Perl speaks NONMEM (PsN) and Xpose

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PsN⁴ Perl speaks NONMEM

http://psn.sf.net   http://xpose.sf.net
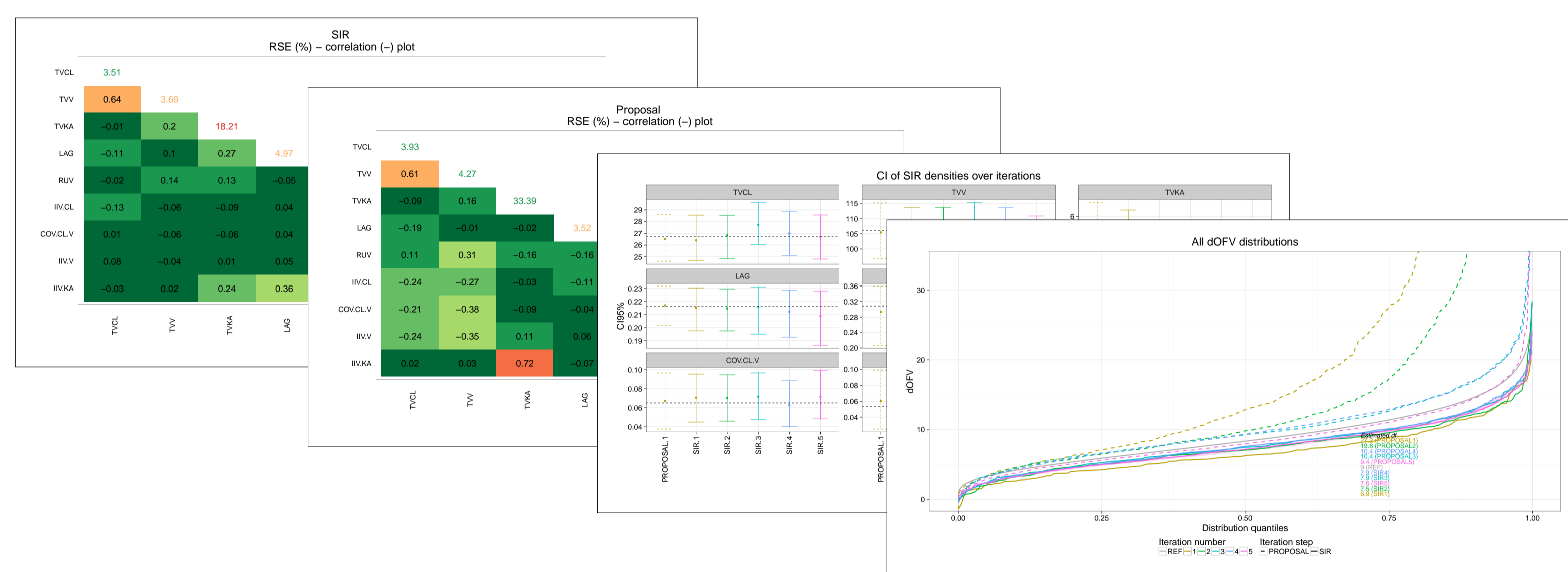
XPOSE

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. PsN4 supports all NONMEM versions from 6.1 through 7.3

New in PsN 4.6.0

- Further advancement of **sir**, a tool for obtaining **parameter uncertainty** faster than with a bootstrap and more accurately than based on the covariance step. The program runs a fully automated iterative procedure and produces easy to use results, as well as diagnostic plots to support their visualization and interpretation [1].
- **Identification of outliers** using simulation and evaluation. New tool: simeval [2]
- **Benchmarking** of combinations of NONMEM control stream settings and/or NONMEM and compiler versions. New tool: benchmark
- Conversion of **NONMEM output to standardized xml** according to the DDMoRe SO format. New tool: nmoutput2so

Automatic diagnostic plots

PsN comes with a set of default templates for diagnostic plots, e.g. for sir and execute. For example `sir run1.mod -rplots=1` will in the run directory create the file PsN_plots_base.pdf containing the following plots:

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 odd-type 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

