How to set historical control limits using the R package predint

Max Menssen

Department of Biostatistics

menssen@cell.uni-hannover.de

25.09.2024

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Introduction

Historical control limits

Institute of
Cell Biology and Biophysics

Leibniz
Universität
Hannover

Aim of the talk

- Validation of the current control (CC) using historical control limits (HCL)
- computed based on historical control data (HCD)

Historical control limits

Institute of Cell Biology and Biophysics | Leibniz Universität Hannover

OECD Test Guidelines:

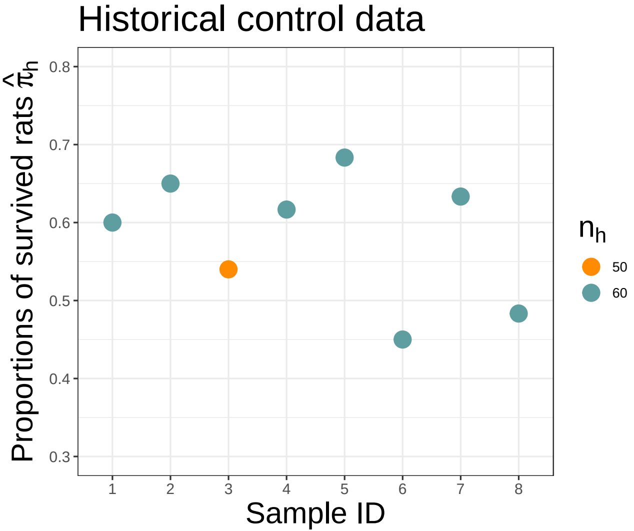
- ... concurrent negative controls should ideally be within the [historical] 95% control limits...

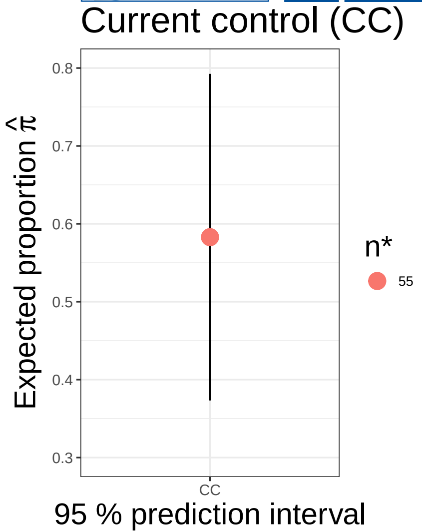
EFSA Scientific opinion (draft)

- ... a statistical comparison of HCD and CC is performed through calculation of a prediction interval (PI) derived from HCD.

[1] **OECD 471:** Bacterial Reverse Mutation Test; **OECD 473:** In Vitro Mammalian Chromosomal Aberration Test; **OECD 490:** In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene; **OECD 2016:** Overview of the set of OECD genetic toxicology test guidelines and updates performed in 2014–2015. **EFSA 2024:** Draft Scientific Opinion on the use and reporting of historical control data for regulatory studies. Public Consultation PC-0856.

Historical control limits (HCL)





[1] **Carlus et al. 2013:** Historical control data of neoplastic lesions in the Wistar Hannover Rat among eight 2-year carcinogenicity studies, Experimental and Toxicologic Pathology, 65(3), 243-253.

Historical control data

Hierarchical design

- n_h experimental units nested within each of the $h = 1, \dots, H$ control groups
- Systematic between-study variation
- Different numbers of experimental units per control group possible ($n_h \neq n_{h'}$)

Assumption

- HCD and CC derive from the same data generating process

Historical control limits

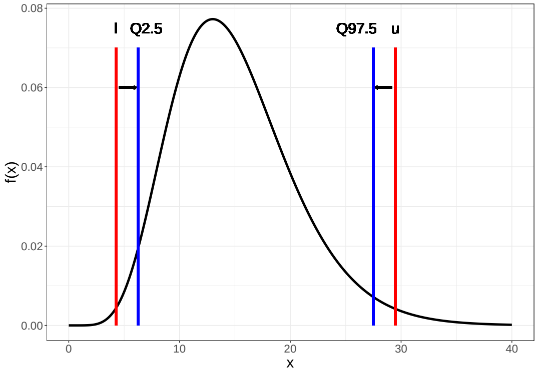
Prediction interval

- $P(l(\boldsymbol{y}) \leq \boldsymbol{y}^* \leq u(\boldsymbol{y})) = 1 - \alpha$

