STP-BRIOCHE : A priori MIPD - Amoxicillin

2027-06-10

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Preface

This book contains all that is related to the a priori MIPD developped in STP-BRIOCHE

1 Covariate simulation

```
library(tidyverse)
library(here)
library(knitr)
library(rriskDistributions) # to fit distributions
library(RColorBrewer)
library(msm) # for truncated normal
library(gt) # for complex tables
library(MASS) # for colinarity
library(tibble)
library(dplyr)
library(tidyr)
library(MASS)
library(ggcorrplot)
library(patchwork)
conflicted::conflicts_prefer(dplyr::filter)
```

```
set.seed(1991)
```

1.1 Objective

```
n_patient <- 625 # number of patients simulated per cohort
```

```
here::i_am("a_priori/For_publication/Simulations/covariate_simulation.qmd")

# Create folder to store published figures
if (!dir.exists(here("a_priori/For_publication/Figures"))) {
  dir.create(here("a_priori/For_publication/Figures"))
}

cov_data <- read_csv(here("a_priori/For_publication/Simulations/cov_distrib_from_papers.csv")
```

From each identified paper, we want to simulate a cohort of patients. For each cohort we want to simulate 625 patients. We define a patient by a vector of covariate values. The covariates of interest are :

- WT : Body weight (kg)
- CRCL : Creatinine clearance (mL/min)
- ICU : Is the patient an ICU patient (=1) or not (=0)
- BURN : Is the patient a burn patient (=1) or not (=0)
- OBESE : Is the patient a obese - BMI > 30 kg/m^2 (=1) or not (=0)
- SEX : Male (=0) or female (=1)
- HT : height (cm)
- AGE : age (years)

To simulate covariate values we use information on the distribution of the covariates taken from the included papers.

We included 4 papers :

- Carlier et al. (2013)
- Fournier et al. (2018)
- Mellon et al. (2020)
- Rambaud et al. (2020)

One issue with the covariate data reported in these papers is that correlations between covariates are not reported and simulating without correlations runs the risk of simulating improbable covariate values. We thus obtained a clinical dataset composed of more than 16000 ICU patients (Johnson et al. (2023)) from which we could derive correlations between covariates of interest. Age, serum creatinine, body weight, sex, height and BMI were obtained for these patients and the creatinine clearance was calculated (in mL/min for Cockroft and Gault and CKD-EPI and in mL/min/1.73 m2 for MDRD (to correspond to Mellon)). A correlation matrix was calculated for each of the respective model development cohorts separately for females and males.

This correlation matrix is used to simulate correlations between the simulated WT, CRCL, AGE, and HT/BMI if necessary to convert CRCL to serum creatinine. (CRCL_MDRD_norm means CRCL in mL/min/1.73 m^2 used for Mellon and CRCL_MDRD in mL/min.). Different correlation matrices are used based on sex. This way two different mutltivariate distributions are simulated based on the two matrices with a number of patients that respects the original article proportions.

We can find correlations for the log-transforms of certain variables. For the covariates where a log-normal distribution fits better the log mean and standard deviation of this distribution will be used to sample log values with a multivariate normal distribution. At the end, the log variables will be retransformed to normal ones.

1.2 Carlier et al. (2013)

1.2.1 Covariate distribution

All patients are ICU patients and we will assume that they are not burn and not obese patients. Creatinine clearance was obtained using the measured urinary equation. Thus for all patients ICU = 1, BURN = 0.

As discussed in the article, renal replacement therapy is an exclusion criterion, therefore the minimum value of creatinine clearance is set to 10 mL/min, any simulated value below 10 mL/min will be resampled. CRCL was calculated using the measured urinary equation.

For WT and CRCL here are the data from the paper :

```
cov_data_carlier <- cov_data |>
  filter(Paper == "Carlier_2013")

cov_data_carlier |>
  filter(Covariate %in% c("WT","CRCL","AGE","BMI")) |>
  kable()
```

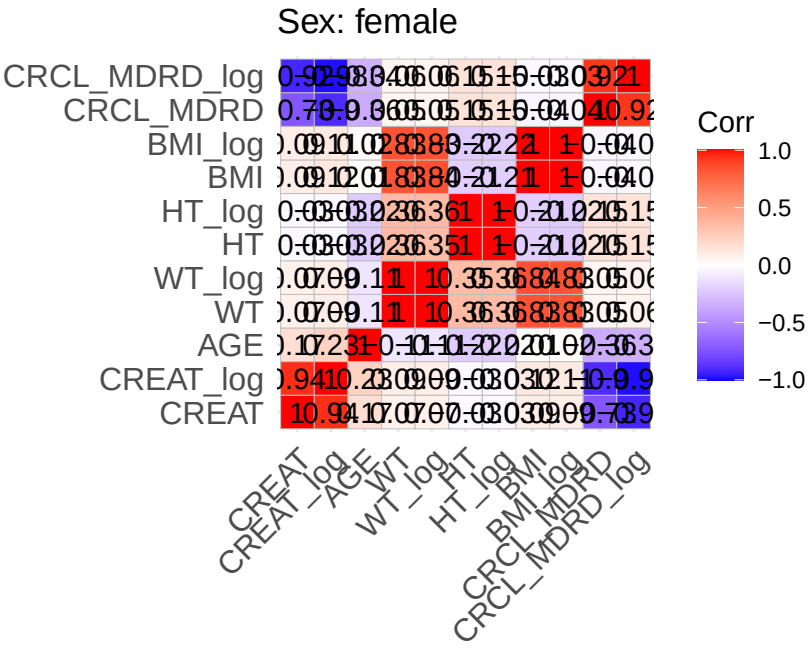
Paper	Covariate	Unit	Median	Q1	Q3	Min	Max
Carlier_2013	WT	kg	75	70	79	NA	NA
Carlier_2013	CRCL	mL/min	102	50	157	10	NA
Carlier_2013	BMI	kg/m^{2}	24	21	25	NA	NA
Carlier_2013	AGE	year	62	58	72	NA	NA

```
cor_matrix_Carlier_F <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Carlier
print(cor_matrix_Carlier_F)
```

```
                CREAT   CREAT_log         AGE          WT      WT_log
CREAT      1.00000000  0.93719806  0.17043554  0.07114115  0.07024583
CREAT_log  0.93719806  1.00000000  0.22904749  0.09016458  0.09019928
AGE        0.17043554  0.22904749  1.00000000 -0.11058359 -0.10874794
WT         0.07114115  0.09016458 -0.11058359  1.00000000  0.99663272
WT_log     0.07024583  0.09019928 -0.10874794  0.99663272  1.00000000
HT        -0.02615290 -0.03452481 -0.22145176  0.36158540  0.35423946
HT_log    -0.02656759 -0.03481661 -0.22200991  0.36341580  0.35641748
BMI        0.09120381  0.11653457  0.01416104  0.83213862  0.83590568
BMI_log    0.08905860  0.11477057  0.01748252  0.82644900  0.83409794
CRCL_MDRD -0.73311938 -0.90200963 -0.35625197  0.05193539  0.05083450
```

```
CRCL_MDRD_log -0.91894029 -0.98323371 -0.33894619  0.05521443  0.05501799
                        HT      HT_log         BMI     BMI_log   CRCL_MDRD
CREAT         -0.02615290 -0.02656759  0.09120381  0.08905860 -0.73311938
CREAT_log     -0.03452481 -0.03481661  0.11653457  0.11477057 -0.90200963
AGE           -0.22145176 -0.22200991  0.01416104  0.01748252 -0.35625197
WT             0.36158540  0.36341580  0.83213862  0.82644900  0.05193539
WT_log         0.35423946  0.35641748  0.83590568  0.83409794  0.05083450
HT             1.00000000  0.99908709 -0.21054270 -0.21983890  0.15405745
HT_log         0.99908709  1.00000000 -0.20907388 -0.21810288  0.15428482
BMI           -0.21054270 -0.20907388  1.00000000  0.99655760 -0.03784624
BMI_log       -0.21983890 -0.21810288  0.99655760  1.00000000 -0.03799028
CRCL_MDRD      0.15405745  0.15428482 -0.03784624 -0.03799028  1.00000000
CRCL_MDRD_log  0.14873339  0.14934183 -0.03146339 -0.03070224  0.92275219
              CRCL_MDRD_log
CREAT           -0.91894029
CREAT_log       -0.98323371
AGE             -0.33894619
WT               0.05521443
WT_log           0.05501799
HT               0.14873339
HT_log           0.14934183
BMI             -0.03146339
BMI_log         -0.03070224
CRCL_MDRD        0.92275219
CRCL_MDRD_log    1.00000000
```

```r
ggcorrplot(cor_matrix_Carlier_F, lab = TRUE, title = "Sex: female")
```

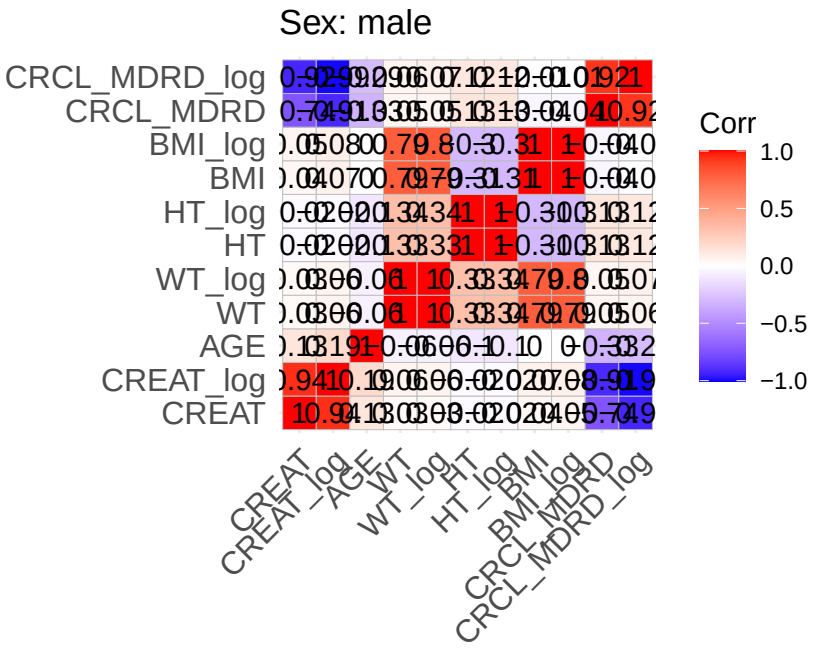



```
cor_matrix_Carlier_M <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Carlier
print(cor_matrix_Carlier_M)
```

```
                    CREAT   CREAT_log          AGE           WT      WT_log
CREAT          1.00000000  0.93656904  0.129584751  0.03477888  0.03489511
CREAT_log      0.93656904  1.00000000  0.191015858  0.06256888  0.06255796
AGE            0.12958475  0.19101586  1.000000000 -0.05978080 -0.05792048
WT             0.03477888  0.06256888 -0.059780801  1.00000000  0.99691085
WT_log         0.03489511  0.06255796 -0.057920475  0.99691085  1.00000000
HT            -0.01562634 -0.02015099 -0.099371429  0.33471772  0.33277207
HT_log        -0.01514335 -0.01943840 -0.098654543  0.33778296  0.33606644
BMI            0.04448518  0.07478234  0.002442579  0.78722872  0.78753911
BMI_log        0.04503665  0.07581809  0.004260007  0.79489820  0.79912510
CRCL_MDRD     -0.73662552 -0.90639303 -0.327115476  0.04508957  0.04511819
CRCL_MDRD_log -0.92158994 -0.98613183 -0.287263519  0.06492902  0.06504475
                      HT      HT_log          BMI      BMI_log   CRCL_MDRD
CREAT         -0.01562634 -0.01514335  0.044485175  0.045036646 -0.73662552
CREAT_log     -0.02015099 -0.01943840  0.074782343  0.075818092 -0.90639303
AGE           -0.09937143 -0.09865454  0.002442579  0.004260007 -0.32711548
WT             0.33471772  0.33778296  0.787228725  0.794898201  0.04508957
WT_log         0.33277207  0.33606644  0.787539107  0.799125098  0.04511819
HT             1.00000000  0.99918214 -0.312182156 -0.300458114  0.12810278
```

```
HT_log          0.99918214  1.00000000 -0.309805459 -0.297640862  0.12729396
BMI            -0.31218216 -0.30980546  1.000000000  0.996020588 -0.03549251
BMI_log        -0.30045811 -0.29764086  0.996020588  1.000000000 -0.03551703
CRCL_MDRD       0.12810278  0.12729396 -0.035492514 -0.035517032  1.00000000
CRCL_MDRD_log   0.11829734  0.11791657 -0.010057809 -0.009333342  0.92462410
                CRCL_MDRD_log
CREAT          -0.921589942
CREAT_log      -0.986131825
AGE            -0.287263519
WT              0.064929019
WT_log          0.065044752
HT              0.118297341
HT_log          0.117916569
BMI            -0.010057809
BMI_log        -0.009333342
CRCL_MDRD       0.924624105
CRCL_MDRD_log   1.000000000
```

```
ggcorrplot(cor_matrix_Carlier_M, lab = TRUE, title = "Sex: male")
```



We are going to fit normal and log-normal distributions to the observed quantiles and select the best fitting one

```r
compute_cv_from_sd_lnorm <- function(sdlog){
  #' Compute the geometric coefficient of variation from the standard deviation of a lognorma
  #'
  #' @param sdlog numeric. standard deviation of the log transformed variable
  #'
  #' @return numeric. geometric coefficient of variation
  sqrt(exp(sdlog^2)-1)
}

extract_cov_param <- function(cov_data, cov_name) {

  #' Get covariate quantiles from covariate characteristics table
  #'
  #' @param cov_data tibble containing the covariate information
  #' @param cov_name character. name of the covariate to select, comes from the Covariate col
  #' @return list with :
  #'  - p : numeric vector of probabilities
  #'  - q : numeric vector of quantiles
  #'  - cov_name : character string containing the covariate name
  #'  - cov_unit : character string containing the unit of the covariate


  cov_filtered_df <- cov_data |>
    filter(Covariate == cov_name) |>
    pivot_longer(
      cols = c(Median, Q1, Q3, Min, Max), # if the format of the csv columns ever changes, tl
      names_to = "p",
      values_to = "q"
    ) |>
    mutate(p = case_match(p, "Median" ~ 0.5, "Q1" ~ 0.25, "Q3" ~ 0.75, "Min" ~ 0.01, "Max" ~
    # if the format of the csv columns ever changes, the code above will need to change
    filter(!is.na(q)) |>
    group_by(Paper) |>
    arrange(p, .by_group = TRUE) |>
    ungroup()

  list(
    p = cov_filtered_df$p,
    q = cov_filtered_df$q,
    cov_name = unique(cov_filtered_df$Covariate),
    cov_unit = unique(cov_filtered_df$Unit)
  )
```

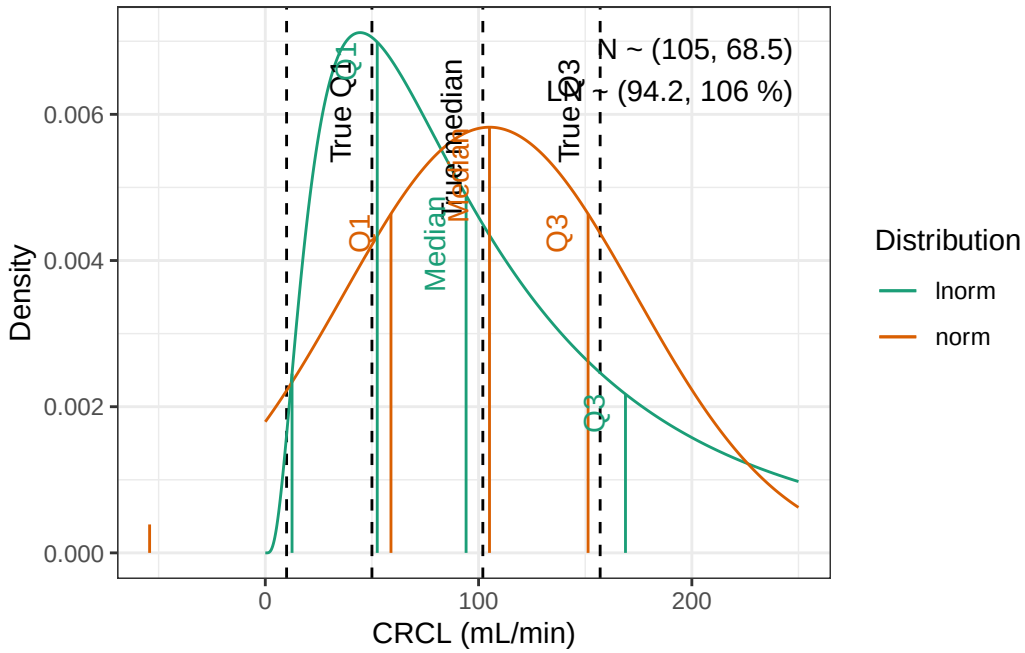
```
}

evaluate_distrib <- function(p, q, cov_name, cov_unit, min_plot, max_plot,tol = 0.001) {
  #' Fit normal and lognormal distribution to observed quantiles
  #' @param p numeric vector of probabilities
  #' @param q numeric vector of quantiles
  #' @param cov_name character string containing the covariate name
  #' @param cov_unit character string containing the unit of the covariate
  #' @param min_plot minimal value of the covariate for which the distribution should be plot
  #' @param max_plot maximal value of the covariate for which the distribution should be plot
  #' @param tol numeric. tolerance value for the fitting algorithm, default is 0.001
  #' @return list with :
  #'  - plot : ggplot2 showing the fitted distributions and the observed covariate
  #'  - lnorm_par : named numeric vector with the lognormal distribution parameters
  #'  - norm_par : named numeric vector with the normal distribution parameters


  lnorm_par <- get.lnorm.par(p = p, q = q, plot = FALSE, show.output = FALSE,tol = tol)
  norm_par <- get.norm.par(p = p, q = q, plot = FALSE, show.output = FALSE,tol=tol)

  #create a dataset with the true percentiles to be able to show them on the plot
  true_percentiles <- tibble(p, q) |>
    mutate(label = case_match(p,
                              0 ~ "True min",
                              0.25 ~ "True Q1",
                              0.5 ~ "True median",
                              0.75 ~ "True Q3",
                              1 ~ "True max"))

  #create a dataset with the percentiles of the fitted distributiosn to be able to show them
  distrib_percentiles <-  tibble(
    probability = p,
    lnorm = qlnorm(probability, meanlog = lnorm_par["meanlog"], sdlog =
                     lnorm_par["sdlog"]),
    norm = qnorm(probability, mean = norm_par["mean"], sd = norm_par["sd"])
  ) |>
    pivot_longer(cols = c(lnorm, norm), names_to = "distrib") |>
    mutate(density = case_match(
      distrib,
      "norm" ~ dnorm(value, mean = norm_par["mean"], sd =
                       norm_par["sd"]),
```

```
    "lnorm" ~ dlnorm(value, meanlog = lnorm_par["meanlog"], sdlog =
                       lnorm_par["sdlog"])
  )) |>
  mutate(label = case_match(probability,
                            0 ~ "Min",
                            0.25 ~ "Q1",
                            0.5 ~ "Median",
                            0.75 ~ "Q3",
                            1 ~ "Max"))


#simulate 1000 datapoints from the fitted distributions to show on the plot
param_data <- tibble(
  variable = seq(min_plot, max_plot, length.out = 1000),
  lnorm = dlnorm(variable, meanlog = lnorm_par["meanlog"], sdlog = lnorm_par["sdlog"]),
  norm = dnorm(variable, mean = norm_par["mean"], sd = norm_par["sd"])
) |>
  pivot_longer(cols = c(lnorm, norm), names_to = "distrib")


plot <- ggplot(param_data, aes(x = variable, y = value, color = distrib)) +
  geom_vline(data = true_percentiles, mapping = aes(xintercept = q),lty = "dashed") +
  geom_line() +
  geom_segment(data = distrib_percentiles, aes(x = value, y = 0, yend =
                                                 density)) +
  theme_bw() +
  scale_color_brewer("Distribution", palette = "Dark2") +
  ylab("Density") +
  xlab(paste0(cov_name, " (", cov_unit, ")")) +
  annotate(
    geom = "text",
    label = paste0(
      "N ~ (",
      signif(norm_par["mean"], 3),
      ", ",
      signif(norm_par["sd"], 3),
      ")\n",
      "LN ~ (",
      signif(exp(lnorm_par["meanlog"]), 3),
      ", ",
      signif(compute_cv_from_sd_lnorm(lnorm_par["sdlog"]), 3) * 100,
      " %)"
```

```
      ),
      x = min(param_data$variable) + 0.99 * diff(range(param_data$variable)),
      y = min(param_data$value) + 0.99 * diff(range(param_data$value)),
      hjust = 1,
      vjust = 1
    )+
    geom_text(
      data = true_percentiles,
      mapping = aes(x = q,label = label,color=NULL),
      show.legend = FALSE,
      y = min(param_data$value) + 0.95 * diff(range(param_data$value)),
      hjust = 1,
      vjust = -1,
      angle = 90
    )+
    geom_text(
      data = distrib_percentiles,
      mapping = aes(x = value, y=density,label = label),
      show.legend = FALSE,
      hjust = 1,
      vjust = -1,
      angle = 90
    )

  list(plot = plot,
       lnorm_par = lnorm_par,
       norm_par = norm_par)

}

fit_cov_wrapper <- function(cov_data, cov_name, min_plot, max_plot, tol = 0.001) {

  #' Wrapper to get covariate quantiles from covariate characteristics table and fit normal a
  #' to observed quantiles
  #'
  #' @param cov_data tibble containing the covariate information
  #' @param cov_name character. name of the covariate to select, comes from the Covariate col
  #' @param min_plot minimal value of the covariate for which the distribution should be plot
  #' @param max_plot maximal value of the covariate for which the distribution should be plot
  #' @param tol numeric. tolerance value for the fitting algorithm, default is 0.001
  #' @return list with :
  #'  - plot : ggplot2 showing the fitted distributions and the observed covariate
```

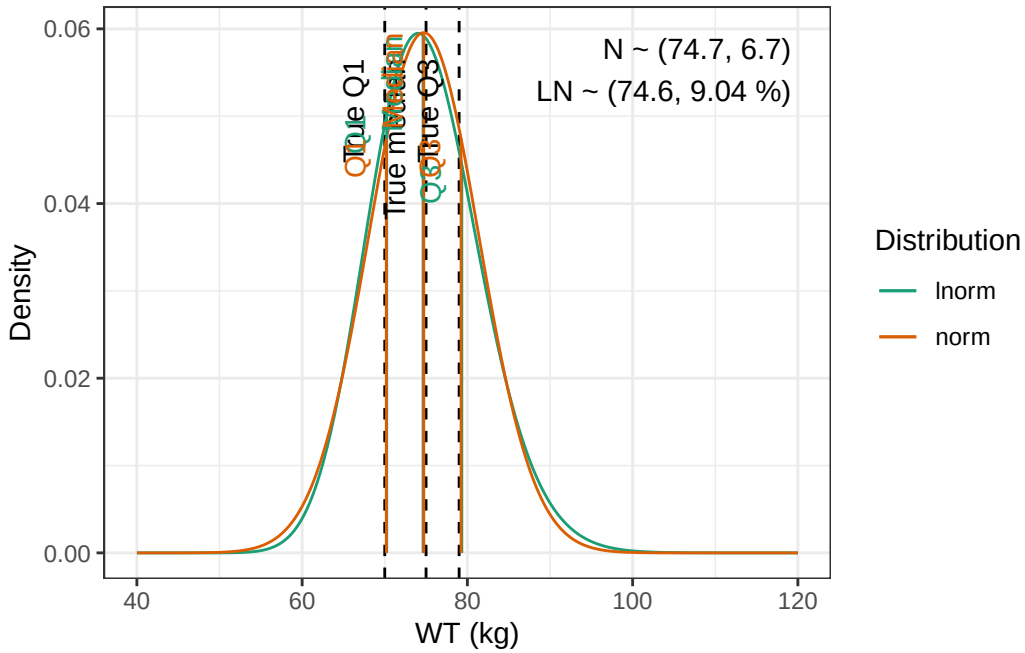
```
  #'  - lnorm_par : named numeric vector with the lognormal distribution parameters
  #'  - norm_par : named numeric vector with the normal distribution parameters


  cov_df <- extract_cov_param(cov_data, cov_name)

  evaluate_distrib(
    p = cov_df$p,
    q = cov_df$q,
    min_plot = min_plot,
    max_plot = max_plot,
    cov_name = cov_df$cov_name,
    cov_unit = cov_df$cov_unit,
    tol = tol
  )

}
```

```
carlier_crcl <- fit_cov_wrapper(
  cov_data = cov_data_carlier,
  cov_name = "CRCL",
  min_plot = 0,
  max_plot = 250
)

carlier_crcl$plot
```



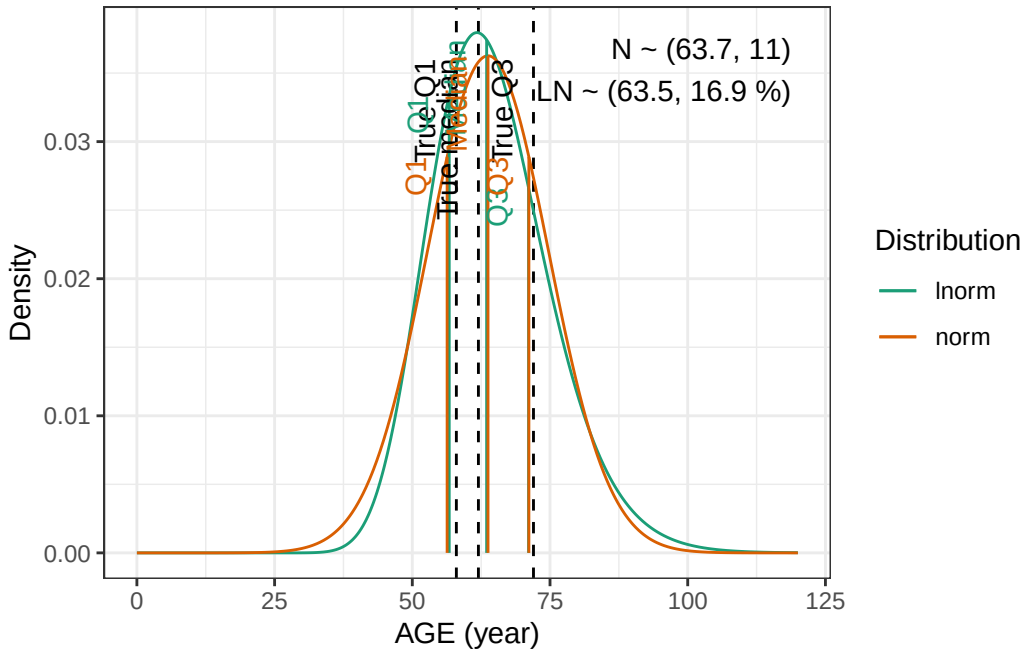
Normal distribution seems better than log-normal.

```
carlier_wt <- fit_cov_wrapper(
  cov_data = cov_data_carlier,
  cov_name = "WT",
  min_plot = 40,
  max_plot = 120
)

carlier_wt$plot
```



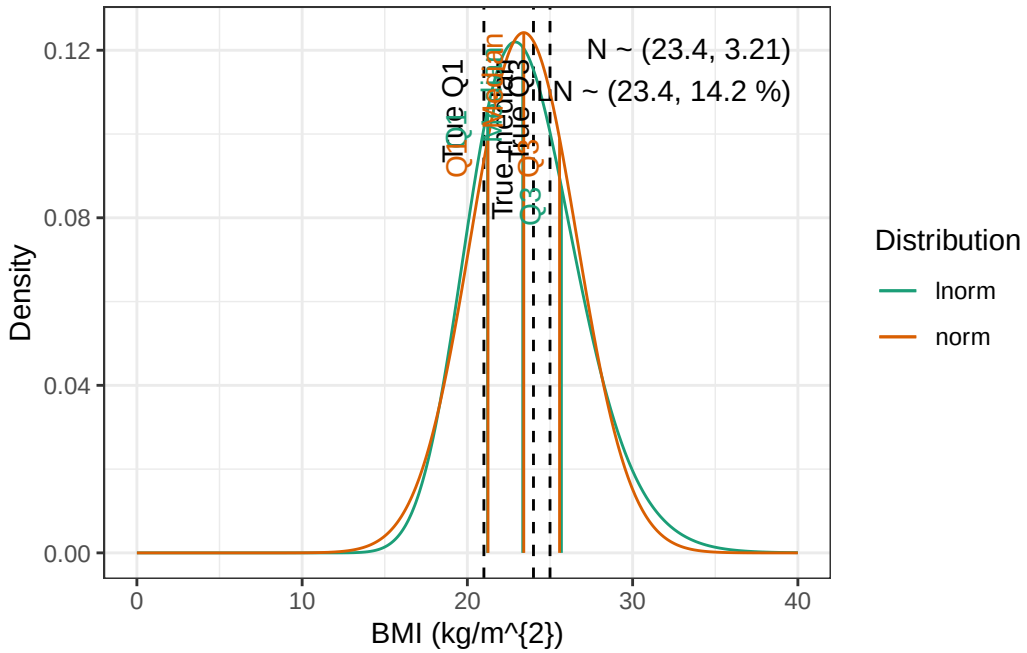
No discernable difference in fit. We have to use the log-normal distribution to be able to calculate height.

```
carlier_age <- fit_cov_wrapper(
  cov_data = cov_data_carlier,
  cov_name = "AGE",
  min_plot = 0,
  max_plot = 120
)

carlier_age$plot
```



No discernible difference in fit. We will use the normal distribution.

```
carlier_bmi <- fit_cov_wrapper(
  cov_data = cov_data_carlier,
  cov_name = "BMI",
  min_plot = 0,
  max_plot = 40,
  tol=0.002
)

carlier_bmi$plot
```



Tolerance was increased to 0.002. No discernible difference in fit. We have to use the log-normal distribution to be able to obtain height.

1.2.2 Simulation of covariates

Covariates will be sampled from the following distributions :

- CRCL : Normal distribution with a minimum of 10 mL/min, with mean 105 mL/min and standard deviation 68.5 mL/min
- WT : Lognormal distribution with mean 74.6 kg, and coefficient of variation 9.04 %
- AGE : Normal distribution with mean 63.7 mL/min and standard deviation 11 years and with a minimum of 18 years
- BMI : Log-normal distribution with mean 3.15 mL/min and standard deviation 0.141 kg/m^{2}

```
sim_norm_without_negatives <- function(n,mean,sd){

  #' Simulate values from normal distribution but resample negative values
  #'
  #' @param n numeric. number of samples to simulate
  #' @param mean numeric. mean of the normal distribution
  #' @param sd numeric. standard deviation of the normal distribtuion
  #' @return numeric vector of n values
```

```
  sim_values <- rnorm(n,mean,sd)
  neg_values <- sim_values[sim_values<=0]
  pos_values <- sim_values[sim_values>0]

  while(length(neg_values)>0){
    new_values <- rnorm(length(neg_values),mean,sd)
    sim_values <- c(pos_values,new_values)
    neg_values <- sim_values[sim_values<=0]
    pos_values <- sim_values[sim_values>0]
    }
  sim_values
}

# Only for normal distribution when the minimum is 10 ml/min, resample below 10
sim_norm_without_dialysis <- function(n,mean,sd){

  #' Simulate values from normal distribution but resample negative values
  #'
  #' @param n numeric. number of samples to simulate
  #' @param mean numeric. mean of the normal distribution
  #' @param sd numeric. standard deviation of the normal distribtuion
  #' @return numeric vector of n values
  sim_values <- rnorm(n,mean,sd)
  neg_values <- sim_values[sim_values<=10]
  pos_values <- sim_values[sim_values>10]

  while(length(neg_values)>0){
    new_values <- rnorm(length(neg_values),mean,sd)
    sim_values <- c(pos_values,new_values)
    neg_values <- sim_values[sim_values<=10]
    pos_values <- sim_values[sim_values>10]
    }
  sim_values
}
# Resimulate subjects younger than 18 years for normally distributed age
sim_norm_without_minors <- function(n,mean,sd){

  #' Simulate values from normal distribution but resample negative values
  #'
  #' @param n numeric. number of samples to simulate
  #' @param mean numeric. mean of the normal distribution
  #' @param sd numeric. standard deviation of the normal distribtuion
```

```
  #' @return numeric vector of n values
  sim_values <- rnorm(n,mean,sd)
  neg_values <- sim_values[sim_values<18]
  pos_values <- sim_values[sim_values>=18]

  while(length(neg_values)>0){
    new_values <- rnorm(length(neg_values),mean,sd)
    sim_values <- c(pos_values,new_values)
    neg_values <- sim_values[sim_values<18]
    pos_values <- sim_values[sim_values>=18]
    }
  sim_values
}
```

The relevant part of the correlation matrix is converted to a covariance matrix by multiplying the already calculated standard deviations of the variables with the diagonal of the correlation matrix. More information can be found at SAS and at stats. A multivariate normal distribution is fitted with resimulation of CRCL below 10 ml/min, AGE below 18 years, and other variables below 0.

