# Lab 4 - ARMD Trial

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For patient $i$ ($i = 1, ..., 234$) at time $t$ ($t = 4, 12, 24, 52$ weeks)

- **Lab2 notation**: $\longrightarrow$ we add a random intercept $b_{0i}$

$$\begin{aligned}
\text{VISUAL}_{it} &= \beta_0 + \beta_1 \cdot \text{VISUAL0}_i + \beta_2 \cdot \text{TIME}_{it} + && (1)\\
&+ \beta_3 \cdot \text{TREAT}_i + \beta_4 \cdot \text{TREAT}_i \cdot \text{TIME}_{it} + && (2)\\
&+ b_{0i} + \epsilon_{it} \ , && (3)\\
& \epsilon_{it} \sim \mathcal{N}(0, \sigma^2_{it}), && (4)\\
& b_{0i} \sim \mathcal{N}(0, \sigma^2 d_{11}) && (5)
\end{aligned}$$

- **Lab3 and Lab4 notation**: $\longrightarrow$ with a random intercept $b_{0i}$

$$\begin{aligned}
\underline{\text{VISUAL}_i} &= \mathbb{X}_i \underline{\beta} + \mathbb{1}_i b_{0i} + \underline{\epsilon_i} && (6)\\
& \underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2 \boldsymbol{\mathcal{R}}_i) \quad \text{where} \quad \boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i && (7)\\
& b_{0i} \sim \mathcal{N}(0, \sigma^2 d_{11}) && (8)
\end{aligned}$$

More in general: $\longrightarrow$ with random intercept and slopes $\underline{b_i} = [b_{0i} \quad b_{1i} \quad ...]'$

$$\begin{aligned}
\underline{\text{VISUAL}_i} &= \mathbb{X}_i \underline{\beta} + \mathbb{Z}_i \underline{b_i} + \underline{\epsilon_i} && (9)\\
& \underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2 \boldsymbol{\mathcal{R}}_i) \quad \text{where} \quad \boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i && (10)\\
& \underline{b_i} \sim \mathcal{N}(\underline{0}, \sigma^2 \boldsymbol{\mathcal{D}}) && (11)
\end{aligned}$$

we know that $\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \, \boldsymbol{\mathcal{D}} \, \mathbb{Z}_i' + \boldsymbol{\mathcal{R}_i}$

- with ´$getVarCov$(model, type = 'conditional')´ we extract $\sigma^2 \boldsymbol{\mathcal{R}}_i$;
- with ´$getVarCov$(model, type = 'marginal')´ we extract $\sigma^2 \boldsymbol{\mathcal{V}}_i$;
- with ´$VarCorr$(model) we extract $\sigma^2 \boldsymbol{\mathcal{D}}$ (also from the summary).

```r
library(nlme)
lm2.form <- visual ~ visual0 + time + treat.f + treat.f:time
```

# Homoscedastic residuals

## Model 16.1 - Random intercept

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \boldsymbol{\mathcal{D}} \mathbb{Z}_i' + \boldsymbol{\mathcal{R}}_i = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} d_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \end{bmatrix} + \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$\Rightarrow \boldsymbol{\mathcal{V}}_i = \begin{bmatrix} 1 + d_{11} & d_{11} & d_{11} & d_{11} \\ d_{11} & 1 + d_{11} & d_{11} & d_{11} \\ d_{11} & d_{11} & 1 + d_{11} & d_{11} \\ d_{11} & d_{11} & d_{11} & 1 + d_{11} \end{bmatrix}$$

Note that the **implied marginal variance-covariance structure** is that of *compound symmetry* with a common correlation equal to $\rho = d_{11}/(1 + d_{11}) > 0$ since $d_{11} > 0$.

$$Var(\text{VISUAL}_{it}) = \sigma^2(d_{11} + 1)$$

```
fm16.1 <- lme(lm2.form, random = ~1|subject, data = armd)
```

## Model 16.2 - Random intercept + slope

### Model 16.2A - General D

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \boldsymbol{\mathcal{D}} \mathbb{Z}_i' + \boldsymbol{\mathcal{R}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$Var(\text{VISUAL}_{it}) = \sigma^2(d_{11} + 2d_{12}\text{TIME}_{it} + d_{22}\text{TIME}_{it}^2 + 1)$$

```r
fm16.2A <- lme(lm2.form, random = ~1 + time | subject, data = armd)
```

**Model 16.2B - Diagonal D**

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \boldsymbol{\mathcal{D}} \mathbb{Z}_i' + \boldsymbol{\mathcal{R}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$Var(\text{VISUAL}_{it}) = \sigma^2(d_{11} + d_{22}\text{TIME}_{it}^2 + 1)$$

```r
fm16.2B <- lme(lm2.form, random = list(subject = pdDiag(~time)), data = armd)
```

# Heteroscedastic residuals: varPower()

## Model 16.3 - Random intercept

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{2\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{2\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{2\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{2\delta} \end{bmatrix}$$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \boldsymbol{\mathcal{D}} \mathbb{Z}_i' + \boldsymbol{\mathcal{R}}_i = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} d_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \end{bmatrix} + \begin{bmatrix} |\text{TIME}_{i1}|^{2\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{2\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{2\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{2\delta} \end{bmatrix}$$

$$\Rightarrow \boldsymbol{\mathcal{V}}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{2\delta} + d_{11} & d_{11} & d_{11} & d_{11} \\ d_{11} & |\text{TIME}_{i2}|^{2\delta} + d_{11} & d_{11} & d_{11} \\ d_{11} & d_{11} & |\text{TIME}_{i3}|^{2\delta} + d_{11} & d_{11} \\ d_{11} & d_{11} & d_{11} & |\text{TIME}_{i4}|^{2\delta} + d_{11} \end{bmatrix}$$

$$Var(\text{VISUAL}_{it}) = \sigma^2(d_{11} + |\text{TIME}_{it}|^{2\delta})$$

```
fm16.3 <- update(fm16.1,
                 weights = varPower(form = ~ time),
                 data = armd)
```

## Model 16.4 - Random intercept + slope

### Model 16.4A - General D

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{2\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{2\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{2\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{2\delta} \end{bmatrix}$$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \boldsymbol{\mathcal{D}} \mathbb{Z}_i' + \boldsymbol{\mathcal{R}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \boldsymbol{\mathcal{R}}_i$$

$$Var(\text{VISUAL}_{it}) = \sigma^2(d_{11} + 2d_{12}\text{TIME}_{it} + d_{22}\text{TIME}_{it}^2 + |\text{TIME}_{it}|^{2\delta})$$

```
fm16.4A <- update(fm16.3,
                  random = ~1 + time | subject,
                  data = armd)
```

### Model 16.4B - Diagonal D

$$\boldsymbol{\mathcal{D}} = \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix}$$

$$\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{2\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{2\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{2\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{2\delta} \end{bmatrix}$$

$$\mathcal{V}_i = \mathbb{Z}_i \, \mathcal{D} \, \mathbb{Z}_i' + \mathcal{R}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \mathcal{R}_i$$

$$Var(\text{VISUAL}_{it}) = \sigma^2 (d_{11} + d_{22}\text{TIME}_{it}^2 + |\text{TIME}_{it}|^{2\delta})$$

```
fm16.4B <- update(fm16.3,
                  random = list(subject = pdDiag(~time)), # Diagonal D
                  data = armd)
```