



ggPMX

Efficient and Versatile R package for Pharmacometrics Model Diagnostic Plots

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Who we are



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Life before ggPMX



Life with ggPMX



Compatible with NONMEM, Monolix, and nlmixr



- **Consistent, reproducible and efficient** workflow
- **Automated generation** of PDF, Word or PNG outputs for reporting purpose
- Advanced Features for **customization** and **stratification**
- High quality graphics, ready-to-use in **submission documents and publications**

List of Diagnostic Plots

Section of modeling report	Description	HA
Main body	Normalized prediction distribution errors versus population predictions (NPD vs. PRED)	✓
	Normalized prediction discrepancies versus time (NPD vs. TIME)	✓
	Individual weighted residuals versus individual predictions (IWRES vs. IPRED)	✓
	Individual weighted residuals versus time (IWRES vs. TIME)	✓
	Visual predictive check (VPC)	✓
Appendix	Distribution and quantile-quantile plot of IWRES	✓
	Distribution and correlation structure of estimated inter-individual random effects (ETA)	✓
	Relationships between estimated inter-individual random effects (ETA) and covariates	✓
	Observations and model predictions per individual (individual fits)	✓
	Observations versus population predictions (DV vs. PRED)	✓
	Observations versus individual predictions (DV vs. IPRED)	✓
	Absolute individual weighted residuals versus individual predictions (IWRES vs. IPRED)	✓

ggPMX - Intuitive & Fast

Comprehensive model diagnostics report with two lines of code

```
library(ggPMX)
```

Controller Creation

```
ctr <- pmx_nm(directory = nonmem_dir_path,  
              file = "my_nonmem_run.lst") NONMEM
```

```
ctr <- pmx_mlxtran(file_name = mlxtran_path) Monolix
```

```
ctr <- pmx_nlmixr(fit) nlmixr
```

Report Generation

```
ctr %>% pmx_report(name      = "ggPMX_Report",  
                  save_dir  = "working_directory",  
                  format    = "report",  
                  extension = "word")
```



ggPMX standing report

/home/baltcir1/ggPMX

23 March, 2020

Table of Contents

Key model diagnostics	2
NPDE vs PRED	2
NPDE vs TIME	3
IWRES vs IPRED	4
IWRES vs TIME	5
Distribution of random effects	6
VPC	7
Supplementary diagnostics	8
Distribution of IWRES	8
QQ plot of IWRES	8
Distribution of IWRES	9
EBE-based diagnostics	10
Distribution and correlation of EBEs	10
EBE vs discrete covariates	11
EBE vs continuous covariates	12
Observations vs predictions	13
DV vs PRED	13
DV vs IPRED	14
Residual plots	15
[IWRES] vs IPRED	15
Individual plots (selection)	16
Stratified key diagnostics	17
NPDE vs TIME by categorical covariates	17
IWRES vs TIME by categorical covariates	18
VPC by categorical covariates	18

ggPMX standing report

/path2output/folder

Table of Contents

Key model diagnostics.....	3
Parameter Table.....	3
NPDE vs PRED.....	4
NPDE vs TIME.....	5
IWRRES vs IPRED.....	6
IWRRES vs TIME.....	7
Distribution of random effects.....	8
VPC.....	9
Supplementary diagnostics.....	10
Distribution of IWRRES.....	10
QQ plot of IWRRES.....	10
Distribution of IWRRES.....	11
EBE-based diagnostics.....	11
Distribution and correlation of EBEs.....	11
EBE vs discrete covariates.....	13
EBE vs continuous covariates.....	14
Observations vs predictions.....	15
DV vs PRED.....	15
DV vs IPRED.....	16
Residual plots.....	17
IWRRES vs IPRED.....	17
Individual plots (selection).....	17
Stratified key diagnostics.....	19
NPDE vs TIME by categorical covariates.....	19
IWRRES vs TIME by categorical covariates.....	20
VPC by categorical covariates.....	20

