Lecture 6 | 31.03.2025

Parametric structures for variance/covariance in mixed models

Some overview

- Consider a linear regression model for repeated measurements within (independent) subjects $i \in \{1, \dots, N\}$ in a form

$$\boldsymbol{Y}_i = \mathbb{X}_i \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i$$

where $\boldsymbol{Y}_i = (Y_{i1}, \dots, Y_{in_i})^\top$ is the subject specific response vector, $\mathbb{X}_i = (\boldsymbol{X}_{i1}, \dots, \boldsymbol{X}_{in_i})^\top$ for $\boldsymbol{X}_{ij} = (X_{ij1}, \dots, X_{ijp})^\top$ and $j = 1, \dots, n_i$ are the subject (and time specific) explanatory vectors (of dimension $p \in \mathbb{N}$) and $\boldsymbol{\beta} = (\beta_1, \dots, \beta_p)^\top$ is the unknown vector of the regression parameters (mean structure) same for all subjects and time points $\boldsymbol{t}_i = (t_{i1}, \dots, t_{in_i})^\top$

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- the variance-covariance structure within each subject is modelled by the vector parameters $\boldsymbol{\alpha} \in \mathbb{R}^q$, such that $\boldsymbol{\varepsilon}_i = (\varepsilon_{i1}, \dots, \varepsilon_{in_i})^\top \sim N_{n_i}(\boldsymbol{0}, \mathbb{V}_i(\boldsymbol{t}_i, \boldsymbol{\alpha}))$
- the stochastic (non-systematic) term of the model—random errors ε_{ij}, for $j = 1, \dots, n_i$, are decomposed into three main parts: the **random effects**, **the serial correlation**, and the **measurement errors**

$$\varepsilon_{ij} = \boldsymbol{z}_{ij}^\top \boldsymbol{w}_i + W_i(t_{ij}) + \omega_{ij}$$

for random vector $\boldsymbol{w}_i$, random process $W_i(t)$, and random variable ω_{ij}

Stochastic properties of the error terms

- **measurement errors** $\omega_{ij} \sim N(0, \tau^2)$ independent for all i and j
  - let $\boldsymbol{\omega}_i = (\omega_{i1}, \ldots, \omega_{in_i})^\top$ and $\boldsymbol{\omega}_i \sim N_{n_i}(\mathbf{0}, \tau^2 \mathbb{I}_i)$, for $\mathbb{I}_i \in \mathbb{R}^{n_i \times n_i}$

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- **serial correlation** represented by random variables $W_i(t_{ij})$ sampled from $N \in \mathbb{N}$ independent copies of a stationary Gaussian process $\{W(t);\ t \in \mathbb{R}\}$, with the zero mean, variance $\sigma^2 > 0$ and the correlation function of the form $\rho(u) = cor(W(t), W(t+u))$
  - random variables $W_{ij} \equiv W_i(t_{ij})$ are independent with respect to subjects $i \in \{1, \ldots, N\}$ but dependent within subjects, i.e., for indexes $j = 1, \ldots, n_i$
  - lets denote $\mathbb{H}_i = (h_{ijk})_{j,k=1}^{n_i}$, where $h_{ijk} = \rho(|t_{ij} - t_{ik}|)$, i.e., the correlation between Y_{ij} and Y_{ik}, taken at the time points t_{ij} and t_{ik}
  - thus, for the vector $\boldsymbol{W}_i = (W_{i1}, \ldots, W_{in_i})^\top$ we have $Var\,\boldsymbol{W}_i = \sigma^2\mathbb{H}_i$

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- **random effects** with normal distribution $\boldsymbol{w}_i \sim N_r(\mathbf{0}, \mathbb{G})$, independent for $i = 1, \dots, N$, with the corresponding explanatory variables $\boldsymbol{z}_{ij} \in \mathbb{R}^r$
  - the random effect $\boldsymbol{w}_i$ is only subject specific (index i) but the explanatory vectors $\boldsymbol{z}_{ij}$ related to this random effects are subject and time specific
  - lets denote $\mathbb{Z}_i = (\boldsymbol{z}_{i1}, \dots, \boldsymbol{z}_{in_i})^\top \in \mathbb{R}^{n_i \times r}$

Parametric models for variance/covariance

Variance/covariance of $\boldsymbol{Y}_i \in \mathbb{R}^{n_i}$ can be expressed as

