dvid column contains values=3 for PK (first endpoint) and dose and =4 for PD (second endpoint). Monolix2016 outputs are found in folder RESULTS/ which contains predictions1.txt and finegrid1.txt for PK predictions, and predictions2.txt and finegrid2.txt for PD predictions. The Endpoint and Controller objects are created as follows:

```r
pkpd_path <- file.path(system.file(package = "ggPMX"), "testdata", "pk_pd")
pkpd_work_dir <- file.path(pkpd_path, "RESULTS")
pkpd_input_file <- file.path(pkpd_path, "pk_pd.csv")

ep <- pmx_endpoint(
  code = "4",
  label = "some_label",
  unit = "some_unit",
  file.code = "2", # will use predictions2.txt and finegrid2.txt
  trans = "log10"
)

ctr <- pmx_mlx(
  directory = pkpd_work_dir,
  input = pkpd_input_file,
  dv = "dv",
  dvid = "dvid",
  endpoint = ep
)
```

```r
## use predictions2.txt as model predictions file .
## use finegrid2.txt as finegrid file .
```

### 2.3.2 A simplified syntax for endpoints (for Monolix, NONMEM and nlmixr)

For NONMEM and nlmixr users, endpoint can be simply specified in the controller creation by e.g. `endpoint = 1`

**NONMEM**

```r
ctr <- pmx_nm(
  directory = nonmem_dir,
  file = "run001.lst",
  endpoint = 1  # # select the first endpoint
  dvid = "DVID"  # # use this column as observation id
)
```

**nlmixr**

```r
```
ctr <- pmx.nlmixr(fit,
    endpoint = 1 ## select the first endpoint
    dvid = "DVID" ## use this column as observation id
)

Also for Monolix users, a simplified syntax for the Endpoint creation exists in the case where the endpoint code matches the files post-fixes (code=1 corresponds to predictions1.txt, code=2 corresponds to predictions2.txt). Instead of passing a pmxEndpoint object as argument of the Controller, the user can specify the numerical value corresponding to the YTYPE/CMT/DVID column.

pmx mlx(
    dvid = "YTYPE", ## use this column as observation id
    endpoint = 1, ## select the first endpoint
    ...) ## other pmx parameters , config, input,etc..

Internally, a pmxEndpoint object will be created, and observations having YTYPE=x will be filtered.

### 2.4 Controller with covariates

Besides the mandatory fields to initialize a Controller, the user can set optional parameters related to covariates. This feature is illustrated below with the Theophylline example.

```r
theophylline_path <- file.path(system.file(package = "ggPMX"), "testdata", "theophylline")
work_dir <- file.path(theophylline_path, "Monolix")
input_data_path <- file.path(theophylline_path, "data_pk.csv")
```

ctr <- pmx mlx(
    directory = work_dir,
    input = input_data_path,
    dv = "Y",
    cats = c("SEX"),
    conts = c("WT0", "AGE0"),
    strats = c("STUD", "SEX")
)

`Conts` are the continuous covariates. `Cats` are categorical covariates used in the model, whereas `strats` are categorical variables that can be used for plot stratification, but are not used as covariates in the model.

The covariates can be accessed using helper functions:

```r
ctr %>% get_cats()
## [1] "SEX"
```

```r
ctr %>% get_conts()
## [1] "WT0" "AGE0"
```

```r
ctr %>% get_strats()
## [1] "STUD" "SEX"
```
## get_covariates()

```r
## [1] "SEX" "WT0" "AGE0"
```

### 2.5 Controller content

The content of the Controller can be seen by printing it:

```r
ctr
```

```r
## pmx object:
##
## |PARAM            | VALUE |
## |:-----------------|--------|
## |working directory| theophylline |
## |Modelling input file| data_pk.csv |
## |dv                | Y |
## |dvid              | DVID |
## |cats              | SEX |
## |conts             | WT0,AGE0 |
## |strats            | STUD,SEX |
##
## |data_name | data_file | data_label |
## |-----------|-----------|-------------|
## |predictions | predictions.txt | model predictions file |
## |estimates   | estimates.txt | parameter estimates file |
## |eta         | indiv_eta.txt | individual estimates of random effects file |
## |finegrid    | finegrid.txt | finegrid file |
## |input       | data_pk.csv | modelling input |
##
## |plot_name | plot_type |
## |-----------|-----------|
## |abs_iwres_ipred | SCATTER |
## |iwres_ipred    | SCATTER |
## |iwres_time     | SCATTER |
## |iwres_dens     | PMX_DENS |
## |iwres_qq       | PMX_QQ |
## |npde_time      | SCATTER |
## |npde_pred      | SCATTER |
## |npde_qq        | PMX_QQ |
## |dv_pred        | SCATTER |
## |dv_ipred       | SCATTER |
## |individual     | IND |
## |eta_hist       | DIS |
## |eta_box        | DIS |
## |eta_matrix     | ETA_PAIRS |
## |eta_cats       | ETA_COV |
## |eta_conts      | ETA_COV |
## |eta_qq         | PMX_QQ |
```
It contains three tables:

- The first table is the Controller configuration. The user can see the working directory, the input modeling dataset name, the dependent variable (DV) name and other fields related to the model (e.g., continuous and discrete covariates).

- The second table lists the ggPMX datasets. The first column (data_name) of this table contains the ggPMX name of the dataset; the second column (data_file) contains the names of the output modeling datasets (for example estimates.txt); in the third column (data_label) contains the dataset description.

- The third table provides the list of available plots in the Generator. It corresponds to Table 3.

### 2.5.1 Plot names

The Controller is a container that stores all plots. To get the list of plots, the function `plot_names()` is used:

```r
ctr %>% plot_names()
```

```
## [1] "abs_iwres_ipred" "iwres_ipred"   "iwres_time"   "iwres_dens"
## [5] "iwres_qq"       "npde_time"   "npde_pred"   "npde_qq"
## [9] "dv_pred"       "dv_ipred"     "individual"  "eta_hist"
## [13] "eta_box"       "eta_matrix"  "eta_cats"    "eta_conts"
## [17] "eta_qq"
```

An alternative way to display the names of the existing plots is by printing the content of the Controller as done above.

ggPMX provides a specialized function to create and update each plot `pmx_plot_xx()` where `xx` is the plot name from the list above.

### 2.5.2 Plot types

Each plot type is a class of similar plots. ggPMX defines the following plot types:

- **SCATTER**: residual plots
- **IND**: individual plots display longitudinal (time course) predictions and data (one panel per individual)
- **DIS**: distribution of empirical Bayes estimates (EBE) histogram or boxplot
- **ETA_PAIRS**: random effects (ETA) distributions and correlations structure
- **ETA_COV**: relationships between random effects (ETA) and continuous or categorical covariates
- **PMX_QQ**: quantile-quantile plot (qq-plot)

The following syntax allows to see which type of plot corresponds to which plot name:

```r
ctr %>% plots()
```

```
## plot_name plot_type plot_function
## 1: abs_iwres_ipred SCATTER pmx_plot_abs_iwres_ipred
## 2: iwres_ipred SCATTER pmx_plot_iwres_ipred
## 3: iwres_time SCATTER pmx_plot_iwres_time
## 4: iwres_dens PMX_DENS pmx_plot_iwres_dens
## 5: iwres_qq PMX_QQ pmx_plot_iwres_qq
```
### ggPMX dataset Description

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Input modeling dataset</td>
</tr>
<tr>
<td>2</td>
<td>Estimated population parameters</td>
</tr>
<tr>
<td>3</td>
<td>Random effects, their standard deviation and residual errors (to calculate shrinkage)</td>
</tr>
<tr>
<td>4</td>
<td>Observations and predictions at times of observations dataset</td>
</tr>
<tr>
<td>5</td>
<td>Additional predictions (at times without observations)</td>
</tr>
</tbody>
</table>

#### Table 1: ggPMX datasets

### 3 Default diagnostic plots

The diagnostic plots of ggPMX are generated by calling the functions `pmx_plot_xx()` where `xx` is a placeholder for the plot name. The list of names of all available plots can be seen via:

```r
ctr %>% plot_names()
```

```
## [1] "abs_iwres_ipred" "iwres_ipred"  "iwres_time"  "iwres_dens"
## [5] "iwres_qq"  "npde_time"   "npde_pred"   "npde_qq"
## [9] "dv_pred"   "dv_ipred"   "individual"  "eta_hist"
## [13] "eta_box"   "eta_matrix" "eta_cats"    "eta_conts"
## [17] "eta_qq"    "pmx_vpc"
```

As a convention, when plots are described as ???Y vs. X???, it is meant that Y is plotted on the vertical axis and X on the horizontal axis.

