Longitudinal data

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Outline

1 Introduction mixed-effects models

Mixed-effects models

- Mixed-effects models take account of dependencies in hierarchical, longitudinal, and other dependent data
- Mixed-effects models have been developed in a variety of disciplines with varying names and terminology
  - Random-effects models (statistics, econometrics)
  - Variance and covariance component analysis (statistics)
  - Hierarchical linear models (education)
  - Multilevel models (sociology)
  - Contextual-effects models (sociology, political science)
  - Random-coefficient models (econometrics)
  - Repeated-measures models (statistics, psychology)

Fox (2016)

Data schema for dependent data

Person	Time	Observ.	Covariates		
1	1	y_{11}	x_{111}	$\dots$	x_{11p}
1	2	y_{12}	x_{121}	$\dots$	x_{12p}
.	.	.	.	$\dots$	.
1	n_1	y_{1n_1}	x_{1n_11}	$\dots$	x_{1n_1p}
.	.	.	.	$\dots$	.
.	.	.	.	$\dots$	.
N	1	y_{N1}	x_{N11}	$\dots$	x_{N1p}
N	2	y_{N2}	x_{N21}	$\dots$	x_{N2p}
.	.	.	.	$\dots$	.
N	n_N	y_{Nn_N}	x_{Nn_N1}	$\dots$	x_{Nn_Np}

- $i = 1, \dots, N$ persons
- $j = 1, \dots, n_i$ time points for person i
- All observations: $\sum_i^N n_i$
- Vector of all observations for person i
  $(\mathbf{y}_i)_{n_i \times 1}$
- Vector of covariates for person i at time point j
  $(\mathbf{x}_{ij})_{p \times 1}$
- All covariates of person i
  $(\mathbf{X}_i)_{n_i \times p}$

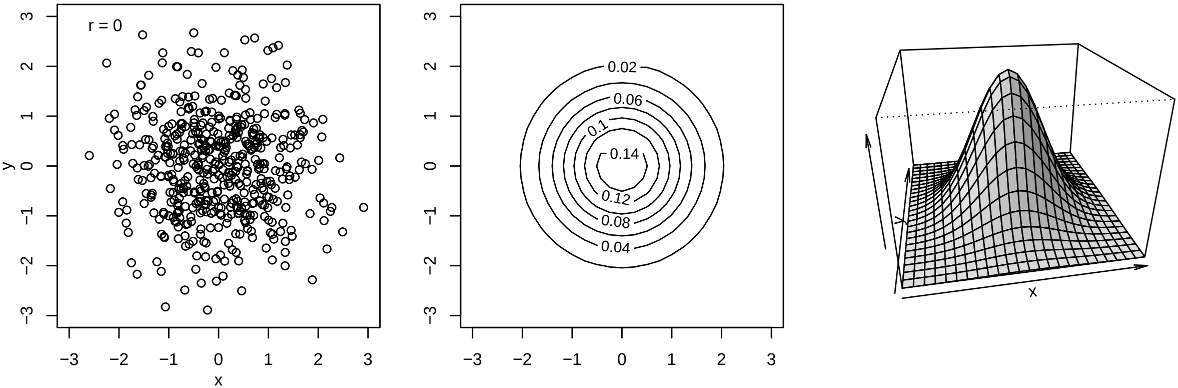
Bivariate data

- Consider two normal random variables X and Y with a correlation ρ_{xy}
- We then have a bivariate normal distribution with mean vector $\boldsymbol{\mu}$ and covariance matrix $\boldsymbol{\Sigma}$

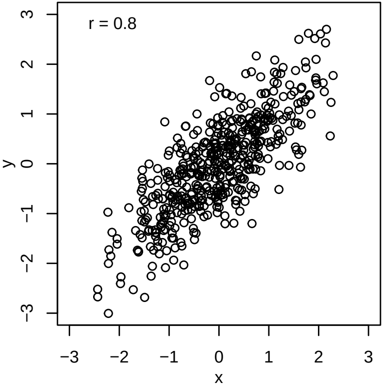
$$\begin{pmatrix} X \\ Y \end{pmatrix} \sim N\left(\boldsymbol{\mu} = \begin{pmatrix} \mu_x \\ \mu_y \end{pmatrix}, \boldsymbol{\Sigma} = \begin{pmatrix} \sigma_x^2 & \sigma_{xy} \\ \sigma_{xy} & \sigma_y^2 \end{pmatrix}\right)$$

