

Model Comparisons

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Simulation to test models

- (Prediction Corrected) Visual Predictive Checks
- Normalized Prediction Distribution Errors (NPDE)

Holford NH. The visual Predictive Check-Superiority to standard diagnostic (Rorschach) plots. Population Approach Group Europe (2005), Abstr 738.

Brendel K, Comets E, Laffont C, Laveille C, Mentré F. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharm Res.* 2006;23(9):2036–2049.

Bergstrand, Martin, Andrew C Hooker, Johan E Wallin, and Mats O Karlsson. “Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models.” *The AAPS Journal* 13, no. 2 (June 2011): 143–51.

Validate by simulation

- `PM_valid <- PM_result$validate(...)`
- Also adds validation to `PM_result$valid`

PM_result\$validate()

```
PM_result$validate(tad = F, binCov, doseC,  
timeC, tadC, limits, ...)
```

PM_result\$validate()

- tad = F, Convert times to time after previous dose
- binCov, Names of covariates to bin (cluster) for pcVPC
- doseC, Number of dose/covariate clusters
- timeC, Number of observation time clusters
- tadC, Number of observation time-after-dose clusters
- limits, Limits as for PM_sim\$run()
- ..., Other parameters to PM_sim\$run(), not normally used

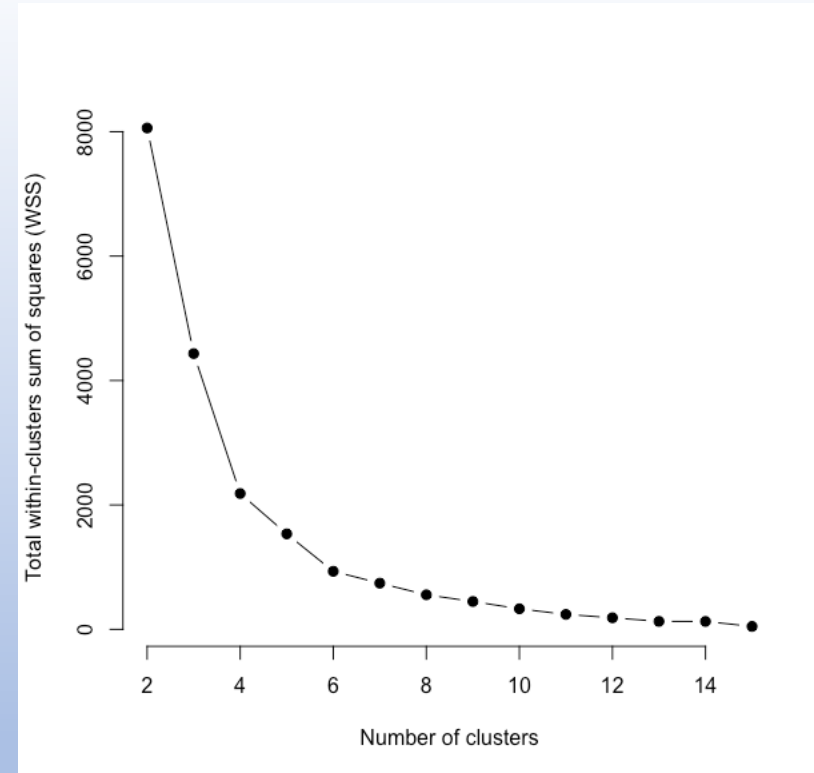
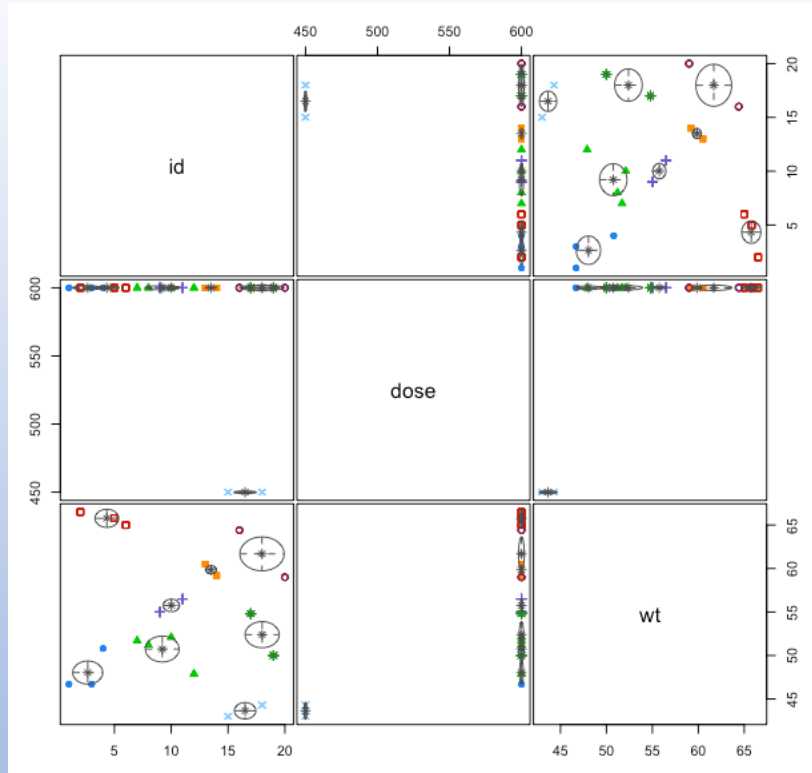
Validation process

