

Crossover Trial

Eamonn O'Brien

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Simulate a tiny crossover trial to show matrices

```
n <- 3 # number of patients

sdB = 1 # between person SD

sdW = 1 # within person SD

beta = c(1, 1, 1, 1) #intercept, main effect, order effect, interaction

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) # Fixed effects

RMat <- model.matrix(~0 + Patient, data = Data) # Random effects

Response <- FMat %*% beta + RMat %*% rnorm(2 * n, 0, sdB) + rnorm(4 *
  n, 0, sdW) # matrix multiplication

Data$Response <- Response
```

Show model matrix for fixed effects

FMat

	(Intercept)	Treatment	Treatment2	OrderSecond
1	1		0	0
2	1		1	1
3	1		0	0
4	1		1	1
5	1		0	0
6	1		1	1
7	1		1	0
8	1		0	1
9	1		1	0
10	1		0	1
11	1		1	0
12	1		0	1

	TreatmentTreatment2:OrderSecond
1	0
2	1
3	0
4	1
5	0
6	1
7	0
8	0
9	0
10	0
11	0
12	0

attr("assign")

[1] 0 1 2 3

attr("contrasts")

attr("contrasts")\$Treatment

[1] "contr.treatment"

attr("contrasts")\$Order

[1] "contr.treatment"

Show model matrix for random effects

RMat

	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6
1	1	0	0	0	0	0
2	1	0	0	0	0	0
3	0	1	0	0	0	0
4	0	1	0	0	0	0
5	0	0	1	0	0	0
6	0	0	1	0	0	0
7	0	0	0	1	0	0
8	0	0	0	1	0	0
9	0	0	0	0	1	0
10	0	0	0	0	1	0
11	0	0	0	0	0	1
12	0	0	0	0	0	1

```
attr(,"assign")
```

```
[1] 1 1 1 1 1 1
```

```
attr(,"contrasts")
```

```
attr(,"contrasts")$Patient
```

```
[1] "contr.treatment"
```

Show the simulated data**Data**

	Patient	Treatment	Order	Response
1	1	Treatment1	First	0.90044056
2	1	Treatment2	Second	2.17446312
3	2	Treatment1	First	0.08296966
4	2	Treatment2	Second	3.32416054
5	3	Treatment1	First	3.78279011
6	3	Treatment2	Second	5.91852214
7	4	Treatment2	First	2.47127984
8	4	Treatment1	Second	2.18119111
9	5	Treatment2	First	1.57344660
10	5	Treatment1	Second	3.91620087
11	6	Treatment2	First	4.21291547
12	6	Treatment1	Second	1.74844783

Fit Model

```
(Fit <- lme4::lmer(Response ~ (1 | Patient) + Treatment * Order,
  data = Data))
```

Linear mixed model fit by REML ['lmerMod']

Formula: Response ~ (1 | Patient) + Treatment * Order

Data: Data

REML criterion at convergence: 34.3185

Random effects:

Groups	Name	Std.Dev.
Patient	(Intercept)	0.9754
Residual		1.3007

Number of obs: 12, groups: Patient, 6

Fixed Effects:

	(Intercept)
	1.58873
TreatmentTreatment2	1.16381
OrderSecond	1.02655
TreatmentTreatment2:OrderSecond	0.02662

```
confint(Fit)
```

	2.5 %	97.5 %
.sig01	0.0000000	2.067994
.sigma	0.6594705	1.983156
(Intercept)	-0.0702044	3.247671
TreatmentTreatment2	-1.1822785	3.509906
OrderSecond	-1.3195459	3.372639
TreatmentTreatment2:OrderSecond	-4.1201312	4.173371

Simulate a very large crossover trial and analyse

```
n <- 5000 # number of patients
sdB = 1 # between person SD
sdW = 1 # within person SD
beta = c(1, 1, 1, 1) #intercept, main effect, order effect, interaction
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) # Fixed effects
RMat <- model.matrix(~0 + Patient, data = Data) # Random effects
Response <- FMat %*% beta + RMat %*% rnorm(2 * n, 0, sdB) + rnorm(4 *
  n, 0, sdW) # matrix multiplication
```


Analyse the large trial

```
summary(Fit <- lme4::lmer(Response ~ (1 | Patient) + Treatment *
  Order, data = Data))
```

Linear mixed model fit by REML ['lmerMod']

Formula: Response ~ (1 | Patient) + Treatment * Order

Data: Data

REML criterion at convergence: 67634.6

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.0925	-0.5539	-0.0042	0.5510	3.6116

Random effects:

Groups	Name	Variance	Std.Dev.
Patient	(Intercept)	0.9815	0.9907
Residual		0.9996	0.9998

Number of obs: 20000, groups: Patient, 10000

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	0.98739	0.01991	49.60
TreatmentTreatment2	0.98838	0.02815	35.11
OrderSecond	1.01532	0.02815	36.07
TreatmentTreatment2:OrderSecond	1.00029	0.04868	20.55

Correlation of Fixed Effects:

	(Intr)	TrtmT2	OrdrSc
TrtmntTrtm2	-0.707		
OrderSecond	-0.707	0.748	
TrtmntT2:OS	0.611	-0.865	-0.865

```
confint(Fit)
```

	2.5 %	97.5 %
.sig01	0.9688031	1.012548
.sigma	0.9860071	1.013720
(Intercept)	0.9483813	1.026405
TreatmentTreatment2	0.9332138	1.043556
OrderSecond	0.9601519	1.070494
TreatmentTreatment2:OrderSecond	0.9048708	1.095703

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] 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      nlme_3.1-140
 [7] formatR_1.7     magrittr_1.5    evaluate_0.14
[10] stringi_1.4.3   minqa_1.2.4     nloptr_1.2.1
[13] Matrix_1.2-17   boot_1.3-22     rmarkdown_1.14
[16] splines_3.6.1   lme4_1.1-21     tools_3.6.1
[19] stringr_1.4.0   xfun_0.8        yaml_2.2.0
[22] compiler_3.6.1  htmltools_0.3.6

This took 17.11 seconds to execute.
```