Random intercept model with a balanced design

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1 Notations

Consider an outcome variable Y measured in n subjects at p occasions. We will index the subjects by $i \in \{1, \ldots, n\}$ and the occasions by $j \in \{1, \ldots, p\}$. During their follow-up each subject is subject to an active ($T = 1$) and a control treatment ($T = 0$) respectively p_1 and p_0 times. We will use the bold notation to denote vector of random variables, e.g. $\mathbf{T}_i = \{T_{i,1}, \ldots, T_{i,p}\}$.

The (data-generating) variance of the outcome will be denoted σ^2. The (data-generating) correlation between any two measurements from a subject will be denoted $r_{j,j'} = \mathbb{C}or(Y_{i,j}, Y_{i,j'}|T_{i,j}, T_{i,j'})$

As a working model we will consider the following random intercept model:

$$Y_{i,j} = \alpha + \beta T_{i,j} + u_i + \boldsymbol{\varepsilon}_{i,j}$$

where $u_i \sim \mathcal{N}(0, \tau)$ and $\varepsilon_{i,j} \sim \mathcal{N}(0, \delta)$. Introducing $\rho = \frac{\tau}{\tau+\delta}$ and $\sigma^2 = \tau + \delta$, we can then express the residual variance-covariance matrix as:

$$\mathbb{V}ar\left[\mathbf{Y}_i|\mathbf{T}_i\right] = \mathbb{V}ar\left[u_i + \boldsymbol{\varepsilon}_i|T_i\right] = \Omega = \sigma^2 R = \sigma^2((1-\rho)I + \rho\mathbf{e}\mathbf{e}^\intercal)$$

where I denotes the $p \times p$ identity matrix and $\mathbf{e}$ a corresponding of size p containing only 1. $\Theta = (\alpha, \beta, \delta, \tau)$ or equivalently $(\alpha, \beta, \rho, \sigma)$ will denote the vector of model parameters and $\boldsymbol{\mu}_i = (\alpha + \beta T_{i1}, \ldots, \alpha + \beta T_{ip})$ the vector of fitted values. Note that since we assume a balanced design and since Ω is unchanged by re-ordering, we can re-order the data such that $\mathbf{T}_i = \mathbf{T}_{i'} = \mathbf{T}$ for all $(i, i') \in \{1, \ldots, n\}^2$.

2 Estimates in a random intercept model

2.1 Theory

Appendix B shows that the Maximum Likelihood estimate of Θ are:

- **mean parameters**: $\widehat{\alpha} = \frac{1}{np} \sum_{i=1}^{n} \sum_{j=1}^{p} (1 - T_{i,j}) Y_{i,j}$
  $\widehat{\beta} = \frac{1}{np} \sum_{i=1}^{n} \sum_{t=1}^{p} (2T_{i,j} - 1) Y_{i,j}$
  $\widehat{\mu}_{i,j} = \widehat{\alpha} - T_{i,j} \widehat{\beta}$
- **variance parameter**: $\widehat{\sigma}^2 = \frac{1}{np} \sum_{i=1}^{n} \sum_{j=1}^{p} (Y_{i,j} - \widehat{\mu}_{i,j})^2$
- **correlation parameter**: $\widehat{\rho} = \frac{1}{p(p-1)/2} \sum_{j=1}^{p} \sum_{j' \in \{1,\ldots,j-1\}} \widehat{\rho}_{j,j'}$
  where for $j \in \{1, \ldots, p\}$, $j' \in \{1, \ldots, j-1\}$, $\widehat{\rho}_{j,j'} = \frac{1}{n} \sum_{i=1}^{n} \frac{(Y_{i,j} - \widehat{\mu}_{i,j})}{\widehat{\sigma}} \frac{(Y_{i,j'} - \widehat{\mu}_{i,j'})}{\widehat{\sigma}}$

i.e. the empirical mean of the outcome, the empirical residual variance, and the average empirical residual correlation.