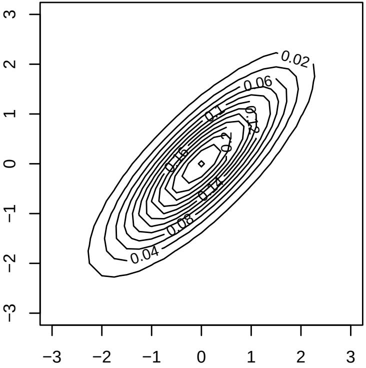
where $\sigma_{xy} = \rho_{xy} \cdot \sigma_x \cdot \sigma_y$

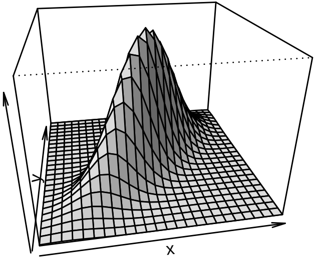
Bivariate data



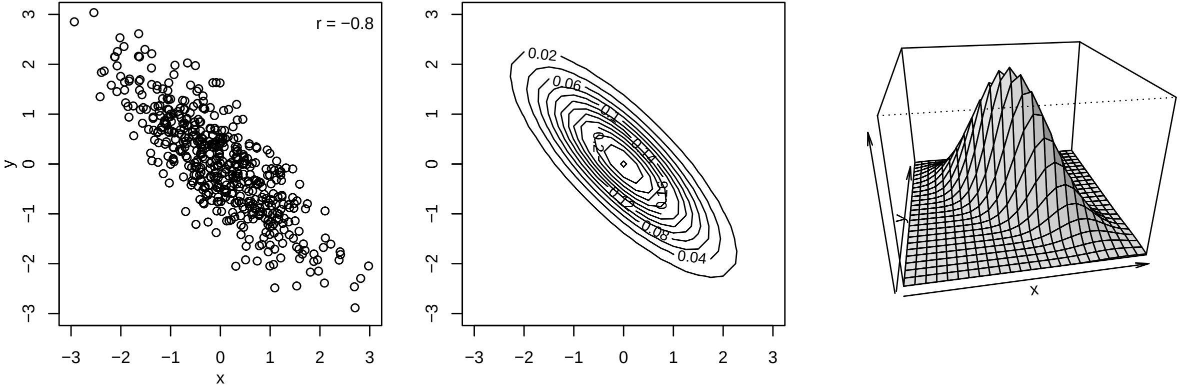
Bivariate data







Bivariate data



Mixed-effects models

- Mixed-effects models are a class of statistical models that include fixed effects as well as random effects
- Fixed effects vs. random effects[1]
  - For fixed effects, only effects of the factor levels used in the present study are considered (manipulated conditions, e. g., assigned groups, but also sex, or other variables . . .)

    → Of interest is how these levels differ
  - For random effects, the factor levels considered in a study are regarded as a (random) sample from some population (e. g., words, raters, subjects, . . .)

    → Of interest are conlusions about the underlying population and its variation

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[1] Some critical discussion on these definitions:
http://andrewgelman.com/2005/01/25/why_i_dont_use/

Crossed random effects

- In many experiments in psychology the reaction of each subject ($j = 1, \ldots, N$) to a complete set of stimuli or items ($k = 1, \ldots, K$) is measured

$$y_{ijk} = \beta_0 + \beta_i x_i + \upsilon_{0j} + \eta_{0k} + \varepsilon_{ijk}$$

with $\varepsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$, $\upsilon_{0j} \overset{iid}{\sim} N(0, \sigma^2_\upsilon)$, and $\eta_{0k} \overset{iid}{\sim} N(0, \sigma^2_\eta)$

