Overview Part 2: longitudinal data

- Examples of longitudinal data
- Linear mixed effects (LME) models with linear time effect
- The variance-covariance matrix of repeated measures
- Correlation structures & covariance pattern models (CPM)
- What to do with baseline measurement?

UMC Utrecht

Epidemiology and Big Data

Mixed Models part 2: Longitudinal Data (Modelling Time)

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Examples of Longitudinal Data

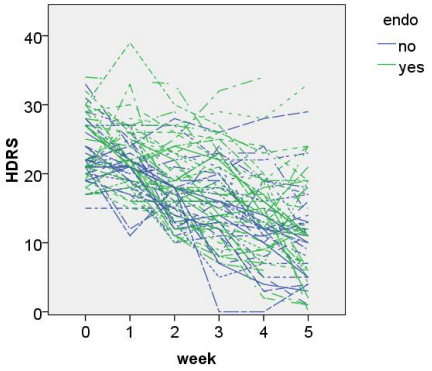
- Example (Reisby et al.)
  - 66 patients
  - with or without endogenous depression
  - depression scores measured weekly at weeks 0 – 5, using Hamilton Depression Rating Scale (HDRS)
  - from week 1 onwards, patients are treated with imipramine
  - **Research question**: is the pattern of HDRS over time different for patients with endogenous and non-endogenous depression?

Longitudinal Data

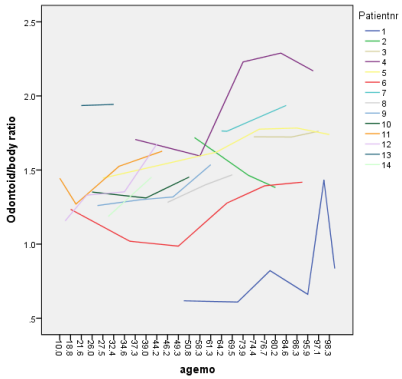
- Longitudinal data:
  - outcome variable measured on individual at several time points
  - observations on one and the same individual will not be independent
  - calls for special analysis techniques
  - time is (usually) the most important level-1 explanatory variable

Examples of Longitudinal Data

Reisby et al.



Stoop et al.



Examples of Longitudinal Data

- Example (Stoop et al. 2012)
  - 14 patients with Hurler syndrome
  - after haematopoietic stem cell transplantation
  - various radiologic measurements, including the odontoid/body ratio
  - **Research question**: what is the pattern of orthopedic manifestations after stem cell transplant?

Example: Reisby Data

Descriptive Statistics (R)

```
> reisby.wide <- reshape(reisby.long, v.names="hdrs", idvar="id",
timevar="week", direction="wide")
> by(reisby.wide[,3:8], reisby.wide$endo, describe)
endo: 0
       var  n  mean   sd median
hdrs.0   1 28 22.79 4.12   22.0
hdrs.1   2 29 20.48 3.83   21.0
hdrs.2   3 28 17.00 4.35   16.5
hdrs.3   4 29 15.34 6.17   16.0
hdrs.4   5 29 12.62 6.72   12.0
hdrs.5   6 27 11.22 6.34   11.0
------------------------------------
endo: 1
       var  n  mean   sd median
hdrs.0   1 33 24.00 4.85   24.0
hdrs.1   2 34 23.00 5.10   22.0
hdrs.2   3 37 19.30 6.08   18.0
hdrs.3   4 36 17.28 6.56   16.5
hdrs.4   5 34 14.47 7.17   14.0
hdrs.5   6 31 12.58 7.96   11.0
```