2.2 Numerical example

We will illustrate the previous result on an example. First we simulate some data in the long format:

```
library(LMMstar)
library(lava)
library(Matrix)

set.seed(1)
dfL <- sampleRem(1e3, n.times = 4, format = "long",
                 mu = c(1,0,0,0), sigma = 1:4, lambda = c(0.5,0.25,2,1))
dfL <- dfL[order(dfL$id),c("id","visit","Y")]
dfL$treatment <- as.numeric(dfL$visit) %% 2
head(dfL)
```

```
  id visit          Y treatment
1  1     1  0.2551614         1
2  1     2  0.7913185         0
3  1     3 -2.1031314         1
4  1     4 -0.4489691         0
5  2     1  1.5637433         1
6  2     2 -0.1637081         0
```

Converting to the wide format facilitate the calculation of the time specific mean, variance, and correlation:

```
dfW <- reshape(dfL[,c("id","visit","Y")],
               direction = "wide", idvar = "id", timevar = "visit")
rbind(mean = colMeans(dfW[,-1]),
      var = apply(dfW[,-1],2,var))
cor(dfW[,-1])
```

```
          Y.1       Y.2       Y.3       Y.4
mean 1.534321 0.2534847  2.101116  1.040294
var  3.770008 1.6149499 47.740082 12.611689
          Y.1       Y.2       Y.3       Y.4
Y.1 1.0000000 0.5515201 0.8579057 0.8330143
Y.2 0.5515201 1.0000000 0.6468049 0.6131780
Y.3 0.8579057 0.6468049 1.0000000 0.9503735
Y.4 0.8330143 0.6131780 0.9503735 1.0000000
```

2.2.1 Maximum likelihood

A random intercept model estimated by Maximum Likelihood (ML) leads to the following results:

```
eML.RI <- lmm(Y~treatment+(1|id), data = dfL, method.fit = "ML")
coef(eML.RI, effects = "all")
```

```
(Intercept)   treatment       sigma     rho(id)
  0.6468893   1.1708292   4.0663607   0.5049300
```

We retrive the empirical means for the intercept and treatment effects:

```
alphaHat <- mean(dfL$Y[dfL$treatment == 0])
betaHat <- mean(dfL$Y[dfL$treatment == 1]) - alphaHat
c(alphaHat, betaHat)
```

```
[1] 0.6468893 1.1708292
```

the empirical squared residuals for the variance:

```
dfL$res <- dfL$Y - alphaHat - dfL$treatment*+betaHat
sqrt(mean(dfL$res^2))
```

```
[1] 4.066361
```

and the empirical residual correlation:

```
dfL$res.normML <- dfL$res/sqrt(mean(dfL$res^2))
dfWres.normML <- reshape(dfL[,c("id","visit","res.normML")],
                         direction = "wide", idvar = "id", timevar = "
   visit")
M.MLcor <- crossprod(as.matrix(dfWres.normML[,-1]))/NROW(dfWres.normML)
mean(M.MLcor[lower.tri(M.MLcor)])
```

```
[1] 0.50493
```

2.2.2 Restricted maximum likelihood

When fitting a random intercept model estimated by Maximum Likelihood (REML):

```
eREML.RI <- lmm(Y~treatment+(1|id), data = dfL, method.fit = "REML")
coef(eREML.RI, effects = "all")
```

```
(Intercept)   treatment       sigma     rho(id)
  0.6468893   1.1708292   4.0678916   0.5051376
```

We retrive the empirical means for the intercept and treatment effects. However we do not 'exactly' retrieve the REML estimate of the residual standard deviation using:

```
sd(dfL$res)
```

```
[1] 4.066869
```

To closer we can get would be using 3 degrees of freedom:

```
NROW(dfL)-sum(tapply(dfL$res^2, dfL$visit, sum))/(coef(eREML.RI, effects =
    "variance"))^2
```

```
   sigma
3.010256
```

We do not 'exactly' retrieve the REML estimate of the residual correlation using the Pearson correlation:

```
dfL$res.normREML <- dfL$res/coef(eREML.RI, effects = "variance")
dfWres.normREML <- reshape(dfL[,c("id","visit","res.normREML")],
                           direction = "wide", idvar = "id", timevar = "
   visit")
M.REMLcor <- crossprod(as.matrix(dfWres.normREML[,-1]))/(NROW(dfWres.
   normREML)-1)
mean(M.REMLcor[lower.tri(M.REMLcor)])
```

```
[1] 0.505055
```

A Inverse of a compound symmetry matrix

Consider the compound symmetry matrix:

$$R = (1-\rho)I + \rho\mathbf{e}\mathbf{e}^\intercal = \rho\left(\frac{1-\rho}{\rho}I + \mathbf{e}\mathbf{e}^\intercal\right)$$

