

Introduction

Context

- Diagnostic graphs used for model evaluation and to guide model building
- diagnostics in non-linear mixed effect models (NLMEM) based on individual estimates or simulations
- Prediction discrepancies (pd) and normalised prediction distribution errors (npde) developed as residuals adapted to NLMEM [1, 2]
- implemented in the npde library for R [3] as well as software like Monolix [4] and NONMEM [5]
- based on simulations from the models, used to assess model predictability (family of predictive checks)

Objectives

- Present new version of the npde library (version 3.1)
 - diagnostic graphs reprogrammed using the standard data visualisation package ggplot2 [6]
 - methods to handle data below the limit of quantification (BQL) [7]
 - covariate plots [8]
- Illustrate reference profiles re-scaling npd/npde while maintaining the shape of the profile [9]

Illustrative example

Warfarin PK data

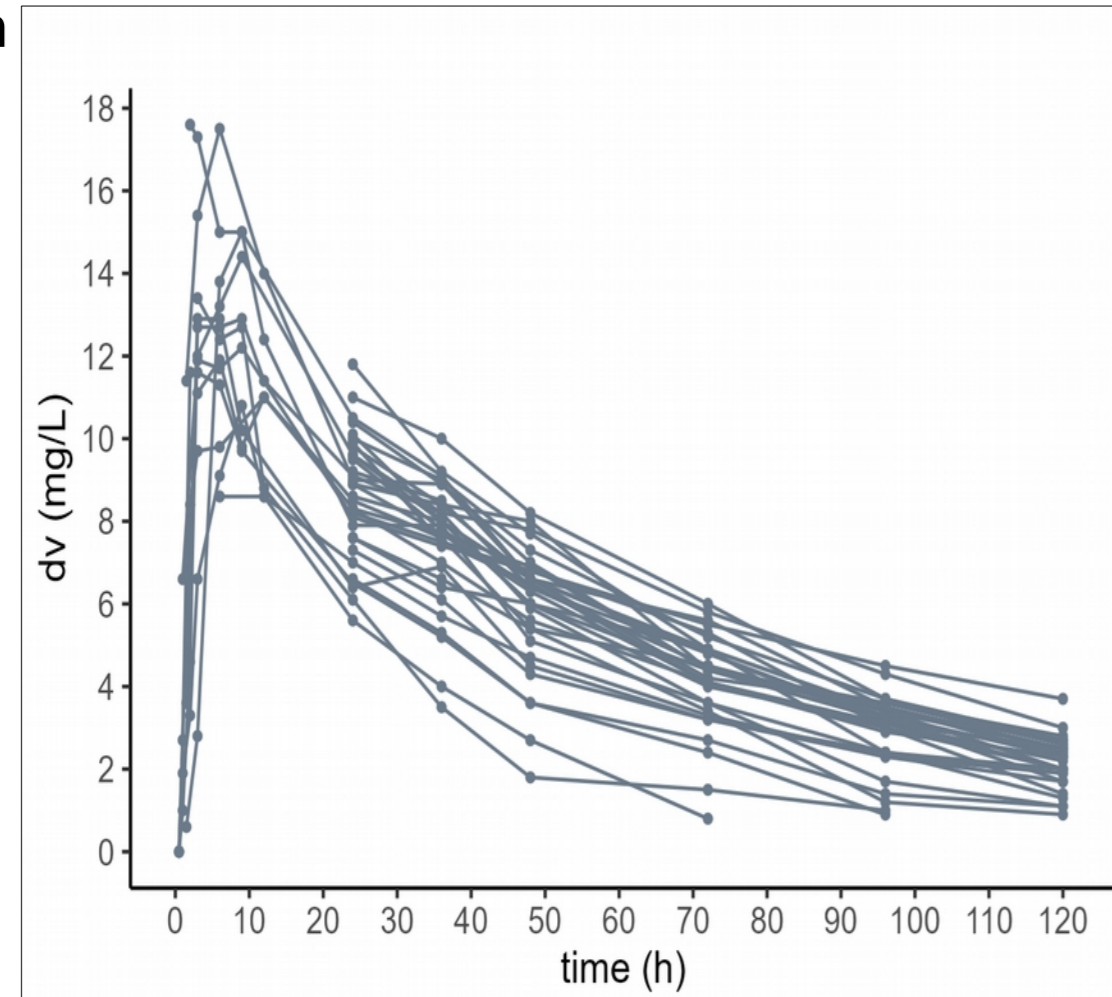
- Dataset [10] collected in a study on warfarin, an anticoagulant drug used in the prevention of thrombosis and thromboembolism
- 32 series of pharmacokinetic measurements after a single dose of 1.5 mg/kg in healthy subjects
- rich sampling up to 120 h
- dataset taken from case-study in Monolix demos
- data in subject i ($i=1, \dots, N$)

