

Crossover Trial Power using Simulation

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Function to simulate crossover trial using lme4 (warning mmessage: boundary (singular) fit: see ?isSingular)

```
# n - number of patients in each order group sdW - within
# patient standard deviation sdB - between patient standard
# deviation beta - coefficient vector c(Intercept, Treatment,
# Order, Treatment:Order)

require("lme4")

simulatec <- function(n = 10, sdW = 4, sdB = 1, beta = c(8, 1,
  0, 0), alpha = 0.05) {

  # generate data
  Patient <- as.factor(rep(1:(2 * n), rep(2, 2 * n)))
  Treatment <- c(rep(c("Treatment1", "Treatment2"), n), rep(c("Treatment2",
    "Treatment1"), n))
  Order <- rep(c("First", "Second"), 2 * n)
  Data <- data.frame(Patient, Treatment, Order)
  FMat <- model.matrix(~Treatment * Order, data = Data)
  RMat <- model.matrix(~0 + Patient, data = Data)
  Response <- FMat %>% beta + RMat %>% rnorm(2 * n, 0, sdB) +
    rnorm(4 * n, 0, sdW)
  Data$Response <- Response

  # analyse
  Fit <- lmer(Response ~ (1 | Patient) + Treatment * Order,
    data = Data)
  Est <- fixef(Fit)[2]
  Ste <- sqrt(vcov(Fit)[2, 2])
  prod(Est + c(-1, 1) * qnorm(1 - alpha/2) * Ste) > 0
}

# power for n=20 and treatment effect 4
mean(replicate(1000, simulatec(n = 20, beta = c(8, 4, 0, 0))))
```

```
[1] 0.868
```

Function to simulate crossover trial using nlme (no warning messages for equivalent analyses compared to lme4)

```
# A random effect very near zero seems to be the reason for
# the warning message using lme4

require(nlme)

simulaten <- function(n = 10, sdW = 4, sdB = 1, beta = c(8, 1,
  0, 0), alpha = 0.05) {

  # generate data
  Patient <- as.factor(rep(1:(2 * n), rep(2, 2 * n)))
  Treatment <- c(rep(c("Treatment1", "Treatment2"), n), rep(c("Treatment2",
    "Treatment1"), n))
  Order <- rep(c("First", "Second"), 2 * n)
  Data <- data.frame(Patient, Treatment, Order)
  FMat <- model.matrix(~Treatment * Order, data = Data)
  RMat <- model.matrix(~0 + Patient, data = Data)
  Response <- FMat %%% beta + RMat %%% rnorm(2 * n, 0, sdB) +
    rnorm(4 * n, 0, sdW)
  Data$Response <- Response

  # analyse
  Fit <- lme(Response ~ Treatment * Order, random = ~1 | Patient,
    data = Data, na.action = "na.omit")
  Est <- fixed.effects(Fit)[2]
  Ste <- sqrt(vcov(Fit)[2, 2])
  prod(Est + c(-1, 1) * qnorm(1 - alpha/2) * Ste) > 0  #(logic: neg*neg = pos, so excludes 0)
}

# power for n=20 and treatment effect 4
mean(replicate(1000, simulaten(n = 20, beta = c(8, 4, 0, 0))))

[1] 0.855
```

Show model matrix for fixed effects

Show model matrix for random effects

Show the simulated data

Fit Model

Simulate a very large crossover trial and analyse

Analyse the large trial

Computing Environment

`sessionInfo()`

R version 3.6.1 (2019-07-05)

Platform: x86_64-w64-mingw32/x64 (64-bit)

Running under: Windows 10 x64 (build 17134)

Matrix products: default

locale:

```
[1] LC_COLLATE=English_United Kingdom.1252
[2] LC_CTYPE=English_United Kingdom.1252
[3] LC_MONETARY=English_United Kingdom.1252
[4] LC_NUMERIC=C
[5] LC_TIME=English_United Kingdom.1252
```

attached base packages:

```
[1] stats      graphics  grDevices  utils      datasets
[6] methods    base
```

other attached packages:

```
[1] nlme_3.1-140  lme4_1.1-21  Matrix_1.2-17 knitr_1.23
```

loaded via a namespace (and not attached):

```
[1] Rcpp_1.0.1      lattice_0.20-38 digest_0.6.20
[4] MASS_7.3-51.4   grid_3.6.1      formatR_1.7
[7] magrittr_1.5     evaluate_0.14    stringi_1.4.3
[10] minqa_1.2.4      nloptr_1.2.1     boot_1.3-22
[13] rmarkdown_1.14   splines_3.6.1    tools_3.6.1
[16] stringr_1.4.0    xfun_0.8         yaml_2.2.0
[19] compiler_3.6.1  htmltools_0.3.6
```

This took 70.51 seconds to execute.