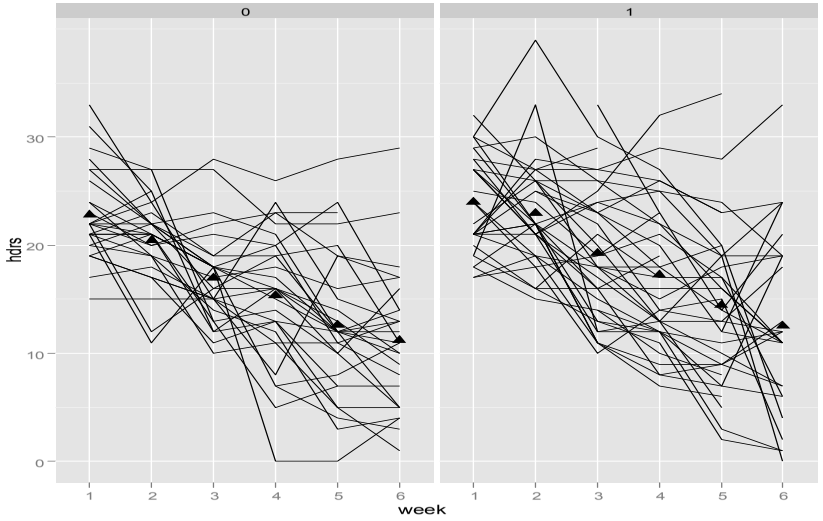
`describe()` function in the **'psych'** package (gives more stats than presented here)

Example: Reisby Data

- Research question: differing patterns over time for the two groups?
  - ➢ fixed effects for intercept, time, group & group*time
  - time continuous or categorical?
- How to deal with multiple measurements?
  - ➢ Random effects
    - intercept?
      - each patient seems to have a different starting point
    - slope of time?
      - could be patients have differing slopes over time

Example: Reisby Data

"Spaghetti Plot" (R, using ggplot2)



Example: Reisby Data

correlations between HDRS measurements (R)

```
> round(cor(reisby.wide[,3:8], use="pairwise.complete.obs"),
digits=2)
```

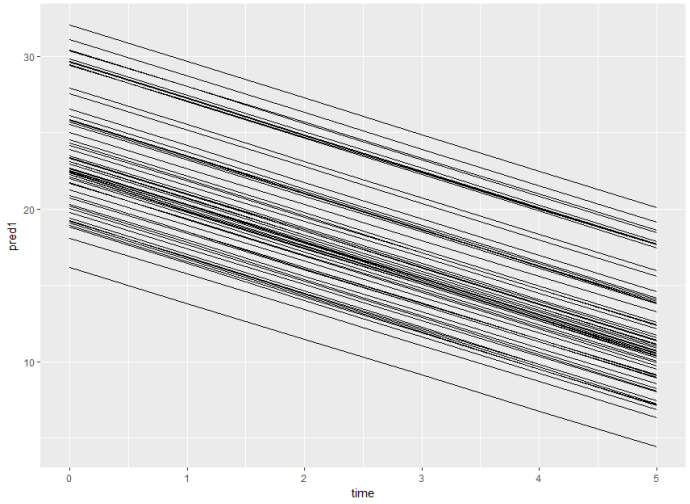
	hdrs.0	hdrs.1	hdrs.2	hdrs.3	hdrs.4	hdrs.5
hdrs.0	1.00	0.49	0.41	0.33	0.23	0.18
hdrs.1	0.49	1.00	0.49	0.41	0.31	0.22
hdrs.2	0.41	0.49	1.00	0.74	0.67	0.46
hdrs.3	0.33	0.41	0.74	1.00	0.82	0.57
hdrs.4	0.23	0.31	0.67	0.82	1.00	0.65
hdrs.5	0.18	0.22	0.46	0.57	0.65	1.00

Linear time effect

- Time technically measured in categories (weeks 1, 2 ...)
- Reasonable to model time as continuous/linear?
  - 1 parameter for slope of HDRS in time
  - need to check whether this assumption is reasonable
    - initial data analysis (spaghetti plot, individual plots)
    - model comparison (lecture 3)

Random intercept with linear time effect

Predicted values from a LME with random intercept and linear time:



Random intercept + random linear time effect

- We can make the assumption that the (linear) time effect is different for each individual by incorporating a random (linear) time effect:
  - $y_{ij} = (\beta_0 + \upsilon_{0i}) + (\beta_1 + \upsilon_{1i}) \cdot time_{ij} + \varepsilon_{ij}$
  - $\varepsilon_{ij} \sim N(0, {\sigma_e}^2)$;
  - $\upsilon_{0i} \sim N(0, {\sigma_{\upsilon 0}}^2)$; $\upsilon_{1i} \sim N(0, {\sigma_{\upsilon 1}}^2)$; $cov(\upsilon_{0i}, \upsilon_{1i}) = \sigma_{\upsilon 01}$
    - This last line can also be written: $\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix} \sim N(0, \boldsymbol{\Sigma}_{\upsilon})$, $\boldsymbol{\Sigma}_{\upsilon} = \begin{bmatrix} {\sigma_{\upsilon 0}}^2 & \sigma_{\upsilon 01} \\ \sigma_{\upsilon 01} & {\sigma_{\upsilon 1}}^2 \end{bmatrix}$
    - $\boldsymbol{\Sigma}_{\upsilon}$ is the *variance-covariance matrix* of the random effects

R output random intercept + random slope model

Parameter estimates of the fixed part of the previous model:

```
 Value Std.Error  DF   t-value p-value
(Intercept) 22.476263 0.7986132 307 28.144117  0.0000
time        -2.365687 0.3134845 307 -7.546425  0.0000
endo         1.988021 1.0747911  64  1.849681  0.0690
time:endo   -0.027056 0.4217258 307 -0.064155  0.9489
```

R output random intercept + random slope model

Parameter estimates of the random part (intercept, slope) of the model:

```
             StdDev   Corr
(Intercept) 3.411893 (Intr)
time        1.441193 -0.285
Residual    3.495500
```

- So:
  - ${\hat{\sigma}_e}^2 = 3.50^2 = 12.22$; ${\hat{\sigma}_{\upsilon 0}}^2 = 3.41^2 = 11.64$; ${\hat{\sigma}_{\upsilon 1}}^2 = 1.44^2 = 2.08$
  - $\widehat{corr}(\upsilon_{0i}, \upsilon_{1i}) = {\hat{\sigma}_{\upsilon 01}}/{(\hat{\sigma}_{\upsilon 0} \cdot \hat{\sigma}_{\upsilon 1})} = -0.285$
    $\rightarrow \hat{\sigma}_{\upsilon 01} = -0.285 \cdot (3.41 \cdot 1.44) = -1.40$

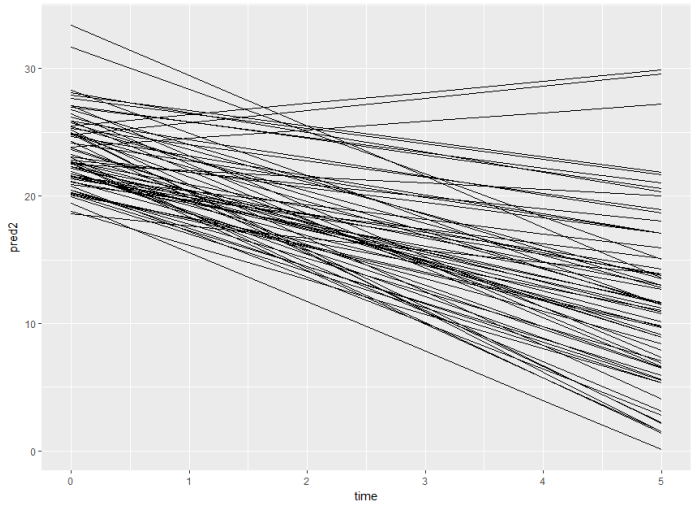
Note: random intercept and slope are negatively correlated (the higher the intercept the more negative the slope); often true in longitudinal data

Interpretation of model

- Intercept (22.48) is average HDRS score when all variables = 0
  - so for patients with exogenous depression (reference) at time = 0
- Estimate for endo (1.99) is average difference in HDRS between endogenous and exogenous patients at time = 0
  - patients with exogenous depression start with average of 22.48
  - patients with endogenous depression start with average of 22.476 + 1.988 = 24.46
- Estimate of random intercept s.d. 3.41 indicates considerable fluctuation around fixed intercepts:
  - patients can start quite a bit higher/lower than average
- "Average" slope is -2.37 for patients with exogenous depression

Random intercept + random linear time effect

Predicted values from a LME with random intercept + random linear time effect:



Interpretation of model, cont.

