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

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2025-03-28

Overview

This project demonstrates two Parametric Empirical Bayes (PEB) methods for deriving personalized reference intervals (prRIs) and reference change values (RCVs). The methods allow for patient-specific cutoffs even when few individual measurements are available.

BV-Based Approach: Uses prior information from established biological variation (BV) estimates (e.g., from the EFLM BV database or your own BV study).

LIS-Based Approach: Uses priors inferred from routine laboratory data housed in a Laboratory Information System (LIS), leveraging local data and real sampling patterns.

Table of Contents

1. Project Sturcutre

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

```
Parametric Empirical Bayes
  |
  |-- 1_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
  |    |-- Establish_LIS_priors.R    # Establish priors from LIS data
  |    |-- PEB_apply_data.csv        # Data for applying PEB (replace with patient data)
  |    `-- LIS_priors_data.csv       # Data for establishing LIS priors (replace with LIS data)
  |
  |-- 2_Monte_Carlo_examples              # For testing PEB on simulated data
  |    |-- BV_priors_Monte_Carlo_example.R     # PEB approach with BV priors (simulation)
  |    `-- LIS_priors_Monte_Carlo_example.R    # PEB approach with LIS priors (simulation)
  |
  `-- 3_Apply_PEB_Excel               # For applying 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)
  |
  |-- LICENSE
  |
  |-- .gitignore
  |
  |-- Parametric_Empirical_Bayes.Rproj
  |
  `-- README.pdf
```

2. Requirements

Ensure you have an up-to-date version of R (4.0 or later). The scripts rely on the following R packages:

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

The scripts will automatically install the required packages if missing.

You may also install them manually:

```
install.packages(c("refineR", "robustbase", "ggplot2", "patchwork",
                   "dplyr", "here", "magrittr", "hms", "knitr", "ggtext"))
```

3. Getting started

Download the project folder (Parametric_Empirical_Bayes).

Open R (or RStudio), and open the `Parametric_Empirical_Bayes.Rproj` file inside the folder.

Check package prerequisites: Confirm you have all the Requirements installed (or let the scripts install them).

4. Workflow

After opening `Paramteric_Emperical_Bayes.Rproj` choose one of two workflows outlined below, depending on which priors are applicable: **1) LIS Priors Workflow** or **2) BV Priors Workflow**.

1) LIS Priors Workflow

Step 1: Prepare the LIS Dataset

- Open `LIS_priors_data.csv`.

- Replace the example data with your own LIS dataset.

- Keep the structure and column names intact (e.g., ID, Result, etc.)

Step 2: Establish LIS Priors

- Open `Establish_LIS_priors.R`.

- Adjust filter options as needed (e.g., age, sex, reference interval filter).

- Run the script. It will:
  - Apply refineR to estimate population mean (mu_pop), population SD (sigma_pop), and Box–Cox lambda.
  - Form result pairs for robust regression to estimate the intraclass correlation (B1).
- Finnaly A summary table will be displayed showing:
  - Population mean

  - Population standard deviation

  - Box–Cox lambda

  - Intraclass correlation (B1)

Step 3: Apply LIS Priors to Patient Data

- Open `PEB_apply_LIS_priors.R`.

- Replace the example data in `PEB_data.csv` with your own patient dataset.

- Copy the LIS priors from the summary table generated in Step 2.

- Run the script to calculate:
  - Personalized Reference Intervals (prRIs)

  - Reference Change Values (RCVs)

2) BV Priors Workflow

Step 1: Prepare the Patient Dataset

- Open `PEB_data.csv`.

- Replace the example data with your own patient dataset.

- Maintain the same data structure.

Step 2: Apply BV Priors

- Open `PEB_apply_BV_priors.R`.

- Enter the known BV parameters (e.g., CVI, CVA, CVG, population mean) or values from the EFLM BV database.

- Run the script to calculate:
  - Personalized Reference Intervals (prRIs)

  - Reference Change Values (RCVs)

5. Script Explanations

5.1 Establish_LIS_priors.R

Purpose:
Estimate prior parameters (population mean, SD, Box–Cox lambda, and intraclass correlation) from routine LIS data using a robust regression framework.

Key Steps:

1. **Replace LIS Example Data**
   Open `LIS_priors_data.csv` and replace the example dataset with your own LIS data. Maintain the same structure.