- HCD: $\boldsymbol{y}$
- Current control: $\boldsymbol{y}^*$

Equal tail probabilities

- $P(l(\boldsymbol{y}) \leq \boldsymbol{y}^*) = 1 - \alpha/2$
- $P(\boldsymbol{y}^* \leq u(\boldsymbol{y})) = 1 - \alpha/2$



Historical control limits

Aim

- Provide methodology for the calculation of prediction intervals for different
  - experimental designs
  - model classes
  - scales

- Ensure for equal tail probabilities

Bootstrap calibration

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Normal approximation

$$\frac{\hat{y}^* - Y^*}{\sqrt{\widehat{var}(\hat{y}^* - Y^*)}} = \frac{\hat{y}^* - Y^*}{\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}} \overset{\text{appr.}}{\sim} N(0,1)$$

Prediction standard error

$$\widehat{se}(\hat{y}^* - Y^*) = \sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}$$

Asymptotic prediction interval

$$[l, u] = \hat{y}^* \pm q_{1-\alpha/2}\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}$$

[1] **Nelson 1982:** Applied life data analysis. Wiley and Sons.

Bootstrap calibration

Standardized framework

- Works for several distributions

Adjust the prediction interval for

- skewed distributions
- hierarchical design of HCD
- simultaneous prediction

Prediction standard error

$$\widehat{se}(\hat{y}^* - Y^*) = \sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}$$

Pointwise prediction interval

$$[l, u] = \hat{y}^* \pm q_{1-\alpha/2}\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}$$

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Bootstrap calibration

- Find substitutes q_l and q_u for $q_{1-\alpha/2}$, that
  - account for possible skewness
  - enable simultaneous prediction

$$\left[l = \hat{y}^* - q_l\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)},\ u = \hat{y}^* + q_u\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)}\right]$$

The R package "predint"

predint

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

```
# Install the package from CRAN
install.packages("predint")

# Install developmental version
devtools::install_github("MaxMenssen/predint")

# Load the package to current R session
library(predint)
```

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Prediction intervals currently available for

- Continuous measurements
  - Linear random effect models
  - `lmer_pi_futmat()`
- Overdispersed binomial data
  - quasi-binomial: `quasi_bin_pi()`
  - beta-binomial: `beta_bin_pi()`
- Overdispersed count data
  - quasi-Poisson: `quasi_pois_pi()`
  - negative-binomial: `neg_bin_pi()`

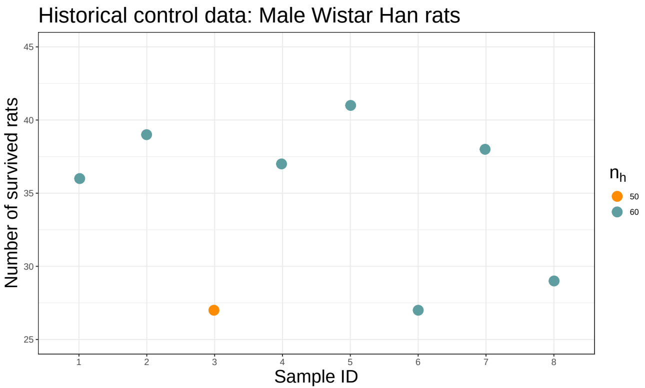
[1] **Menssen and Schaarschmidt 2022:** Prediction intervals for all of M future observations based on linear random effects models, Statistica Neerlandica, 76(3), 283-308. **Menssen et al. 2024:** Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control arXiv:2404.05282 (under review). **Menssen and Rathjens 2024:** Prediction intervals for overdispersed binomial endpoints and their application to historical control data arXiv:2407.13296 (under review).