- Interaction endo*time (-0.027) is difference in slope endogenous vs. exogenous
  - per time unit (1 week) the HDRS score decreases on average by 2.37 (exog)
  - per time unit (1 week) the HDRS score decreases on average by 2.39 (endog)
- Estimate of random slope s.d. 1.44, so for individuals the slope can be quite a bit steeper or flatter, may even be positive for some patients (as seen in the plot).

LMM matrix formulation & var-covar matrix

- Recall model linear mixed model:
  - $y_{ij} = \beta_0 + \beta_1 X_{1ij} + \upsilon_{0i} + \upsilon_{1i} X_{1ij} + \varepsilon_{ij}$
- In matrix formulation:
  - $\boldsymbol{Y}_i = \boldsymbol{X}_i \cdot \boldsymbol{\beta} + \boldsymbol{Z}_i \cdot \upsilon_i + \boldsymbol{\varepsilon}_i$
  - where $\boldsymbol{X}_i$ is the covariate matrix of the fixed effect(s) and $\boldsymbol{Z}_i$ the design matrix of the random effect(s)
- Variance-covariance matrix of repeated measures y:
  - $Var(\boldsymbol{Y}_i) = \boldsymbol{Z}_i \cdot \boldsymbol{\Sigma}_\upsilon \cdot \boldsymbol{Z}_i{}' + {\sigma_e}^2 \cdot \boldsymbol{I}_{n_i}$
  - variance-covariance matrix of outcome for a patient's measurements depends on covariance matrix of random effects $\boldsymbol{\Sigma}_\upsilon$ and residual variance σ_e^2
  - the number and variances of the random effects and their correlation(s) determine part of the variance-covariance matrix

Random intercept + random linear time effect

- Given what we learned last week, the previous analysis (with linear effects for time) is "all" we could do
- What if we think it is unreasonable to use time as continuous?
- Add time as categorical to the fixed effects – and then?
  - some add time as linear to the random effects
  - others choose to tackle time as a categorical variable in the random part of the model as well

LMM matrix formulation & var-covar matrix

$$Var(\boldsymbol{Y}_i) = \boldsymbol{Z}_i \cdot \boldsymbol{\Sigma}_U \cdot \boldsymbol{Z}_i{}' + \sigma_e{}^2 \cdot \boldsymbol{I}_{n_i}$$

$$= \begin{pmatrix} s' & t & h & i & n & g \\ m & e & s & s & y & - \\ (d & e & p & e & n & ds \\ & & o & n & & \\ r & a & n & d & o & m \\ e & ff & e & c & t & s) \end{pmatrix} + \sigma_e^2 \cdot \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

CPMs & var-covar matrix

Another possibility for modelling longitudinal data:

- $\boldsymbol{Y}_i = \boldsymbol{X}_i \cdot \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i$
  - No random effects!
  - How do we take into account the correlation between measurements on same person?
- Variance-covariance matrix of repeated measures y is now:
  - $Var(\boldsymbol{Y}_i) = Var(\boldsymbol{\varepsilon}_i) = \boldsymbol{\Sigma}$

CPMs & var-covar matrix

- We know the residuals are not independent, so we need to assume correlation for $\boldsymbol{\Sigma}$:

$$\boldsymbol{\Sigma} = \begin{pmatrix} & t & h & i & s & \\ s & h & o & u & l & d \\ b & e & & c & o & r- \\ r & e & c & t & l & y \\ c & o & m & p & l & - \\ i & c & a & t & e & d! \end{pmatrix}$$

- We can use different correlation structures to model $\boldsymbol{\Sigma}$ directly
- We call this type of model a *covariance pattern model* (CPM)
- Some also call them "GEE-type covariance structures"

Example: Reisby Data

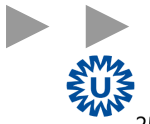
Possibilities for modelling correlated measures