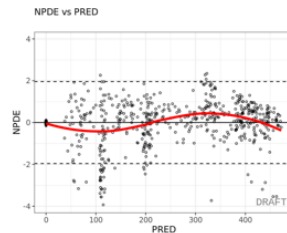
Key model diagnostics

Parameter Table

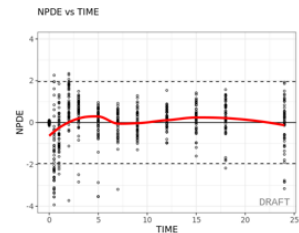
Parameter estimates (15 lines)

Parameter	Value	Relative Standard Error	Shrinkage
CL_pop	3.1e-01	8%	
ka_pop	2.9e-01	7%	
V_pop	2.3e+00	6%	
omega_CL	2.2e-01	11%	11%
omega_ka	1.0e-01	75%	74%
omega_V	3.9e-02	280%	95%
beta_CL_SEX_0	0.0e+00	fixed	
beta_CL_SEX_1	-1.0e-01	78%	
beta_CL_STUD_1	0.0e+00	fixed	
beta_CL_STUD_2	1.2e-01	59%	
beta_CL_SAGE0	-5.7e-02	140%	
beta_CL_WT0	-1.6e-01	136%	
beta_V_WT0	1.8e-01	74%	
b	2.9e-01	3%	
		comp. with var	

