Parametric Empirical Bayes (PEB) Approaches for Personalized Reference Intervals and Reference Change Values

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Overview

This project demonstrates two Parametric Empirical Bayes (PEB) methods for deriving personalized reference intervals (prRIs) and reference change values (RCVs).

The BV-based approach uses priors derived from established biological variation (BV) estimates. The LIS-based approach uses priors inferred from routine laboratory data via the LIS (Laboratory Information System).

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Requirements

Make sure you have the following R packages installed:

```
refineR
robustbase
ggplot2
patchwork
dplyr
here
magrittr
hms
knitr
ggtext
```

The scripts will automatically install the required packages if missing.

Project Files

The project files are organized in **folders** with the following structure:

```
Parametric Empirical Bayes
  |-- Parameteric_Emperical_Bayes.Rproj
  |
  |-- README.pdf
  |
  |-- PEB_main                    # For applying the PEB and establishing LIS-priors
  |   |-- PEB_apply_LIS_priors.R # PEB prRIs and RCVs from LIS priors
  |   |-- PEB_apply_BV_priors.R  # PEB prRIs and RCVs from BV priors
  |   |-- Establis_LIS_priors.R  # Establish priors from LIS data
  |   |-- PEB_data.csv           # Data used in PEB.R (replace with acutal patient data)
  |   `-- LIS_priors_data.csv    # Data used in LIS_priors.R (replace with acutal LIS data)
  |
  |-- Monte_Carlo_examples                    # For testing the PEB on simulated data
  |   |-- BV_priors_Monte_Carlo_example.R     # PEB approach with BV priors
  |   `-- LIS_priors_Monte_Carlo_example.R    # PEB approach with LIS priors
  |
  `-- Excel_PEB                       # For applying the PEB in Excel
      |-- Apply_PEB_BV_priors.xlsx    # Determines the prRI and RCV in excel (BV-priors)
      `-- Apply_PEB_LIS_priors.xlsx   # Determines the prRI and RCV in excel (LIS-priors)
```

Setup

1. **Download and Open Project:**
   - Save the project folder and open the R project file `Paramteric_Emperical_Bayes.Rproj`.
2. **Establish LIS Priors:**
   - Open `LIS_priors.R`.
     - Replace the example dataset with your LIS data (maintain the same data structure).
     - Adjust filters as needed (e.g., age, sex, sample timing).
     - The script uses `refineR` and `robustbase` to estimate the LIS priors.
3. **Calculate prRIs and RCVs:**
   - Open `PEB_apply_LIS_priors.R` or `PEB_apply_BV_priors.R`.
     - Replace the example dataset in `PEB_data.csv` with your actual data.
     - Specify which priors to use (BV or LIS) by updating the parameters.
     - The script calculates personalized reference intervals (prRIs) & reference change values (RCVs).

Note: Update the file paths, delimiters, and date-time formats in the scripts as needed.

Script Explanations

LIS_priors.R

Purpose:
Estimates prior parameters: population mean, standard deviation, and intraclass correlation, from LIS data using a Box-Cox transformation and robust regression.

Key Steps:

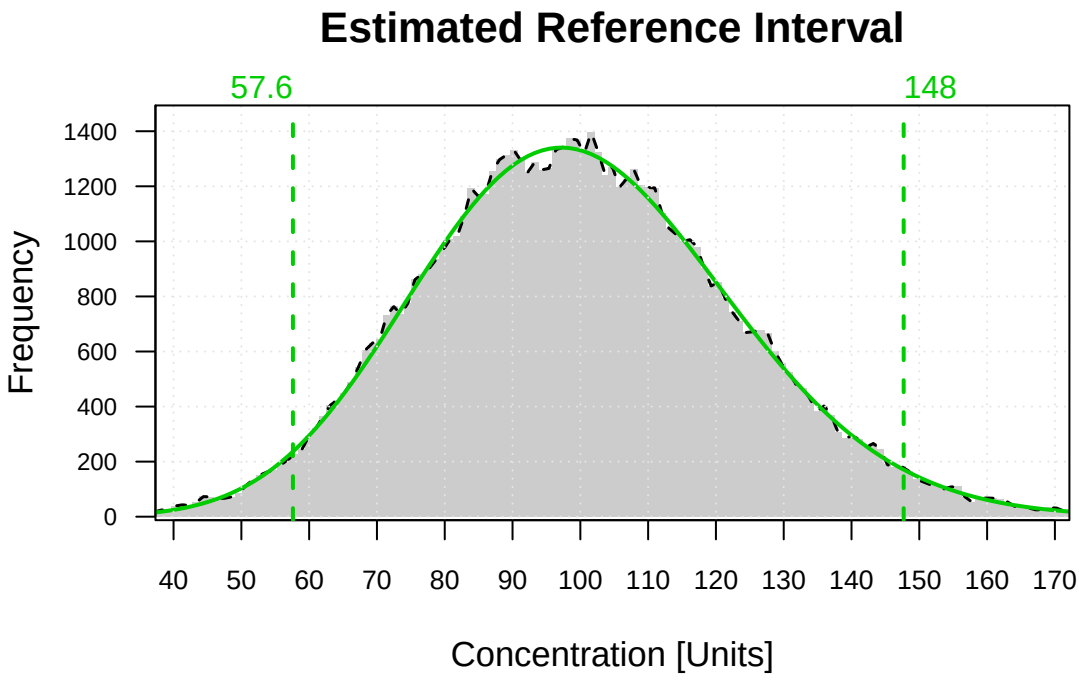
2) Parameter Setup: Select filters you wish to apply to the LIS data. For example:

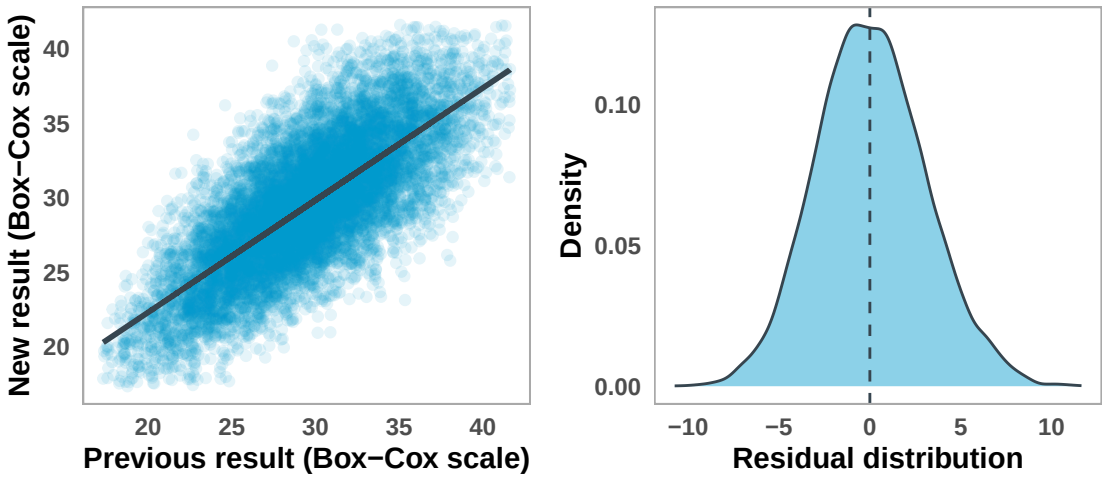
```
# Filter activation flags:
activate_age_filter         <- TRUE  # Activate the age filter?
activate_sex_filter         <- TRUE   # Activate the sex filter?
activate_24hr_filter        <- TRUE   # Activate the 24-hour filter for pairing?
activate_ref_interval_filter<- TRUE   # Activate the reference interval filter?

# Basic filter parameters:
filter_age_min <- 18           # Minimum age
filter_sex     <- c("F")       # Included Sex

# Reference interval filter (here: central 99%)
ref_percetile_lower <- 0.005
ref_percetile_upper <- 0.995
```

2) Data Loading: Load the patient data from PEB_data.csv. Replace these data with actual LIS data:

```
file_path <- here("PEB_main","LIS_priors_data.csv")
```

3) Determine LIS priors: Running the remaining script will apply refineR and robust regression to the LIS data to determine the priors:





B1 = 0.753 at the Box−Cox scale **B1 = 0.655**

Table 1: Summary of LIS Priors

LIS_priors	Value
Box-Cox lambda	0.6554470
Population SD (Box-Cox scale)	4.7348252
Population Mean (Box-Cox scale)	29.4994000
Intraclass Correlation - B1 (Box-Cox scale)	0.7532327

PEB_apply_LIS_priors.R

Purpose:
Applies the PEB approach (LIS-priors) to compute personalized reference intervals (prRIs) and reference change values (RCVs).