$$y_i = \{y_{i1}, \dots, y_{in_i}\}$$

- Statistical model

$$y_{ij} = f(t_{ij}, \theta_i) + g(t_{ij}, \theta_i, \sigma) \varepsilon_{ij}$$

with $\varepsilon_{ij} \sim N(0, 1)$



Construction of the model

- Stepwise model building
- Two-compartment model, with first-order absorption and a time delay
 - Log-normal distributions for parameters $\theta_i \sim LN(\mu, \Omega)$
 - Combined error model
- Covariate effects
 - age (centered on 30 yr) effect on CL
 - weight (centered on 70 kg) effect on CL and V_1
 - gender effect on CL and V_1 (NS in fit on V_1 , for illustration purposes)

Model evaluation using npd and npde

Model evaluation

- Test the hypothesis (H_0): {data in a validation dataset V can be described by a population model M_L build in a learning dataset L }
 - $L=V$ for internal evaluation
 - M_L defined by its structure (f, g , distributions) and the population parameters $\Psi=(\mu, \Omega, \sigma)$

Computing npd and npde

- Prediction discrepancies pd_{ij} defined as the value of the cumulative predictive distribution for the observation y_{ij}

$$pd_{ij} = F_{ij}(y_{ij}) = \int_{-\infty}^{y_{ij}} p_i(y|\Psi) dy = \int_{-\infty}^{y_{ij}} \int p_i(y|\theta_i) p(\theta_i) d\theta_i dy$$

- no closed form in non-linear models
 - computed using the same simulations as for Visual Predictive Checks (VPC) [11]
- under H_0 , $pd_{ij} \sim U(0, 1)$
- inflation of type I error of a test based on pd due to repeated measurements [1]
- Accounting for correlated observations within a subject
 - decorrelate observations and simulations using the empirical variance-covariance matrix V_i for each subject
 - V_i computed using the simulated data
- Standard residuals usually obey a normal distribution => normalised versions of **pd** and **pde**
 - npd**: normalised prediction discrepancies
 - npde**: normalised prediction distribution error
 - under H_0 , **npd** $\sim N(0, 1)$ (with inflation) and **npde** $\sim N(0, 1)$

Graphs and tests

- Tests for pde and npde
 - Files required
 - original data, with at least one ID column, one time column (or independent variable) and one
 - simulated data:
 - recommended: at least 1000 simulations
- Prediction intervals
 - for unbalanced designs, bin the predictors on the X axis [12] before computing the percentiles

