Advanced dataanalysis and statistical modelling, Week 9

Mixed effects models - II

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DTU Compute

- Fixed effects
- Block and main effects
- Random effects

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lme

- random.efftects… differences from the fixed.effects

Outline

1. The general linear mixed model
   - Random coefficient regression lines - example
2. REML - estimation
3. Repeated measurements setup (Correlation structure)
4. Model development

Oversigt

Remember the general linear mixed model

A general linear mixed model can be presented in matrix notation by:

$$\mathbf{Y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{U} + \varepsilon, \quad \text{where } \mathbf{U} \sim N(0, \mathbf{\Psi}) \text{ and } \varepsilon \sim N(0, \mathbf{\Sigma}).$$

- $\mathbf{Y}$ is the observation vector
- $\mathbf{X}$ is the design matrix for the fixed effects
- $\boldsymbol{\beta}$ is the vector containing the fixed effect parameters
- $\mathbf{Z}$ is the design matrix for the random effects
- $\mathbf{U}$ is the vector of random effects
  - It is assumed that $\mathbf{U} \sim N(\mathbf{0}, \mathbf{\Psi})$
  - cov$(U_i, U_j) = G_{i,j}$ (typically $\mathbf{\Psi}$ has a very simple structure (for instance diagonal))
- $\boldsymbol{\varepsilon}$ is the vector of residual errors
  - It is assumed that $\varepsilon \sim N(\mathbf{0}, \mathbf{\Sigma})$
  - cov$(\varepsilon_i, \varepsilon_j) = R_{i,j}$ (typically $\mathbf{\Sigma}$ is diagonal, but we shall later see some useful exceptions for repeated measurements)

The distribution of $\mathbf{Y}$

From the model description:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{U} + \boldsymbol{\varepsilon}, \quad \text{where } \mathbf{U} \sim N(0, \boldsymbol{\Psi}) \text{ and } \boldsymbol{\varepsilon} \sim N(0, \boldsymbol{\Sigma}).$$

We can compute the mean vector $\boldsymbol{\mu} = E(\mathbf{Y})$ and covariance matrix $\mathbf{V} = \text{var}(\mathbf{Y})$:

$$\begin{aligned}
\boldsymbol{\mu} &= E(\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{U} + \boldsymbol{\varepsilon}) = \mathbf{X}\boldsymbol{\beta} \quad \text{[All other terms have mean zero]} \\
\mathbf{V} &= \text{var}(\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{U} + \boldsymbol{\varepsilon}) \quad \text{[from model]} \\
&= \text{var}(\mathbf{X}\boldsymbol{\beta}) + \text{var}(\mathbf{Z}\mathbf{U}) + \text{var}(\boldsymbol{\varepsilon}) \quad \text{[all terms are independent]} \\
&= \text{var}(\mathbf{Z}\mathbf{U}) + \text{var}(\boldsymbol{\varepsilon}) \quad \text{[variance of fixed effects is zero]} \\
&= \mathbf{Z}\text{var}(\mathbf{U})\mathbf{Z}^T + \text{var}(\boldsymbol{\varepsilon}) \quad [\mathbf{Z} \text{ is constant}] \\
&= \mathbf{Z}\boldsymbol{\Psi}\mathbf{Z}^T + \boldsymbol{\Sigma} \quad \text{[from model]}
\end{aligned}$$

So $\mathbf{Y}$ follows a multivariate normal distribution:

$$\mathbf{Y} \sim N(\mathbf{X}\boldsymbol{\beta}, \mathbf{Z}\boldsymbol{\Psi}\mathbf{Z}^T + \boldsymbol{\Sigma})$$

General linear mixed effects models

It follows from the independence of $\boldsymbol{U}$ and $\boldsymbol{\epsilon}$ that

$$\mathrm{D}\left[\begin{pmatrix}\boldsymbol{\epsilon}\\ \boldsymbol{U}\end{pmatrix}\right] = \begin{pmatrix}\boldsymbol{\Sigma} & \mathbf{0}\\ \mathbf{0} & \boldsymbol{\Psi}\end{pmatrix}$$

The model may also be interpreted as a *hierarchical model*

$$\boldsymbol{U} \sim N(\mathbf{0}, \boldsymbol{\Psi})$$
$$\boldsymbol{Y}|\boldsymbol{U} = \boldsymbol{u} \sim N(\boldsymbol{X\beta} + \boldsymbol{Zu}, \boldsymbol{\Sigma})$$

One-way model with random effects - example

The one-way model with random effects

$$Y_{ij} = \mu + U_i + e_{ij}$$

We can formulate this as

$$\boldsymbol{Y} = \boldsymbol{X}\beta + \boldsymbol{Z}\boldsymbol{U} + \boldsymbol{\epsilon}$$

with

$$\begin{aligned}
\boldsymbol{X} &= \mathbf{1}_N \\
\beta &= \mu \\
\boldsymbol{U} &= (U_1, U_2, \ldots, U_k)^T \\
\boldsymbol{\Sigma} &= \sigma^2 \boldsymbol{I}_N \\
\boldsymbol{\Psi} &= \sigma_u^2 \boldsymbol{I}_k
\end{aligned}$$

where $\mathbf{1}_N$ is a column of 1's. The i, j'th element in the $N \times k$ dimensional matrix $\boldsymbol{Z}$ is 1, if y_{ij} belongs to the i'th group, otherwise it is zero.