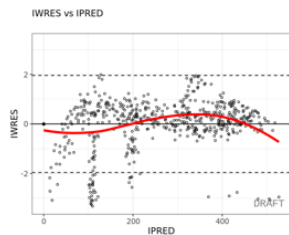
NPDE vs PRED



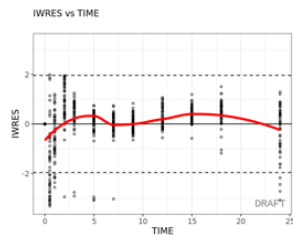
NPDE vs TIME



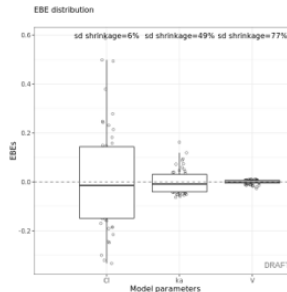
IWRRES vs IPRED



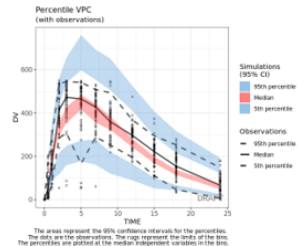
IWRRES vs TIME



Distribution of random effects



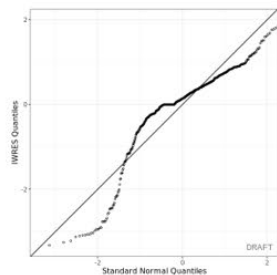
VPC



Supplementary diagnostics

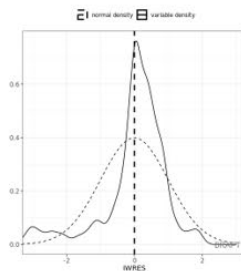
Distribution of IWRES

QQ plot of IWRES



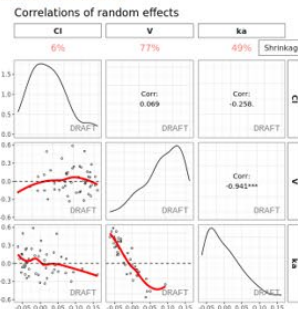
Distribution of IWRES

Density plot of IWRES



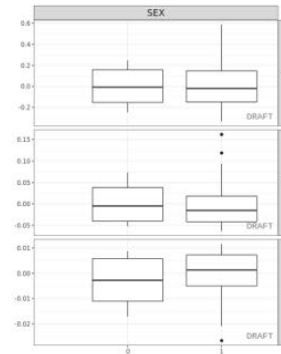
EBE-based diagnostics

Distribution and correlation of EBEs



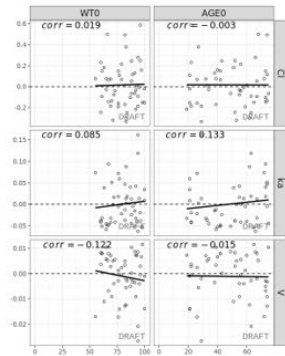
EBE vs discrete covariates

EBE vs. covariates



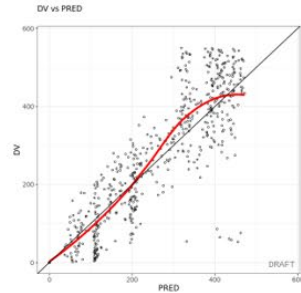
EBE vs continuous covariates

EBE vs. covariates



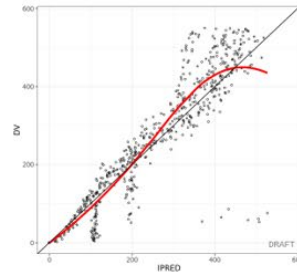
Observations vs predictions

DV vs PRED



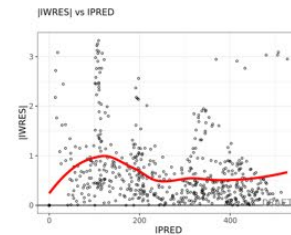
DV vs IPRED

DV vs IPRED

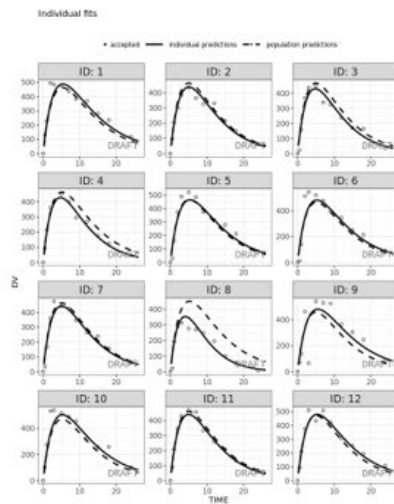


Residual plots

[IWRES] vs IPRED

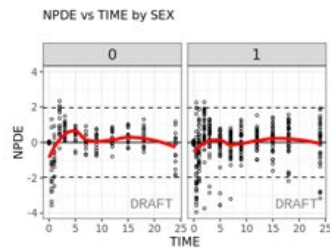


Individual plots (selection)



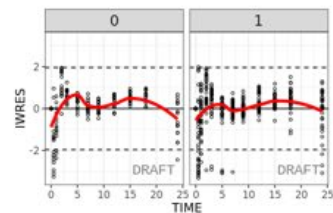
Stratified key diagnostics

NPDE vs TIME by categorical covariates

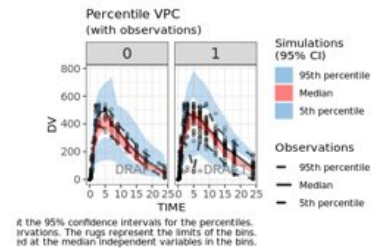


IWRES vs TIME by categorical covariates

IWRES vs TIME by SEX



VPC by categorical covariates



Software-Specific Requirements

NONMEM

- Version ≥ 7.2
- Same output table setting as xpose

Monolix

- Version ≥ 2016
- Run at least the following Monolix tasks:
 - Population Parameters
 - EBEs
 - Standard errors
 - Plots
- Export Chart data
- Select at least the following plots to be displayed and saved:
 - **individual fits** and
 - **scatter plot of the residuals**

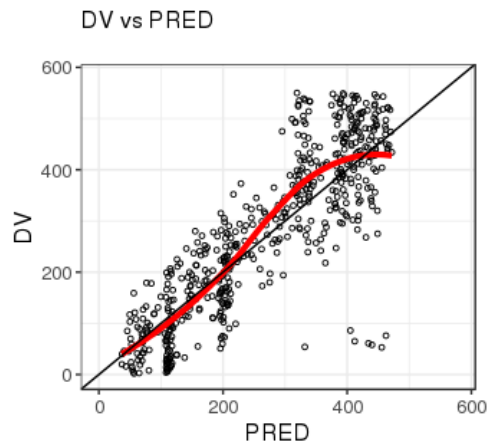
nlmixr/nlmixr2

- nlmixr > 2.0 for censoring support
- nlmixr output object
- Note: VPC of ggPMX with nlmixr currently not working

