Calculation of drugs bioequivalence using MIXED effects model

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In this tutorial the calculation of pharmacokinetic parameters will be demonstrated using raw pharmacokinetic data using MIXED effects model.

Cmax

```
# upload packges
library(writexl)
library(readxl)
library(nlme)
# temporarily turn off warnings
options(warn=0)

# Import and data preprocessing (set working directory)
setwd('/Users/valer/Desktop/R_project/')
path_ <- getwd()
path_ <- "C:/Users/valer/Desktop/R_project/project 4/total.xlsx"

# loading data containing test and reference datasheets
loading_data <- function(path_, sheet_) {
  # reading file
  data <- read_excel(path = path_, sheet = sheet_)
  return (data)
}

# dataset for drug product (dataset for Cmax)
data_test <- loading_data(path_, "Cmax_")
```

```r
# select columns
cols <- c('Subject', 'Sequence', 'Period', 'Treatment')
data_test[,cols] <- data.frame(apply(data_test[cols], 2, as.factor))
data_test
```

```
# A tibble: 54 x 5
   Subject   Sequence Period Treatment  Cmax
   <chr>     <chr>    <chr>  <chr>     <dbl>
 1 Subject_1 TR       1      T          1.85
 2 Subject_1 TR       2      R          1.87
 3 Subject_2 TR       1      T          1.17
 4 Subject_2 TR       2      R          1.13
 5 Subject_3 TR       1      T          1.80
 6 Subject_3 TR       2      R          1.88
 7 Subject_4 TR       1      T          1.77
 8 Subject_4 TR       2      R          1.67
 9 Subject_5 TR       1      T          1.20
10 Subject_5 TR       2      R          1.3
# i 44 more rows
```

Fittng data to MIXED effects model

```r
# R formula for the model
Result = lme(log(Cmax) ~ Sequence + Period + Treatment, random=~1|Subject,
             data = data_test)
summary(Result)
```

```
Linear mixed-effects model fit by REML
  Data: data_test
        AIC       BIC   logLik
  -36.33569 -24.86355 24.16784

Random effects:
 Formula: ~1 | Subject
        (Intercept)   Residual
StdDev:   0.2149787 0.05690634

Fixed effects:  log(Cmax) ~ Sequence + Period + Treatment
                 Value  Std.Error DF   t-value p-value
(Intercept)  0.4753565 0.05941706 25  8.000338  0.0000
```

```
SequenceTR  -0.0957943 0.08424202 25 -1.137132  0.2663
Period2      0.0434427 0.01548794 25  2.804938  0.0096
TreatmentT   0.0339851 0.01577345 25  2.154575  0.0410
 Correlation:
           (Intr) SqncTR Perid2
SequenceTR -0.682
Period2    -0.130  0.000
TreatmentT -0.123 -0.007  0.000

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-1.9591423 -0.4245167  0.1027731  0.3081176  1.7356000

Number of Observations: 54
Number of Groups: 27
```

```
# variances from the standard deviation
VarCorr(Result)
```

```
Subject = pdLogChol(1)
            Variance    StdDev
(Intercept) 0.046215833 0.21497868
Residual    0.003238332 0.05690634
```

```
# 90% of log scale difference
ci = intervals(Result, 0.9)
```

```
# 90% CI of GMR
exp(ci$fixed["TreatmentT", ])
```

```
   lower     est.    upper
1.007067 1.034569 1.062823
```

Cmax

Calculated point estimate equals to 1.03, the lower limit equals to 1.01, the upper limit equals to 1.06. This concludes that the both drugs are bioequivalent (limits are within 0.80 - 1.25).