Institute of Cell Biology and Biophysics
Leibniz Universität Hannover

Binomial data: Survival incidence

HCD: Survival incidence

```
##   surv dead
## 1   36   24
## 2   39   21
## 3   27   23
## 4   37   23
## 5   41   19
## 6   27   33
## 7   38   22
## 8   29   31
```



1 **Carlus et al. 2013:** Historical control data of neoplastic lesions in the Wistar Hannover Rat among eight 2-year carcinogenicity studies, Experimental and Toxicologic Pathology, 65(3), 243-253.

HCD: Survival incidence

Aim

- Predict the number of rats that survived the two year period
- Current control group: $n^* = 55$ rats

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Beta-binomial assumption

- $var(Y_h) = \phi_h n_h \pi(1-\pi)$ with $\phi_h = 1 + (n_h - 1)\rho$
- $var(Y^*) = \phi^* n^* \pi(1-\pi)$ with $\phi^* = 1 + (n^* - 1)\rho$

- π binomial proportion
- ρ intra-class correlation
  - Overdispersion $\rho > 0$

Prediction standard error

- $\widehat{se}(\hat{y}^* - Y^*) = \sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)} = \sqrt{\frac{\hat{\phi}^* n^{*2} \hat{\pi}(1-\hat{\pi})}{\sum_h n_h} + \hat{\phi}^* n^* \hat{\pi}(1-\hat{\pi})}$

[1] **Menssen and Schaarschmidt 2019:** Prediction intervals for overdispersed binomial data with application to historical controls. Statistics in Medicine, 38(14), 2652-2663.

HCD: Survival incidence

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

BS-calibrated interval

$$\left[l = n^* \hat{\pi} - q_l \sqrt{\frac{\hat{\phi}^* n^{*2} \hat{\pi}(1-\hat{\pi})}{\sum_h n_h} + \hat{\phi}^* n^* \hat{\pi}(1-\hat{\pi})}, \right.$$

$$\left. u = n^* \hat{\pi} + q_u \sqrt{\frac{\hat{\phi}^* n^{*2} \hat{\pi}(1-\hat{\pi})}{\sum_h n_h} + \hat{\phi}^* n^* \hat{\pi}(1-\hat{\pi})} \right]$$

[1] **Menssen and Rathjens 2024:** Prediction intervals for overdispersed binomial endpoints and their application to historical control data arXiv:2404.05282 (under review).

HCD: Survival incidence

```
bb_predint <- beta_bin_pi(histdat = f24a,
                          newsize=55)

bb_predint$rho # 0.01169135
# phi_star = 1 + 54 * 0.011 = 1.63

summary(bb_predint)
```

```
## Pointwise 95 % prediction interval for one future observation
##
##      lower    upper newsize y_star_hat       ql       qu  pred_se
## 1 20.53592 42.81963      55   32.06383 2.039219 1.902637 5.653101
##
## Bootstrap calibration was done for each prediction limit separately
##  using a modified  version of Menssen and Schaarschmidt 2022
```

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Prediction interval on observation scale (y^*)

- $[l, u] = [20.53, 43.59]$

Prediction interval on proportion scale ($\hat{\pi}^*$)

- $[l/n^*, u/n^*] = [20.53/55, 43.59/55] = [0.37, 0.79]$

Discussion

Discussion

Historical control limits

- HCD based validation of CC is mandatory
- Literature on prediction intervals for hierarchical designs is relatively scarce
- More research is needed!

R package predint

- Prediction intervals for three important scales
- Coverage probabilities close to the nominal level
- Provides methodology for self-implementation

[1] **Menssen and Schaarschmidt 2019:** Prediction intervals for overdispersed binomial data with application to historical controls. Statistics in Medicine, 38(14), 2652-2663. **Menssen and Schaarschmidt 2022:** Prediction intervals for all of M future observations based on linear random effects models, Statistica Neerlandica, 76(3), 283-308. **Menssen et al. 2024:** Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control arXiv:2404.05282 (under review). **Menssen and Rathjens 2024:** Prediction intervals for overdispersed binomial endpoints and their application to historical control data arXiv:2407.13296 (under review).