The Sherman-Morrison formula indicates that:

$$\begin{aligned} R^{-1} &= \rho^{-1}\left(\frac{\rho}{1-\rho}I - \frac{\rho^2}{(1-\rho)^2}\frac{\mathbf{e}\mathbf{e}^\intercal}{1+\frac{\rho}{1-\rho}\mathbf{e}^\intercal\mathbf{e}}\right) = \frac{1}{1-\rho}I - \frac{\rho}{(1-\rho)^2}\frac{\mathbf{e}\mathbf{e}^\intercal}{1+\frac{\rho}{1-\rho}p} \\ &= \frac{1}{1-\rho}I - \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{(1-\rho)^2+\rho(1-\rho)p} = \frac{1}{1-\rho}\left(I - \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right) \end{aligned}$$

B Estimates in a random intercept model

The log-likelihood of a random intercept model can be written:

$$\mathcal{L}(\Theta|\mathbf{Y},\mathbf{T}) = \sum_{i=1}^{n}\left(-\frac{m}{2}\log(2\pi) - \frac{1}{2}\log|\Omega| - \frac{1}{2}(\mathbf{Y}_i - \boldsymbol{\mu}_i)^\intercal\Omega^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i)\right)$$

and the corresponding restricted likelihood:

$$\mathcal{L}^R(\Theta|\mathbf{Y},\mathbf{T}) = \mathcal{L}(\Theta|\mathbf{Y},\mathbf{T}) + \frac{p}{2}\log(2\pi) - \frac{1}{2}\log\left(\left|\sum_{i=1}^{n}\mathbf{Z}_i^\intercal\Omega^{-1}\mathbf{Z}_i\right|\right)$$

where $\mathbf{Z}_i = (1, \mathbf{T}_i)$ is the design matrix w.r.t. subject i.

B.1 Mean parameters

The score equation w.r.t. the mean parameters is identical when considering the log-likelihood or the restricted log-likelihood. Using the expression of R^{-1} found in appendix B we get:

$$\begin{bmatrix}0\\0\end{bmatrix} = \begin{bmatrix}\sum_{i=1}^n e^\intercal\Omega^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i))\\ \sum_{i=1}^n \mathbf{T}^\intercal\Omega^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i)\end{bmatrix} = \begin{bmatrix}\frac{1}{\sigma^2(1-\rho)}\sum_{i=1}^n e^\intercal\left(I - \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right)(\mathbf{Y}_i - \boldsymbol{\mu}_i)\\ \frac{1}{\sigma^2(1-\rho)}\sum_{i=1}^n \mathbf{T}^\intercal\left(I - \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right)(\mathbf{Y}_i - \boldsymbol{\mu}_i)\end{bmatrix}$$

which is equivalent to:

$$\begin{aligned} \begin{bmatrix}0\\0\end{bmatrix} &= \begin{bmatrix}\sum_{i=1}^n\left(e^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) - \frac{\rho p\mathbf{e}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i)}{1+\rho(p-1)}\right)\\ \sum_{i=1}^n\left(\mathbf{T}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) - \frac{\rho p_1\mathbf{e}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i)}{1+\rho(p-1)}\right)\end{bmatrix} \\ &= \begin{bmatrix}\left(1 - \frac{\rho p}{1+\rho(p-1)}\right)\sum_{i=1}^n e^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i)\\ \sum_{i=1}^n \mathbf{T}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) - \frac{\rho p_1}{1+\rho(p-1)}\sum_{i=1}^n \mathbf{e}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i)\end{bmatrix} \end{aligned}$$

Using that $1 - \frac{\rho p}{1+\rho(p-1)} = 1 + \rho(p-1) - \rho p = 1 - \rho > 0$ and substracting p_1/p times equation 1 from equation 2 we get:

$$\begin{bmatrix} 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^n e^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) \\ \sum_{i=1}^n \mathbf{T}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) - \frac{p_1}{p} \sum_{i=1}^n \mathbf{e}^\intercal(\mathbf{Y}_i - \boldsymbol{\mu}_i) \end{bmatrix}$$

Denoting the by $\widehat{\alpha} = \frac{1}{np} \sum_{i=1}^n \sum_{t=1}^p (1 - T_{it}) Y_{it}$ and $\widehat{\beta} = \frac{1}{np} \sum_{i=1}^n \sum_{t=1}^p T_{it} Y_{it} - \widehat{\alpha}$ the empirical mean over timepoints and patients under control and under treatment. The former equations are equivalent to:

$$\begin{bmatrix} 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \widehat{\alpha} - \alpha + p_1(\widehat{\beta} - \beta) \\ p_1(\widehat{\alpha} + \widehat{\beta} - \alpha - \beta) - \frac{p_1}{p}(\widehat{\alpha} - \alpha + p_1(\widehat{\beta} - \beta)) \end{bmatrix}$$
$$\begin{bmatrix} 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \widehat{\alpha} - \alpha + (\widehat{\beta} - \beta) \\ (\widehat{\alpha} - \alpha + \widehat{\beta} - \beta) - \frac{1}{p}(\widehat{\alpha} - \alpha + p_1(\widehat{\beta} - \beta)) \end{bmatrix}$$

