Dealing with BQL data in normalised prediction distribution errors: a new version of the npde library for R

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Objective: This poster presents a new version of the npde library [1] for R [2]. We propose methods to handle data below the limit of quantification (BQL) [3] and new diagnostic graphs [4].

Introduction

- Model diagnostics
  - diagnostic graphs used for model evaluation and to guide model building
  - prediction discrepancies (pd) and normalised prediction distribution errors (npde) developed for nonlinear mixed effect models [5, 6]
  - implemented in the npde library for R [1] as well as software like Monolix [7] and NONMEM [8]
  - based on simulations from the models, used to assess model predictability (family of predictive checks)
- Limit of quantification present in analytical methods
  - data below the limit of quantification (BQL) frequently encountered in PK/PD studies
  - example : viral load counts in HIV often become BQL soon after the beginning of treatment
- BQL data often omitted from diagnostic graphs, inducing bias [9]
  - alternative solution proposed here: impute pd/npde for BQL data
  - evaluated using a simulation study, extending work presented in PAGE 2011 [3]

Methods

Statistical models

Model for observation y_{ij}

$$y_{ij} = f(\theta_i, x_{ij}) + g(\theta_i, \gamma, x_{ij})\varepsilon_{ij}$$

where:

- subject i ($i = 1, \ldots N$), with n_i observations $\mathbf{y}_i = \{y_{i1}, \ldots, y_{in_i}\}$ at times t_{ij}
- f: structural model, common to all subjects
- g: residual error model, eg $g(\theta_i, x_{ij}) = a + b\ f^c(\theta_i, x_{ij})$
- individual parameters θ_i
  - often modelled parametrically as a function h of fixed effects μ and random effects η_i:

$$\theta_i = h(\mu, \eta_i) \text{ where } \eta \sim \mathcal{N}(0, \Omega)$$

  - in PK/PD, h is frequently a log-normal transformation, such that for the p^{th} component:

$$\theta_{i(p)} = \mu_{(p)}\ e^{\eta_{i(p)}}$$

Prediction discrepancies and prediction distribution errors

- F_{ij}: cumulative distribution function (cdf) of the predictive distribution of Y_{ij} under model M^B
  - F_{ij} obtained using Monte-Carlo simulations
  - K datasets $V^{sim(k)}$ simulated under model M^B using the design of the validation dataset V ($\mathbf{y}_i^{sim(k)}$: vector of simulated observations for the i^{th} subject in the k^{th} simulation)
  - same simulations used to obtain Visual Predictive Check (VPC)
- prediction discrepancy for observation y_{ij}

$$\text{pd}_{ij} = F_{ij}(y_{ij}) \approx \frac{1}{K}\sum_{k=1}^{K} \delta_{ijk}$$

  - where $\delta_{ijk} = 1$ if $y_{ij}^{sim(k)} < y_{ij}$ and 0 otherwise
  - pd expected to follow $\mathcal{U}(0,1)$ under the model
  - within-subject correlations introduced when multiple observations are available for each subject [5]
  - option to jitter pd to avoid ties (option `ties=FALSE`) by adding a random sample from $\mathcal{U}(0, 1/K)$ to each value
- prediction distribution errors
  - decorrelation using empirical mean $E_{\text{emp}\,i}$ and empirical variance-covariance matrix $\text{var}(\mathbf{y}_i)$ over the K simulations for simulated and observed data:

$$\mathbf{y}_i^{sim(k)*} = \mathbf{V}_{\text{emp}\,i}^{-1/2}(\mathbf{y}_i^{sim(k)} - E_{\text{emp}\,i})$$
$$\mathbf{y}_i^{*} = \mathbf{V}_{\text{emp}\,i}^{-1/2}(\mathbf{y}_i - E_{\text{emp}\,i})$$

  - pde obtained using decorrelated values and transformed to a normal distribution using the inverse of the normal cdf

$$\text{pde}_{ij} = F_{ij}^*(y_{ij}^*) \approx \frac{1}{K}\sum_{k=1}^{K} \delta_{ijk}^*$$
$$\text{npde}_{ij} = \Phi^{-1}(\text{pde}_{ij}) \quad \sim \mathcal{N}(0,1) \text{ under } H_0$$