- Model correlation of measurements *implicitly* (linear mixed effects model):
  - repeated observations are level-1 variables nested within patient (=level 2)
    - random intercept per patient or random intercept per patient + random slope for week per patient or...
    - random effects and their covariance determine structure of var-covar matrix
- Model correlation of measurements *explicitly* (CPM):
  - incorporate a covariance structure of the residuals into the model
  - (usually) assumes equally spaced time intervals
- Combination of the two (mixed regression models with autocorrelated errors)

Observed var-cov matrix Reisby dataset

```
> round(var(reisby.wide[,3:8], use="pairwise.complete.obs"), digits = 2)

       hdrs.0 hdrs.1 hdrs.2 hdrs.3 hdrs.4 hdrs.5
hdrs.0  20.55  10.11  10.14  10.09   7.19   6.28
hdrs.1  10.11  22.07  12.28  12.55  10.26   7.72
hdrs.2  10.14  12.28  30.09  25.13  24.63  18.38
hdrs.3  10.09  12.55  25.13  41.15  37.34  23.99
hdrs.4   7.19  10.26  24.63  37.34  48.59  30.51
hdrs.5   6.28   7.72  18.38  23.99  30.51  52.12
```



Various correlation structures

- nlme has numerous correlation structures for linear ~~mixed~~ models
- Most common/realistic for longitudinal data
  - unstructured
  - autoregressive of order 1: AR(1)
- Bad ideas:
  - uncorrelated (independent)
  - compound symmetry
- Correlations pertain to the residuals within each of the subjects after correcting for fixed (and perhaps random) effects

Independent correlation structure

- The independent (scaled identity) correlation structure assumes residuals to be independent, as if they came from different subjects
- All variances are assumed equal, all correlations are assumed 0
- This is the assumption in ordinary linear regression/ANOVA

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma^2 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma^2 \end{pmatrix} = \sigma^2 \cdot \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Independent correlation structure

- Analyzing the data from the Reisby example using time (categorical), tx and time*tx and an independent correlation structure amounts to doing a two-way ANOVA (all observations are assumed to be independent)
- Even when observations are in fact (nearly) independent, the design of the study was to take random patients, and measure these multiple times, not to take random samples at each time point
- (like doing OLS regr on schools data)

➢ Preferable to analyze data as being repeated (and thus correlated)!

Compound symmetry correlation structure

- A covariance pattern model with a compound symmetry pattern for the residuals is equivalent to a linear mixed model with a random intercept per patient
  - when we treat time the same way (here: as categorical) in the fixed parts of both models
- For data without missing values, these two models are also equivalent to a repeated measures ("split-plot") ANOVA

Compound symmetry correlation structure

- The compound symmetry (exchangeable) correlation structure assumes correlations between all time points to be equal, irrespective of the length of the time intervals.
- All variances are assumed equal, all correlations too:

$$\begin{pmatrix} \sigma^2+{\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 \\ {\sigma_0}^2 & \sigma^2+{\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 \\ {\sigma_0}^2 & \sigma^2 & \sigma^2+{\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 \\ {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & \sigma^2+{\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 \\ {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & \sigma^2+{\sigma_0}^2 & {\sigma_0}^2 \\ {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & {\sigma_0}^2 & \sigma^2+{\sigma_0}^2 \end{pmatrix} = (\sigma_0{}^2+\sigma^2)\begin{pmatrix} 1 & \rho & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho & \rho \\ \rho & \rho & 1 & \rho & \rho & \rho \\ \rho & \rho & \rho & 1 & \rho & \rho \\ \rho & \rho & \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & \rho & \rho & 1 \end{pmatrix}$$

- Note: $\rho = {\sigma_0}^2 / (\sigma_0{}^2+\sigma^2)$, with ${\sigma_0}^2$ the variance between patients
- ρ is known as the intraclass correlation coefficient, the correlation between observations within a cluster
  - also: proportion of total variance accounted for by clustering

