Statistical models for longitudinal data : Linear Mixed Model

A. Latouche

STA 112

Learning objectives

- ▶ Be able to understand the importance of longitudinal models (in epidemiology)

- ▶ Be able to understand the rationale of using mixed models

- ▶ Be able to formulate, run, and interpret results of mixed models for longitudinal data

Outline

- ▶ Introduction: definition of longitudinal data and objective of their analysis

- ▶ Application of mixed models to longitudinal data

Definitions: Main study designs

- Cross-sectional design:
    - Definition: one single measurement (outcome) per individual
    - Example: measure height in a sampled population
- Multivariate designs:
    - Definition: several outcomes measured in each participant
    - Example: measure height and arm length in a sampled population
- Repeated measures designs
    - Definition: the outcome(s) is (are) measured several times in each participant
    - Example: measure both arm lengths in each participants
- Longitudinal designs
    - Definition: repeated measures occur at different time points
        - ⇒ need to follow-up in time the studied population
    - Example: follow the arm length at different ages
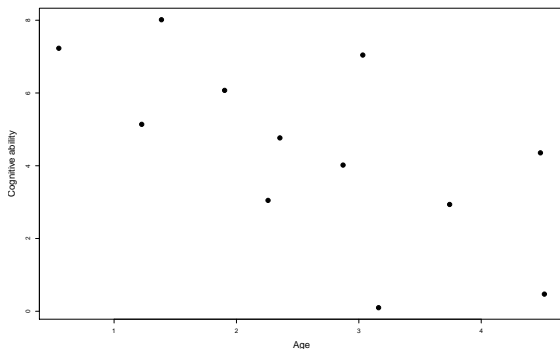   - ⇒ repeated measures are not necessarily longitudinal

Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.
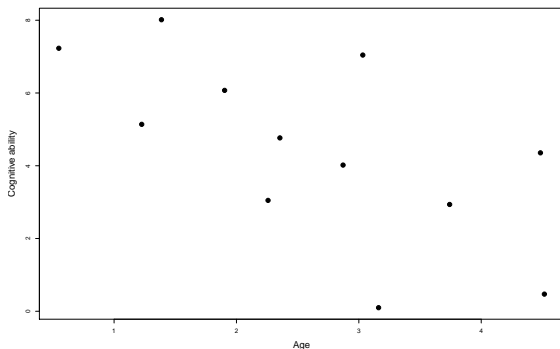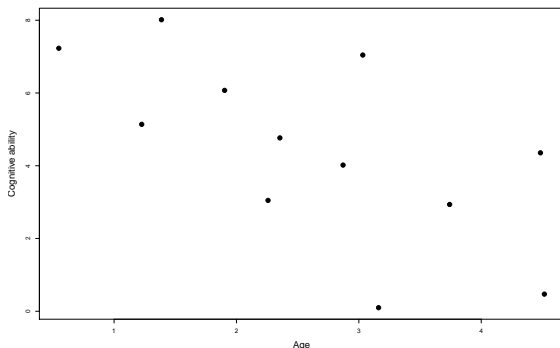
Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.

$\Rightarrow$ data show a general decreasing cognitive ability with age
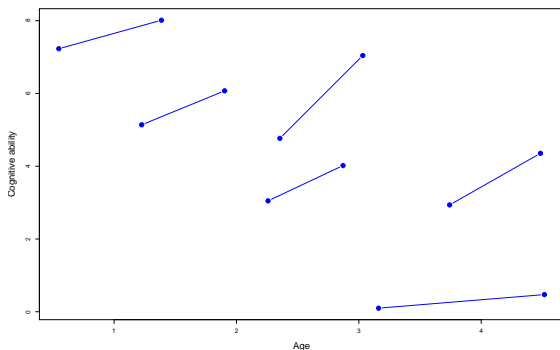
Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.

⇒ data show a general decreasing cognitive ability with age
⇒ this assumes that all observations are independent (*i.e.* two measures in one child ⇔ one measure in two children)

Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.

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⇒ need to account for the intra-individual correlation

Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.

⇒ need to account for the intra-individual correlation
⇒ this suggest that the value observed at the second time points
depends of the first measured value
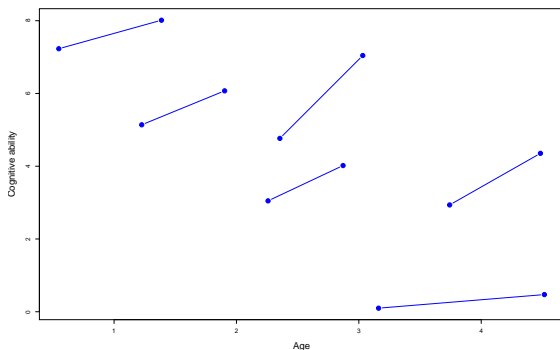
Overview of longitudinal data

Example: cognitive ability was measured in 6 children twice in time.
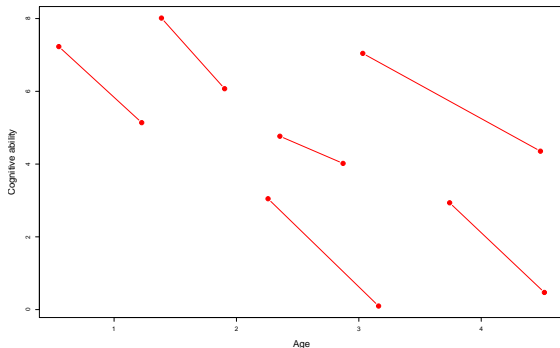
Overview of longitudinal data