The proportion of males is 0.85 in the original article, so the number of males is 531 and the number of females is 94 to add up to 625.

```
mean_WT_log <- as.numeric(carlier_wt$lnorm_par["meanlog"])
sd_WT_log <- as.numeric(carlier_wt$lnorm_par["sdlog"])
mean_BMI_log <- as.numeric(carlier_bmi$lnorm_par["meanlog"])
sd_BMI_log <- as.numeric(carlier_bmi$lnorm_par["sdlog"])
r_M <- 0.34 # Pearson correlation between HT_log and WT_log for males
r_F <- 0.36 # Pearson correlation for females

# sd is different based on sex
mean_HT_log = (mean_WT_log - mean_BMI_log) / 2
sd_HT_M_log = (-r_M * sd_WT_log + sqrt(r_M^2 * sd_WT_log^2 - sd_WT_log^2 + sd_BMI_log^2))/2 #
sd_HT_F_log = (-r_F * sd_WT_log + sqrt(r_F^2 * sd_WT_log^2 - sd_WT_log^2 + sd_BMI_log^2))/2 #

correlated_simulation <- function(n, means, cov_matrix) {
  set.seed(1991)
  collected <- matrix(NA, 0, length(means))
  colnames(collected) <- names(means)

  while (nrow(collected) < n) {
    batch <- MASS::mvrnorm(n = n, mu = means, Sigma = cov_matrix)
```

```
    colnames(batch) <- names(means)

    valid <- batch[, "AGE"] >= 18 &
             batch[, "CRCL_MDRD"] >= 10

    batch_valid <- batch[valid, , drop = FALSE]
    collected <- rbind(collected, batch_valid)
  }

  collected[1:n, , drop = FALSE]
}

means <- c(
  CRCL_MDRD = carlier_crcl$norm_par["mean"],
  WT_log    = carlier_wt$lnorm_par["meanlog"],
  AGE       = carlier_age$norm_par["mean"],
  HT_log    = mean_HT_log
)

sds_M <- c(
  CRCL_MDRD = carlier_crcl$norm_par["sd"],
  WT_log    = carlier_wt$lnorm_par["sdlog"],
  AGE       = carlier_age$norm_par["sd"],
  HT_log    = sd_HT_M_log
)

sds_F <- c(
  CRCL_MDRD = carlier_crcl$norm_par["sd"],
  WT_log    = carlier_wt$lnorm_par["sdlog"],
  AGE       = carlier_age$norm_par["sd"],
  HT_log    = sd_HT_F_log
)

covariates <- c("CRCL_MDRD", "WT_log", "AGE", "HT_log")

names(means) <- covariates

# Correlation and Covariance Matrix
cor_carlier_M <- cor_matrix_Carlier_M[covariates, covariates]
cov_matrix_M <- diag(sds_M) %*% cor_carlier_M %*% diag(sds_M)
eigen(cov_matrix_M)$values
```

```
[1] 4.705706e+03 1.077951e+02 8.326780e-03 1.446538e-03
```

```r
cor_carlier_F <- cor_matrix_Carlier_F[covariates, covariates]
cov_matrix_F <- diag(sds_F) %*% cor_carlier_F %*% diag(sds_F)
eigen(cov_matrix_F)$values
```

```
[1] 4.708164e+03 1.053367e+02 8.259148e-03 1.338558e-03
```

```r
# Simulate
sim_data_M <- correlated_simulation(n = 531, means = means, cov_matrix = cov_matrix_M)
sim_data_M <- as_tibble(sim_data_M) %>%
  mutate(SEX = 0)

sim_data_F <- correlated_simulation(n = 94, means = means, cov_matrix = cov_matrix_F)
sim_data_F <- as_tibble(sim_data_F) %>%
  mutate(SEX = 1)

sim_data <- rbind(sim_data_M, sim_data_F)

# Put the covariates together
sim_cov_carlier <- tibble(
  Paper = "Carlier_2013",
  ID_within_paper = 1:n_patient,
  ICU = 1,
  BURN = 0,
  OBESE = 0,
  CRCL = sim_data$CRCL_MDRD,
  WT_log   = sim_data$WT_log,
  AGE  = sim_data$AGE,
  HT_log  = sim_data$HT_log,
  SEX = sim_data$SEX
)

# Add OBESE variable and reconvert logWT to WT
sim_cov_carlier <- sim_cov_carlier %>%
  mutate(WT = exp(WT_log),
         HT = (exp(HT_log))*100,
         BMI = WT / (HT/100)^2,
         OBESE = ifelse(BMI > 30, 1, 0))

summary_sim_cov_carlier <- sim_cov_carlier |>
  pivot_longer(cols = c(ICU,BURN,OBESE,CRCL,WT,AGE,BMI),
```

```
                names_to = "Covariate") |>
  summarise(.by = c(Covariate,Paper),
            Min = min(value),
            Q1 = quantile(value, 0.25),
            Median = quantile(value, 0.5),
            Q3 = quantile(value, 0.75),
            Max = max(value))
```

```
cov_carlier_compare <- summary_sim_cov_carlier |>
  rename_with(~ paste0(.x, "_sim"), -one_of("Covariate", "Paper")) |>
  left_join(rename_with(
    cov_data_carlier,
    ~ paste0(.x, "_true"),
    -one_of("Covariate", "Paper", "Unit")
  )) |>
  relocate(Covariate, .after = Paper) |>
  relocate(Unit, .after = Covariate)

cov_carlier_compare |>
  gt() |>
  fmt_scientific() |>
    tab_spanner(columns = starts_with("Min"),
                label = "Min") |>
      tab_spanner(columns = starts_with("Q1"),
                label = "Q1") |>
      tab_spanner(columns = starts_with("Median"),
                label = "Median") |>
      tab_spanner(columns = starts_with("Q3"),
                label = "Q3") |>
  tab_spanner(columns = starts_with("Max"),
                label = "Max")
```

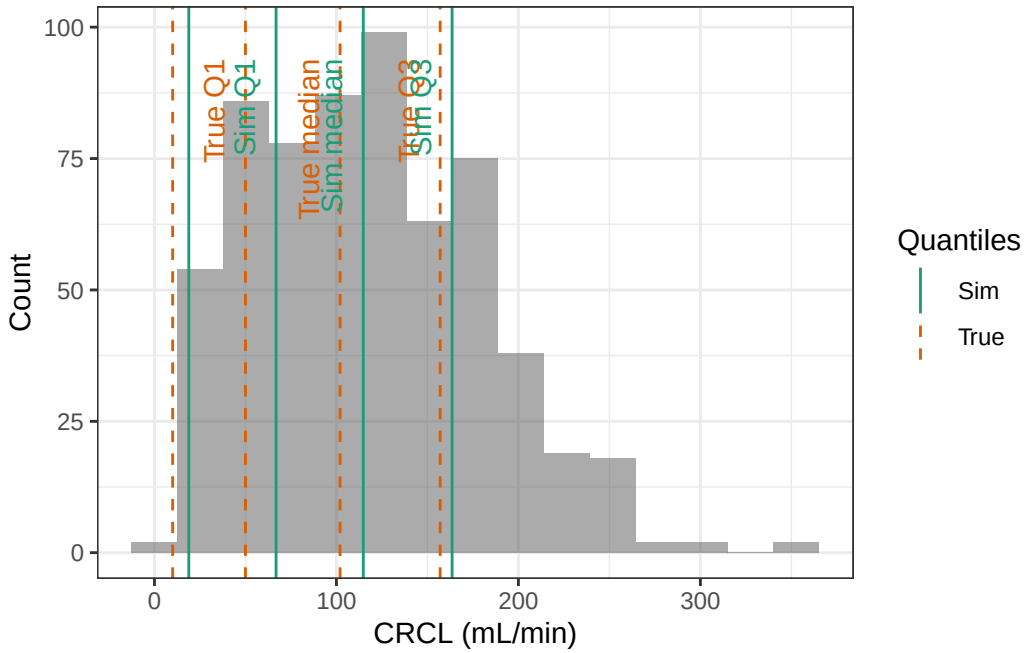
```
evaluate_cov_sim <- function(p, q, cov_name, cov_unit, cov_sim) {
  #' Plot simulated covariate distribution versus observed quantiles from the paper
  #' @param p numeric vector of probabilities
  #' @param q numeric vector of quantiles
  #' @param cov_name character string containing the covariate name
  #' @param cov_unit character string containing the unit of the covariate
  #' @param cov_sim tibble containing the simulated values for the covariate
  #' @return ggplot2 showing the distributions of the simulated covariate and the observed co
```

			Min		Q1		M
Paper	Covariate	Unit	Min_sim	Min_true	Q1_sim	Q1_true	Median_sim
Carlier_2013	ICU	Unitless	1.00	1.00	1.00	1.00	1.0
Carlier_2013	BURN	Unitless	0.00	0.00	0.00	0.00	0.0
Carlier_2013	OBESE	Unitless	0.00	0.00	0.00	0.00	0.0
Carlier_2013	CRCL	mL/min	1.18×10^1	1.00×10^1	6.68×10^1	5.00×10^1	1.15×10
Carlier_2013	WT	kg	5.89×10^1	NA	7.02×10^1	7.00×10^1	7.47×10
Carlier_2013	AGE	year	2.84×10^1	NA	5.38×10^1	5.80×10^1	6.30×10
Carlier_2013	BMI	kg/m^{2}	1.66×10^1	NA	2.19×10^1	2.10×10^1	2.32×10

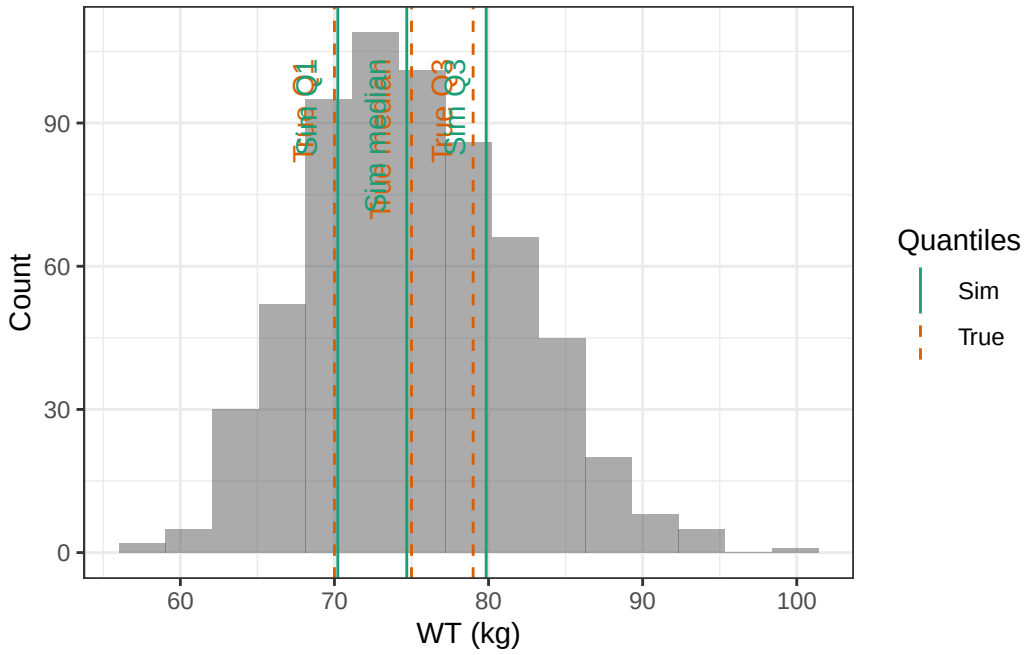
```
  #create a dataset with the true percentiles to be able to show them on the plot
  true_percentiles <- tibble(p, q) |>
    mutate(label = case_match(p,
                              0 ~ "True min",
                              0.25 ~ "True Q1",
                              0.5 ~ "True median",
                              0.75 ~ "True Q3",
                              1 ~ "True max"))

  #create a dataset with the percentiles of the fitted distributions to be able to show them
   sim_percentiles <-  tibble(
    probability = p,
    q = quantile(pull(cov_sim,cov_name),p)
  ) |>
        mutate(label = case_match(probability,
                              0 ~ "Sim min",
                              0.25 ~ "Sim Q1",
                              0.5 ~ "Sim median",
                              0.75 ~ "Sim Q3",
                              1 ~ "Sim max"))

# create an initial histogram in order to be able to extract statistics of the binned covaria
hist_ini <- ggplot(cov_sim, aes(x = .data[[cov_name]])) +
  geom_histogram(bins=15)

hist_data <- layer_data(hist_ini)

plot <- ggplot(hist_data) +
  geom_rect(aes(xmin=xmin,xmax=xmax, ymin=0, ymax=count),
```

```
            alpha = 0.5) +
    geom_vline(data = true_percentiles,
               mapping = aes(xintercept = q,color = "True"),
               lty = "dashed") +
    geom_vline(data = sim_percentiles,
               mapping = aes(xintercept = q,color = "Sim"),
               lty = "solid") +
    theme_bw() +
    ylab("Count") +
    xlab(paste0(cov_name, " (", cov_unit, ")"))  +

    geom_text(
      data = true_percentiles,
      mapping = aes(x = q, label = label, color = "True"),
      show.legend = FALSE,
      y = 0.95*max(hist_data$ymax),
      hjust = 1,
      vjust = -1,
      angle = 90
    ) +
    geom_text(
      data = sim_percentiles,
      mapping = aes(x = q, label = label, color = "Sim"),
      show.legend = FALSE,
      y = 0.95*max(hist_data$ymax),
      hjust = 1,
      vjust = -1,
      angle = 90
    ) +
    scale_color_brewer(name = "Quantiles",
                       palette ="Dark2")
  plot
}

plot_sim_cov_wrapper <- function(cov_data,cov_name,cov_sim){
  cov_df <- extract_cov_param(cov_data, cov_name)

evaluate_cov_sim(cov_df$p,cov_df$q,cov_df$cov_name,cov_df$cov_unit,
                 cov_sim)
}
```

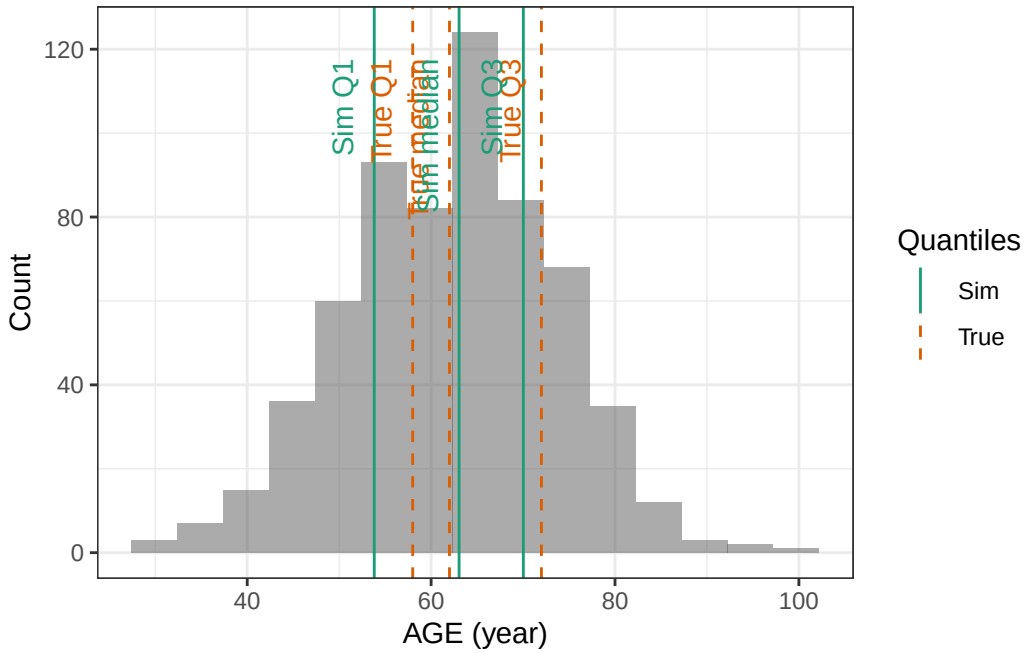
```
plot_sim_cov_wrapper(cov_data_carlier,"CRCL",sim_cov_carlier)
```



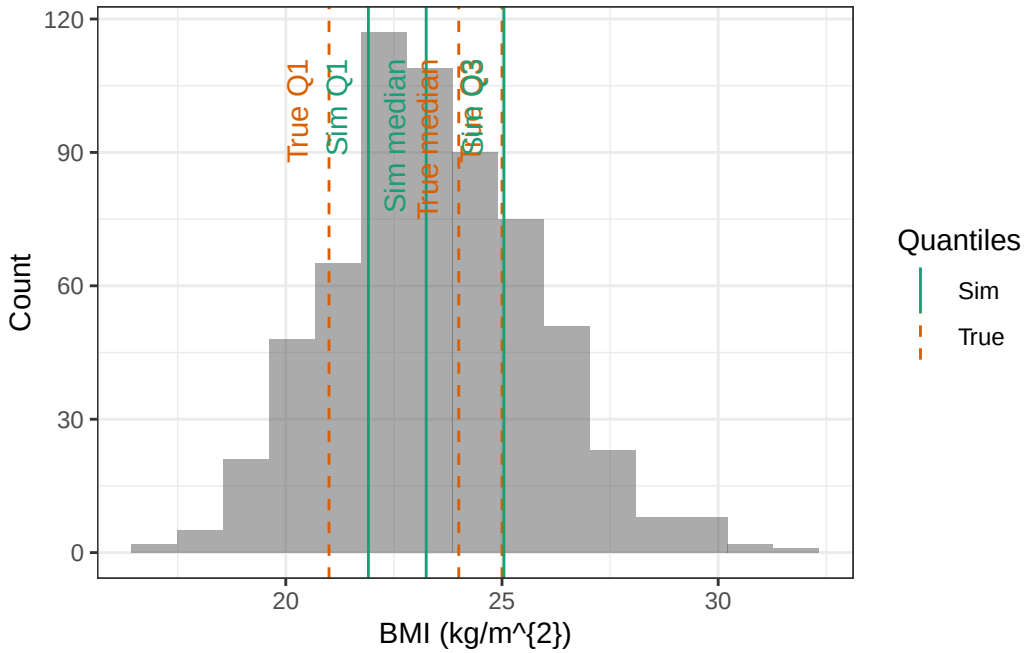

```
plot_sim_cov_wrapper(cov_data_carlier,"WT",sim_cov_carlier)
```



```
plot_sim_cov_wrapper(cov_data_carlier,"AGE",sim_cov_carlier)
```

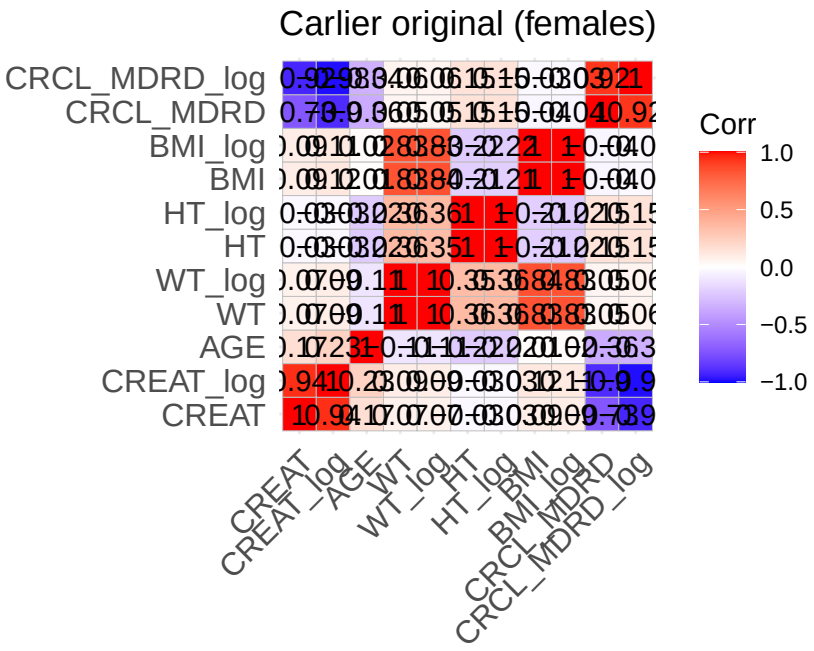



```
plot_sim_cov_wrapper(cov_data_carlier,"BMI",sim_cov_carlier)
```

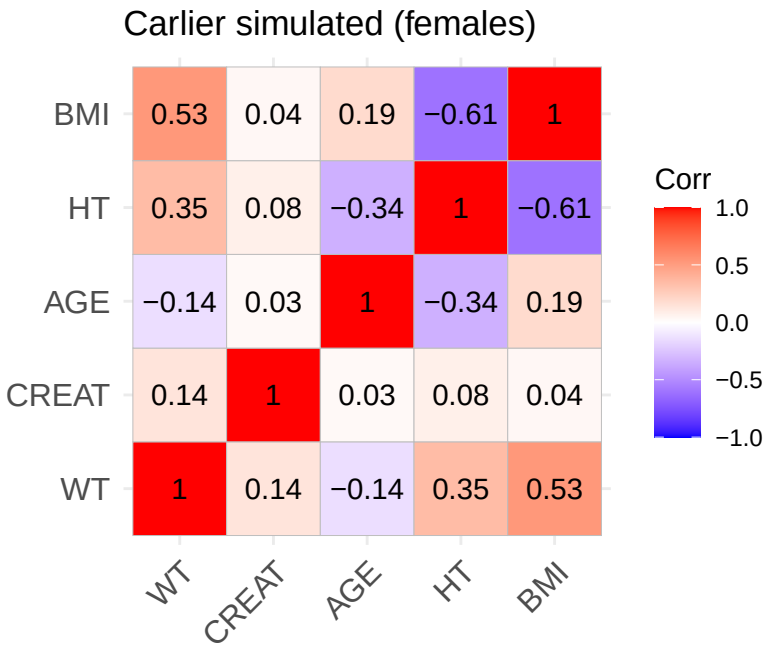


Then, based on BMI and WT, height (HT) is calculated to be able to calculate the body surface area (BSA). CRCL was calculated using the measured urinary equation, and as we have know information about the urinary volume or urinary creatinine concentration, we cannot reconvert CRCL to CREAT based on this equation. The most recommended equation is CKD-EPI, however as different exponents are used based on the value of CREAT, it can't be used for reconversion of CRCL to CREAT. Thus, the second best equation, MDRD is used.

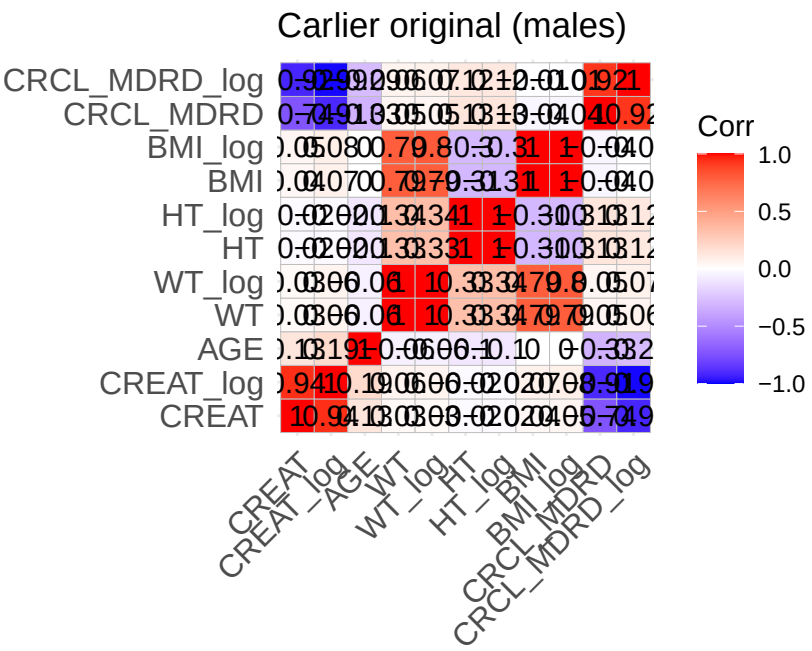
```
reconvert_MDRD <- function(AGE, CRCL, SEX) {
    # Mutliply by 0.742 for females
    sex_factor <- ifelse(SEX == 0, 1, 0.742)

    # Calculate DFG
   CREAT <- (CRCL / (175 * (AGE^(-0.203)) * sex_factor))^(-1 / 1.154)

  return(CREAT)
}

sim_cov_carlier <- sim_cov_carlier %>%
  mutate(
    BSA = (WT^0.425 * (HT^0.725) * 0.007184), # Calculate body surface area based on Dubois&
    CRCL = CRCL * (1.73 /BSA) # convert mL/min to mL/min/1.73 m2
  )
sim_cov_carlier$CREAT <- mapply(reconvert_MDRD, sim_cov_carlier$AGE, sim_cov_carlier$CRCL, s
sim_cov_carlier <- sim_cov_carlier %>%
  dplyr::select(Paper, ID_within_paper, ICU, BURN, OBESE, CREAT, WT, BSA, BMI, AGE, SEX, HT)

# Calculate the simulated correlation matrices separately for the two sexes to compare with
sim_cov_carlier_M <- sim_cov_carlier %>% filter(SEX == 0)
sim_cov_carlier_F <- sim_cov_carlier %>% filter(SEX == 1)

cor_sim_M <- cor(sim_cov_carlier_M %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "comple
cor_sim_F <- cor(sim_cov_carlier_F %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "comple

ggcorrplot(cor_matrix_Carlier_F, lab = TRUE, title = "Carlier original (females)")
```



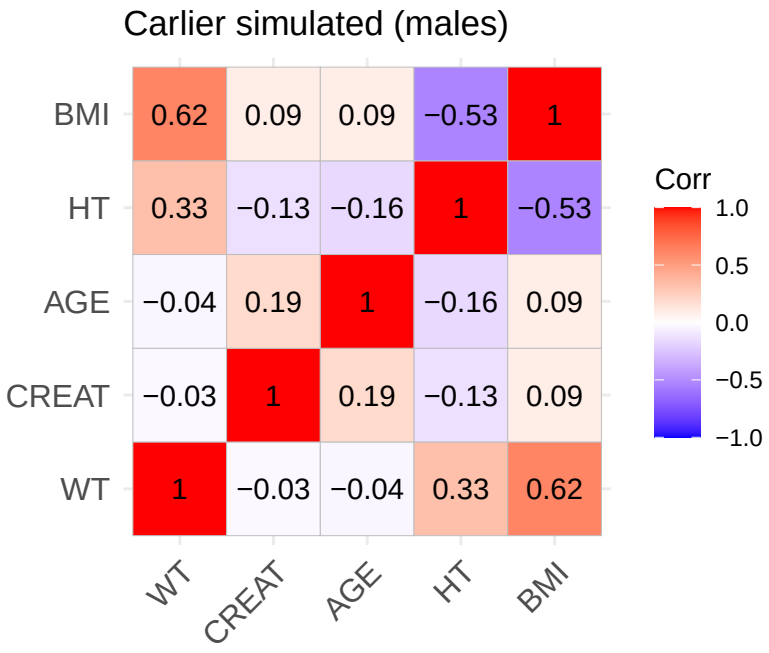

```
Carlier_F <- ggcorrplot(cor_sim_F, lab = TRUE, title = "Carlier simulated (females)")
Carlier_F
```



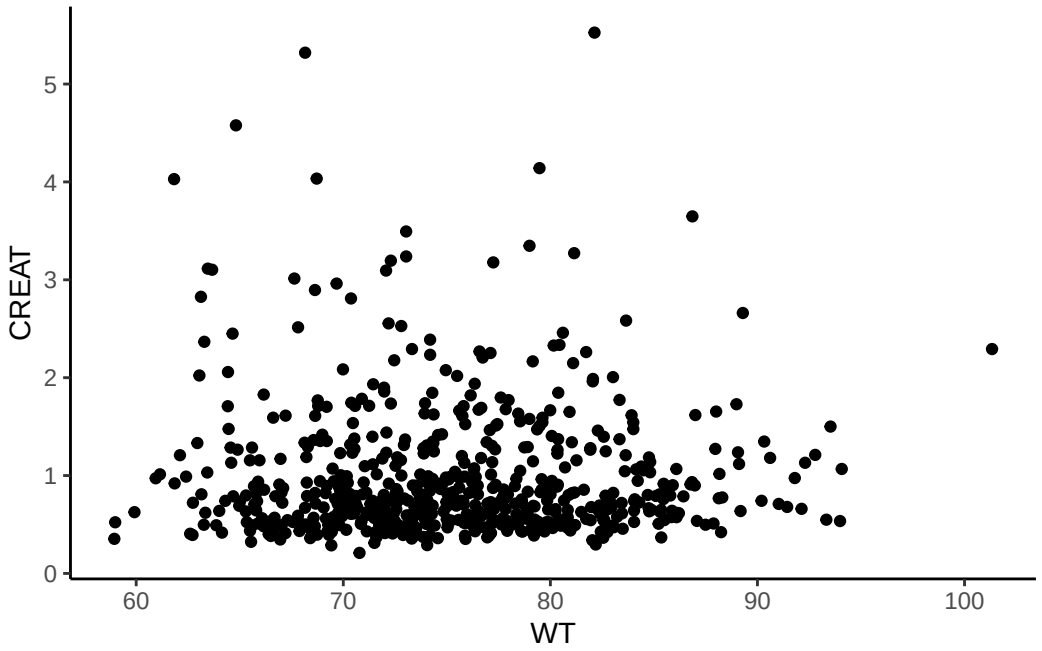
```
ggcorrplot(cor_matrix_Carlier_M, lab = TRUE, title = "Carlier original (males)")
```




```
Carlier_M <- ggcorrplot(cor_sim_M, lab = TRUE, title = "Carlier simulated (males)")
Carlier_M
```




```
plot_codistribution_cov <- function(data,covariate_x,covariate_y){
data |>
  dplyr::select(any_of(c(covariate_x,covariate_y))) |>
  ggplot(aes(x=.data[[covariate_x]],
             y=.data[[covariate_y]]))+
  geom_point()+
  theme_classic()
}

plot_codistribution_cov(sim_cov_carlier,covariate_x = "WT",covariate_y = "CREAT")
```



1.3 Fournier et al. (2018)

1.4 General considerations about the paper

This study includes only 21 patients, thus deriving distributions from the reported covariates values might be difficult

1.4.1 Covariate distribution

All patients are ICU patients with burns who are assumed to be non obese. Creatinine clearance is calculated based on the Cockcroft & Gault equation, whose output is in mL/min, so there is no need to calculate BSA. Thus for all patients ICU = 1, BURN = 1 and OBESE=0.

It is not mentioned in the article if certain patients are on renal replacement therapy, therefore we assume that they are not, and set the minimum value of creatinine clearance to 10 mL/min. CRCL was estimated using the Cockroft and Gault equation.

For AGE, not the median and IQR is given but the mean (50.1) and standard deviation (24.3). As we cannot compare the simulated distribution to the true one, so we suppose that the distribution follows a normal distribution.

The proportion of males in the original article is 0.762.

Neither BMI nor HT or BSA are provided in the article, thus the height is simulated based on the height obtained from the MIMIC clinical dataset (normal distribution with mean of 169 and sd of 10.3).

For WT, AGE and CRCL here are the data from the paper :

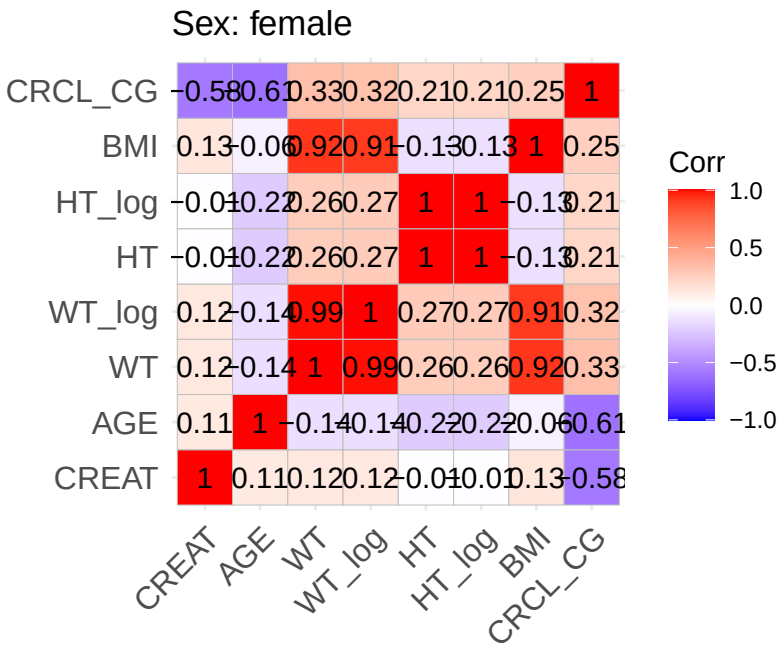
```
cov_data_fournier <- cov_data |>
  filter(Paper == "Fournier_2018")

cov_data_fournier |>
  filter(Covariate %in% c("WT","CRCL","AGE")) |>
  kable()
```

Paper	Covariate	Unit	Median	Q1	Q3	Min	Max
Fournier_2018	WT	kg	72.4	67	83.6	NA	NA
Fournier_2018	CRCL	mL/min	128.0	65	150.0	10	NA
Fournier_2018	AGE	year	50.1	NA	NA	NA	NA

```
cor_matrix_Fournier_F <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Fourni
print(cor_matrix_Fournier_F)
```

```
              CREAT         AGE          WT      WT_log          HT       HT_log
CREAT    1.00000000  0.11092068  0.1240980  0.1236777 -0.01115272 -0.01163038
AGE      0.11092068  1.00000000 -0.1411092 -0.1377268 -0.21810675 -0.21757157
WT       0.12409798 -0.14110923  1.0000000  0.9910295  0.26291857  0.26261857
WT_log   0.12367767 -0.13772678  0.9910295  1.0000000  0.27210890  0.27214801
HT      -0.01115272 -0.21810675  0.2629186  0.2721089  1.00000000  0.99936169
HT_log  -0.01163038 -0.21757157  0.2626186  0.2721480  0.99936169  1.00000000
BMI      0.13219801 -0.06085883  0.9199729  0.9108563 -0.12595561 -0.12641807
CRCL_CG -0.57789581 -0.60548019  0.3271195  0.3230419  0.20870474  0.20811864
                BMI    CRCL_CG
CREAT    0.13219801 -0.5778958
AGE     -0.06085883 -0.6054802
WT       0.91997291  0.3271195
WT_log   0.91085635  0.3230419
HT      -0.12595561  0.2087047
HT_log  -0.12641807  0.2081186
BMI      1.00000000  0.2518084
CRCL_CG  0.25180837  1.0000000
```

```
ggcorrplot(cor_matrix_Fournier_F, lab = TRUE, title = "Sex: female")
```

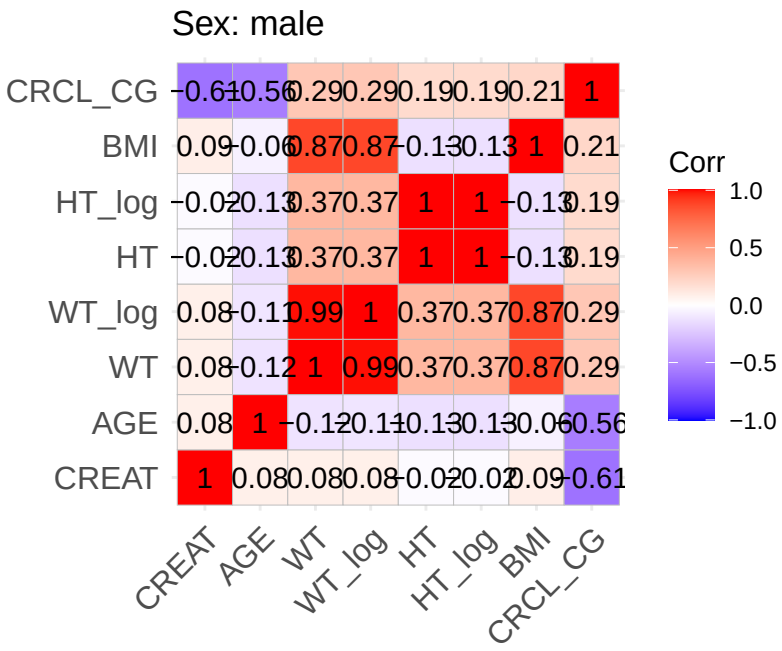



```
cor_matrix_Fournier_M <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Fourni
print(cor_matrix_Fournier_M)
```

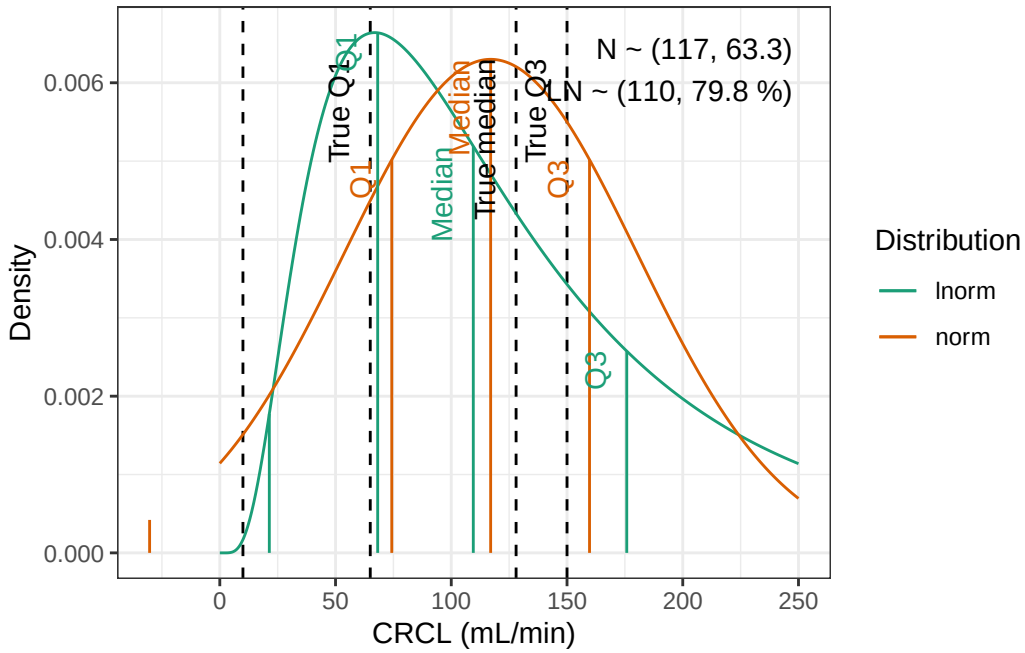
```
               CREAT         AGE          WT      WT_log          HT      HT_log
CREAT     1.00000000  0.08421679  0.07887415  0.07757763 -0.01796103 -0.01782471
AGE       0.08421679  1.00000000 -0.11683417 -0.11039865 -0.13268497 -0.13114182
WT        0.07887415 -0.11683417  1.00000000  0.99316445  0.36730646  0.36578272
WT_log    0.07757763 -0.11039865  0.99316445  1.00000000  0.36989373  0.36884368
HT       -0.01796103 -0.13268497  0.36730646  0.36989373  1.00000000  0.99929302
HT_log   -0.01782471 -0.13114182  0.36578272  0.36884368  0.99929302  1.00000000
BMI       0.09421423 -0.05819520  0.87199105  0.86717872 -0.12604976 -0.12807159
CRCL_CG  -0.60813562 -0.55803721  0.29302773  0.28921272  0.18756329  0.18568377
                BMI     CRCL_CG
CREAT    0.09421423 -0.6081356
AGE     -0.05819520 -0.5580372
WT       0.87199105  0.2930277
WT_log   0.86717872  0.2892127
HT      -0.12604976  0.1875633
HT_log  -0.12807159  0.1856838
BMI      1.00000000  0.2145950
```

```
CRCL_CG  0.21459503  1.0000000
```

```
ggcorrplot(cor_matrix_Fournier_M, lab = TRUE, title = "Sex: male")
```

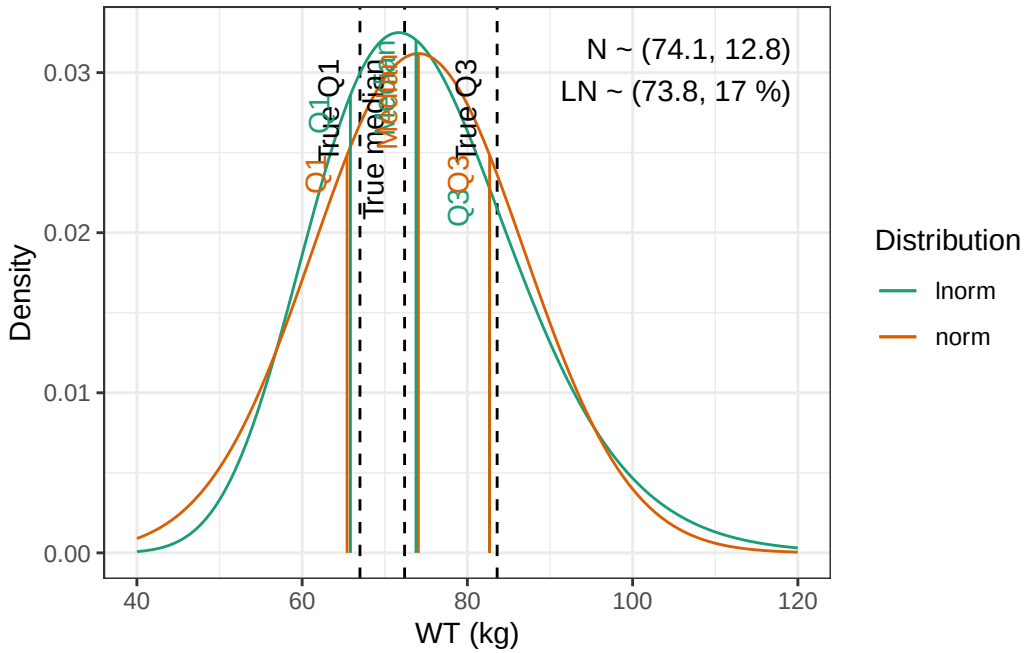



```
fournier_crcl <- fit_cov_wrapper(
  cov_data = cov_data_fournier,
  cov_name = "CRCL",
  min_plot = 0,
  max_plot = 250,
  tol=0.002
)

fournier_crcl$plot
```



Tolerance was increased to 0.002 to have a fit for log-normal. Normal distribution is better suited.

```
fournier_wt <- fit_cov_wrapper(
  cov_data = cov_data_fournier,
  cov_name = "WT",
  min_plot = 40,
  max_plot = 120
)

fournier_wt$plot
```



In this case the log-normal distribution quantiles are closer to the true quantiles than the normal ones. We will take the log-normal ones.