BQL VPC

Categorized continuous data
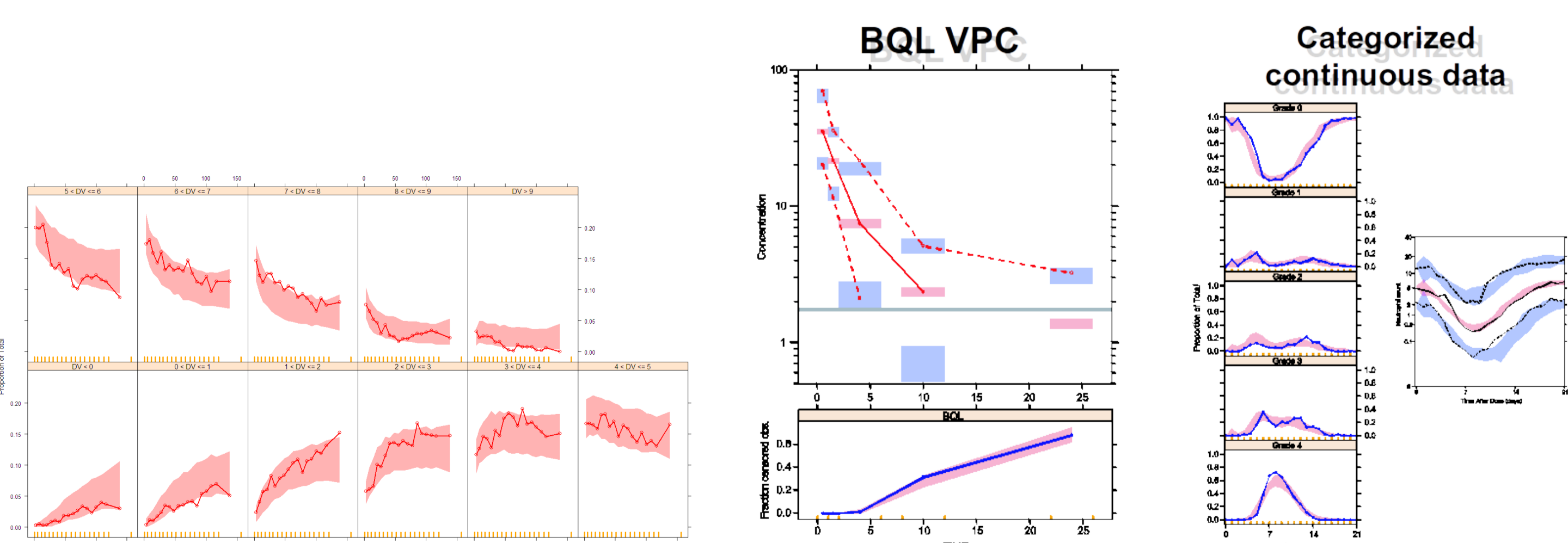
What is Xpose?

Xpose is an open-source R package for post-processing of NONMEM (and PsN) output. It takes one or more standard NONMEM table files (or PsN result files) as input and generates graphs or other analyses. Xpose tries to make it easier for a modeler to use diagnostics in an intelligent manner.

Features of Xpose

- **Tools for for data visualization and data checkout:** Graphs and tables intended to summarize raw data, for example concentrations versus time or histograms of the covariates.
- **Model evaluation tools:** Plots and tables created to evaluate all aspects of a pharmacometric model. Including:

  Visual Predictive Check
  Conditional weighted residuals vs. Time after dose (Run 1.cwres.vpc)