- Data are completely crossed: all subjects work on all items

		Subject				
		1	2	3	...	20
	1	1	1	1	...	1
	2	1	1	1	...	1
Item	3	1	1	1	...	1
	⋮	⋮	⋮	⋮	⋮	⋮
	10	1	1	1	...	1

Crossed random effects

```
> head(dat, 12)
   id  cond   item  av
1   1 cond1 item01 105
2   1 cond1 item02 116
3   1 cond1 item03 104
4   1 cond1 item04  81
5   1 cond1 item05  99
6   1 cond1 item06 109
7   1 cond1 item07 100
8   1 cond1 item08 103
9   1 cond1 item09  89
10  1 cond1 item10  94
11  2 cond1 item01 107
12  2 cond1 item02 100
```

```
> xtabs( ~ item + id, dat)
        id
item     1 2 3 4 5 6 7 8 9 ... 20
  item01 1 1 1 1 1 1 1 1 1 ...  1
  item02 1 1 1 1 1 1 1 1 1 ...  1
  item03 1 1 1 1 1 1 1 1 1 ...  1
  item04 1 1 1 1 1 1 1 1 1 ...  1
  item05 1 1 1 1 1 1 1 1 1 ...  1
  item06 1 1 1 1 1 1 1 1 1 ...  1
  item07 1 1 1 1 1 1 1 1 1 ...  1
  item08 1 1 1 1 1 1 1 1 1 ...  1
  item09 1 1 1 1 1 1 1 1 1 ...  1
  item10 1 1 1 1 1 1 1 1 1 ...  1
```

Nested random effects

- We talk about nested random effects, when certain levels of one factor are combined only with certain leves of another factor (factors are nested within each other)
- The standard example for a nested design are students in classes in schools

$$y_{ijk} = \beta_0 + \upsilon_{0i} + \eta_{0ij} + \varepsilon_{ijk}$$

with $\varepsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$, $\upsilon_{0i} \overset{iid}{\sim} N(0, \sigma_\upsilon^2)$, and $\eta_{0ij} \overset{iid}{\sim} N(0, \sigma_\eta^2)$

		Classes									
		1	2	3	4	5	6	7	8	9	10
	1	n_1	n_2	.	.	.	.	.	.	.	.
	2	.	.	n_3	n_4	.	.	.	.	.	.
Schools	3	.	.	.	.	n_5	n_6	.	.	.	.
	4	.	.	.	.	.	.	n_7	n_8	.	.
	5	.	.	.	.	.	.	.	.	n_9	n_{10}

Nested random effects

```
> head(dat, 12)
   id   class  school  av
1   1 class01 school1 105
2   2 class01 school1  93
3   3 class01 school1 119
4   4 class01 school1  94
5   5 class01 school1 107
6   6 class01 school1 100
7   7 class01 school1  98
8   8 class01 school1 108
9   9 class01 school1 108
10 10 class01 school1  91
11 11 class01 school1  75
12 12 class01 school1  76
```

```
> xtabs(~school + class, dat, sparse = TRUE)
school1 19 17  .  .  .  .  .  .  .  .
school2  .  . 23 21  .  .  .  .  .  .
school3  .  .  .  . 18 20  .  .  .  .
school4  .  .  .  .  .  . 19 21  .  .
school5  .  .  .  .  .  .  .  . 23 19
```

Linear model

- We have observations $(y_i, x_{i1}, \ldots, x_{ip})$ with $i = 1, \ldots, N$ and the stochastical model

$$y_i = \beta_0 + \beta_1 \cdot x_{i1} + \ldots + \beta_p \cdot x_{ip} + \varepsilon_i$$

$$\varepsilon_i \overset{iid}{\sim} N(0, \sigma^2)$$

- In matrix notation

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i$$

which corresponds to

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ \vdots \\ y_N \end{pmatrix} = \begin{pmatrix} 1 & x_{11} & x_{12} & \ldots & x_{1p} \\ 1 & x_{21} & x_{22} & \ldots & x_{2p} \\ 1 & x_{31} & x_{32} & \ldots & x_{3p} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & x_{N1} & x_{N2} & \ldots & x_{Np} \end{pmatrix} \cdot \begin{pmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \\ \vdots \\ \varepsilon_N \end{pmatrix}$$