So $\widehat{\beta} - \beta = -\frac{1}{p_1}(\widehat{\alpha} - \alpha)$ and:

$$0 = (\widehat{\alpha} - \alpha) \left(1 - \frac{1}{p_1} - \frac{1}{p} + 1 \right)$$

Since design $p_0 \geq 1$ and $p \geq 2$ so $2 - \frac{1}{p_1} - \frac{1}{p} \geq 0.5$. It follows that $\alpha = \widehat{\alpha}$ and therefore $\beta = \widehat{\beta}$: the maximum likelihood (ML) and restricted maximum likelihood (REML) estimates of the mean parameters are the empirical means in the appropriate subgroups.

B.2 Correlation parameter (ML)

The ML score equation w.r.t the correlation parameter is:

$$\begin{aligned} 0 &= -\frac{n}{2} tr \left(\Omega^{-1} \frac{\partial \Omega}{\partial \rho} \right) + \frac{1}{2} \sum_{i=1}^n (\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)^\intercal \Omega^{-1} \frac{\partial \Omega}{\partial \rho} \Omega^{-1} (\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i) \\ &= -\frac{n}{2} tr \left(R^{-1} \frac{\partial R}{\partial \rho} \right) + \frac{1}{2\sigma^2} tr \left(R^{-1} \frac{\partial R}{\partial \rho} R^{-1} \sum_{i=1}^n (\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)^\intercal \right) \end{aligned}$$

We first explicit the first term:

$$\begin{aligned} R^{-1} \frac{\partial R}{\partial \rho} &= \frac{1}{1-\rho} \left(I - \frac{\rho \mathbf{e}\mathbf{e}^\intercal}{1 + \rho(p-1)} \right) (-I + \mathbf{e}\mathbf{e}^\intercal) \\ &= \frac{1}{1-\rho} \left(-I + \mathbf{e}\mathbf{e}^\intercal + \frac{\rho \mathbf{e}\mathbf{e}^\intercal}{1 + \rho(p-1)} - \frac{\rho p \mathbf{e}\mathbf{e}^\intercal}{1 + \rho(p-1)} \right) \\ &= \frac{1}{1-\rho} \left(-I + \mathbf{e}\mathbf{e}^\intercal \frac{1 + \rho(p-1) + \rho - \rho p}{1 + \rho(p-1)} \right) \end{aligned}$$

$$= \frac{1}{1-\rho}\left(-I + \frac{\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right)$$

Thus:

$$tr\left(R^{-1}\frac{\partial R}{\partial \rho}\right) = \frac{p}{1-\rho}\left(-1 + \frac{1}{1+\rho(p-1)}\right) = -\frac{p\rho(p-1)}{(1-\rho)(1+\rho(p-1))}$$

We now consider:

$$\begin{aligned}
R^{-1}\frac{\partial R}{\partial \rho}R^{-1} &= \frac{1}{(1-\rho)^2}\left(-I + \frac{\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right)\left(I - \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)}\right) \\
&= \frac{1}{(1-\rho)^2}\left(-I + \frac{\rho\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)} + \frac{\mathbf{e}\mathbf{e}^\intercal}{1+\rho(p-1)} - \frac{\rho p\mathbf{e}\mathbf{e}^\intercal}{(1+\rho(p-1))^2}\right) \\
&= \frac{1}{(1-\rho)^2}\left(-I + \mathbf{e}\mathbf{e}^\intercal\frac{\rho+\rho^2(p-1)+1+\rho(p-1)-\rho p}{(1+\rho(p-1))^2}\right) \\
&= \frac{1}{(1-\rho)^2}\left(-I + \mathbf{e}\mathbf{e}^\intercal\frac{\rho^2(p-1)+1}{(1+\rho(p-1))^2}\right)
\end{aligned}$$

We now consider the matrix $\frac{1}{n}\sum_{i=1}^n(\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)^\intercal$ and denote by:

- $\left(\widetilde{\sigma}_1^2, \dots, \widetilde{\sigma}_p^2\right) = \left(\frac{1}{n}\sum_{i=1}^n(Y_{i,1} - \widehat{\mu}_{i,1})^2, \dots, \frac{1}{n}\sum_{i=1}^n(Y_{i,p} - \widehat{\mu}_{i,p})^2\right)$ its diagonal elements. The tilde notation is used instead of the hat notation to stress that they generally differ from the time-specific empirical variance estimator (which would center the residuals at each timepoint). Note that their average equal the empirical residual variance: $\widehat{\sigma}^2 = \frac{1}{p}\sum_{j=1}^p \widetilde{\sigma}_j^2$.