As an example, a plot of individual weighted residuals (IWRES) versus time (with default settings) can be generated using a single-line code:

```r
ctr %>% pmx_plot_iwres_time
```
The complete list of available plots per plot type (given in parenthesis) is given below:

- Residual plots (SCATTER)
  
  ```
  ctr %>% pmx_plot_dv_pred
  ctr %>% pmx_plot_dv_ipred
  ctr %>% pmx_plot_iwres_time
  ctr %>% pmx_plot_npde_time
  ctr %>% pmx_plot_iwres_ipred
  ctr %>% pmx_plot_abs_iwres_ipred
  ctr %>% pmx_plot_npde_pred
  ```

- Empirical Bayes Estimates (EBE), also called “eta”, histogram and boxplot (DIS)
  
  ```
  ctr %>% pmx_plot_eta_hist
  ctr %>% pmx_plot_eta_box
  ```

- Individual plots (IND)
  
  ```
  ctr %>% pmx_plot_individual(which_pages = 1)
  ```

- QQ-plots (PMX_QQ)
Distribution and correlation structure of random effects (**ETA_PAIRS**)

## 4 Visual Predictive Checks (VPC)

### 4.1 Initialization

In order to generate VPCs a simulation dataset is required. Creation of VPC is slightly different depending on the fitting software used (Monolix, NONMEM or nlmixr).

#### 4.1.1 Models fitted with Monolix (versions 2016 and later)

Monolix users, need to run a simulation with simulx. Here’s an example code:

```r
## Create simulated object using simulx
mysim <- simulx(project=project_dir, nrep=100) #
## Retrieve simulated dataset (assumed to be in y1)
simdata <- mysim$LIDV
```

For use with ggPMX, it is required that the IDs are reverted to the original IDs as in the modelling dataset for ggPMX.

```r
## Need to revert the original IDs as in modeling dataset for ggPMX
## Rename IDs column to same name as in modeling dataset, e.g.
## ???id??? in the example below
simdata <- simdata %>%
  mutate(newId = as.numeric(as.character(id))) %>%
  left_join(., mysim$originalId) %>%
  mutate(id = as.numeric(as.character(oriId))) %>%
  select(-oriId, -newId) %>%
data.table::data.table()
```

```r
## It's highly recommended to store your simulation as .csv
vpc_file <- write.csv(simdata, file = "my_VPC.csv", quote=FALSE, row.names = FALSE)
```

**pmx_sim** creates a simulation object. It takes the following arguments:

Argumentss

1. **file** character path to the simulation file
2. **irun** character name of the simulation column
3. **idv** character name of the ind. variable
4. **dv** character name of the observation variable

Within pmx vpc controller, it is called like:
theoph_path <- file.path(
  system.file(package = "ggPMX"), "testdata",
  "theophylline"
)
WORK_DIR <- file.path(theoph_path, "Monolix")
input_file <- file.path(theoph_path, "data_pk.csv")
vpc_file <- file.path(theoph_path, "sim.csv")

ctr <- pmx_mlx(
  directory = WORK_DIR,
  input = input_file,
  dv = "Y",
  cats = c("SEX"),
  conts = c("WT0", "AGE0"),
  strats = "STUD",
  settings = pmx_settings(
    use.labels=TRUE,
    cats.labels=list(
      SEX=c("0"="Male","1"="Female")
    )
  ),
  sim = pmx_sim(
    file = vpc_file,
    irun ="rep",
    idv="TIME"
  )
)

4.1.2 Models fitted with NONMEM (versions 7.2 and later)

It is required to provide simulation tables to generate VPCs. Furthermore, it is highly recommended that simulation tables have a “sim”-suffix and are kept with the same naming convention as for the prediction tables (e.g sdtab001sim, catab001sim). In this case they’re automatically recognized by the run number (runno) or by the model file if specified there. For post-hoc simulation it is possible to include an additional simfile:

ctr <- pmx_nm(
  directory = model_dir,
  file = "modelfile.ctl" #or .lst
  simfile = "simulation_modelfile.ctl" #or .lst
)

Important: When simulations are performed post-hoc and the controller is generated by run number, the reader might load the wrong .ext file (used for parameters). A warning message is displayed.

4.1.3 Models fitted with nlmixr

For nlmixr users, the VPC is generated automatically with the controller creation and turned on by default vpc = TRUE.
4.2 VPC plot

The plot options are described in ?pmx_plot_vpc function.

