Applied Statistics - Mixed Effects Models
ARMD Trial

May 17, 2023

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

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

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

```
library(nlme)
lm1.form <- visual ~ -1 + visual0 + time.f + treat.f:time.f
```

Model 9.1 - $< \delta >$-group

Time-specific variance: $\epsilon_{it} \sim \mathcal{N}(0, \sigma_t^2)$

$$\sigma_t = \begin{cases} \sigma_1 \\ \sigma_2 \\ \sigma_3 \\ \sigma_4 \end{cases} = \begin{cases} \sigma \cdot 1 & \text{if } t = 1 \text{ (4 weeks);} \\ \sigma \cdot \delta_2 & \text{if } t = 2 \text{ (12 weeks);} \\ \sigma \cdot \delta_3 & \text{if } t = 3 \text{ (24 weeks);} \\ \sigma \cdot \delta_4 & \text{if } t = 4 \text{ (52 weeks).} \end{cases}$$

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

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

Model 9.2 - - varPower($\cdot$) time ($< \delta, v_{it} >$-group)

$\epsilon_{it} \sim \mathcal{N}(0, \sigma_{it}^2)$
varPower($\cdot$) time
$\underline{\delta} = \delta$ (scalar) since we do not include any stratification in the model

$$\begin{aligned}
\sigma_{it} &= \sigma \cdot \lambda_{it} \\
&= \sigma \cdot \lambda(\ \delta,\ \text{TIME}_{it}\ ) \\
&= \sigma \cdot |\text{TIME}_{it}|^{\delta} \quad \text{since } \lambda \text{ is varPower}(\cdot)
\end{aligned}$$

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

Notation 1: $\epsilon_{it} \sim \mathcal{N}(0, \sigma_{it}^2)$
Notation 2: $\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2 \boldsymbol{\mathcal{R}}_i)$ where $\boldsymbol{\mathcal{R}}_i = \boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i$
$\underline{\delta} = \delta$ (scalar) since we do not include any stratification in the model
Notation 1: $\epsilon_{it} \sim \mathcal{N}(0, \sigma_{it}^2)$ where

$$\begin{aligned}
\sigma_{it} &= \sigma \cdot \lambda_{it} \\
&= \sigma \cdot \lambda(\ \delta,\ \text{TIME}_{it}\ ) \\
&= \sigma \cdot |\text{TIME}_{it}|^{\delta} \quad \text{since } \lambda \text{ is varPower}(\cdot)
\end{aligned}$$

Notation 2: $\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\boldsymbol{\Lambda}_i \boldsymbol{\mathcal{C}}_i \boldsymbol{\Lambda}_i))$ where

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

and

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

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

We want to modify $\boldsymbol{\mathcal{C}}_i$, allowing the visual acuity measurements for the same individual to be correlated, while keeping the same $\boldsymbol{\Lambda}_i$. We make use of the empirical Semivariogram for choosing the appropriate correlation structure.

Model 12.1 - corCompSymm($\cdot$)

Compound Symmetry Correlation Structure
$\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i))$ where

$$\mathbf{\Lambda}_i = \begin{bmatrix} |\mathrm{TIME}_{i1}|^\delta & 0 & 0 & 0 \\ 0 & |\mathrm{TIME}_{i2}|^\delta & 0 & 0 \\ 0 & 0 & |\mathrm{TIME}_{i3}|^\delta & 0 \\ 0 & 0 & 0 & |\mathrm{TIME}_{i4}|^\delta \end{bmatrix}$$

and

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix}$$

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

Model 12.2 - corAR1($\cdot$)

Heteroscedastic Autoregressive Residual Errors
$\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i))$ where

$$\mathbf{\Lambda}_i = \begin{bmatrix} |\mathrm{TIME}_{i1}|^\delta & 0 & 0 & 0 \\ 0 & |\mathrm{TIME}_{i2}|^\delta & 0 & 0 \\ 0 & 0 & |\mathrm{TIME}_{i3}|^\delta & 0 \\ 0 & 0 & 0 & |\mathrm{TIME}_{i4}|^\delta \end{bmatrix}$$

and

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

```
weights = varPower(form = ~time)
correlation = corAR1(form = ~tp|subject)
fm12.2 <- gls(lm1.form,
              weights = weights,
              correlation = correlation,
              data = armd)
```

Model 12.3 - corSymm($\cdot$)

General correlation matrix for Residual Errors
$\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i))$ where

$$\mathbf{\Lambda}_i = \begin{bmatrix} |\text{TIME}_{i1}|^\delta & 0 & 0 & 0 \\ 0 & |\text{TIME}_{i2}|^\delta & 0 & 0 \\ 0 & 0 & |\text{TIME}_{i3}|^\delta & 0 \\ 0 & 0 & 0 & |\text{TIME}_{i4}|^\delta \end{bmatrix}$$

and

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \rho_{14} \\ \rho_{12} & 1 & \rho_{23} & \rho_{24} \\ \rho_{13} & \rho_{23} & 1 & \rho_{34} \\ \rho_{14} & \rho_{24} & \rho_{34} & 1 \end{bmatrix}$$

