

# Longitudinal clinical trial using linear mixed-effects models

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```
# upload packages
library(readxl)
library(tidyverse) # get for tibble
library(ggplot2)
library(ggplot2)
library(DescTools)
library(lmerTest)
library(huxtable) # printing pretty table
library(lme4)
library(lattice)
library(simr)
# temporarily turn off warnings
options(warn=0)

# Import and data preprocessing

# set working directory
path_ <- "C:/Users/valer/Desktop/R_project/Project 7/data.xlsx"

# loading data containing test and reference datasheets
loading_data <- function(path_, sheet_) {

  # reading file
  data <- read_excel(path = path_, sheet = sheet_)
  return (data)
}

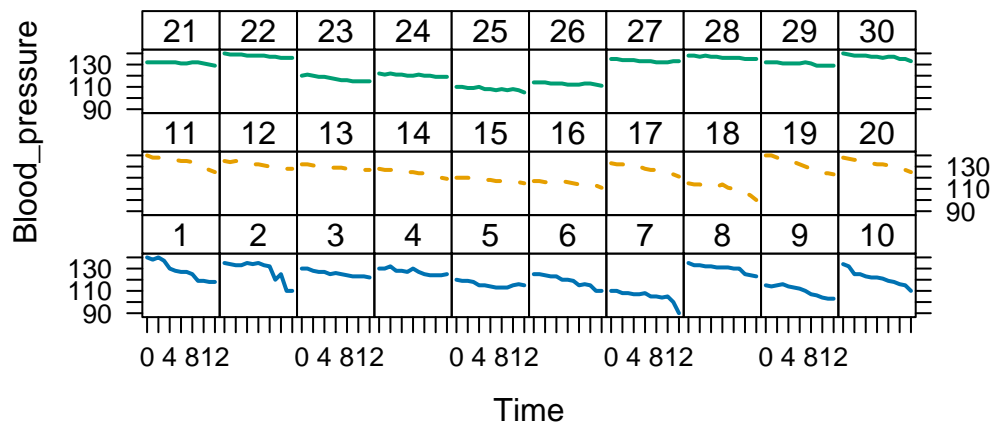
# dataset for the test medicinal product
data_test <- loading_data(path_, "data")
```

```
# printing the first rows
head(data_test)
```

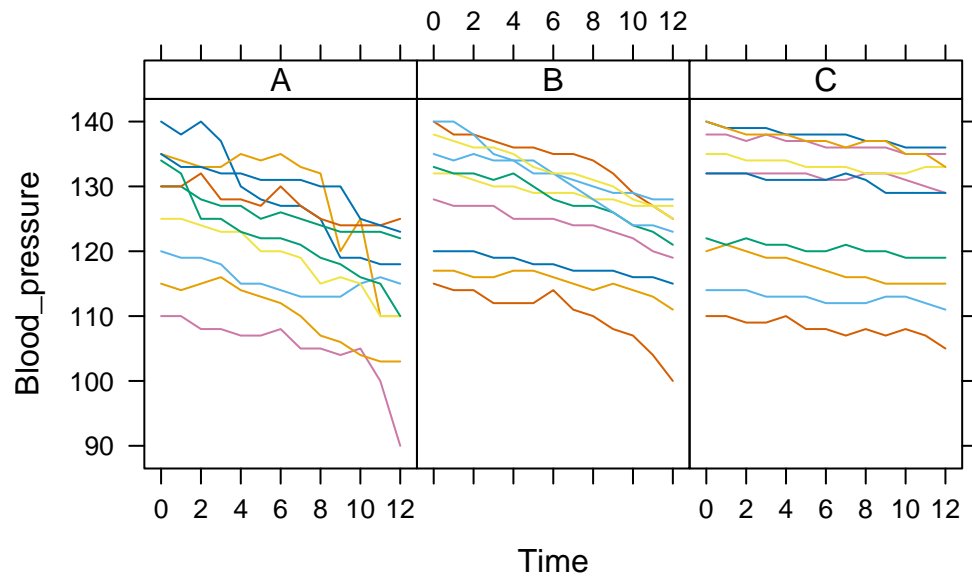
Subject	Treatment	Age	Sex	Time	Blood_pressure
1	A	40	M	0	140
1	A	40	M	1	138
1	A	40	M	2	140
1	A	40	M	3	137
1	A	40	M	4	130
1	A	40	M	5	128

Treatment C is a placebo, Treatment B is 10 mg drug dose, Treatment A is 20 mg drug dose

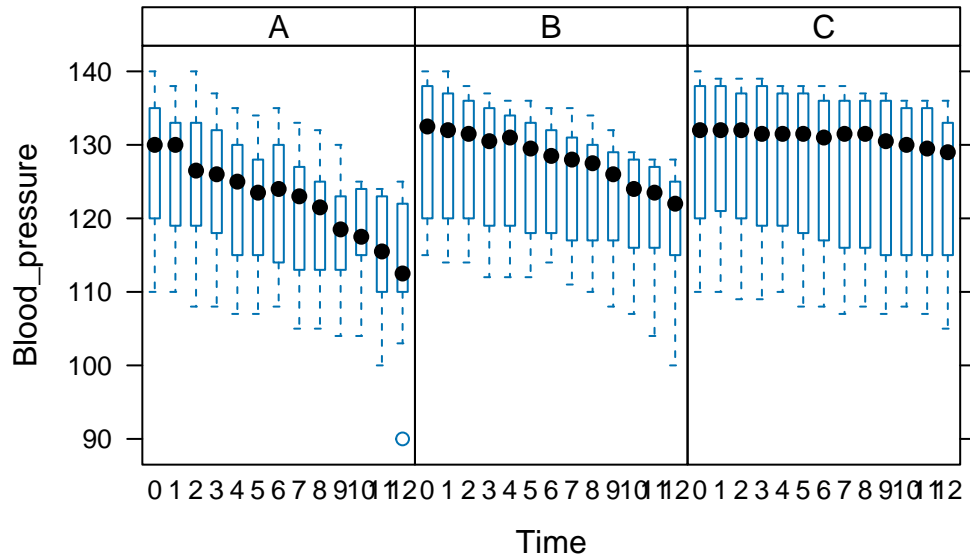
```
print(xyplot(Blood_pressure~Time|as.factor(Subject),type="l",groups=Treatment,
strip=strip.custom(bg="white"), lty=c(1,8), lwd=2,
layout=c(10,4), data_test))
```