4.2.1 Default

%>% pmx_plot_vpc

4.2.2 Scatter/Percentile

By default the vpc plot is percentile ; , but we can plot the scatter type:

%>% pmx_plot_vpc(type ="scatter")
### 4.2.3 Binning

```r
ctr %> pmx_plot_vpc(bin=pmx_vpc_bin(style = "kmeans",n=5))
```

Areas represent the 95% confidence intervals for the percentiles. The dots are the observations. The rugs represent the limits of the bins. The percentiles are plotted at the median independent variables in the bins.

### 4.2.4 Stratification

```r
ctr %> pmx_plot_vpc(strat.facet="SEX",facets=list(nrow=2))
```

Areas represent the 95% confidence intervals for the percentiles. The dots are the observations. The rugs represent the limits of the bins. The percentiles are plotted at the median independent variables in the bins.
4.2.5 Monolix-like customisation

User can customize the options to get a Monolix-like display.

```r
ctr %>% pmx_plot_vpc(
  strat.facet="SEX",
  facets=list(nrow=2),
  type="percentile",
  is.draft = FALSE,
  pi = pmx_vpc_pi(interval = c(0.1,0.9),
                  median=list(color="green"),
                  extreme= list(color="green")),
  obs = pmx_vpc_obs(color="blue",shape=18,size=2),
  ci = pmx_vpc_ci(interval = c(0.1,0.9)),
)```
5 Diagnostics report

A report (in pdf and docx format) containing all default diagnostic plots can be created using the `pmx_report` function. The `format` can take three different values:

- **report**: produces a pdf and a docx file (named `name.pdf` and `name.png` specified in argument `name`, located in `save_dir`) with default diagnostic plots
- **plots**: produces a folder named `ggpmx_GOF` located in `save_dir` that contains all default diagnostic plots, each in a pdf and png file. The different plots are numerated in order to have an unique identifier for each plot (ex: `ebe_box-1.pdf`). This is necessary for having correct footnotes that indicated the path to the source file (for submission reports).
*both*: is a combination of both options above.

Example:

```r
ctr %>% pmx_report(name='Diagnostic_plots2',
  save_dir = work_dir,
  format='both')
```

Note that running the same command first with the option “format='plots'” and then with the option “format='report'” will remove the `ggpmx_GOF` folder.

Note also that by default, the report will have the DRAFT label on all plots. The label can be removed by using the settings argument in the Controller creation.

The user can customize the default report by creating a “template”. To create a template, the user should create first a default report with the following command:

```r
ctr %>% pmx_report(name='Diagnostic_plots1',
  save_dir = work_dir,
  format='report')
```

The Rmarkdown (.Rmd) file is the “template”. The user can modify the Rmarkdown file as desired (ex: changing the size of some figures) and save the modified file. The new template can be used with the following command:

```r
ctr %>% pmx_report(name='Diagnostic_plots3',
  save_dir = work_dir,
  format='report',
  template=file.path(work_dir,'Diagnostic_plots1.Rmd'))
```

6 Customizing plots

Any particular plot can be customized in two ways:

- Specifying options in each call of a plot (on the fly, recommended):

  ```r
  ctr %>% pmx_plot_xx(list of options)
  ```

- Customizing a type of plot for all subsequent calls in the session by modifying the Controller:

  ```r
  ctr %>% pmx_update(???xx???, list of options)
  ```

Help(pmx_gpar) lists some options.

Help(pmx_plot_xx) lists some possible parameters to update a particular plot.

To obtain an exhaustive list of possible options for a particular plot, use the following:

```r
ctr %>% get_plot_config("xx")
```
6.1 Visualization of BLQs (Monolix and NONMEM)

It is possible to visualize BLQ (below the limit of quantification) values in the individual plots. For this, `bloq` needs to be specified using the `pmx_bloq` function (see example below with the `pmx_mlxtran()` function).

```r
ctr %>% pmx_mlxtran(file_name = mlx_file, bloq=pmx_bloq(cens = "??BLQ???, limit = "??LIMIT???"))
ctr %>% pmx_plot_individual()
```

6.2 Simulated BLOQ (Monolix 2018 and later)

Monolix users may want to plot simulated BLQs. This is possible for outputs with Monolix 2018 and later. An additional dataset is loaded (sim_blq), which will be used for plotting instead the regular “predictions”-dataset.

The `sim_blq` statement can be specified within the plot (locally) ...