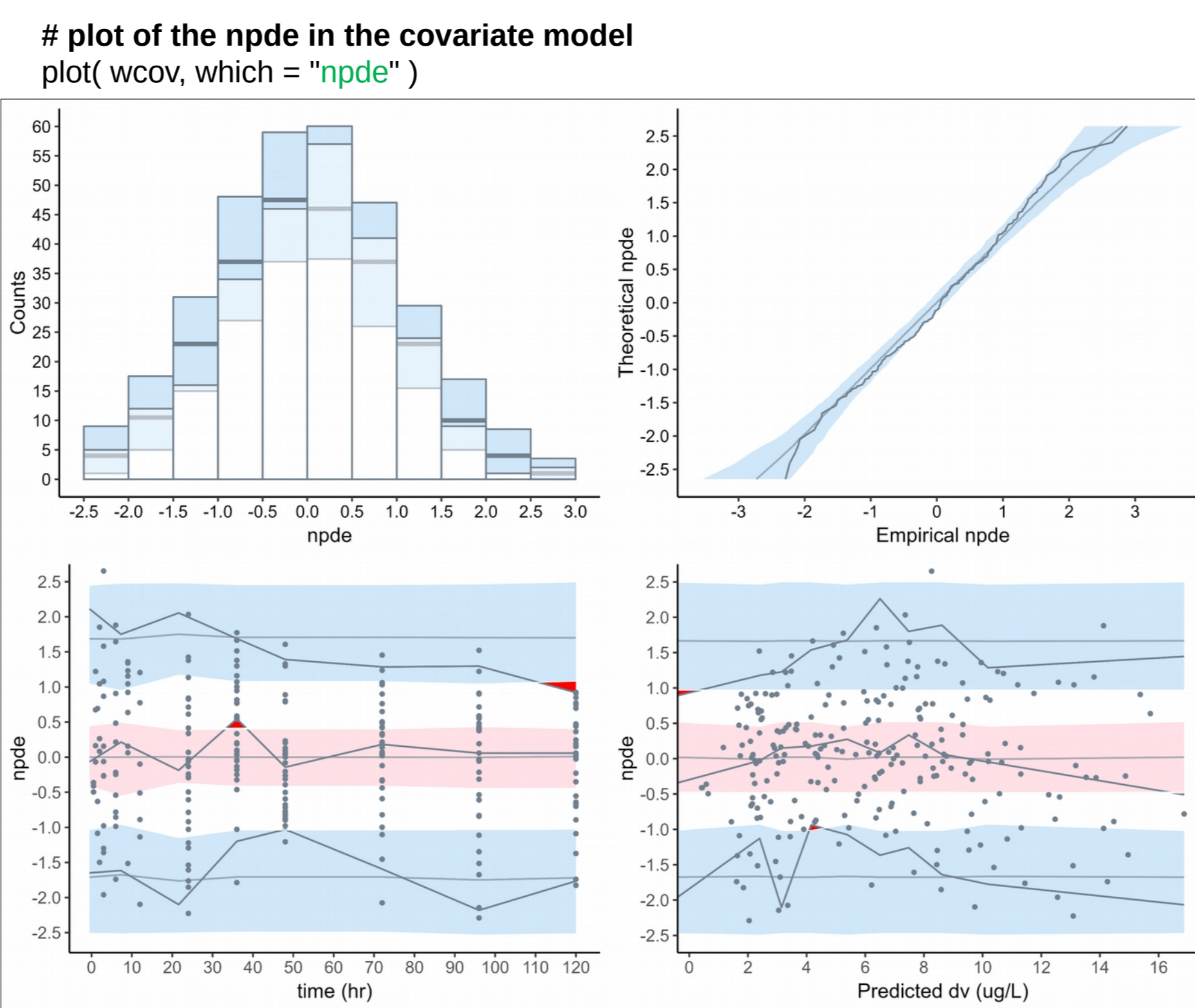
Evaluating the warfarin model

- Simulations performed using simlux and the Mlxtran project used to estimate the parameters on the real data.
 - 1000 simulations using the design of the original data performed for each model
- Two datasets containing simulated data associated with the warfarin data
 - simwarfarinBase: simulated according to a base model without covariates (M_{base})
 - simwarfarinCov: simulated using the covariate model (M_{cov})
 - not included in the package due to size constraints on CRAN
 - can be downloaded directly from the github repository of npde <https://github.com/ecomets/npde30/tree/main/keep/data>

