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Perl speaks NONMEM (PsN)

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<https://uupharmacometrics.github.io/PsN>

What is PsN?

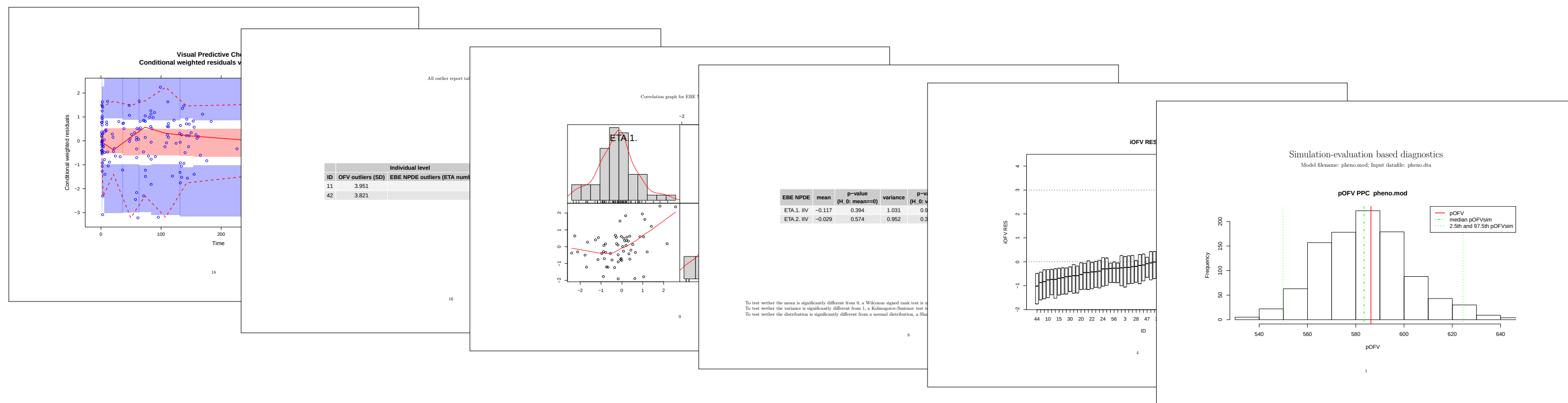
PsN is a toolbox for population PK/PD model building using NONMEM. It has a broad functionality ranging from simple wrapping of nmfe runs and parameter estimate extraction to advanced computer-intensive statistical methods and NONMEM job handling in large distributed computing systems. All PsN tools support NONMEM 7.3 and later and many tools also support NONMEM versions as old as NONMEM 6.1.

New in PsN 4.8.0

- A new tool, **qa**, for fast and automatic assumption assessment and quality assurance of models [1][2][3][4][5]
- A new tool, **transform**, to manipulate model files. For example to automatically add IOV or Box-Cox transform ETAs.
- A new optional directory structure using a subdirectory for each model via the option `-model_subdir` (see below)
- The addition of support for vpc for mixture models [6]
- Second order approximation added to the linearize tool [7]
- The presentation of meta data (i.e. start time, NONMEM version etc) in a new file, **meta.yaml**, which is in a both human and computer readable format

Automatic diagnostic plots

PsN can create and run an R script based on a template. PsN comes with a set of default templates, e.g. for simeval, but the user can easily modify these templates or create new ones for specific projects. For example, `simeval pheno.mod -samples=1000 -rplots=2` will, by default, create the file `PsN_simeval_plots.pdf` with the following plots (and more) in the run directory:



Model diagnostics using PsN and Xpose

VPC/NPC

- PsN controls the simulation of new datasets and does the computation needed for the VPC or NPC. Xpose is invoked via the `-rplots` option.
`vpc run22.mod -samples=1000 -rplots=1`
- Options to handle different types of data e.g.:
 - Categorical data
 - Censored continuous (e.g. BLQ) data
 - Categorized continuous data
 - Survival data
- Options to perform prediction corrected VPC and prediction + variability corrected VPC
`vpc run22.mod -samples=1000 -predcorr -rplots=1`
- Wide range of customizable binning and stratification settings
`vpc run22.mod -samples=1000 -stratify_on=DOSE -rplots=1`
- Automatic handling of log transformed data