……

AUCt

```
# dataset for the drug product dataset for AUC(0-t)
data_test <- loading_data(path_, "AUCt_")

# select columns
cols <- c('Subject', 'Sequence', 'Period', 'Treatment')
data_test[,cols] <- data.frame(apply(data_test[cols], 2, as.factor))
data_test
```

```
# A tibble: 54 x 5
   Subject   Sequence Period Treatment  AUCt
   <chr>     <chr>    <chr>  <chr>     <dbl>
 1 Subject_1 TR       1      T         10.2
 2 Subject_1 TR       2      R         12.3
 3 Subject_2 TR       1      T          6.63
 4 Subject_2 TR       2      R          5.56
 5 Subject_3 TR       1      T          7.24
 6 Subject_3 TR       2      R          8.13
 7 Subject_4 TR       1      T          5.5
 8 Subject_4 TR       2      R          4.6
 9 Subject_5 TR       1      T          6.6
10 Subject_5 TR       2      R          5.5
# i 44 more rows
```

```
# R formula for the model
Result = lme(log(AUCt) ~ Sequence + Period + Treatment, random=~1|Subject,
             data = data_test)
summary(Result)
```

```
Linear mixed-effects model fit by REML
  Data: data_test
       AIC     BIC   logLik
  1.781262 13.2534 5.109369

Random effects:
 Formula: ~1 | Subject
        (Intercept)  Residual
StdDev:   0.2082549 0.1187839
```

```
Fixed effects:  log(AUCt) ~ Sequence + Period + Treatment
                 Value  Std.Error DF  t-value p-value
(Intercept)  2.1524055 0.06399896 25 33.63188  0.0000
SequenceTR  -0.1643873 0.08649854 25 -1.90046  0.0690
Period2     -0.0356695 0.03232889 25 -1.10333  0.2804
TreatmentT   0.0159990 0.03286274 25  0.48684  0.6306
 Correlation:
           (Intr) SqncTR Perid2
SequenceTR -0.647
Period2    -0.253  0.000
TreatmentT -0.238 -0.014  0.000

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-1.3807822 -0.5599341 -0.1569549  0.5112270  1.5780603

Number of Observations: 54
Number of Groups: 27
```

```
# variances from the standard deviation
VarCorr(Result)
```

```
Subject = pdLogChol(1)
            Variance   StdDev
(Intercept) 0.04337011 0.2082549
Residual    0.01410962 0.1187839
```

```
# 90% of log scale difference
ci = intervals(Result, 0.9)
```

```
# 90% CI of GMR
exp(ci$fixed["TreatmentT", ])
```

```
    lower      est.     upper
0.9606596 1.0161277 1.0747985
```

AUCt

Calculated point estimate equals to 1.02, the lower limit equals to 0.96, the upper limit equals to 1.07. This concludes that the both drugs are bioequivalent (limits are within 0.80 - 1.25).

AUCinf

```
# dataset for the drug product dataset for AUCinf
data_test <- loading_data(path_, "AUCinf_")

# select columns
cols <- c('Subject', 'Sequence', 'Period', 'Treatment')
data_test[,cols] <- data.frame(apply(data_test[cols], 2, as.factor))
data_test
```

```
# A tibble: 54 x 5
   Subject   Sequence Period Treatment AUCinf
   <chr>     <chr>    <chr>  <chr>      <dbl>
 1 Subject_1 TR       1      T           12
 2 Subject_1 TR       2      R           10.4
 3 Subject_2 TR       1      T            7.2
 4 Subject_2 TR       2      R            8.3
 5 Subject_3 TR       1      T            9.5
 6 Subject_3 TR       2      R            9.8
 7 Subject_4 TR       1      T            6.4
 8 Subject_4 TR       2      R            4.5
 9 Subject_5 TR       1      T            7.6
10 Subject_5 TR       2      R            6.3
# i 44 more rows
```

```
# R formula for the model
Result = lme(log(AUCinf) ~ Sequence + Period + Treatment, random=~1|Subject,
             data = data_test)
summary(Result)
```

```
Linear mixed-effects model fit by REML
  Data: data_test
       AIC      BIC    logLik
  17.37804 28.85018 -2.689021

Random effects:
 Formula: ~1 | Subject
        (Intercept)  Residual
StdDev:   0.2870361 0.1216102
```

```
Fixed effects:  log(AUCinf) ~ Sequence + Period + Treatment
                 Value  Std.Error DF   t-value p-value
(Intercept)  2.0910197 0.08325587 25 25.115582  0.0000
SequenceTR   0.0713134 0.11541703 25  0.617876  0.5422
Period2     -0.0312600 0.03309810 25 -0.944464  0.3540
TreatmentT   0.0169099 0.03367910 25  0.502088  0.6200
 Correlation:
           (Intr) SqncTR Perid2
SequenceTR -0.665
Period2    -0.199  0.000
TreatmentT -0.188 -0.010  0.000

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.04133372 -0.42094810  0.04766206  0.42221395  1.47430340

Number of Observations: 54
Number of Groups: 27
```

```
# variances from the standard deviation
VarCorr(Result)
```

```
Subject = pdLogChol(1)
            Variance   StdDev
(Intercept) 0.08238975 0.2870361
Residual    0.01478904 0.1216102
```

```
# 90% of log scale difference
ci = intervals(Result, 0.9)
```

```
# 90% CI of GMR
exp(ci$fixed["TreatmentT", ])
```

```
    lower      est.     upper
0.9601951 1.0170536 1.0772791
```

AUCinf

Calculated point estimate equals to 1.02, the lower limit equals to 0.96, the upper limit equals to 1.07. This concludes that the both drugs are bioequivalent (limits are within 0.80 - 1.25).