1.4.2 Simulation of covariates

Covariates will be sampled from the following distributions :

- CRCL : Normal distribution with mean 117.016 mL/min and standard deviation 63.3 mL/min
- WT : Lognormal distribution with mean 73.8 kg, and coefficient of variation 17 %
- AGE : Supposed normal distribution with mean of 50.1 years and standard deviation of 24.3

The proportion of males is 0.762 in the original article, so the number of males is 476 and the number of females is 149 to add up to 625.

```
correlated_simulation <- function(n, means, cov_matrix) {
  set.seed(1991)
  collected <- matrix(NA, 0, length(means))
  colnames(collected) <- names(means)

  while (nrow(collected) < n) {
    batch <- MASS::mvrnorm(n = n, mu = means, Sigma = cov_matrix)
```

```
    colnames(batch) <- names(means)

    valid <- batch[, "AGE"] >= 18 &
             batch[, "CRCL_CG"] >= 10

    batch_valid <- batch[valid, , drop = FALSE]
    collected <- rbind(collected, batch_valid)
  }

  collected[1:n, , drop = FALSE]
}

means <- c(
  CRCL_CG = fournier_crcl$norm_par["mean"],
  WT_log      = fournier_wt$lnorm_par["meanlog"],
  AGE     = 50.1,
  HT = 169
)

sds <- c(
  CRCL_CG = fournier_crcl$norm_par["sd"],
  WT_log      = fournier_wt$lnorm_par["sdlog"],
  AGE     = 24.3,
  HT = 10.3
)

covariates <- c("CRCL_CG", "WT_log", "AGE", "HT")

names(means) <- covariates

# Correlation and Covariance Matrix
cor_fournier_M <- cor_matrix_Fournier_M[covariates, covariates]
cov_matrix_M <- diag(sds) %*% cor_fournier_M %*% diag(sds)
eigen(cov_matrix_M)$values
```

```
[1] 4218.3820076  387.0322287  102.1295861    0.0230053
```

```
cor_fournier_F <- cor_matrix_Fournier_F[covariates, covariates]
cov_matrix_F <- diag(sds) %*% cor_fournier_F %*% diag(sds)
eigen(cov_matrix_F)$values
```

```
[1] 4.253434e+03 3.545807e+02 9.952763e+01 2.398513e-02
```

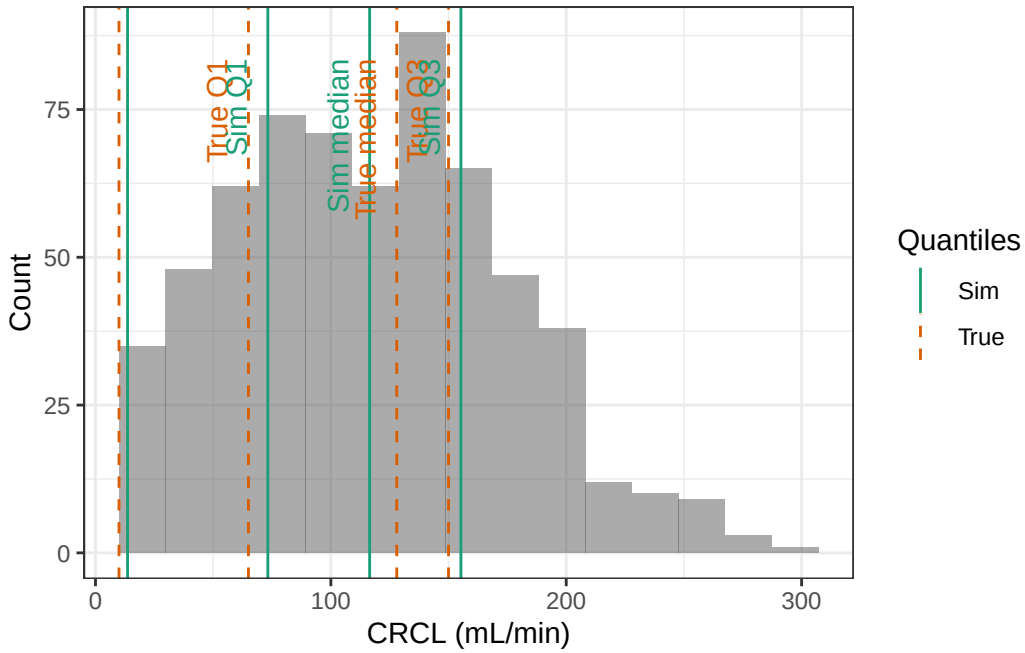
```r
# Simulate
sim_data_M <- correlated_simulation(n = 476, means = means, cov_matrix = cov_matrix_M)
sim_data_M <- as_tibble(sim_data_M) %>%
  mutate(SEX = 0)

sim_data_F <- correlated_simulation(n = 149, means = means, cov_matrix = cov_matrix_F)
sim_data_F <- as_tibble(sim_data_F) %>%
  mutate(SEX = 1)

sim_data <- rbind(sim_data_M, sim_data_F)

# Put the covariates together
sim_cov_fournier <- tibble(
  Paper = "Fournier_2018",
  ID_within_paper = 1:n_patient,
  ICU = 1,
  BURN = 1,
  OBESE = 0,
  CRCL = sim_data$CRCL_CG,
  WT_log   = sim_data$WT_log,
  AGE  = sim_data$AGE,
  HT  = sim_data$HT,
  SEX = sim_data$SEX)

sim_cov_fournier <- sim_cov_fournier %>%
  mutate(WT = exp(WT_log))

summary_sim_cov_fournier <- sim_cov_fournier |>
  pivot_longer(cols = c(ICU,BURN,OBESE,CRCL,WT,AGE),
               names_to = "Covariate") |>
  summarise(.by = c(Covariate,Paper),
            Min = min(value),
            Q1 = quantile(value, 0.25),
            Median = quantile(value, 0.5),
            Q3 = quantile(value, 0.75),
            Max = max(value))

paste0("The proportion of males is ", round(mean(sim_cov_fournier$SEX == 0), 3), " compared t
```

```
[1] "The proportion of males is 0.762 compared to the original 0.762."
```

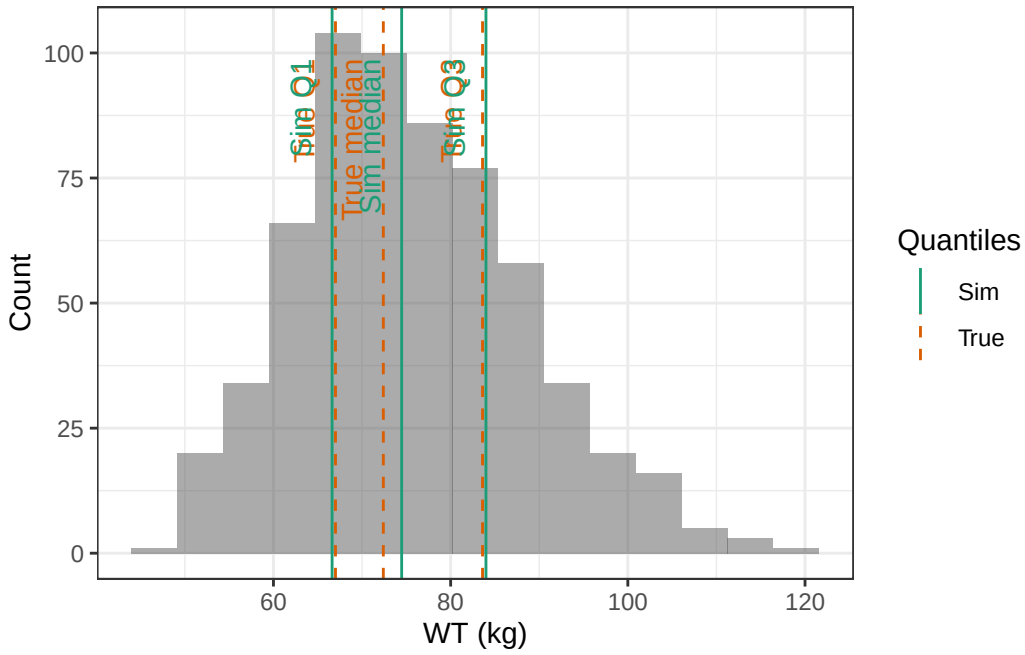
			Min		Q1		M
Paper	Covariate	Unit	Min_sim	Min_true	Q1_sim	Q1_true	Median_sim
Fournier_2018	ICU	Unitless	1.00	1.00	1.00	1.00	1.00
Fournier_2018	BURN	Unitless	1.00	1.00	1.00	1.00	1.00
Fournier_2018	OBESE	Unitless	0.00	0.00	0.00	0.00	0.00
Fournier_2018	CRCL	mL/min	1.01×10^{1}	1.00×10^{1}	7.32×10^{1}	6.50×10^{1}	1.16×10^{2}
Fournier_2018	WT	kg	4.53×10^{1}	NA	6.66×10^{1}	6.70×10^{1}	7.45×10^{1}
Fournier_2018	AGE	year	1.80×10^{1}	NA	3.49×10^{1}	NA	5.03×10^{1}

```
cov_fournier_compare <- summary_sim_cov_fournier |>
  rename_with(~ paste0(.x, "_sim"), -one_of("Covariate", "Paper")) |>
  left_join(rename_with(
    cov_data_fournier,
    ~ paste0(.x, "_true"),
    -one_of("Covariate", "Paper", "Unit")
  )) |>
  relocate(Covariate, .after = Paper) |>
  relocate(Unit, .after = Covariate)

cov_fournier_compare |>
  gt() |>
  fmt_scientific() |>
    tab_spanner(columns = starts_with("Min"),
                label = "Min") |>
      tab_spanner(columns = starts_with("Q1"),
                label = "Q1") |>
      tab_spanner(columns = starts_with("Median"),
                label = "Median") |>
      tab_spanner(columns = starts_with("Q3"),
                label = "Q3") |>
  tab_spanner(columns = starts_with("Max"),
                label = "Max")
```

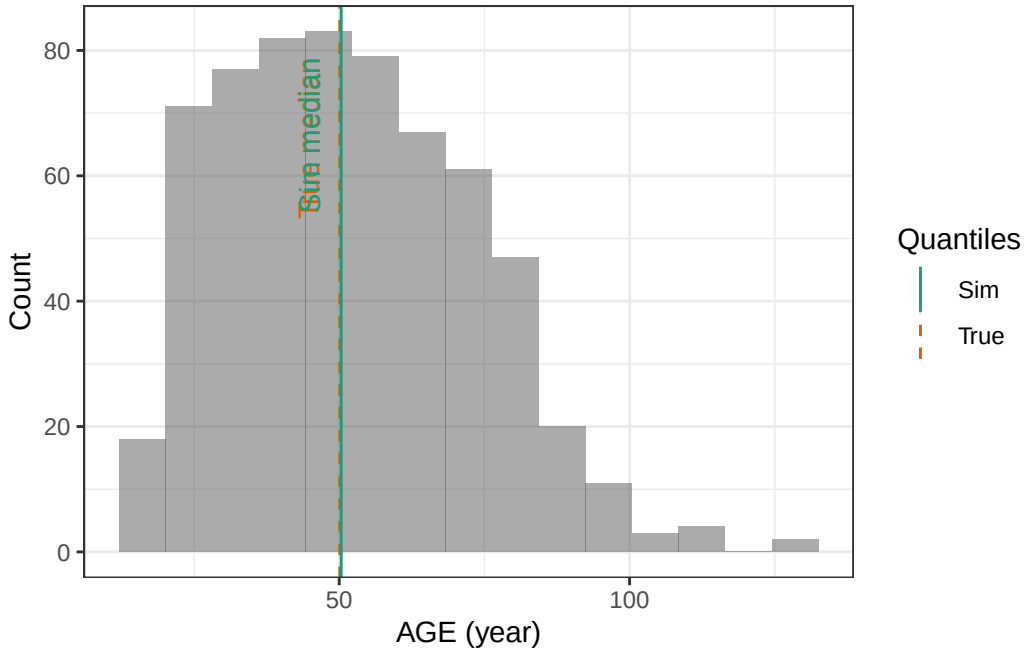
```
plot_sim_cov_wrapper(cov_data_fournier,"CRCL",sim_cov_fournier)
```




```
plot_sim_cov_wrapper(cov_data_fournier,"WT",sim_cov_fournier)
```



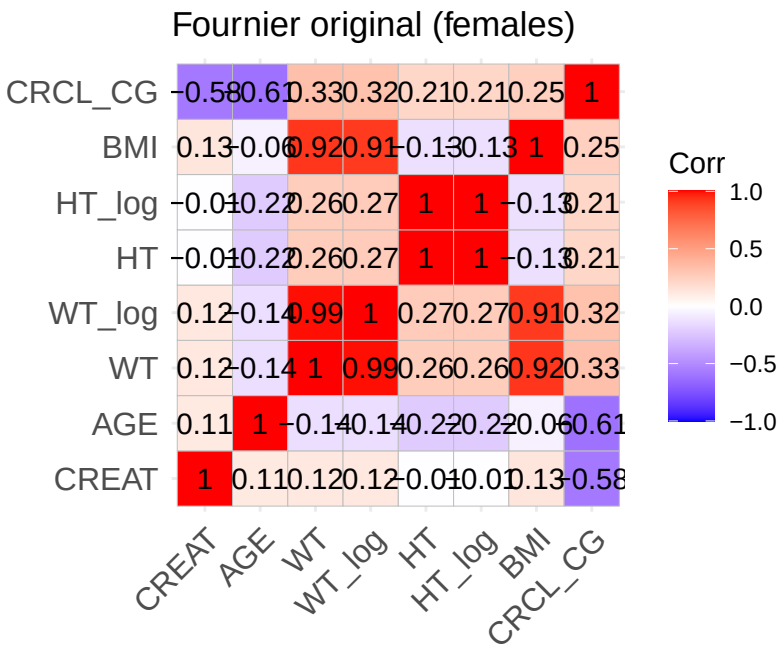
```
plot_sim_cov_wrapper(cov_data_fournier,"AGE",sim_cov_fournier)
```



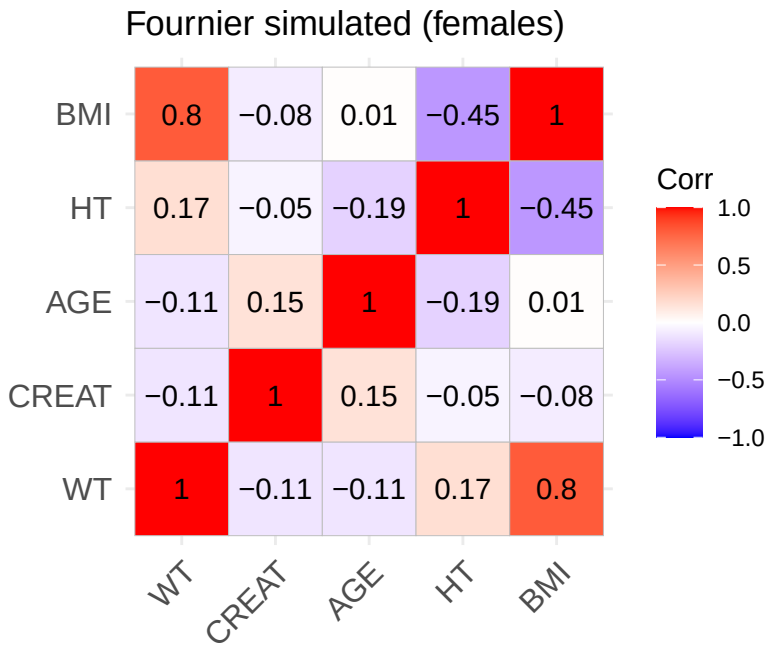
Then, based on the BMI and WT, the height (HT) is calculated to be able to calculate the body surface area (BSA). CRCL is reconverted to serum creatinine (CREAT) based on the Cockroft and Gault equation.

```
reconvert_CG <- function(AGE, CRCL, SEX, WT) {
    # Mutliply by 0.85 for females
    sex_factor <- ifelse(SEX == 0, 1, 0.85)

    # Calculate DFG
    CREAT = ((140 - AGE) * WT * sex_factor) / (CRCL * 72)

  return(CREAT)
}

sim_cov_fournier$CREAT <- mapply(reconvert_CG, sim_cov_fournier$AGE, sim_cov_fournier$CRCL, s
sim_cov_fournier <- sim_cov_fournier %>%
  mutate(
     BSA = (WT^0.425 * (HT^0.725) * 0.007184),
     BMI = WT / (HT/100)^2,
     OBESE = ifelse(BMI > 30, 1, 0)
  ) %>%
```

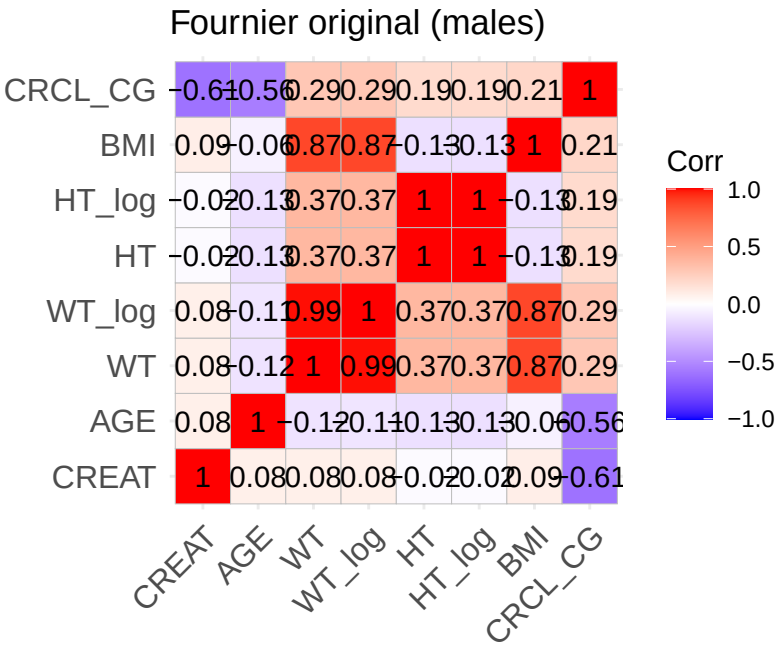
```
  dplyr::select(Paper, ID_within_paper, ICU, BURN, OBESE, CREAT, WT, BSA, BMI, AGE, SEX, HT)
# Calculate the simulated correlation matrices separately for the two sexes to compare with t
sim_cov_fournier_M <- sim_cov_fournier %>% filter(SEX == 0)
sim_cov_fournier_F <- sim_cov_fournier %>% filter(SEX == 1)

cor_sim_M <- cor(sim_cov_fournier_M %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "comple
cor_sim_F <- cor(sim_cov_fournier_F %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "comple

ggcorrplot(cor_matrix_Fournier_F, lab = TRUE, title = "Fournier original (females)")
```



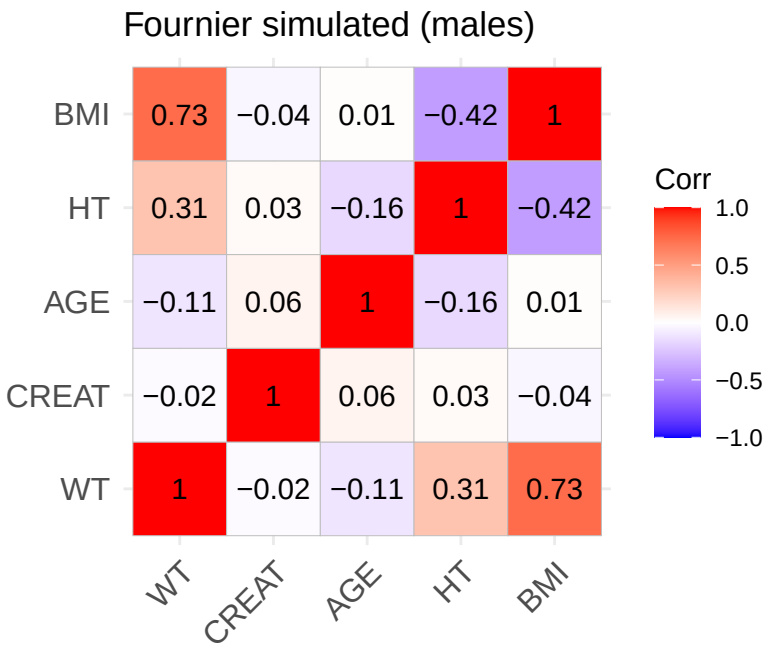

```
Fournier_F <- ggcorrplot(cor_sim_F, lab = TRUE, title = "Fournier simulated (females)")
Fournier_F
```



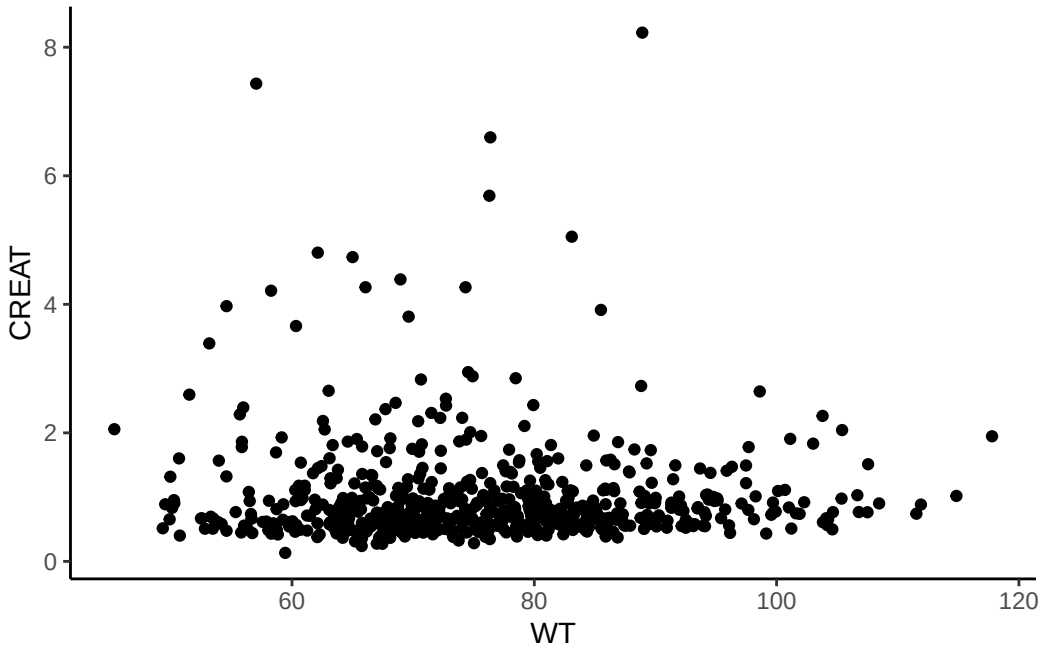

```
ggcorrplot(cor_matrix_Fournier_M, lab = TRUE, title = "Fournier original (males)")
```



```
Fournier_M <- ggcorrplot(cor_sim_M, lab = TRUE, title = "Fournier simulated (males)")
Fournier_M
```




```
plot_codistribution_cov(sim_cov_fournier,covariate_x = "WT",covariate_y = "CREAT")
```



1.5 Mellon et al. (2020)

1.5.1 Covariate distribution

Patients are obese, but otherwise healthy, meaning that they are not in intensive care and not burn victims. They are all obese (BMI > 30 kg/m^2). Creatinine clearance is calculated based on the MDRD equation. Thus for all patients ICU = 0, BURN = 0, OBESE=1.

For WT, BMI and CRCL here are the data from the paper :

```
cov_data_mellon <- cov_data |>
  filter(Paper == "Mellon_2020")

cov_data_mellon |>
  filter(Covariate %in% c("WT","CRCL", "AGE", "BMI", "BMI_log")) |>
  kable()
```

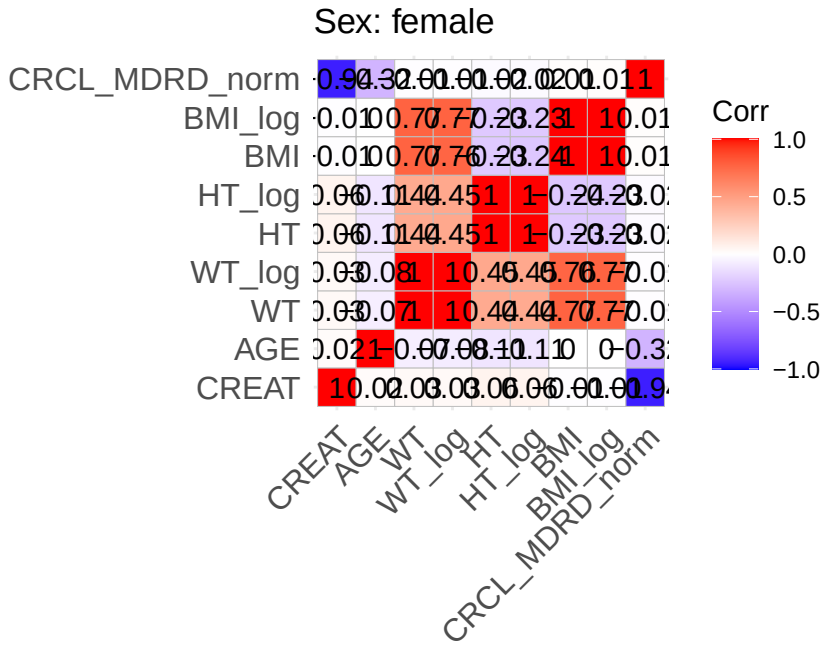
Paper	Covariate	Unit	Median	Q1	Q3	Min	Max
Mellon_2020	WT	kg	109.3	NA	NA	88.00	151.50
Mellon_2020	CRCL	mL/min/1.73m^{2}	94.0	NA	NA	62.00	133.00
Mellon_2020	BMI	kg/m^{2}	40.6	NA	NA	35.20	67.30

Paper	Covariate	Unit	Median	Q1	Q3	Min	Max
Mellon_2020	BMI_log	kg/m^{2}	3.7	NA	NA	3.56	4.21
Mellon_2020	CRCL	ml/min	NA	NA	NA	NA	NA
Mellon_2020	AGE	year	51.7	NA	NA	22.90	62.90

```
cor_matrix_Mellon_F <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Mellon_
print(cor_matrix_Mellon_F)
```

```
                    CREAT          AGE           WT       WT_log           HT
CREAT           1.000000000  0.022643469  0.03125540  0.031968067  0.05795702
AGE             0.022643469  1.000000000 -0.07488881 -0.077065515 -0.11168121
WT              0.031255400 -0.074888809  1.00000000  0.997431167  0.43988528
WT_log          0.031968067 -0.077065515  0.99743117  1.000000000  0.45364368
HT              0.057957020 -0.111681207  0.43988528  0.453643683  1.00000000
HT_log          0.057716460 -0.110775924  0.43501172  0.448949779  0.99935506
BMI            -0.006435320 -0.004011043  0.76869713  0.758978914 -0.23142245
BMI_log        -0.006781559 -0.004085614  0.77244329  0.765197692 -0.22615779
CRCL_MDRD_norm -0.936664533 -0.319596180 -0.00640208 -0.006556334 -0.02317188
                    HT_log          BMI      BMI_log CRCL_MDRD_norm
CREAT           0.05771646 -0.006435320 -0.006781559   -0.936664533
AGE            -0.11077592 -0.004011043 -0.004085614   -0.319596180
WT              0.43501172  0.768697132  0.772443287   -0.006402080
WT_log          0.44894978  0.758978914  0.765197692   -0.006556334
HT              0.99935506 -0.231422452 -0.226157792   -0.023171879
HT_log          1.00000000 -0.237225021 -0.231732528   -0.023241184
BMI            -0.23722502  1.000000000  0.997187131    0.009471973
BMI_log        -0.23173253  0.997187131  1.000000000    0.009607333
CRCL_MDRD_norm -0.02324118  0.009471973  0.009607333    1.000000000
```

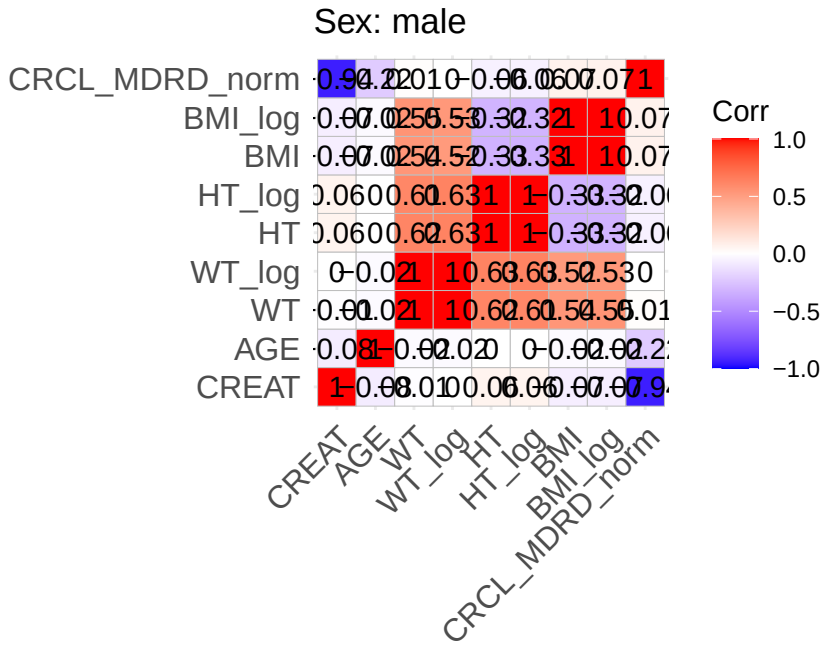
```
ggcorrplot(cor_matrix_Mellon_F, lab = TRUE, title = "Sex: female")
```




```
cor_matrix_Mellon_M <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Mellon_M
print(cor_matrix_Mellon_M)
```

```
                      CREAT          AGE           WT       WT_log           HT
CREAT           1.000000000 -0.079420098 -0.005155970 -0.002021643  0.062039693
AGE            -0.079420098  1.000000000 -0.020403922 -0.018224696 -0.002835067
WT             -0.005155970 -0.020403922  1.000000000  0.997694029  0.617330996
WT_log         -0.002021643 -0.018224696  0.997694029  1.000000000  0.634363996
HT              0.062039693 -0.002835067  0.617330996  0.634363996  1.000000000
HT_log          0.061429587 -0.001756480  0.613093576  0.631018266  0.999227265
BMI            -0.070072797 -0.019345942  0.535836189  0.518641232 -0.328796339
BMI_log        -0.069673338 -0.020297428  0.545596150  0.528796578 -0.319827206
CRCL_MDRD_norm -0.940158336 -0.215895006  0.007018922  0.003387753 -0.059982333
                     HT_log         BMI      BMI_log CRCL_MDRD_norm
CREAT            0.06142959 -0.07007280 -0.06967334   -0.940158336
AGE             -0.00175648 -0.01934594 -0.02029743   -0.215895006
WT               0.61309358  0.53583619  0.54559615    0.007018922
WT_log           0.63101827  0.51864123  0.52879658    0.003387753
HT               0.99922726 -0.32879634 -0.31982721   -0.059982333
HT_log           1.00000000 -0.33401211 -0.32475168   -0.059647213
BMI             -0.33401211  1.00000000  0.99775044    0.069173500
BMI_log         -0.32475168  0.99775044  1.00000000    0.069388818
CRCL_MDRD_norm  -0.05964721  0.06917350  0.06938882    1.000000000
```

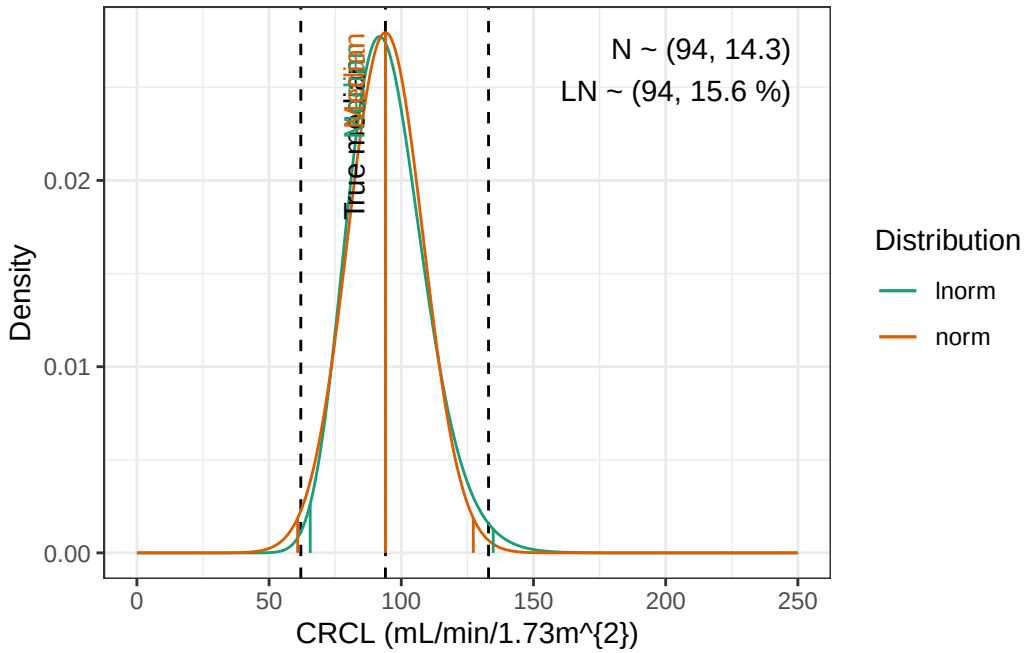
```
ggcorrplot(cor_matrix_Mellon_M, lab = TRUE, title = "Sex: male")
```



Mellon is different from the other papers as CRCL is given as ml/min/1.73m^{2} based on the MDRD equation, and instead of Q1 and Q3, the minimum and maxiumum of the covariates is given (apart from BMI). Another particularity is that due to the particularity of the subjects (obesity), the distribution of body weight is positively (right) skewed. Positively skewed distribution is relatively rare, so it is not easy to find a distribution function to describe it. Beta distribution needs scaling the data between 0 and 1. and 4 parameter stable distribution et gamma distribution have several parameters that need to be defined, and in the absence of the original data, it is not possible to estimate these parameters.