Linear mixed-effects model

- The linear mixed-effects model has the general form

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \boldsymbol{\upsilon}_i + \boldsymbol{\varepsilon}_i$$

  with fixed effects $\boldsymbol{\beta}$, random effects $\boldsymbol{\upsilon}_i$, and the design matrices $\mathbf{X}_i$ and $\mathbf{Z}_i$ and the assumptions

$$\boldsymbol{\upsilon}_i \overset{iid}{\sim} N(\mathbf{0}, \boldsymbol{\Sigma}_\upsilon), \qquad \boldsymbol{\varepsilon}_i \overset{iid}{\sim} N(\mathbf{0}, \sigma^2 \mathbf{I}_{n_i})$$

- This implies for the marginal covariance matrix

$$Cov(\mathbf{y}_i) = \boldsymbol{\Sigma}_i = \mathbf{Z}_i \boldsymbol{\Sigma}_\upsilon \mathbf{Z}_i' + \sigma^2 \mathbf{I}_{n_i}$$

Linear mixed-effects model

$$
\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ \vdots \\ y_N \end{pmatrix} = \begin{pmatrix} 1 & x_{11} & x_{12} & \dots & x_{1p} \\ 1 & x_{21} & x_{22} & \dots & x_{2p} \\ 1 & x_{31} & x_{32} & \dots & x_{3p} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & x_{N1} & x_{N2} & \dots & x_{Np} \end{pmatrix} \cdot \begin{pmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix} + \begin{pmatrix} z_{10} & z_{11} & \dots & z_{1q} & \dots \\ z_{20} & z_{21} & \dots & z_{2q} & \dots \\ z_{30} & z_{31} & \dots & z_{3q} & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ z_{N0} & z_{N1} & \dots & z_{Nq} & \dots \end{pmatrix} \cdot \begin{pmatrix} \upsilon_{10} \\ \vdots \\ \upsilon_{1q} \\ \upsilon_{20} \\ \vdots \\ \upsilon_{Nq} \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \\ \vdots \\ \varepsilon_N \end{pmatrix}
$$

Linear mixed-effects model

- Random intercept model

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \upsilon_{0i} + \varepsilon_i$$

with $\upsilon_{0i} \overset{iid}{\sim} N(0, \sigma_\upsilon^2)$, $\varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$, υ_{0i} and ε_{ij} i.i.d.

- Random slope model

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \upsilon_{0i} + \upsilon_{1i} x_{ij} + \varepsilon_i$$

with

$$\begin{pmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{pmatrix} \overset{iid}{\sim} N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \boldsymbol{\Sigma}_\upsilon = \begin{pmatrix} \sigma_{\upsilon_0}^2 & \sigma_{\upsilon_0 \upsilon_1} \\ \sigma_{\upsilon_0 \upsilon_1} & \sigma_{\upsilon_1}^2 \end{pmatrix} \right)$$

$$\varepsilon_i \overset{iid}{\sim} N(\mathbf{0}, \sigma^2 \mathbf{I}_{n_i})$$

2 Sleep study

Longitudinal data

- Longitudinal data consist of repeated measurements on the same subject taken over time
  - are special cases of mixed-effects models
  - contain a time covariate
  - time trends within and between subjects are of interest
- We will look at an example from the `lme4` package[2]

```
library(lme4)
data(sleepstudy)
?sleepstudy
str(sleepstudy)
summary(sleepstudy)
head(sleepstudy)
```

[2] The example can be found in a book draft by Douglas Bates: http://lme4.r-forge.r-project.org/ or the JSS paper on `lme4`: https://www.jstatsoft.org/article/view/v067i01

