Referenced Visual Predictive Check (rVPC)

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Abstract

The prediction-corrected VPC (pcVPC) [1] reduces the variance in the observed data and in the model distributions by normalizing to an "identically distributed" situation for all individuals. The computation of the prediction correction factor for each bin separately, limits this method to situations of balanced data within each bin. The goal is to extend the prediction-corrected VPC to situations of sparse and unbalanced data by avoiding binning on the independent variable (idv) scale and to show:

1. The equivalence of the new rVPC method to the pcVPC in cases of balanced data.
2. The robustness of the rVPC in cases of sparse and unbalanced data.

In addition to model evaluation, the rVPC is to provide a base for discussion with clinicians on dosing adequacy in untypical individuals.

Introduction

Mixed effect PopPK/PD models are widely assessed for adequacy by graphical comparison of the model-based simulations versus the experimentally observed data. The prediction correction is effected to good approximation for simulated and for observed data by multiplying by the ratio of the median of the model-based predicted value at the respective time point over the predicted value itself. The definition of the median is straightforward in the ideal case of complete data at all time points. In practice, however, sampling time points differ between individuals, and in order to compute the summary sample measures that are to be compared, like quantiles, the simulated and the observed data need to be binned in a set of time intervals. This poster presents techniques that aim at eliminating the problems arising from unbalanced data within time bins for the simulated data and and at alleviating these problems for the observed data.

Material and Methods

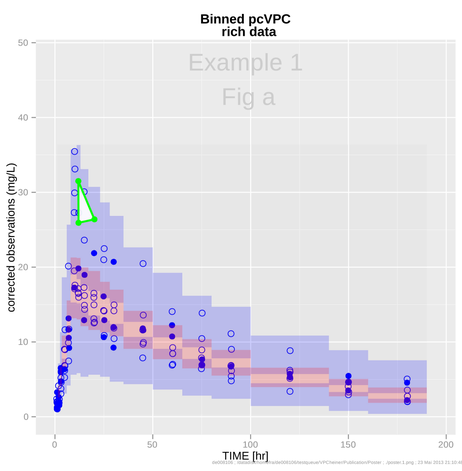
The first example data set describes 8 subjects grouped into two dose-groups. Following a 1-hour infusion, 18 data points were collected per individual. For such rich data, the prediction works as described by Bergstrand [1]. The sparse and unbalanced data is obtained by randomly deleting 97 of the 144 data points, keeping only 47, ie 33%.
The NONMEM-fit itself is remarkably robust against this data reduction:
The results for the main model parameters fitted for the original and for the mutilated data set as obtained by the model fitting program NONMEM [2] (FOCE) agree within 5%.
The second example data set is based on Case Study 1 of the American College of Clinical Pharmacology [4]. It comprises 1500 observations in 100 subjects grouped in two dose groups treated with an IV bolus of 100 mg and 250 mg, respectively. A reduced data set of 223 observations in 94 subjects was generated by drawing randomly without replacement (1 to 7 observations per subject).

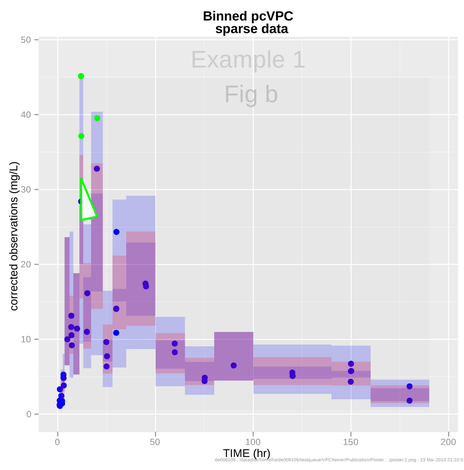
Results

pcVPC [3]: For the simple case of lower bound equal to zero, the prediction correction formula for each time point has the form:

$$pcDV_{ij} = DV_{ij} \cdot \frac{median_{bin}(PRED_{ij})}{PRED_{ij}} \qquad \begin{array}{l} DV \triangleq Dependent\ Variable(Observation) \\ PRED \triangleq Population\ Prediction \end{array}$$

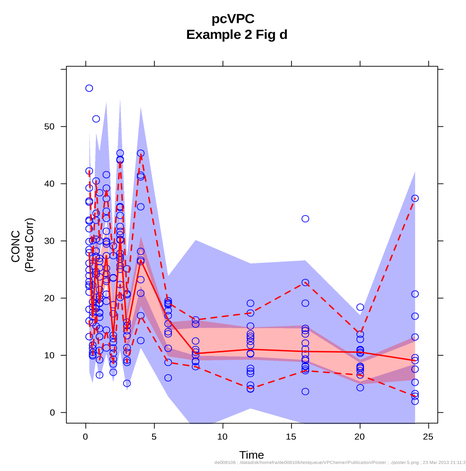
The problem of the pcVPC lies in the binned median for unbalanced data (Fig. b).