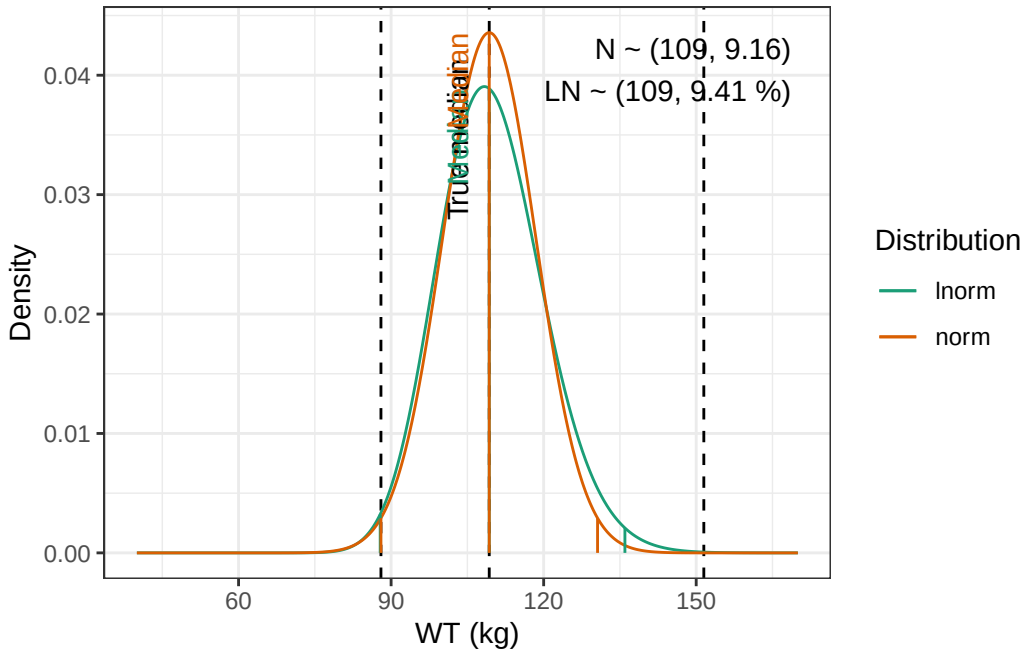
The proportion of males is 0.148.

```
mellon_crcl <- fit_cov_wrapper(
  cov_data = cov_data_mellon,
  cov_name = "CRCL",
  min_plot = 0,
  max_plot = 250
)

mellon_crcl$plot
```



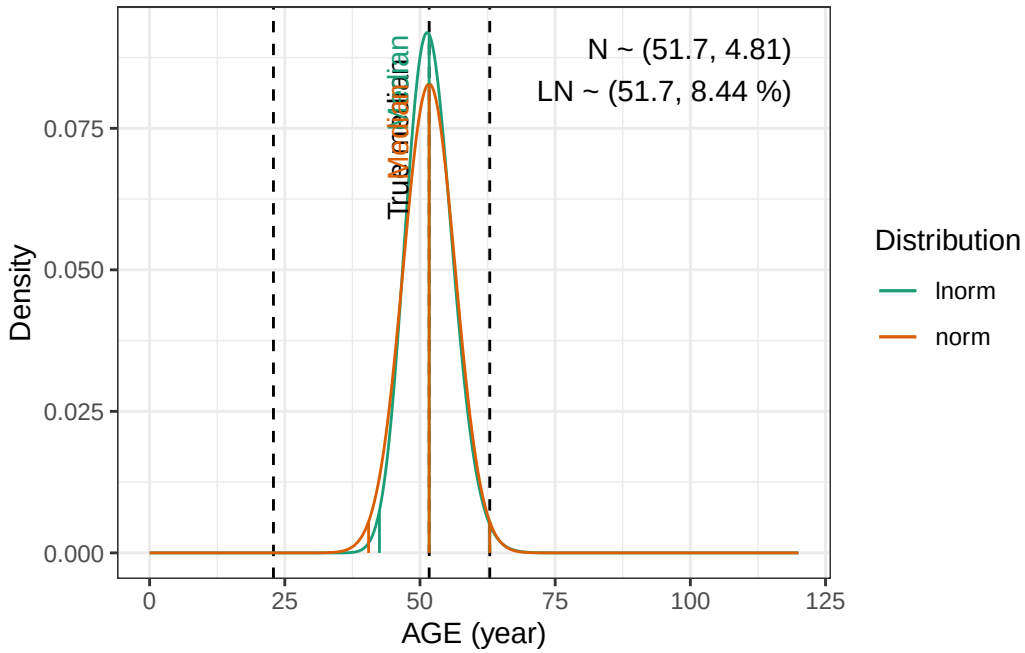
Similar fits; normal distribution is selected.

```
mellon_wt <- fit_cov_wrapper(
  cov_data = cov_data_mellon,
  cov_name = "WT",
  min_plot = 40,
  max_plot = 170
)

mellon_wt$plot
```



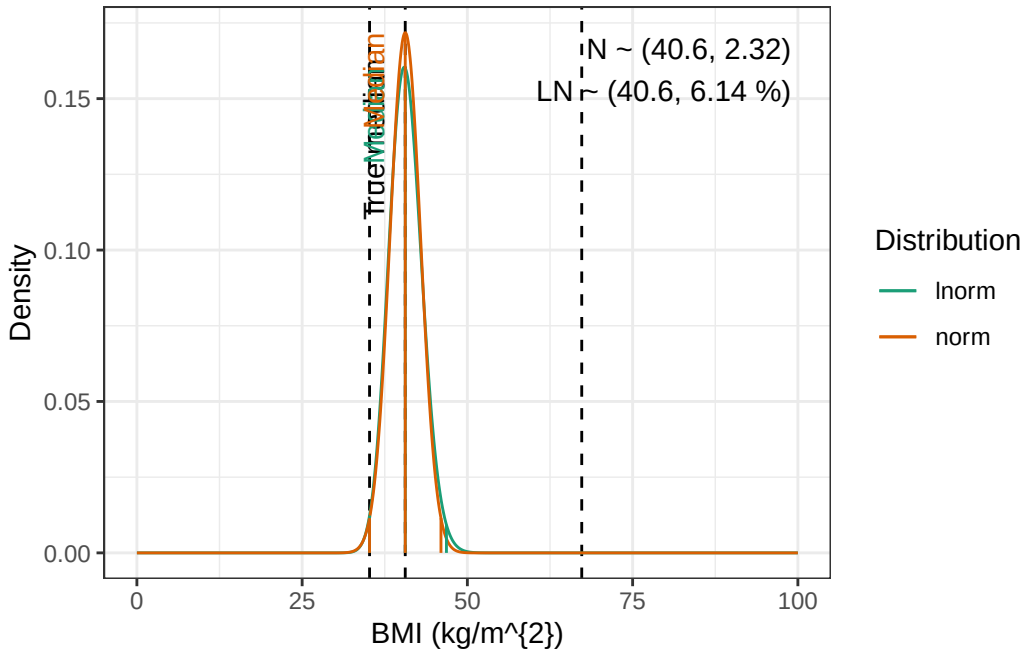
Log-normal distribution fits slightly better than normal.

```
mellon_age <- fit_cov_wrapper(
  cov_data = cov_data_mellon,
  cov_name = "AGE",
  min_plot = 0,
  max_plot = 120
)

mellon_age$plot
```

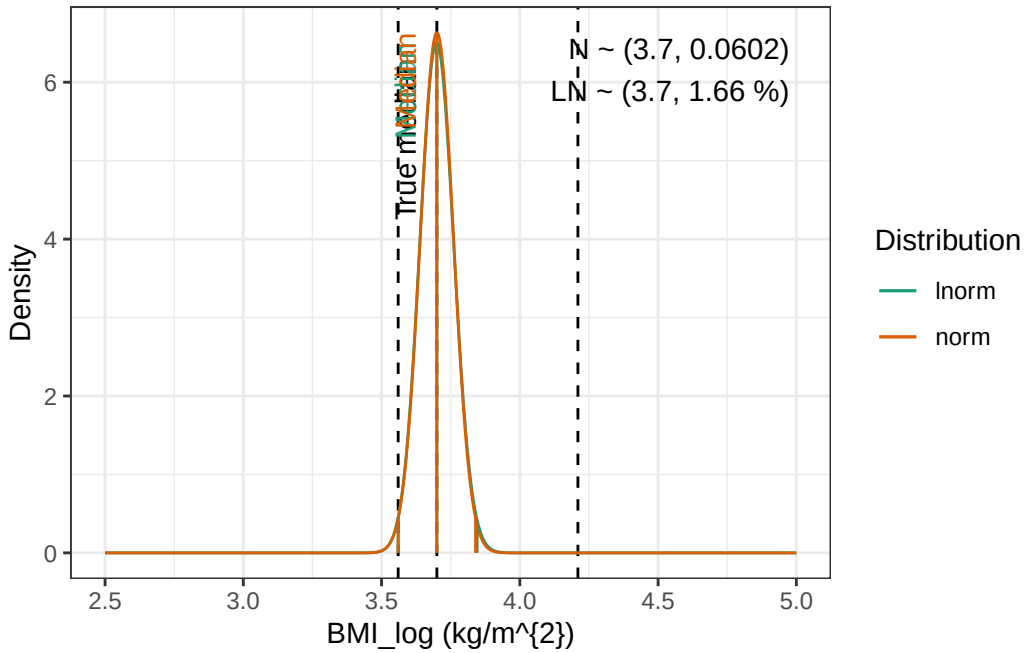


Normal distribution fits a bit better.

```
mellon_bmi <- fit_cov_wrapper(
  cov_data = cov_data_mellon,
  cov_name = "BMI",
  min_plot = 0,
  max_plot = 100,
  tol = 0.001
)

mellon_bmi$plot
```




```
mellon_bmi_log <- fit_cov_wrapper(
  cov_data = cov_data_mellon,
  cov_name = "BMI_log",
  min_plot = 2.5,
  max_plot = 5,
  tol = 0.001
)

mellon_bmi_log$plot
```



Log-normal distribution fits a bit better.

1.5.2 Simulation of covariates

Covariates will be sampled from the following distributions :

- CRCL : Normal distribution from which negative values have been resampled, with mean 94 mL/min and standard deviation 14.3 mL/min
- WT : Log-normal distribution with mean 109 kg, and coefficient of variation 9.41 %
- AGE : Normal distribution with mean 2.84×10^{22} years, and standard deviation 4.81 %
- BMI : Log-normal distribution with mean 40.6 kg/m^2, and coefficient of variation 6.14 %

The proportion of males is 0.148 in the original article, so the number of males is 93 and the number of females is 532 to add up to 625.

```
correlated_simulation <- function(n, means, cov_matrix) {
  set.seed(1991)
  collected <- matrix(NA, 0, length(means))
  colnames(collected) <- names(means)

  while (nrow(collected) < n) {
    batch <- MASS::mvrnorm(n = n, mu = means, Sigma = cov_matrix)
```

```
    colnames(batch) <- names(means)

    valid <- batch[, "AGE"] >= 18 &
             batch[, "CRCL_MDRD_norm"] >= 10 &
             batch[, "BMI_log"] > 3.401197 # log(30)

    batch_valid <- batch[valid, , drop = FALSE]
    collected <- rbind(collected, batch_valid)
  }

  collected[1:n, , drop = FALSE]
}

means <- c(
  CRCL_MDRD_norm = mellon_crcl$norm_par["mean"],
  WT_log      = mellon_wt$lnorm_par["meanlog"],
  AGE     = mellon_age$norm_par["mean"],
  BMI_log     = mellon_bmi$lnorm_par["meanlog"]
)

sds <- c(
  CRCL_MDRD_norm = mellon_crcl$norm_par["sd"],
  WT_log      = mellon_wt$lnorm_par["sdlog"],
  AGE = mellon_age$norm_par["sd"],
  BMI_log     = mellon_bmi$lnorm_par["sdlog"]
)

covariates <- c("CRCL_MDRD_norm", "WT_log", "AGE", "BMI_log")

names(means) <- covariates

# Correlation and Covariance Matrix
cor_mellon_M <- cor_matrix_Mellon_M[covariates, covariates]
cov_matrix_M <- diag(sds) %*% cor_mellon_M %*% diag(sds)
eigen(cov_matrix_M)$values
```

```
[1] 2.050769e+02 2.197051e+01 1.024041e-02 2.320348e-03
```

```
cor_mellon_F <- cor_matrix_Mellon_F[covariates, covariates]
cov_matrix_F <- diag(sds) %*% cor_mellon_F %*% diag(sds)
eigen(cov_matrix_F)$values
```

```
[1] 2.064991e+02 2.054837e+01 1.132511e-02 1.194553e-03
```

```r
# Simulate
sim_data_M <- correlated_simulation(n = 93, means = means, cov_matrix = cov_matrix_M)
sim_data_M <- as_tibble(sim_data_M) %>%
  mutate(SEX = 0)

sim_data_F <- correlated_simulation(n = 532, means = means, cov_matrix = cov_matrix_F)
sim_data_F <- as_tibble(sim_data_F) %>%
  mutate(SEX = 1)

sim_data <- rbind(sim_data_M, sim_data_F)

# Put the covariates together
sim_cov_mellon <- tibble(
  Paper = "Mellon_2020",
  ID_within_paper = 1:n_patient,
  ICU = 0,
  BURN = 0,
  OBESE = 1,
  CRCL = sim_data$CRCL_MDRD_norm,
  WT_log   = sim_data$WT_log,
  AGE  = sim_data$AGE,
  BMI_log  = sim_data$BMI_log,
  SEX = sim_data$SEX)

sim_cov_mellon <- sim_cov_mellon %>%
  mutate(WT = exp(WT_log),
         BMI = exp(BMI_log))

summary_sim_cov_mellon <- sim_cov_mellon |>
  pivot_longer(cols = c(ICU,BURN,OBESE,CRCL,WT,AGE),
               names_to = "Covariate") |>
  summarise(.by = c(Covariate,Paper),
            Min = min(value),
            Q1 = quantile(value, 0.25),
            Median = quantile(value, 0.5),
            Q3 = quantile(value, 0.75),
            Max = max(value))
```

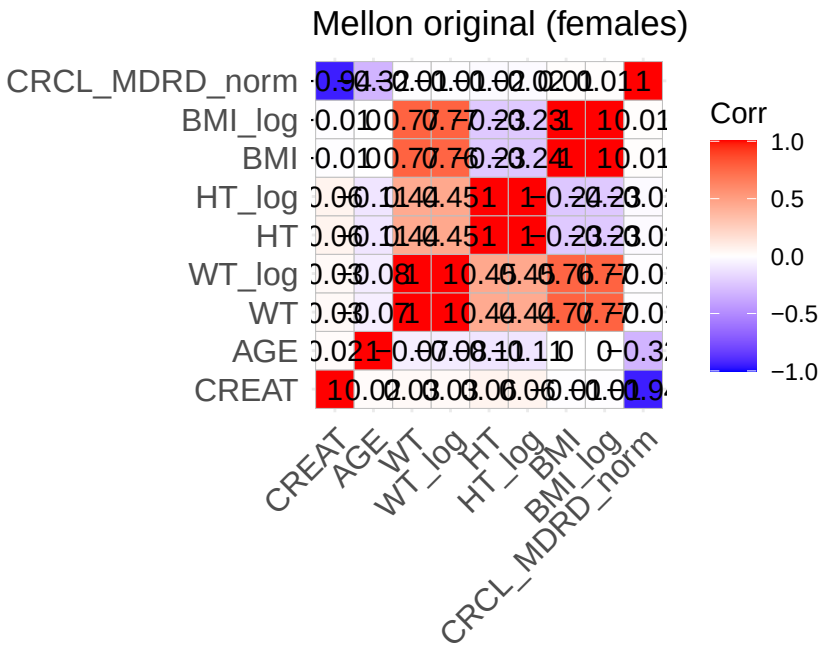
```r
sim_cov_mellon <- sim_cov_mellon %>%
  dplyr::select(Paper, ID_within_paper, ICU, BURN, OBESE, CRCL, WT, AGE, BMI, SEX)
```

			Min		Q1		
Paper	Covariate	Unit	Min_sim	Min_true	Q1_sim	Q1_true	Me
Mellon_2020	ICU	Unitless	0.00	0.00	0.00	0.00	
Mellon_2020	BURN	Unitless	0.00	0.00	0.00	0.00	
Mellon_2020	OBESE	Unitless	1.00	1.00	1.00	1.00	
Mellon_2020	CRCL	mL/min/1.73m^{2}	5.18×10^{1}	6.20×10^{1}	8.24×10^{1}	NA	9.
Mellon_2020	CRCL	ml/min	5.18×10^{1}	NA	8.24×10^{1}	NA	9.
Mellon_2020	WT	kg	8.10×10^{1}	8.80×10^{1}	1.02×10^{2}	NA	1.
Mellon_2020	AGE	year	3.51×10^{1}	2.29×10^{1}	4.87×10^{1}	NA	5.

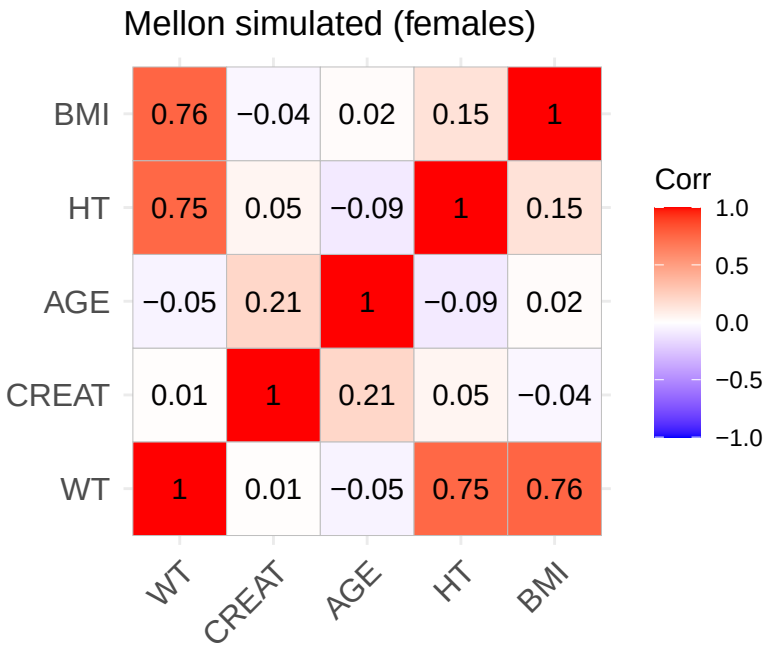
```
cov_mellon_compare <- summary_sim_cov_mellon |>
  rename_with(~ paste0(.x, "_sim"), -one_of("Covariate", "Paper")) |>
  left_join(rename_with(
    cov_data_mellon,
    ~ paste0(.x, "_true"),
    -one_of("Covariate", "Paper", "Unit")
  )) |>
  relocate(Covariate, .after = Paper) |>
  relocate(Unit, .after = Covariate)

cov_mellon_compare |>
  gt() |>
  fmt_scientific() |>
  tab_spanner(columns = starts_with("Min"),
              label = "Min") |>
  tab_spanner(columns = starts_with("Q1"),
              label = "Q1") |>
  tab_spanner(columns = starts_with("Median"),
              label = "Median") |>
  tab_spanner(columns = starts_with("Q3"),
              label = "Q3") |>
  tab_spanner(columns = starts_with("Max"),
              label = "Max")
```

Then, based on the BMI and WT, the height (HT) is calculated to be able to calculate the body surface area (BSA). CRCL is reconverted to serum creatinine (CREAT) based on the MDRD equation.

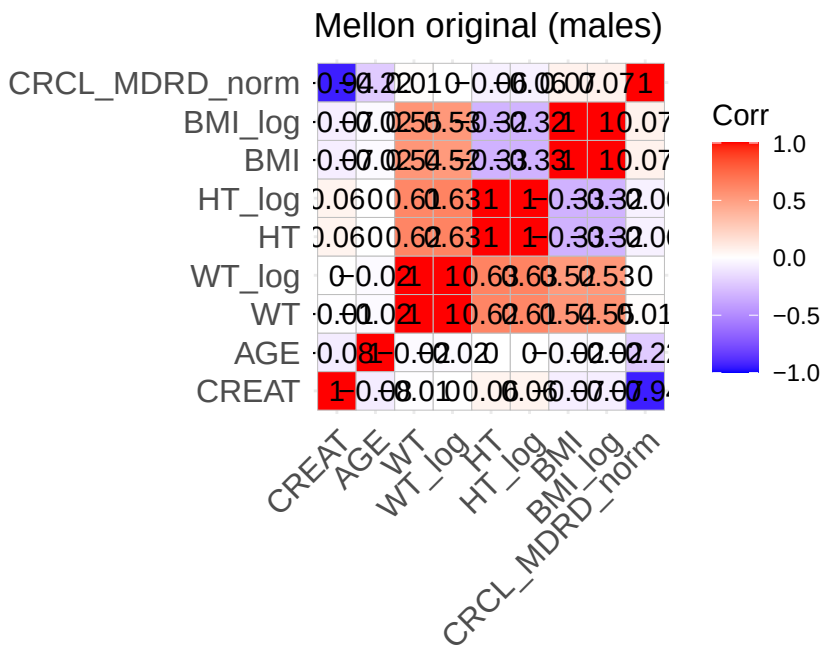
```r
reconvert_MDRD <- function(AGE, CRCL, SEX) {
    # Mutliply by 0.85 for females
    sex_factor <- ifelse(SEX == 0, 1, 0.742)

    # Calculate DFG
   CREAT <- (CRCL / (175 * (AGE^(-0.203)) * sex_factor))^(-1 / 1.154)

  return(CREAT)
}

sim_cov_mellon$CREAT <- mapply(reconvert_MDRD, sim_cov_mellon$AGE, sim_cov_mellon$CRCL, sim_
sim_cov_mellon <- sim_cov_mellon %>%
  mutate(
   HT = sqrt(WT/BMI) * 100, # mutliplied by 100 to convert m to cm
    BSA = (WT^0.425 * (HT^0.725) * 0.007184),
    OBESE = ifelse(BMI > 30, 1, 0)
  ) %>%
  dplyr::select(Paper, ID_within_paper, ICU, BURN, OBESE, CREAT, WT, BSA, BMI, AGE, SEX, HT)

# Calculate the simulated correlation matrices separately for the two sexes to compare with t
sim_cov_mellon_M <- sim_cov_mellon %>% filter(SEX == 0)
sim_cov_mellon_F <- sim_cov_mellon %>% filter(SEX == 1)

cor_sim_M <- cor(sim_cov_mellon_M %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "complete
cor_sim_F <- cor(sim_cov_mellon_F %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "complete

ggcorrplot(cor_matrix_Mellon_F, lab = TRUE, title = "Mellon original (females)")
```



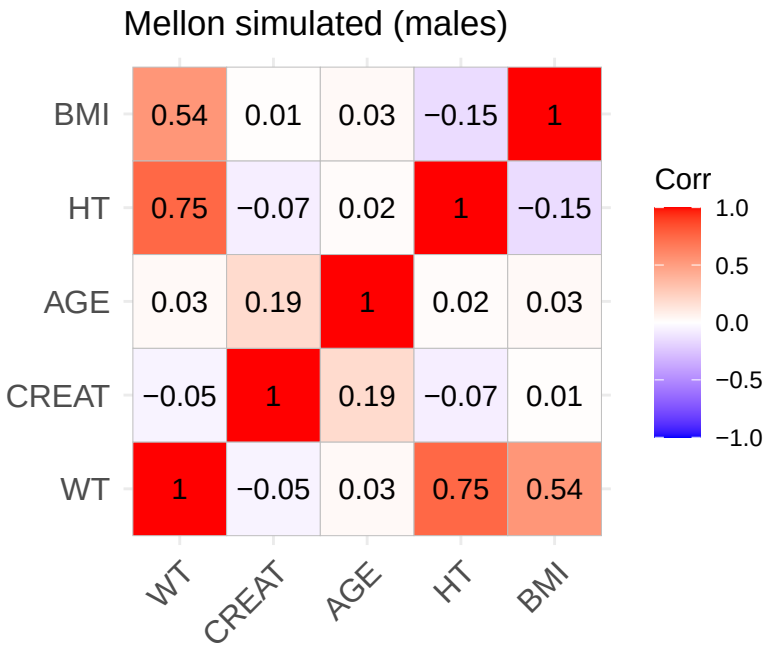

```
Mellon_F <- ggcorrplot(cor_sim_F, lab = TRUE, title = "Mellon simulated (females)")
Mellon_F
```



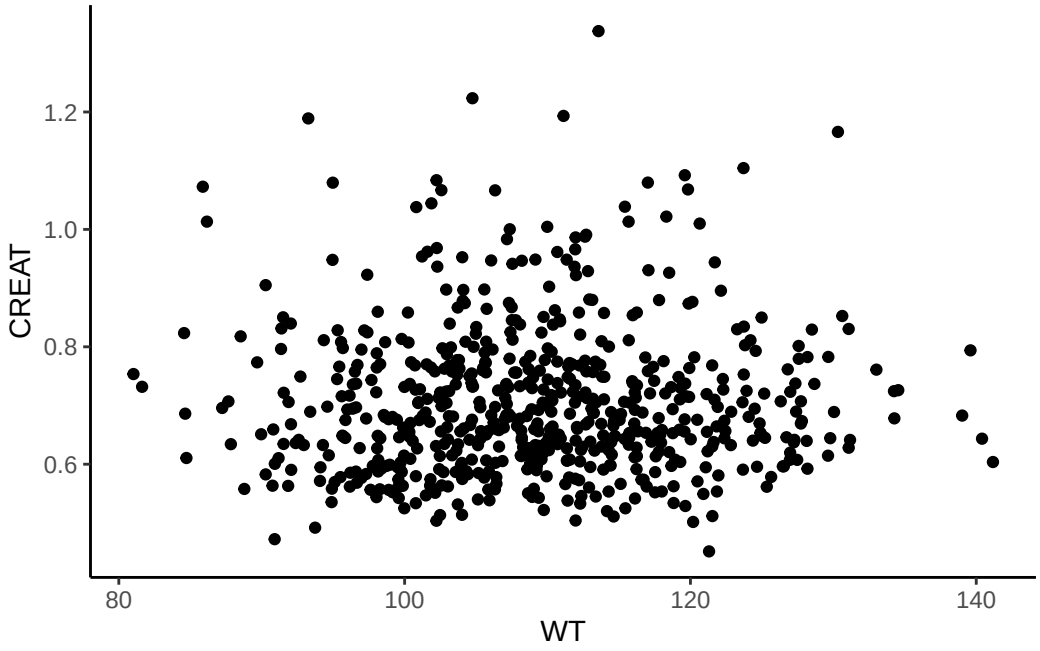
```
ggcorrplot(cor_matrix_Mellon_M, lab = TRUE, title = "Mellon original (males)")
```




```
Mellon_M <- ggcorrplot(cor_sim_M, lab = TRUE, title = "Mellon simulated (males)")
Mellon_M
```




```
plot_codistribution_cov(sim_cov_mellon,covariate_x = "WT",covariate_y = "CREAT")
```



1.6 Rambaud et al. (2020)

1.6.1 Covariate distribution

All patients are ICU patients with endocarditis. They are not considered to be burn victims or obese. Creatinine clearance was calculated using the CKD-EPI equation. Thus for all patients ICU = 1, BURN = 0 and OBESE=0. In this paper, the distribution of serum creatinine is given (in micromol/L), so it can be directly simulated instead of reconverting CRCL. The proportion of males is 0.794.

For WT and CRCL here are the data from the paper :

```
cov_data_rambaud <- cov_data |>
  filter(Paper == "Rambaud_2020")

cov_data_rambaud |>
  filter(Covariate %in% c("WT","CREAT","AGE","HT")) |>
  kable()
```

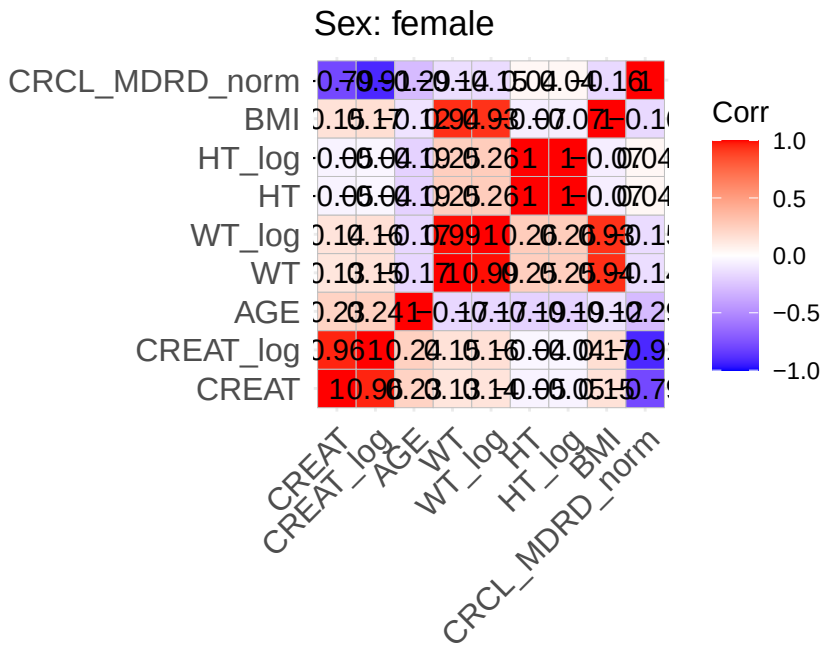
Paper	Covariate	Unit	Median	Q1	Q3	Min	Max
Rambaud_2020	WT	kg	76	69	87.0	NA	NA
Rambaud_2020	HT	cm	170	166	175.0	NA	NA
Rambaud_2020	AGE	year	72	62	80.5	NA	NA
Rambaud_2020	CREAT	micromol/L	87	73	115.5	NA	NA

```
cor_matrix_Rambaud_F <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Rambaud
print(cor_matrix_Rambaud_F)
```

```
                    CREAT   CREAT_log         AGE          WT      WT_log
CREAT           1.00000000  0.96241769  0.2320510  0.1329905  0.1360852
CREAT_log       0.96241769  1.00000000  0.2429180  0.1521950  0.1565402
AGE             0.23205099  0.24291801  1.0000000 -0.1726236 -0.1683232
WT              0.13299046  0.15219495 -0.1726236  1.0000000  0.9894565
WT_log          0.13608520  0.15654017 -0.1683232  0.9894565  1.0000000
HT             -0.04892509 -0.04044581 -0.1889338  0.2517176  0.2592944
HT_log         -0.04916482 -0.04082750 -0.1894298  0.2520660  0.2599500
BMI             0.15464517  0.17128168 -0.1162404  0.9435277  0.9336719
CRCL_MDRD_norm -0.78792478 -0.91391033 -0.2872002 -0.1410118 -0.1466372
                       HT      HT_log         BMI CRCL_MDRD_norm
CREAT          -0.04892509 -0.04916482  0.1546452    -0.78792478
```

```
CREAT_log       -0.04044581 -0.04082750  0.1712817    -0.91391033
AGE             -0.18893375 -0.18942976 -0.1162404    -0.28720016
WT               0.25171756  0.25206601  0.9435277    -0.14101184
WT_log           0.25929441  0.25994996  0.9336719    -0.14663719
HT               1.00000000  0.99970438 -0.0747791     0.04109155
HT_log           0.99970438  1.00000000 -0.0742787     0.04153856
BMI             -0.07477910 -0.07427870  1.0000000    -0.15925725
CRCL_MDRD_norm   0.04109155  0.04153856 -0.1592572     1.00000000
```

```
ggcorrplot(cor_matrix_Rambaud_F, lab = TRUE, title = "Sex: female")
```

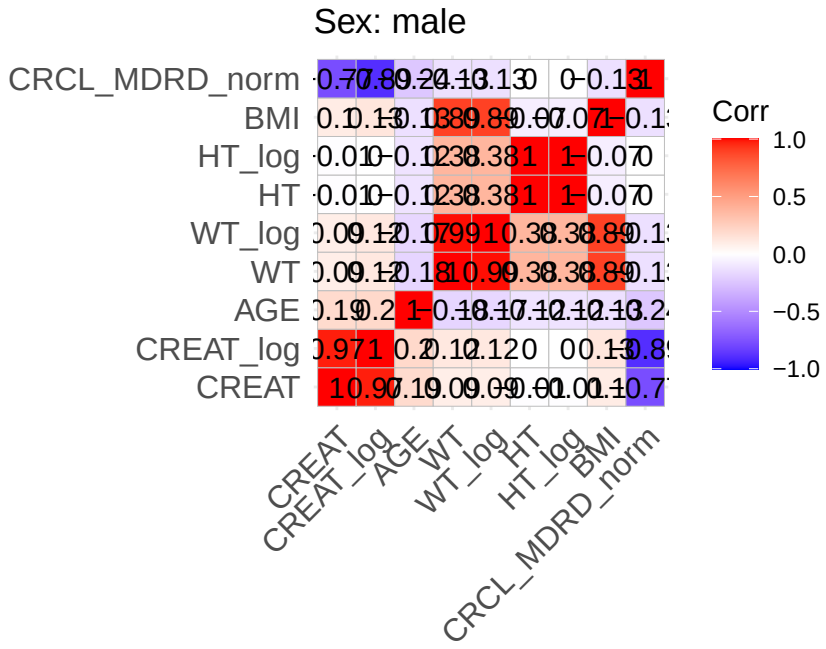



```
cor_matrix_Rambaud_M <- readRDS(here("a_priori/For_publication/Simulations/cor_matrix_Rambaud
print(cor_matrix_Rambaud_M)
```

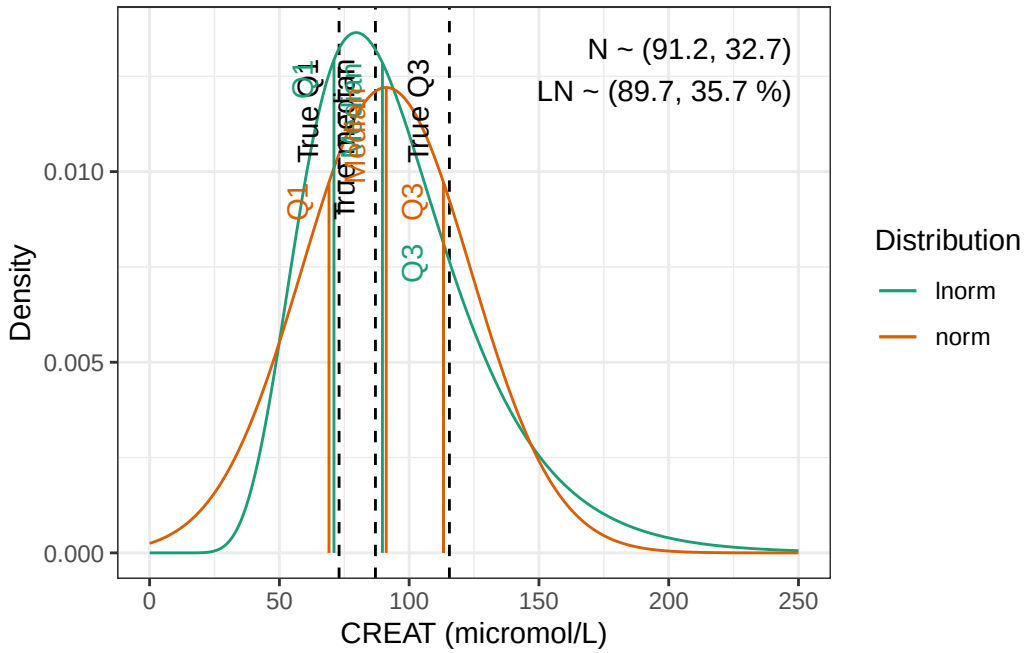
```
                    CREAT     CREAT_log         AGE          WT      WT_log
CREAT           1.000000000  0.9686820232  0.1909639  0.09370644  0.09181062
CREAT_log       0.968682023  1.0000000000  0.1982311  0.12356685  0.12378068
AGE             0.190963871  0.1982311079  1.0000000 -0.18051719 -0.17233815
WT              0.093706437  0.1235668470 -0.1805172  1.00000000  0.99225399
WT_log          0.091810623  0.1237806818 -0.1723382  0.99225399  1.00000000
HT             -0.005710820  0.0007327162 -0.1229902  0.37551772  0.37978066
HT_log         -0.005537361  0.0010029509 -0.1228308  0.37500256  0.37967684
```

```
BMI             0.103837382  0.1331126943 -0.1347419  0.89436959  0.88815355
CRCL_MDRD_norm -0.769174641 -0.8857730397 -0.2449519 -0.12508733 -0.12881176
                         HT       HT_log          BMI CRCL_MDRD_norm
CREAT          -0.0057108200 -0.005537361  0.10383738   -0.769174641
CREAT_log       0.0007327162  0.001002951  0.13311269   -0.885773040
AGE            -0.1229902101 -0.122830828 -0.13474194   -0.244951935
WT              0.3755177211  0.375002564  0.89436959   -0.125087326
WT_log          0.3797806561  0.379676845  0.88815355   -0.128811758
HT              1.0000000000  0.999598212 -0.07118055   -0.003915605
HT_log          0.9995982117  1.000000000 -0.07162513   -0.004244813
BMI            -0.0711805452 -0.071625134  1.00000000   -0.133475436
CRCL_MDRD_norm -0.0039156049 -0.004244813 -0.13347544    1.000000000
```

```
ggcorrplot(cor_matrix_Rambaud_M, lab = TRUE, title = "Sex: male")
```