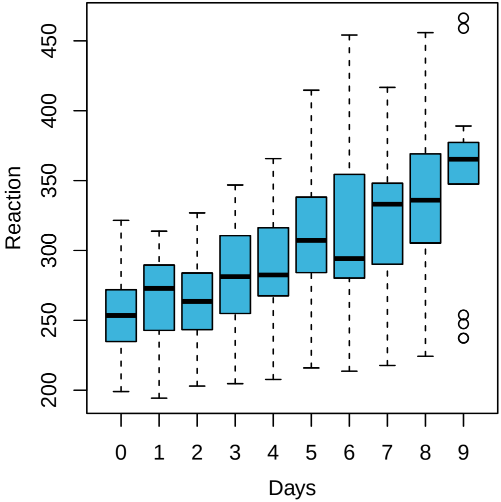
Sleep study

- Average reaction time per day for subjects in a sleep deprivation study
- On day 0, the subjects had their normal amount of sleep
- Starting that night they were restricted to 3 hours of sleep per night
- Observations represent the average reaction time on a series of tests given each day to each subject

A data frame with 180 observations on the following 3 variables

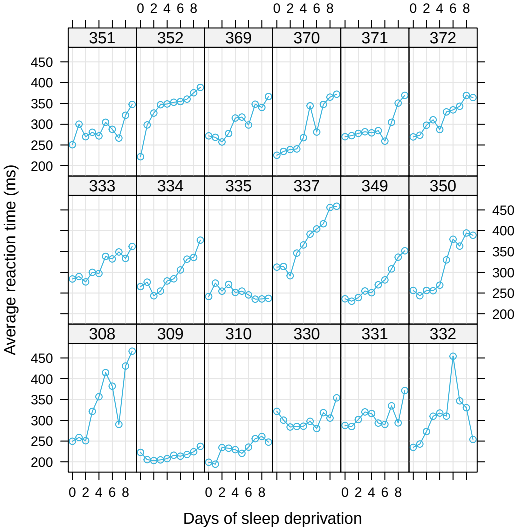
`Reaction`	Average reaction time (ms)
`Days`	Number of days of sleep deprivation
`Subject`	Subject number on which the observation was made

Visualization of data




```
boxplot(Reaction ~ Days, sleepstudy)
```

Visualization of individual data




```
library(lattice)

xyplot(Reaction ~ Days | Subject,
  data = sleepstudy,
  type = c("g","b"),
  xlab = "Days of sleep deprivation",
  ylab = "Average reaction time (ms)",
  aspect = "xy")
```

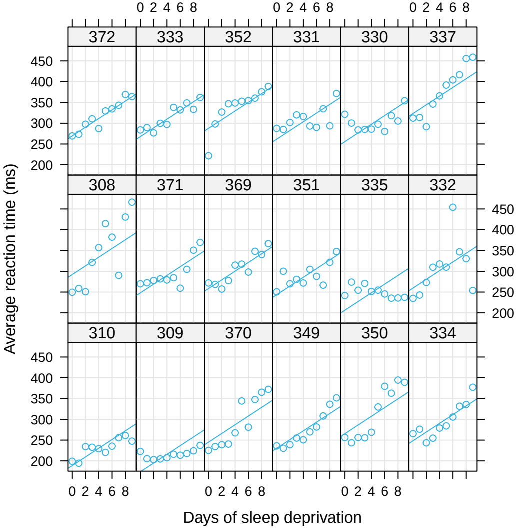
Random intercept model

- The random intercept model adds a random intercept for each subject

$$y_{ij} = \beta_0 + \beta_1\, Days_{ij} + \upsilon_{0i} + \varepsilon_i$$

with $\upsilon_{0i} \overset{iid}{\sim} N(0, \sigma_\upsilon^2)$, $\varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$

- The slope is identical for each subject (and the population)



Random intercept model

```
lme0 <- lmer(Reaction ~ Days + (1 | Subject), sleepstudy)
summary(lme0)

# model matrices
X <- model.matrix(~ Days, sleepstudy)
Z <- model.matrix(~ 0 + Subject, sleepstudy)

# coefficients
coef(lme0)
fixef(lme0)
ranef(lme0)
```

Random slope model

- The random slope model adds a random intercept and a random slope for each subject