- User supplies covariates which are parameters in model equations
- Pmetrics suggests number of clusters based on doses and covariates
- Observations then inspected for clustering

Cluster doses/covariates

```
> valid_2 <- exRes2$validate(limits = NA)
Covariates in your data file: wt, africa, age, gender, height
Enter any covariates to be binned, separated by commas (<Return> for none): wt
Now optimizing clusters for dose/covariates.
First step is a Gaussian mixture model analysis, followed by an elbow plot.
Press <Return> to start cluster analysis for dose, wt:
Now performing Gaussian mixture model analysis.fitting ...
|=====| 100%
Most likely number of clusters is 8.
Press <Return> to see classification plot:
Press <Return> to see elbow plot:
```

Dose/covariate cluster plots



Cluster observation times

Now clustering for actual sample times...

Press <Return> to start cluster analysis for sample times:

fitting ...

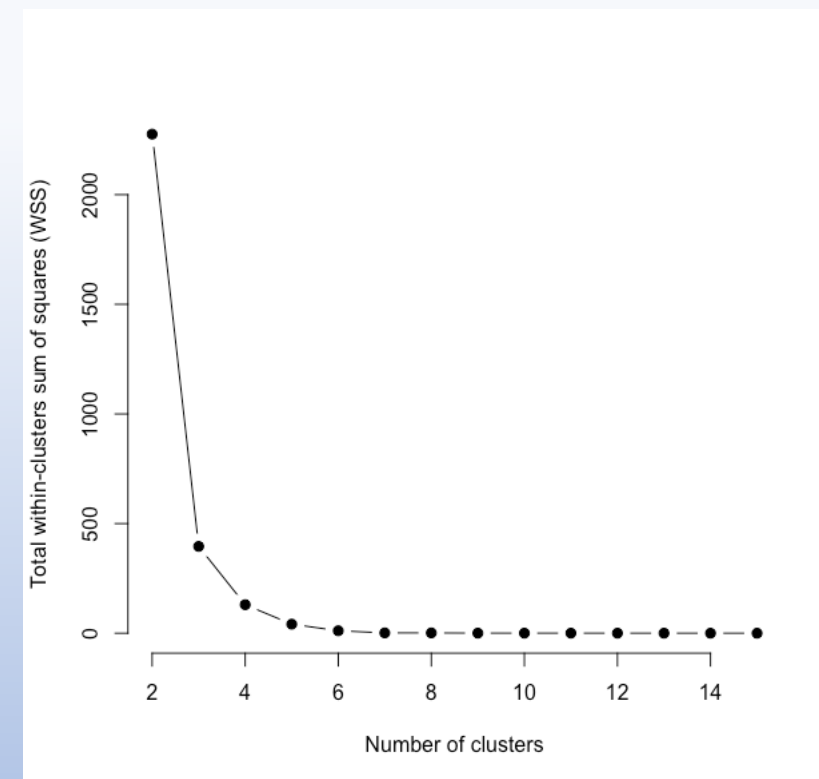
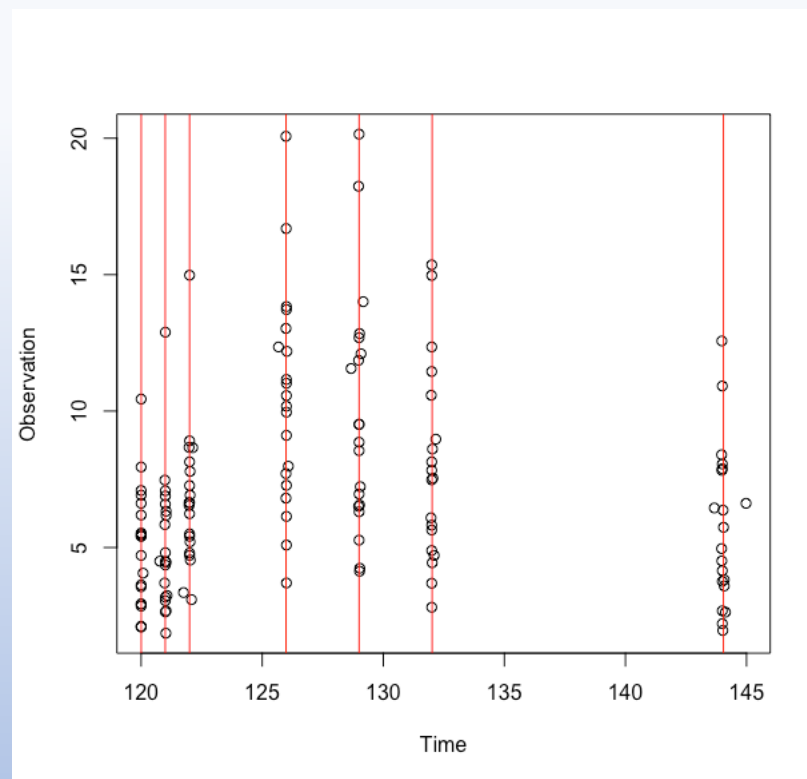
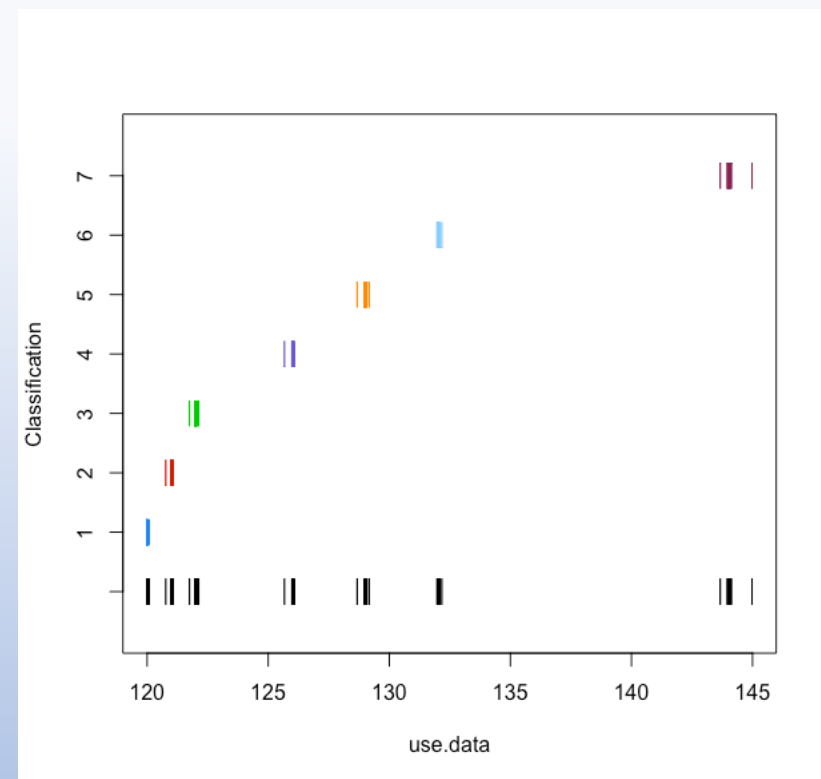
|=====| 100%

Most likely number of clusters is 7.