- $\forall (j,j') \in \{1,\dots,p\}$ such that $j \neq j'$, we denote the off diagonal elements by $\widehat{\sigma}^2\widehat{\rho}_{j,j'}$ where $\widehat{\rho}_{j,j'} = \widehat{\rho}_{j',j} = \frac{1}{n}\sum_{i=1}^n \frac{Y_{i,j}-\widehat{\mu}_{i,j}}{\widehat{\sigma}}\frac{Y_{i,j'}-\widehat{\mu}_{i,j'}}{\widehat{\sigma}}$ its off diagonal elements.

Then:

$$\begin{aligned}
&tr\left(R^{-1}\frac{\partial R}{\partial \rho}R^{-1}\sum_{i=1}^n(\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \widehat{\boldsymbol{\mu}}_i)^\intercal\right) \\
&= \frac{n\widehat{\sigma}^2}{(1-\rho)^2}\left(p\left(-1 + \frac{\rho^2(p-1)+1}{(1+\rho(p-1))^2}\right) + \frac{2\rho^2(p-1)+2}{(1+\rho(p-1))^2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right) \\
&= \frac{n\widehat{\sigma}^2}{(1-\rho)^2}\left(p\left(\frac{-2\rho(p-1)-\rho^2(p-1)^2+\rho^2(p-1)}{(1+\rho(p-1))^2}\right) + \frac{2\rho^2(p-1)+2}{(1+\rho(p-1))^2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right) \\
&= \frac{n\widehat{\sigma}^2}{(1-\rho)^2(1+\rho(p-1))^2}\left(p\rho(p-1)\left(-2-\rho(p-2)\right) + \left(2\rho^2(p-1)+2\right)\sum_{j<j'}\widehat{\rho}_{j,j'}\right)
\end{aligned}$$

The score equation becomes:

$$0 = \frac{np(p-1)}{2(1-\rho)^2(1+\rho(p-1))^2}\left(\rho(1-\rho)(1+\rho(p-1)) - \frac{\widehat{\sigma}^2}{\sigma^2}\rho\left(2+\rho(p-2)\right) + \frac{\rho^2(p-1)+1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)$$

$$= \frac{np(p-1)(\rho^2(p-1)+1)}{2(1-\rho)^2(1+\rho(p-1))^2}\left(\rho\frac{(1-\rho)(1+\rho(p-1)) - \frac{\widehat{\sigma}^2}{\sigma^2}\left(2+\rho(p-2)\right))}{\rho^2(p-1)+1} + \frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)$$

Using that $(1-\rho)(1+\rho(p-1)) = 1-\rho+\rho(p-1)-\rho^2(p-1) = -\rho^2(p-1)+\rho(p-2)+1 = -(\rho^2(p-1)+1)+\rho(p-2)+2$, it follows that:

$$\begin{aligned}
0 &= \frac{np(p-1)\rho^2(p-1)+1}{2(1-\rho)^2(1+\rho(p-1))^2}\left(-\rho+\rho\frac{\rho(p-2)+2-\frac{\widehat{\sigma}^2}{\sigma^2}\left(2+\rho(p-2)\right))}{\rho^2(p-1)+1} + \frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right) \\
&= \frac{np(p-1)\rho^2(p-1)+1}{2(1-\rho)^2(1+\rho(p-1))^2}\left(-\rho-\rho\left(\frac{\widehat{\sigma}^2}{\sigma^2}-1\right)\frac{2+\rho(p-2)}{1+\rho^2(p-1)} + \frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)
\end{aligned}$$

Since the first term is strictly positive ($0<\rho<1$ and $p>1$) we can simplify and get that:

$$\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'} = \rho+\rho\left(\frac{\sigma^2}{\widehat{\sigma}^2}-1\right)\frac{2+\rho(p-2)}{1+\rho^2(p-1)} \tag{1}$$

B.3 Variance parameter (ML)