```r
ctr %>% pmx_mlxtran(file_name = mlx_file))
ctr %>% pmx_plot_iwres_ipred(sim_blq = TRUE)
```

... or within the controller (globally). If this statement is used within the controller, all corresponding plots will plot simulated BLOQs by default.

```r
ctr %>% pmx_mlxtran(file_name = mlx_file, sim_blq = TRUE))
ctr %>% pmx_plot_iwres_ipred()
```

6.3 Customizing global settings - `pmx_settings()`

The user can define a Controller with global settings that will be applied to all plots. For example remove draft annotation, use abbreviation definitions to define axis labels, etc.

A settings object is defined by using the function `pmx_settings()`. The created object is passed as the parameter “settings” to `pmx()`. By doing so, the settings are defined globally and apply to all plots. For a complete list of global settings with their corresponding default values, please consult the ggPMX Help (`?pmx_settings`).

```r
## set one or more settings
my_settings <- pmx_settings(  
is.draft = FALSE,  
use.abbrev = TRUE,  
...)
```

### set other settings parameters here

```r
ctr <-  
  pmx_mlx(  
    ...,  
    ## put here other pmx parameters  
    settings = my_settings  
  )
```

6.3.1 Remove DRAFT label globally

By default in the “standing” configuration, a DRAFT label is printed on all plots. In order to switch this label off, the user sets the `is.draft` option of `pmx_settings()` to `FALSE`. 
6.3.2 Use abbreviation definitions

The standing configuration initializes all plots using abbreviations for axis labels. Each abbreviation has its corresponding definition. To get the list of abbreviation:

```r
ctr %>% get_abbrev
```

## AIC : Akaike information criterion
## BIC : Bayesian information criterion
## BLQ : Below the limit of quantification
## COAR : Clinical Operations Analytics and Regions
## DV : Dependent variable
## ETA : Inter-individual random effect
## EBE : Empirical Bayes estimate
## FO : First order
## FOCE : First order conditional estimation
## FOCEI : First order conditional estimation with interaction
## IIV : Inter-individual variability
## IPRED : Individual prediction
## LRT : Likelihood ratio test
## M&S : Modeling & Simulation
## NLME : Nonlinear mixed-effects (model)
## NPD : Normalized prediction discrepancy
## NPDE : Normalized prediction distribution error
## OCP : Oncology Clinical Pharmacology
## OFV : Objective function value
## PD : Pharmacodynamics
## PK : Pharmacokinetics
## PDF : Probability density function
## SAEM : Stochastic approximation of the expectation-minimization algorithm
## VPC : Visual predictive check
## PRED : Population parameters predictions
## EPRED : Population averaged predictions
## IWRES : Individual weighted residuals
## |IWRES| : |Individual weighted residuals|
## NVS : Novartis internal report
## HA : Report submitted to Health Authorities
## TIME : Time after first dose (hours)

You can update one abbreviation to set a custom label

```r
ctr %>% set_abbrev(TIME="TIME after the first dose")
```

Using use.abbrev flag you can use abbreviation definition to set axis labels:

```r
ctr <- theophylline(settings=pmx_settings(use.abbrev = TRUE))
ctr %>% set_abbrev(TIME="Custom TIME axis")
ctr %>% pmx_plot_npde_time
```
6.3.3 Use `finegrid.txt` file for individual plots

within Monolix, user can choose to not use finegrid file even if it is present.

```r
ctr <- theophylline()
ctr %>% pmx_plot_individual(use.finegrid = FALSE)
```

## USE predictions data set
6.3.4 Set stratification color legend

In case of color stratification user can customize the legend. For example here using the `ggplot2::scale_color_manual`:
Another way to do it is to define a global `scales.color` parameter that will be applied to all plots with `strat.color`:

```r
ctr <- theophylline()
ctr %>% pmx_plot_npde_time(strat.color="STUD") +
  ggplot2::scale_color_manual(
    "Study",
    labels=c("Study 1","Study 2"),
    values=c("1"="green","2"="blue"))
```

NPDE vs TIME

Another way to do it is to define a global `scales.color` parameter that will be applied to all plots with `strat.color`:

```r
ctr <- theophylline(
  settings=
    pmx_settings(
      color.scales=list(
        "Study",
        labels=c("Study 1","Study 2"),
        values=c("1"="orange","2"="magenta"))
    )
)

ctr %>% pmx_plot_npde_time(strat.color="STUD")
```
6.3.5 Define labels of categorical variables

In case of faceting by stratification user can redefine categorical labels to have more human readable strips. Lables are defined within `cats.labels` argument and user can use them by setting `use.labels` to TRUE.

