

Exploring tidyvpc, an Efficient and Versatile Toolkit for Performing Visual Predictive Checks (VPCs) in Pharmacometrics Models.



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Background

- Visual predictive check (VPC) is a core simulation-based diagnostic tool for evaluating nonlinear mixed effects models [1]. However, this can be computationally intensive and time-consuming.
- tidyvpc, an R package [2], was developed as a versatile and comprehensive toolkit to improve speed and facilitate construction of both continuous and categorical VPCs from a single simulation run.
- tidyvpc is software agnostic, i.e. simulations can be performed in different software used to fit the data such as NONMEM, Phoenix NLME/RsNLME, Monolix, and R (e.g. nlmixr2, mrgsim, rxode2).
- The package employs the data.table package and various performance optimizations to enhance computational efficiency.
- The tidyverse-style syntax facilitates streamlined data manipulation and flexible VPC construction—supporting diverse binning and stratification strategies, handling of censored data, and prediction-correction methods.
- The tidyvpc package also integrates with Certara.VPCResults [3], which utilizes a Shiny application to provide an interactive user-friendly interface for parameterizing and plotting VPCs on the fly.
- The tidyvpc package is currently available for installation on GitHub [2] and CRAN [4].

Objective

- To explore a use case example of the tidyvpc package for creating continuous VPCs.

Methods

- The hypothetical PK model used to generate datasets in this example was a one-compartment model with first-order absorption and elimination.
- The “observed” dataset consisted of 300 virtual IDs with fixed intensive sampling scheduled after the first dose (8 samples over 10 hours) and sparse sampling following the second dose (4 samples over 24 hours).
- Two continuous (age, weight) and three categorical (sex, study, patient status) covariates were included in the dataset.
- VPC simulation data table was generated from \$SIM block in NONMEM version 7.5.1 for 100 simulations.
- VPC plots were generated using tidyvpc package in R version 4.3.1. The functions implemented were:

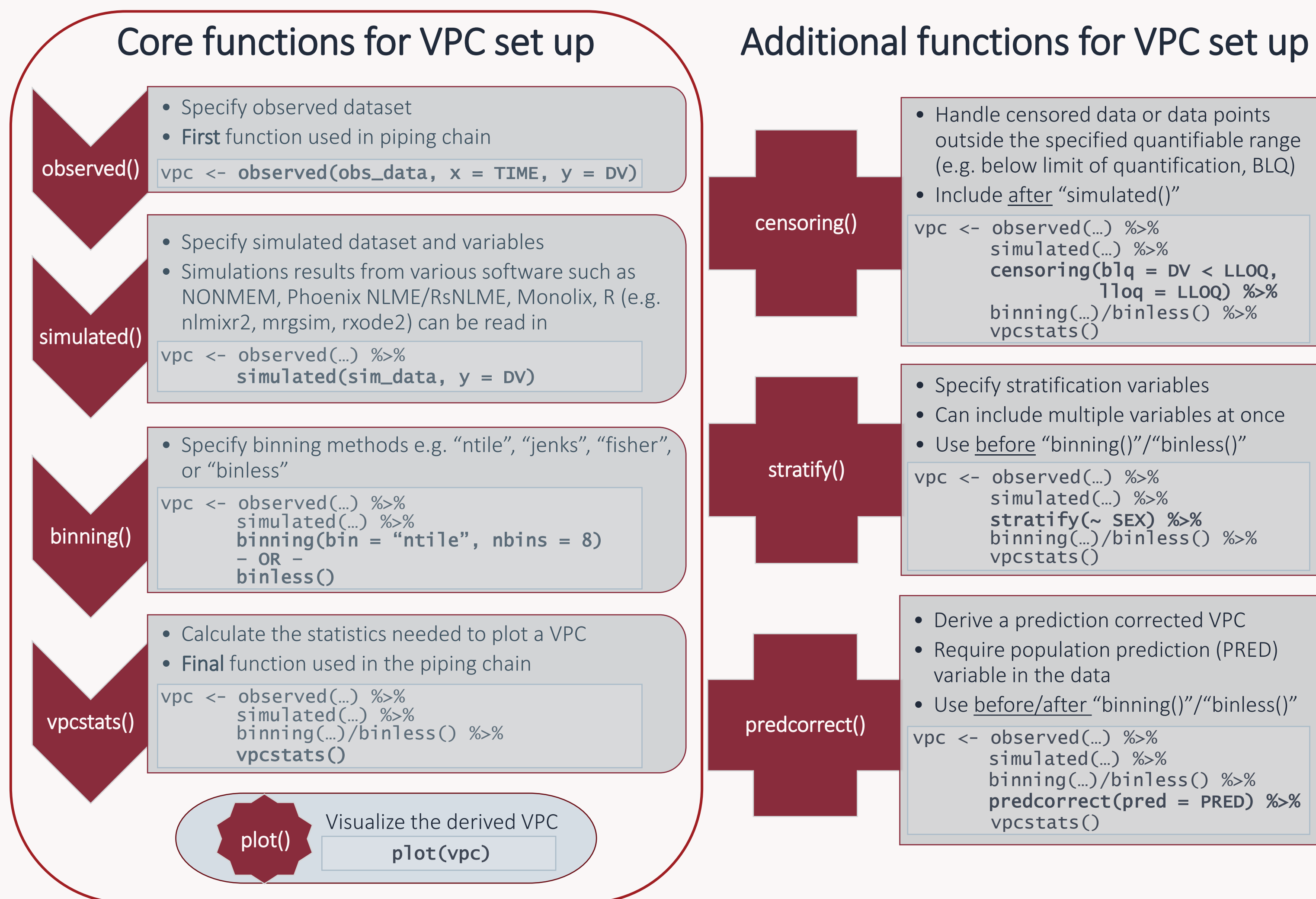