Discussion

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Take home messages

- Methodology in line with OECD and EFSA requirements
- Methodology is validated
- Applicable for other purposes
  - ADA cut-points
  - Sheward control charts

[1] **Menssen and Schaarschmidt 2019:** Prediction intervals for overdispersed binomial data with application to historical controls. Statistics in Medicine, 38(14), 2652-2663. **Menssen and Schaarschmidt 2022:** Prediction intervals for all of M future observations based on linear random effects models, Statistica Neerlandica, 76(3), 283-308. **Menssen et al. 2024:** Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control arXiv:2404.05282 (under review). **Menssen and Rathjens 2024:** Prediction intervals for overdispersed binomial endpoints and their application to historical control data arXiv:2407.13296 (under review).

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Thank you!

Institute of Cell Biology and Biophysics
Leibniz Universität Hannover

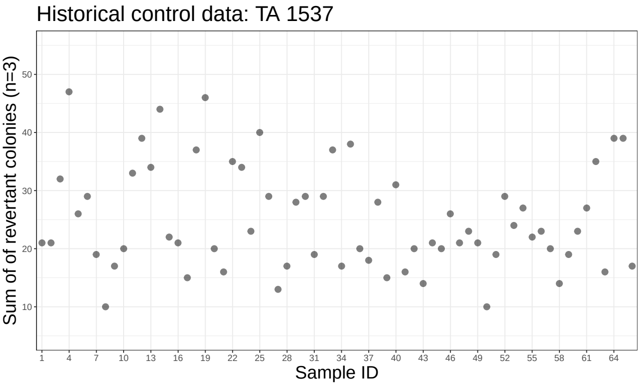
Appendix

Count data: No. of revertant colonies (Ames test)

HCD: Count data

HCD

```
##   colonies plates
## 1       27      3
## 2       14      3
## 3       17      3
## 4       29      3
## 5       21      3
## 6       17      3
```



[1] **Tarone 1982:** The Use of Historical Control Information in Testing for a Trend in Poisson Means. Biometrics, 457-462.

HCD: Count data

Current trial

```
##   dose colonies plates
## 1  0.0       10      3
## 2  0.3       18      3
## 3  1.0       21      3
## 4  3.3       16      3
## 5 10.0       35      3
```

Aim

- Validation of the control group
- $y^* = 10$ revertant colonies
- $n^* = 3$ petri dishes

[1] **Tarone 1982:** The Use of Historical Control Information in Testing for a Trend in Poisson Means. Biometrics, 457-462.

HCD: Count data

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Quasi-Poisson assumption

- $var(Y_h) = \phi n_h \lambda$
- $var(Y^*) = \phi n^* \lambda$
- Overdispersion $\phi > 1$

Prediction standard error

- $\widehat{se}(\hat{y}^* - Y^*) = \sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y^*)} = \sqrt{\frac{\hat{\phi} n^{*2} \hat{\lambda}}{\sum_h n_h} + \hat{\phi} n^* \hat{\lambda}}$

[1] **Menssen et al. 2024:** Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control arXiv:2404.05282 (under review).

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

BS-calibrated interval

$$\left[l = n^* \hat{\lambda} - q_l \sqrt{\frac{\hat{\phi} n^{*2} \hat{\lambda}}{\sum_h n_h} + \hat{\phi} n^* \hat{\lambda}},\right.$$

$$\left. u = n^* \hat{\lambda} + q_u \sqrt{\frac{\hat{\phi} n^{*2} \hat{\lambda}}{\sum_h n_h} + \hat{\phi} n^* \hat{\lambda}}\right]$$

[1] **Menssen et al. 2024:** Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control arXiv:2404.05282 (under review).

HCD: Count data

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

```
qp_predint <- quasi_pois_pi(histdat = tarone_hcd,
                             newdat = tarone_ad[1, 2:3])

qp_predint$phi # 3.182295
```