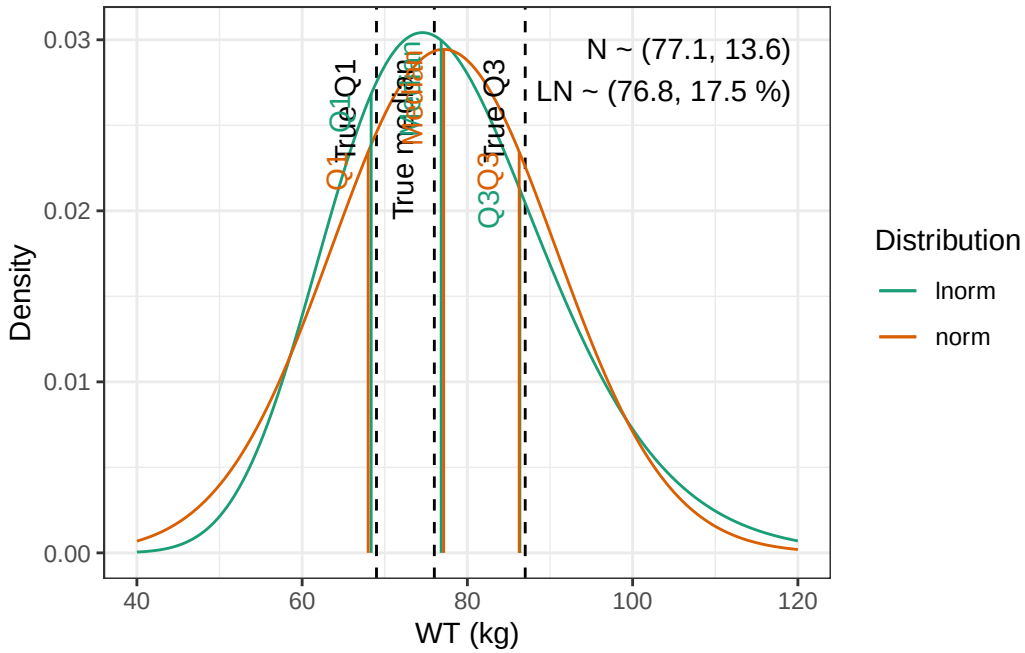



```
rambaud_creat <- fit_cov_wrapper(
  cov_data = cov_data_rambaud,
  cov_name = "CREAT",
  min_plot = 0,
  max_plot = 250
)

rambaud_creat$plot
```



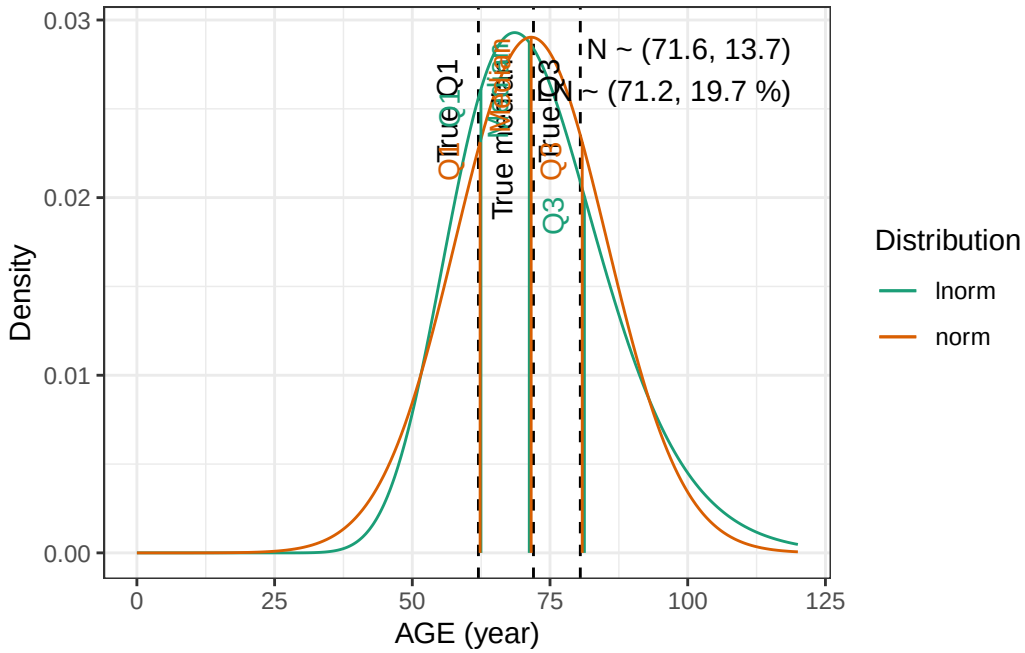
Log-normal distribution fits the best the data, so it is selected.

```
rambaud_wt <- fit_cov_wrapper(
  cov_data = cov_data_rambaud,
  cov_name = "WT",
  min_plot = 40,
  max_plot = 120
)

rambaud_wt$plot
```



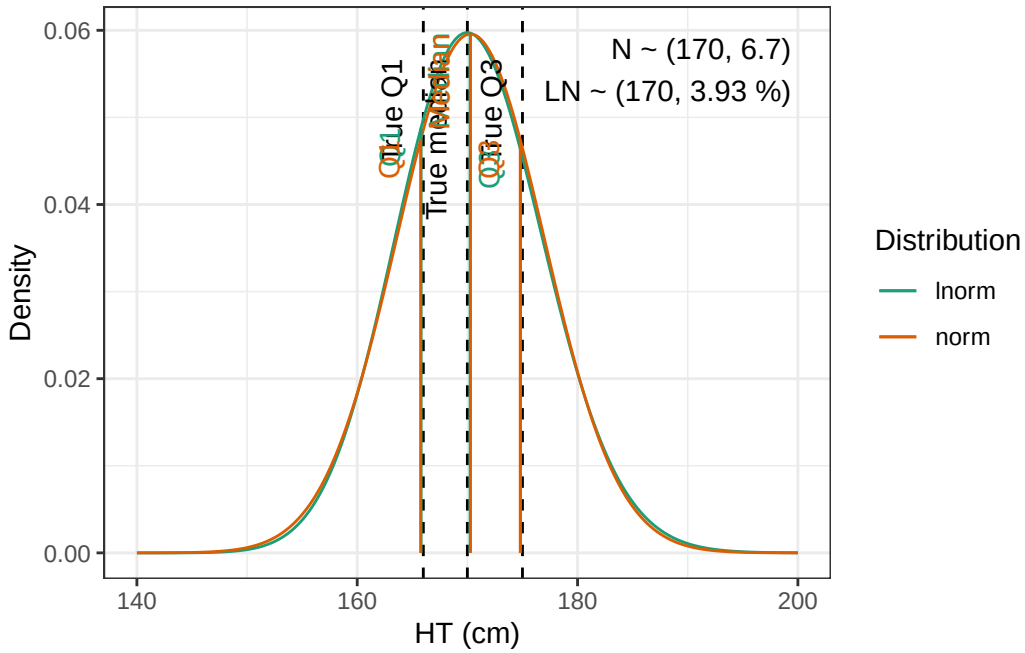
No discernable difference between the two fits. The log-normal distribution is selected.

```
rambaud_age <- fit_cov_wrapper(
  cov_data = cov_data_rambaud,
  cov_name = "AGE",
  min_plot = 0,
  max_plot = 120
)

rambaud_age$plot
```



No discernable difference, so normal distribution is selected, as age usually follows a normal distribution.

```
rambaud_ht <- fit_cov_wrapper(
  cov_data = cov_data_rambaud,
  cov_name = "HT",
  min_plot = 140,
  max_plot = 200
)

rambaud_ht$plot
```



No discernable difference. Log-normal distribution is selected.

1.6.2 Simulation of covariates

Covariates will be sampled from the following distributions :

- CREAT : Log-normal distribution with a minimum 10 micromol/L with mean 89.7 micromol/L and standard deviation 0.346 micromol/L
- WT : Normal distribution with resampling of negative values with mean 76.8 kg, and standard deviation 17.3 %
- AGE : Normal distribution with resampling of negative values with mean 1.22×10^{31} years, and coefficient of variation 1370 %
- HT : Normal distribution with resampling of negative values with mean 170 cm, and standard deviation 3.93 %

The proportion of males is 0.794 in the original article, so the number of males is 496 and the number of females is 129 to add up to 625.

```
correlated_simulation <- function(n, means, cov_matrix) {
  set.seed(1991)
  collected <- matrix(NA, 0, length(means))
  colnames(collected) <- names(means)
```

```
  while (nrow(collected) < n) {
    batch <- MASS::mvrnorm(n = n, mu = means, Sigma = cov_matrix)
    colnames(batch) <- names(means)

    valid <- batch[, "AGE"] >= 18 &
             batch[, "CREAT_log"] < 5.991465 # log(400) corresponding to CRCL of 10 mL/min f

    batch_valid <- batch[valid, , drop = FALSE]
    collected <- rbind(collected, batch_valid)
  }

  collected[1:n, , drop = FALSE]
}

means <- c(
  CREAT_log = rambaud_creat$lnorm_par["meanlog"],
  WT_log      = rambaud_wt$lnorm_par["meanlog"],
  AGE     = rambaud_age$norm_par["mean"],
  HT_log      = rambaud_ht$lnorm_par["meanlog"]
)

sds <- c(
  CREAT_log = rambaud_creat$lnorm_par["sdlog"],
  WT_log     = rambaud_wt$lnorm_par["sdlog"],
  AGE = rambaud_age$norm_par["sd"],
  HT_log     = rambaud_ht$lnorm_par["sdlog"]
)

covariates <- c("CREAT_log", "WT_log", "AGE", "HT_log")

names(means) <- covariates

# Correlation and Covariance Matrix
cor_rambaud_M <- cor_matrix_Rambaud_M[covariates, covariates]
cov_matrix_M <- diag(sds) %*% cor_rambaud_M %*% diag(sds)
eigen(cov_matrix_M)$values
```

```
[1] 1.888441e+02 1.160604e-01 2.831560e-02 1.302147e-03
```

```
cor_rambaud_F <- cor_matrix_Rambaud_F[covariates, covariates]
cov_matrix_F <- diag(sds) %*% cor_rambaud_F %*% diag(sds)
eigen(cov_matrix_F)$values
```

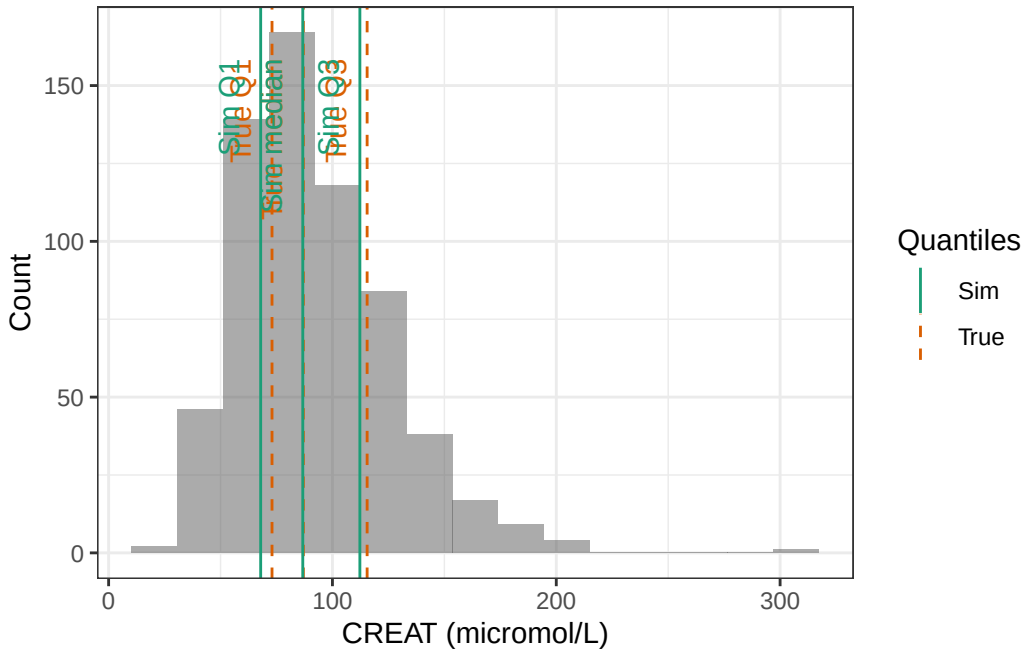
```
[1] 1.888465e+02 1.143105e-01 2.761902e-02 1.396003e-03
```

```
# Simulate
sim_data_M <- correlated_simulation(n = 496, means = means, cov_matrix = cov_matrix_M)
sim_data_M <- as_tibble(sim_data_M) %>%
  mutate(SEX = 0)

sim_data_F <- correlated_simulation(n = 129, means = means, cov_matrix = cov_matrix_F)
sim_data_F <- as_tibble(sim_data_F) %>%
  mutate(SEX = 1)

sim_data <- rbind(sim_data_M, sim_data_F)

# Put the covariates together
sim_cov_rambaud <- tibble(
  Paper = "Rambaud_2020",
  ID_within_paper = 1:n_patient,
  ICU = 1,
  BURN = 0,
  OBESE = 0,
  CREAT_log = sim_data$CREAT_log,
  WT_log   = sim_data$WT_log,
  AGE  = sim_data$AGE,
  HT_log  = sim_data$HT_log,
  SEX = sim_data$SEX)

sim_cov_rambaud <- sim_cov_rambaud %>%
  mutate(CREAT = exp(CREAT_log),
         HT = exp(HT_log),
         WT = exp(WT_log))

summary_sim_cov_rambaud <- sim_cov_rambaud |>
  pivot_longer(cols = c(ICU,BURN,OBESE,CREAT,WT,AGE,HT),
               names_to = "Covariate") |>
  summarise(.by = c(Covariate,Paper),
            Min = min(value),
            Q1 = quantile(value, 0.25),
            Median = quantile(value, 0.5),
            Q3 = quantile(value, 0.75),
            Max = max(value))
```

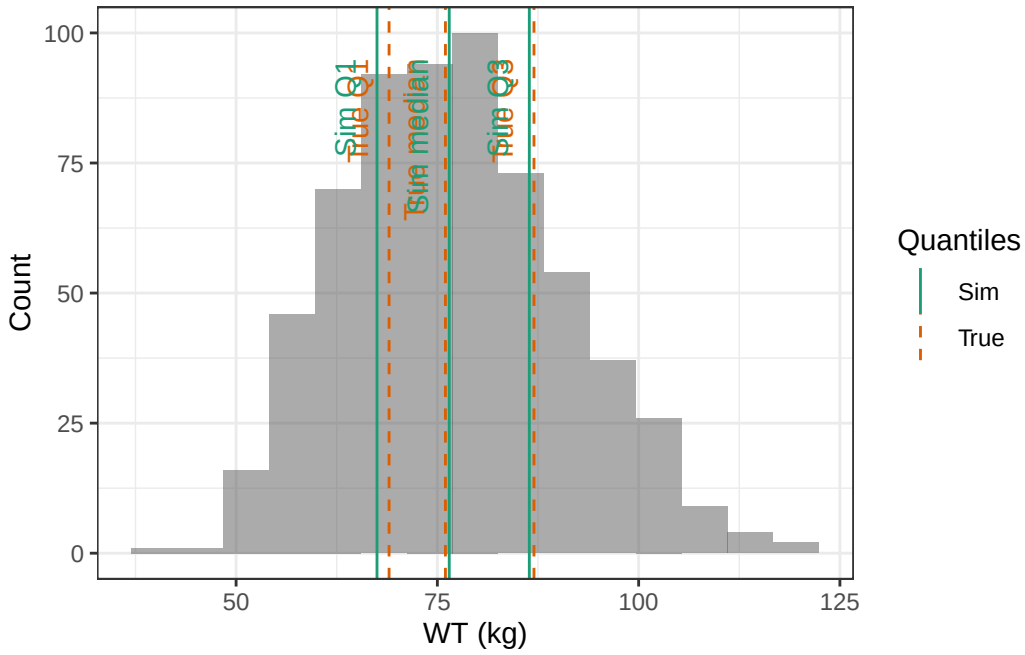
			Min		Q1		
Paper	Covariate	Unit	Min_sim	Min_true	Q1_sim	Q1_true	Median_
Rambaud_2020	ICU	Unitless	1.00	1.00	1.00	1.00	
Rambaud_2020	BURN	Unitless	0.00	0.00	0.00	0.00	
Rambaud_2020	OBESE	Unitless	0.00	0.00	0.00	0.00	
Rambaud_2020	CREAT	micromol/L	2.08×10^{1}	NA	6.79×10^{1}	7.30×10^{1}	$8.67 \times$
Rambaud_2020	WT	kg	4.13×10^{1}	NA	6.75×10^{1}	6.90×10^{1}	$7.65 \times$
Rambaud_2020	AGE	year	1.97×10^{1}	NA	6.04×10^{1}	6.20×10^{1}	$7.08 \times$
Rambaud_2020	HT	cm	1.50×10^{2}	NA	1.64×10^{2}	1.66×10^{2}	$1.69 \times$

```
cov_rambaud_compare <- summary_sim_cov_rambaud |>
  rename_with(~ paste0(.x, "_sim"), -one_of("Covariate", "Paper")) |>
  left_join(rename_with(
    cov_data_rambaud,
    ~ paste0(.x, "_true"),
    -one_of("Covariate", "Paper", "Unit")
  )) |>
  relocate(Covariate, .after = Paper) |>
  relocate(Unit, .after = Covariate)

cov_rambaud_compare |>
  gt() |>
  fmt_scientific() |>
    tab_spanner(columns = starts_with("Min"),
                label = "Min") |>
      tab_spanner(columns = starts_with("Q1"),
                label = "Q1") |>
      tab_spanner(columns = starts_with("Median"),
                label = "Median") |>
      tab_spanner(columns = starts_with("Q3"),
                label = "Q3") |>
  tab_spanner(columns = starts_with("Max"),
                label = "Max")
```

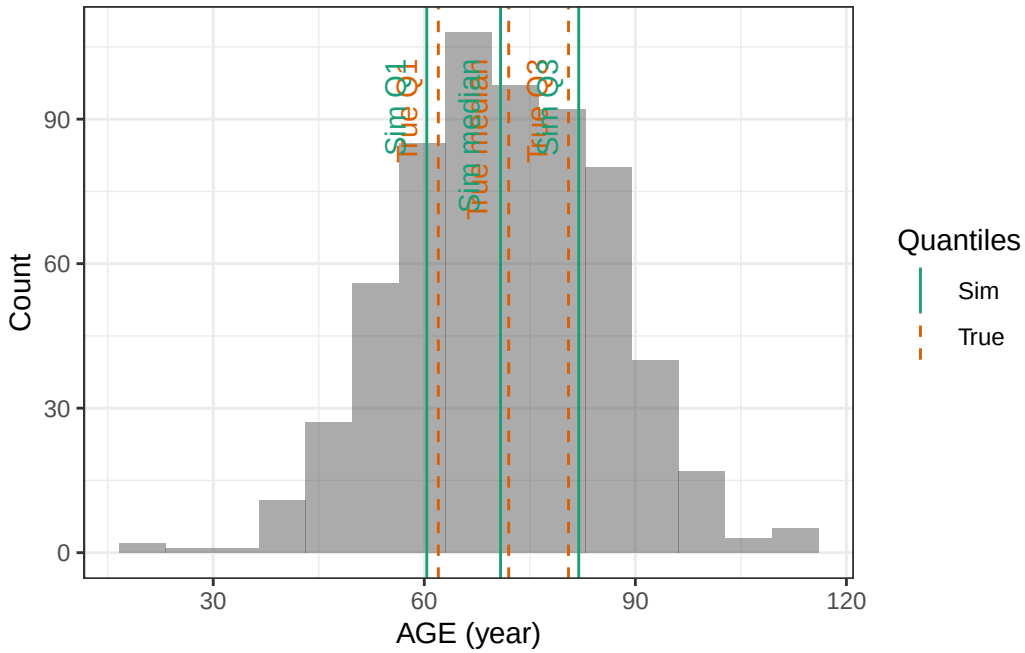
```
plot_sim_cov_wrapper(cov_data_rambaud,"CREAT",sim_cov_rambaud)
```



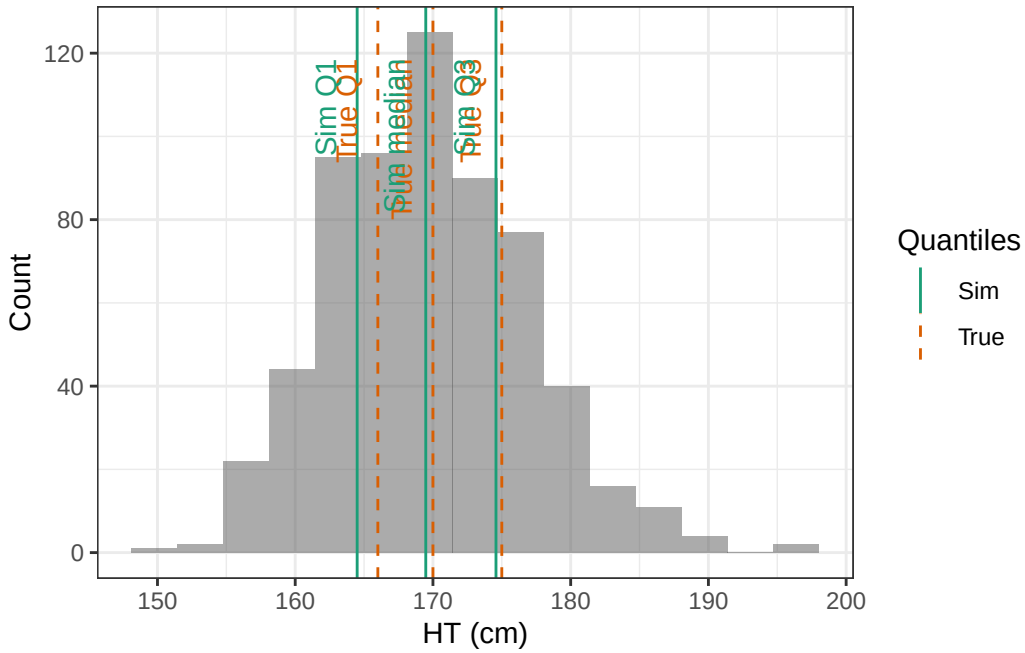

```
plot_sim_cov_wrapper(cov_data_rambaud,"WT",sim_cov_rambaud)
```



```
plot_sim_cov_wrapper(cov_data_rambaud,"AGE",sim_cov_rambaud)
```

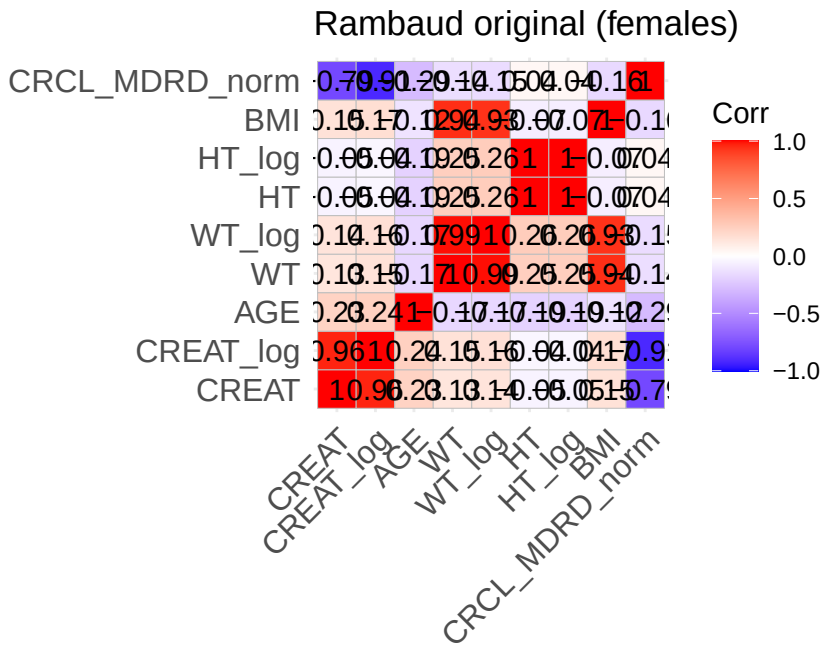



```
plot_sim_cov_wrapper(cov_data_rambaud,"HT",sim_cov_rambaud)
```

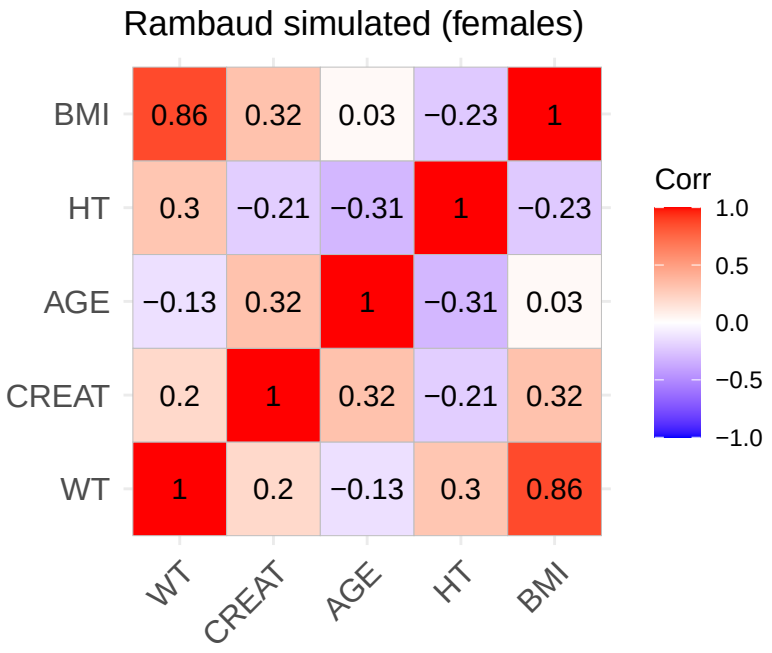


CREAT is converted from micromol/L to mg/dL.

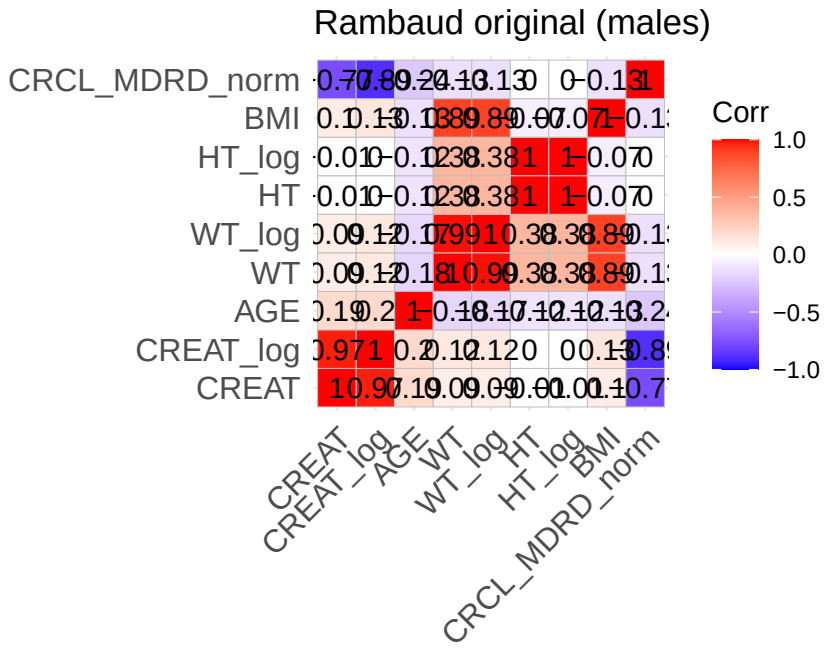
```
sim_cov_rambaud <- sim_cov_rambaud %>%
  mutate(
    BSA = (WT^0.425 * (HT^0.725) * 0.007184),
    CREAT = CREAT/88.4,
    BMI = WT / (HT/100)^2,
    OBESE = ifelse(BMI > 30, 1, 0)
  ) %>%
  dplyr::select(Paper, ID_within_paper, ICU, BURN, OBESE, CREAT, WT, BSA, BMI, AGE, SEX, HT)

# Calculate the simulated correlation matrices separately for the two sexes to compare with t
sim_cov_rambaud_M <- sim_cov_rambaud %>% filter(SEX == 0)
sim_cov_rambaud_F <- sim_cov_rambaud %>% filter(SEX == 1)

cor_sim_M <- cor(sim_cov_rambaud_M %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "complet
cor_sim_F <- cor(sim_cov_rambaud_F %>% dplyr::select(WT, CREAT, AGE, HT, BMI), use = "complet

ggcorrplot(cor_matrix_Rambaud_F, lab = TRUE, title = "Rambaud original (females)")
```



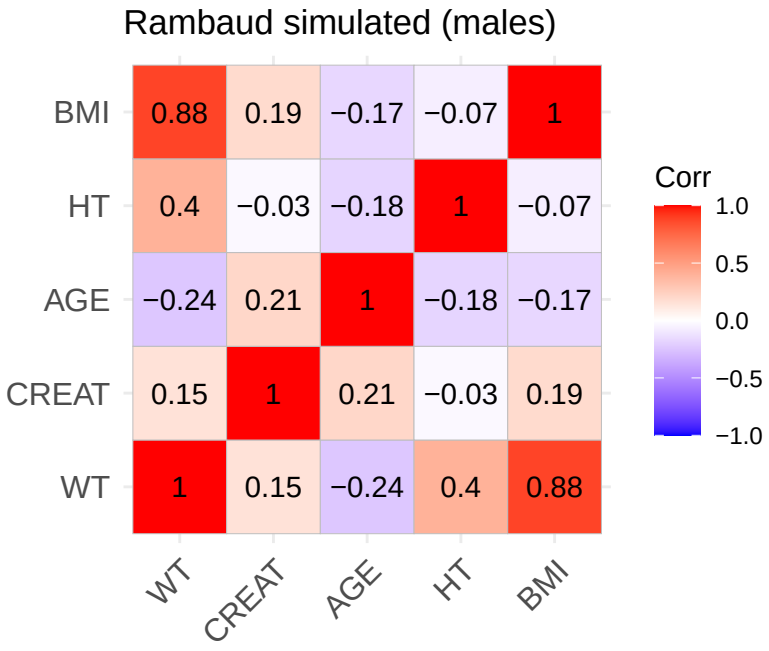

```
Rambaud_F <- ggcorrplot(cor_sim_F, lab = TRUE, title = "Rambaud simulated (females)")
Rambaud_F
```




```
ggcorrplot(cor_matrix_Rambaud_M, lab = TRUE, title = "Rambaud original (males)")
```



```
Rambaud_M <- ggcorrplot(cor_sim_M, lab = TRUE, title = "Rambaud simulated (males)")
Rambaud_M
```



1.7 Final covariate table

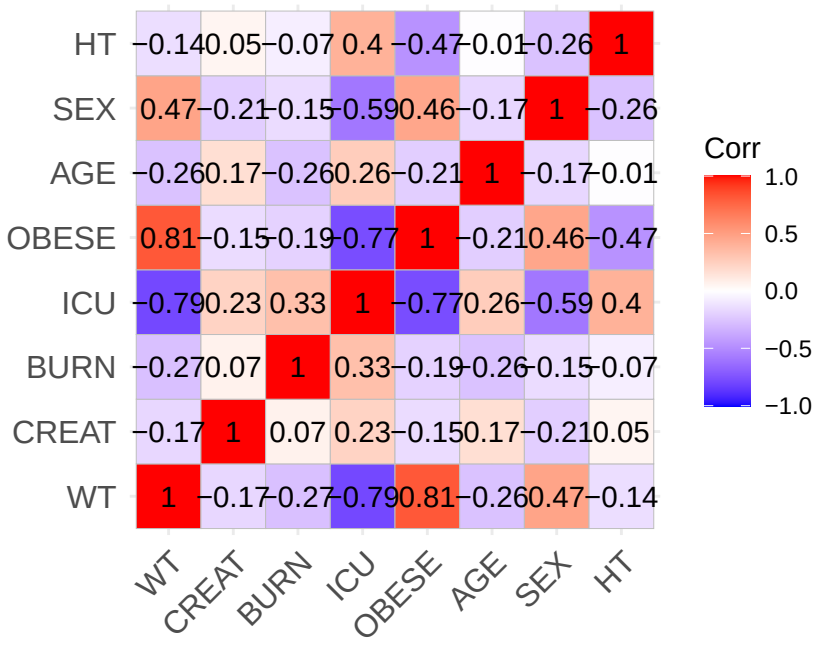
Make the final covariate dataset with 2500 sets of covariates in a way that in each 100 sets, we have 25-25 from each covariate's cohort, as later, each dosing regimen will be simulated for 100 sets of covariates, and it is important that the 4 cohorts are equally represented.

Also, for the concentration simulation part, we have to know before applying the models, if a patient needs a different regiment due to his renal failure or not. That is why an additional IR column is added where 1 indicates a renal failure patient who needs a dose adjustement. For Carlier, the MDRD equation is used, and for Fournier, the Cockroft and Gault. For Mellon and Rambaud, all patients have 0 in the IR column, as it is not explicited in the articles that a dose adjustement was applied to renal failure patients.

```
# Patchwork simulated correlation plots
corr_simulated <- (Carlier_F + Fournier_F + Mellon_F + Rambaud_F +
  Carlier_M + Fournier_M + Mellon_M + Rambaud_M) +
  plot_layout(ncol = 4, nrow = 2, byrow = TRUE)
ggsave(filename = here("a_priori/For_publication/Figures/S1.jpg"),
```

```
       plot = corr_simulated,
       width = 14, height = 8, dpi = 300)

# Row-bind the datasets to have 25 subjects from each in a sample of 100
datasets <- list(sim_cov_carlier, sim_cov_fournier, sim_cov_mellon, sim_cov_rambaud)

interleave_rows <- function(datasets, chunk_size) {
  n_chunks <- nrow(datasets[[1]]) / chunk_size
  interleaved <- do.call(rbind, lapply(1:n_chunks, function(i) {
    do.call(rbind, lapply(datasets, function(dataset) {
      dataset[((i - 1) * chunk_size + 1):(i * chunk_size), ]
    }))
  }))
  return(interleaved)
}

COV <- interleave_rows(datasets, chunk_size = 25)

# Convert Paper column to MODEL_COHORT column which indicates the model that is used to simul
COV <- COV %>%
  mutate(MODEL_COHORT = case_when(
    Paper == "Carlier_2013" ~ "CARLIER",
    Paper == "Fournier_2018" ~ "FOURNIER",
    Paper == "Mellon_2020" ~ "MELLON",
    Paper == "Rambaud_2020" ~ "RAMBAUD")
  )

# Adding ID
COV$ID <- seq(1:2500)

# CRCL calculation functions
calculate_MDRD <- function(AGE, CREAT, SEX) {
  # Mutliply by 0.742 for females
    sex_factor <- ifelse(SEX == 0, 1, 0.742)
    eGFR <- 175 * (CREAT^(-1.154)) * AGE^(-0.203) * sex_factor
    return(eGFR)
}

calculate_CG <- function(AGE, CREAT, SEX, WT) {
  sex_factor <- ifelse(SEX == 0, 1, 0.85)
  eGFR <- ((140 - AGE) * WT * sex_factor) / (CREAT * 72)
  return(eGFR)
```

```r
}

# Add 1 for dose adjustement for CRCL < 30 mL/min for Carlier and Fournier
COV <- COV %>%
  rowwise() %>%
  mutate(
    CRCL = case_when(
      MODEL_COHORT == "CARLIER" ~ calculate_MDRD(AGE, CREAT, SEX) * (BSA / 1.73),
      MODEL_COHORT == "FOURNIER" ~ calculate_CG(AGE, CREAT, SEX, WT),
      TRUE ~ NA_real_
    ),
    IR = case_when(
      MODEL_COHORT == "CARLIER" & CRCL < 30 ~ 1,
      MODEL_COHORT == "FOURNIER" & CRCL < 30 ~ 1,
      MODEL_COHORT %in% c("MELLON", "RAMBAUD") ~ 0,
      TRUE ~ 0
    )
  ) %>%
  ungroup()

COV <- COV %>%
  dplyr::select(ID, MODEL_COHORT, WT, CREAT, BURN, ICU, OBESE, BSA, AGE, SEX, HT, IR)

# Export to csv
write.csv(COV, here("a_priori/For_publication/Data/COV.csv"), quote = F, row.names = F)

# Check correlation (Pearson)
cor_sim <- cor(COV %>% dplyr::select(WT, CREAT, BURN, ICU, OBESE, AGE, SEX, HT), use = "compl
ggcorrplot(cor_sim, lab = TRUE)
```


HT
SEX
AGE
OBESE
ICU
BURN
CREAT
WT
WT
CREAT
BURN
ICU
OBESE
AGE
SEX
HT
Corr
1.0
0.5
0.0
−0.5
−1.0

2 Simulation of concentrations and secondary PK parameters

```
library(mrgsolve)
library(here)
library(tidyverse)
library(mapbayr)
library(MESS)
library(ggplot2)
library(dplyr)
library(patchwork) # To put different plots on the same grid
library(tableone)
library(knitr)
conflicted::conflicts_prefer(dplyr::filter)
conflicted::conflicts_prefer(dplyr::select)
```

The objective is to simulate concentrations and secondary PK parameters (Cmax, Cmin & AUC) using 4 validated PopPK models for amoxicillin. The 4 papers are:

- Carlier et al. (2013)
- Fournier et al. (2018)
- Mellon et al. (2020)
- Rambaud et al. (2020)

The original Rambaud model was non-parametric which was approximated using a parametric model (details in "Rambaud_validation.html").