```r
ctr <- theophylline(
  settings= pmx_settings(
    cats.labels=list(
      SEX=c("0"="M", "1"="F"),
    )))
```
```r
ctr <- theophylline(
  settings = pmx_settings(
    cats.labels = list(
      SEX = c("0" = "M", "1" = "F"),
      STUD = c("1" = "Study 1", "2" = "Study 2")
    ),
    use.labels = TRUE
  )
)

ctr %>% pmx_plot_npde_time(strat.facet = -SEX)
```
NPDE vs TIME by SEX

ctr %>% pmx_plot_eta_box(strat.facet = ~SEX)
7 Appendix

7.1 Generic Controller creation with pmx()

The function pmx() is the generic function for creating a Controller, currently only works with Monolix. The user needs to specify a set of arguments such as the path to the model directory, the software used for model fitting (Monolix), the name of a configuration. A list of all existing configurations is provided in the Appendix. All mandatory arguments of pmx() are listed in Table 2.

The example below defines a Controller with the standing (standard) configuration.
Table 2: Mandatory arguments of pmx() function

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 sys</td>
<td>Software used for model fitting (Monolix or nlmixr)</td>
<td>mlx, mlx2018, nm</td>
</tr>
<tr>
<td>2 config</td>
<td>A pre-defined configuration is a set of default settings</td>
<td>standing</td>
</tr>
<tr>
<td>3 directory</td>
<td>Path to the directory containing model output files</td>
<td></td>
</tr>
<tr>
<td>4 input</td>
<td>Path to input modeling dataset (dataset used for model fitting)</td>
<td></td>
</tr>
<tr>
<td>5 dv</td>
<td>Measurable variable name, as defined in the input modeling dataset</td>
<td>DV, LIDV, LNDV, Y, etc.</td>
</tr>
<tr>
<td>6 dvid</td>
<td>Endpoint (output) name, as defined in the input modeling dataset</td>
<td>DVID, YTYPE, CMT, etc.</td>
</tr>
</tbody>
</table>

```r
theophylline_path <- file.path(system.file(package = "ggPMX"), "testdata", "theophylline")
work_dir <- file.path(theophylline_path, "Monolix")
input_data_path <- file.path(theophylline_path, "data_pk.csv")