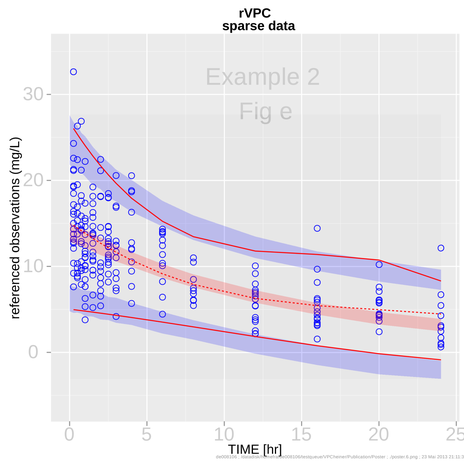


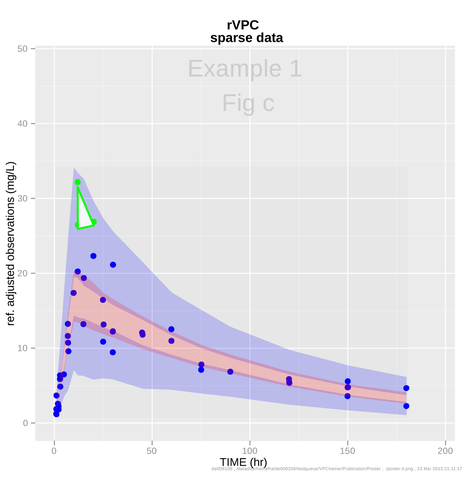


refDV: The calculation of of the correction factor was done in NONMEM by adding a second profile with reference values for the individual covariate variables and dose in the data set and resetting the model to baseline.

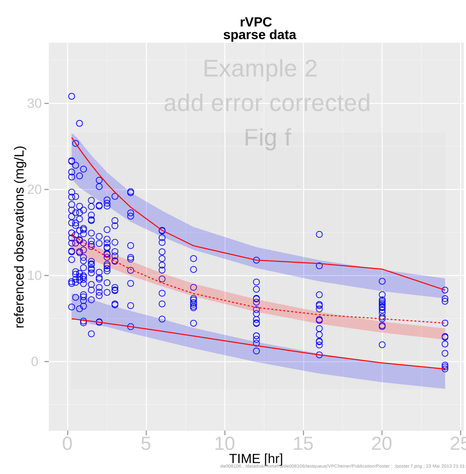
$$refDV_{ij} = f(x_{ij}^{ref}, \phi_i^{ref}) \cdot (1 + \varepsilon_{ij}^{rel}) + \varepsilon_{ij}^{add}; \quad refDV_{ij}^{example\,1} = \frac{R_i^{ref} \cdot WT_i}{R_i \cdot WT_{ref}} \cdot DV_{ij} \qquad \begin{array}{l} WT \triangleq \text{Weight} \\ R \triangleq Rate \end{array}$$







Example 1: Open circles indicated observations of the full data set that were dropped in the reduced data set.Colored bands represent the 95% intervals of the 5% (blue), 50% (red) and 95% (blue) quantiles of the simulated observations. Three exemplary adjusted observations (green) are plotted in all plots. The reference position of them in plot (a) is marked as green contour triangle in all plots. Fig a shows the correct prediction correction (pcVPC) because the data are balanced; Fig c shows the correct pc calculated as reference prediction correction (rVPC). For example 1 exists a direct calculation (closed solution) for the reference prediction correction



Example 2:

- Fig d shows the pcVPC as it is implemented in PsN/XPOSE [3,1]
- The red line in Fig (e,f) are calculated with the tool Quantile Regression (R-package quantreg) a statistical methods for estimating and drawing inferences about conditional quantile functions. [4,5]
- Fig f rVPC with additional error correction.

Conclusions

- The rVPC method allows to adjust the observations and the simulations in the VPC to any reference set of covariate values of choice, irrespective of sparseness and unbalancedness of the data without need to stratify into subgroups (bins) while maintaining the familiar shape of the PK/PD time profiles.
- The binning method described by Bergstrand [1] works well for rich and balanced data. It requires tests with various choices of binning to make sure that the results do not depend on it.
- Quantile regression is a useful tool to show the central tendency of the adjusted observations.

Acknowledgements

1. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. The AAPS Journal. 2011;p. 1–9.
2. Bauer RJ. NONMEM Users Guide: Introduction to NONMEM 7.2.0. ICON Development Solutions; 2011.
3. Lindbom L, Pihlgren P, Jonsson EN, Jonsson N. PsN Toolkit–a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005 Sep;79(3):241–257.
4. R Development Core Team. R: A Language and En-vironment for Statistical Computing. Vienna, Austria; 2010. ISBN 3-900051-07-0. Available from: http://www.R-project.org/.
5. Koenker R. quantreg: Quantile Regression; 2012. R3 package version 4.81.

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