One way ANOVA with random block effect

Consider again the model:

$$Y_{ij} = \mu + \alpha_i + B_j + \varepsilon_{ij},\ B_j \sim N(0, \sigma_B^2),\ \varepsilon_{ij} \sim N(0, \sigma^2),\ i = 1, 2,\ j = 1, 2, 3$$

Calculation of $\boldsymbol{\mu}$ and $\mathbf{V}$ gives:

$$\boldsymbol{\mu} = \begin{pmatrix} \mu + \alpha_1 \\ \mu + \alpha_2 \\ \mu + \alpha_1 \\ \mu + \alpha_2 \\ \mu + \alpha_1 \\ \mu + \alpha_2 \end{pmatrix},\ \mathbf{V} = \begin{pmatrix} \sigma^2 + \sigma_B^2 & \sigma_B^2 & 0 & 0 & 0 & 0 \\ \sigma_B^2 & \sigma^2 + \sigma_B^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2 + \sigma_B^2 & \sigma_B^2 & 0 & 0 \\ 0 & 0 & \sigma_B^2 & \sigma^2 + \sigma_B^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2 + \sigma_B^2 & \sigma_B^2 \\ 0 & 0 & 0 & 0 & \sigma_B^2 & \sigma^2 + \sigma_B^2 \end{pmatrix}$$

Notice that two observations from the same block are correlated.

Random coefficient regression lines - example

The table shows the length in [mm] of the ramus bone for five randomly selected boys in the age 8-10 years. For each boy the bone length was measured four times, at age 8, 8.5, 9 and 9.5 years.
Also estimated parameters of a fixed effects model.

	Reduced age, $x_i = \text{age} - 8.75$					
Boy	-0.75	-0.25	0.25	0.75	β_{i1}	β_{i2}
A	52.5	53.2	53.3	53.7	53.175	0.74
B	51.2	53.0	54.3	54.5	53.250	2.24
C	51.2	51.4	51.6	51.9	51.525	0.46
D	52.1	52.8	53.7	55.0	53.400	1.92
E	50.7	51.7	52.7	53.3	52.100	1.76
Average	51.54	52.42	53.12	53.68	52.690	1.424

Example: Ramus bone length

If interested in these specific five boys - a fixed effects model:

$$Y_{ij} = \beta_{i1} + x_{ij}\beta_{i2} + \epsilon_{ij},\ i = 1, 2, \ldots, 5;\ j = 1, 2, 3, 4, \tag{1}$$

where ϵ_{ij} are assumed independent $N(0, \sigma^2)$-distributed.

In R one might have used a formula like

```
> formula = ramus ~ Boy+agered+Boy:agered
```

Example: Ramus bone length - random coef. regression

However, since we are not interested in the individual boys as such, but consider them as a sample of boys, so we will use a *random effects* model. The observations from the i'th boy are modelled by

$$\boldsymbol{Y}_i = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{X}\boldsymbol{U}_i + \boldsymbol{\epsilon}_i,\ i = 1, 2, \ldots, k$$

where the two-dimensional random effect contains the random deviations from the overall values of the intercept and slope, and where

$$\boldsymbol{U}_i \sim N_2(\mathbf{0}, \sigma^2\boldsymbol{\Psi}), \ \ \boldsymbol{\epsilon}_i \sim N_{n_i}(\mathbf{0}, \sigma^2\boldsymbol{I}_{n_i}) \ , \tag{2}$$

and where $\boldsymbol{U}_i, \boldsymbol{U}_j$ are mutually independent for $i \neq j$, and $\boldsymbol{\epsilon}_i$ and $\boldsymbol{\epsilon}_j$ are mutually independent for $i \neq j$, and further are $\boldsymbol{U}_i$ and $\boldsymbol{\epsilon}_j$ independent. The covariance matrix $\boldsymbol{\Psi}$ denotes the covariance matrix in the population distribution of intercepts and slopes with the measurement error σ^2 extracted as a factor.

Example: Ramus bone length - random coef. regression

The marginal distribution of $\boldsymbol{Y}_i$ under the model is given by

$$\boldsymbol{Y}_i \sim N_{n_i}(\boldsymbol{X}\boldsymbol{\beta}, \sigma^2[\boldsymbol{I}_{n_i} + \boldsymbol{X}\boldsymbol{\Psi}\boldsymbol{X}^T]),$$

It is noticed that the distribution is influenced as well by the design matrix $\boldsymbol{X}$, as by the covariance matrix $\boldsymbol{\Psi}$ in the distribution of $\boldsymbol{U}$.

Example: Ramus bone length - random coef. regression

The fixed effects part of the model leads to estimates of the overall values of the parameters. These overall estimates for the intercept and slope are $\hat{\beta}_1 = 52.69$ and $\hat{\beta}_2 = 1.424$.

The random effects part of the model can be specified as

$$\widehat{\sigma}^2 \widehat{\boldsymbol{\Psi}} = 0.2939^2 \begin{pmatrix} 7.7312 & 4.0573 \\ 4.0573 & 6.2072 \end{pmatrix} = \begin{pmatrix} 0.8173^2 & 0.3506 \\ 0.3506 & 0.7323^2 \end{pmatrix} \tag{3}$$

where the estimated correlation coefficient (0.586) is used to state the off-diagonal value of the covariance matrix $\widehat{\boldsymbol{\Psi}}$.

In conclusion it is seen that the average length of the ramus bone for boys at age 8.75 is 52.69 [mm], and the average growth rate is 1.42 [mm/year]. Finally, the correlation coefficient shows a positive relation between the length of the ramus bone at age 8.75 and the growth rate.

Oversigt

The likelihood function

- The *likelihood* L is a function of model parameters and observations
- For given parameter values L returns a measure of the probability of observing $\mathbf{y}$
- The *log likelihood* ℓ for a mixed linear model is:

$$\ell(\mathbf{y}, \boldsymbol{\beta}, \boldsymbol{\psi}) \propto -\frac{1}{2}\left\{\log|\mathbf{V}(\boldsymbol{\psi})| + (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T(\mathbf{V}(\boldsymbol{\psi}))^{-1}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta})\right\}$$

- Here $\boldsymbol{\psi}$ is the variance parameters (σ^2 and σ_B^2 in our example)
- A natural estimate is to choose the parameters that make our observations most likely:

$$(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\psi}}) = \underset{(\boldsymbol{\beta},\boldsymbol{\psi})}{\text{argmax}}\, \ell(\mathbf{y}, \boldsymbol{\beta}, \boldsymbol{\psi})$$

- This is the *maximum likelihood (ML)* method

The restricted/residual maximum likelihood method

- The maximum likelihood method tends to give (slightly) too low estimates of the random effects parameters. We say it is *biased downwards*
- The simplest example is:

  $(x_1, \ldots, x_N) \sim N(\mu, \sigma^2)$ i.i.d.
  $\hat{\sigma}^2 = \frac{1}{n}\sum(x_i - \overline{x})^2$ is the maximum likelihood estimate, but
  $\hat{\sigma}^2 = \frac{1}{n-1}\sum(x_i - \overline{x})^2$ is generally preferred, because it is *unbiased*
- The *restricted/residual maximum likelihood (REML)* method modifies the maximum likelihood method by maximizing:

$$\ell_{re}(\mathbf{y}, \boldsymbol{\beta}, \boldsymbol{\psi}) \propto -\frac{1}{2}\left\{\log|\mathbf{V}(\boldsymbol{\psi})| + (\mathbf{y}-\mathbf{X}\boldsymbol{\beta})^T(\mathbf{V}(\boldsymbol{\psi}))^{-1}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}) + \log|\mathbf{X}^T(\mathbf{V}(\boldsymbol{\psi}))^{-1}\mathbf{X}|\right\}$$

  which gives unbiased estimates (at least in balanced cases)
- The REML method is generally preferred in mixed models

ML vs. REML, simplest example

Consider again the model:

$$Y_i = \mu + \varepsilon_i; \qquad \varepsilon_i \sim N(0, \sigma^2), \;\; i = 1, 2, ..., n$$

the likelihood of (μ, σ^2) is

$$l([\mu, \sigma^2]; \mathbf{y}) \propto -\frac{n}{2} \log(\sigma^2) - \frac{1}{2\sigma^2} \sum_i (y_i - \mu)^2$$

and hence

$$\frac{\partial l([\mu, \sigma^2]; \mathbf{y})}{\partial \mu} = -\frac{1}{\sigma^2} \sum_i (y_i - \mu) = \frac{1}{\sigma^2} \left(n\mu - \sum_i y_i \right)$$

and the MLE of μ is $\hat{\mu} = \bar{y}$, and $E[\hat{\mu}] = \mu$.

ML, simplest example (σ^2)

$$\frac{\partial l([\mu,\sigma^2];\mathbf{y})}{\partial\sigma^2} = -\frac{n}{2\sigma^2} + \frac{1}{2(\sigma^2)^2}\sum_i (y_i-\mu)^2$$

and the MLE of σ^2 is $\hat{\sigma}^2_{ML} = \frac{1}{n}\sum_i (y_i-\mu)^2$, replacing μ with $\hat{\mu}$ gives $\hat{\sigma}^2_{ML} = \frac{1}{n}\sum_i (y_i-\bar{y})^2$. Taking the expectation

$$\begin{aligned}
E[\hat{\sigma}^2_{ML}] =& \frac{1}{n}\sum_i E\left[(Y_i-\bar{Y})^2\right] \\
=& \frac{1}{n}\sum_i E\left[(Y_i+\mu-\mu-\bar{Y})^2\right] \\
=& \frac{1}{n}\sum_i \left(E\left[(Y_i+\mu)^2\right] + E\left[(\bar{Y}-\mu)^2\right] - 2E\left[(Y_i+\mu)(\bar{Y}-\mu)\right]\right) \\
=& \frac{1}{n}\sum_i \left(\sigma^2 + \frac{\sigma^2}{n} - 2\frac{\sigma^2}{n}\right) = \sigma^2\left(1-\frac{1}{n}\right)
\end{aligned}$$

REML, simplest example (σ^2)

The modification term for the likelihood in the model is

$$\frac{1}{2}\log|\mathbf{X}^T V^{-1}\mathbf{X}| = \frac{1}{2}\log\left(\frac{n}{\sigma^2}\right) = \frac{1}{2}\left(\log(n) - \log(\sigma^2)\right)$$

and hence

$$\frac{\partial l_{RE}([\mu,\sigma^2];\mathbf{y})}{\partial\sigma^2} = -\frac{n}{2\sigma^2} + \frac{1}{2(\sigma^2)^2}\sum_i (y_i-\mu)^2 + \frac{1}{2\sigma^2}$$

and the REML estimate of σ^2 is $\hat{\sigma}^2_{REML} = \frac{1}{n-1}\sum_i (y_i-\mu)^2$, replacing μ with $\hat{\mu}$ gives $\hat{\sigma}^2_{REML} = \frac{1}{n-1}\sum_i (y_i-\bar{y})^2$. Taking the expectation

$$\begin{aligned} E[\hat{\sigma}^2_{REML}] =& \frac{1}{n-1}\sum_i\left(\sigma^2 + \frac{\sigma^2}{n} - 2\frac{\sigma^2}{n}\right) \\ =& \frac{1}{n-1}n\sigma^2\left(1-\frac{1}{n}\right) = \sigma^2 \end{aligned}$$

ML vs. REML, simple example

Consider again the model:

$$Y_{ij} = \mu + B_j + \varepsilon_{ij},\ \ B_j \sim N(0, \sigma_B^2),\ \ \varepsilon_{ij} \sim N(0, \sigma^2),\ \ i = 1, 2,\ \ j = 1, 2, 3$$

Calculation of $\boldsymbol{\mu}$ and $\mathbf{V}$ gives:

$$\boldsymbol{\mu} = \begin{pmatrix} \mu \\ \mu \\ \mu \\ \mu \\ \mu \\ \mu \end{pmatrix},\ \ \mathbf{V} = \begin{pmatrix} \sigma^2+\sigma_B^2 & \sigma_B^2 & 0 & 0 & 0 & 0 \\ \sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2+\sigma_B^2 & \sigma_B^2 & 0 & 0 \\ 0 & 0 & \sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2+\sigma_B^2 & \sigma_B^2 \\ 0 & 0 & 0 & 0 & \sigma_B^2 & \sigma^2+\sigma_B^2 \end{pmatrix}$$