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

Model 12.3.b - corSymm($\cdot$) and varIdent($\cdot$)

We now re-fit the model 12.3 with the most general variance function (varIdent) which allows arbitrary (positive) variances of the visual acuity measurements made at different timepoints.
$\underline{\epsilon_i} \sim \mathcal{N}(\underline{0}, \sigma^2(\mathbf{\Lambda}_i \boldsymbol{\mathcal{C}}_i \mathbf{\Lambda}_i))$ where

$$\mathbf{\Lambda}_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \delta_2 & 0 & 0 \\ 0 & 0 & \delta_3 & 0 \\ 0 & 0 & 0 & \delta_4 \end{bmatrix}$$

and

$$\boldsymbol{\mathcal{C}}_i = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \rho_{14} \\ \rho_{12} & 1 & \rho_{23} & \rho_{24} \\ \rho_{13} & \rho_{23} & 1 & \rho_{34} \\ \rho_{14} & \rho_{24} & \rho_{34} & 1 \end{bmatrix}$$

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

Multilevel Models

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

- **Notation 1**: $\longrightarrow$ we add a random intercept b_{0i}

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

- **Notation 2**:

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

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

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

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

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

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

Homoscedastic residuals

Model 16.1 - Random intercept

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

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

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \, \tilde{\boldsymbol{\mathcal{D}}} \, \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} d_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \end{bmatrix} + \begin{bmatrix} \sigma^2 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & \sigma^2 \end{bmatrix}$$

$$\Rightarrow \boldsymbol{\mathcal{V}}_i = \begin{bmatrix} \sigma^2 + d_{11} & d_{11} & d_{11} & d_{11} \\ d_{11} & \sigma^2 + d_{11} & d_{11} & d_{11} \\ d_{11} & d_{11} & \sigma^2 + d_{11} & d_{11} \\ d_{11} & d_{11} & d_{11} & \sigma^2 + d_{11} \end{bmatrix}$$

Note that the **implied marginal variance-covariance structure** is that of *compound symmetry* with a common correlation equal to $\rho = d_{11}/(\sigma^2 + d_{11}) > 0$ since $d_{11} > 0$.

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

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

Model 16.2 - Random intercept + slope

Model 16.2A - General D

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

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

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \, \tilde{\boldsymbol{\mathcal{D}}} \, \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} \sigma^2 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & \sigma^2 \end{bmatrix}$$

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

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

Model 16.2B - Diagonal D

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

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

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \tilde{\boldsymbol{\mathcal{D}}} \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} \sigma^2 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & \sigma^2 \end{bmatrix}$$

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

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

Heteroscedastic residuals: varPower()

Model 16.3 - Random intercept

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

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

Defining $\sigma_t^2 = \sigma^2 \cdot |\text{TIME}_{it}|^{2\delta}$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \tilde{\boldsymbol{\mathcal{D}}} \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} d_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \end{bmatrix} + \begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix}$$

$$\Rightarrow \boldsymbol{\mathcal{V}}_i = \begin{bmatrix} \sigma_1^2 + d_{11} & d_{11} & d_{11} & d_{11} \\ d_{11} & \sigma_2^2 + d_{11} & d_{11} & d_{11} \\ d_{11} & d_{11} & \sigma_3^2 + d_{11} & d_{11} \\ d_{11} & d_{11} & d_{11} & \sigma_4^2 + d_{11} \end{bmatrix}$$

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

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

Model 16.4 - Random intercept + slope

Model 16.4A - General D

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

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

Defining $\sigma_t^2 = \sigma^2 \cdot |\text{TIME}_{it}|^{2\delta}$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \tilde{\boldsymbol{\mathcal{D}}} \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix}$$

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

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

Model 16.4B - Diagonal D

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

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

Defining $\sigma_t^2 = \sigma^2 \cdot |\text{TIME}_{it}|^{2\delta}$

$$\boldsymbol{\mathcal{V}}_i = \mathbb{Z}_i \tilde{\boldsymbol{\mathcal{D}}} \mathbb{Z}_i' + \tilde{\boldsymbol{\mathcal{R}}}_i = \begin{bmatrix} 1 & 4 \\ 1 & 12 \\ 1 & 24 \\ 1 & 52 \end{bmatrix} \begin{bmatrix} d_{11} & 0 \\ 0 & d_{22} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 4 & 12 & 24 & 52 \end{bmatrix} + \begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix}$$

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

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