ADDITIONAL FEATURES AND GRAPHS IN THE NEW npde LIBRARY FOR R

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Objective: (i) present new features of the npde library 2.2 to compute npde (normalised prediction distribution errors) and npd (normalised prediction discrepancies) [1, 2, 3] in R, with methods to handle data below the limit of quantification (BQL) [4], covariate plots [5] and prediction intervals [6]; (ii) propose a new method to re-scale npd/npde while maintaining the shape of the profile.

INTRODUCTION

- Model diagnostics
  - used for model evaluation and to guide model building
  - npd and npde developed for nonlinear mixed effect models [1, 2]
  - based on simulations from the models, used to assess model predictability (family of predictive checks)
  - implemented in the npde library for R [3, 7] as well as software like Monolix [8] and NONMEM [9]
- Recent extensions to npde
  - tests and graphs for covariate models [5]
  - prediction intervals for graphs [6]
  - imputation method to handle data below the quantification limit (BQL) [4]
- New feature proposed here: plot using transformed npd/npde preserving the shape of the profile

Computing pd, npd and npde

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 as $\theta_i = h(\mu, \eta_i, z_i)$ (μ: fixed effects; $\eta_i \sim \mathcal{N}(0, \Omega)$: random effects; z_i: known covariates)
- F_{ij}: cumulative distribution function (cdf) of the predictive distribution of Y_{ij} under model M^B 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 pd_{ij} for observation y_{ij} defined as $F_{ij}(y_{ij})$
  - pd expected to follow $\mathcal{U}(0, 1)$ under the model
  - inverse transformation to normal distribution yields npd
  - within-subject correlations introduced when multiple observations are available for each subject [1]
- Prediction distribution errors
  - decorrelation using the empirical mean and the empirical variance-covariance matrix over the K simulations for simulated and observed data
  - pde obtained as pd using decorrelated values and transformed to a normal distribution using the inverse of the normal cdf

HANDLING BQL DATA

Methods

- Omitting BQL data from diagnostic graphs may introduce bias [10]
- Instead, compute pd for a censored observation y_{ij}^{cens} by imputation [4]
  - 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 censored observations using the simulated distribution F_{ij} (Fig 1) in both original and simulated datasets
  - decorrelate using the imputed datasets

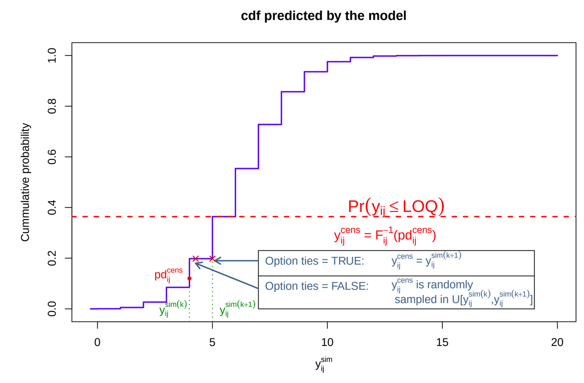

***Figure 1:** Imputing pd_{ij}^{cens} and y_{ij}^{cens}*

Illustrative example

- Simulated data based on real data from the COPHAR 3-ANRS 134 multicenter clinical trial [11]
  - M_T: protocol and model based on real data, with N=50 subjects
  - HIV viral load decrease during antiretroviral treatment following a bi-exponential model

$$f(\theta_i, x_{ij}) = \log_{10}(P_{1i} e^{-\lambda_{1i} x_{ij}} + P_{2i} e^{-\lambda_{2i} x_{ij}})$$

  - measurements of viral loads 0, 24, 56, 84, 112, 168 days after initiation of treatment
  - limit of quantification of 40 to 50 cp/mL (depending on the assay)
- simulations settings
  - simulation of 1000 datasets under M_T to compute pd and npde
  - V_T: 1 dataset simulated with M_T
  - V_F: 1 dataset simulated assuming λ_2 divided by 2
- Datasets analysed first uncensored, then assuming LOQ=50 cp/mL

Diagnostic graphs with BQL data

- Standard diagnostics to detect model misspecification
  - scatterplots of npd/npde versus time or predictions
  - distribution plots

