Mixed Effects Models Module

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For patient i ($i = 1, ..., 234$) at time t ($t = 1\,(4\text{ wks}),\ 2\,(12\text{ wks}),\ 3\,(24\text{ wks}),\ 4\,(52\text{ wks})$)

- **Notation 1**: model equation at the level of statistical units it

$$\text{VISUAL}_{it} = \beta_{0t} + \beta_1 \cdot \text{VISUAL0}_i + \beta_{2t} \cdot \text{TREAT}_i + \epsilon_{it} \quad \text{with} \quad \boxed{\epsilon_{it} \sim \mathcal{N}(0, \sigma^2)}$$

- **Notation 2**: model equation at the patient level i

$$\underline{\text{VISUAL}_i} = \mathbb{X}_i \underline{\beta} + \underline{\epsilon_i}$$

$$\begin{bmatrix} \text{VISUAL}_{i1} \\ \text{VISUAL}_{i2} \\ \text{VISUAL}_{i3} \\ \text{VISUAL}_{i4} \end{bmatrix} \equiv \underline{\text{VISUAL}_i} \quad \text{and} \quad \begin{bmatrix} \epsilon_{i1} \\ \epsilon_{i2} \\ \epsilon_{i3} \\ \epsilon_{i4} \end{bmatrix} \equiv \boxed{\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \boldsymbol{\mathcal{R}}_i)} \text{ where } \boldsymbol{\mathcal{R}}_i = \sigma^2 \boldsymbol{R}_i = \sigma^2 \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i$$

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

$$\mathbb{X}_i \underline{\beta} = \begin{bmatrix} 1 & 0 & 0 & 0 & \text{VISUAL0}_i & \text{TREAT}_i & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \text{VISUAL0}_i & 0 & \text{TREAT}_i & 0 & 0 \\ 0 & 0 & 1 & 0 & \text{VISUAL0}_i & 0 & 0 & \text{TREAT}_i & 0 \\ 0 & 0 & 0 & 1 & \text{VISUAL0}_i & 0 & 0 & 0 & \text{TREAT}_i \end{bmatrix} \cdot \begin{bmatrix} \beta_{0\,4\text{wks}} \\ \beta_{0\,12\text{wks}} \\ \beta_{0\,24\text{wks}} \\ \beta_{0\,52\text{wks}} \\ \beta_1 \\ \beta_{2\,4\text{wks}} \\ \beta_{2\,12\text{wks}} \\ \beta_{2\,24\text{wks}} \\ \beta_{2\,52\text{wks}} \end{bmatrix}$$

```r
# formula
lm1.form <- visual ~ -1 + time.f + visual0 + treat.f:time.f
```

1 Standard Model: $\boxed{\epsilon_{it} \sim \mathcal{N}(0, \sigma^2)}$

```r
# Model 6.1
fm6.1 <- lm(lm1.form, data = armd)
```

In Sections 2 and 3 we relax the variance homogeneity assumption: we want to model $\boldsymbol{\Lambda}_i$, (while $\boldsymbol{\mathcal{C}}_i$ is still diagonal). We mainly employ **Notation 1**.

2 Known Variance Weights: $\boxed{\epsilon_{it} \sim \mathcal{N}(0, \sigma^2_{it})}$

where, for instance, we assume $\sigma_{it} = \sigma_t = \sigma \cdot \sqrt{\text{TIME}_t}$, i.e.,

$$\sigma_t = \begin{cases} \sigma_1 \\ \sigma_2 \\ \sigma_3 \\ \sigma_4 \end{cases} = \begin{cases} \sigma \cdot \sqrt{4} & \text{if } t = 1 \text{ (4 weeks)}; \\ \sigma \cdot \sqrt{12} & \text{if } t = 2 \text{ (12 weeks)}; \\ \sigma \cdot \sqrt{24} & \text{if } t = 3 \text{ (24 weeks)}; \\ \sigma \cdot \sqrt{52} & \text{if } t = 4 \text{ (52 weeks)}. \end{cases}$$

```r
# Model 9.0
weights = varFixed(value = ~time)
# the variance covariate needs to be continuous: time.f doesn't work!
fm9.0 <- gls(lm1.form, weights = weights, data = armd)
```