  - **Overall goodness of fit assessment:** Xpose has a number of composite displays (multiple graphs and tables of different kinds on the same page) that provide diagnostics for multiple aspects of the fit and summarize a NONMEM run.
  - **Numerical evaluations:** summaries of and tools to create numerical diagnostics.
  - **Population and individual prediction based diagnostics:** plots that use PRED and IPRED to diagnose the appropriateness of the model.
  - **Residual based diagnostics:** Plots that use residuals to diagnose the appropriateness of the model.
  - **Parameter distribution diagnostics:** Plots of parameter distributions.
  - **Simulation based diagnostics:** Mirror plots, visual predictive checks (VPC), numerical predictive checks (NPC).
- **Model comparison tools:** Graphs for comparing various aspects of two models fit to the same data.
- **Model development tools:** Used to help the modeler decide what to do next with the model. Most of these functions focus on aspects of covariate inclusion.
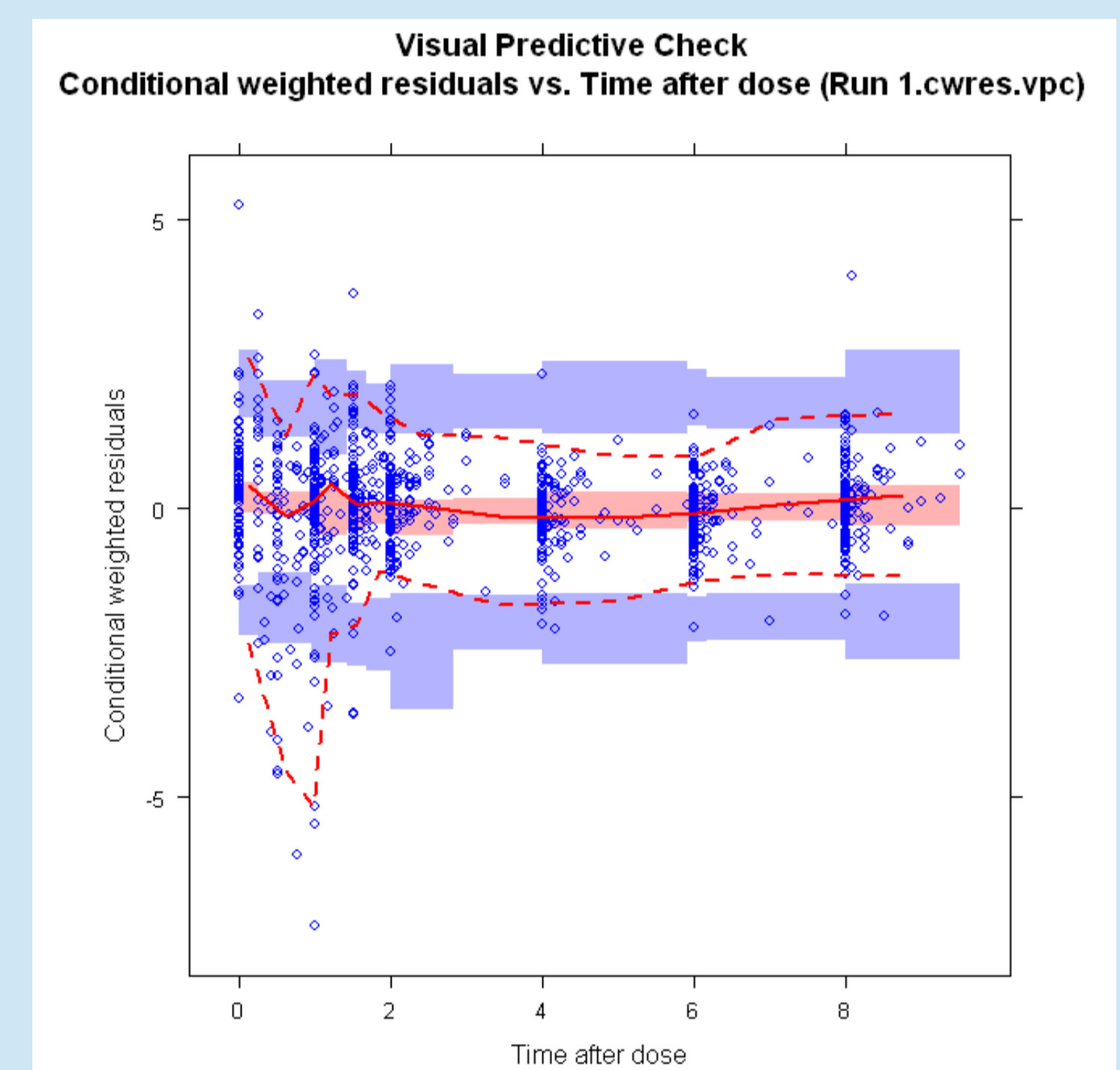
Randomization test

- PsN randomizes the dataset (e.g. based on treatment group) and controls the estimation from both the base model and the full model. The -rplots option makes PsN call Xpose to create the plot.
  `randtest -samples=1000 -randomization_column=DOSE`
  `    run89.mod -base_model=run0.mod -rplots=1`
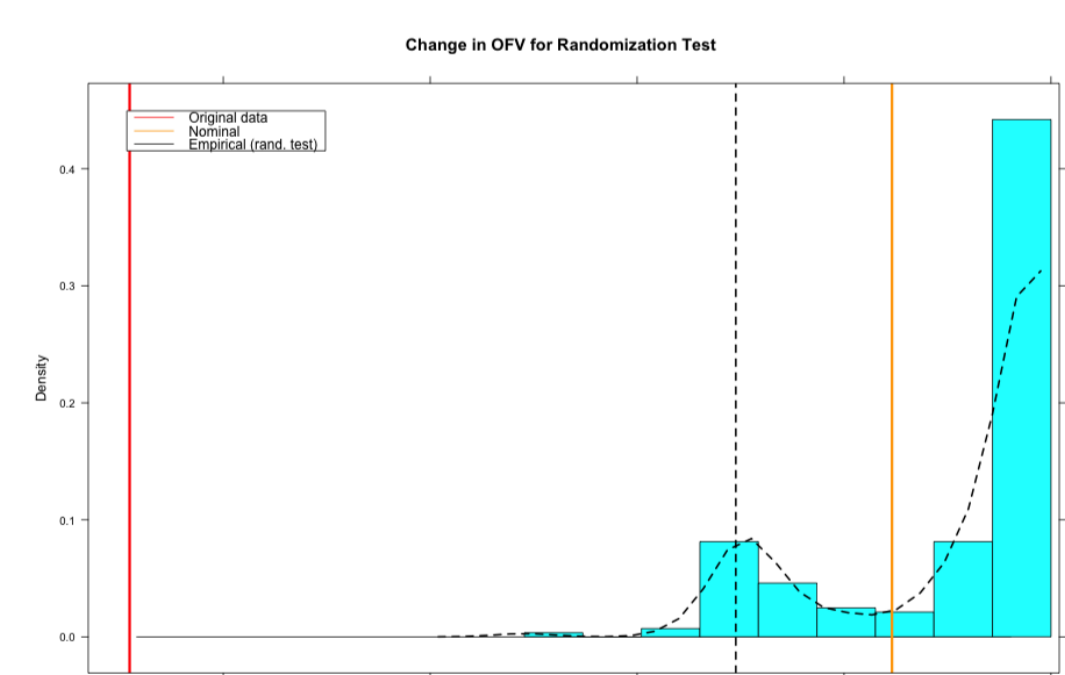
Bootstrap of the stepwise covariate covariate model building (SCM) tool