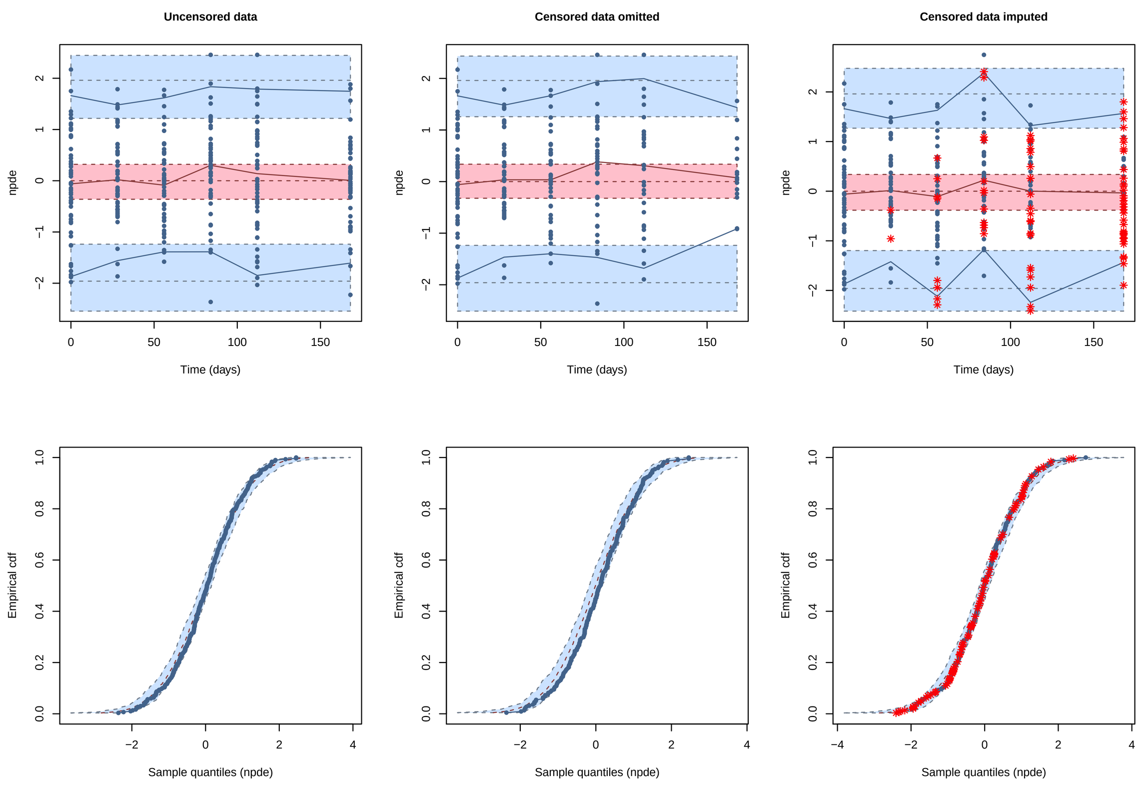

***Figure 2:** Scatterplot of npde versus time (top) and empirical cdf (bottom) for simulated dataset V_T: uncensored dataset (left), dataset after censoring using LOQ=50 cp/mL, removing the values below BQL from the plot (middle) or imputing BQL value (right).*

- Trend in both plots for V_T when omitting BQL data (more visible in scatterplot)
  - imputation of BQL data corrects this pattern