3 Variance Functions: $\boxed{\epsilon_{it} \sim \mathcal{N}(0, \sigma^2_{it})}$

3.1 `varIdent(·)` - $< \delta >$-group

$$\epsilon_{it} \sim \mathcal{N}(0, \sigma^2_t), \quad \text{s.t.} \quad \sigma_t = \begin{cases} \sigma_1 \\ \sigma_2 \\ \sigma_3 \\ \sigma_4 \end{cases} = \begin{cases} \sigma \cdot 1 & \text{if } t = 1 \text{ (4 weeks)}; \\ \sigma \cdot \delta_2 & \text{if } t = 2 \text{ (12 weeks)}; \\ \sigma \cdot \delta_3 & \text{if } t = 3 \text{ (24 weeks)}; \\ \sigma \cdot \delta_4 & \text{if } t = 4 \text{ (52 weeks)}. \end{cases}$$

we get: $\delta_2 = \frac{\sigma_2}{\sigma_1}$; $\delta_3 = \frac{\sigma_3}{\sigma_1}$; $\delta_4 = \frac{\sigma_4}{\sigma_1}$

```r
# Model 9.1
weights = varIdent(form = ~1|time.f)
fm9.1 <- gls(lm1.form, weights = weights, data = armd)
```

3.2 `varPower(·)` - $<\delta>$-group

- We do not include any stratification in the model

$$\epsilon_{it} \sim \mathcal{N}(0, \sigma_{it}^2) \quad \text{s.t.} \quad \begin{aligned} \sigma_{it} &= \sigma \cdot \lambda_{it} \\ &= \sigma \cdot \lambda(\ \delta,\ \text{TIME}_{it}\ ) \\ &= \sigma \cdot |\text{TIME}_{it}|^{\delta} \quad \text{since } \lambda \text{ is } \texttt{varPower}(\cdot) \end{aligned}$$

Following Notation 2, this could be written as $\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i))$ s.t.

$$\mathbf{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{\delta} \end{bmatrix} \quad \text{and} \quad \boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

```r
# Model 9.2
weights = varPower(form = ~time)
fm9.2 <- gls(lm1.form, weights = weights, data = armd)
```

- We include stratification in the model

$$\epsilon_{it} \sim \mathcal{N}(0, \sigma_{it}^2) \quad \text{s.t.} \quad \begin{aligned} \sigma_{it} &= \sigma \cdot \lambda_{it} \\ &= \sigma \cdot \lambda(\ \underline{\delta},\ \text{TIME}_{it}\ ) \\ &= \sigma \cdot \lambda(\ [\delta_1, \delta_2]',\ \text{TIME}_{it}\ ) \\ &= \begin{cases} \sigma \cdot |\text{TIME}_{it}|^{\delta_1} & \text{if active} \\ \sigma \cdot |\text{TIME}_{it}|^{\delta_2} & \text{if placebo} \end{cases} \end{aligned}$$

```r
# Model 9.3
weights = varPower(form = ~time|treat.f)
fm9.3 <- gls(lm1.form, weights = weights, data = armd)
```

In Section 4 we also relax the independence assumption; we mainly employ **Notation 2**. Specifically, we want to modify $\boldsymbol{\mathcal{C}}_i$, allowing the visual acuity measurements for the same individual to be correlated.

4 Correlation Structure: $\boxed{\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2 \mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i)}$

4.1 `corCompSymm(·)` (& `varPower(·)`)

Compound Symmetry Correlation Structure

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix} \quad \text{and} \quad \mathbf{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^{\delta} & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^{\delta} & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^{\delta} & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^{\delta} \end{bmatrix}$$

```r
# Model 12.1
correlation = corCompSymm(form = ~1|subject)
weights = varPower(form = ~time)
fm12.1 <- gls(lm1.form,
              weights = weights,
              correlation = correlation,
              data = armd)
```

4.2 `corAR1(·)` (& `varPower(·)`)

Heteroscedastic Autoregressive Residual Errors

$$\mathcal{C}_i = \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix} \quad \text{and} \quad \mathbf{\Lambda}_i = \begin{bmatrix} |\mathrm{TIME}_{i1}|^\delta & 0 & 0 & 0 \\ 0 & |\mathrm{TIME}_{i2}|^\delta & 0 & 0 \\ 0 & 0 & |\mathrm{TIME}_{i3}|^\delta & 0 \\ 0 & 0 & 0 & |\mathrm{TIME}_{i4}|^\delta \end{bmatrix}$$

```r
# Model 12.2
correlation = corAR1(form = ~tp|subject)
# using (form = ~1 | subject) would be a mistake
weights = varPower(form = ~time)
fm12.2 <- gls(lm1.form,
              weights = weights,
              correlation = correlation,
              data = armd)
```