Results

- npde computed using the function `autonpde()`
 - original data: warfarin
 - specify columns containing grouping (ID), independent variable (x) and dependent variable (Y)
 - optionally specify columns containing covariate information
 - simulated data: simwarfarinCov
 - the first 3 columns must be simulated ID, simulated X and simulated Y in this order
- Default plots produced automatically for **npd** after run
 - many plots available using the `plot()` function with `plot.type` set to different values (see documentation)
 - select metric of interest using the argument `which`

```
# compute the npde for the covariate model (here also load dose as a covariate)
wcov <- autonpde(namobs = warfarin, namsim = simwarfarinCov,
  iid = 1, ix = 2, iy = 4, icov = c(3,6:8), namsav = "warCov",
  units = list(x = "h", y = "mg/L", covariates = c("mg", "kg", "yr")))
# plot of the npde in the covariate model
plot(wcov, which = "npde")
```



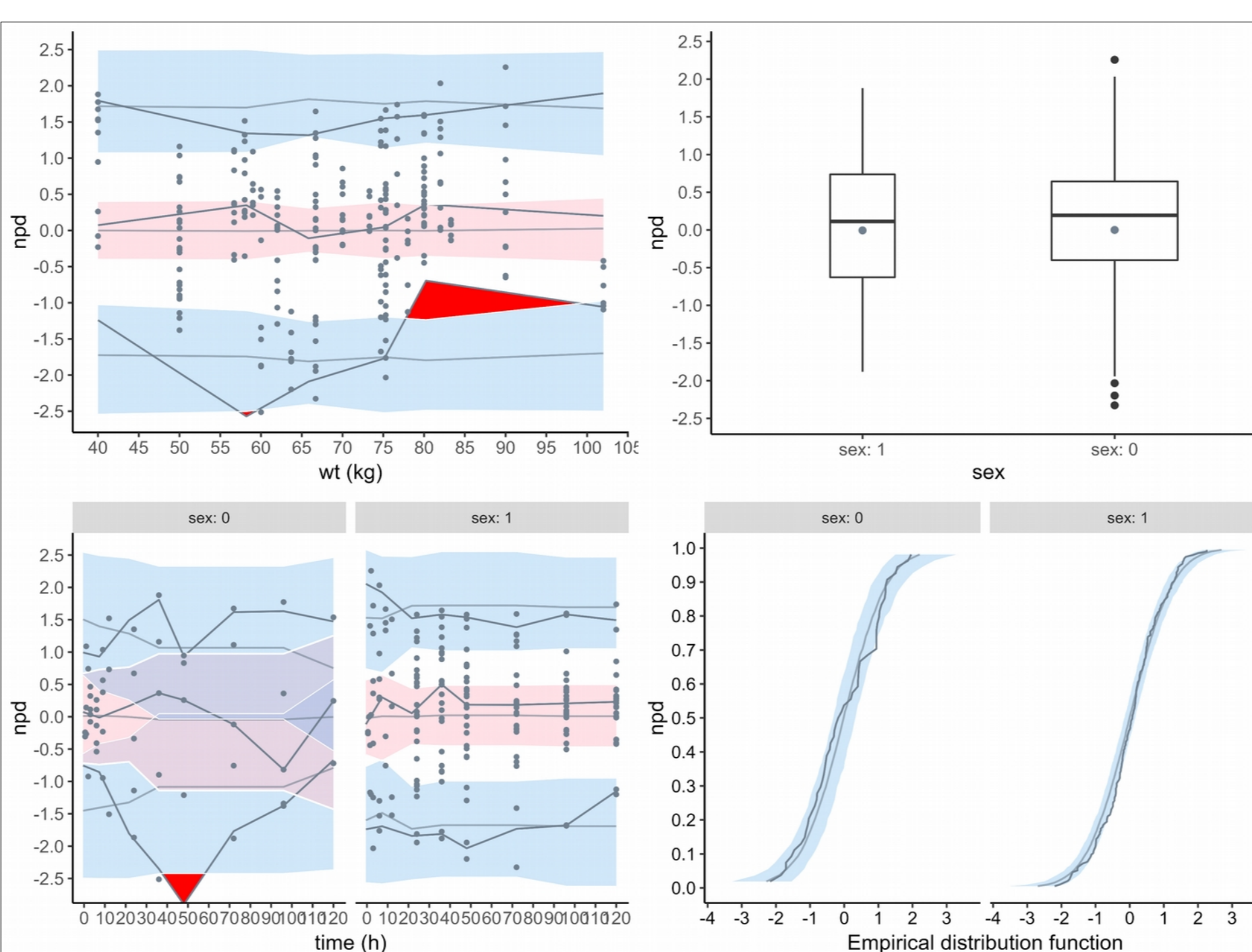
Default plots produced for M_{cov} : Histogram of the npde with the density of the standard normal distribution overlaid (upper left). Quantile-quantile plot of the npde versus the expected standard normal distribution (upper right). Scatterplot of npde versus time (lower left). Scatterplot of npde versus predicted Y (lower right).