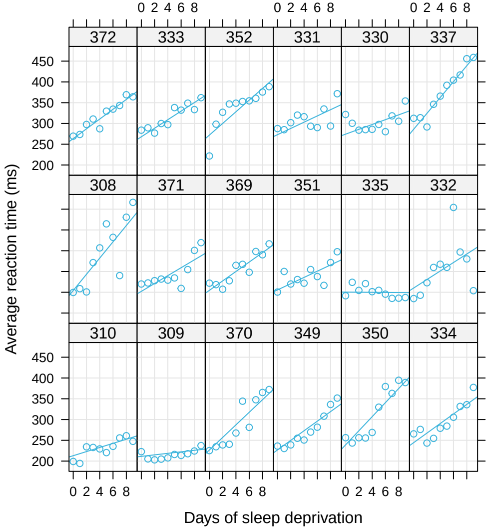
$$y_{ij} = \beta_0 + \beta_1 \, Days_{ij} + \upsilon_{0i} + \upsilon_{1i} \, Days_{ij} + \varepsilon_{ij}$$

with

$$\begin{pmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{pmatrix} \overset{iid}{\sim} N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \boldsymbol{\Sigma}_\upsilon = \begin{pmatrix} \sigma^2_{\upsilon_0} & \sigma_{\upsilon_0 \upsilon_1} \\ \sigma_{\upsilon_0 \upsilon_1} & \sigma^2_{\upsilon_1} \end{pmatrix} \right)$$

$$\varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2_\varepsilon)$$

- Individual slopes for each subject



Random slope model

```
lme1 <- lmer(Reaction ~ Days + (Days | Subject), sleepstudy)
summary(lme1)

# model matrices
X <- model.matrix(~ Days, sleepstudy)
Z <- model.matrix(~ 0 + Subject + Subject:Days, sleepstudy)

# coefficients
coef(lme1)
fixef(lme1)
ranef(lme1)
```

Model with uncorrelated random effects

- We will now consider a model without correlated random effects

$$y_{ij} = \beta_0 + \beta_1 Days_{ij} + \upsilon_{0i} + \upsilon_{1i} Days_{ij} + \varepsilon_{ij}$$

with

$$\boldsymbol{\upsilon} \overset{iid}{\sim} N\left(\mathbf{0}, \boldsymbol{\Sigma}_\upsilon = \begin{pmatrix} \sigma^2_{\upsilon_0} & 0 \\ 0 & \sigma^2_{\upsilon_1} \end{pmatrix}\right) \quad \text{and} \quad \varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2_\varepsilon)$$

```r
lme2 <- lmer(Reaction ~ Days + (Days || Subject), sleepstudy)
summary(lme2)

# likelihood-ratio test
anova(lme1, lme2)
# confidence intervals
confint(lme2)
```

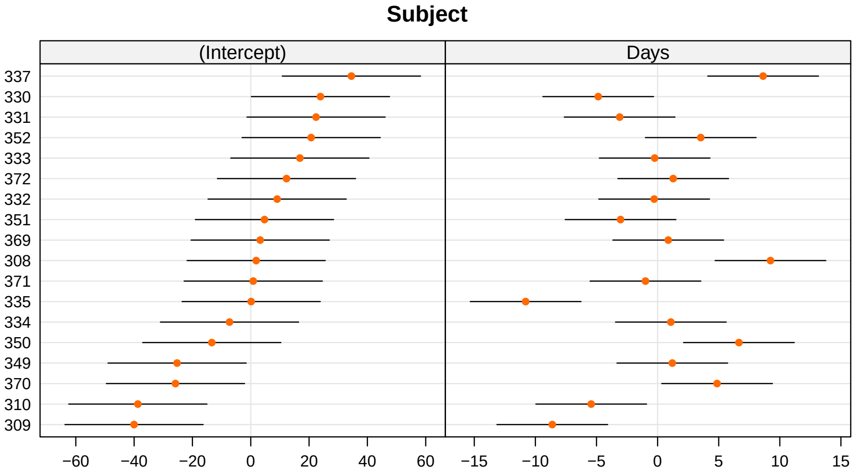
Confidence intervals and interpretation

- The results indicate that the extra parameter $\sigma_{\upsilon_0 \upsilon_1}$ does not produce a significantly better fit
- Results show that we have a significant effect for days with an average increase in reaction time of 10.47 ms for each day of sleep deprivation
- We get an estimate of $\sigma_{\upsilon_0} = 24.17$ for the standard deviation of reaction time for subjects and a standard deviation of $\sigma_{\upsilon_1} = 5.80$ for the dependence of reaction time on days of sleep deprivation