ctr <- pmx(
  sys = "mlx",
  directory = work_dir,
  input = input_data_path,
  dv = "Y",
)
```

Note that the column “DVID” of data_pk.csv does not exist; however it is not needed here because there is only one single output of the model. As dvid is a mandatory argument, which is automatically set to “DVID” if dvid is missing.

The input dataset can be provided to ggPMX via its location (as in the example above) or as a data frame (maybe give an example). The modeling output datasets have to be in the location that is indicated as working directory (work_dir in the example above).

### 7.2 Software requirements

ggPMX is compatible with Monolix versions 2016 and later, NONMEM version 7.2 and later, and nlmixr.

#### 7.2.1 Monolix

In order to be able to produce all available diagnostic plots, the following tasks should be executed in Monolix during the model fitting procedure:

- Population parameters;
- Individual parameters (EBEs);
- Standard errors;
- Plots.

In addition, make sure to export charts data (In Monolix 2018: Settings -> Preferences -> Export -> switch on the Export charts data button). Select at least the following plots to be displayed and saved: individual fits and scatter plot of the residuals.

#### 7.2.2 NONMEM

NONMEM Version 7.2/7.3/7.4 Preferred output tables according ???sdtab, patab, cotab, catab??? convention Simulation are required for creation of VPC (e.g. sdtab1sim)
7.2.3 nlmixr

Fit objects need to be generated by nlmixr and have data attached. Standard errors are required (a successful covariance plot) for full diagnostic checks. Can use `bootstrapFit()` to get standard error estimates if necessary.

7.3 Plots table

The main target of ggPMX is to create a report containing the following plots (see abbreviation list below):

<table>
<thead>
<tr>
<th>Plot Name</th>
<th>ggPMX type</th>
<th>ggPMX name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Scatter plot of NPDE vs population predictions</td>
<td>SCATTER</td>
<td>npde_pred</td>
</tr>
<tr>
<td>2 Scatter plot of NPDE vs time</td>
<td>SCATTER</td>
<td>npde_time</td>
</tr>
<tr>
<td>3 Scatter plot of IWRES vs time</td>
<td>SCATTER</td>
<td>iwres_time</td>
</tr>
<tr>
<td>4 Scatter plot of observations vs population predictions</td>
<td>SCATTER</td>
<td>dv_pred</td>
</tr>
<tr>
<td>5 Scatter plot of observations vs individual predictions</td>
<td>SCATTER</td>
<td>dv_ipred</td>
</tr>
<tr>
<td>6 Scatter plot of absolute value of IWRES vs individual predictions</td>
<td>SCATTER</td>
<td>abs_iwres_ipred</td>
</tr>
<tr>
<td>7 Scatter plot of IWRES vs individual predictions</td>
<td>SCATTER</td>
<td>iwres_ipred</td>
</tr>
<tr>
<td>8 Plots of observations and model predictions per individual</td>
<td>IND</td>
<td>individual</td>
</tr>
<tr>
<td>9 Histogram of EBE</td>
<td>DIS</td>
<td>ebe_hist</td>
</tr>
<tr>
<td>10 Boxplot of EBE</td>
<td>DIS</td>
<td>ebe_box</td>
</tr>
<tr>
<td>11 Distribution and quantile-quantile plot of IWRES</td>
<td>QQ</td>
<td>qq_iwres</td>
</tr>
<tr>
<td>12 Distribution and correlation structure of RE (‘ETA’)</td>
<td>ETA_PAIRS</td>
<td>eta_matrix</td>
</tr>
<tr>
<td>13 Relationships between RE and categorical covariates</td>
<td>ETA_COV</td>
<td>eta_cats</td>
</tr>
<tr>
<td>14 Relationships between RE and continuous covariates</td>
<td>ETA_COV</td>
<td>eta_conts</td>
</tr>
<tr>
<td>15 Visual predictive check (VPC)</td>
<td>VPC</td>
<td>vpc</td>
</tr>
</tbody>
</table>

Table 3: List of all diagnostic plots

Abbreviations:

- NPDE: normalized prediction distribution errors
- IWRES: individual weighted residuals
- EBE: empirical Bayes estimates
- RE: random effects
- VPC: visual predictive check

7.4 ggPMX main functions

ggPMX implements few functions to generate and manipulate diagnostic plots. (Should we list pmx and pmx_mlx separately and say the differences? Or it’s maybe clear from the previous sections.)

(Apparently, it’s not the full list. Add all functions.) The design of the package is around the central object: the controller. It can introspected or piped using the %>% operand.

Note that:

The controller is an \texttt{R6} object, it behaves like a reference object. Some functions (methods) can have a side effect on the controller and modify it internally. Technically speaking we talk about chaining not piping here. However, using \texttt{pmx_copy} user can work on a copy of the controller.
### Table 4: List of all ‘ggPMX’ functions

<table>
<thead>
<tr>
<th>Function name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1 pmx, or pmx_mlx</td>
<td>Creates a controller</td>
</tr>
<tr>
<td>2 2 plot_names or plots</td>
<td>Lists controller plots</td>
</tr>
<tr>
<td>3 3 get_data</td>
<td>Lists controller data</td>
</tr>
<tr>
<td>4 4 get_plot</td>
<td>Prints a plot</td>
</tr>
<tr>
<td>5 5 set_plot</td>
<td>Creates a new plot</td>
</tr>
<tr>
<td>6 6 pmx_update</td>
<td>Updates an existing plot</td>
</tr>
<tr>
<td>7 7 pmx_filter</td>
<td>Filters globally the data of the current session</td>
</tr>
<tr>
<td>8 8 pmx_copy</td>
<td>Returns a deep copy of the controller</td>
</tr>
</tbody>
</table>

#### 7.5 ggPMX graphical parameters

Graphical parameters in ggPMX are set internally using the `pmx_gpar` function. A number of graphical parameters can be set for the different plot types.