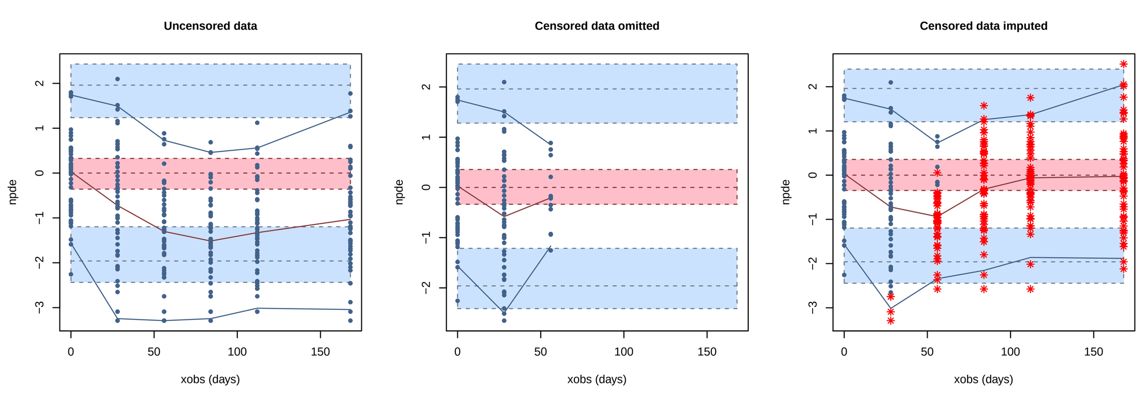

***Figure 3:** Scatterplot of npde versus time for simulated dataset V_F: uncensored dataset (left), dataset after censoring using LOQ=50 cp/mL, removing the values below BQL from the plot (middle) or imputing BQL value (right).*

- For V_F, model misspecification more apparent with imputed values
  - however, power to detect misspecification decreases with fraction of BQL data [4]

TRANSFORMED NPD/NPDE

Methods

- Compute mean E_j and standard deviation SD_j of simulated $y_{ij}^{sim(k)}$ for each value x_j of x, and define:

$$tnpde_{ij} = E_j + SD_j\, npde_{ij}$$

  - same equation for npd_{ij}
- Unbalanced design: similar procedure after binning on the X-axis [12]
- All or part of the simulations can be used to obtain a reference profile

Illustration (uncensored dataset)

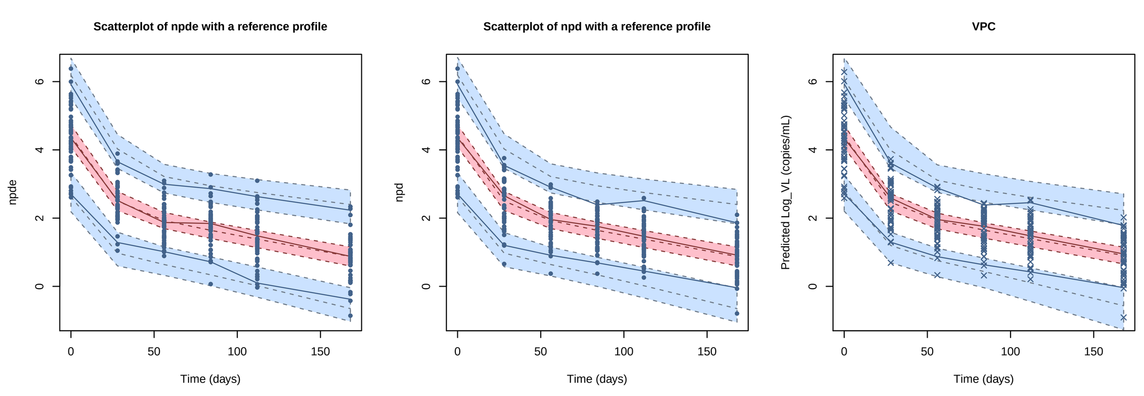

***Figure 4:** Scatterplot of npde (left) and npd (middle) versus time with a reference profile as described in methods; VPC (right).*

- The addition of the reference plot shows the evolution of the process
  - both npd and npde scatterplots show a pattern similar to VPC
- The distribution of npde accounts for within subject correlations
  - the width of the prediction interval is scaled with the same factor as the npde themselves
- The method adapts easily to datasets including BQL data since the reference profile uses (non censored) simulated data

ASSESSING COVARIATE MODELS

Methods

Two methods proposed [5]:

- test the relationship between npde and a covariate
  - categorical covariates: Wilcoxon test
  - continuous covariates: correlation test
  - scatterplots or whisker plots versus the covariate
- test distribution of npde after splitting by the values of the covariate
  - discretise by quantiles for continuous covariates
- Bonferroni correction for multiple tests

Illustrative example

- Same model and protocol as above, adding a covariate effect
  - simulation of a binary covariate (values: 0/1 with a proportion of 50/50)
  - $V_{T\ cov}$: value of λ_2 divided by 2 compared to the population value in subjects with cov=1
  - simulations used to compute npde:
    - previous simulations assuming no covariate effect (M_T)
    - simulations with the same covariate model as for $V_{T\ cov}$ ($M_{T\ cov}$)
- Plots shown for uncensored data

