Capacities of NPDE, VPC and pvcVPC at detecting model misspecification: a simulation study of a pharmacokinetic model showed no apparent difference

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Background

- VPC (Visual Predictive Check), pvcVPC (prediction- and variability-corrected VPC)[1] , and NPDE (Normalised-Prediction Distribution Errors)[2] are three simulation-based model evaluation methods
- VPC is a within-bin comparison of the empirical distribution of the observations with the corresponding model-based predictions.
- pvcVPC is the same methodology as VPC except that the observations are previously "corrected". Correction consists in prediction and variability correction of the observed and simulated data.
- NPDE are individual comparisons of each observation with the corresponding model-based prediction,
- pvcVPC and NPDE have the capacity to detect model misspecification in the additional context of covariate heterogeneity
- Unfortunately, there is no information in the literature comparing their performances

Objectives

- To investigate the capacity of these different methods at detecting a misspecified model in the context of high non-linearity and covariate heterogeneity

Conclusion

In a situation with a non-linear model and heterogeneity coming from a covariate, pvcVPC did not completely remove the heterogeneity of the prediction distribution across covariate levels but this did not prevent the detection of the model misspecification. The NPDE method could detect the same model misspecification.

Methods

- To assess the extent by which the pvcVPC corrects for heterogeneity and how the prediction distribution would be homogeous after correction, the distribution of the prediction (defined by $Y_i = f(\theta_i) + \varepsilon_i$ for an individual i at a specified time point with θ_i the vector of the individual parameters and ε_i the residual error) before and after correction were obtained after simulation of 1000 PK profiles for a range of covariate value (using R v. 2.15.2). The PK profiles were simulated by a model included high non-linearity because the correction would expectedly be difficult. This process has been done in two situations defined by two different experimental designs and a pair of a true and a wrong models (see Table 1).
- To investigate the capacity of these different methods at detecting a misspecified model (wrong model), NPDE, VPC and pvcVPC were generated after estimation of the true and the wrong model on a dataset simulated with the true model including 5 subjects per covariate and dose level (using NONMEM v.7.2 and PsN v.3.5.3).

Table 1. ***Description the situations 1 and 2, the study design and features of the True/Wrong models (differences are highlighted in bold).***

	Situation 1		Situation 2	
	True model	**Wrong model**	**True model**	**Wrong model**
Type of model	**2 cp PK model**	**1 cp PK model**	**2 cp PK model**	**1 cp PK model**
Absorption	Bolus, no KA	Bolus, no KA	First Order	First Order
Elimination	Linear			
Residual error model	Additive on a log scale			
Individual parameters including the covariate	V1 = TVV1 * (WT/70) * EXP(ETA(1)) **V2 = TVV2 * ((WT/70)**3) * EXP(ETA(2))** CL = TVCL * ((WT/70)**0.75) * EXP(ETA(3))	**V = TVV * ((WT/70)**3) * EXP(ETA(1))** CL = TVCL * ((WT/70)**0.75) * EXP(ETA(2))	KA = TVKA * COVA * EXP(ETA(4))	KA = TVKA * COVA * EXP(ETA(4))
Typical parameters values	**TVV1 = 10 L ; TVV2 = 300 L ; TVQ = 10 L/h** **TVCL = 2 L/h** Residual error: W = 0.2	TVV = 40 L ; TVCL = 3 L/h Residual error: W = 0.2	TVV1 = 209 L ; **TVV2= 530 L ; TVQ = 53 L/h** **TVCL = 19 L/h ; TVKA = 0.001 h^{-1}** Residual error: W = 0.2	TVV = 209 L ; **TVCL = 25 L/h ;** **TVKA = 0.0007 h^{-1}** Residual error: W = 0.2
Inter-individual variability (variance)	OMV1 = 0.5 ; OMV2 = 0.5 ; OMQ = 0.5 OMCL = 0.5	OMV = 0.5 ; OMCL = 0.5	OMV2 = 0.2 ; OMV3 = 0.2 ; OMCL = 0.2 OMKA = 0.5	OMV = 0.2 ; OMCL = 0.2 ; OMKA = 0.5
Covariate values	Weight in kg (WT) : 40, 60, 80, 100, 120		COVA : 1, 2, 4, 8, 16, 32, 64, 128, 256, 512, 1024, 2048, 4096	
Dose	100 mg or 300 mg at t=0, one single dose		10 mg at t=0, one single dose	

Results

- The results for the situation 1 and 2 were similar. Below the results for the situation 2 with the wrong model are presented. It was the worse situation where *a priori* the correction will have the most difficulty to compensate heterogeneity.