The ML score equation w.r.t the variance parameter is:

$$\begin{aligned}
0 &= -\frac{n}{2}tr\left(\Omega^{-1}\frac{\partial\Omega}{\partial\sigma^2}\right) + \frac{1}{2}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal\Omega^{-1}\frac{\partial\Omega}{\partial\sigma^2}\Omega^{-1}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i) \\
&= -\frac{n}{2}tr\left(\sigma^{-2}R^{-1}R\right) + \frac{1}{2\sigma^4}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal R^{-1}RR^{-1}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i) \\
&= -\frac{np}{2\sigma^2} + \frac{1}{2\sigma^4}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal R^{-1}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)
\end{aligned}$$

Using the expression of R^{-1} found in appendix B we get:

$$\begin{aligned}
0 &= -\frac{np}{2\sigma^2} + \frac{1}{2\sigma^4(1-\rho)}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal\left(I-\frac{\rho\mathbf{e}\mathbf{e}^\intercal}{(1-\rho)+\rho p}\right)(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i) \\
&= -\frac{np}{2\sigma^2} + \frac{1}{2\sigma^4(1-\rho)}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i) \\
&\quad - \frac{\rho}{2\sigma^4(1-\rho)((1-\rho)+\rho p)}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal\mathbf{e}\mathbf{e}^\intercal(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i) \\
&= -\frac{np}{2\sigma^2} + \frac{np\widehat{\sigma}^2}{2\sigma^4(1-\rho)} - \frac{\rho np^2}{2\sigma^4(1-\rho)((1-\rho)+\rho p)}\frac{1}{n}\sum_{i=1}^{n}\left(\frac{1}{p}\sum_{i=1}^{n}Y_{i,j}-\widehat{\mu}_{i,j}\right)^2
\end{aligned}$$

Since:

$$\frac{1}{n}\sum_{i=1}^{n}\left(\frac{1}{p}\sum_{j=1}^{p}Y_{i,j}-\widehat{\mu}_{i,j}\right)^2 = \frac{1}{np^2}\sum_{i=1}^{n}\sum_{j=1}^{p}\sum_{j'=1}^{p}\left(Y_{i,j}-\widehat{\mu}_j\right)\left(Y_{i,j'}-\widehat{\mu}_{j'}\right)$$

$$=\frac{\widehat{\sigma}^2}{p^2}\left(p+2\sum_{j<j'}\widehat{\rho}_{j,j'}\right)=\frac{\widehat{\sigma}^2}{p}\left(1+(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)$$

we obtain:

$$0=-\frac{np}{2\sigma^2}+\frac{np\widehat{\sigma}^2}{2\sigma^4(1-\rho)}-\frac{\rho np\widehat{\sigma}^2}{2\sigma^4(1-\rho)((1-\rho)+\rho p)}\left(1+(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)$$
$$0=-\frac{np\widehat{\sigma}^2}{2\sigma^4}\left(\frac{\sigma^2}{\widehat{\sigma}^2}-\frac{1}{(1-\rho)}+\frac{\rho}{(1-\rho)((1-\rho)+\rho p)}\left(1+(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\right)$$

Since

$$\begin{aligned}&-\frac{1}{(1-\rho)}+\frac{\rho}{(1-\rho)^2+\rho(1-\rho)p}\left(1+(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\\&=-\frac{1}{(1-\rho)}\left(1-\frac{\rho}{1+\rho(p-1)}-\frac{\rho(p-1)}{1+\rho(p-1)}\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\\&=-\frac{1}{(1-\rho)(1+\rho(p-1))}\left(1+\rho(p-2)-\rho(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\end{aligned}$$

We get:

$$\begin{aligned}0&=-\frac{np\widehat{\sigma}^2}{2\sigma^4}\left(\frac{\sigma^2}{\widehat{\sigma}^2}-\frac{1}{(1-\rho)(1+\rho(p-1))}\left(1+\rho(p-2)-\rho(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\right)\\&=-\frac{np\widehat{\sigma}^2}{2\sigma^4}\left(\frac{\sigma^2}{\widehat{\sigma}^2}-\frac{1}{1+\rho(p-2)-\rho^2(p-1)}\left(1+\rho(p-2)-\rho(p-1)\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)\right)\\&=-\frac{np\widehat{\sigma}^2}{2\sigma^4}\left(\frac{\sigma^2}{\widehat{\sigma}^2}-1-\frac{\rho(p-1)\left(\rho-\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}\right)}{1+\rho(p-2)-\rho^2(p-1)}\right)\end{aligned}$$