QA

Quality assurance, QA, is a new diagnostics tool that will aid in assessing different aspects or assumptions and quality of a model [1]. A qa run will separately cover the structural model, parameter model, residual error model, covariate model as well as outliers and influential individuals of a given model. A QA run gives comprehensive input to where a model might have weaknesses. The main result table shown below gives a modeller input on how much alternative models would impact OFV. Other figures and tables give more detailed information.

	dOFV	Additional parameters
Structural Model		
TIME	7.7	9
TAD	7.6	8
PRED	6.5	9
Parameter Variability Model		
Full OMEGA Block	2.6	1
Box-Cox Transformation	2.2	2
Additional ETA	NA	
t-distribution	0.0	2
Interoccasion variability	NA	
Covariates		
FREM	4.5	4
CLAPGR-4	2.5	1
Residual Error Model		
dtbs	13.9	2
time varying	8.0	2
Influential Individuals		
None		
Outliers		
Subject 42	0.4	

Figure 1: Overview of QA results from QA report

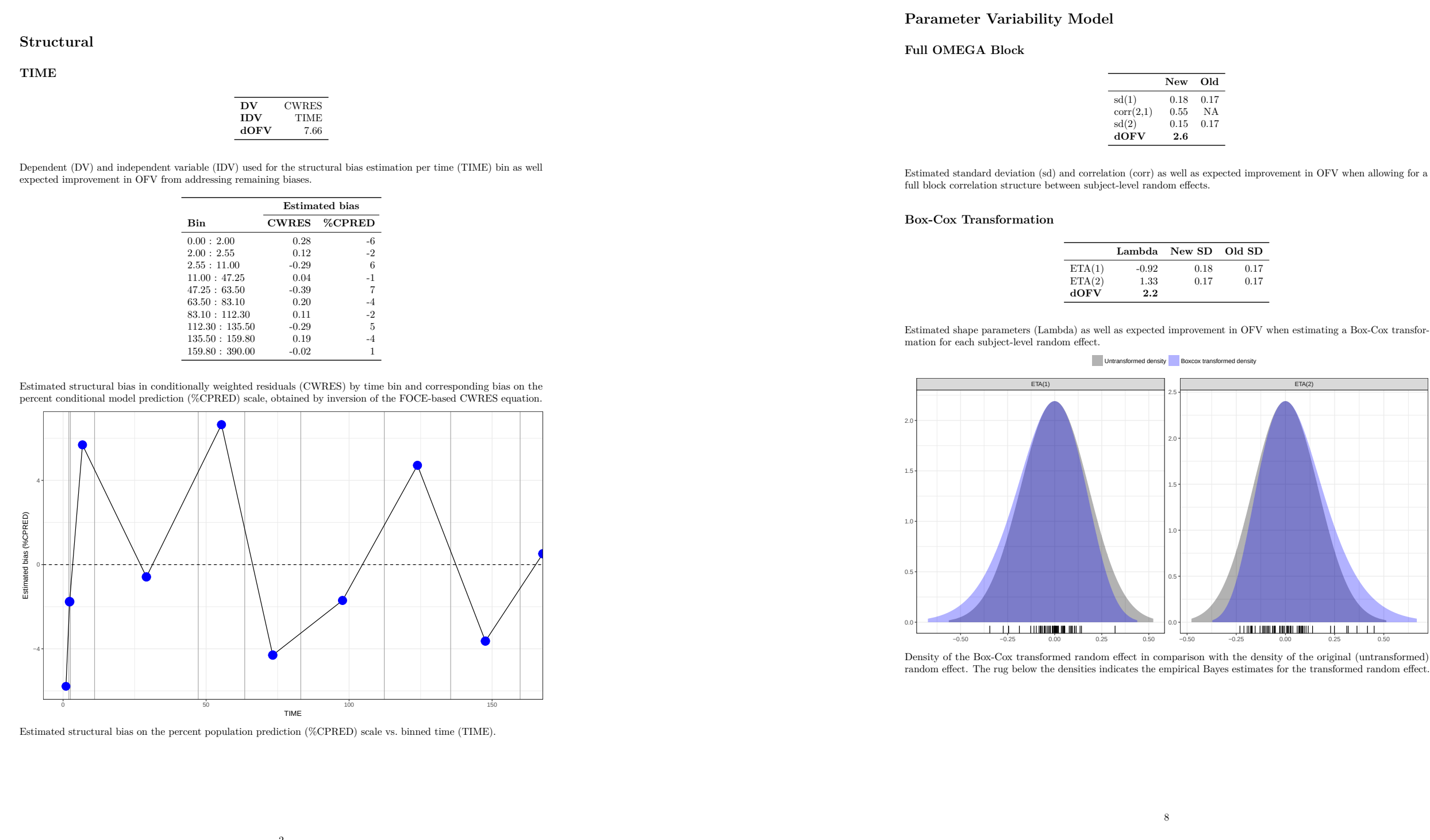


Figure 2: Estimated structural bias

Figure 3: Full omega black and Box-Cox transformation

New optional directory structure

A new optional directory structure has been introduced. The option `-model_subdir`, which is available for all PsN tools, will activate the new structure. It adds a new subdirectory for each model putting all run directories and result files pertaining to a model in its own directory. As an example consider the starting directory structure below. The top directory contains two models and datasets.

```
mydir/
├── run1.csv
├── run1.mod
├── run2.csv
└── run2.mod
```

After running `execute` and `bootstrap` on both models two directories called `run1` and `run2` will be created. These would contain the run directories as well as the generated result files. Compare with the default flat directory on the right where results from the different models are intermixed. (Note that the `sdtab` would need to have different names and that it would be wise to use the `-directory` option to keep track of the different run directories in the default scenario.)