4.3 `corSymm(·)` (& `varPower(·)`)

$$\mathcal{C}_i = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \rho_{14} \\ \rho_{12} & 1 & \rho_{23} & \rho_{24} \\ \rho_{13} & \rho_{23} & 1 & \rho_{34} \\ \rho_{14} & \rho_{24} & \rho_{34} & 1 \end{bmatrix} \quad \text{and} \quad \mathbf{\Lambda}_i = \begin{bmatrix} |\mathrm{TIME}_{i1}|^\delta & 0 & 0 & 0 \\ 0 & |\mathrm{TIME}_{i2}|^\delta & 0 & 0 \\ 0 & 0 & |\mathrm{TIME}_{i3}|^\delta & 0 \\ 0 & 0 & 0 & |\mathrm{TIME}_{i4}|^\delta \end{bmatrix}$$

```r
# Model 12.3
correlation = corSymm(form = ~tp|subject)
weights = varPower(form = ~time)
fm12.3 <- gls(lm1.form,
              weights = weights,
              correlation = correlation,
              data = armd)
```

4.4 `corSymm(·)` (& `varIdent(·)`)

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \rho_{14} \\ \rho_{12} & 1 & \rho_{23} & \rho_{24} \\ \rho_{13} & \rho_{23} & 1 & \rho_{34} \\ \rho_{14} & \rho_{24} & \rho_{34} & 1 \end{bmatrix} \quad \text{and} \quad \boldsymbol{\Lambda}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \delta_2 & 0 & 0 \\ 0 & 0 & \delta_3 & 0 \\ 0 & 0 & 0 & \delta_4 \end{bmatrix}$$

```r
# Model 12.3.b
correlation = corSymm(form = ~tp|subject)
weights = varIdent(form = ~1|time.f)
fm12.3.b <- gls(lm1.form,
                weights = weights,
                correlation = correlation,
                data = armd)
```

5 Linear Mixed Models

For patient i ($i = 1, ..., 234$) at time t ($t = 1\,(4\text{ wks}),\ 2\,(12\text{ wks}),\ 3\,(24\text{ wks}),\ 4\,(52\text{ wks})$)

- **Notation 1**: We define our new model and add a random intercept b_{0i}

  $\text{VISUAL}_{it} = \beta_0+\beta_1\cdot\text{VISUAL0}_i+\beta_2\cdot\text{TIME}_{it}+\beta_3\cdot\text{TREAT}_i+\beta_4\cdot\text{TREAT}_i\cdot\text{TIME}_{it}+b_{0i}+\epsilon_{it}$

  with $\epsilon_{it} \sim \mathcal{N}(0, \sigma^2_{it})$ and $b_{0i} \sim \mathcal{N}(0, \sigma^2 d_{11})$

- **Notation 2**: Model equation at the patient level i

$$\underline{\text{VISUAL}_i} = \mathbb{X}_i\underline{\beta} + \underline{1}_i b_{0i} + \underline{\epsilon_i}$$

  with $\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \boldsymbol{\mathcal{R}}_i)$ where $\boldsymbol{\mathcal{R}}_i = \sigma^2\boldsymbol{R}_i = \boldsymbol{\Lambda}_i\boldsymbol{\mathcal{C}}_i\boldsymbol{\Lambda}_i$ and $b_{0i} \sim \mathcal{N}(0, \sigma^2 d_{11})$

$$\begin{bmatrix}\text{VISUAL}_{i1}\\ \text{VISUAL}_{i2}\\ \text{VISUAL}_{i3}\\ \text{VISUAL}_{i4}\end{bmatrix} \equiv \underline{\text{VISUAL}_i} \quad \text{and} \quad \begin{bmatrix}\epsilon_{i1}\\ \epsilon_{i2}\\ \epsilon_{i3}\\ \epsilon_{i4}\end{bmatrix} \equiv \underline{\epsilon_i} \quad \text{and} \quad \begin{bmatrix}1\\1\\1\\1\end{bmatrix} \equiv \underline{1}_i$$