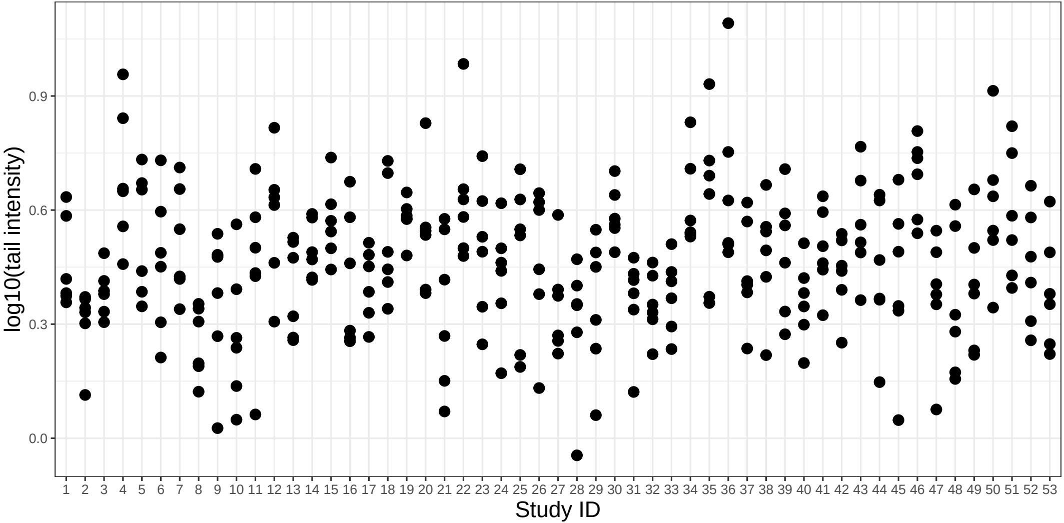
HCD: Count data

```r
summary(qp_predint)
```

```
## Pointwise 95 % prediction interval for one future observation
##
##   colonies plates    lower    upper y_star_hat       ql
## 1       10      3 10.04798 44.81337   25.06061 1.668496
##         qu  pred_se cover
## 1 2.195312 8.997699 FALSE
##
## ATTENTION: Not all future observations are covered
##
## Bootstrap calibration was done for each prediction limit separately
##  using a modified  version of Menssen and Schaarschmidt 2022
```

Continuous data: Comet assay

HCD: Comet assay



HCD: Comet assay

Experimental design

- log10(Tail intensity)
- Six rats per control group
- Rats nested in historical control groups

Model

- One way random effects model
- $y_{i(h)} = \mu + a_h + e_{i(h)}$
- $a_h \sim N(0, \sigma_a^2)$ σ_a^2: Between study variation
- $e_{i(h)} \sim N(0, \sigma_e^2)$ σ_e^2: Within study variation

Random effects models

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Historical observations

$$\boldsymbol{Y} = \mathbf{1}\mu + \boldsymbol{ZU} + \epsilon$$

$$\boldsymbol{ZU} = (\boldsymbol{Z}_1, \ldots, \boldsymbol{Z}_C) \begin{pmatrix} \boldsymbol{U}_1 \\ \vdots \\ \boldsymbol{U}_C \end{pmatrix} = \sum_{c=1}^{C} \boldsymbol{Z}_c \boldsymbol{U}_c$$

$$var(\boldsymbol{Y}) = \boldsymbol{\Sigma} = \sum_{c=1}^{C} \boldsymbol{Z}_c \boldsymbol{Z}_c^T \sigma_c^2 + \boldsymbol{I}\sigma_{C+1}^2$$

$$\boldsymbol{Y} \sim MVN(\mathbf{1}\mu, \boldsymbol{\Sigma})$$

$$Y \sim N(\mu, \sigma_1^2 + \sigma_2^2, \ldots, \sigma_{C+1}^2)$$

[1] Searle et al. 2006

Random effects models

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Current observations

$$\boldsymbol{Y}^* = \mathbf{1}\mu + \boldsymbol{Z}^* \boldsymbol{U}^* + \epsilon^*$$

$$\boldsymbol{Z}^* \boldsymbol{U}^* = (\boldsymbol{Z}^*{}_1, \ldots, \boldsymbol{Z}^*{}_C) \begin{pmatrix} \boldsymbol{U}^*{}_1 \\ \vdots \\ \boldsymbol{U}^*{}_C \end{pmatrix} = \sum_{c=1}^{C} \boldsymbol{Z}^*{}_c \boldsymbol{U}^*{}_c$$

$$var(\boldsymbol{Y}^*) = \boldsymbol{\Sigma}^* = \sum_{c=1}^{C} \boldsymbol{Z}_c^* \boldsymbol{Z}_c^{*T} \sigma_c^2 + \boldsymbol{I}^* \sigma_{C+1}^2$$