Fixed effect parameters

$$l(\beta,\psi;\mathbf{y}) = -\frac{1}{2}\log|\mathbf{V}| - \frac{1}{2}(\mathbf{y}-\mathbf{X}\beta)^T\mathbf{V}^{-1}(\mathbf{y}-\mathbf{X}\beta)$$

$$l_\beta(\beta,\psi;\mathbf{y}) = \frac{1}{2}\mathbf{X}^T\left(\mathbf{V}^{-1}\mathbf{y} - \mathbf{V}^{-1}\mathbf{X}\beta\right)$$

$$\mathbf{V}^{-1} = \frac{1}{\sigma^4 + 2\sigma^2\sigma_B^2}\begin{pmatrix} \sigma^2+\sigma_B^2 & -\sigma_B^2 & 0 & 0 & 0 & 0 \\ -\sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2+\sigma_B^2 & -\sigma_B^2 & 0 & 0 \\ 0 & 0 & -\sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2+\sigma_B^2 & -\sigma_B^2 \\ 0 & 0 & 0 & 0 & -\sigma_B^2 & \sigma^2+\sigma_B^2 \end{pmatrix}$$

$$\mathbf{X}^T\mathbf{V}^{-1}\mathbf{y} = \frac{\sigma^2}{\sigma^4 + 2\sigma^2\sigma_B^2}\sum_i\sum_j y_{ij}$$

$$\mathbf{X}^T\mathbf{V}^{-1}\mathbf{X} = \frac{6\sigma^2}{\sigma^4 + 2\sigma^2\sigma_B^2}$$

Fixed effect parameter

$$
\begin{aligned}
l_\beta(\beta, \psi; \mathbf{y}) =& 0 \Rightarrow \\
\frac{\sigma^2}{\sigma^4 + 2\sigma^2\sigma_B^2} \sum_i \sum_j y_{ij} =& \frac{6\sigma^2\beta}{\sigma^4 + 2\sigma^2\sigma_B^2} \Rightarrow \\
\hat{\beta} =& \frac{1}{6} \sum_i \sum_j y_{ij} \\
=& \bar{\bar{y}}
\end{aligned}
$$

also

$$
\begin{aligned}
E[l_\beta(\beta, \psi; \mathbf{y})] =& \mathbf{X}^T(\mathbf{V}^{-1}E[\mathbf{y}] - \mathbf{V}^{-1}\mathbf{X}\beta) \\
=& \mathbf{X}^T(\mathbf{V}^{-1}\mathbf{X}\beta - \mathbf{V}^{-1}\mathbf{X}\beta) = 0
\end{aligned}
$$

Estimation of σ^2

$$l_{\sigma^2}(\beta,\psi;\mathbf{y}) = -\frac{1}{2}\frac{\partial}{\partial\sigma^2}\log|\mathbf{V}| - \frac{1}{2}(\mathbf{y}-\mathbf{X}\beta)^T\frac{\partial}{\partial\sigma^2}\mathbf{V}^{-1}(\mathbf{y}-\mathbf{X}\beta)$$

$$\begin{aligned}
|\mathbf{V}| =& (\sigma^4 + 2\sigma^2\sigma_B^2)^3 \\
\log|\mathbf{V}| =& 3\log(\sigma^4 + 2\sigma^2\sigma_B^2) \\
\frac{\partial}{\partial\sigma^2}\log|\mathbf{V}| =& 6\frac{\sigma^2 + \sigma_B^2}{\sigma^4 + 2\sigma^2\sigma_B^2}
\end{aligned}$$

Estimation of σ^2

$$\frac{\partial \mathbf{V}^{-1}}{\partial \sigma^2} = -\frac{2(\sigma^2+\sigma_B^2)}{(\sigma^4+2\sigma^2\sigma_B^2)^2}\begin{pmatrix} \sigma^2+\sigma_B^2 & -\sigma_B^2 & 0 & 0 & 0 & 0 \\ -\sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2+\sigma_B^2 & -\sigma_B^2 & 0 & 0 \\ 0 & 0 & -\sigma_B^2 & \sigma^2+\sigma_B^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2+\sigma_B^2 & -\sigma_B^2 \\ 0 & 0 & 0 & 0 & -\sigma_B^2 & \sigma^2+\sigma_B^2 \end{pmatrix}$$

$$+\frac{1}{\sigma^4+2\sigma^2\sigma_B^2}\mathbf{I}$$

with $e_{ij} = y_{ij} - x_i\hat{\beta}$ we get

$$\mathbf{e}^T\frac{\partial \mathbf{V}^{-1}}{\partial \sigma^2}\mathbf{e} = -\frac{2(\sigma^2+\sigma_B^2)}{(\sigma^4+2\sigma^2\sigma_B^2)^2}\left((\sigma^2+\sigma_B^2)\sum_{i,j} e_{ij}^2 - 2\sigma_B^2\sum_j e_{1j}e_{2j}\right)$$

$$+\frac{1}{\sigma^4+2\sigma^2\sigma_B^2}\sum_{i,j} e_{ij}^2$$

Estimation of σ^2

$$\begin{aligned}
E[e_{ij}^2] =& E[(y_{ij} - \hat{\beta})^2] \\
=& \sigma^2 + \sigma_B^2 + V[\hat{\beta}] \\
E[e_{1j}e_{2j}] =& E[(y_{1j} - \hat{\beta})(y_{2j} - \hat{\beta})] \\
=& \sigma_B^2 + V[\hat{\beta}] \\
V[\hat{\beta}] =& (\mathbf{X}^T\mathbf{V}^{-1}\mathbf{X})^{-1} \\
=& \frac{1}{6}(\sigma^2 + 2\sigma_B^2)
\end{aligned}$$

and

$$E\left[\mathbf{e}^T\frac{\partial \mathbf{V}^{-1}}{\partial \sigma^2}\mathbf{e}\right] = -\frac{6(\sigma^2+\sigma_B^2)}{(\sigma^4+2\sigma^2\sigma_B^2)} - \frac{6(V[\hat{\beta}] - \frac{1}{3}(\sigma^2+2\sigma_B^2))}{(\sigma^2+2\sigma_B^2)^2}$$