Figure 1. ***Prediction distribution at t = 1h after 10 mg administration. Dashed lines represents percentiles: the 1st quartile in green, the median in red and the 3rd quartile in blue. (a) prediction (y_{ij}) distribution are heterogeneous across the covariate values as it is expected for a large covariate range. (b) prediction ($pvcy_{ij}$) distribution have same mean, same standard error but there is still some degrees of heterogeneity in shape.***

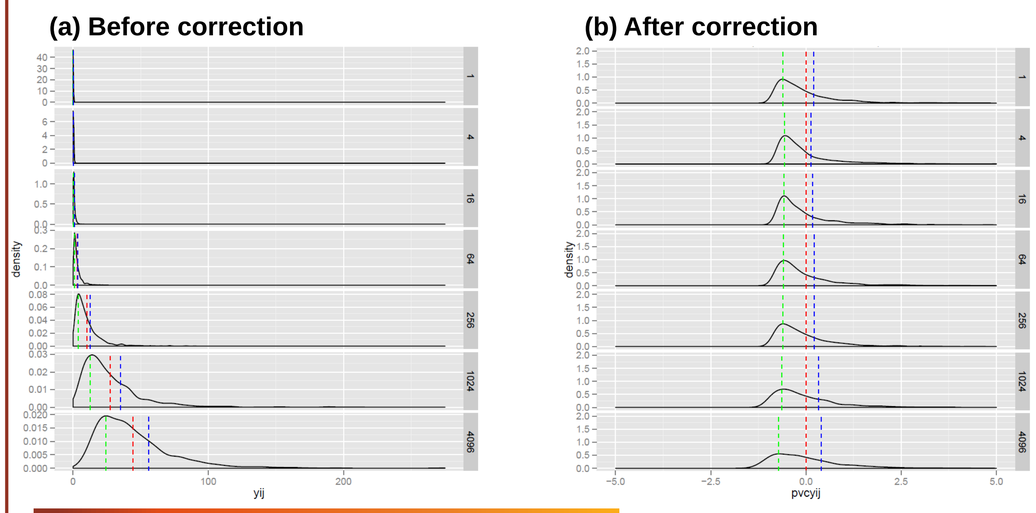
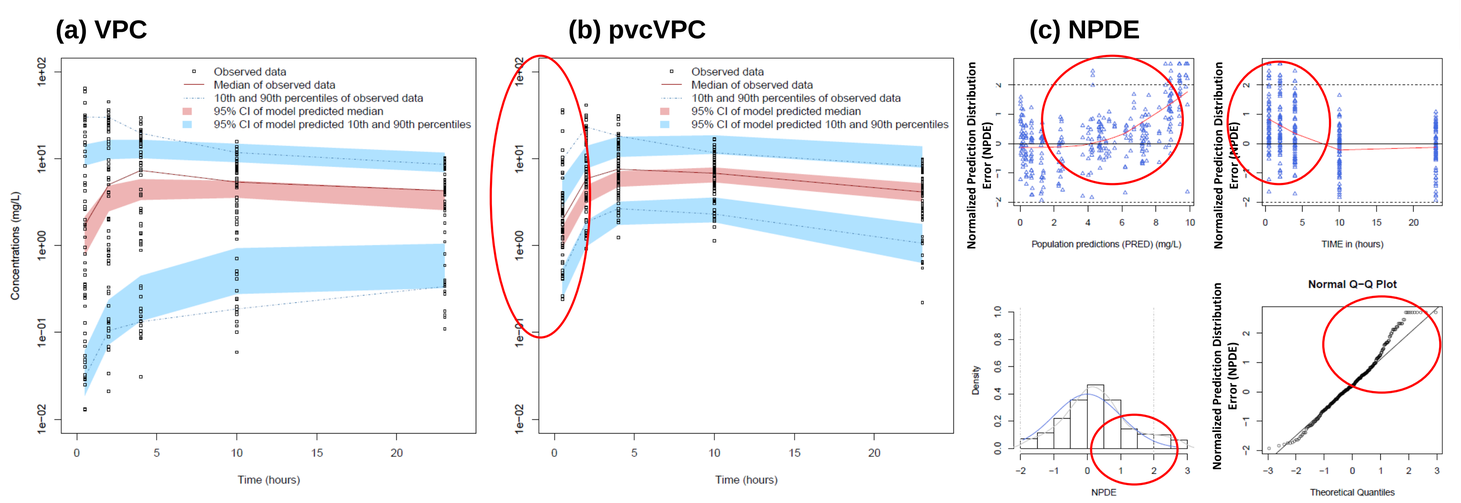


Figure 2. ***The wrong model is rejected by (a) VPC, (b) pvcVPC and (c) NPDE***



Discussion

- Prediction distribution before correction in the two situations were very different depending on the covariate value.
- NPDE and pvcVPC take into account heterogeneity due to the covariate while VPC does not.
- Further investigation on how NPDE and pvcVPC could handle heterogeneity would include:
  - Unbalanced design in simulation scenarios with doses in mg/kg.
  - Impact assessment of data not collected at the same time but with different time point within windows around a time point.

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2. Comets E, Brendel K, Mentre F. Computing normalized prediction distribution errors to evaluate nonlinear mixed-effects models : the npde add-on package for R. Computer Methods and Programs in Biomedecine, 2008, 90:154-166

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