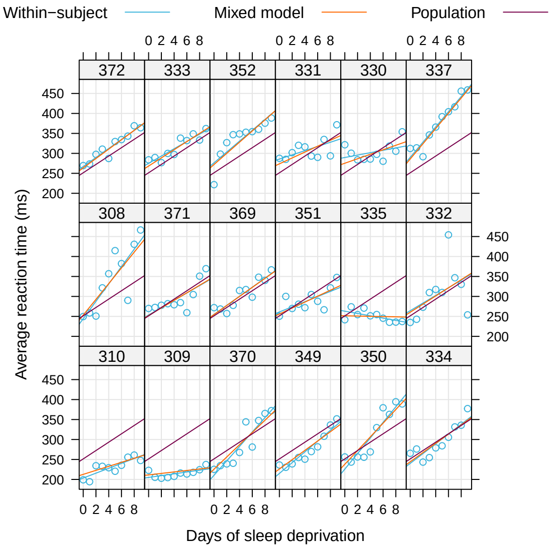
Examining random effects and predictions

```
coef(lme2)
fixef(lme2)
ranef(lme2)

# correlational structure for intercepts and slopes
dotplot(ranef(lme2, condVar = TRUE),
        scales = list(x = list(relation = "free")))[[1]]

# predictions for all subjects
predict(lme2)
```

Examining random effects and predictions



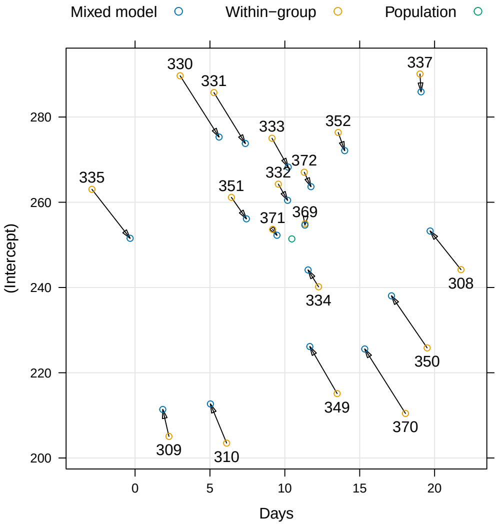
Examining random effects and predictions



- Within-subject regression line shows regression line fitted to data for each individual
- Population regression line shows fixed effects for mixed-effects model
- Mixed model regression line shows individual regression lines as predicted by mixed-effects models

Shrinkage

- When per-subject slopes and intercepts calculated from a mixed-effects model are compared to estimated slopes and intercepts within subjects, estimates from mixed-effects model are closer to the population estimates (the fixed effects)
- This pattern is sometimes described as *shrinkage* of coefficients toward the population values
- The more within-subject variance, the stronger parameters *shrink* towards the population parameters



Assumptions

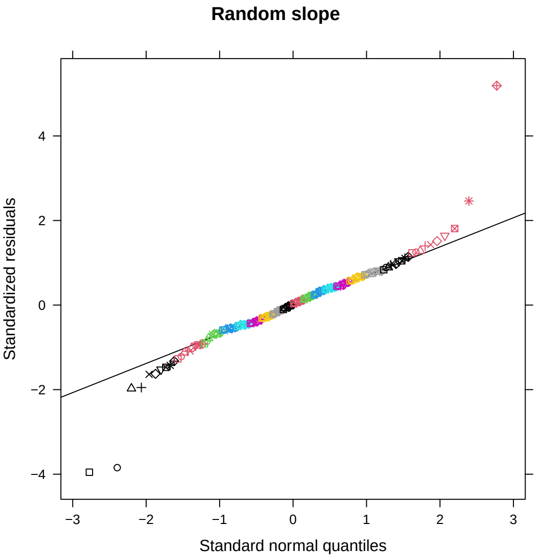
- Assumptions can be checked visually
- Normality assumption

```
qqmath(lme2,
       col = sleepstudy$Subject,
       pch = sleepstudy$Days)
```