Handling data below the limit of quantification

Computation of pd [3]:

- for a censored observation y_{ij}^{cens}, compute probability of being under LOQ, $\Pr(y_{ij}^{cens} \leq \text{LOQ})$, from the predictive distribution
- set pd_{ij}^{cens} to a value randomly sampled from $\mathcal{U}[0, \Pr(y_{ij}^{cens} \leq \text{LOQ})]$

Computation of npde:

- impute pd for the all censored values in the dataset
- use the predictive distribution to impute censored observations to the value in the simulated distribution F_{ij} corresponding to that quantile (see figure 1)

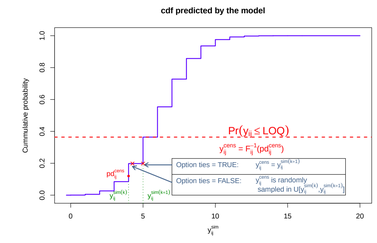

Figure 1: *Imputing censored observation using* pd.

- apply the same procedure to the simulated datasets
- decorrelate using the imputed datasets

Simulation study

Data

- Real data from the COPHAR 3-ANRS 134 multicenter clinical trial [10]
  - 35 naïve HIV-infected patients treated once daily with atazanavir, ritonavir and tenofovir/emtricitabine during 24 weeks
  - measurements of viral loads 0, 24, 56, 84, 112, 168 days after initiation of treatment
  - limit of quantification of the assay: 40 or 50 copies/mL
  - HIV viral load decrease during treatment described by a bi-exponential model $f(\theta_i, x_{ij}) = \log_{10}(P_{1i}e^{-\lambda_{1i}x_{ij}} + P_{2i}e^{-\lambda_{2i}x_{ij}})$
- Simulation settings: extension of work presented in [3]
  - protocol and model based on real data, with N=50 subjects
  - simulations under H_0 (same model V_t used to simulate data and compute pd and npde)
    - parameters shown in table 1 based on (rounded) parameter estimates from the real data, obtained using the SAEM algorithm in MONOLIX 3.2 [7]
    - correlation between P_1 and P_2: $\rho_{(\eta_{P_1}, \eta_{P_2})} = 0.8$
    - additive error: $\sigma_{inter} = 0.14$

	P_1 (copie/mL)	P_2 (copie/mL)	λ_1 (day^{-1})	λ_2 (day^{-1})
True model V_t, S_{high}	25000 (2.1)	250 (1.4)	0.2 (0.3)	0.02 (0.3)
S_{low}	25000 (0.3)	250 (0.3)	0.2 (0.3)	0.02 (0.3)

Table 1: *Population mean and (% IIV) used as parameter values in the simulation study, for the true models in two settings with high and low variability.*

  - simulations under different model misspecifications, with two levels of variability
    - changes in the fixed effect λ_2: V_{fix_1} (λ_2=0.04), V_{fix_2} (λ_2=0.01)
    - changes in the variability of λ_2: V_{var_1} ($\omega(\lambda_2)$=0.9), V_{var_2} ($\omega(\lambda_2)$=0.1)
    - simulations under H_0 used to compute npde for each dataset simulated under a misspecified model
  - two levels of interindividual variability investigated: S_{high} and S_{low}
- Evaluation of the proposed method to handle BQL data:
  - global test comparing the distribution of npde to N(0,1) by combining a test of mean, a test of variance, and a test of normality with a Bonferroni correction [6]
  - simulation under H_0: assessment of type I error
  - assessment of power to detect a given model misspecification
  - 1000 simulations in each scenario
    - for each dataset, 3 analyses, with data censored assuming LOQ=0 (no censoring), 20 or 50 cp/mL respectively