```
print(xyplot(Blood_pressure~Time|Treatment,type="l",data_test,
            groups=as.factor(Subject),
            strip=strip.custom(bg="white")))
```



```
print(bwplot(Blood_pressure~as.factor(Time)|Treatment,data_test, xlab="Time",
            strip=strip.custom(bg="white")))
```



From these figures the obvious trend is revealed; i.e., that on average blood pressure, declines at a faster rate in Treatment A than in Treatment B, and in Treatment B is faster than in Treatment C. The rate and extent of decline varies across the 30 patients.

## Longitudinal Modeling

Model will have Subject as random effect, while Treatment and Time will be considered as fixed effects.

```
# fit Model 2
mod2DBP = lmer(Blood_pressure~Treatment+Time+(1|Subject), data_test)
summary(mod2DBP)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: Blood_pressure ~ Treatment + Time + (1 | Subject)
Data: data_test
```

```
REML criterion at convergence: 1978.7
```

```
Scaled residuals:
```

Min	1Q	Median	3Q	Max
-5.6936	-0.4642	0.0425	0.4945	3.4594

Random effects:

Groups	Name	Variance	Std.Dev.
Subject	(Intercept)	85.642	9.254
Residual		6.473	2.544

Number of obs: 390, groups: Subject, 30

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	125.72857	2.94221	27.26815	42.733	<2e-16 ***
TreatmentB	4.32308	4.15065	27.00000	1.042	0.307
TreatmentC	5.42308	4.15065	27.00000	1.307	0.202
Time	-0.77143	0.03443	359.00000	-22.405	<2e-16 ***

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	TrtmnB	TrtmnC
TreatmentB	-0.705		
TreatmentC	-0.705	0.500	
Time	-0.070	0.000	0.000

Conclusion

It is observed that Treatment A (dose 20 mg) at initial timepoint equals to 125.7, and this is statistically significant. As the time goes on (-0.77 coefficient) the effect of a drug is increasing while the effects of treatment B (10 mg) and Treatment C (placebo) decrease the blood pressure to much lesser extent. Treatment B and Treatment C both are not statistically significant.

```
# adding Age and Sex to the model
# fit Model 3 include Age effect
mod3DBP = lmer(Blood_pressure~Treatment+Time+Age+(1|Subject), data_test)
summary(mod3DBP)
```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [

lmerModLmerTest]

Formula: Blood\_pressure ~ Treatment + Time + Age + (1 | Subject)

Data: data\_test

REML criterion at convergence: 1978.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-5.6971	-0.4669	0.0475	0.4924	3.4540

Random effects:

Groups	Name	Variance	Std.Dev.
Subject	(Intercept)	86.281	9.289
Residual		6.473	2.544

Number of obs: 390, groups: Subject, 30

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	119.32897	7.73660	26.03711	15.424	1.3e-14 ***
TreatmentB	4.25733	4.16668	26.00000	1.022	0.316
TreatmentC	5.05050	4.18679	26.00000	1.206	0.239
Time	-0.77143	0.03443	359.00000	-22.405	< 2e-16 ***
Age	0.21916	0.24489	26.00000	0.895	0.379

---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	TrtmnB	TrtmnC	Time
TreatmentB	-0.253			
TreatmentC	-0.176	0.499		
Time	-0.027	0.000	0.000	
Age	-0.924	-0.018	-0.099	0.000

the addition of the Age variable does not statistically significant change the model.

```
anova(mod2DBP, mod3DBP)
```

npar	AIC	BIC	logLik	-2*log(L)	Chisq	Df	Pr(>Chisq)
6	2e+03	2.02e+03	-993	1.99e+03			
7	2e+03	2.03e+03	-992	1.98e+03	0.91	1	0.34

```
# fit Model 4 including Age and Sex  
mod4DBP = lmer(Blood_pressure~Treatment+Time+Age+Sex+(1|Subject), data_test)
```

```
# test the Sex effect  
anova(mod3DBP, mod4DBP)
```

npars	AIC	BIC	logLik	-2*log(L)	Chisq	Df	Pr(>Chisq)
7	2e+03	2.03e+03	-992	1.98e+03			
8	2e+03	2.03e+03	-992	1.98e+03	0.755	1	0.385

This gives a p-value indicating that Age and Sex are not a statistically significant effect.