- $Var\,\boldsymbol{Y}_i = Var(\varepsilon_i) = Var\left[\boldsymbol{z}_{ij}^\top \boldsymbol{w}_i + W_i(t_{ij}) + \omega_{ij}\right] = \mathbb{Z}_i \mathbb{G} \mathbb{Z}_i^\top + \underbrace{\sigma^2 \mathbb{H}_i + \tau^2 \mathbb{I}_i}_{\mathbb{R}_i \text{ in SAS}}$

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- the overall variance-covariance structure for $Var\,\boldsymbol{Y}_i$ will be a block-diagonal matrix with squared matrices of the types $n_i \times n_i$ in the diagonal

Example: correlation & variogram

❏ Let $\rho(x)$ denote the **correlation function** and $\gamma(x)$ denotes the **variogram function**, $\gamma(x) = \sigma^2(1 - \rho(x))$, for $x \geq 0$ and $\sigma^2 > 0$
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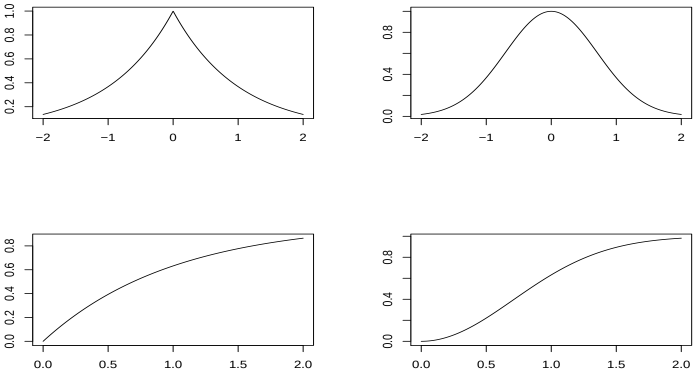
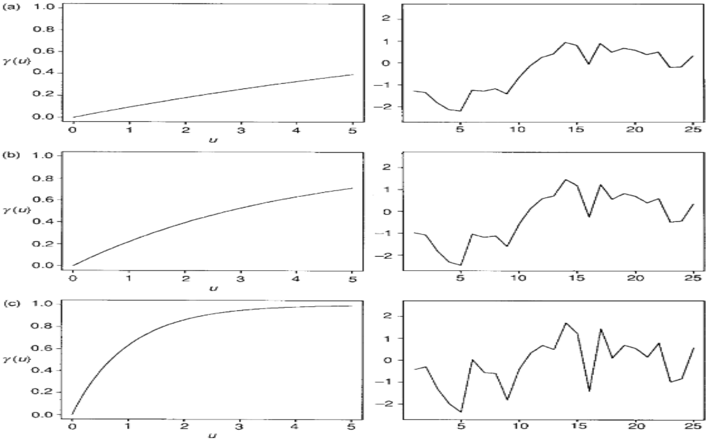
$\rho(x) = \exp\{-\phi|x|\}, \phi = 1$ $\rho(x) = \exp\{-\phi x^2\}, \phi = 1$



Exponential correlation model vs. Gaussian correlation model

Parametric models for variance/covariance

Considering both models—the exponential model and the Gaussian correlation model—the role of the $\phi > 0$ parameter is the same—as the value of ϕ increases, the variograms rises more sharply and the simulated realizations are less smooth (Fig. 5.1., Diggle et al., 2002)



Exponential correlation model: from top to bottom, $\phi = 0.1$, $\phi = 0.25$, and $\phi = 1.0$

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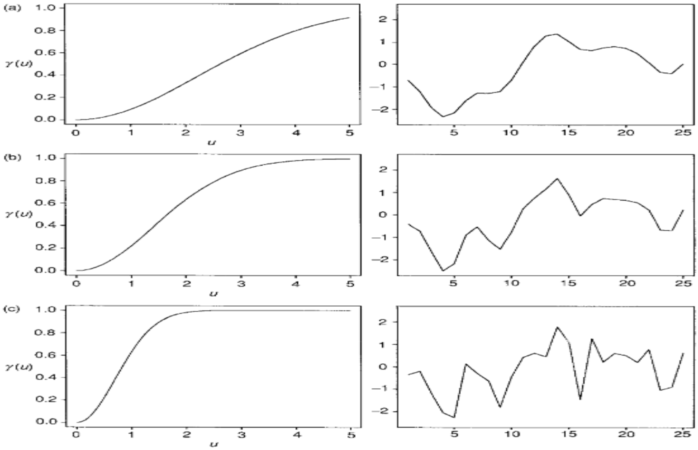