Unstructured correlation for Reisby data

Estimated from model with time (cat), endo & time*endo, no random effects

```
       [,1]  [,2]  [,3]  [,4]  [,5]  [,6]
[1,] 19.63 10.40  6.34  8.09  6.73  4.50
[2,] 10.40 20.87 10.26 10.69  8.33  5.02
[3,]  6.34 10.26 25.90 22.36 23.99 20.88
[4,]  8.09 10.69 22.36 38.44 32.03 29.90
[5,]  6.73  8.33 23.99 32.03 46.89 38.77
[6,]  4.50  5.02 20.88 29.90 38.77 60.19
```


Unstructured correlation

$$\begin{pmatrix} \theta_{11} & \theta_{12} & \theta_{13} & \theta_{14} & \theta_{15} & \theta_{16} \\ \theta_{21} & \theta_{22} & \theta_{23} & \theta_{24} & \theta_{25} & \theta_{26} \\ \theta_{31} & \theta_{32} & \theta_{33} & \theta_{34} & \theta_{35} & \theta_{36} \\ \theta_{41} & \theta_{42} & \theta_{43} & \theta_{44} & \theta_{45} & \theta_{46} \\ \theta_{51} & \theta_{52} & \theta_{53} & \theta_{54} & \theta_{55} & \theta_{56} \\ \theta_{61} & \theta_{62} & \theta_{63} & \theta_{64} & \theta_{65} & \theta_{66} \end{pmatrix}$$

- Variances at each time point different
- All covariances among time points may be different (note that $\theta_{12} = \theta_{21}$)
- Flexible structure!
- Costly structure: 21 df needed for 6 time points!

AR1 with homogeneous variances for Reisby data

Estimated from model with time (cat), tx & time*tx, no random effects

```
        [,1]    [,2]   [,3]   [,4]    [,5]    [,6]
[1,] 35.0510 23.1050 15.231 10.040  6.6183  4.3627
[2,] 23.1050 35.0510 23.105 15.231 10.0400  6.6183
[3,] 15.2310 23.1050 35.051 23.105 15.2310 10.0400
[4,] 10.0400 15.2310 23.105 35.051 23.1050 15.2310
[5,]  6.6183 10.0400 15.231 23.105 35.0510 23.1050
[6,]  4.3627  6.6183 10.040 15.231 23.1050 35.0510
  Standard Deviations: 5.9204 5.9204 5.9204 5.9204 5.9204 5.9204
```

(Homogeneous) autoregressive of order 1 (AR1) correlation

$$\sigma^2 \cdot \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 & \rho^4 & \rho^5 \\ \rho & 1 & \rho & \rho^2 & \rho^3 & \rho^4 \\ \rho^2 & \rho & 1 & \rho & \rho^2 & \rho^3 \\ \rho^3 & \rho^2 & \rho & 1 & \rho & \rho^2 \\ \rho^4 & \rho^3 & \rho^2 & \rho & 1 & \rho \\ \rho^5 & \rho^4 & \rho^3 & \rho^2 & \rho & 1 \end{pmatrix}$$

- Note: observations per subject assumed to be taken at equally-spaced intervals
- AR(1) assumes all observations 1 time unit apart have same correlations (ρ)
- Observations 2 units apart have corr ρ^2, obs 3 units apart ρ^3, etc.
- Outcome has same variance (σ^2) across all time points

"Covariance patterns" of linear mixed models

- A random intercept model implies a compound symmetry structure for all data combined
- A linear mixed model with random intercept and random slope also implies a certain correlation structure for the data, but this is by no means a simple structure
  - recall: $Var(\boldsymbol{Y}_i) = \boldsymbol{Z}_i \cdot \boldsymbol{\Sigma}_{\mathcal{U}} \cdot \boldsymbol{Z}_i{}' + {\sigma_e}^2 \cdot \boldsymbol{I}_{n_i}$
  - structure depends on the estimates for ${\sigma_{\mathcal{U}0}}^2$, ${\sigma_{\mathcal{U}1}}^2$, and $\sigma_{\mathcal{U}01}$, but *usually* the variances increase for later time points and correlations decrease when time points are further apart
  - this is exactly what we observed for our data set, so this model might fit the data quite well