Estimation of σ^2

$$
\begin{aligned}
E[l_{\sigma^2}(\sigma^2, \sigma_B^2; \hat{\beta})] &= -\frac{6}{2}\frac{\sigma^2+\sigma_B^2}{\sigma^4+2\sigma^2\sigma_B^2} + \frac{6}{2}\frac{\sigma^2+\sigma_B^2}{\sigma^4+2\sigma^2\sigma_B^2} - \frac{1}{2}\frac{1}{\sigma^2+2\sigma_B^2} \\
&= -\frac{1}{2}\frac{1}{\sigma^2+2\sigma_B^2} < 0
\end{aligned}
$$

The REML correction term is (apart from the factor $-1/2$ (cf. (5.57))

$$
\begin{aligned}
\log|\mathbf{X}\mathbf{V}^{-1}\mathbf{X}| &= \log\left(\frac{1}{V[\hat{\beta}]}\right) = \log(6) - \log(\sigma^2 + 2\sigma_B^2) \\
\frac{\partial}{\partial\sigma^2}\log|\mathbf{X}\mathbf{V}^{-1}\mathbf{X}| &= -\frac{1}{\sigma^2+2\sigma_B^2}
\end{aligned}
$$

Estimation of σ_B^2

By similar calculation

$$E[l_{\sigma_B^2}(\sigma_B^2, ..)] = -\frac{1}{\sigma^2 + 2\sigma_B^2} < 0$$

The REML correction term is

$$\log|\mathbf{X}\mathbf{V}^{-1}\mathbf{X}| = \log\left(\frac{1}{V[\hat{\beta}]}\right) = \log(6) - \log(\sigma^2 + 2\sigma_B^2)$$

$$\frac{\partial}{\partial\sigma_B^2}\log|\mathbf{X}\mathbf{V}^{-1}\mathbf{X}| = -\frac{2}{\sigma^2 + 2\sigma_B^2}$$

Estimation of random effects

- Formally, the random effects, $\boldsymbol{U}$ are not parameters in the model, and the usual likelihood approach does not make much sense for “estimating” these random quantities.
- It is, however, often of interest to assess these “latent”, or “state” variables.
- We formulate a so-called *hierarchical likelihood* by writing the joint density for observable as well as unobservable random quantities.

$$
\begin{aligned}
f(\mathbf{y}, \mathbf{u}; \beta, \psi) =& f_{Y|u}(\mathbf{y}; \beta) f_U(\mathbf{u}; \psi) \\
=& \frac{1}{(\sqrt{2})^N \sqrt{|\mathbf{\Sigma}|}} e^{-\frac{1}{2}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}-\mathbf{Z}\boldsymbol{u})^T \mathbf{\Sigma}^{-1}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}-\mathbf{Z}\boldsymbol{u})} \times \\
& \frac{1}{(\sqrt{2})^q \sqrt{|\mathbf{\Psi}|}} e^{-\frac{1}{2}\mathbf{u}^T \mathbf{\Psi}^{-1} \mathbf{u}}
\end{aligned}
$$

Estimation of random effects

- *Hierarchical likelihood* (Remember, the short notation $\boldsymbol{\Psi}$ for $\boldsymbol{\Psi}(\boldsymbol{\psi})$ is used)

$$
\begin{aligned}
l(\boldsymbol{\beta}, \boldsymbol{\psi}, \boldsymbol{u}) =& -\frac{1}{2}\log(|\boldsymbol{\Sigma}|) - \frac{1}{2}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta} - \mathbf{Z}\boldsymbol{u})^T \boldsymbol{\Sigma}^{-1}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta} - \mathbf{Z}\boldsymbol{u}) \\
& -\frac{1}{2}\log(|\boldsymbol{\Psi}|) - \frac{1}{2}\mathbf{u}^T\boldsymbol{\Psi}^{-1}\mathbf{u} \\
l_{\boldsymbol{u}}(\boldsymbol{\beta}, \boldsymbol{\psi}, \boldsymbol{u}) =& \mathbf{Z}^T\boldsymbol{\Sigma}^{-1}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta} - \mathbf{Z}\boldsymbol{u}) - \boldsymbol{\Psi}^{-1}\mathbf{u}
\end{aligned}
$$

- By putting the derivative of the hierarchical likelihood equal to zero and solving with respect to $\boldsymbol{u}$ one finds that the estimate $\widehat{\boldsymbol{u}}$ is solution to

$$
(\boldsymbol{Z}^T\boldsymbol{\Sigma}^{-1}\boldsymbol{Z} + \boldsymbol{\Psi}^{-1})\boldsymbol{u} = \boldsymbol{Z}^T\boldsymbol{\Sigma}^{-1}(\boldsymbol{y} - \boldsymbol{X}\boldsymbol{\beta})
$$

  where the estimate $\widehat{\boldsymbol{\beta}}$ is inserted in place of $\boldsymbol{\beta}$.

- The solution is termed the *best linear unbiased predictor*
- Unceartainty of $\hat{\boldsymbol{u}}$ can be assessed through the observed Fisher information

$$
\boldsymbol{I}(\hat{\boldsymbol{u}}) = (\boldsymbol{Z}^T\boldsymbol{\Sigma}^{-1}\boldsymbol{Z} + \boldsymbol{\Psi}^{-1})
$$

REML or ML

- When we want to estimate model parameters - especially variance parameters - we should use REML
- But when we want to compute the likelihood ratio test we should use ML.
- The `lme()` function defaults to REML, and can use ML by specifying

```
> fit<-lme(y~A, random=~1|B, method="ML")
```

Oversigt

The repeated measurements setup

- Several "individuals"
- Several measurements on each individual
- Two measurements on the same individual might be correlated
- Might even be highly correlated if "close" and less correlated if "far apart"
- Typical example:
  - 20 individuals from relevant population
  - Half get drug A and half get drug B
  - Measured every week for two months