$$\mathbb{X}_i\underline{\beta} = \begin{bmatrix}1 & \text{VISUAL0}_i & 4 & \text{TREAT}_i & 4\cdot\text{TREAT}_i\\ 1 & \text{VISUAL0}_i & 12 & \text{TREAT}_i & 12\cdot\text{TREAT}_i\\ 1 & \text{VISUAL0}_i & 24 & \text{TREAT}_i & 24\cdot\text{TREAT}_i\\ 1 & \text{VISUAL0}_i & 52 & \text{TREAT}_i & 52\cdot\text{TREAT}_i\end{bmatrix} \cdot \begin{bmatrix}\beta_0\\ \beta_1\\ \beta_2\\ \beta_3\\ \beta_4\end{bmatrix}$$

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

$$\underline{\text{VISUAL}_i} = \mathbb{X}_i\underline{\beta} + \mathbb{Z}_i\underline{b_i} + \underline{\epsilon_i}$$

  with $\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \boldsymbol{\mathcal{R}}_i)$ where $\boldsymbol{\mathcal{R}}_i = \sigma^2\boldsymbol{R}_i$ and $\underline{b_i} \sim \mathcal{N}(\underline{0}, \boldsymbol{\mathcal{D}})$ where $\boldsymbol{\mathcal{D}} = \sigma^2\boldsymbol{D}$
  for instance, we can choose TIME to be our slope:

$$\mathbb{Z}_i = \begin{bmatrix}1 & 4\\ 1 & 12\\ 1 & 24\\ 1 & 52\end{bmatrix} \quad \text{and} \quad \underline{b_i} = \begin{bmatrix}b_{0i}\\ b_{1i}\end{bmatrix}$$

```
# formula
lm2.form <- visual ~ visual0 + time + treat.f + treat.f:time
```

we know that $\boldsymbol{\mathcal{V}}_i = \sigma^2\boldsymbol{V}_i = \sigma^2[\mathbb{Z}_i\,\boldsymbol{D}\,\mathbb{Z}_i' + \boldsymbol{R}_i]$

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

5.1 Homoscedastic residuals

5.1.1 Random intercept only

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

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

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

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

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 $d_{11} > 0$.

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

```
# Model 16.1
# with lme4 library
fm16.1mer <- lmer(visual ~ visual0 + time * treat.f + (1|subject),
                  data = armd)
# with nlme library
fm16.1 <- lme(lm2.form, random = ~1|subject, data = armd)
```

5.1.2 Random intercept & slope

- **General $\boldsymbol{D}$**

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

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

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

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

```
# Model 16.2A
# with lme4 library
fm16.2mer <- lmer(visual ~ visual0 + time * treat.f + (1+time|subject),
                  data = armd, control=lmerControl(optimizer="bobyqa",
                                                   optCtrl=list(maxfun=2e5)))
# with nlme library
fm16.2A <- lme(lm2.form, random = ~1 + time | subject, data = armd)
```

- **Diagonal $\boldsymbol{D}$**

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

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

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

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

```
# Model 16.2B
# with lme4 library
fm16.2dmer <- lmer(visual ~ visual0 + time * treat.f +
                   (1|subject) + (0 + time|subject),
                   data = armd, control=lmerControl(optimizer="bobyqa",
                                                    optCtrl=list(maxfun=2e5)))
# with nlme library
fm16.2B <- lme(lm2.form, random = list(subject = pdDiag(~time)), data = armd)
```

5.2 Heteroscedastic residuals: `varPower(·)`

5.2.1 Random intercept only

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

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

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

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

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

```
# Model 16.3 - nlme library only
fm16.3 <- lme(lm2.form, random = ~1|subject,
              weights = varPower(form = ~ time), data = armd)
```

5.2.2 Random intercept & slope

- **General $\boldsymbol{D}$**

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

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

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

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

```r
# Model 16.4A - nlme library only
fm16.4A <- update(fm16.3,
                  random = ~1 + time | subject,
                  data = armd)
```

- **Diagonal $\boldsymbol{D}$**

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

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

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

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

```r
# Model 16.4B - nlme library only
fm16.4B <- update(fm16.3,
                  random = list(subject = pdDiag(~time)), # Diagonal D
                  data = armd)
```