Key Steps:

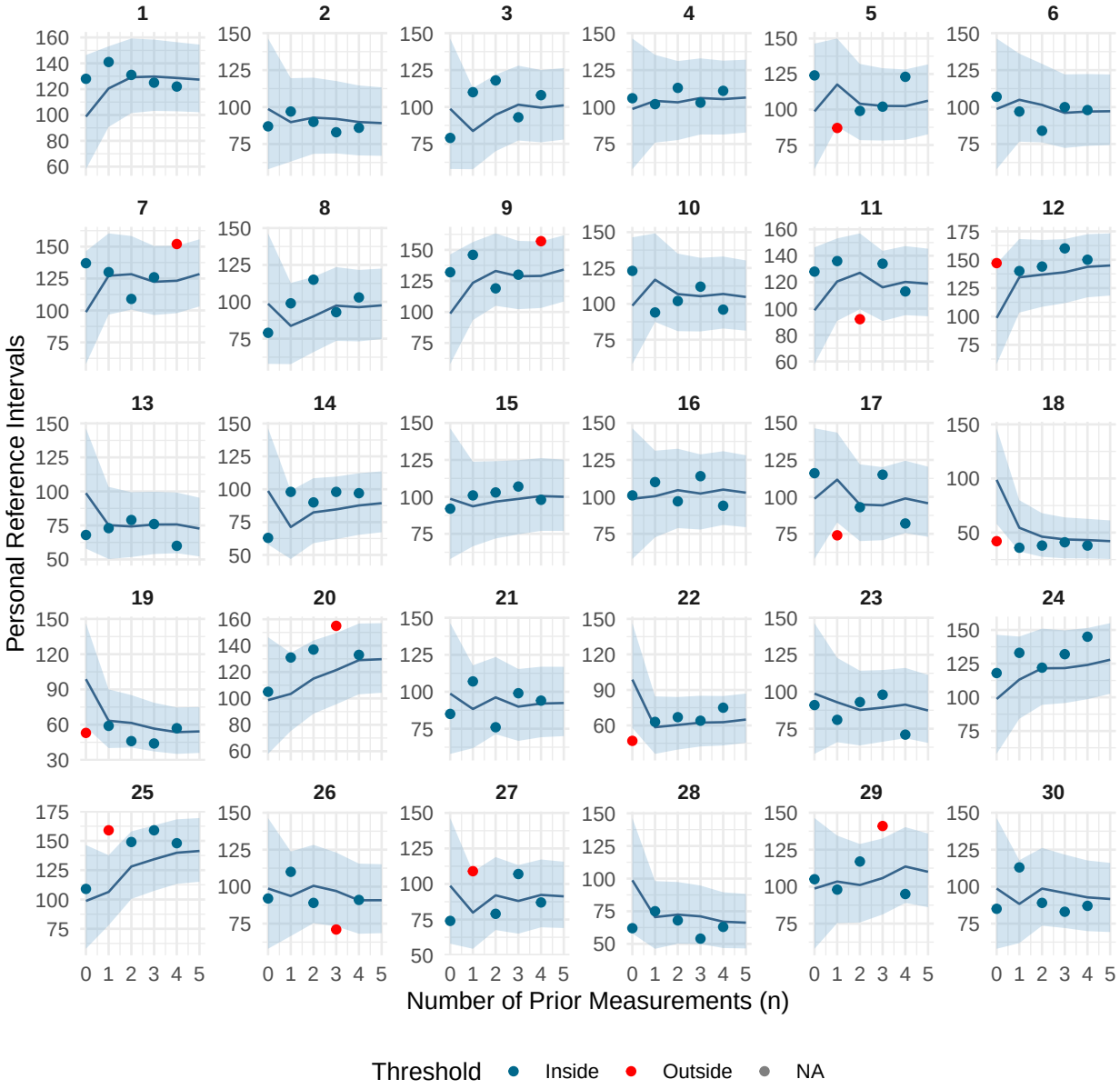
1) Parameter Setup: Input the established LIS priors and specify the significance level:

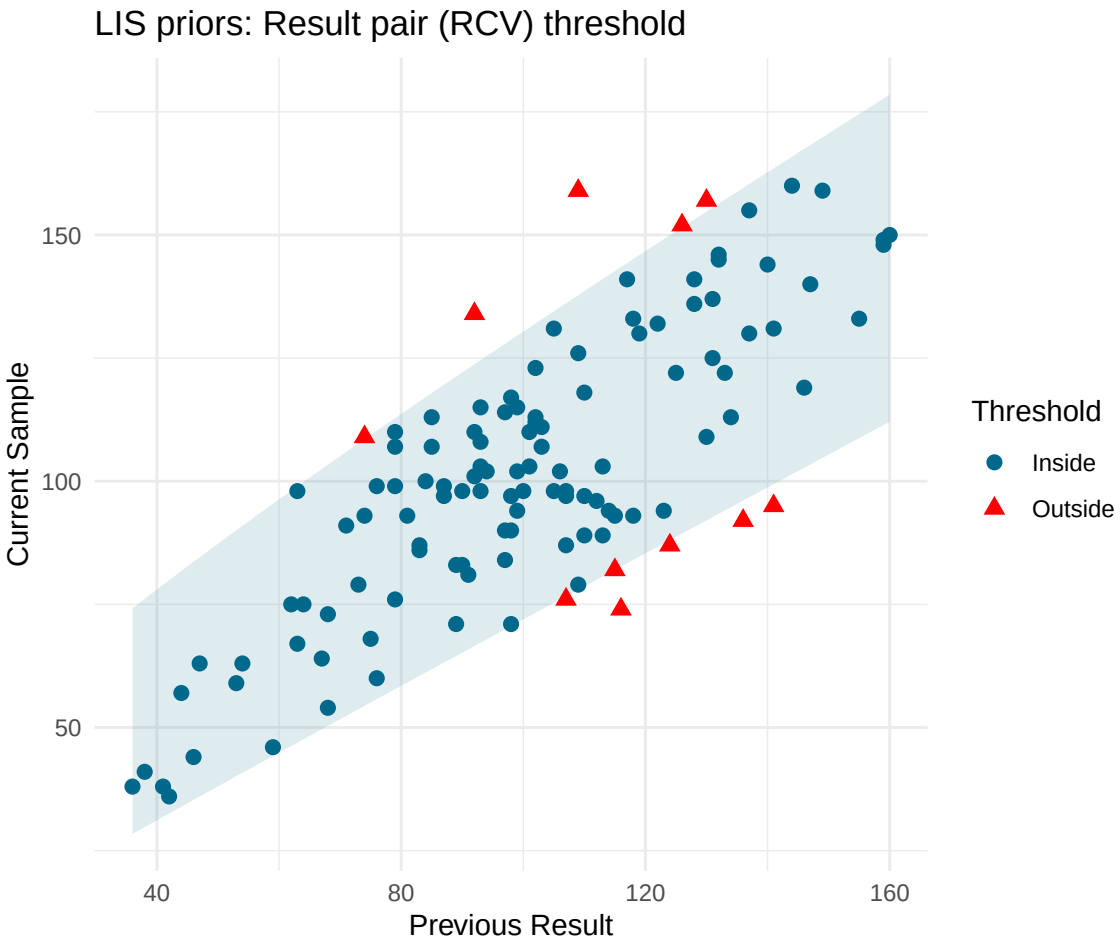
```
################################################################################
# 1) Define LIS priors
################################################################################
lambda    <- 0.655447  # Box-Cox transformation parameter
B1        <- 0.7533967 # Intraclass correlation on the Box-Cox scale
sigma_pop <- 4.653029  # Population SD on the Box-Cox scale
mu_pop    <- 29.42723  # Population mean on the Box-Cox scale

# Significance level
alpha   <- 0.05
z_score <- qnorm(1 - alpha / 2)
```

2) Data Loading: Load the patient data from PEB_data.csv. Replace these data with actual patient data:

```
df <- read.csv(here("PEB_main", "PEB_data.csv"), stringsAsFactors = FALSE)
df$measurement <- as.numeric(df$measurement)
```

3) prRI and RCV Calculations: Running the remaining script it will output the the prRI and RCV thresholds:


Personal Reference Intervals
Number of Prior Measurements (n)
Threshold
Inside
Outside
NA



PEB_apply_BV_priors.R

Same as **PEB_apply_BV_priors.R** just with BV priors (e.g. from the EFLM BV database)

LIS_priors_Monte_Carlo_example.R &

BV_priors_Monte_Carlo_example.R:

Purpose:
Simulates nested data and applies the PEB approach. These scripts are included to provide proof of concept for the assumptions underlying the BV and LIS priors. They may also be used to test the limitations of the approach or to further develop the approach, such as alternative methods for establishing priors.

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Contact

For questions, suggestions, or contributions, feel free to reach out to the project maintainer.