New diagnostic graphs with BQL data

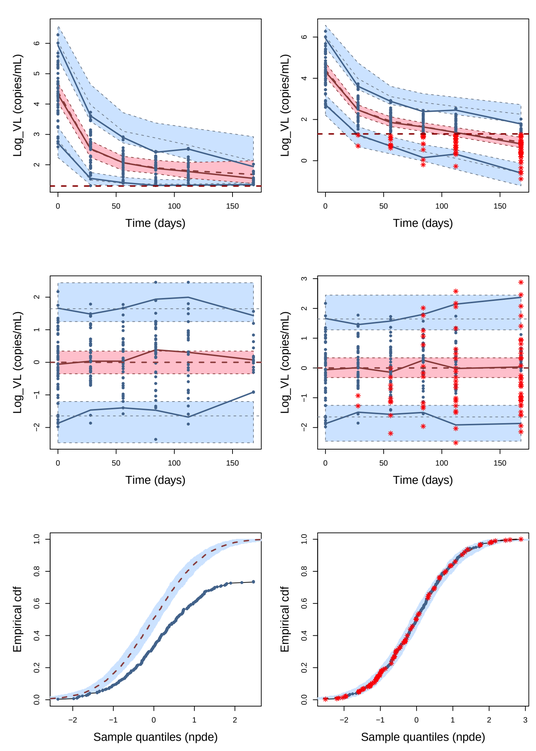

Figure 2: *Diagnostic plots for one simulated dataset under H_0, censored at LOQ=20 cp/mL, omitting BQL data (left); imputing using the cdf method (right). Top: VPC; Middle: scatterplot of* npde *versus time; Bottom: empirical cdf for* npde, *with prediction bands*

- Strong trend in all plots when omitting BQL
  - imputation of BQL corrects this pattern
- Prediction bands very useful to assess model adequacy

Results of the simulation study

- Results shown in table 2 (1000 datasets for each scenario)
- Simulation under H_0: in bold, results different from 5%
  - comparison between imputing BQL data (new method) and omitting BQL from the observed data
  - large increase in type I error for the global test [6] when omitting BQL from the data in the presence of censored data
  - only slight inflation when accounting for BQL data by imputation

		D_{rich}, S_{high}			D_{rich}, S_{low}		
		LOQ (cp/mL)			LOQ (cp/mL)		
	Data	0	20	50	0	20	50
Type I error, omitting BQL	V_{true}	5.4	**25.8**	**46.9**	5.6	**23.9**	**64.3**
imputing BQL		5.4	**6.5**	**7.0**	5.1	4.8	5.4
Power, imputing BQL	V_{fix_1}	100	100	98.8	100	100	99.9
	V_{fix_2}	100	100	99.7	100	100	100
	V_{var_1}	100	78.7	53.6	100	100	99.4
	V_{var_2}	14.2	11.2	8.2	30.5	30.7	17.8

Table 2: *Type I error under H_0 and power under alternative assumptions, for the global test on npde. Evaluation performed on 1000 simulated datasets, depending on censoring (LOQ=0, 20, 50 cp/mL)*

- Simulations with model misspecification
  - high power to detect model misspecification on the value of the second slope
  - much lower power for model misspecification on variability on this parameter, especially with high proportions of BQL
  - decrease in power as IIV increases
- Further simulations presented in [11]

New features of the npde library

- Extensive overhaul of the first version
  - switching to the S4 class system
  - generic methods (`print`, `plot`, `summary`) now apply
- Major changes for the user
  - the function no longer returns a list, but an object
  - using the method `summary` creates a list from which the same elements as previously can be returned (retro-compatibility)
  - pd are now computed by default
  - new options for main functions (with default arguments) and plots
- New plots: VPC, empirical cumulative distribution functions, prediction intervals added to all the plots, plots split by covariates
- Methods to handle BQL data evaluated by a simulation study
  - increased power to detect model misspecification, compared to simply omitting BQL data from the dataset (full results in [11])
  - correction for biases in diagnostic plots
  - as expected, decrease in power when the proportion of BQL increases, since the imputation is based on the model

New version available on the CRAN shortly (installation as any other R package through the GUI or in command line).

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