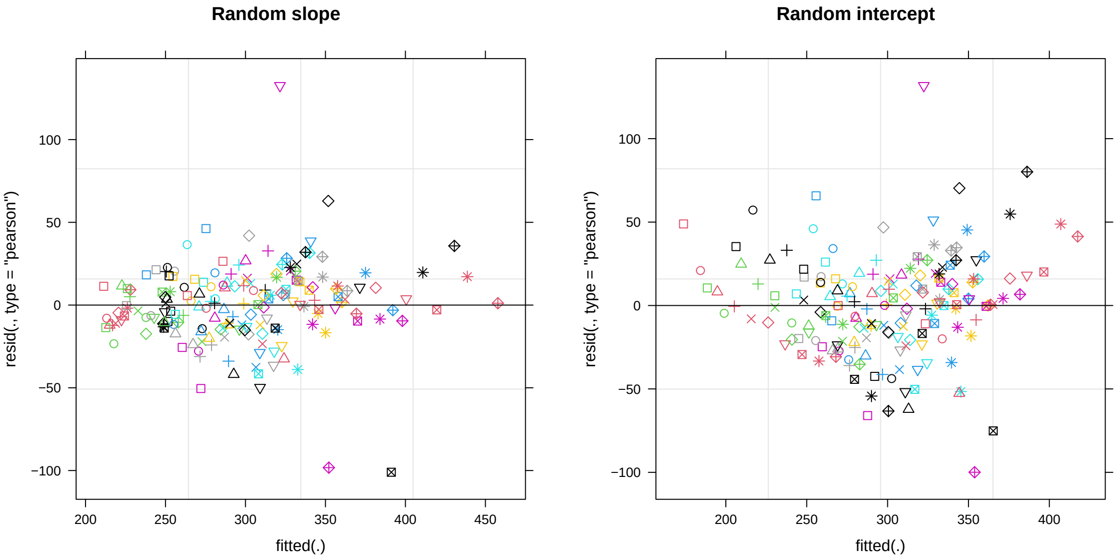
- Independence assumption

```
plot(lme2,
       col = sleepstudy$Subject,
       pch = sleepstudy$Days)
```

https://bbolker.github.io/morelia_2018/notes/mixedlab.html



Assumptions



3 Parameter estimation

Maximum Likelihood Estimation

- The maximum likelihood principle was introduced by R. A. Fisher
  - It can be used for almost all estimation problems, also complex ones
  - The resulting estimation functions have many desirable properties
- Obtaining the MLE $\hat{\vartheta}$ takes the following steps
  1. Generate the log-likelihood
  $$\log L(\vartheta)$$
  2. Take the derivative of the log-likelihood with respect to parameter ϑ
  $$(\log L)'(\vartheta) = \frac{d \log L(\vartheta)}{d\vartheta}$$
  3. Set the derivative equal to 0
  $$(\log L)'(\hat{\vartheta}) = 0$$
  4. Solve the resulting equation for the estimator $\hat{\vartheta}$

Restricted Maximum Likelihood Estimation

- The restricted maximum likelihood (REML) approach is a form of Maximum Likelihood Estimation
- In particular, REML is used as a method for fitting linear mixed-effects models
- In contrast to traditional Maximum Likelihood Estimation, REML can produce unbiased estimates of variance and covariance parameters
- MLE and REML do not outmatch each other, both can be used
- REML is the default in `lme4`, but if we want to conduct likelihood ratio tests, only MLE estimates are valid

References

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015).Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Bates, D. M. (2010). lme4: Mixed-effects modeling with R.

Fox, J. (2016). *Applied regression analysis and generalized linear models*. Sage Publications.