Gaussian correlation model: from top to bottom, $\phi = 0.1$, $\phi = 0.25$, and $\phi = 1.0$

Serial correlation (only) model (Case I)

- From the three possible variance/covariance terms in the expansion

$$Var\,\boldsymbol{Y} = Var(\varepsilon) = \mathbb{Z}\mathbb{G}\mathbb{Z}^{\top} + \sigma^2\mathbb{H} + \tau^2\mathbb{I}$$

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- This implies that $Var(\varepsilon) = \sigma^2\mathbb{H}$ respectively, $Cov(\varepsilon_j, \varepsilon_k) = \sigma^2\rho(|t_j - t_k|)$ with the corresponding variogram of the form $\gamma(u) = \sigma^2(1 - \rho(u))$, $u \geq 0$
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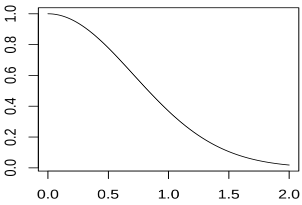
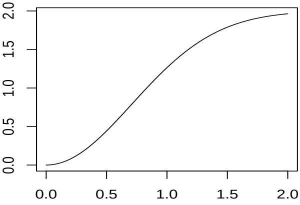


$\gamma(x) = \sigma^2(1-\rho(x))$, $\sigma^2 = 2$



Ante-dependence model (Alternative for Case I)

- Assuming a direct dependence on previous observations in a sense that ε_j taken at the time point $t_j > t_{j-1} > t_{j-2} > \dots$ depends explicitly on some previous k errors $\varepsilon_{j-1}, \dots, \varepsilon_{j-k}$ *(ante-dependence of order k)*
- This is also well known as the k-order Markov model or an autoregressive sequence of the order $k \in \mathbb{N}$—denoted as $AR(k)$
- $AR(1)$ model formally: $\varepsilon_j = \alpha\varepsilon_{j-1} + \omega_j$, for ω_j being $i.i.d.$ from $N(0, \sigma^2)$, for $\varepsilon_0 \sim N(0, \sigma^2/(1-\alpha))$
- However, the ante-dependence model can be problematic for situations with unequally spaced repeated observations within the subject (*and two different but not equivalent formulations are possible*)
- On the other hand, small orders $k \in \mathbb{N}$ can be suitable for the likelihood estimation (straightforward to get the joint distribution/density of ε_i)
- In addition, the ante-dependence property is not preserved when incorporating, for instance, the measurements errors

Serial correlation + measurement errors (Case II)

- Models where there are no random effects present and the variance of ε_i reduces to

$$Var(\varepsilon) = \sigma^2 \mathbb{H} + \tau^2 \mathbb{I}$$

- The variance of ε_j is captured by the sum $\tau^2 + \sigma^2$ with the corresponding variogram function $\gamma(u) = \tau^2 + \sigma^2(1 - \rho(u))$
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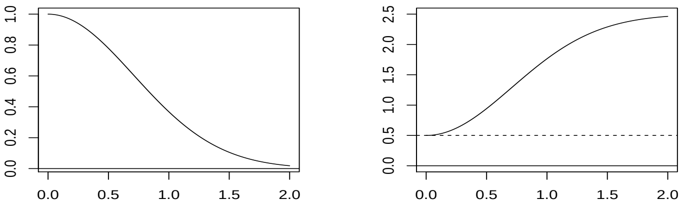

Random intercept model (Case III)

- The simplest example of a general model with three variance/covariance terms in the decomposition where $z_{ij} = 1$ and $w_i \sim N(0, \nu^2)$
- The variance of ε_j is $Var\varepsilon_j = \nu^2 + \sigma^2 + \tau^2$ and the corelation within the whole vector ε is captured by the matrices $\mathbb{H}$ and $\mathbb{J}$ (Diggle, 1988)
- $Var(\varepsilon) = \nu^2\mathbb{J} + \sigma^2\mathbb{H} + \tau^2\mathbb{I}$ with the correlation function $\rho(x)$ and the variogram function $\gamma(u) = \tau^2 + \sigma^2(1 - \rho(u))$
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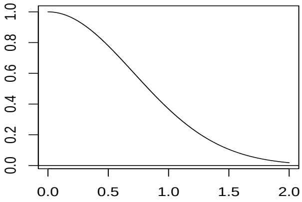
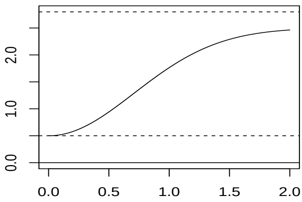