Press <Return> to see classification plot:

Press <Return> to see cluster plot: |

Time cluster plots



Choose your time clusters

Enter:

<1> for 7 clusters

<2> for a different number of automatically placed clusters

<3> to manually specify cluster centers

Visual Predictive Check

- Simulate using the mean/median population parameter values
- Compare the distribution of simulated observations to the distribution of measured observations in the population

Problems with VPC

- Covariates
- Different dosage regimens used in population

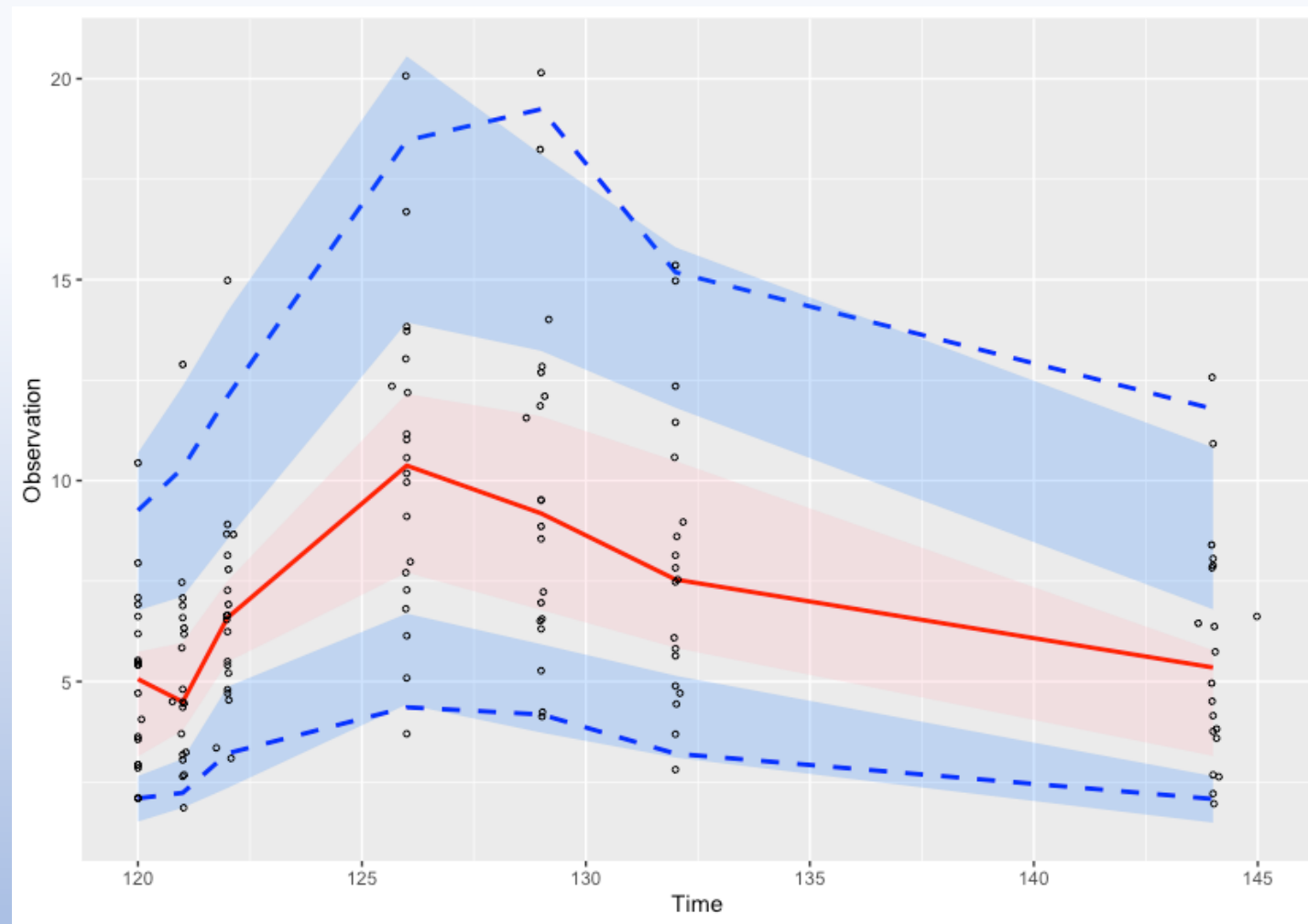
pcVPC

- Simulate based on median values for each cluster and population means, covariances for parameters
- Simulate using all data, correcting each observation for cluster median