The only route of administration is intraveinous infusion.

Three types of infusion are simulated:

- intermittent (duration = 0.5 h),
- extended (1-2 hours),
- continuous .

There are 8 different dosing schemes. For each model cohort the dosing scheme that was in the original article is used for simulation. For patients with renal failure (IR = CRCL $<$ 30 mL/min), a different dosing scheme is applied if it is explicited in the articles (*i. e.* Carlier, Fournier). For Mellon, there was a single administration in the original model. To have a dosing scheme compatible with the clinical context in which we want to apply our methods, administration frequency is set to every 6 h for intermittent administrations. ID means a set of covariates, not a subject (to make data manipulation easier later).

144 observations are simulated for each subject to have a sufficient number of observations after the first dose, as well as during a steady-state interdose interval. Observations are simulated for the period between the first and second doses and for the same duration for the first interdose interval that is entirely at steady-state. The number of observations has been determined to have at least three observations during the first interdose interval for all dosing schemes. For example, in the case of an intermittent infusion of 0.5 g q6h, there is an observation in each 5 minutes between 0 and 6 h & between 24 h and 30 h (if steady-state is reached at 22 h). This means, that not only the dosing grid changes for each dosing scheme, but the observation grid as well.

```
here::i_am("a_priori/For_publication/Simulations/Simulation_Carlier_Fournier_Mellon_Rambaud.
# Import or generate the file with the covariates (COV)
COV <- read.csv(here("a_priori/For_publication/Data/COV.csv"), quote = "")
set.seed(1991)
```

First, the dataset needs to be created with all the information that mrgsolve needs for the simulation. In the function create_dosing_data, the input data is created for all the lines that contain an administered dose.

```
# Function to create dosing grid (lines where there is an administered dose)
create_dosing_data <- function(id_range, amt, ii, rate, cmt, time_seq) {
  COV1 <- COV %>% dplyr::filter(ID %in% id_range)

  ID <- id_range            # ID range for the regimen

  # Create base dosing data
  dosing_data <- data.frame(
    ID = ID,
    amt = rep(amt, length(ID)),   # Dose amount in mg
    ii = rep(ii, length(ID)),     # Interdose interval in h
    rate = rep(rate, length(ID)), # Infusion rate
    evid = rep(1, length(ID)),    # EVID
    cmt = cmt                     # Compartment
  )
```

```
  # Add covariates from COV.csv
  dosing_data <- cbind(dosing_data, COV1[, setdiff(names(COV1), "ID")])

  # Repeat dosing data for all time points
  dosing_repeated <- dosing_data[rep(1:nrow(dosing_data), each = length(time_seq)), ]
  time <- rep(time_seq, times = length(ID))

  # Combine with time
  final_dosing_data <- cbind(dosing_repeated, time)
  return(final_dosing_data)
}
```

Then, the information is created for all the lines, that do not contain a dose, but an observation. The latest possible time is 120 h, as amoxicillin has a short half life and all subjects have had a complete steady-state dosing interval by then.

```
# Function to create observation grid (lines with concentration measurement)
create_observation_data <- function(id_range, obs_length) {
  COV1 <- COV %>% dplyr::filter(ID %in% id_range)
 # Extract covariates for the specified range
  ID <- id_range            # ID range for the regimen

  # Create base observation data (as these are lines with concentrations, AMT, II, RATE and
  obs_data <- data.frame(
    ID = ID,                      # ID meaning a set of covariates
    amt = rep(0, length(ID)),     # Dose amount in mg
    ii = rep(0, length(ID)),      # Interdose interval in h
    rate = rep(0, length(ID)),    # Infusion rate
    evid = rep(0, length(ID)),    # EVID
    cmt = "CENTRAL"               # Central compartment
  )

  # Add covariates
  obs_data <- cbind(obs_data, COV1[, setdiff(names(COV1), "ID")])

  # Repeat observation data for all observation times
  obs_repeated <- obs_data[rep(1:nrow(obs_data), each = obs_length), ]
  time <- rep(seq(from = 0, to = 120, length.out = obs_length), times = length(ID))    # Lates

  # Combine with time
  final_obs_data <- cbind(obs_repeated, time)
```

```
  return(final_obs_data)
}
```

To remove outliers, the non-physiological PK parameter values are resimulated (at most 100 times per value) using the *simeta* function of mrgsolve. A central volume of distribution smaller than 3 L (the volume of plasma) and a clearance higher than 180 L/h (normal blood flow) is considered non-physiological. (However, the maximum simulated clearance is around 100 L/h, so its resimulation is unnecessary.)

Simulations are done using the mrgsolve models in .cpp format. To find the interdose interval which is entirely in steady-state, first, the time to reach steady state (TSS) has to be calculated.

$$K_{10} = \frac{CL}{V_c}$$

$$K_{12} = \frac{Q}{V_c}$$

$$K_{21} = \frac{Q}{V_p}$$

$$L_2 = \frac{(K_{10} + K_{12} + K_{21}) - \sqrt{(K_{10} + K_{12} + K_{21})^2 - 4K_{10}K_{21}}}{2}$$

$$t_{1/2} = \frac{ln(2)}{L_2}$$

We can consider that steady state is reached when the concentration is 90 % of the steady state concentration, which corresponds to a time of 3.3 times the half life (as $1 - e^{(-k_e \cdot t)} = 0.9$).

First, concentrations are simulated for all data points between 0 and 120 h, then the results are filtered to choose the first interdose interval and the first interdose interval entirely in steady-state.

```
# Function to simulate based on mrgsolve models
simulate_mrgsim <- function(sim_final, model, interval) {
  sim_results <- mrgsim(model, sim_final) %>% as.data.frame()

  return(sim_results)
}
```

Then, the filtered dataset, and the covariates will be put together, and the observation and dosing grids will be simulated based on the functions defined earlier. The dosing scheme is added as three columns (DOSE, FREQuency, DURation). Each model control stream is used two times for each simulation. Once, to simulate IPRED and Y (and $Cmax_{\text{ind}}$, $Cmin_{\text{ind}}$ and AUC_{ind} which are based on IPRED), then a second time, the omega matrix is set to 0 to simulate PRED (and CMAX_PRED and AUC_PRED based on PRED). PRED are typical concentrations which do not contain inter-individual variability. IPRED has inter-individual variability incorporated, and Y has both inter-and intra-individual variability.

```
# Function to merge covariates and finalize
finalize_results <- function(sim_results, id_range, model, dose, freq, dur) {
  COV1 <- COV %>% dplyr::filter(ID %in% id_range)

  # Merge with simulation results
  result <- merge(sim_results, COV1, by = "ID", all.x = TRUE)

  result <- result %>%
    mutate(MODEL = model, DOSE_ADM = dose, FREQ = freq, DUR = dur) %>%
    distinct(ID, TIME = time, .keep_all = TRUE)

  return(result)
}

generate_model_regimen <- function(model_name, cpp_file, regimens, sim_dur) {
  model <- mread(model = cpp_file)
  model_zero <- zero_re(model)
  COV <- read.csv(here("a_priori/For_publication/Data/COV.csv"), quote = "")

  regimen_assignments <- list()

  for (cohort_name in unique(COV$MODEL_COHORT)) {
    cohort_cov <- COV %>% filter(MODEL_COHORT == cohort_name)
    cohort_regimens <- regimens[sapply(regimens, function(x) x$model_cohort == cohort_name)]

    for (ir_value in unique(cohort_cov$IR)) {
      eligible_ids <- cohort_cov %>% filter(IR == ir_value) %>% pull(ID)

      matched_regimens <- cohort_regimens[seq_along(cohort_regimens) %% length(unique(cohort_

      # Distribute eligible subjects evenly across relevant dosing regimens
      id_splits <- split(eligible_ids, rep(1:length(matched_regimens), length.out = length(el

      for (i in seq_along(matched_regimens)) {
```

```
      matched_regimens[[i]]$assigned_ids <- id_splits[[i]]
      regimen_assignments <- append(regimen_assignments, list(matched_regimens[[i]]))
    }
  }
}

# Simulate for the assigned regimens
regimen_results <- list()
for (regimen in regimen_assignments) {
  if (length(regimen$assigned_ids) == 0) next

  dose <- regimen$dose
  interval <- regimen$interval
  duration <- regimen$duration
  id_range <- regimen$assigned_ids

  dosing_times <- seq(0, sim_dur - interval, by = interval)
  obs_length <- (sim_dur / interval) * sim_dur + 1

  dose_data <- create_dosing_data(
    id_range = id_range,
    amt = dose,
    ii = interval,
    rate = dose / duration,
    cmt = "CENTRAL",
    time_seq = dosing_times
  )

  obs_data <- create_observation_data(id_range = id_range, obs_length = obs_length)
  sim_data <- rbind(dose_data, obs_data) %>% arrange(ID, time, desc(evid))

  processed_data <- simulate_mrgsim(sim_data, model, interval)
  processed_data_zero <- simulate_mrgsim(sim_data, model_zero, interval)

  finalized_data <- finalize_results(
    sim_results = processed_data,
    id_range = id_range,
    model = model_name,
    dose = dose,
    freq = interval,
    dur = duration
  )
```

```
    pred_data <- processed_data_zero %>%
      select(ID, time, PRED = IPRED, AUC_PRED = AUC, Cmax_PRED = Cmax)

    merged_data <- finalized_data %>% left_join(pred_data, by = c("ID", "time"))
    regimen_results <- append(regimen_results, list(merged_data))
  }

  combined_results <- do.call(rbind, regimen_results)
  return(combined_results)
}
```

8 different dosing schemes are used depending on the model cohort.

```
# Define regimen parameters for all models. For each regimen, we take a different batch of 1
regimens <- list(
  list(model_cohort = "CARLIER", ir_group = 0, dose = 1000, interval = 6, duration = 0.5),
  list(model_cohort = "CARLIER", ir_group = 1, dose = 1000, interval = 8, duration = 0.5),
  list(model_cohort = "FOURNIER", ir_group = 0, dose = 1000, interval = 6, duration = 2),
  list(model_cohort = "FOURNIER", ir_group = 0, dose = 1500, interval = 6, duration = 1),
  list(model_cohort = "FOURNIER", ir_group = 0, dose = 2000, interval = 6, duration = 2),
  list(model_cohort = "FOURNIER", ir_group = 0, dose = 2000, interval = 8, duration = 1),
  list(model_cohort = "FOURNIER", ir_group = 1, dose = 500, interval = 8, duration = 2),
  list(model_cohort = "MELLON", ir_group = 0, dose = 1000, interval = 6, duration = 0.5),
  list(model_cohort = "RAMBAUD", ir_group = 0, dose = 12000, interval = 24, duration = 24),
  list(model_cohort = "RAMBAUD", ir_group = 0, dose = 14000, interval = 24, duration = 24)
)

# Total simulation time
sim_dur <- 120
```

Finally, the simulations are done with each respective model, the results are merged and a MODEL column is added to identify the model used for the simulation of each concentration.

```
results_Carlier <- generate_model_regimen("amox_Carlier", here("a_priori/For_publication/Simu
results_Fournier <- generate_model_regimen("amox_Fournier", here("a_priori/For_publication/Si
results_Mellon <- generate_model_regimen("amox_Mellon", here("a_priori/For_publication/Simula
results_Rambaud <- generate_model_regimen("amox_Rambaud", here("a_priori/For_publication/Simu

# Combine results from the simulation
all_results_raw <- dplyr::bind_rows(
  results_Carlier,
```

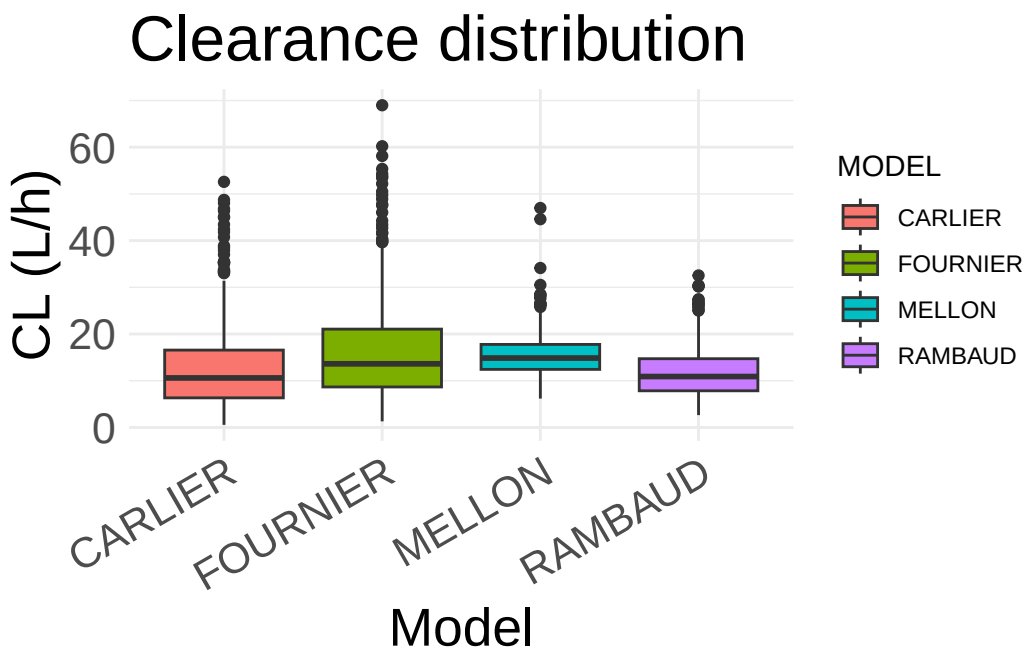
```
  results_Fournier,
  results_Mellon,
  results_Rambaud
)

# Add MODEL column indicating the model which is used for the simulation
all_results_raw <- all_results_raw %>%
  dplyr::mutate(MODEL = case_when(
    MODEL == "amox_Carlier" ~ "CARLIER",
    MODEL == "amox_Fournier" ~ "FOURNIER",
     MODEL == "amox_Mellon" ~ "MELLON",
    MODEL == "amox_Rambaud" ~ "RAMBAUD")
  ) %>%
  distinct()

# Filter based on steady-state based on the reference (true) clearance and volume
ref_values <- all_results_raw %>%
  filter(MODEL == MODEL_COHORT) %>%
  group_by(ID) %>%
  slice(1) %>%
  select(ID, Vc, CL, Q, Vp)
all_results <- all_results_raw %>%
  left_join(ref_values, by = "ID", suffix = c("", "_ref")) %>%
  mutate(K10 = CL_ref/Vc_ref,
  K12 = Q_ref/Vc_ref,
  K21 = Q_ref/Vp_ref,
  L2 = ((K10+K12+K21)-((K10+K12+K21)**2-4*K10*K21)**0.5)/2,
  TSS = ceiling((3.3 * (0.693 / L2)) / FREQ) * FREQ) %>%
  dplyr::filter((TIME >= 0 & TIME <= (0 + FREQ)) | (TIME >= TSS & TIME <= (TSS + FREQ)))
```

2.0.1 Concentrations (PRED, IPRED, Y)

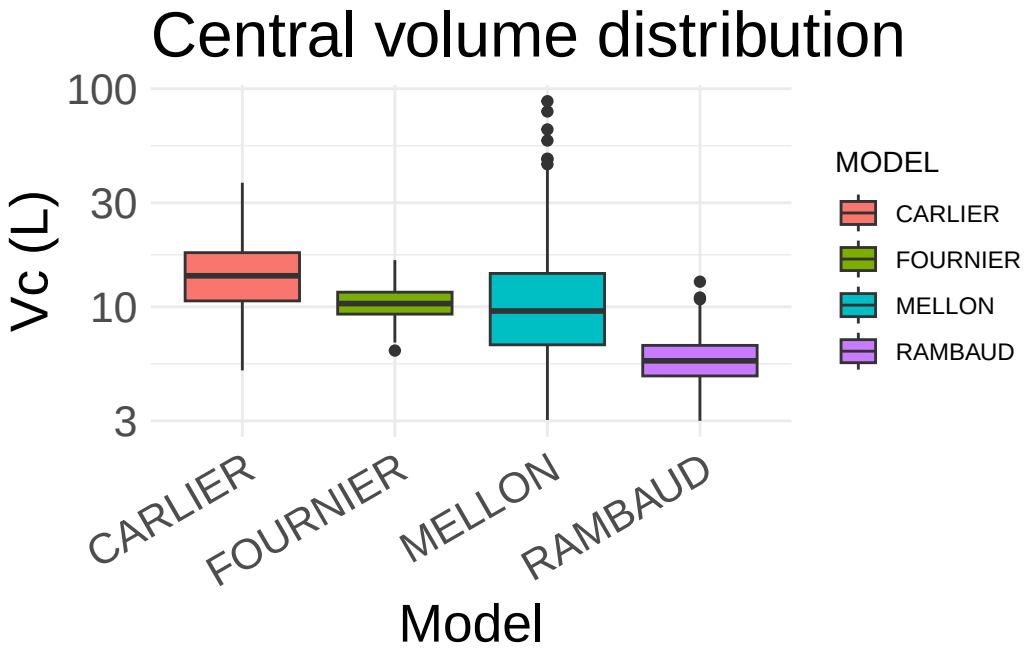
Below quantification limit observations are removed (M1 method). LLOQ concentrations for each model can be found in "mrgsolve/LLOQ.txt".

```
AMOX_SIM <- all_results %>%
  select(ID, TIME, PRED, IPRED, Y, WT, CREAT, BURN, ICU, OBESE, AGE, SEX, HT, BSA, MODEL, MO
  distinct()

# Add a variable called REFERENCE which is 1 for the the line where the model used for simula
AMOX_SIM <- AMOX_SIM %>%
```

```r
  mutate(REFERENCE = if_else(MODEL == MODEL_COHORT, 1, 0))

# Dataset to plot CL
summarized_SIM <- AMOX_SIM %>%
  filter(REFERENCE==1) %>%
  distinct(ID, MODEL, CL, Vc)

# Box plot for CL
plot_CL <- ggplot(summarized_SIM, aes(x = MODEL, y = CL, fill = MODEL)) +
  geom_boxplot() +
  theme_minimal() +
  labs(title = "Clearance distribution", x = "Model", y = "CL (L/h)") +
  theme(
    axis.text.x = element_text(angle = 30, hjust = 1),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=24),
  )

plot_CL
```



```r
# Box plot for Vc
plot_V <- ggplot(summarized_SIM, aes(x = MODEL, y = Vc, fill = MODEL)) +
  geom_boxplot() +
  theme_minimal() +
  scale_y_log10() +
  labs(title = "Central volume distribution", x = "Model", y = "Vc (L)") +
  theme(
    axis.text.x = element_text(angle = 30, hjust = 1),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=24),
  )

plot_V
```




```r
AMOX_SIM_QL2 <- AMOX_SIM %>%
  group_by(ID, TIME) %>%
  mutate(IPRED = IPRED[REFERENCE == 1]) %>%
  ungroup()


# Create test data by taking 2400 subjects (24 from each dosing scheme and 6-6 for each model
```

```r
SIM_test <- AMOX_SIM_QL2 %>%
  dplyr::filter(
    ID %% 100 >= 1 & ID %% 100 <= 6 |
      ID %% 100 >= 26 & ID %% 100 <= 31 |
      ID %% 100 >= 51 & ID %% 100 <= 56 |
      ID %% 100 >= 76 & ID %% 100 <= 81
  )

# Create training data by taking 7600 subjects (76 from each dosing scheme and 19-19 for eac
SIM_train <- AMOX_SIM_QL2 %>%
  dplyr::filter(
    ID %% 100 >= 7 & ID %% 100 <= 25 |
      ID %% 100 >= 32 & ID %% 100 <= 50 |
      ID %% 100 >= 57 & ID %% 100 <= 75 |
      ID %% 100 >= 82 & ID %% 100 <= 100
  )

# Dataset identifyer
IPRED_train_compare <- SIM_train %>% mutate(Dataset = "Train")
IPRED_test_compare <- SIM_test %>% mutate(Dataset = "Test")

# Combine the three datasets
combined_IPRED <- bind_rows(IPRED_train_compare, IPRED_test_compare)

# Compare the train and test sets
vars <- c("CREAT", "WT", "IPRED", "CL", "Vc")
tableOne7 <- CreateTableOne(vars = vars, strata = "Dataset", data = combined_IPRED)
tableOne8<-print(tableOne7, nonnormal = c("CREAT", "WT", "IPRED", "CL", "Vc"), printToggle=F

kableone(tableOne7)
```

	Test	Train	p	test
n	579196	1809816		
CREAT (mean (SD))	0.95 (0.58)	0.93 (0.59)	<0.001	
WT (mean (SD))	84.40 (18.68)	84.38 (18.09)	0.416	
IPRED (mean (SD))	26.71 (29.17)	24.81 (27.43)	<0.001	
CL (mean (SD))	14.24 (7.99)	14.47 (8.10)	<0.001	
Vc (mean (SD))	11.07 (6.00)	11.03 (5.85)	<0.001	

```
kableone(tableOne8)
```

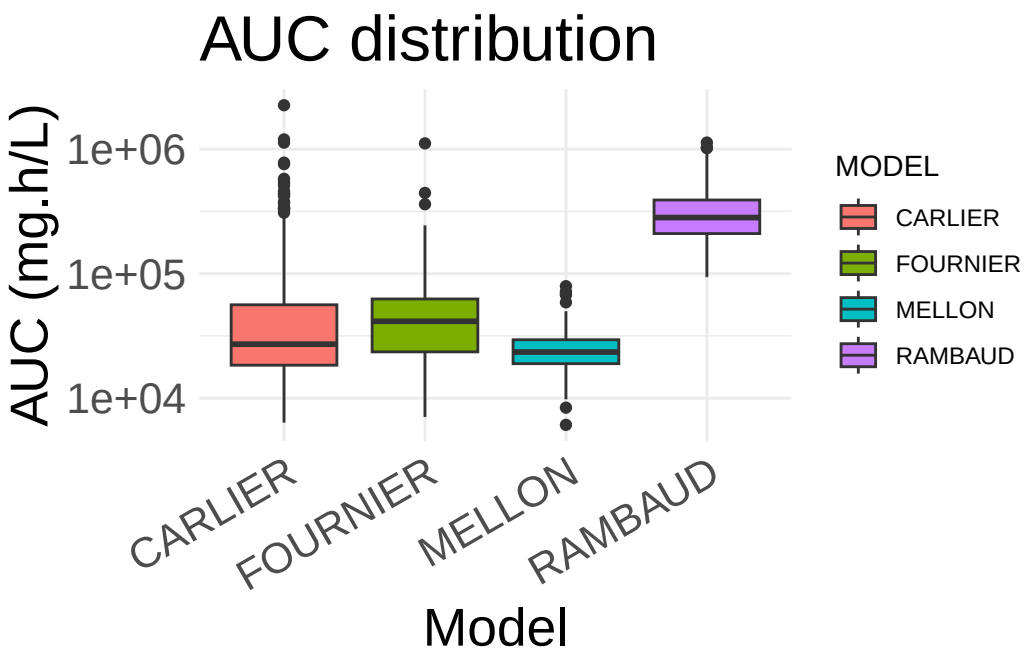
	Test	Train	p	test
n	579196	1809816		
CREAT (median [range])	0.76 [0.24, 5.32]	0.77 [0.13, 8.23]	<0.001	nonnorm
WT (median [range])	80.04 [41.33, 139.60]	79.99 [47.36, 141.17]	<0.001	nonnorm
IPRED (median [range])	17.07 [0.00, 207.50]	14.79 [0.00, 338.56]	<0.001	nonnorm
CL (median [range])	12.90 [0.57, 79.94]	13.30 [0.55, 109.60]	<0.001	nonnorm
Vc (median [range])	9.98 [3.02, 72.94]	10.07 [3.00, 87.63]	0.801	nonnorm

2.0.2 Exposure (AUC)

AUC is calculated based on the sum of the integrals of IPRED values and cumulated for both the steady-state and non stead-state inter-dose interval.

```
AMOX_AUC1 <- all_results %>%
  group_by(ID, MODEL) %>%
  summarize(
    ID = first(ID),
    MODEL = first(MODEL),
    MODEL_COHORT = first(MODEL_COHORT),
    AUC_IND = sum(AUC, na.rm = TRUE), #total AUC (based on IPRED)
    AUC_PRED = sum(AUC_PRED, na.rm = TRUE), #total AUC (based on PRED)
    WT = first(WT),
    CREAT = first(CREAT),
    BURN = first(BURN),
    ICU = first(ICU),
    OBESE = first(OBESE),
    AGE = first(AGE),
    SEX = first(SEX),
    HT = first(HT),
    DUR = first(DUR),
    FREQ = first(FREQ),
    DOSE_ADM = first(DOSE_ADM),
    TSS = first(TSS),
    Vc = first(Vc),
    CL = first(CL)
  ) %>%
```

```r
  mutate(REFERENCE = if_else(MODEL == MODEL_COHORT, 1, 0)) # Add a variable called REFERENCE

summarized_AUC <- AMOX_AUC1 %>%
  dplyr::filter(REFERENCE==1) %>%
  distinct(ID, MODEL, AUC_IND)

# Add a variable called REFERENCE which is 1 for the the line where the model used for simula
  AMOX_AUC1 <- AMOX_AUC1 %>%
  group_by(ID) %>%
  mutate(AUC_IND = AUC_IND[REFERENCE == 1]) %>%
  ungroup()

# Box plot for AUC
plot_AUC <- ggplot(summarized_AUC, aes(x = MODEL, y = AUC_IND, fill = MODEL)) +
  geom_boxplot() +
  scale_y_log10() +
  theme_minimal() +
  labs(title = "AUC distribution", x = "Model", y = "AUC (mg.h/L)") +
  theme(
    axis.text.x = element_text(angle = 30, hjust = 1),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=24),
  )

plot_AUC
```




```r
# Create test data by taking 2400 subjects (24 from each dosing scheme and 6-6 for each model
AUC_test <- AMOX_AUC1 %>%
  dplyr::filter(
    ID %% 100 >= 1 & ID %% 100 <= 6 |
      ID %% 100 >= 26 & ID %% 100 <= 31 |
      ID %% 100 >= 51 & ID %% 100 <= 56 |
      ID %% 100 >= 76 & ID %% 100 <= 81
  )

# Create training data by taking 7600 subjects (76 from each dosing scheme and 19-19 for each
AUC_train <- AMOX_AUC1 %>%
  dplyr::filter(
    ID %% 100 >= 7 & ID %% 100 <= 25 |
      ID %% 100 >= 32 & ID %% 100 <= 50 |
      ID %% 100 >= 57 & ID %% 100 <= 75 |
      ID %% 100 >= 82 & ID %% 100 <= 100
  )

# Dataset identifyer
AUC_train_compare <- AUC_train %>% mutate(Dataset = "Train")
AUC_test_compare <- AUC_test %>% mutate(Dataset = "Test")

# Combine the three datasets
```

```r
combined_AUC <- bind_rows(AUC_train_compare, AUC_test_compare)

# Compare the train and test sets
vars <- c("CREAT", "WT", "AUC_IND", "CL", "Vc")
tableOne <- CreateTableOne(vars = vars, strata = "Dataset", data = combined_AUC)
tableOne2 <- print(tableOne, nonnormal = c("CREAT", "WT", "AUC_IND", "CL", "Vc"), printToggle

kableone(tableOne2)
```

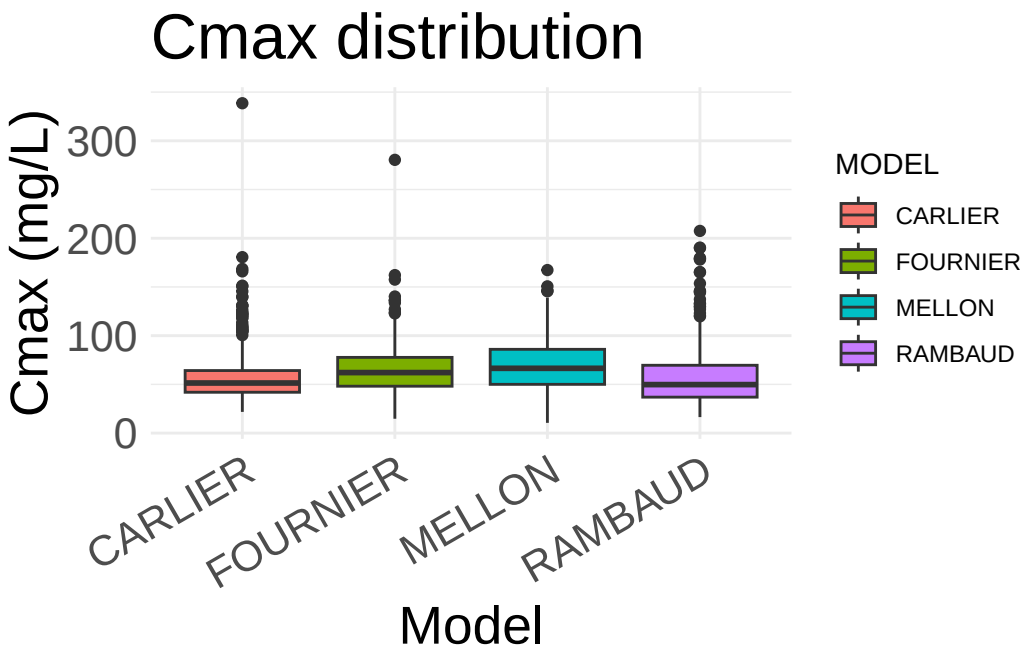
	Test	Train	p	test
n	2400	7500		
CREAT (median [range])	0.76 [0.24, 5.32]	0.77 [0.13, 8.23]	0.099	nonnorm
WT (median [range])	80.03 [41.33, 139.60]	79.99 [47.36, 141.17]	0.771	nonnorm
AUC_IND (median [range])	40639.31 [7061.75, 1196253.42]	37471.44 [6102.14, 2252604.68]	0.003	nonnorm
CL (median [range])	12.92 [0.57, 79.94]	13.30 [0.55, 109.60]	0.208	nonnorm
Vc (median [range])	9.98 [3.02, 72.94]	10.06 [3.00, 87.63]	0.987	nonnorm

2.0.3 Maximal concentration (Cmax)

Cmax is the true Cmax, not the highest observed concentration.

```r
AMOX_CMAX1 <- all_results %>%
  group_by(ID, MODEL) %>%
  summarize(
    ID = first(ID),
    MODEL = first(MODEL),
    MODEL_COHORT = first(MODEL_COHORT),
    CMAX_IND = max(Cmax, na.rm = TRUE),  # Cmax based on IPRED
    CMAX_PRED = max(Cmax_PRED, na.rm = TRUE), # Cmax based on PRED
    WT = first(WT),
    CREAT = first(CREAT),
    BURN = first(BURN),
    ICU = first(ICU),
    OBESE = first(OBESE),
    AGE = first(AGE),
    SEX = first(SEX),
    HT = first(HT),
```

```
    DUR = first(DUR),
    FREQ = first(FREQ),
    DOSE_ADM = first(DOSE_ADM),
    TSS = first(TSS),
    Vc = first(Vc),
    CL = first(CL)
  ) %>%
  mutate(REFERENCE = if_else(MODEL == MODEL_COHORT, 1, 0)) %>% # Add a variable called REFERE
  mutate(CON = ifelse(DUR == 24, 1, 0))

summarized_CMAX <- AMOX_CMAX1 %>%
  dplyr::filter(REFERENCE==1) %>%
  distinct(ID, MODEL, CMAX_IND)

# Add a variable called REFERENCE which is 1 for the the line where the model used for simula
  AMOX_CMAX1 <- AMOX_CMAX1 %>%
  group_by(ID) %>%
  mutate(CMAX_IND = CMAX_IND[REFERENCE == 1]) %>%
  ungroup()

# Box plot for Cmax
plot_CMAX <- ggplot(summarized_CMAX, aes(x = MODEL, y = CMAX_IND, fill = MODEL)) +
  geom_boxplot() +
  theme_minimal() +
  labs(title = "Cmax distribution", x = "Model", y = "Cmax (mg/L)") +
  theme(
    axis.text.x = element_text(angle = 30, hjust = 1),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=24),
  )

plot_CMAX
```




```r
# Create test data by taking 2400 subjects (24 from each dosing scheme and 6-6 for each model
CMAX_test <- AMOX_CMAX1 %>%
  dplyr::filter(
    ID %% 100 >= 1 & ID %% 100 <= 6 |
      ID %% 100 >= 26 & ID %% 100 <= 31 |
      ID %% 100 >= 51 & ID %% 100 <= 56 |
      ID %% 100 >= 76 & ID %% 100 <= 81
  )

# Create training data by taking 7600 subjects (76 from each dosing scheme and 19-19 for each
CMAX_train <- AMOX_CMAX1 %>%
  dplyr::filter(
    ID %% 100 >= 7 & ID %% 100 <= 25 |
      ID %% 100 >= 32 & ID %% 100 <= 50 |
      ID %% 100 >= 57 & ID %% 100 <= 75 |
      ID %% 100 >= 82 & ID %% 100 <= 100
  )

# Dataset identifier
CMAX_train_compare <- CMAX_train %>% mutate(Dataset = "Train")
CMAX_test_compare <- CMAX_test %>% mutate(Dataset = "Test")

# Combine the three datasets
```

```r
combined_CMAX <- bind_rows(CMAX_train_compare, CMAX_test_compare)

# Compare the train and test sets
vars <- c("CREAT", "WT", "CMAX_IND", "CL", "Vc")
tableOne3 <- CreateTableOne(vars = vars, strata = "Dataset", data = combined_CMAX)
tableOne4<-print(tableOne3, nonnormal = c("CREAT", "WT", "CMAX_IND", "CL", "Vc"), printToggle

kableone(tableOne4)
```

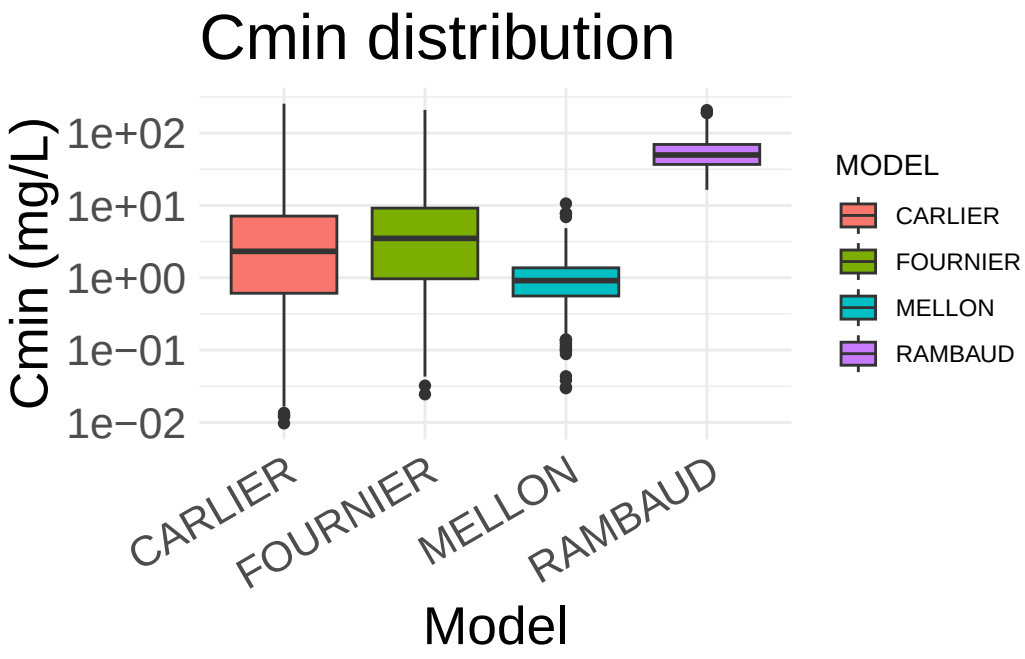
	Test	Train	p	test
n	2400	7500		
CREAT (median [range])	0.76 [0.24, 5.32]	0.77 [0.13, 8.23]	0.099	nonnorm
WT (median [range])	80.03 [41.33, 139.60]	79.99 [47.36, 141.17]	0.771	nonnorm
CMAX_IND (median [range])	57.55 [14.56, 207.50]	56.90 [10.51, 338.56]	0.084	nonnorm
CL (median [range])	12.92 [0.57, 79.94]	13.30 [0.55, 109.60]	0.208	nonnorm
Vc (median [range])	9.98 [3.02, 72.94]	10.06 [3.00, 87.63]	0.987	nonnorm