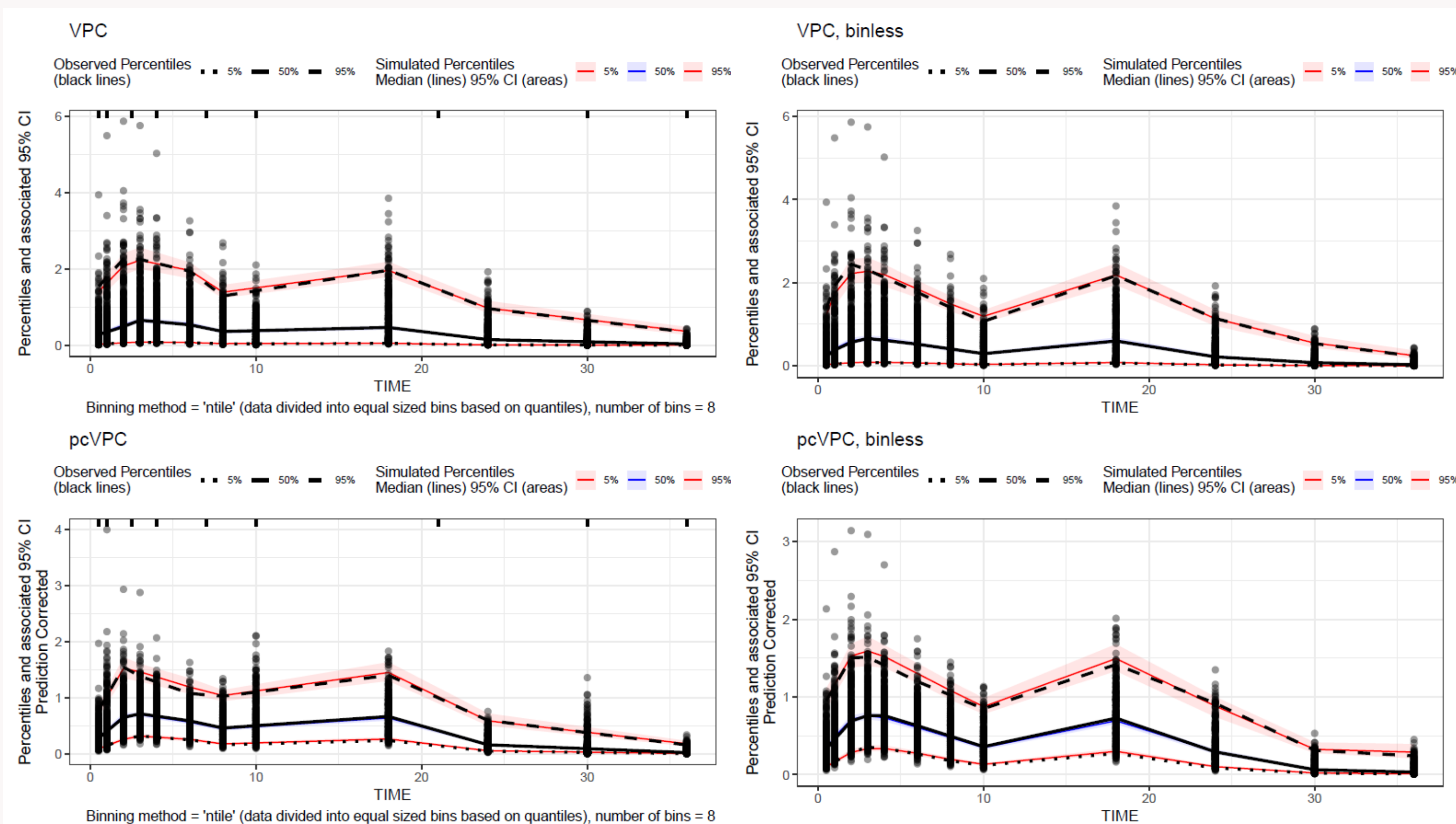


