Perl speaks NONMEM (PsN)

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PsN^4 Perl speaks NONMEM

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 7.4.3 and many tools also support NONMEM versions as old as NONMEM 6.1.

New in PsN 4.9.0

- Many improvements to the quality assurance tool **qa**.
- New option `parameters` to **sumo** makes comparing model parameters and OFV easier
- R code for plotting has been moved to an R package **PsNR**
- Stratification for **crossval**
- New option -debug_rmd to keep the tex and md files when using `-rplots`
- New clean level 5 to remove the entire rundirectory

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:

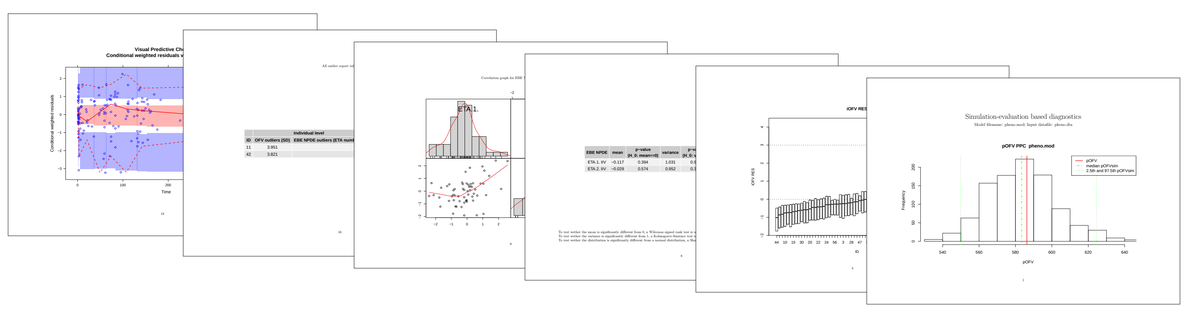

Figure 1: Selection of automatically generated diagnostics available in PsN.

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 the tool that received most attention in this release. QA was introduced last year, it is a diagnostics tool that will aid in assessing different aspects or assumptions and quality of a model [1]. In contrast to traditional diagnostics, QA automatically evaluates a multitude of different model modifications and presents the expected impact in terms of change in OFV to the user. The tool utilizes proxy models (linearization and CWRES based) to perform these evaluations in a fraction of the estimation time for a full non-linear mixed effect model. With one simple command, such as:

```
qa run1.mod -parameters=CL,V,KA -continuous=AGE,WT -categorical=SEX
```

the tool will test:

1. Structural model misspecifications
2. A full OMEGA block
3. Box-Cox transformation of all random effects
4. Addition of new random effects
5. t-distributed random effects
6. Addition of interoccasion variability
7. Improvement through covariates univariately
8. Joint improvement of all covariates
9. Six different residual error models
10. Impact of influential individuals
11. Impact of outlying individuals and observations

The results of this evaluation are summarized in PDF report with an overview table for at-a-glance checking as well as detailed tables and figures for in-depth diagnosis.

	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 2: Overview table of QA results in the PDF report

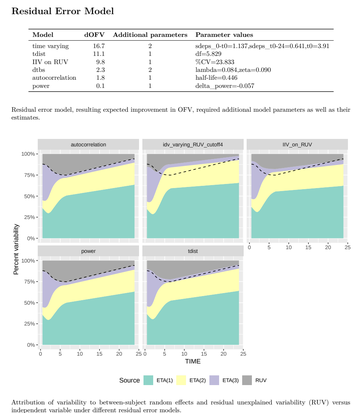

Figure 3: Details section for residual error modifications

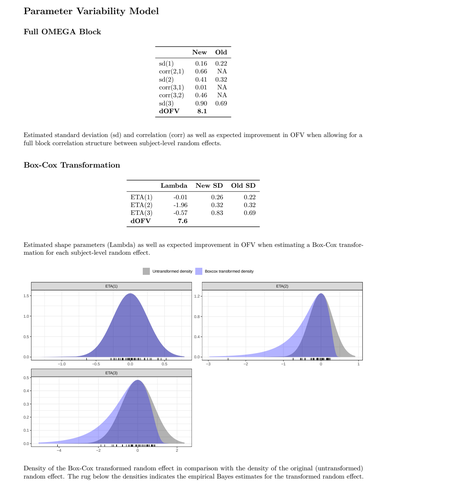

Figure 4: Details section for full omega block and Box-Cox transformation

Utility scripts

PsN also provides various small helpers to simplify common modelling tasks, such as:

- Assessing model sensitivity to initial parameter estimates

```
parallel_retries run1.mod -min_retries=10 -degree=0.2
```

- Test different initial estimates for one theta

```
benchmark run1.mod -theta_inits=2:none,0.1,0.5,1,2
```

- Test different initial estimates for a set of thetas

```
benchmark run1.mod -theta_inits=CL:none,1,2,3,,V:none,1,2,3
```

- Clean files from a rundirectory after the run was finished

```
psn_clean bootstrap_dir1 -level=4 -no-interactive
```

- Box-cox transform etas in a model

```
transform boxcox run1.mod -etas=1
```

- Compare estimates of two or more models

```
sumo run1.lst run2.lst -parameters
```

[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.