2.0.4 Trough concentration (Cmin)

The trough concentration is the last concentration for the steady-state interdose interval

```r
# Add CMIN column by taking the last steady-state concentration
AMOX_CMIN1 <- AMOX_SIM_QL2 %>%
  group_by(ID, MODEL) %>%
  arrange(TIME) %>%
  mutate(CMIN_IND = last(IPRED[TIME == max(TIME)])) %>%
  mutate(CMIN_PRED = last(PRED[TIME == max(TIME)])) %>%
  slice_max(TIME, n = 1, with_ties = FALSE) %>%
  ungroup() %>%
  distinct(ID, MODEL, CMIN_IND, .keep_all = TRUE) %>%
  mutate(CON = ifelse(DUR == 24, 1, 0))

summarized_CMIN <- AMOX_CMIN1 %>%
  dplyr::filter(REFERENCE==1)

# Add a variable called REFERENCE which is 1 for the the line where the model used for simula
  AMOX_CMIN1 <- AMOX_CMIN1 %>%
  group_by(ID) %>%
  mutate(CMIN_IND = CMIN_IND[REFERENCE == 1]) %>%
```

```
  ungroup()

# Box plot for CL before removing the outliers
plot_CMIN <- ggplot(summarized_CMIN, aes(x = MODEL, y = CMIN_IND, fill = MODEL)) +
  geom_boxplot() +
  scale_y_log10() +
  theme_minimal() +
  labs(title = "Cmin distribution", x = "Model", y = "Cmin (mg/L)") +
  theme(
    axis.text.x = element_text(angle = 30, hjust = 1),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=24),
  )

plot_CMIN
```




```
# Create test data by taking 2400 subjects (24 from each dosing scheme and 6-6 for each model
CMIN_test <- AMOX_CMIN1 %>%
  dplyr::filter(
    ID %% 100 >= 1 & ID %% 100 <= 6 |
      ID %% 100 >= 26 & ID %% 100 <= 31 |
```

```
      ID %% 100 >= 51 & ID %% 100 <= 56 |
      ID %% 100 >= 76 & ID %% 100 <= 81
  )

# Create training data by taking 7600 subjects (76 from each dosing scheme and 19-19 for eac
CMIN_train <- AMOX_CMIN1 %>%
  dplyr::filter(
    ID %% 100 >= 7 & ID %% 100 <= 25 |
      ID %% 100 >= 32 & ID %% 100 <= 50 |
      ID %% 100 >= 57 & ID %% 100 <= 75 |
      ID %% 100 >= 82 & ID %% 100 <= 100
  )

# Dataset identifyer
CMIN_train_compare <- CMIN_train %>% mutate(Dataset = "Train")
CMIN_test_compare <- CMIN_test %>% mutate(Dataset = "Test")

# Combine the three datasets
combined_CMIN <- bind_rows(CMIN_train_compare, CMIN_test_compare)

# Compare the train and test sets
vars <- c("CREAT", "WT", "CMIN_IND", "CL", "Vc")
tableOne5 <- CreateTableOne(vars = vars, strata = "Dataset", data = combined_CMIN)
tableOne6 <- print(tableOne5, nonnormal = c("CREAT", "WT", "CMIN_IND", "CL", "Vc"), printTogg

kableone(tableOne6)
```

	Test	Train	p	test
n	2400	7500		
CREAT (median [range])	0.76 [0.24, 5.32]	0.77 [0.13, 8.23]	0.099	nonnorm
WT (median [range])	80.03 [41.33, 139.60]	79.99 [47.36, 141.17]	0.771	nonnorm
CMIN_IND (median [range])	3.26 [0.02, 207.50]	2.75 [0.01, 254.67]	0.007	nonnorm
CL (median [range])	12.91 [0.57, 79.94]	13.30 [0.55, 109.60]	0.193	nonnorm
Vc (median [range])	9.98 [3.02, 72.94]	10.06 [3.00, 87.63]	0.987	nonnorm

```
# Export to csv
write.csv(CMIN_train, here("a_priori/For_publication/Data/AMOX_CMIN_TRAIN.csv"), row.names =
write.csv(CMIN_test, here("a_priori/For_publication/Data/AMOX_CMIN_TEST.csv"), row.names = F
```

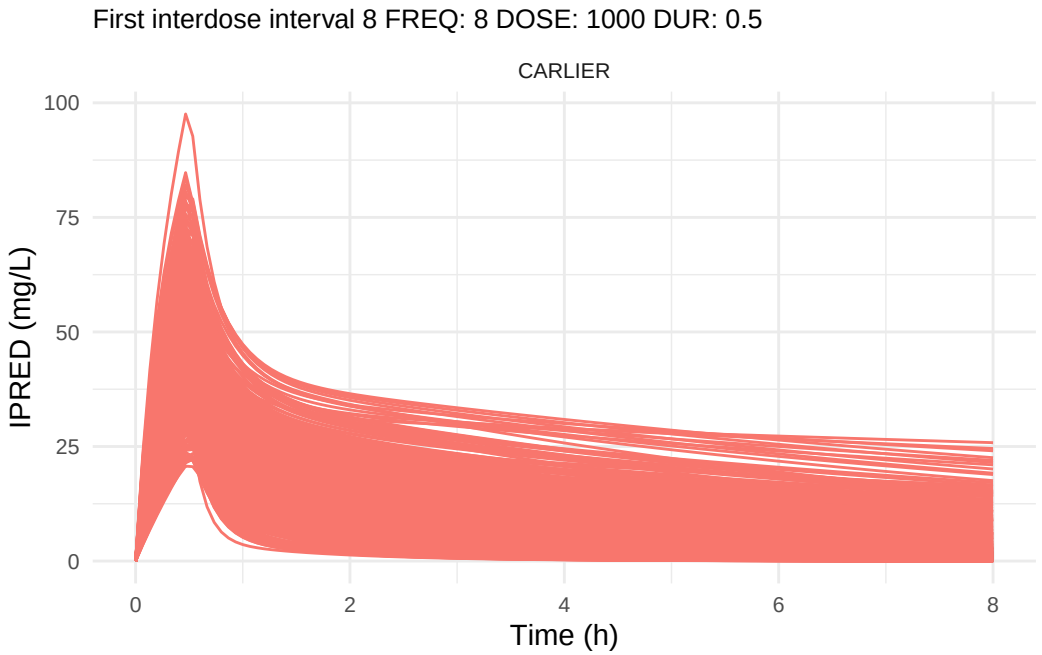
2.1 Data visualization stratified by dosing schemes

The following graphs show the individual observed concentration-time curves for the data stratified by model. One graph shows the concentration-time curves for the first interdose interval and the other graph for the interdose interval after the dose which permits to reach steady state.

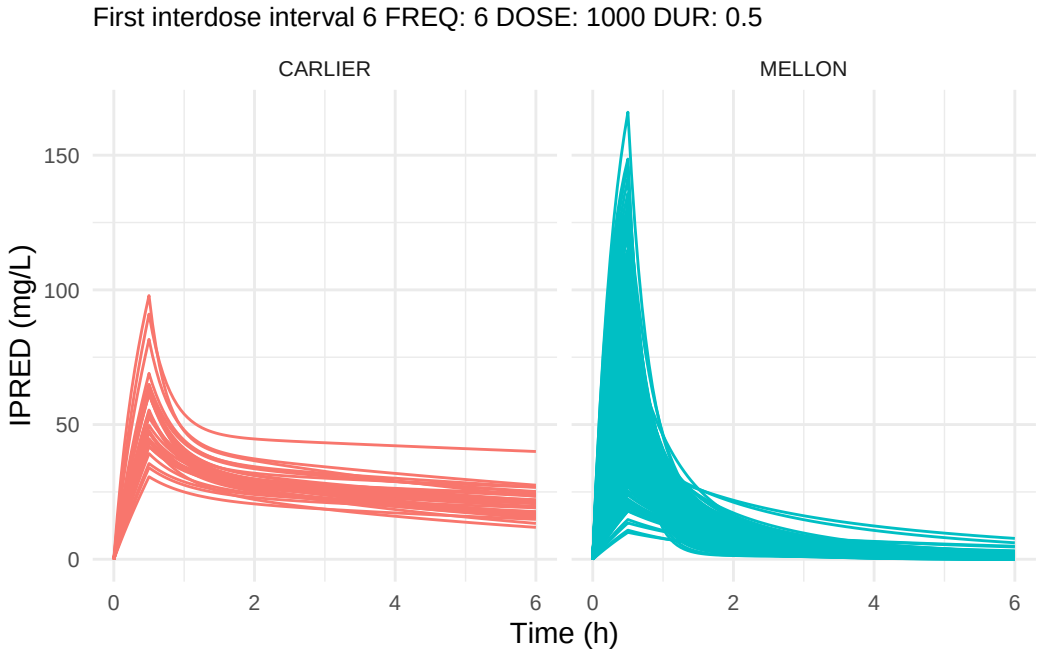
```
# Add dosing scheme as a categorical variable (to separate dosing schemes)
data <- AMOX_SIM %>%
  mutate(DOSING_SCHEME = paste("FREQ:", FREQ, "DOSE:", DOSE_ADM, "DUR:", DUR, sep = " "))

data_ref <- data %>% dplyr::filter(REFERENCE == 1)

dosing_schemes <- unique(data$DOSING_SCHEME)

# Loop through each dosing scheme
plot_dosing_schemes <- function(data_ref, dosing_schemes) {
  plot_list_before <- list()
  plot_list_after <- list()

  for (i in seq_along(dosing_schemes)) {
    scheme <- dosing_schemes[i]

    # Extract FREQ (=interdose interval)
    scheme_data <- subset(data_ref, DOSING_SCHEME == scheme)
    freq_value <- unique(scheme_data$FREQ)


    # Split data before and after SS
    data_before <- subset(scheme_data, TIME <= freq_value)
    data_after <- subset(scheme_data, TIME > TSS) %>%
      mutate(TIME = TIME - TSS)  # Adjust time so that it means time after SS dose

    # Plot for before SS
    plot_list_before[[i]] <- ggplot(data_before, aes(x = TIME, y = IPRED, color = MODEL, grou
      geom_line() +
      facet_wrap(~MODEL) +
      theme_minimal() +
      labs(
        title = paste("First interdose interval", freq_value, scheme),
        x = "Time (h)",
        y = "IPRED (mg/L)",
```

```
        color = "MODEL"
      ) +
      theme(
        plot.title = element_text(size=10),
        strip.text = element_text(size = 8),
        axis.text = element_text(size = 8),
        legend.position = "none"
      )

    # Plot for after SS is reached
    plot_list_after[[i]] <- ggplot(data_after, aes(x = TIME, y = IPRED, color = MODEL, group
      geom_line() +
      facet_wrap(~MODEL) +
      theme_minimal() +
      labs(
        title = paste("Steady-state", freq_value, scheme),
        x = "Time after steady-state dose (h)",
        y = "IPRED (mg/L)",
        color = "MODEL"
      ) +
      theme(
        plot.title = element_text(size=10),
        strip.text = element_text(size = 8),
        axis.text = element_text(size = 8),
        legend.position = "none"
      )
  }

  list(before = plot_list_before, after = plot_list_after)
}

conc_profile_plots <- plot_dosing_schemes(data_ref, dosing_schemes)
conc_profile_plots
```

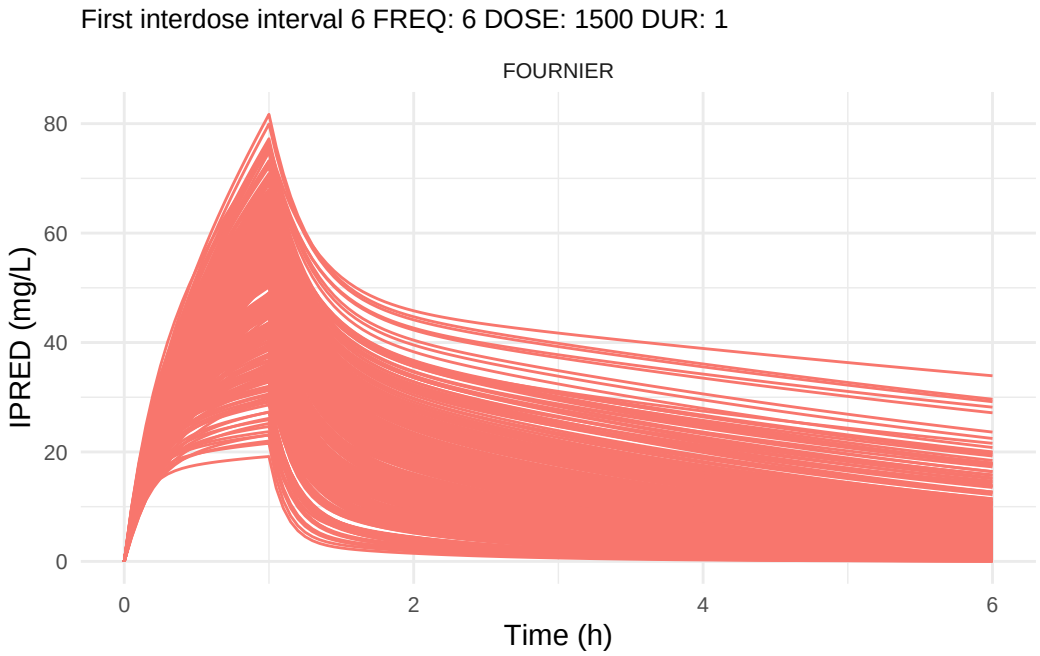
```
$before
$before[[1]]
```


First interdose interval 8 FREQ: 8 DOSE: 1000 DUR: 0.5
CARLIER
IPRED (mg/L)
100
75
50
25
0
0
2
4
6
8
Time (h)

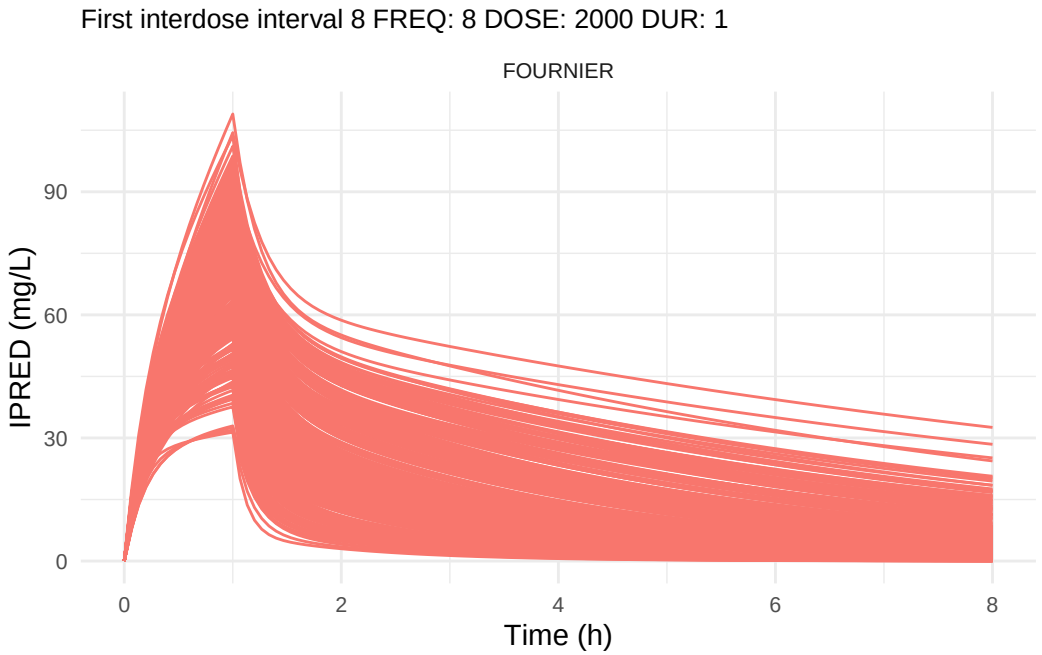
```
$before[[2]]
```


First interdose interval 6 FREQ: 6 DOSE: 1000 DUR: 0.5
CARLIER
MELLON
IPRED (mg/L)
150
100
50
0
0
2
4
6
Time (h)

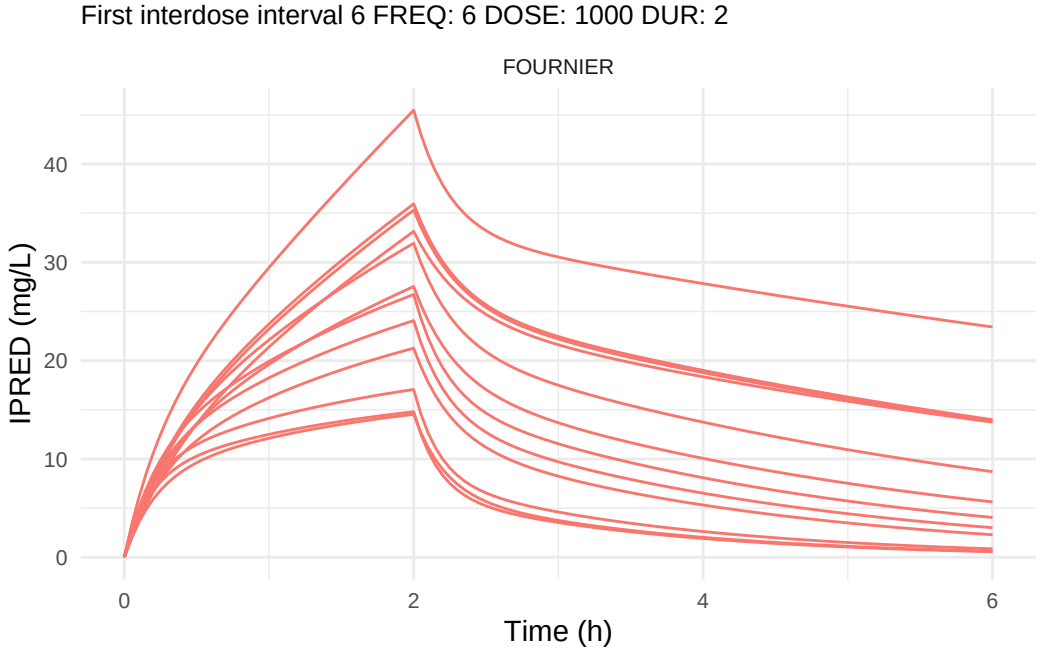
```
$before[[3]]
```



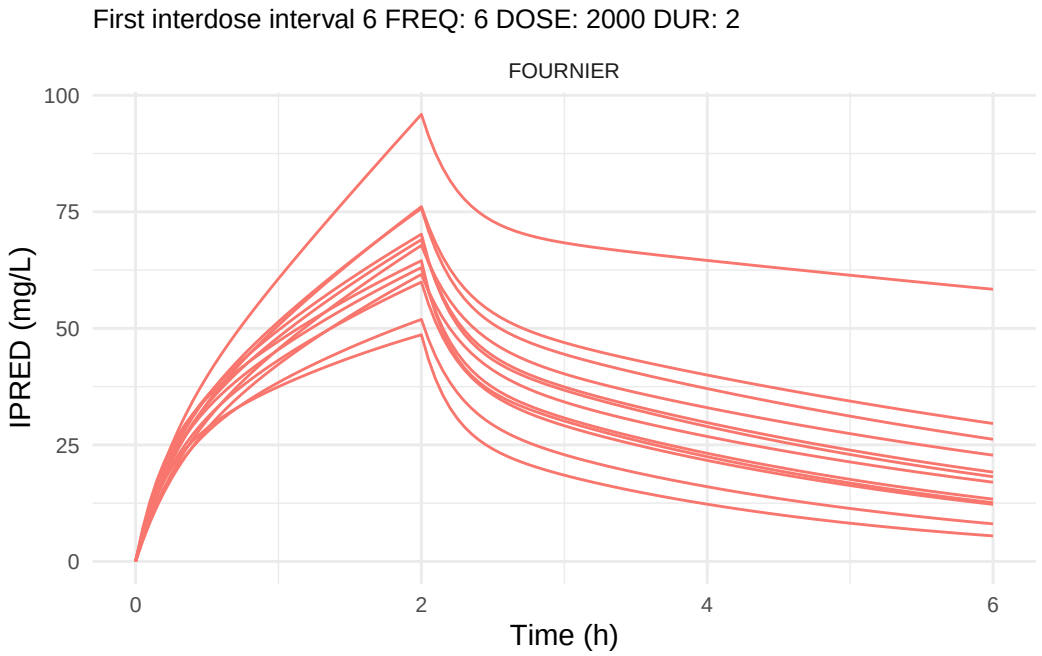

```
$before[[4]]
```


First interdose interval 8 FREQ: 8 DOSE: 2000 DUR: 1
FOURNIER
IPRED (mg/L)
0
30
60
90
0
2
4
6
8
Time (h)

```
$before[[5]]
```

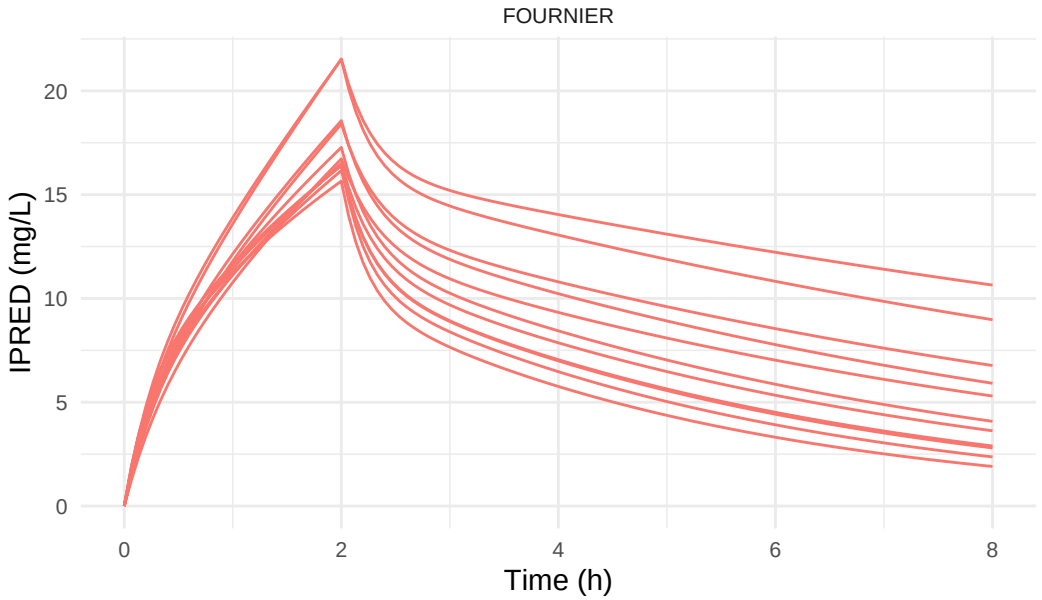

First interdose interval 6 FREQ: 6 DOSE: 1000 DUR: 2
FOURNIER
IPRED (mg/L)
0
10
20
30
40
0
2
4
6
Time (h)

```
$before[[6]]
```



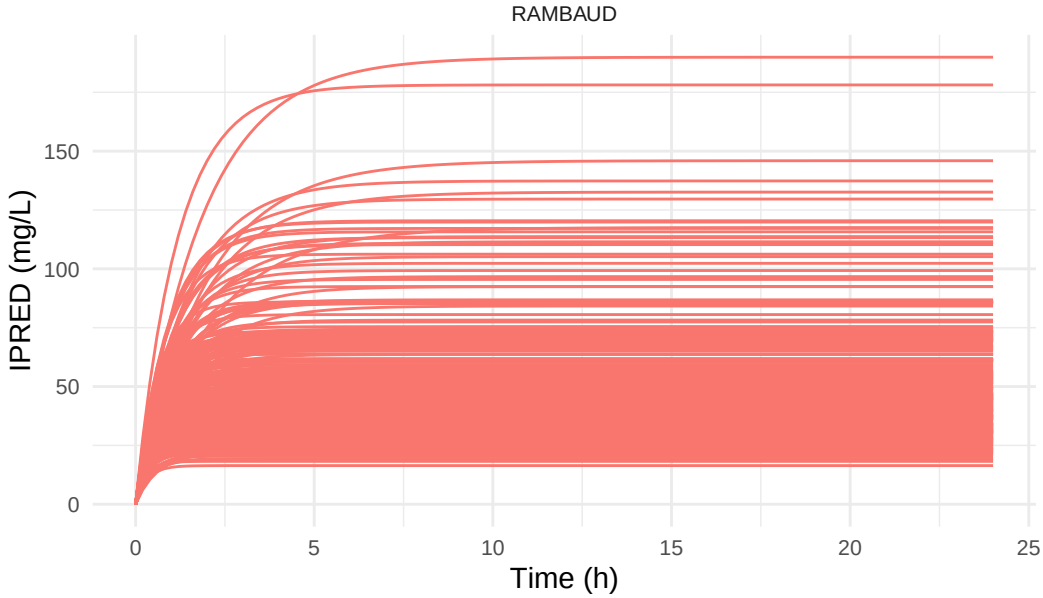

```
$before[[7]]
```

First interdose interval 8 FREQ: 8 DOSE: 500 DUR: 2

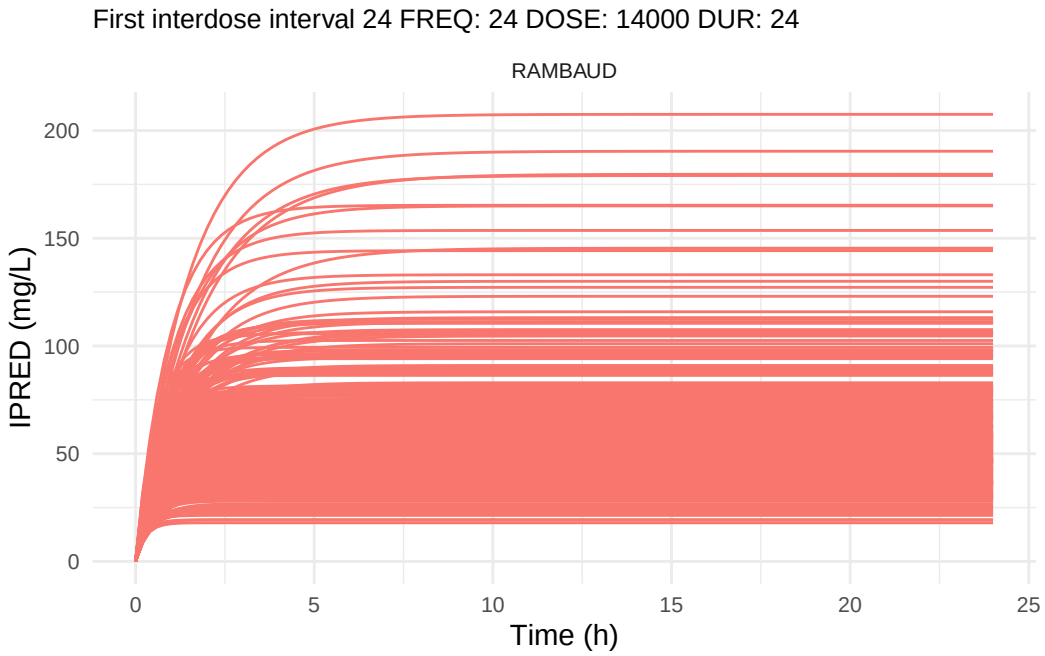


`$before[[8]]`

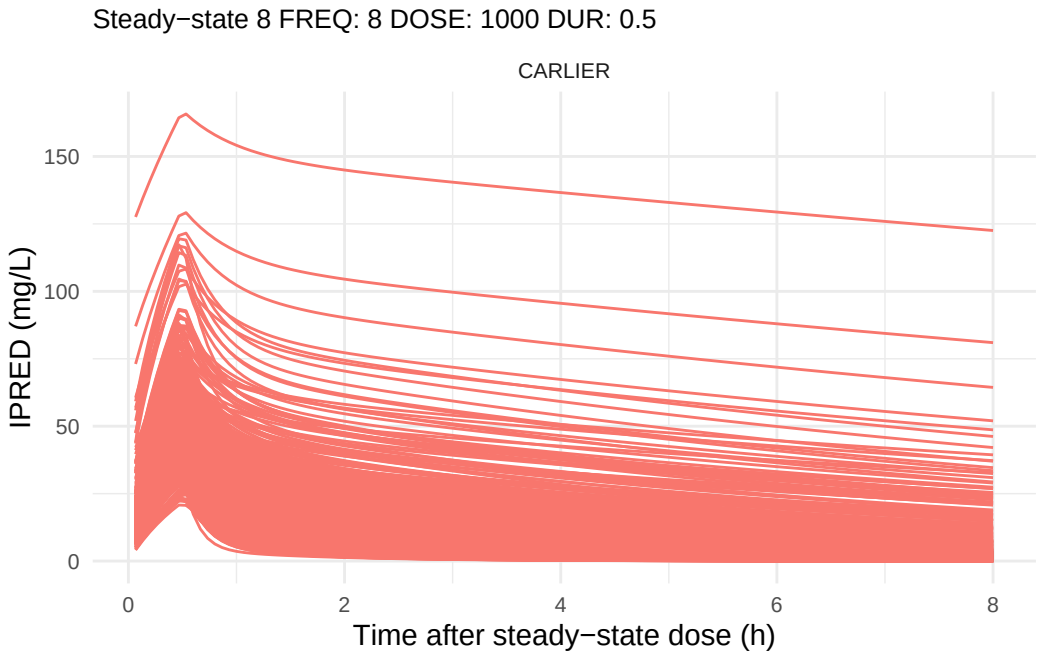
First interdose interval 24 FREQ: 24 DOSE: 12000 DUR: 24



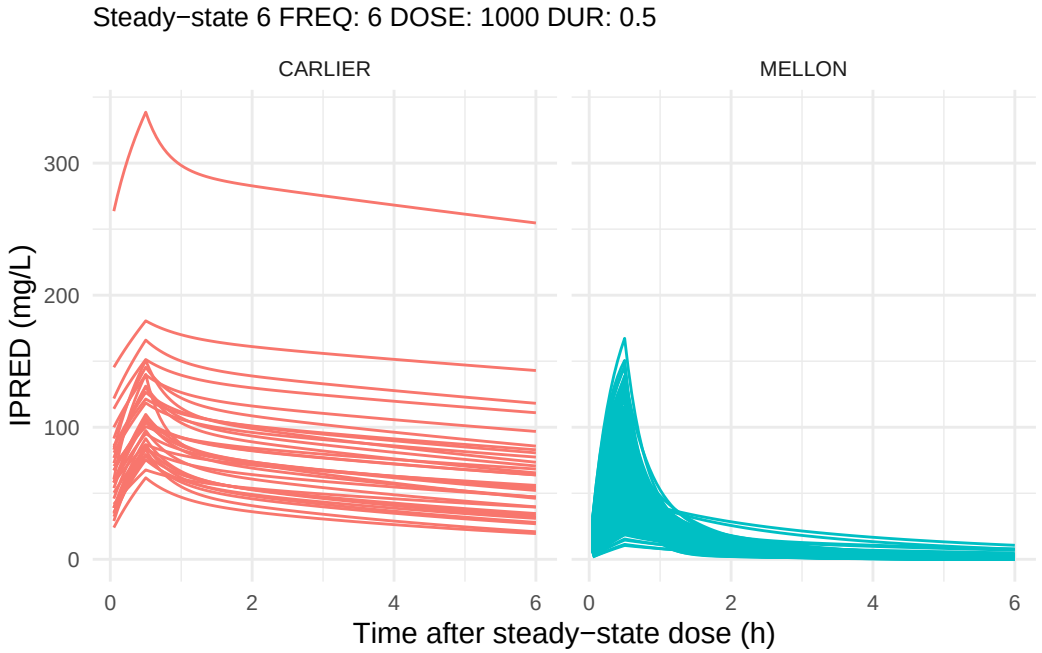
```
$before[[9]]
```



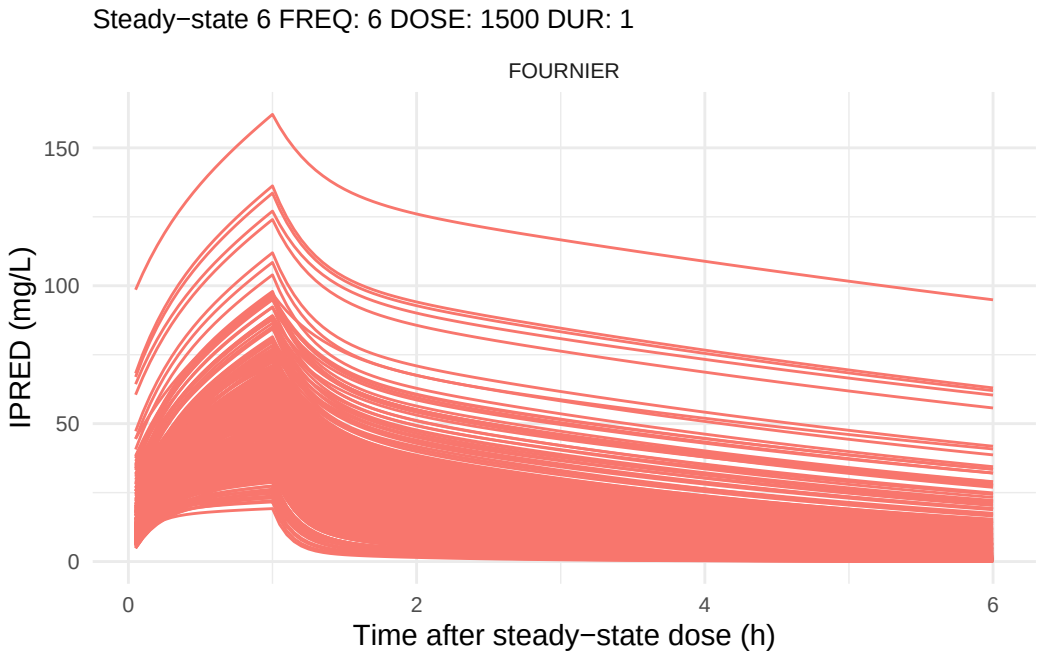

```
$after
$after[[1]]
```


Steady−state 8 FREQ: 8 DOSE: 1000 DUR: 0.5
CARLIER
IPRED (mg/L)
150
100
50
0
0
2
4
6
8
Time after steady−state dose (h)

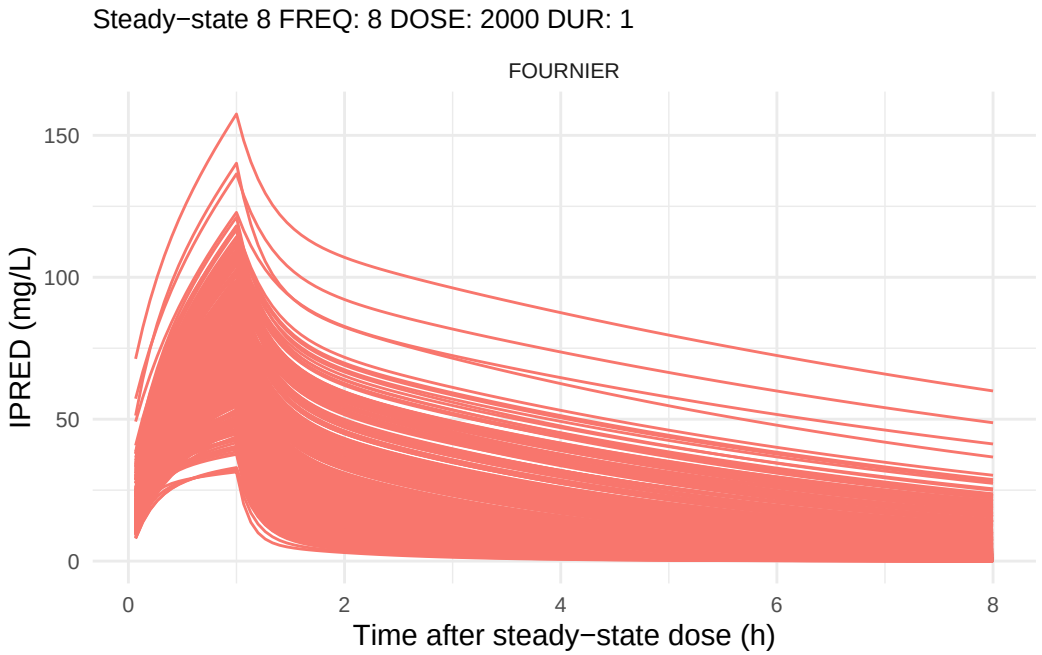
`$after[[2]]`


Steady−state 6 FREQ: 6 DOSE: 1000 DUR: 0.5
CARLIER
MELLON
IPRED (mg/L)
300
200
100
0
0
2
4
6
Time after steady−state dose (h)