```
mydir/
├── run1/
│   ├── bootstrap_dir1/
│   ├── modelfit_dir1/
│   ├── run1.lst
│   └── sdtab
├── run2/
│   ├── bootstrap_dir1/
│   ├── modelfit_dir1/
│   ├── run2.lst
│   └── sdtab
├── run1.csv
├── run1.mod
├── run2.csv
└── run2.mod
```

```
mydir/
├── bootstrap_dir1/
├── bootstrap_dir2/
├── modelfit_dir1/
├── modelfit_dir2/
├── run1.csv
├── run1.lst
├── run1.mod
├── run2.csv
├── run2.lst
├── run2.mod
└── sdtab
```

The model subdirectory feature was sponsored by
Boehringer
Ingelheim

[1] Mats O. Karlsson, Svetlana Freiberga, Gunnar Yngman, Rikard Nordgren, and Sebastian Ueckert. Extensive and automatic assumption assessment of pharmacometric models. *PAGE 27 (2018) Abstr 8754*, 2018.

[2] Rikard Nordgren, Sebastian Ueckert, Svetlana Freiberga, and Mats O. Karlsson. Faster methods for case deletion diagnostics: dofv and linearized dofv. *PAGE 27 (2018) Abstr 8683*, 2018.

[3] Gunnar Yngman, Rikard Nordgren, Svetlana Freiberga, and Mats O. Karlsson. Linearization of full random effects modeling (frem) for time-efficient automatic covariate assessment. *PAGE 27 (2018) Abstr 8750*, 2018.

[4] Sebastian Ueckert, Svetlana Freiberga, Gunnar Yngman, and Mats O. Karlsson. Understanding sources of variability: The variability attribution plot. *PAGE 27 (2018) Abstr 8659*, 2018.

[5] Moustafa M. A. Ibrahim, Sebastian Ueckert, Svetlana Freiberga, Maria C. Kjellsson, and Mats O. Karlsson. Model-based post-processing of cwres for assessment of prediction bias. *PAGE 27 (2018) Abstr 8716*, 2018.

[6] Usman Arshad, Estelle Chasseloup, Rikard Nordgren, and Mats O. Karlsson. Development of visual predictive checks accounting for multimodal parameter distributions in mixture models. *PAGE 27 (2018) Abstr 8600*, 2018.

[7] Yasunori Aoki, Joakim Nyberg, and Mats O. Karlsson. Second order taylor expansion of likelihood-based models for fast covariate and random effect model building. *PAGE 27 (2018) Abstr 8751*, 2018.