NPDE

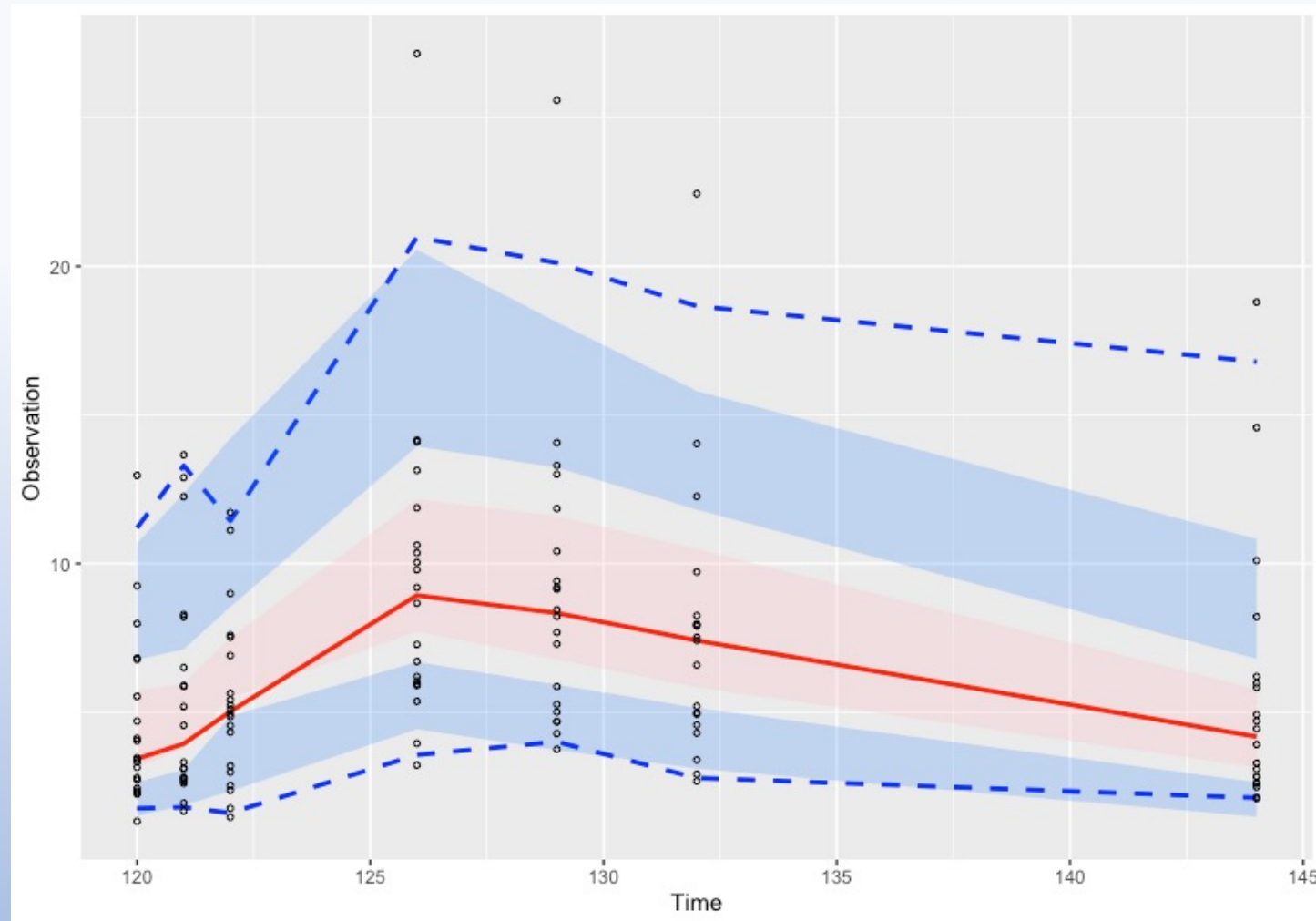
- Normalized prediction distribution errors
- Simulate from each subject using the population parameters but their own covariates, doses, etc.
- Decorrelate and center measured and simulated observations
- Calculate the z-score of the measured observation with respect to the simulated observations at the same time