Figure 1: VPC and pcVPC plots, both bin and binless



Abbreviation list

BLQ = below limit of quantification; CI = confidence interval; LLOQ = lower limit of quantification; pcVPC = prediction-corrected visual predictive check; VPC = visual predictive check

References

- Nguyen TH et al. CPT Pharmacometrics Syst Pharmacol. 2017 Feb;6(2):87-109.
- Barriere O, Rich B, Craig J, Mouksassi S (2024). tidyvpc: VPC Percentiles and Prediction Intervals. R package version 1.5.1, <https://github.com/certara/tidyvpc>.
- Craig J, Talley M (2024). Certara.VPCResults: Generate Visual Predictive Check (VPC) from Shiny GUI. R package version 3.0.0, <https://certara.github.io/R-VPCResults/>.
- <https://cran.r-project.org/web/packages/tidyvpc/index.html>.

Figure 2: VPC and pcVPC plots with censoring

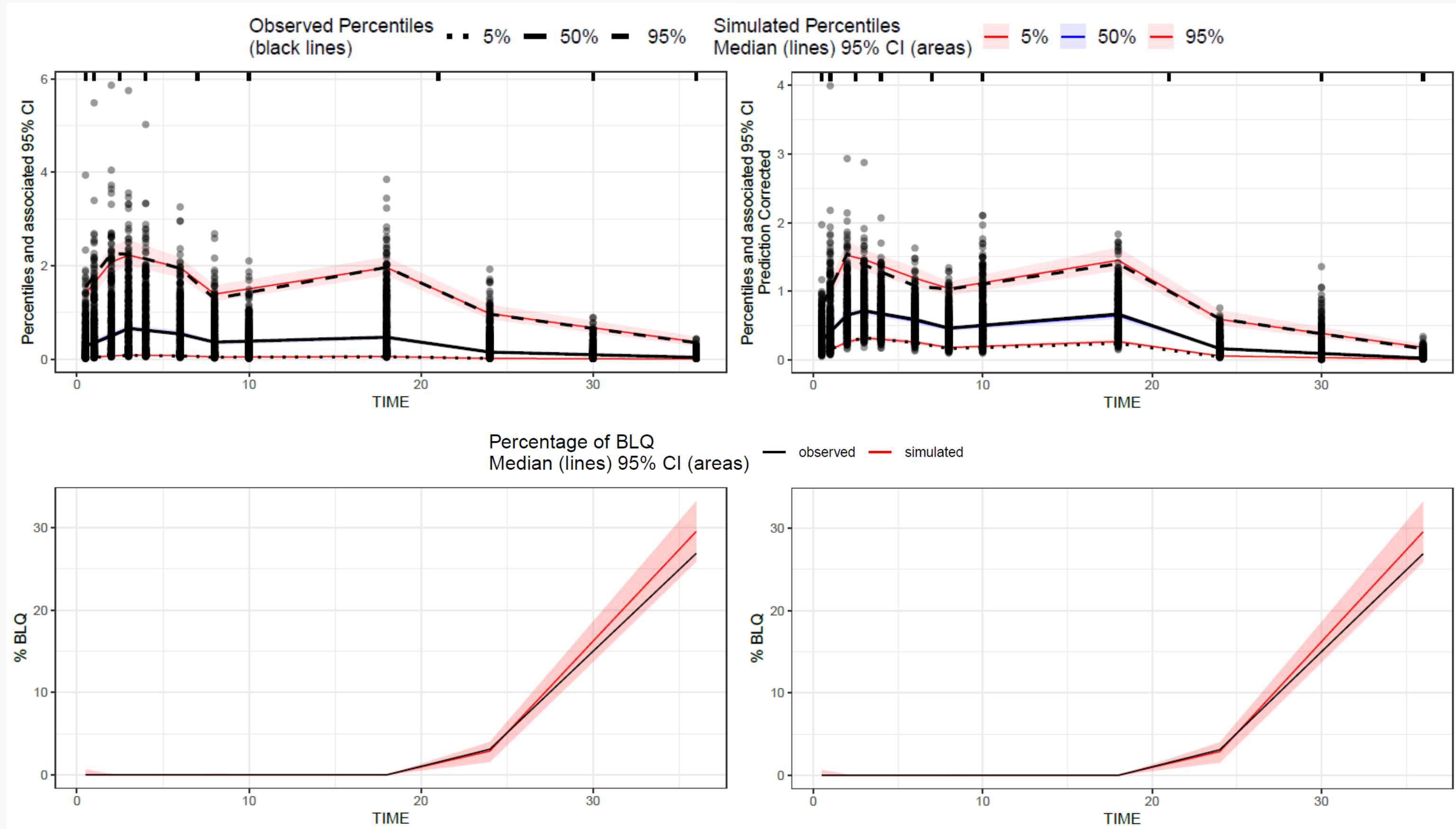
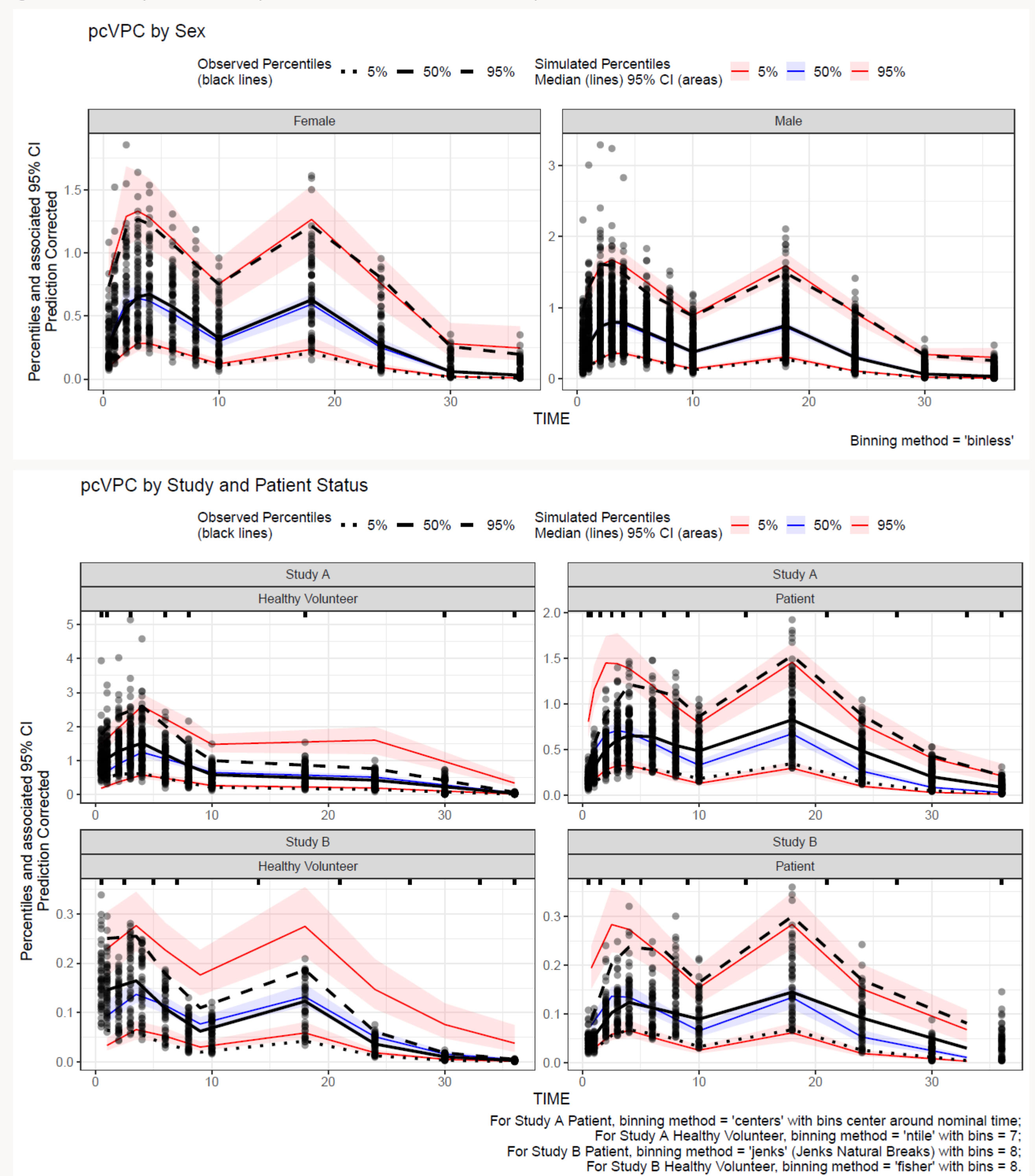


Figure 3: pcVPC plots stratified by selected covariates of interest



Results

- More than 100 variants of VPCs could be generated from a single simulation file for this example using the tidyvpc package.
- Eleven versions of VPCs were explored (8 shown): standard VPCs (both bin and binless, Figure1, top panels); pcVPCs (both bin and binless, Figure 1 bottom panels); VPC with BLQ censoring (Figure 2, left panel); pcVPC with BLQ censoring (Figure 2, right panel); and two examples of categorical stratification scenarios: pcVPC by sex (Figure 3, top panels) and pcVPC by study and patient status (Figure 3, bottom panels).
- The VPC set up and customizations were performed post-simulation in R. Once the code is set up, the generation time for these plots was less than 5 minutes.

Conclusions

- The tidyvpc package offers a fast, flexible and effective approach to generating continuous VPCs.
- This approach significantly reduces the computational and time burdens associated with performing VPCs and supports the routine inclusion of VPCs as a diagnostic tool during model development process.



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