```r
args(pmx_gpar)
```

```r
## function (labels, axis.title, axis.text, ranges, is.smooth, smooth, 
## is.band, band, is.draft, draft, discrete, is.identity_line, 
## identity_line, scale_x_log10, scale_y_log10, color.scales, 
## is.legend, legend.position) 
## NULL
```

More information can be found in the help document `?pmx_gpar` and in the examples that follow.

#### 7.6 Pre-defined configurations

For the moment we are mainly using standing configuration. In the next release user can specify configuration either by creating a custom yaml file or an R configuration object. Also ggPMX will create many helper functions to manipulate the configuration objects.

#### 7.7 Shrinkage

#### 7.8 Default call

The shrinkage is a computation within controller data. In general it is used to annotate the plots. Although one can get it independently from any plot using `pmx_comp_shrink`. It is part of the `pmx_compt_xx` layer( In the future we will add , `pmx_comp_cor`, `pmx_comp_summary`,...)

Here the basic call:

```r
ctr %>% pmx_comp_shrink
```

```r
## EFFECT OMEGA SHRINK POS FUN
## 1: Cl 0.22485 0.1125175 0.2934250 var
## 2: V 0.03939 0.9469996 0.0057915 var
## 3: ka 0.10024 0.7423478 0.0810850 var
```
We get the shrinkage for each effect (SHRINK column).
The same values can be shown on distribution plot, for example:

```r
ctr %>% pmx_plot_eta_box
```

**EBE distribution**

![EBE distribution plot]

```
ctr %>% pmx_plot_eta_hist
```
You can add or remove shrinkage annotation using `is.shrink` argument (TRUE by default):

```r
ctr %>% pmx_plot_eta_box(is.shrink = FALSE)
```
### 7.9 Var function

You can compute shrinkage by applying either standard deviation `sd` or variance `var`:

```r
ctr %>% pmx_comp_shrink( fun = "var")
```

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>OMEGA</th>
<th>SHRINK</th>
<th>POS</th>
<th>FUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>0.22485</td>
<td>0.1125175</td>
<td>0.2934250</td>
<td>var</td>
</tr>
<tr>
<td>V</td>
<td>0.03939</td>
<td>0.9469996</td>
<td>0.0057915</td>
<td>var</td>
</tr>
<tr>
<td>ka</td>
<td>0.10024</td>
<td>0.7423478</td>
<td>0.0810850</td>
<td>var</td>
</tr>
</tbody>
</table>

```r
ctr %>% pmx_plot_eta_box( shrink=list(fun = "var"))
```
7.10 Shrinkage and stratification

Shrinkage can be applied after stratification:

```r
ctr %>% pmx_comp_shrink(strat.facet = ~SEX)
```

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>SEX</th>
<th>OMEGA</th>
<th>SHRINK</th>
<th>POS</th>
<th>FUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>1</td>
<td>0.22485</td>
<td>-0.08032359</td>
<td>0.29342500</td>
<td>var</td>
</tr>
<tr>
<td>Cl</td>
<td>0</td>
<td>0.22485</td>
<td>0.51828810</td>
<td>0.12378000</td>
<td>var</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>0.03939</td>
<td>0.94628054</td>
<td>0.00579150</td>
<td>var</td>
</tr>
<tr>
<td>V</td>
<td>0</td>
<td>0.03939</td>
<td>0.94818243</td>
<td>0.00437235</td>
<td>var</td>
</tr>
<tr>
<td>ka</td>
<td>1</td>
<td>0.10024</td>
<td>0.70737008</td>
<td>0.08108500</td>
<td>var</td>
</tr>
<tr>
<td>ka</td>
<td>0</td>
<td>0.10024</td>
<td>0.80907530</td>
<td>0.03676950</td>
<td>var</td>
</tr>
</tbody>
</table>

or by grouping like:

```r
ctr %>% pmx_comp_shrink(strat.color = "SEX")
```

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>SEX</th>
<th>OMEGA</th>
<th>SHRINK</th>
<th>POS</th>
<th>FUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
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<td>0.29342500</td>
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<tr>
<td>V</td>
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<td>0.03939</td>
<td>0.94628054</td>
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<tr>
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<tr>
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<td>0.70737008</td>
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<tr>
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<td>0.80907530</td>
<td>0.03676950</td>
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</tr>
</tbody>
</table>

We can
ctr %>% pmx_plot_eta_hist(is.shrink = TRUE, strat.facet = ~SEX, facets=list(scales="free_y"))

or

ctr %>% pmx_plot_eta_box(is.shrink = TRUE, strat.facet = "SEX", facets=list(scales="free_y", ncol=2))
EBE distribution by SEX

Model parameters

EBEs

sd shrinkage=31%  sd shrinkage=77%  sd shrinkage=56%

sd shrinkage=−4%  sd shrinkage=77%  sd shrinkage=46%

0 1

0.6

0.4

0.2

0.0

-0.2

-0.4

-0.6

Cl  V  ka

Cl  V  ka

DRAFT

DRAFT

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