VPC



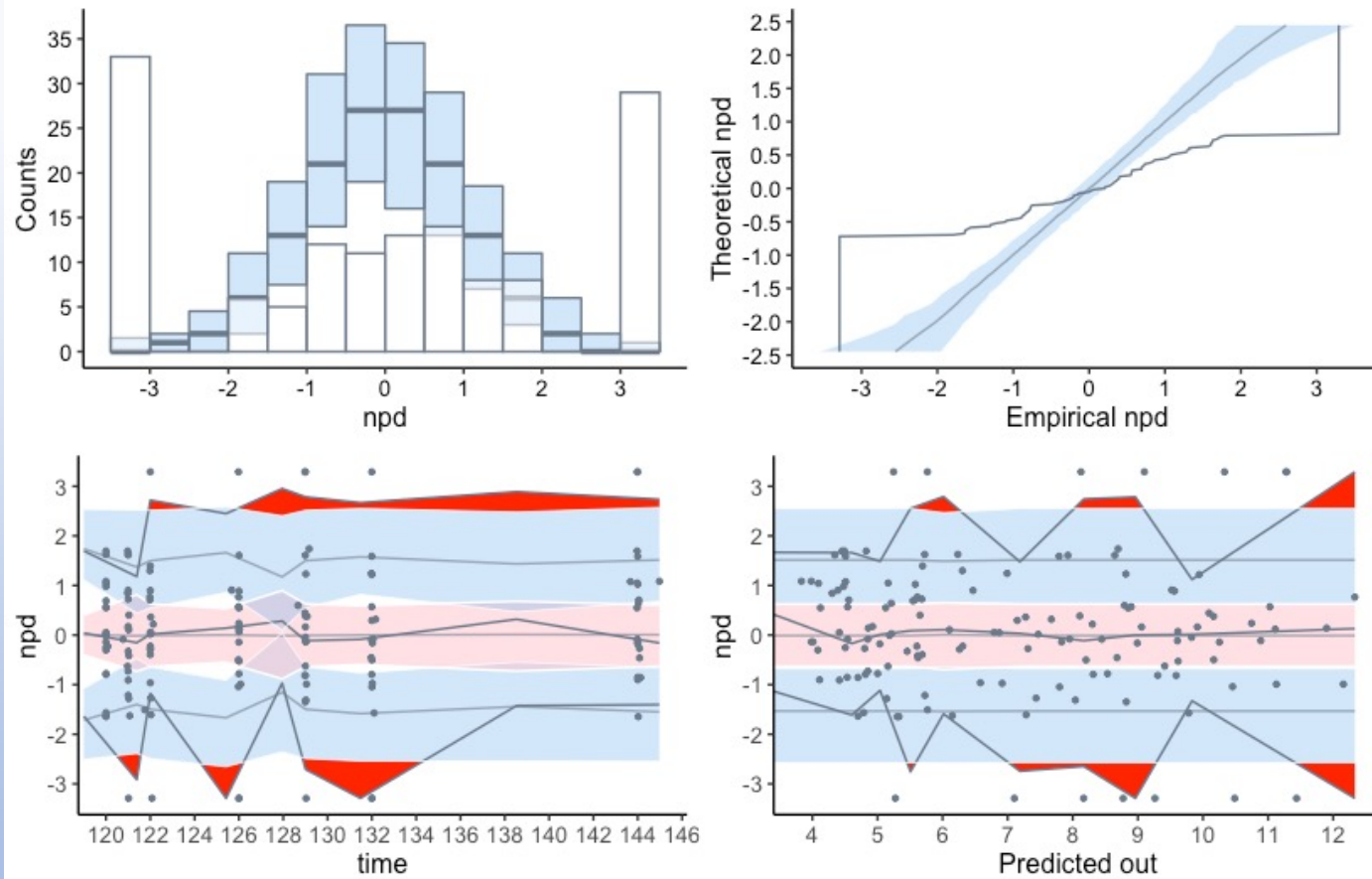
```
valid1$plot()
```


pcVPC



```
valid1$plot(type = "pcvpc")
```

NPDE



```
valid1$plot(type = "npde")
```

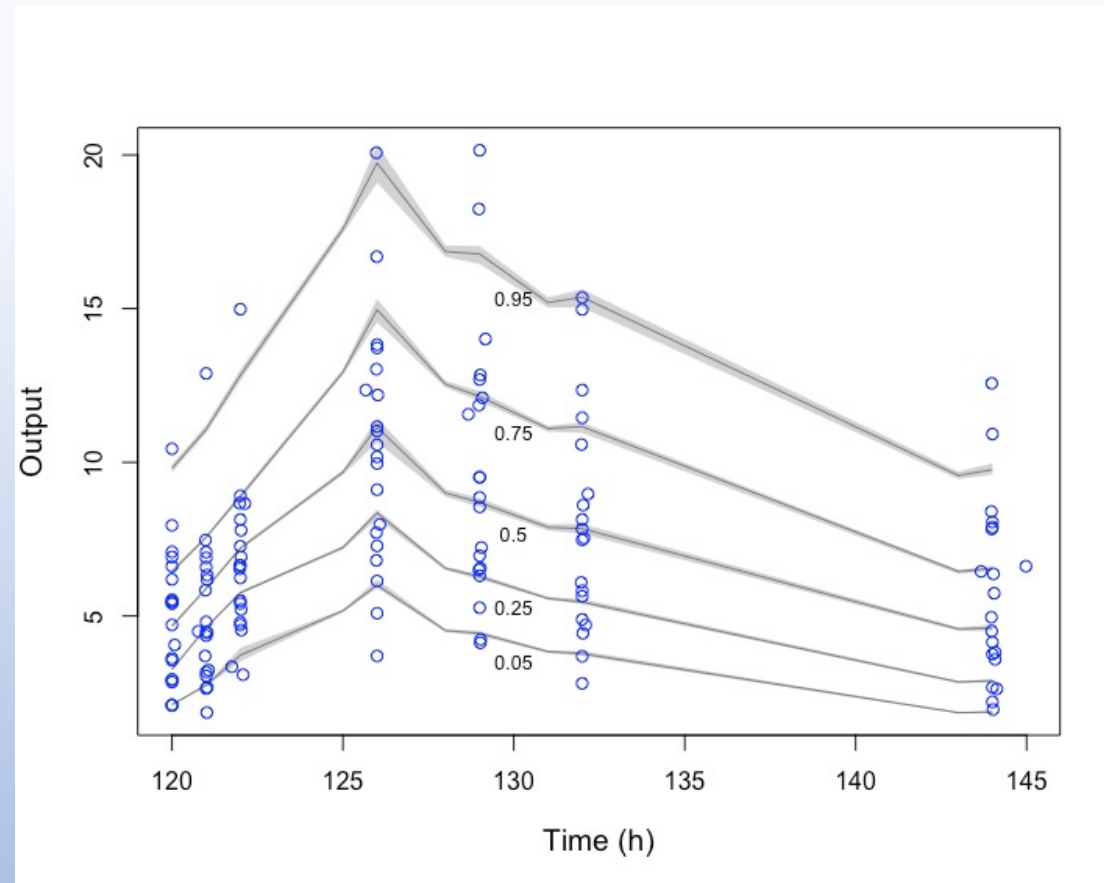
plot.PMsim

```
PM_sim$plot(..., obs, ocol = "blue", ...)
```

obs ... a PMop object, e.g. PM_result\$op

ocol ... Color to plot the observations

Plot



```
npc.1 <- sim1$plot(obs = run1$op, binSize = 1, log = F)
```

NPC

```
> npc.1
```

	quantile	prop.less	pval
1	0.05	0.106	0.007665045
2	0.25	0.311	0.108583850
3	0.50	0.545	0.338380239
4	0.75	0.811	0.130933637
5	0.95	0.939	0.545915167

Proportion of observations between 5th and 95th simulated percentiles: 0.894, P=0.772

Comparing models

```
PM_compare(x, y, ..., icen = "median", outeq =  
1, plot = F)
```

PM_compare: x, y,...

- x, y, ... are any number of PM_result objects

PM_compare

- `PM_compare(run1, run2)`

run	type	nsub	nvar	par	converge	-2*LL	aic	bic
1	NPAG	20	4	Ka Ke V Tlag1	FALSE	440.2	450.6	464.9
2	NPAG	20	4	Ka Ke V0 Tlag1	FALSE	439.7	450.2	464.4
popBias	popImp	popPer_RMSE			postBias	postImp	postPer_RMSE	pval
1.329	18.64	46.16			-0.10297	0.9813	12.31	NA
1.424	17.44	43.07			-0.09176	0.9982	12.40	0.609

PM_compare

- `PM_compare(run1, run2, plot=T)`

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