Since $\frac{np\widehat{\sigma}^2}{2\sigma^4}\neq 0$ and using equation Equation 1, we obtain:

$$0=\frac{\sigma^2}{\widehat{\sigma}^2}-1+\frac{\rho^2(p-1)\left(\frac{\sigma^2}{\widehat{\sigma}^2}-1\right)\frac{2+\rho(p-2)}{1+\rho^2(p-1)}}{1+\rho(p-2)-\rho^2(p-1)}=\left(\frac{\sigma^2}{\widehat{\sigma}^2}-1\right)\left(1+\frac{\rho^2(p-1)\frac{2+\rho(p-2)}{1+\rho^2(p-1)}}{(1-\rho)(1+\rho(p-1))}\right)$$

The second term is strictly positive: it is clear when $p>2$ because all terms are positive or null and one is added. When $p=1$ then $2+\rho(p-2)=2-\rho>0$ because $\rho<1$. So we must have $\sigma^2=\widehat{\sigma}^2$. Plugging this value in the score equation for the correlation parameter leads to:

$$\rho=\frac{1}{p(p-1)/2}\sum_{j<j'}\widehat{\rho}_{j,j'}$$

B.4 Correlation parameter (REML)

The REML score equation w.r.t the correlation parameter is the same as the ML score equation with the additional term:

$$\begin{aligned}
&\frac{1}{2}tr\left(\left(X^\intercal\Omega^{-1}X\right)^{-1}\left(X^\intercal\Omega^{-1}\frac{\partial\Omega}{\partial\rho}\Omega^{-1}X\right)\right)\\
=&\frac{1}{2\sigma^4}tr\left(\left(X^\intercal R^{-1}X\right)^{-1}\left(X^\intercal R^{-1}\frac{\partial R}{\partial\rho}R^{-1}X\right)\right)
\end{aligned}$$

Using from appendix C that:

$$\left(X^\intercal R^{-1}X\right)^{-1}=\frac{1}{p-p_1}\begin{bmatrix}1+\rho(p-p_1-1) & -(1-\rho)\\ -(1-\rho) & \frac{p}{p_1}(1-\rho)\end{bmatrix}$$

and that:

$$\begin{aligned}
R^{-1}\frac{\partial R}{\partial\rho}R^{-1} &= \frac{1}{(1-\rho)^2}\left(-I+\mathbf{e}\mathbf{e}^\intercal\frac{\rho^2(p-1)+1}{(1+\rho(p-1))^2}\right)\\
X^\intercal R^{-1}\frac{\partial R}{\partial\rho}R^{-1}X &= \frac{1}{(1-\rho)^2}\left(-X^\intercal X+X^\intercal\mathbf{e}\mathbf{e}^\intercal X\frac{\rho^2(p-1)+1}{(1+\rho(p-1))^2}\right)\\
&= \frac{1}{(1-\rho)^2}\left(-\begin{bmatrix}p & p_1\\ p_1 & p\end{bmatrix}+\begin{bmatrix}p^2 & pp_1\\ pp_1 & p_1^2\end{bmatrix}\frac{\rho^2(p-1)+1}{(1+\rho(p-1))^2}\right)
\end{aligned}$$

which does not seems to simplify, i.e. the trace has a complicated expression.

B.5 Variance parameter (REML)

The REML score equation w.r.t the variance parameter is the same as the ML score equation with the additional term:

$$\begin{aligned}
&\frac{1}{2}tr\left(\left(X^\intercal\Omega^{-1}X\right)^{-1}\left(X^\intercal\Omega^{-1}\frac{\partial\Omega}{\partial\sigma^2}\Omega^{-1}X\right)\right)\\
&=\frac{1}{2\sigma^2}tr\left(\left(X^\intercal\Omega^{-1}X\right)^{-1}\left(X^\intercal\Omega^{-1}X\right)\right)=\frac{2}{2\sigma^2}
\end{aligned}$$

leading to

$$\sigma^2=\frac{1}{np-2}\sum_{i=1}^{n}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)^\intercal R^{-1}(\mathbf{Y}_i-\widehat{\boldsymbol{\mu}}_i)$$