Single Plot Functions

- Plots visualized using the functions `pmx_plot_xx()`, where xx is a placeholder for the plot name. First argument is always the controller (use piping!)
- Example:

```
ctr %>% pmx_plot_dv_pred()  
ctr %>% pmx_plot_npde_time()  
ctr %>% pmx_plot_eta_box()  
ctr %>% pmx_plot_eta_matrix()  
ctr %>% pmx_plot_individual()  
ctr %>% pmx_plot_vpc()
```



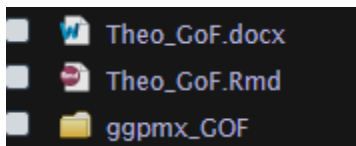
Generating a Diagnostics Report: `pmx_report()`

- 3 report formats available (word, pdf, html) – by default, Word document (only) is generated

```
ctr %>% pmx_report( name      = "Report_ggPMX",    # Report Filename
                    save_dir = "work_dir",        # Directory Path to Report
                    format   = "report",          # Create just a report
                    extension= "word")            # Report Format
```

- Possibility to create a folder containing all figures (`format = "both"`), saved as individual files:

ggpmx_GOF 6/9/2021 10:44 AM File folder



Name	Date modified	Type	Size
abs_ivres_ipred-13.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	112 KB
dv_ipred-12.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	104 KB
dv_pred-11.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	86 KB
eta_box-5.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	35 KB
eta_cats-9.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	30 KB
eta_conts-10.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	113 KB
eta_matrix-8.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	70 KB
indiv-14.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	43 KB
ivres_dens-7.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	10 KB
ivres_ipred-3.pdf	6/9/2021 10:44 AM	Adobe Acrobat D...	112 KB

Key features

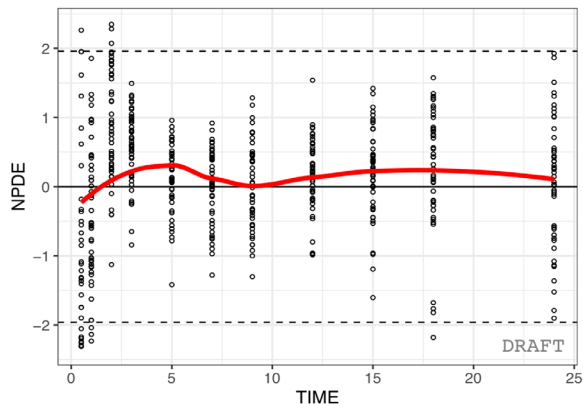
- **Graphical customization**
- **Multiple endpoints**
- **VPC**
- **Stratification** and filtering
- Censoring
- Shrinkage
- Parameter table

Plots customization – on the fly

Default setting

```
ctr %>% pmx_plot_npde_time()
```

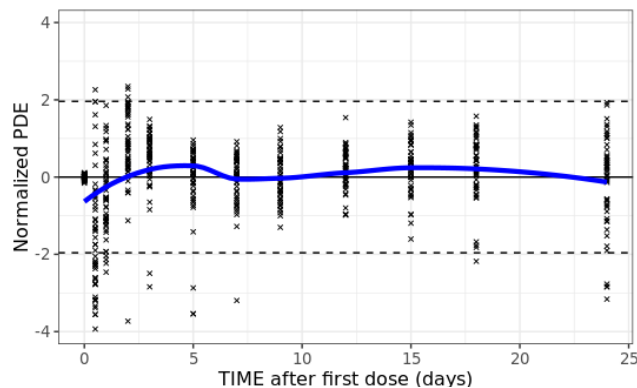
NPDE vs TIME



Updating labels and graphical settings

```
ctr %>% pmx_plot_npde_time(  
  smooth = list(color = "blue"),  
  point = list(shape = 4),  
  is.draft = FALSE,  
  labels = list(x = "TIME after first dose (days)",  
    y = "Normalized PDE"))
```