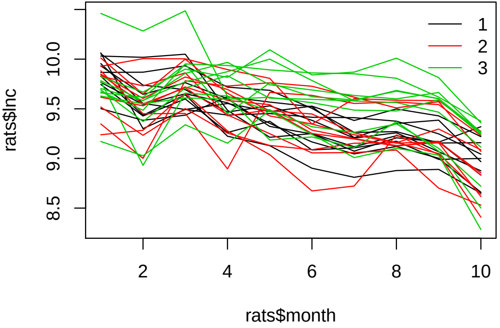
To pretend all observations are independent can lead to wrong conclusions

		Month									
Dose	Cage	1	2	3	4	5	6	7	8	9	10
1	1	20584	15439	17376	14785	11189	10366	8725	9974	9576	6849
1	2	23265	16956	16200	12934	13763	11893	9949	10490	8674	7153
1	3	17065	12429	14757	10524	11783	8828	9016	9635	8028	8099
1	4	19265	19316	20598	16619	16092	13422	10532	10614	9466	9494
1	5	21062	14095	13267	12543	12734	12268	12219	11791	10379	8463
1	6	23456	10939	13270	14089	12986	13723	11878	13338	12442	10094
1	7	13383	11899	12531	15081	14295	13650	9988	11518	11915	7844
1	8	22717	22434	23151	13163	10029	10408	9119	10188	9549	11153
1	9	17437	13950	15535	14199	11540	9568	8481	9143	8117	5765
1	10	18546	12520	15394	10137	9218	7343	6702	7173	7257	5708
2	11	18536	16827	19185	12445	13227	10412	9855	9169	9639	6853
2	12	18831	14043	16493	12562	10397	8568	8599	8818	6011	5062
2	13	15016	13765	16648	14537	13929	10778	9897	9225	9491	5523
2	14	22276	15497	22024	15616	12440	11454	10290	9456	9567	7003
2	15	18943	14834	18403	16232	13085	12679	10489	9495	10896	8836
2	16	13598	10233	13392	10457	9236	8847	9445	9501	8509	5656
2	17	20498	22136	22094	19825	18157	11452	14809	14564	14503	10643
2	18	19586	12710	12745	7294	15757	15296	14097	14308	13933	10210
2	19	11474	8108	17714	16795	17364	16766	15016	13475	14349	8698
2	20	10284	10760	15628	10692	8420	5842	6138	10271	8435	4486
3	21	18459	15805	19924	18337	24197	18790	19333	22234	18291	11595
3	22	16186	11750	16470	18637	14862	14695	14458	14228	12909	9079
3	23	9614	8319	11375	9446	13157	11153	10540	11476	8976	6123
3	24	15688	15016	20929	12706	17351	15089	14605	15952	14795	10434
3	25	15864	13169	20991	20655	19763	19180	19003	18172	15025	11790
3	26	17721	14489	19085	21333	17011	16148	15280	14762	15745	10477
3	27	17606	7558	15646	15194	13036	10316	8172	8977	8378	3962
3	28	34907	29247	35831	15093	9754	10061	9042	11732	8716	4922
3	29	15189	14046	14909	14713	14999	14201	13184	13073	14639	10330
3	30	16388	14538	17548	19416	22034	17761	14488	16068	14773	10595

Example: Activity of rats

Summary of experiment:

- 3 treatments: 1, 2, 3 (concentration)
- 10 cages per treatment
- 10 contiguous months
- The response is activity ($\log$(count) of intersections of light beam during 57 hours)



Separate analysis for each time–point

- Select a fixed time point
- The observations at that time (one from each individual) are independent
- Do a separate analysis for the observations at that time
- This is not wrong, but (possibly) a lot of information is waisted
- This can be done for several time–points, but
  - Difficult to reach a coherent conclusion
  - Sub–tests are not independent
  - Tempting to select time–points that supports out preference
  - Mass significance: If many tests are carried out at 5% level some might be significant by chance. (Bonferroni correction: Use significance level $0.05/n$ instead of 0.05)

Analysis of summary statistic

- Choose a single measure to summarize the individual curves
- This again reduces the data set to independent observations
- Popular choices of summary measures:
  - Average over time
  - Slope in regression with time (or higher order polynomial coefficients)
  - Total increase (last point minus first point)
  - Area under curve (AUC)
  - Maximum or minimum point
- Good method with few and easily checked assumptions
- Information may be lost
- Important to choose a good summary measure

Simple mixed model

- Add "individual" (here cage) as a random effect
- Makes measurements on same individual correlated (as we have seen)
- This model uses all observations instead of reducing to one observation per individual
- Unfortunately equally correlated no matter if they are "close" or "far apart"
- Can be considered first step in modelling the actual covariance structure
- Usually only good for short series
- This model is also known as the split–plot model for repeated measurements (with "individuals" as main–plots and the single measurements as sub–plots)

Rats data analyzed via the simple mixed model approach

- The model can now be enhanced to:

$$\texttt{lnc}_i = \mu + \alpha(\texttt{treatm}_i) + \beta(\texttt{month}_i) + \gamma(\texttt{treatm}_i, \texttt{month}_i) + d(\mathsf{cage}_i) + \varepsilon_i,$$

with $\varepsilon_i \sim N(0, \sigma^2)$ and $d(\mathsf{cage}_i) \sim N(0, \sigma_d^2)$ all independent.