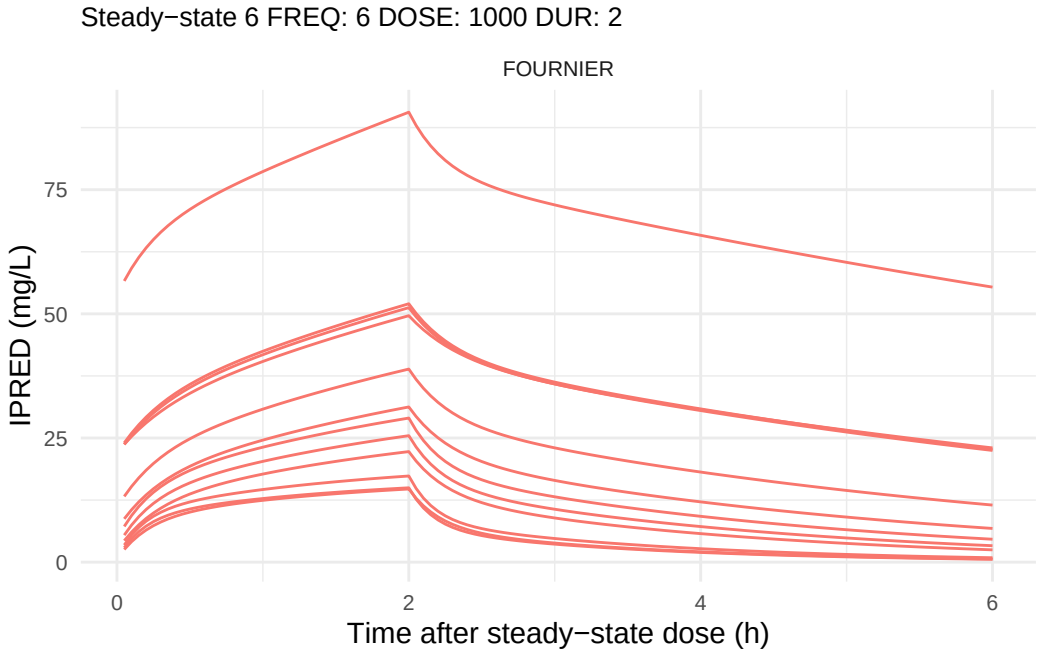
```
$after[[3]]
```



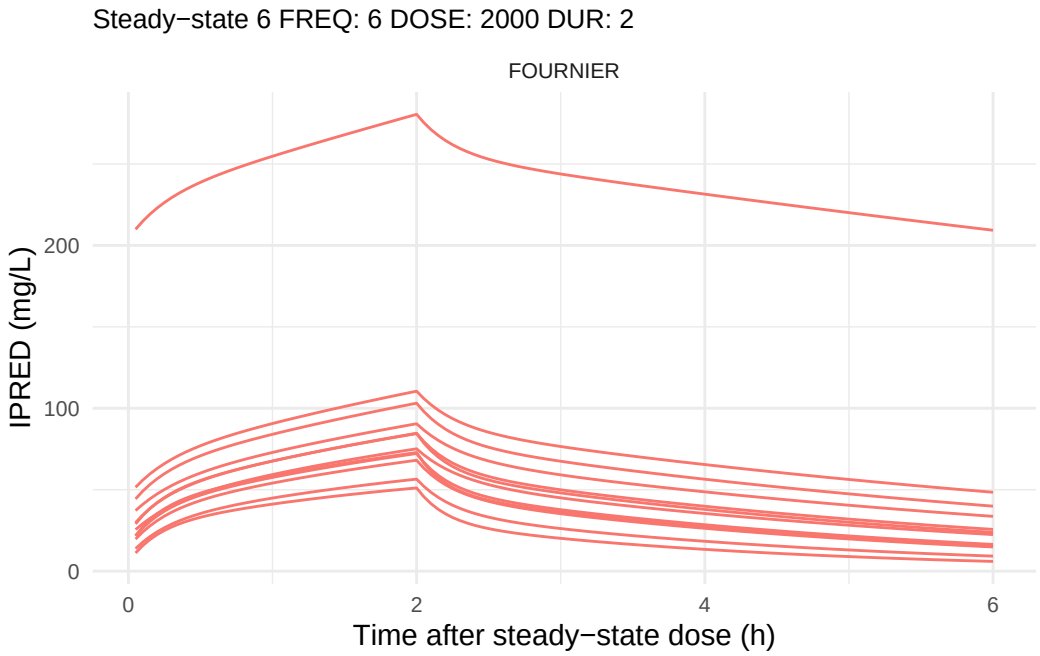

```
$after[[4]]
```


Steady−state 8 FREQ: 8 DOSE: 2000 DUR: 1
FOURNIER
150
100
50
0
IPRED (mg/L)
0
2
4
6
8
Time after steady−state dose (h)

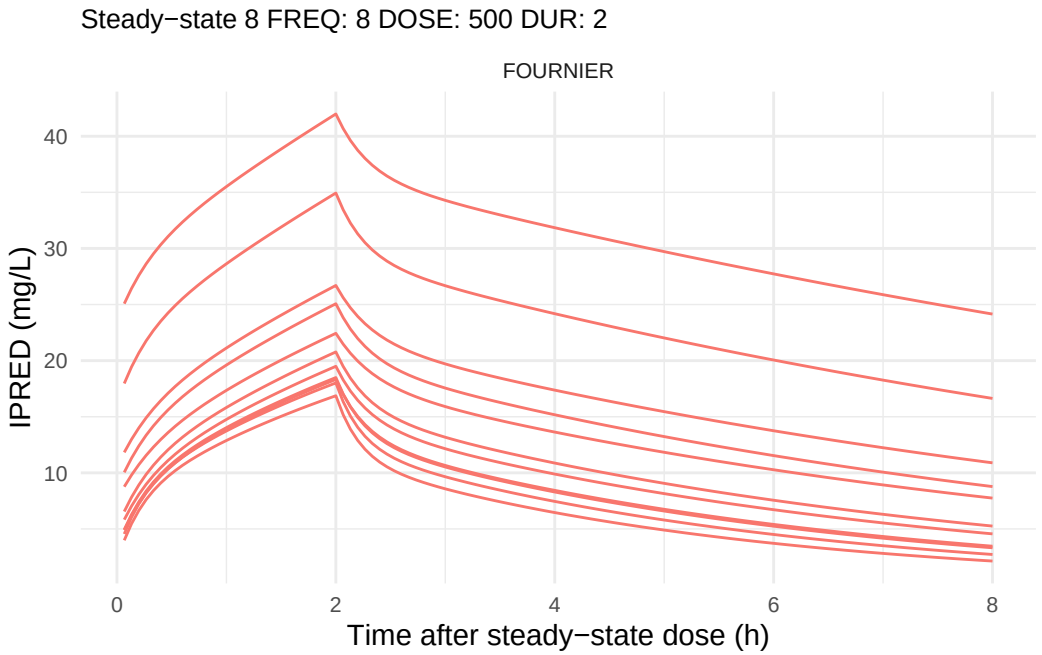
`$after[[5]]`


Steady−state 6 FREQ: 6 DOSE: 1000 DUR: 2
FOURNIER
75
50
25
0
IPRED (mg/L)
0
2
4
6
Time after steady−state dose (h)

```
$after[[6]]
```



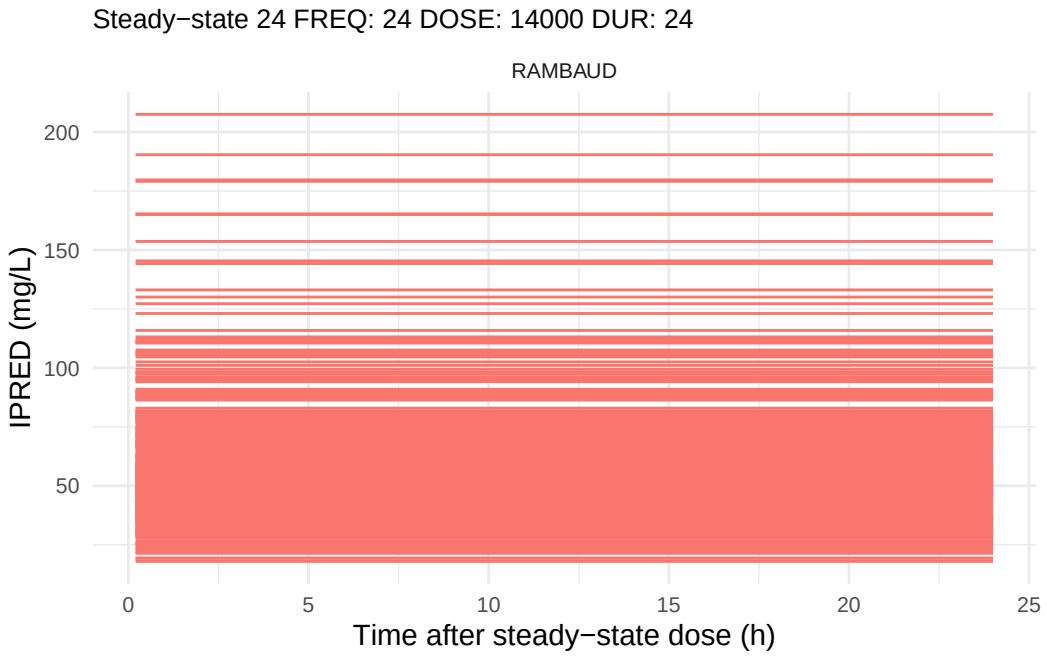

```
$after[[7]]
```


Steady−state 8 FREQ: 8 DOSE: 500 DUR: 2
FOURNIER
IPRED (mg/L)
40
30
20
10
0
2
4
6
8
Time after steady−state dose (h)

```
$after[[8]]
```


Steady−state 24 FREQ: 24 DOSE: 12000 DUR: 24
RAMBAUD
IPRED (mg/L)
150
100
50
0
5
10
15
20
25
Time after steady−state dose (h)

```
$after[[9]]
```



Visualization of 5th, 50th and 95th percentiles (5th and 95th percentiles in dashed)

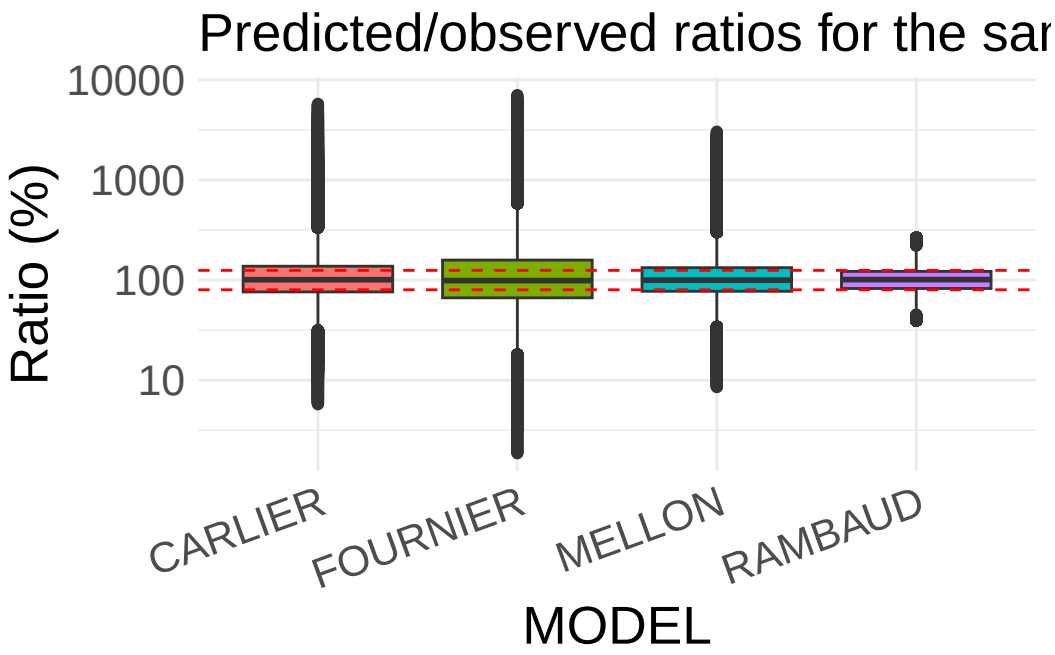
```r
# The data is binned to 40 bins to make it smoother
data_percentiles_ref <- data_ref %>% filter(TIME > TSS) %>%
      mutate(TIME = TIME - TSS) |>
  mutate(TIME_bin = ntile(TIME, 40)) %>%
  group_by(DOSING_SCHEME, MODEL, TIME_bin) %>%
  summarise(
    P5 = quantile(IPRED, 0.05, na.rm = TRUE),
    P50 = quantile(IPRED, 0.50, na.rm = TRUE),
    P95 = quantile(IPRED, 0.95, na.rm = TRUE),
    TIME = median(TIME, na.rm = TRUE),
    .groups = 'drop'
  )

# Loop through each dosing scheme
plot_percentiles <- function(data_percentiles_ref, dosing_schemes) {
  library(ggplot2)
  library(patchwork)
```

```
  plot_list_ref <- list()

  for (i in seq_along(dosing_schemes)) {
    plot_list_ref[[i]] <- ggplot(
      subset(data_percentiles_ref, DOSING_SCHEME == dosing_schemes[i]),
      aes(x = TIME)
    ) +
      geom_line(aes(y = P5, color = MODEL), linetype = "dashed") +
      geom_line(aes(y = P50, color = MODEL), size = 1) +
      geom_line(aes(y = P95, color = MODEL), linetype = "dashed") +
      theme_minimal() +
      labs(
        title = paste(dosing_schemes[i]),
        x = "Time post steady-state (binned)",
        y = "IPRED (mg/L)",
        color = "MODEL"
      ) +
      theme(
        plot.title = element_text(size = 10),
        axis.text = element_text(size = 8),
        strip.text = element_text(size = 8),
        legend.position = "bottom"
      )
  }

  return(plot_list_ref)
}


percentile_plots <- plot_percentiles(data_percentiles_ref, dosing_schemes)
```

Visualization of the inter-individual variability of models by dividing PRED (predicted) values by IPRED (observed) both generated by the same model.

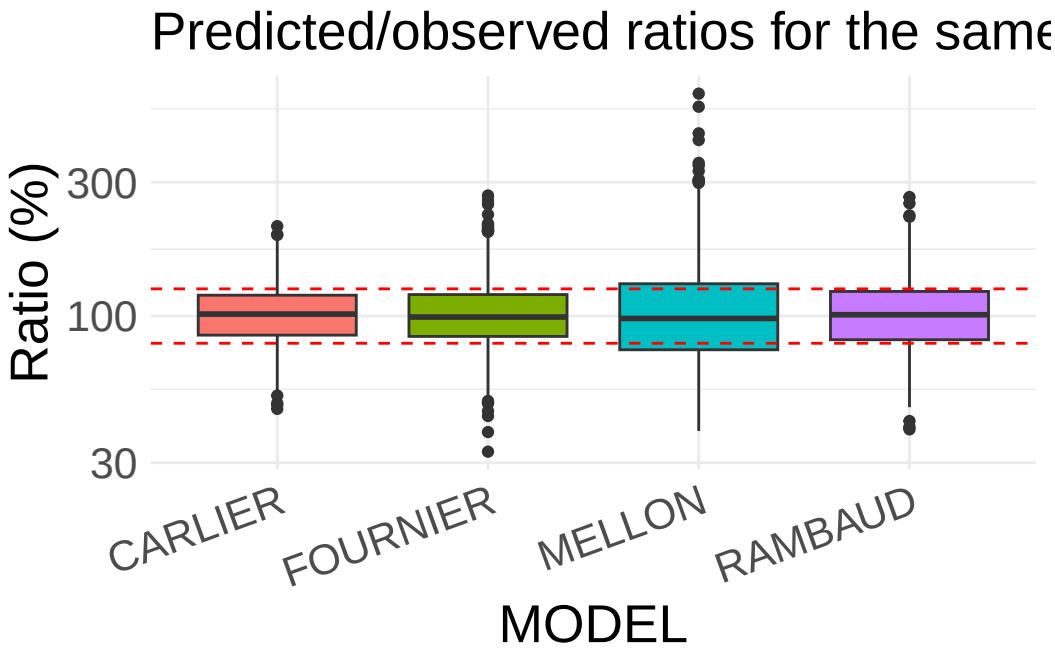
```
# IPRED

# Divide each PRED by the IPRED reference
 AMOX_SIM_QL3 <- AMOX_SIM_QL2 %>%
  group_by(ID, TIME, MODEL) %>%
  filter(REFERENCE == 1) |>
  mutate(
    ratio = (PRED / IPRED) * 100
```

```
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
stratified_ratios_SIM <- ggplot( AMOX_SIM_QL3, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  scale_y_log10() +
  labs(
    title = "Predicted/observed ratios for the same model",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

stratified_ratios_SIM
```



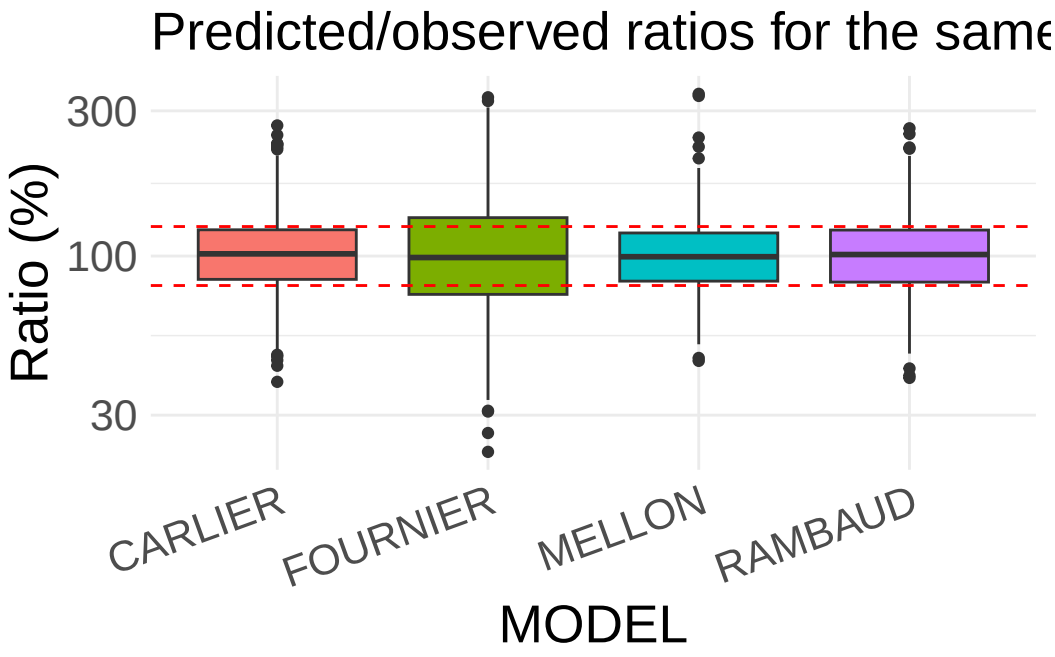

```
# CMAX
# Divide each PRED by the IPRED reference
AMOX_CMAX2 <- AMOX_CMAX1 %>%
  filter(REFERENCE == 1) |>
  group_by(ID, MODEL) %>%
  mutate(
    ratio = (CMAX_PRED / CMAX_IND) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
stratified_ratios_CMAX <- ggplot(AMOX_CMAX2, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Predicted/observed ratios for the same model (Cmax)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
```

```
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

stratified_ratios_CMAX + scale_y_log10()
```



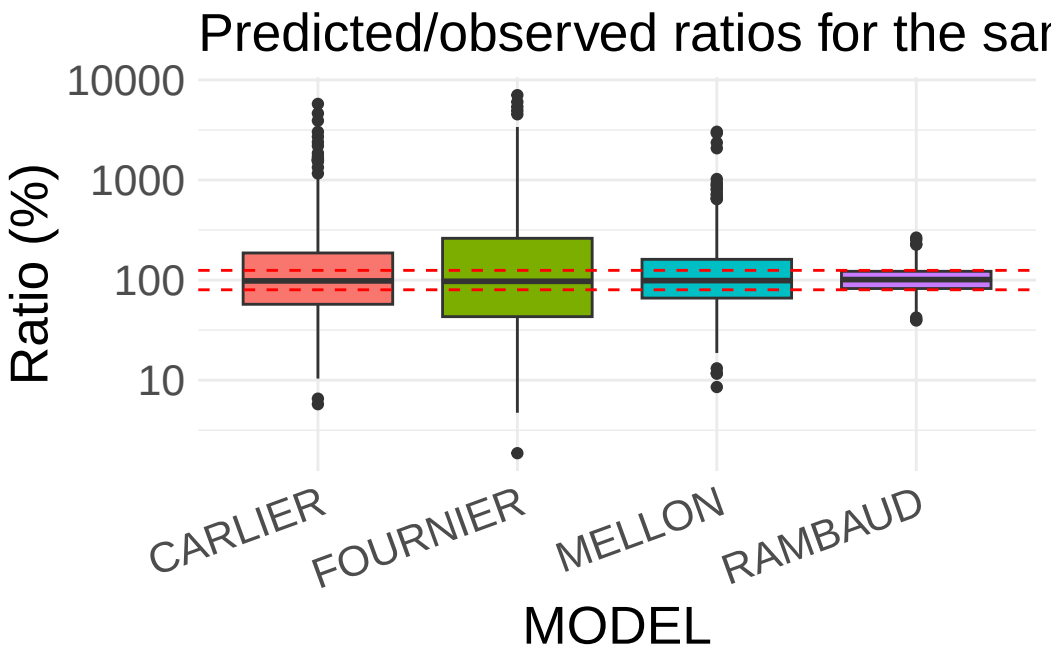

```
# AUC
# Divide each PRED by the IPRED reference
AMOX_AUC2 <- AMOX_AUC1 %>%
  filter(REFERENCE == 1) |>
  group_by(ID, MODEL) %>%
  mutate(
    ratio = (AUC_PRED / AUC_IND) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
stratified_ratios_AUC <- ggplot(AMOX_AUC2, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
```

```
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Predicted/observed ratios for the same model (AUC)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

stratified_ratios_AUC + scale_y_log10()
```




```
# CMIN
# Divide each PRED by the IPRED reference
AMOX_CMIN2 <- AMOX_CMIN1 %>%
  filter(REFERENCE == 1) |>
  group_by(ID, MODEL) %>%
```

```
  mutate(
    ratio = (CMIN_PRED / CMIN_IND) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
stratified_ratios_CMIN <- ggplot(AMOX_CMIN2, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Predicted/observed ratios for the same model (Cmax)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

stratified_ratios_CMIN + scale_y_log10()
```

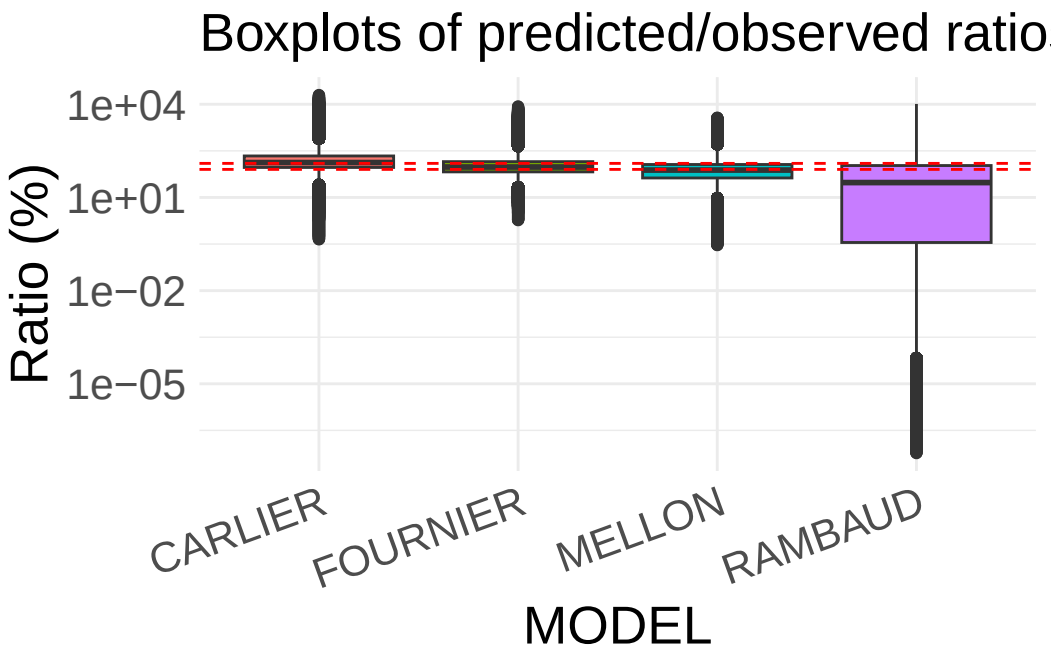


2.2 Model performance

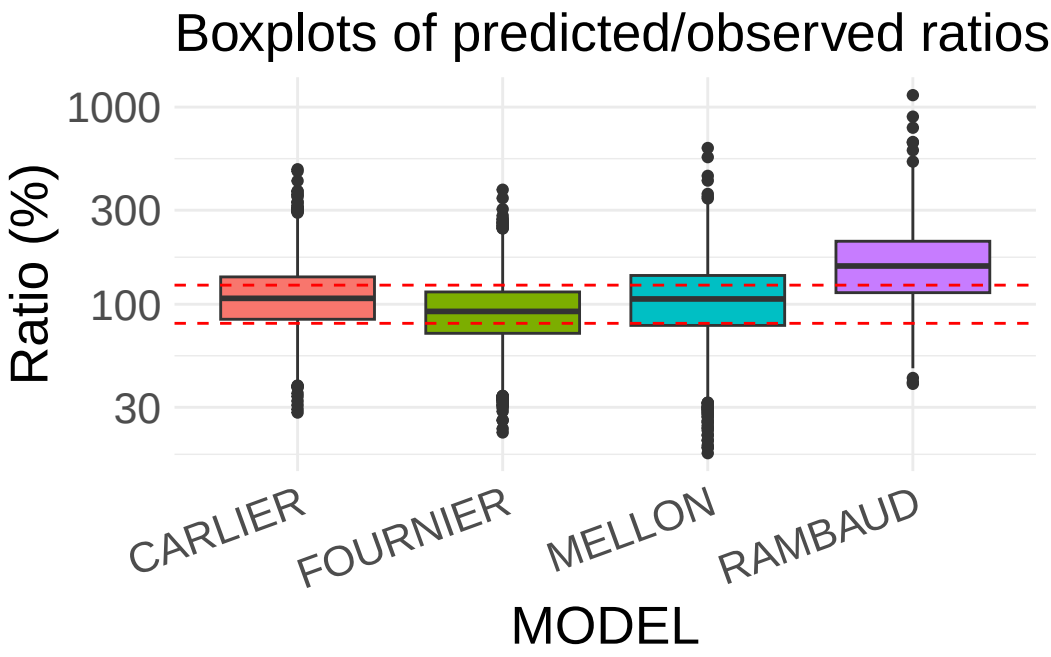
In this section, the focus is no longer solely on observed concentrations (IPRED), but the performance of the models is explored by illustrating how the predicted concentrations (PRED) for **all** the cohorts (not just for covariates on which the model was developed) compare the the observed concentration. Visualization of PRED/IPRED ratios. In all cases we compare PRED (predicted) values to a reference IPRED (observed), which is the IPRED of the model whose cohort was used to simulate a particular set of covariates. Red lines indicate the bioequivalence range of 80-125 %.

```
# IPRED

# Divide each PRED by the IPRED reference
data2 <- AMOX_SIM_QL2 %>%
  group_by(ID, TIME) %>%
  mutate(
    ref_IPRED = first(IPRED[REFERENCE == 1], default = NA),
    ratio = (PRED / ref_IPRED) * 100
  ) %>%
  ungroup()
```

```r
# Boxplot of ratios stratified by model
perf_SIM <- ggplot(data2, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  scale_y_log10() +
  labs(
    title = "Boxplots of predicted/observed ratios",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

perf_SIM
```

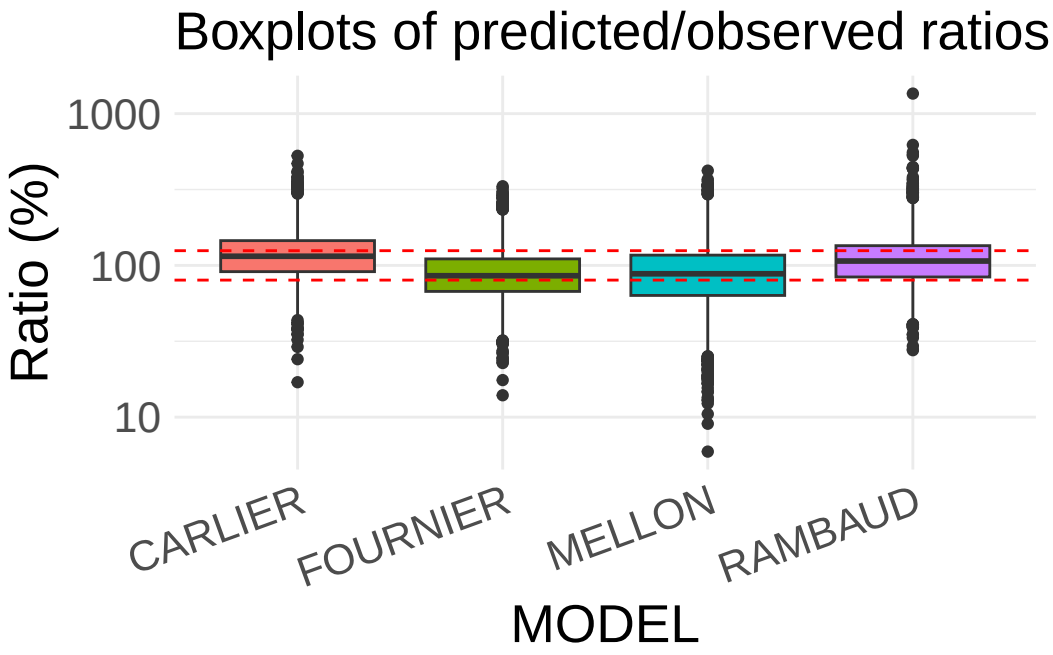


```r
# CMAX
# Divide each PRED by the IPRED reference
AMOX_CMAX3 <- AMOX_CMAX1 %>%
  group_by(ID) %>%
  mutate(
    ref_CMAX = first(CMAX_IND[REFERENCE == 1], default = NA),
    ratio = (CMAX_PRED / ref_CMAX) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
perf_CMAX <- ggplot(AMOX_CMAX3, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Boxplots of predicted/observed ratios (Cmax)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

perf_CMAX + scale_y_log10()
```



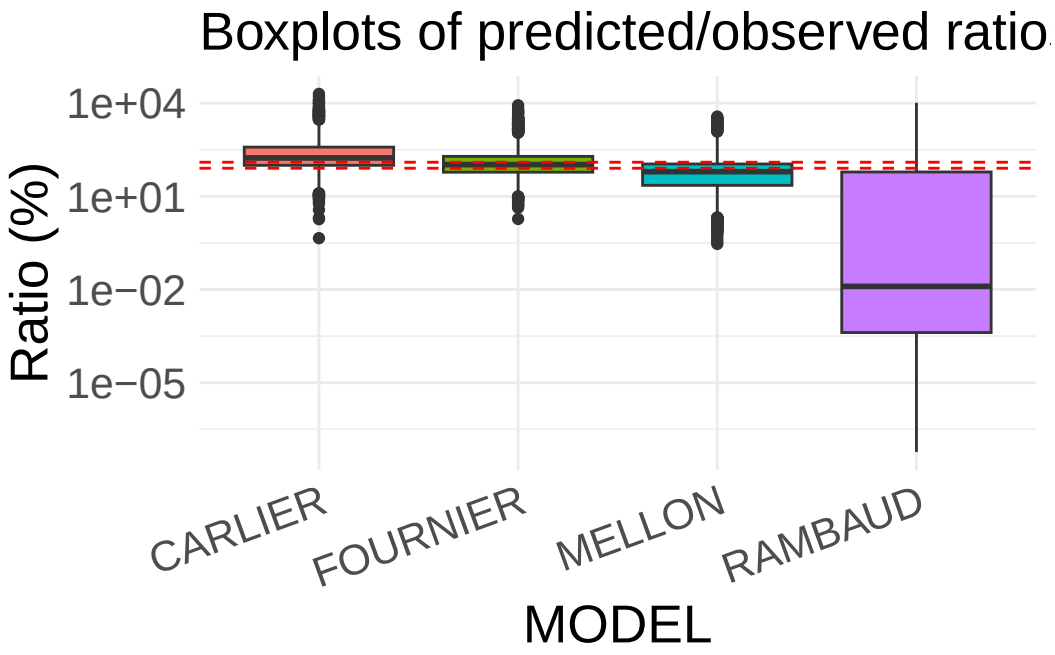

```r
# AUC
# Divide each PRED by the IPRED reference
AMOX_AUC3 <- AMOX_AUC1 %>%
  group_by(ID) %>%
  mutate(
    ref_AUC = first(AUC_IND[REFERENCE == 1], default = NA),
    ratio = (AUC_PRED / ref_AUC) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
perf_AUC <- ggplot(AMOX_AUC3, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
  scale_y_log10() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Boxplots of predicted/observed ratios (AUC)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
```

```
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

perf_AUC
```




```
# CMIN
# Divide each PRED by the IPRED reference
AMOX_CMIN3 <- AMOX_CMIN1 %>%
  group_by(ID) %>%
  mutate(
    ref_CMIN = first(CMIN_IND[REFERENCE == 1], default = NA),
    ratio = (CMIN_PRED / ref_CMIN) * 100
  ) %>%
  ungroup()

# Boxplot of ratios stratified by model
perf_CMIN <- ggplot(AMOX_CMIN3, aes(x = MODEL, y = ratio, fill = MODEL)) +
  geom_boxplot() +
```

```
  scale_y_log10() +
  geom_hline(yintercept = 80, linetype = "dashed", color = "red") +
  geom_hline(yintercept = 125, linetype = "dashed", color = "red") +
  labs(
    title = "Boxplots of predicted/observed ratios (CMIN)",
    x = "MODEL",
    y = "Ratio (%)"
  ) +
  theme_minimal() +
  theme(legend.position = "none") +
  theme(
    axis.text.x = element_text(angle = 20, hjust = 1, size = 16),
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 20),
    plot.title = element_text(size=20),
  )

perf_CMIN
```



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Fournier, Anne, Sylvain Goutelle, Yok-Ai Que, Philippe Eggimann, Olivier Pantet, Farshid Sadeghipour, Pierre Voirol, and Chantal Csajka. 2018. "Population Pharmacokinetic Study of Amoxicillin-Treated Burn Patients Hospitalized at a Swiss Tertiary-Care Center." *Antimicrobial Agents and Chemotherapy* 62 (9): e00505–18. https://doi.org/10.1128/AAC.00505-18.

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Mellon, G, K Hammas, C Burdet, X Duval, C Carette, N El-Helali, L Massias, F Mentré, S Czernichow, and A -C Crémieux. 2020. "Population Pharmacokinetics and Dosing Simulations of Amoxicillin in Obese Adults Receiving Co-Amoxiclav." *Journal of Antimicrobial Chemotherapy* 75 (12): 3611–18. https://doi.org/10.1093/jac/dkaa368.

Rambaud, Antoine, Benjamin Jean Gaborit, Colin Deschanvres, Paul Le Turnier, Raphaël Lecomte, Nathalie Asseray-Madani, Anne-Gaëlle Leroy, et al. 2020. "Development and Validation of a Dosing Nomogram for Amoxicillin in Infective Endocarditis." *The Journal of Antimicrobial Chemotherapy* 75 (10): 2941–50. https://doi.org/10.1093/jac/dkaa232.