$\gamma(x)$, $\sigma^2 = 2$, $\tau^2 = 0.5$, $\nu^2 = 0.3$



Random intercept and slope model (Case IV)

- More general model allows for some form of nonstationarity—the variability within the subject now depends on the time
- The random effects are now $\boldsymbol{w}_i \sim N_2(\mathbf{0}, \mathbb{G})$ and for simplicity we assume that $\mathbb{G} = \nu^2\mathbb{I}$, the covariates are $\boldsymbol{z}_{ij} = (1, t_{ij})^\top$
- The variance of ε_j is $\nu^2(1 + t_j^2) + \sigma^2 + \tau^2$ and the whole variance/covariance structure of ε is $Var\varepsilon = \mathbb{Z}\mathbb{G}\mathbb{Z}^\top + \sigma^2\mathbb{H} + \tau^2\mathbb{I}$, where the matrix $\mathbb{Z}\mathbb{G}\mathbb{Z}^\top$ is a $n \times n$ matrix with elements $\{\nu^2(1 + t_j t_k)\}_{j,k=1}^n$

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- How can be this structure revealed with the sample variogram?

$$\widehat{\gamma}_i(u) = \frac{1}{2(n-u)} \sum_{j=u+1}^{n} \left[\varepsilon_{ij} - \varepsilon_{i(j-u)}\right]^2, \quad \text{for } u \in \{0, \dots, n-1\}$$

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(note, that for the sample variogram we always have $\widehat{\gamma}_i(0) = 0$ and, moreover, parameter ν^2 can not be estimated from one subject only)

Four cases example

Example $N = 50$ independent subjects observed repeatedly for $T = 20$ times (the measurement error variance $\tau^2 = 0.5$; serial correlation $W(t) = 0.2W(t-1) + e_t$; random intercept variance $\nu_1^2 = 1$; random slope variance $\nu_2^2 = 0.5$)

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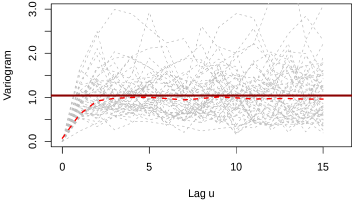

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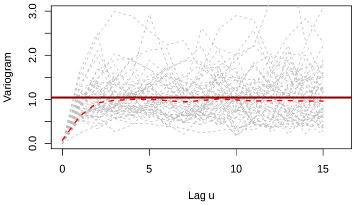

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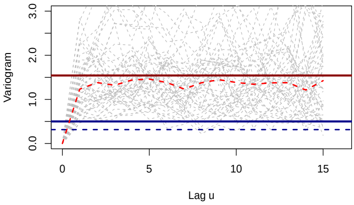

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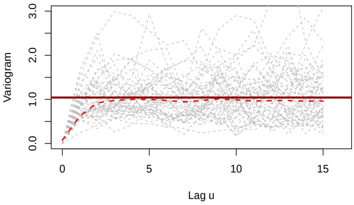

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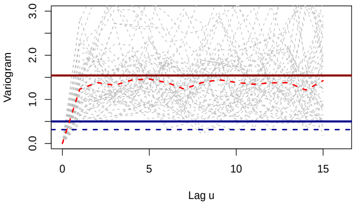
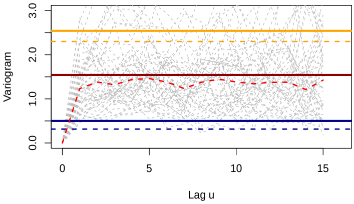


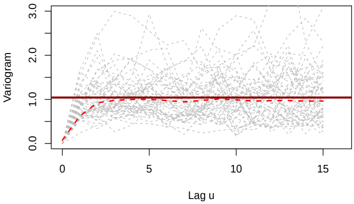
- $Var(\varepsilon_{ij}) = \nu^2 + \sigma^2 + \tau^2$