- The covariance structure of this model is:

$$\mathsf{cov}(y_{i_1}, y_{i_2}) = \begin{cases} 0 & \text{, if } \mathsf{cage}_{i_1} \neq \mathsf{cage}_{i_2} \\ \sigma_d^2 & \text{, if } \mathsf{cage}_{i_1} = \mathsf{cage}_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma_d^2 + \sigma^2 & \text{, if } i_1 = i_2 \end{cases}$$

- This model is implemented in R by:

```
> library(nlme)
> fit.mm<-lme(lnc~month+treatm+month:treatm, random = ~1|cage, data=rats)
```

Different view on the mixed model approach

- Any linear mixed model can be expressed as:

$$\mathbf{Y} \sim N(\mathbf{X}\boldsymbol{\beta}, \mathbf{Z}\boldsymbol{\Psi}\mathbf{Z}^T + \boldsymbol{\Sigma}),$$

- The total covariance of all observations are described by

$$\mathbf{V} = \mathbf{Z}\boldsymbol{\Psi}\mathbf{Z}^T + \boldsymbol{\Sigma}$$

- The $\mathbf{Z}\boldsymbol{\Psi}\mathbf{Z}^T$ part is specified through the random effects of the model
- The $\boldsymbol{\Sigma}$ part has so far been $\sigma^2\mathbf{I}$, but now we will put some structure into $\boldsymbol{\Sigma}$
- For instance the structure known from the simple mixed model

$$\text{cov}(y_{i_1}, y_{i_2}) = \begin{cases} 0 & , \text{ if } \texttt{individual}_{i_1} \neq \texttt{individual}_{i_2} \\ \sigma^2_{\texttt{individual}} & , \text{ if } \texttt{individual}_{i_1} = \texttt{individual}_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma^2_{\texttt{individual}} + \sigma^2, & \text{ if } i_1 = i_2 \end{cases}$$

- This structure is known as *compound symmetry*

Activity of rats analyzed via compound symmetry model

- The model is the same as the random effects model, but specified directly

$$\begin{aligned}
\textbf{lnc} &\sim N(\boldsymbol{\mu}, \mathbf{V}), \quad \text{where} \\
\mu_i &= \mu + \alpha(\texttt{treatm}_i) + \beta(\texttt{month}_i) + \gamma(\texttt{treatm}_i, \texttt{month}_i), \text{ and} \\
V_{i_1,i_2} &= \begin{cases} 0 & , \text{ if cage}_{i_1} \neq \text{cage}_{i_2} \\ \sigma_d^2 & , \text{ if cage}_{i_1} = \text{cage}_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma_d^2 + \sigma^2 & , \text{ if } i_1 = i_2 \end{cases}
\end{aligned}$$

- Implemented in R by:

```
> fit.cs<-gls(lnc~month+treatm+month:treatm,
+             correlation=corCompSymm(form=~1|cage),
+             data=rats)
```

- A `random=...` statement adds random effects, but a `correlation=...` statement writes a structure directly into the $\boldsymbol{\Sigma}$–matrix

Comparing

- Notice I had to use `gls()` instead of `lme()`, but only because `lme()` does not allow models with no random effects.
- But `lme()` also has a `correlation=...` argument
- Is it the same model?

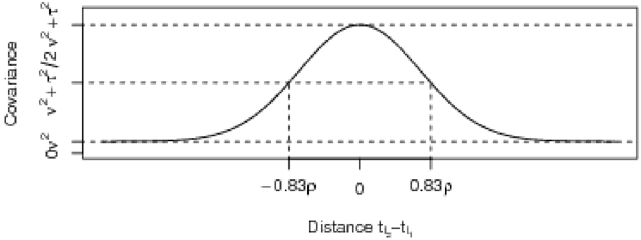
```
> fit.cs<-gls(lnc~month+treatm+month:treatm,
+             correlation=corCompSymm(form=~1|cage),
+             data=rats, method="ML")
> logLik(fit.cs)
```

```
> fit.mm<-lme(lnc~month+treatm+month:treatm,
+             random = ~1|cage,
+             data=rats, method="ML")
> logLik(fit.mm)
```

Gaussian model of spatial correlation

- Covariance structures depending on "how far" observations are apart are known as *spatial*
- The following covariance structure has been proposed for repeated measurements

$$V_{i_1,i_2}=\begin{cases}0 & \text{, if } \texttt{individual}_{i_1} \neq \texttt{individual}_{i_2} \\ \nu^2+\tau^2\exp\left\{\frac{-(t_{i_1}-t_{i_2})^2}{\rho^2}\right\} & \text{, if } \texttt{individual}_{i_1} = \texttt{individual}_{i_2} \text{ and } i_1 \neq i_2 \\ \nu^2+\tau^2+\sigma^2 & \text{, if } i_1 = i_2\end{cases}$$



Rats data via spatial Gaussian correlation model

- The entire model is:

$$
\begin{aligned}
\textbf{lnc} &\sim N(\boldsymbol{\mu}, \mathbf{V}), \text{ where} \\
\mu_i &= \mu + \alpha(\texttt{treatm}_i) + \beta(\texttt{month}_i) + \gamma(\texttt{treatm}_i, \texttt{month}_i), \text{ and} \\
V_{i_1,i_2} &= \begin{cases} 0 & , \text{ if } \mathsf{cage}_{i_1} \neq \mathsf{cage}_{i_2} \\ \nu^2 + \tau^2 \exp\left\{ \frac{-(\texttt{month}_{i_1} - \texttt{month}_{i_2})^2}{\rho^2} \right\} & , \text{ if } \mathsf{cage}_{i_1} = \mathsf{cage}_{i_2} \\ & \quad \text{and } i_1 \neq i_2 \\ \nu^2 + \tau^2 + \sigma^2 & , \text{ if } i_1 = i_2 \end{cases}
\end{aligned}
$$

- This model is implemented by:

```
> fit.gau <- lme(lnc~month+treatm+month:treatm,
+                random=~1|cage,
+                correlation=corGaus(form=~as.numeric(month)|cage,nugget=TRUE)
+                data=rats)
```

Parametrization

- The model outputs are not exactly how we set up the model:

$$
\begin{aligned}
\texttt{(Intercept)} &= \nu \\
\texttt{(Residual)} &= \sqrt{\tau^2 + \sigma^2} \\
\texttt{(range)} &= \rho^2 \\
\texttt{(nugget)} &= \sigma^2/(\tau^2 + \sigma^2)
\end{aligned}
$$

- So we can get our estimates by:

```
> nu.sq<-0.1404056^2
> sigma.sq<-0.2171559^2*0.2186743
> tau.sq<-0.2171559^2-sigma.sq
> rho.sq<-2.3863954
> c(nu.sq=nu.sq, sigma.sq=sigma.sq, tau.sq=tau.sq, rho.sq=rho.sq)


     nu.sq   sigma.sq     tau.sq     rho.sq
0.01971373 0.01031196 0.03684473 2.38639540
```