NPDE vs TIME



Multiple endpoint models

- ggPMX produces **one diagnostics report per endpoint**
- The endpoint is defined within the controller:
 - to filter the observations dataset
 - to keep only the values corresponding to the endpoint of interest

```
# Controller Creation for PD data (DVID==2)
ctrPD <- pmx_nm(directory = work_dir, dv = "DVID", endpoint = 2)
```

- One report per endpoint, e.g. one pmx_report per controller

```
ctrPD %>% pmx_report(      name      = "Report_ggPMX_PD", # Report Filename
                           save_dir  = "work_dir",       # Directory Path to Report
                           format    = "report",         # Report Setting
                           extension= "word")             # Report Format
```

VPC – Controller creation

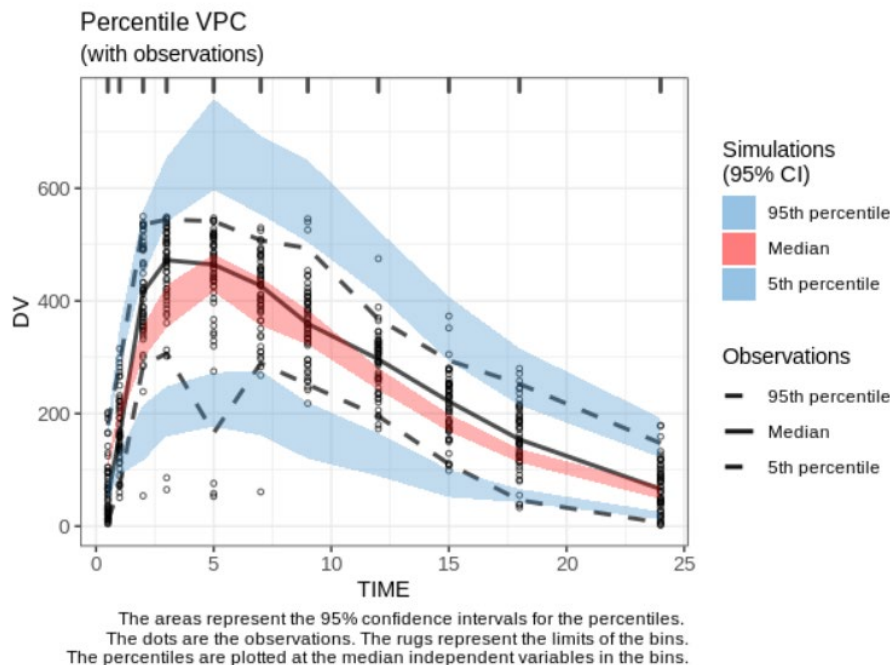
- User needs to provide a simulation dataset at the controller creation
- Use your preferred simulation software/package to create the simulation dataset containing (at least) the following columns:
 - ID: individual identifiers
 - REP: simulation replicate number
 - TIME: time
 - DV: dependent variable
- Create a “simulation object” using **pmx_sim()** and pass it as an argument of the controller function

Example:

```
# Enable VPC functionality for a Monolix controller
ctr <- pmx_mlxttran(file_name = mlxttran_path,
                   sim = pmx_sim(file = "sim.csv", irun = "REP", idv = "TIME"))
```