$$\boldsymbol{Y}^* \sim MVN(\mathbf{1}\mu, \boldsymbol{\Sigma}^*)$$

$$Y^* \sim N(\mu, \sigma_1^2 + \sigma_2^2, \ldots, \sigma_{C+1}^2)$$

[1] Menssen & Schaarschmidt 2022

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Overview about the data

```
## 'data.frame':    318 obs. of  3 variables:
##  $ y_log10: num  0.357 0.374 0.634 0.585 0.419 ...
##  $ run    : Factor w/ 53 levels "1","2","3","4",..: 1 1 1 1 1 1 2 2 2 2
##  $ id     : Factor w/ 53 levels "6","12","18",..: 1 2 3 4 5 6 7 8 9 10
```

HCD: Comet assay

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Model

- One way random effects model
- $y_{i(h)} = \mu + a_h + e_{i(h)}$

Fit the model

```
# Fit the model
comet_fit <- lme4::lmer(y_log10 ~ 1 + (1|run), data=comet_hcd)
```

HCD: Comet assay

Prediction intervals with `lmer_pi_futmat()`

- Works with random effects models fit with `lme4::lmer()`
- Factorial designs (hierarchical, cross-classified, ...)
- Random effects must be specified as `(1|ran_eff)`
- Provides PI on observation level

HCD: Comet assay

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Pointwise PI: One future rat

```r
# Pointwise PI on log10 scale
pred_int_pw <- lmer_pi_futmat(model=comet_fit,
                              newdat=1,
                              traceplot=FALSE)
summary(pred_int_pw)
```

```
## Pointwise 95 % prediction interval for one future observation
##
##       lower     upper y_star_hat        q   pred_se
## 1 0.1081695 0.8180777  0.4631236 1.961172 0.1809908
##
## Bootstrap calibration was done following Menssen and Schaarschmidt 2022
```

HCD: Comet assay

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Simultaneous PI: One concurrent control with six rats

- $var(\boldsymbol{Y}^*) = \boldsymbol{\Sigma}^* = \sum_{c=1}^{C} \boldsymbol{Z}_c^* \boldsymbol{Z}_c^{*T} \sigma_c^2 + \boldsymbol{I}^* \sigma_C^2 + 1$
- Provide list of $\boldsymbol{Z}_c^*$ via `futmat_list`

Simultaneous PI: One concurrent control with six rats

```
# Variance components
lme4::VarCorr(comet_fit)
```

```
##  Groups   Name        Std.Dev.
##  run      (Intercept) 0.088005
##  Residual             0.157444
```

HCD: Comet assay


```r
fml[["run"]]
```

```
##      [,1]
## [1,]    1
## [2,]    1
## [3,]    1
## [4,]    1
## [5,]    1
## [6,]    1
```

```r
fml[["Residual"]]
```

```
##      [,1] [,2] [,3] [,4] [,5] [,6]
## [1,]    1    0    0    0    0    0
## [2,]    0    1    0    0    0    0
## [3,]    0    0    1    0    0    0
## [4,]    0    0    0    1    0    0
## [5,]    0    0    0    0    1    0
## [6,]    0    0    0    0    0    1
```

Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

Simultaneous PI: One concurrent control with six rats

```
# Simultaneous PI on log10 scale
pred_int_si1 <- lmer_pi_futmat(model=comet_fit,
                               futmat_list=fml,
                               traceplot=FALSE)
```

Simultaneous PI: One concurrent control with six rats

```r
summary(pred_int_si1)
```

```
## Simultaneous 95 % prediction interval for 6 future observations
##
##          lower     upper y_star_hat        q   pred_se
## 1 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
## 2 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
## 3 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
## 4 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
## 5 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
## 6 -0.01543098 0.9416782  0.4631236 2.644082 0.1809908
##
## Bootstrap calibration was done following Menssen and Schaarschmidt 2022
```

Simultaneous PI: One concurrent control with six rats

```
# ggplot based graphic
plot(pred_int_si1)+
  ylab("log10(tail intensity) ")+
  theme(text = element_text(size = 15))
```