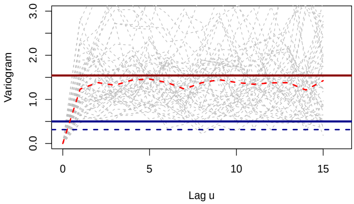
Four cases example

Example $N = 50$ independent subjects observed repeatedly for $T = 20$ times (the measurement error variance $\tau^2 = 0.5$; serial correlation $W(t) = 0.2W(t-1) + e_t$; random intercept variance $\nu_1^2 = 1$; random slope variance $\nu_2^2 = 0.5$)

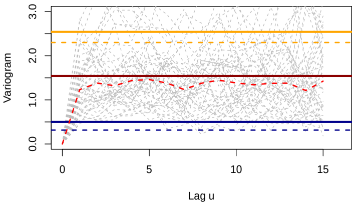
- $Var(\varepsilon_{ij}) = \sigma^2$



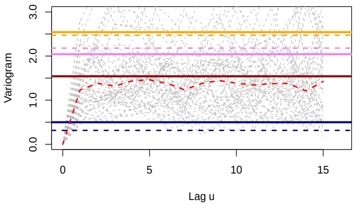
- $Var(\varepsilon_{ij}) = \sigma^2 + \tau^2$



- $Var(\varepsilon_{ij}) = \nu^2 + \sigma^2 + \tau^2$



- $Var(\varepsilon_{ij}) = \boldsymbol{z}^\top \mathbb{G} \boldsymbol{z} + \sigma^2 + \tau^2$



Random effects and measurement error

- Serial correlation appear to be quite natural feature for the longitudinal data analysis but in some applications the effects of the serial correlation may be dominated by the random effects and measurement errors
- Particularly, if $\sigma^2 > 0$ is small compared to $\nu^2 + \tau^2$ than the random effects and the measurement errors are crucial ones to be accounted for
- The model error ε_{ij} reduces to $\boldsymbol{z}_{ij}^\top \boldsymbol{w}_i + \omega_{ij}$ and the corresponding variance/covariance structure is of the form $Var \boldsymbol{\varepsilon} = \mathbb{Z}\mathbb{G}\mathbb{Z}^\top + \tau^2\mathbb{I}$
- The simplest scenario involves the random intercept only, meaning that $\mathbb{Z}\mathbb{G}\mathbb{Z}$ reduces to the matrix $\mathbb{J}$ and $Var \boldsymbol{\varepsilon} = \nu^2\mathbb{J} + \tau^2\mathbb{I}$
- More complex scenario may involve random effects $\boldsymbol{z}_{ij} = (1, \mathbb{I}_{\{i \in \mathcal{S}\}})^\top$ which for $\mathbb{G} = \mathbb{I}$ reduces to the variance $Var \varepsilon_{ij} = \nu^2 + \nu^2\mathbb{I}_{\{i \in S\}} + \tau^2$
  (i.e., heterogeneity between the groups $i \in S$ and $i \notin S$ for some subset $S \subset \{1, \dots, N\}$)

Model selection & model building

- **Practical utilization of the model**
  - firstly, it is important to be able to validly answer the question of interest
  - statistical inference—statistical tests and confidence intervals/regions
- **Conditional mean structure**
  - exploratory in terms of some visualization tools (plots, graphs, etc.)
  - modeling in terms of the model matrix $\mathbb{X}$
- **Designe of experiment**
  - many existing problems could be avoided by a proper experiment planning
  - balanced data, proper randomization, treatment assignments, etc.
- **Variace/covariance structure**
  - exploratory in terms of some residuals inspection
  - effects of unobserved covariates,

Different covariance structures in SAS

See, for instance, the implementation of `PROC MIXED` in SAS and the corresponding SAS help/tutorial

- variance components
- compound symmetry
- unstructured
- autoregressive
- spatial
- ...

SAS Documentation at https://documentation.sas.com

Model diagnostics

The main idea of the statistical modeling process in general...

model formulation $\rightarrow$ **model estimation** $\longleftrightarrow$ **model diagnostics** $\rightarrow$ **statistical inference**

Model diagnostics

The main idea of the statistical modeling process in general...

model formulation $\rightarrow$ **model estimation** $\longleftrightarrow$ **model diagnostics** $\rightarrow$ **statistical inference**

- **The mean structure**
  - simple empirical characteristics, data scatterplots
  - simple summary plots/graphs (e.g., boxplots)
  - ...

- **The variance/covariance structure**
  - variance-covariance (correlation) matrix estimation
  - sample correlogram/variogram functions (or alternatives)
  - residual inspection and various residual plots
  - ...