The npd can be:

- plot versus a covariate using `plot.type = "cov.scatter"` selecting the covariate with `which.cov=""`
- split by covariate: for instance, the scatter plots of npde versus time may be split by gender by requesting a plot of type `plot.type="x.scatter"` with the `covsplit=TRUE` argument.
- regrouped as boxplots for each category with `plot.type="covariates"`

evaluating covariate models

```
xwt.covscatt <- plot(wcov, plot.type = "cov.scatter", which.cov = "wt", bin.method = "optimal")
xsex.box <- plot(wcov, plot.type = "covariates", which.cov = "sex")
xsex.scatt <- plot(wcov, plot.type = "x.scatter", covsplit = TRUE, which.cov = "sex")
xsex.ecdf <- plot(wcov, plot.type = "ecdf", covsplit = TRUE, which.cov = "sex")
grid.arrange(grobs = list(xwt.covscatt, xsex.box[1]), xsex.scatt, xsex.ecdf,
  nrow = 2, ncol = 2)
```



User-defined grid plot to assess covariate models: Scatter plot of the npd versus weight (upper left). Boxplots of npd for both gender categories (upper right). Scatterplot of npde versus time split by gender (lower left). Empirical distribution function split by gender (lower right).

Transformed npde

Methods

- Compute for each value x_t of the predictor x the mean $\mathbb{E}_{t_{ij}}$ and standard deviation $SD_{t_{ij}}$ of the simulations corresponding to the selected reference profile for that time

$$\mathbb{E}_{t_{ij}} = \frac{1}{I_R K} \sum_{k=1}^K \sum_{i \in I_R} y_{ij}^{sim(k)}$$

$$Var_{t_{ij}} = \frac{1}{I_R (K-1)} \sum_{k=1}^K \sum_{i \in I_R} (y_{ij}^{sim(k)} - \mathbb{E}_{t_{ij}})^2$$

with I_R = set of individuals corresponding to the reference profile

- Compute the transformed npde at time t_{ij} as:

$$tnpde_{ij} = \mathbb{E}_{t_{ij}} + SD_{t_{ij}} npde_{ij}$$

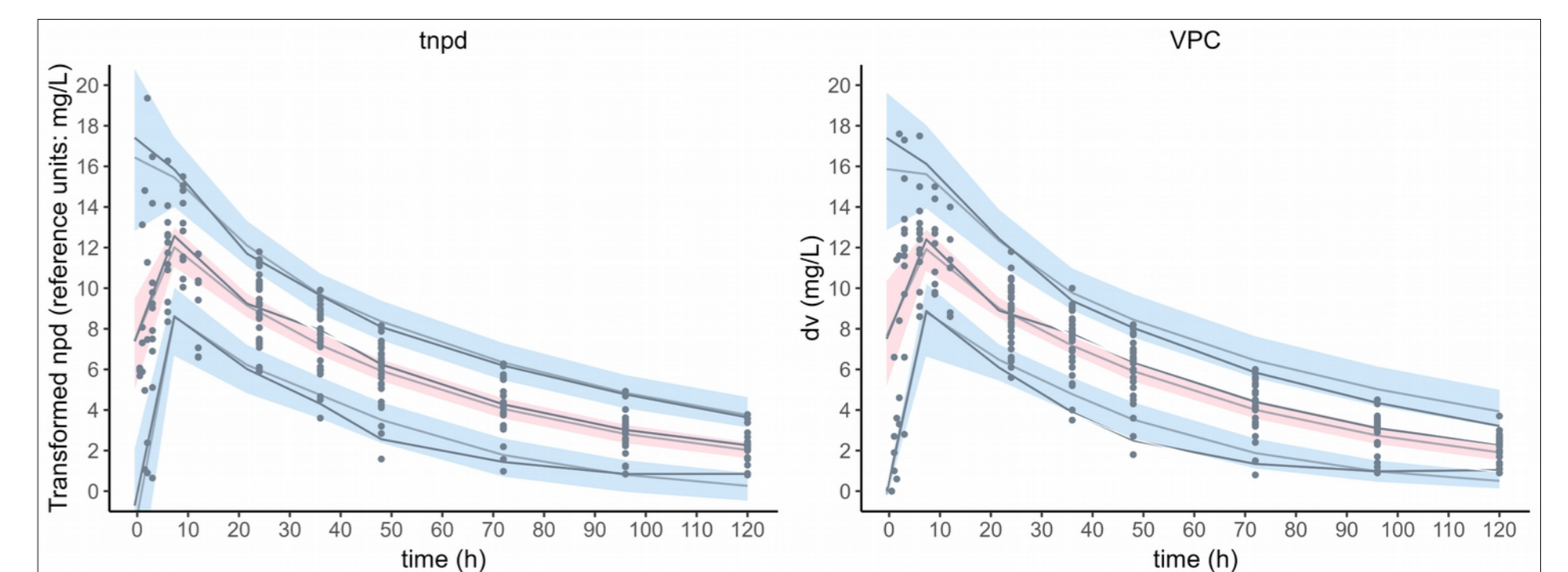
- same equation for npd_{ij}
- all or part of the simulations can be used to obtain a reference profile
- Unbalanced design: bin the predictors as for prediction intervals and compute the mean and SD for each bin, which are used within each bin to compute the transformed tnpde

Reference profile over all subjects

- Transformed npd profile using all subjects to define the reference profile (the variability reflects that of the full dataset)
 - provide an alternative to residual plots by adding the typical evolution of Y
 - below, shown side-by-side with a VPC plot

transformed npd profile using all subjects

```
plot.tnpd <- plot(wcov, plot.type = "x.scatter", ref.prof = "all", main = "tnpd",
  ylim = c(0, 20))
# VPC
plot.vpc <- plot(wcov, plot.type = "vpc", main = "VPC")
# Grid plot
grid.arrange(grobs = list(plot.tnpd, plot.vpc), nrow = 1, ncol = 2)
```