- PsN creates a number of bootstrap datasets and then runs the SCM. Linearization of the process for faster run times is possible.
  `boot_scm linear.scm`
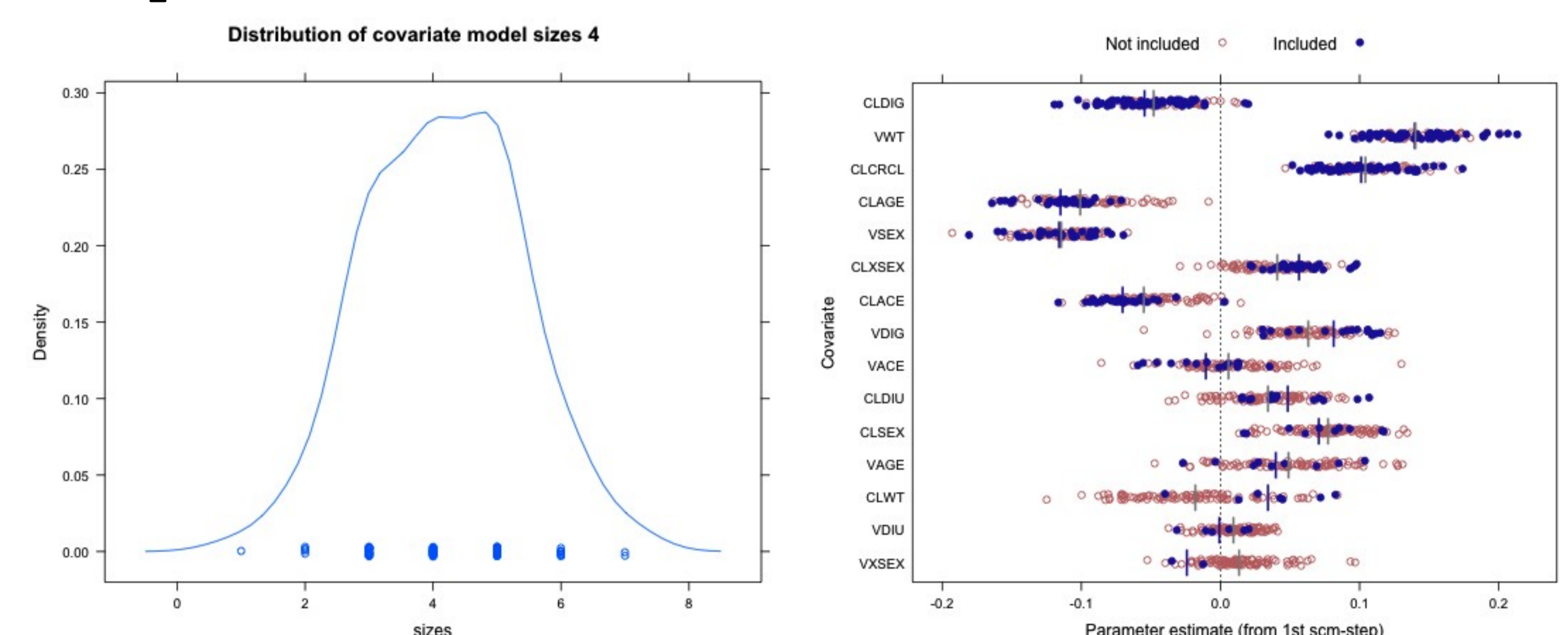
Distribution of covariate model sizes 4

[1] A. G. Dosne, M. Bergstrand, and M. O. Karlsson. Determination of appropriate settings in the assessment of parameter uncertainty distributions using sampling importance resampling (SIR). *PAGE 24 (2015) Abstr 3546*, 2015.

[2] A. Largajolli, S. Jönsson, and M. O. Karlsson. The OFVPPC: A simulation objective function based diagnostic. *PAGE 23 (2014) Abstr 3208*, 2014.