VPC - Default setting

```
ctr %>% pmx_plot_vpc()
```

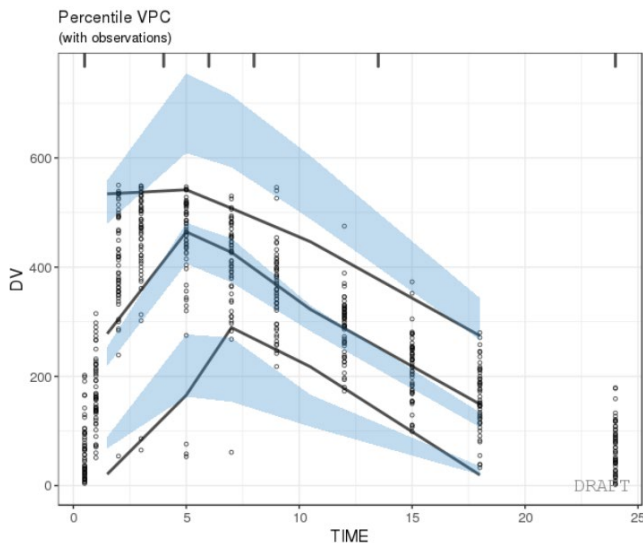


- Legend automatically updated when statistical summaries are changed

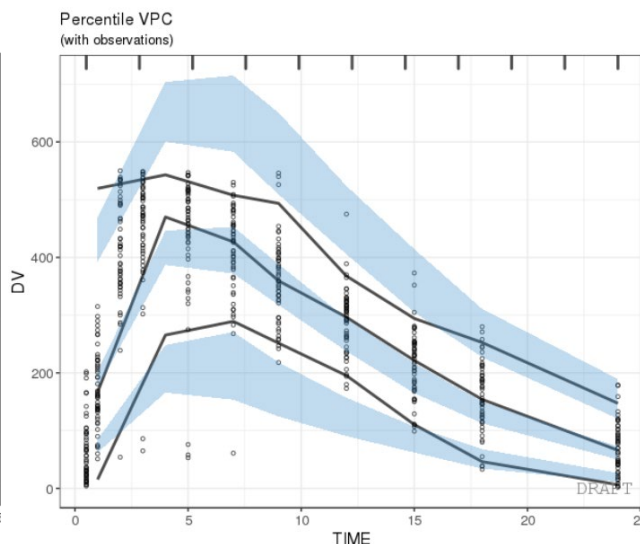
VPC – change the bins

1. `ctr %>% pmx_plot_vpc(bin = pmx_vpc_bin(style = "kmeans", n=5))`
2. `ctr %>% pmx_plot_vpc(bin = pmx_vpc_bin(style = "equal", n=10))`

1.



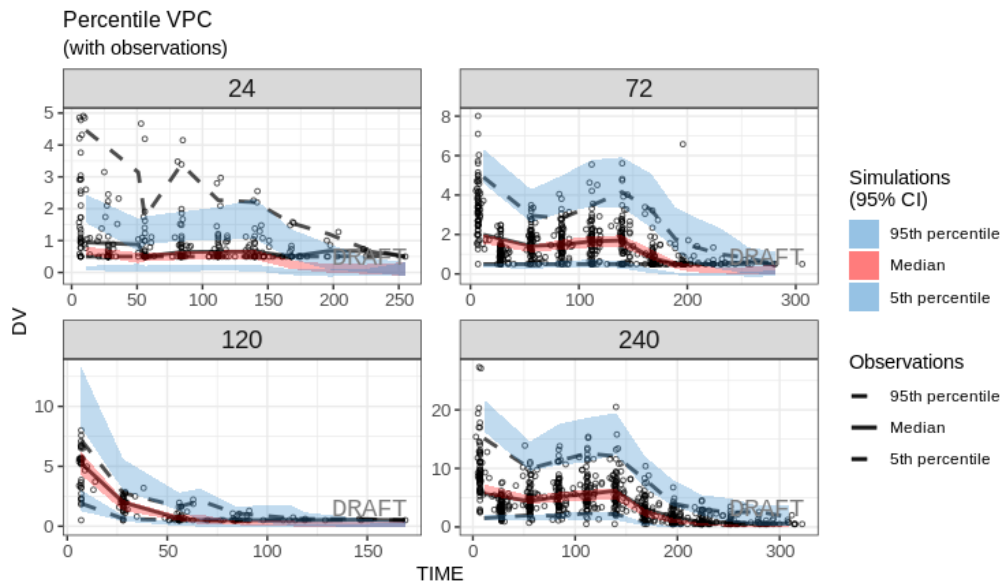
2.