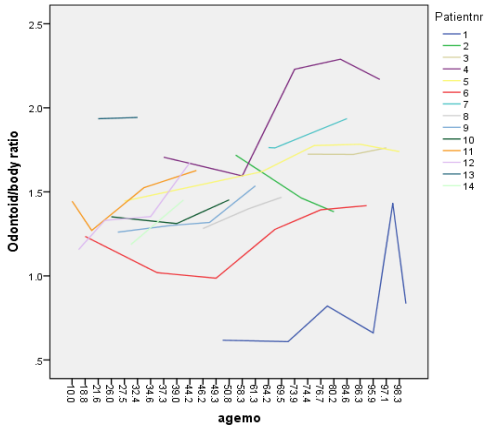
AR1 with *heterogeneous* variances for Reisby data

Estimated from model with time (cat), tx & time*tx, no random effects

```
      [,1]  [,2]  [,3]  [,4]  [,5]  [,6]
[1,] 22.98 16.29 11.18  7.76  5.42  4.09
[2,] 16.29 27.12 18.62 12.92  9.02  6.81
[3,] 11.18 18.62 30.05 20.85 14.56 10.99
[4,]  7.76 12.92 20.85 33.98 23.73 17.91
[5,]  5.42  9.02 14.56 23.73 38.92 29.38
[6,]  4.09  6.81 10.99 17.91 29.38 52.11
```

- Heterogeneous variances probably fit the data better than homogeneous

Back to Stoop, et al.



- How would we model data from Stoop, et al.?
  - time: discreet or continuous?
  - LME or CPM?
  - time: linear? quadratic?
  - Theory vs. practice....

Covariance patterns linear mixed models

Random intercept + random slope model (fixed time categorical*):

```
Marginal variance covariance matrix
        1       2       3       4       5       6
1 23.8600 10.239  8.838  7.4364  6.0349  4.6334
2 10.2390 23.134 11.590 12.2660 12.9420 13.6170
3  8.8380 11.590 26.562 17.0960 19.8480 22.6010
4  7.4364 12.266 17.096 34.1440 26.7550 31.5840
5  6.0349 12.942 19.848 26.7550 45.8800 40.5680
6  4.6334 13.617 22.601 31.5840 40.5680 61.7700
```

*Strange thing to do?

Reisby Example, use baseline HDRS as covariate

- Select only time >0, use hdrs.base as covariate in mixed model with random intercept, random slope, fixed time & endo
- What do you expect will happen to:
  - ...the estimate of the fixed intercept?
  - ...the estimate of the fixed effect of endo?
  - ...the estimate of the fixed effect of time?

What to do with baseline measurement?

- In clinical trials, a baseline measurement of outcome often taken before randomization
  - Is baseline an "outcome"?
    - yes: use as first outcome measurement in mixed model?
    - no: ignore?
    - no: use as covariate in model?
- In an observational study, there is no experimental intervention
  - Usually then "baseline" is the first of the measured outcomes
- In Reisby example, baseline HDRS is before patients are treated, but there is no randomization
  - Is baseline HDRS an outcome?

Summary longitudinal data

- Longitudinal data is a specific form of multilevel data
  - measurements within patients, challenge is in modelling time properly
- Time can be continuous or discrete
  - discrete: everyone measured at a few specific time points
    - but, with 3+ measurements per person and approximately linear time trends, you could still consider modelling data as continuous
  - continuous: measurements at different times for different individuals
- We can account for correlation of measurements over time
  - explicitly: variance-covariance matrix of residuals (CPMs)
    - primarily when everyone (theoretically) measured at same time points
  - implicitly: random intercept, random slope for time (LMEs)
  - (both explicitly & implicitly: LMEs with autocorrelated errors)
- "Baseline" measurement of outcome has different meaning depending on study design

Reisby Example, use baseline HDRS as covariate

- Select only time >0, use hdrs.base as covariate in mixed model with random intercept, random slope, fixed time & endo
- What do you expect will happen to:
  - …the variance of the random intercept?
  - …the variance of the random slope?
  - …the residual variance?