Comparing variance structures

- Comparing the three different variance structures
  - independent
  - simple correlation within cage
  - spatial Gaussian correlation structure

```
> fit.id <- lm(lnc~month+treatm+month:treatm, data=rats) # WRONG independent m
> fit.mm <- lme(lnc~month+treatm+month:treatm,
+               random = ~1|cage,
+               data=rats, method="ML")
> fit.gau<- lme(lnc~month+treatm+month:treatm,
+               random=~1|cage,
+               correlation=corGaus(form=~as.numeric(month)|cage,nugget=TRUE),
+               data=rats, method="ML")
> anova(fit.gau,fit.mm,fit.id)
```

```
        Model df        AIC       BIC    logLik   Test  L.Ratio p-value
fit.gau     1 34 -157.37587 -31.44726 112.68793
fit.mm      2 32  -34.78917  83.73187  49.39459 1 vs 2 126.5867  <.0001
fit.id      3 31   63.47860 178.29585  -0.73930 2 vs 3 100.2678  <.0001
```

- Which shows that spatial Gaussian correlation structure is preferable.

Other spatial correlation structures

- R has a lot of build–in correlation structures. A few examples are:

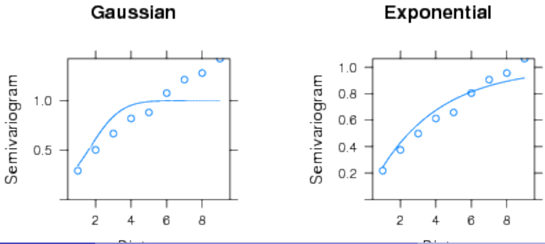
Write in R	**Name**	**Correlation term**
`corGaus`	Gaussian	$\tau^2 \exp\{\frac{-(t_{i_1}-t_{i_2})^2}{\rho^2}\}$
`corExp`	exponential	$\tau^2 \exp\{\frac{-\lvert t_{i_1}-t_{i_2}\rvert}{\rho}\}$
`corAR1`	autoregressive(1)	$\rho^{\lvert i_1-i_2\rvert}$
`corSymm`	unstructured	$\tau^2_{i_1,i_2}$

- Unfortunately it can be very difficult to choose — especially for “short” individual series
- General advice:
  - Keep it simple: Numerical problems often occur with (too) complicated structures
  - Graphical methods: Especially for “long” series the variogram is useful
  - Information criteria: AIC or BIC can be used as guideline
  - Try to cross–validate your main conclusion(s) by one of the “simple” methods

The semi-variogram

- A variogram compares the model predicted correlation (or rather one minus) to empirical estimates of the correlation at different distances.
- The empirical estimates will be uncertain at large distances

```
> fit.gau<- lme(lnc~month+treatm+month:treatm, random=~1|cage,
+               correlation=corGaus(form=~as.numeric(month)|cage,nugget=TRUE),
+               data=rats)
> fit.exp<- lme(lnc~month+treatm+month:treatm, random=~1|cage,
+               correlation=corExp(form=~as.numeric(month)|cage,nugget=TRUE),
+               data=rats)
> plot(Variogram(fit.gau), main='Gaussian')
> plot(Variogram(fit.exp), main='Exponential')
```



Comparing by AIC

- Remember to run with `method="ML"`

```
> fit.gau<- lme(lnc~month+treatm+month:treatm, random=~1|cage,
+               correlation=corGaus(form=~as.numeric(month)|cage,nugget=TRUE),
+               data=rats, method="ML")
> fit.exp<- lme(lnc~month+treatm+month:treatm, random=~1|cage,
+               correlation=corExp(form=~as.numeric(month)|cage,nugget=TRUE),
+               data=rats, method="ML")
> anova(fit.gau,fit.exp)
```

```
        Model df       AIC       BIC   logLik
fit.gau     1 34 -157.3759 -31.44726 112.6879
fit.exp     2 34 -163.3743 -37.44572 115.6872
```

- So also in favor of exponential structure.

Reducing mean value structure

- Remember to run with `method="ML"`

```
> fit.exp.1<-lme(lnc~month+treatm+month:treatm, random=~1|cage,
+                correlation=corExp(form=~as.numeric(month)|cage,nugget=TRUE),
+                data=rats, method="ML")
> fit.exp.2<-lme(lnc~month+treatm, random=~1|cage,
+                correlation=corExp(form=~as.numeric(month)|cage,nugget=TRUE),
+                data=rats, method="ML")
> anova(fit.exp.2,fit.exp.1)
```

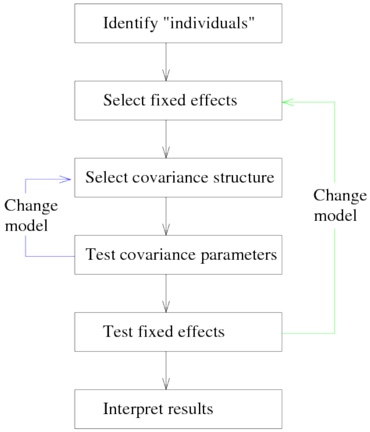
```
          Model df       AIC        BIC    logLik   Test  L.Ratio p-value
fit.exp.2     1 16 -167.1792 -107.91867  99.58959
fit.exp.1     2 34 -163.3743  -37.44572 115.68716 1 vs 2 32.19514  0.0208
```

- So interaction term is significant.

Oversigt

Diagram of analysis

- Select covariance structure from
  - knowledge about the experiment
  - guided by information criteria
  - guided by variogram
- Covariance parameters are tested by likelihood ratio test
- The green arrow is often omitted by the argument that a non–significant simplification of the mean structure should not change the covariance structure much



Summary

1. The general linear mixed model
   - Random coefficient regression lines - example
2. REML - estimation
3. Repeated measurements setup (Correlation structure)
4. Model development