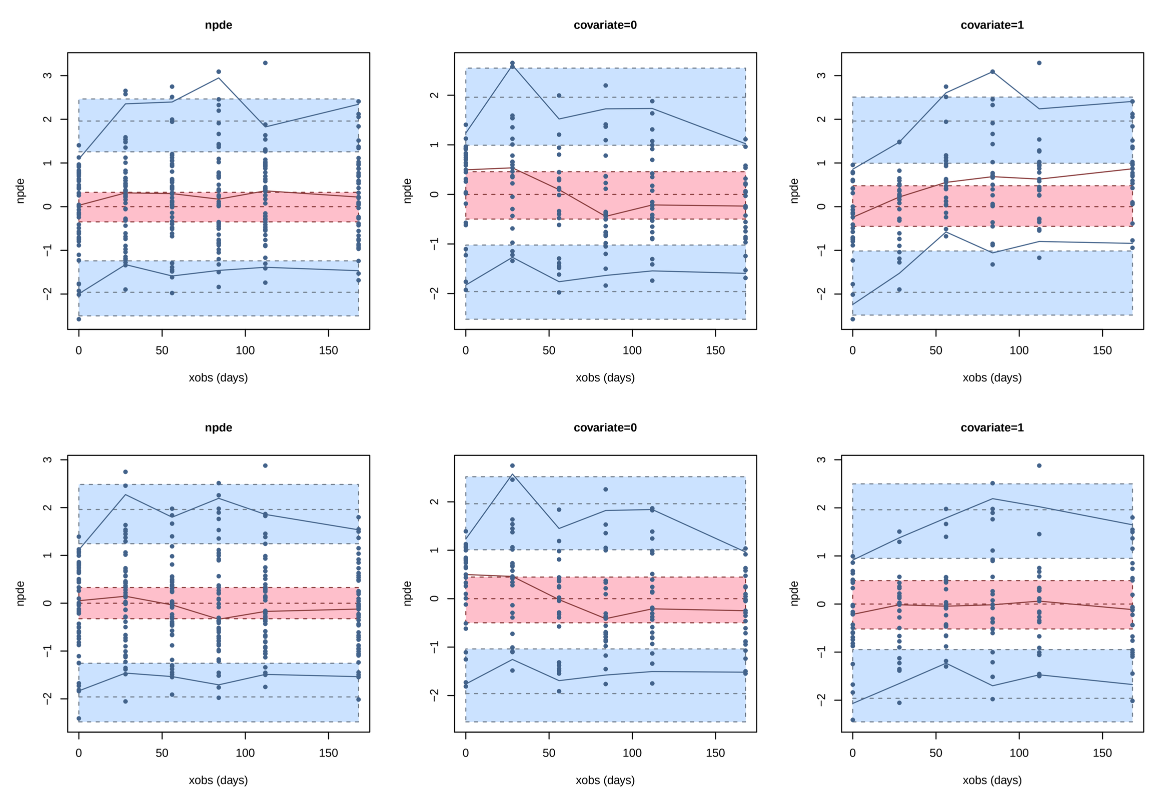

***Figure 5:** Scatterplot of npde versus time for $V_{T\ cov}$, with simulations under M_T (no covariate model, top) and under $M_{T\ cov}$ (with covariate model, bottom). On each line: scatterplot regardless of the value of the covariate (left), and for the two levels of the covariate (middle and right).*

- Plots stratified by the value of the covariate allow to assess model misspecification level by level
  - model misspecification picked up on plot for covariate level 1 (top right), and on the overall plot (top left)
  - no trend when the same covariate model is used for both simulated and observed data (bottom plots)

CONCLUSION

- Simulation-based diagnostics for non-linear mixed effect models
- Methods to handle BQL data evaluated by a simulation study [4]
  - increased power to detect model misspecification, compared to simply omitting BQL data from the dataset
  - 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
- Transformed npd/npde
  - similar visual interpretation as VPC while retaining the statistical properties of npd/npde
  - naturally handle design heterogeneity without stratifying
  - the reference profile can be computed using all or part of the simulations
- Library npde for R: current version 2.2 available on the CRAN
  - diagnostic graphs: VPC, empirical cumulative distribution functions, probability of being BQL, scatterplots versus X or predictions
  - prediction intervals added to all the plots: very useful to assess model adequacy
  - plots can also be split by covariates

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