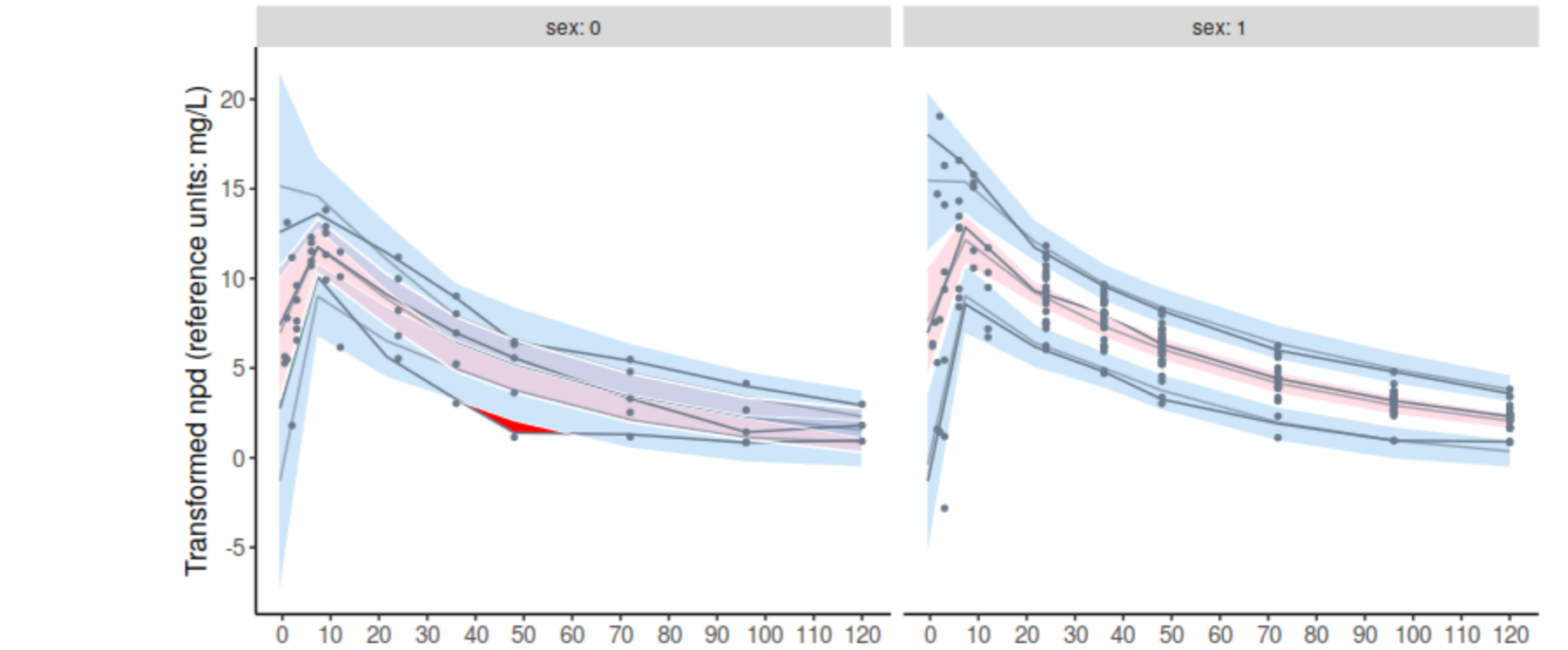
Scatterplot of tnpd versus time with a reference profile obtained over all subjects (left); VPC (right).

Reference profile by covariate

- Reference profiles can be tailored to categories of a covariate
 - the variability now reflects the expected variability within each category

transformed npd profile split by gender

```
plot(wcov, plot.type = "x.scatter", ref.prof = "covariate", which.cov = "sex", covsplit = TRUE)
```



Conclusion / Perspectives

Library npde for R

- Simulation-based diagnostics for non-linear mixed effect models
 - naturally handle design heterogeneity without stratifying
 - part of the recommended diagnostics for NLMEM [13]
- Current version 3.1 available on CRAN (repository for R packages) and on dedicated github
 - many plots available
 - diagnostic graphs: VPC, empirical cdf, probability of being BQL, scatterplots versus X or predictions
 - prediction intervals added to all the plots to assess model adequacy
 - plots can also be split by covariates
 - user-defined grids can be used to arrange different ggplot objects
 - Transformed npd/npde
 - similar visual interpretation as VPC while retaining the statistical properties of npd/npde
 - the reference profile can be computed using all or part of the simulations, or tailored to covariates such as dose group

Future work on the npde library

- Include recent extensions
 - npd for time-to-event model
 - npd for models describing categorical data

Development code available on github

Website for documentation

https://iame-researchcenter.github.io/npde_bookdown/

Userguide with detailed examples

https://github.com/ecomets/npde30/blob/main/userguide_npde_3.1.pdf

Download site from GitHub repository

<https://github.com/iame-researchCenter/npde>

References

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