2. **Adjust Filter Settings**
   In the script, modify the filtering parameters such as:

   - Age and sex filters
   - Reference interval trimming
   - 24-hour gap between sample pairs

```
# 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
```
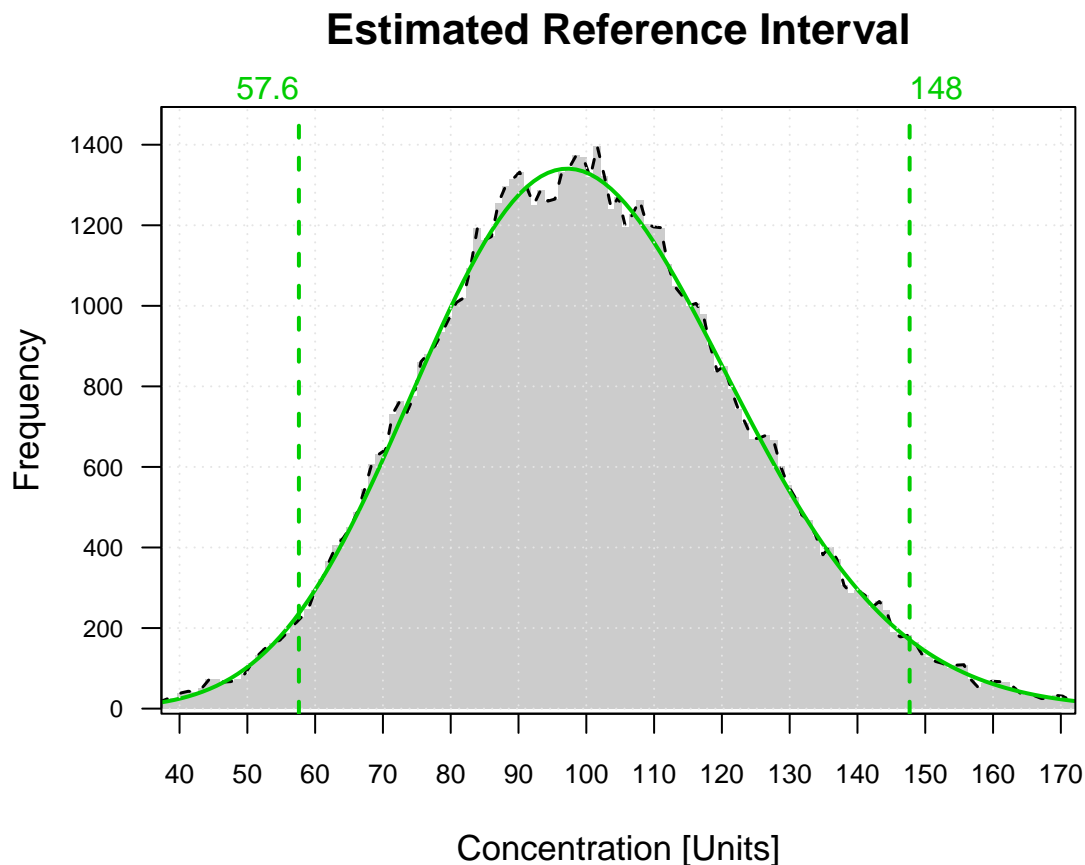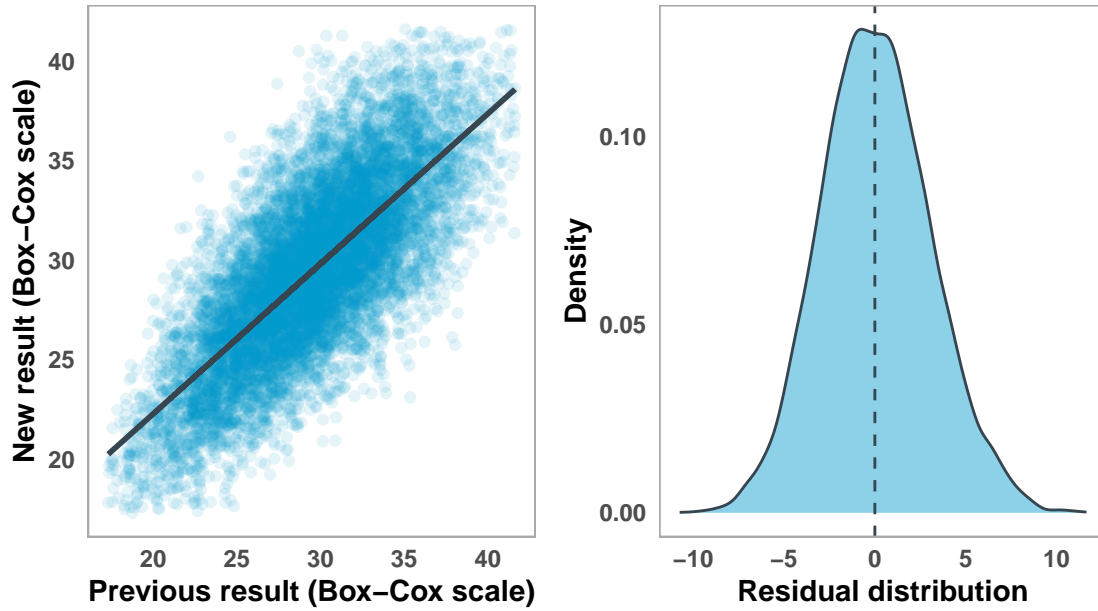
3. **Run the Script**
   The script will:

   - Estimate priors using `refineR` and `robustbase`

Estimated Reference Interval

B1 = 0.753 at the Box–Cox scale **lambda = 0.655**

4. **LIS priors table output**
   A summary table containing the LIS priors:

Table 1: Summary of LIS Priors

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

5.2 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
sigma_pop <- 4.653029  # Population SD on the Box-Cox scale
mu_pop    <- 29.42723  # Population mean on the Box-Cox scale
B1        <- 0.7533967 # Intraclass correlation 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:

LIS priors: Result pair (RCV) threshold
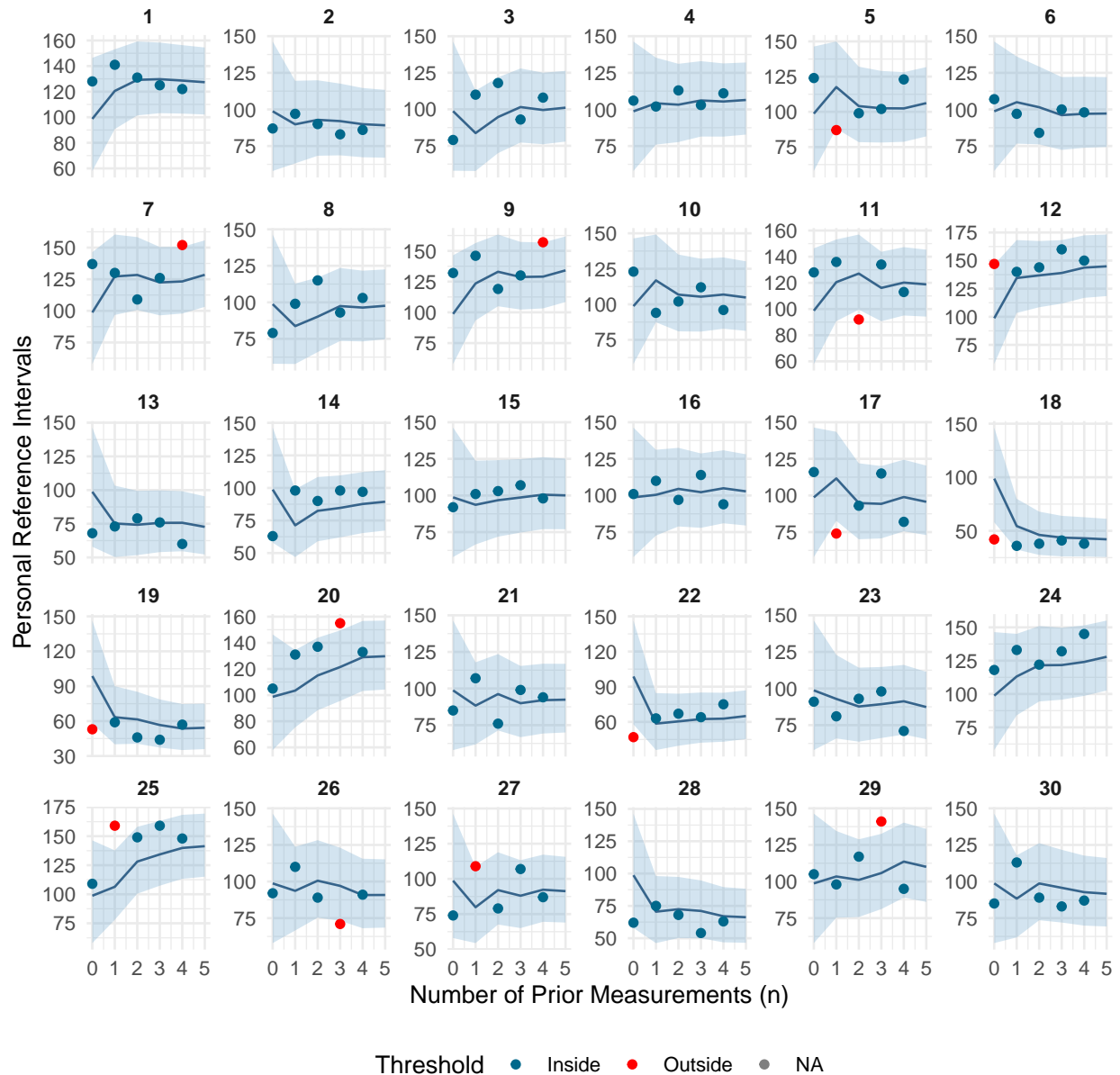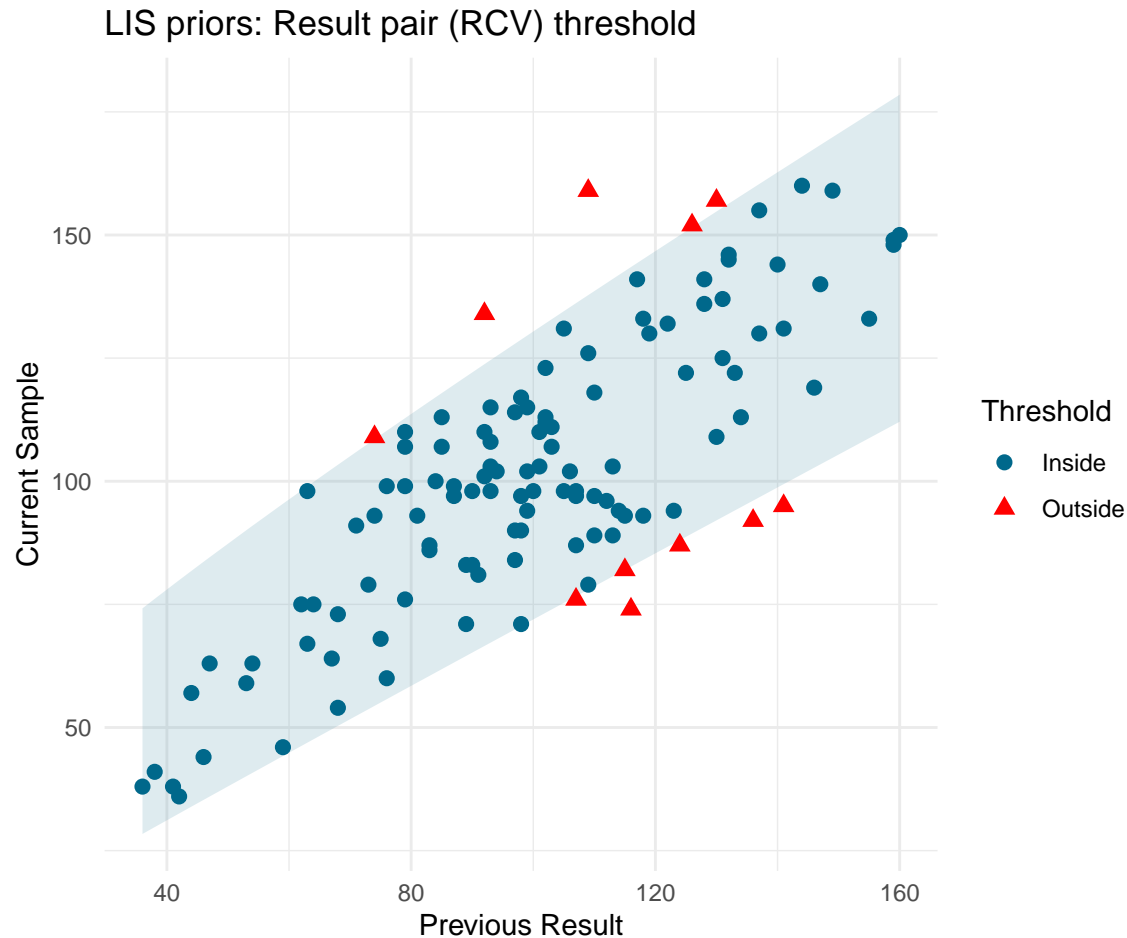
5.3 PEB_apply_BV_priors.R

Does the same as PEB_apply_LIS_priors.R but uses known BV parameters (CVI, CVA, CVG).

Key steps: 1) Specify BV priors: e.g., from published data or your own BV study.

2) Log-transform patient data (assuming variance is proportional to the mean).

3) Apply the iterative PEB formula on the log scale.

4) Back-transform the intervals and highlight flagged values by RCV or prRIs.

5.4 LIS_priors_Monte_Carlo_example.R &

BV_priors_Monte_Carlo_example.R:

Both scripts demonstrate how to simulate nested data and apply the PEB approach. They provide:

Synthetic data generation with chosen CVI, CVG and CVA.

Provides a proof of concept for the two approaches: BV and LIS priors in the PEB framework.

The script may also be used to test limitations of the approach (different distributions or pathological noise) or to further develop the approach, such as alternative methods for establishing priors.

6 Contact

For questions, suggestions, or contributions, please contact:

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