C Standard error of the treatment effect in a balanced random intercept model

Consider a random intercept model including single binary covariate (called treatment):

$$Y_{it} = \mu + \beta T_{it} + \alpha_i + \varepsilon_{it}$$

where $\alpha_i \sim \mathcal{N}(0, \tau)$ and $\varepsilon_{it} \sim \mathcal{N}(0, \delta)$. Denote $\rho = \frac{\tau}{\tau+\delta}$ and $\sigma^2 = \tau + \delta$ such that:

$$\mathbb{V}ar\left[Y_{it}\right] = \Omega = \sigma^2 R = \sigma^2((1-\rho)I + \rho e e^\intercal)$$

where I and e were defined in section A. The inverse of R was also explicit in section A and when multiplied the $p \times 2$ matrix $X = (1, T)$ where T is either 0 or 1, respectively p_0 and p_1 times, we get:

$$\begin{aligned}
X^\intercal R^{-1} X &= \frac{1}{1-\rho} X^\intercal X - \frac{\rho X^\intercal e e^\intercal X}{(1-\rho)^2 + \rho(1-\rho)p} \\
&= \frac{1}{1-\rho}\left(X^\intercal X - \frac{\rho X^\intercal e e^\intercal X}{1+\rho(p-1)}\right) \\
&= \frac{1}{1-\rho}\left(\begin{bmatrix} p & p_1 \\ p_1 & p_1 \end{bmatrix} - \frac{\rho}{1+\rho(p-1)}\begin{bmatrix} p^2 & pp_1 \\ pp_1 & p_1^2 \end{bmatrix}\right) \\
&= \frac{1}{(1-\rho)(1+\rho(p-1))}\begin{bmatrix} p + p\rho(p-1) - \rho p^2 & p_1 + p_1\rho(p-1) - \rho p p_1 \\ p_1 + p_1\rho(p-1) - \rho p p_1 & p_1 + p_1\rho(p-1) - \rho p_1^2 \end{bmatrix} \\
&= \frac{1}{(1-\rho)(1+\rho(p-1))}\begin{bmatrix} p(1-\rho) & p_1(1-\rho) \\ p_1(1-\rho) & p_1(1+\rho(p-p_1-1)) \end{bmatrix}
\end{aligned}$$

whose inverse is:

$$\begin{aligned}
\left(X^\intercal R^{-1} X\right)^{-1} &= \frac{(1-\rho)(1+\rho(p-1))}{p_1 p(1-\rho)(1+\rho(p-p_1-1)) - p_1^2(1-\rho)^2}\begin{bmatrix} p_1(1+\rho(p-p_1-1)) & -p_1(1-\rho) \\ -p_1(1-\rho) & p(1-\rho) \end{bmatrix} \\
&= \frac{1+\rho(p-1)}{p_1 p(1+\rho(p-p_1-1)) - p_1^2(1-\rho)}\begin{bmatrix} p_1(1+\rho(p-p_1-1)) & -p_1(1-\rho) \\ -p_1(1-\rho) & p(1-\rho) \end{bmatrix} \\
&= \frac{1+\rho(p-1)}{(p-p_1) + \rho(p^2 - pp_1 - p + p_1)}\begin{bmatrix} 1+\rho(p-p_1-1) & -(1-\rho) \\ -(1-\rho) & \frac{p}{p_1}(1-\rho) \end{bmatrix} \\
&= \frac{1}{p-p_1}\begin{bmatrix} 1+\rho(p-p_1-1) & -(1-\rho) \\ -(1-\rho) & \frac{p}{p_1}(1-\rho) \end{bmatrix}
\end{aligned}$$

So in the random intercept model, the standard error of the treatment estimator will be:

$$\sigma_{\widehat{\beta}} = \sqrt{\sigma_0^2(1-\rho)\frac{p}{np_1(p-p_1)}} = \sqrt{\frac{\delta}{n}\frac{p}{p_1(p-p_1)}}$$

In a design with as many observations under treatment as under control $p_1 = p/2$ and the expression simplifies into.

$$\sigma_{\widehat{\beta}} = \sqrt{\frac{4\delta}{np}} = \sqrt{\frac{2\delta}{np_1}}$$

From section B we deduce that:

$$\sigma_{\widehat{\beta}} = \sqrt{\frac{\left(1 - \frac{1}{p(p-1)/2}\sum_{t \neq t'} \rho_{t,t'}\right)\sigma^2}{n}\frac{p}{p_1(p-p_1)}}$$

which in a design with as many observations under treatment as under control simplifies to:

$$\sigma_{\widehat{\beta}} = \sqrt{\frac{2\left(1 - \frac{1}{p(p-1)/2}\sum_{t \neq t'} \rho_{t,t'}\right)\sigma^2}{np_1}}$$

Note: when using a t-test on the change based only on the first observation under each treatment the variance is:

$$\sigma_{\widehat{\beta}} = \sqrt{\frac{2(1-\rho_{1,p+1})\sigma^2}{n}}$$