- Package `classInt` is used for binning
- Various binning methods available (*fixed*, *sd*, *equal*, *pretty*, *quantile*, *kmeans*, *hclust* or *jenks*)

VPC - stratification

```
ctr %>% pmx_plot_vpc(bin = pmx_vpc_bin(style = "equal"),  
                    strat.facet = "DOSE",  
                    facets = list(scales = "free"))
```

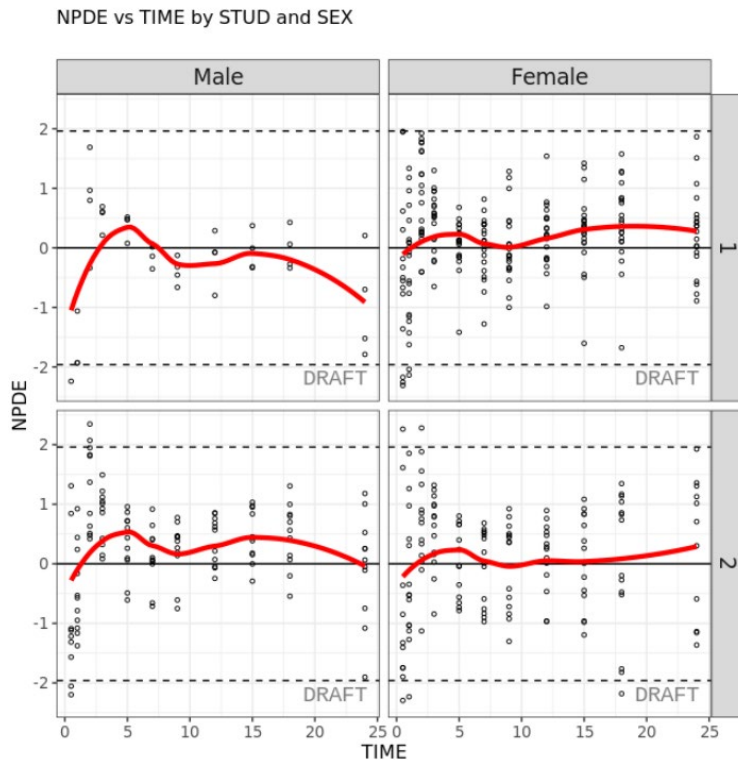


The areas represent the 95% confidence intervals for the percentiles.
The dots are the observations. The rugs represent the limits of the bins.
The percentiles are plotted at the median independent variables in the bins.

Stratification

- Using arguments *strat.facet* (discrete) or *strat.color* (continuous) in *pmx_plot_xxx()*.
- Allows two-dimensional stratification

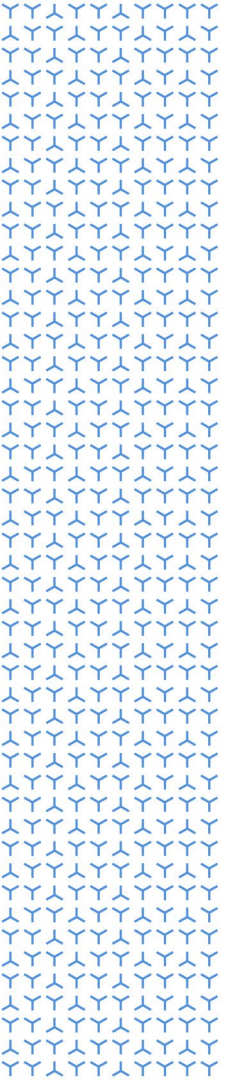
```
ctr %>% pmx_plot_npde_time(strat.facet = STUD~SEX)
```



Documentation & Help

- Latest ggPMX version available on GitHub and CRAN
- Documentation & Training Material on Github
<https://github.com/ggPMXdevelopment/ggPMX>
- Vignette (User Guide)





Thank you

Acknowledgements

- Christian Bartels
- Andrzej Bienczak
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