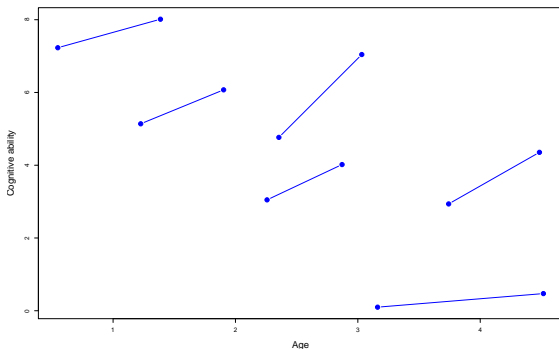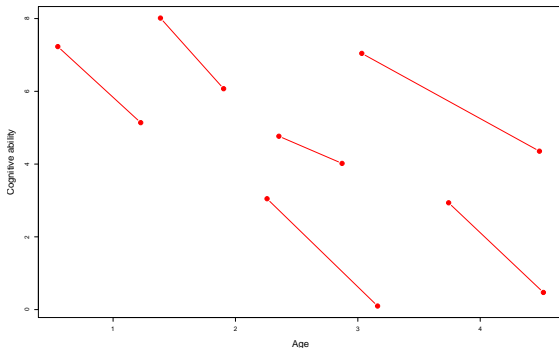Example: cognitive ability was measured in 6 children twice in time.

⇒ depending on how the two observations per individual correlate, data may suggest very different trends.

Main features of longitudinal data

- Conclusions:
  - By nature longitudinal data exhibit strong intra-individual correlations: the value observed at time t depends on the one(s) observed before

    $\Rightarrow$ this correlation defines individual-specific features driving the observed outcome

- In a linear model context:
  - Variable intercepts: irrespective of age children may have different cognitive abilities (heterogeneous population)
  - Variable slopes: the evolution of cognitive abilities with age may be different from one child to another: some may be faster than others (heterogeneous response to age).

$\Rightarrow$ How to account for individual heterogeneity in an linear model?

From linear to linear mixed models

▶ Formulation of the linear model for the jth observation of individual i:

$$Y_{ij} = \alpha + \beta X_{ij} + \epsilon_{ij},$$

where:

- ▶ Y_{ij} is the measured outcome (e.g. the the jth cognitive ability measure of child i)
- ▶ X_{ij} is the observed value for the predictive value (e.g the age on the ith child at the jth measurement)
- ▶ α is the intercept (e.g the average cognitive ability at birth)
- ▶ β is the regression coefficient defining how much the outcome should vary for a one-unit increase in X
- ▶ ϵ_{ij} is the residual error measuring the deviation from the linear relationship (e.g. the luck when child i took his/her j^{th} cognitive test)

From linear to linear mixed models

Main assumptions:

- For a given individual i, there is no correlation between the Y_{ij} (*e.g* the data are the same as having one measure in $I \times J$ children)

- The intercept is the same for all individual (*e.g.* all children have the same ability at birth)

- The slope does not depend on the individual (*e.g* cognitive abilities will evolve in a similar fashion in all children)

- The residuals error are independent and identically distributed (*e.g.* the luck while taking the test does not depend on the individual nor of the time)

▶ Formulation of the linear mixed model:

$$Y_{ij} = (\alpha + u_{0i}) + (\beta + u_{1i})X_{ij} + \epsilon_{ij},$$

where

- ▶ u_{0i} is the random intercept: modelling baseline individual heterogeneity (*e.g* difference in cognitive ability at birth)
- ▶ u_{1i} is the random slope: modelling individual heterogeneity in the X-Y relationship (*e.g.* differences in the age-related evolution of cognitive ability)
- ▶ Main assumption: both u_{0i} and u_{1i} are assumed Gaussian centered on 0 with variance σ_0, σ_1 respectively.

Summary: Principle of the linear mixed models
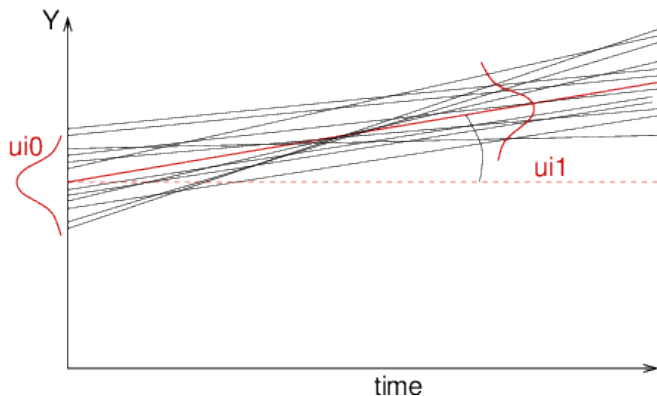
- Random intercept measures heterogeneity at baseline
- Random slope measures heterogeneity at the end of follow-up
- Note: random effects are centered on 0

Linear mixed models in practice

- ▶ Step 1: data inspection
  - ⇒ do data need to account for time-related intra-individual correlation (*i.e.* is there a need for a mixed model?)
- ▶ Step 2: model formulation
  - ⇒ should the model include a random intercept and/or slope?
- ▶ Step 3: model estimation
  - ⇒ what are the fixed effect and random effects estimates?
- ▶ Step 4: results interpretation
  - ⇒ what do the fixed effect and random effects estimates suggest?

Worked example: sleep deprivation study

- Study outline
  - Aim: assess the effect of sleep deprivation on cognitive performances
  - Design: during their follow-up, several truck drivers were restricted to 3 hours sleep per night and their cognitive performance was assessed each day
  - Outcome measurement: the cognitive performance was assessed by measuring their reaction time for several stimulation, and the mean reaction time (in ms) is reported.
  - Question: is the reaction time changing with time? Does the reaction time deteriorates with an increase of sleep deprivation?

Worked example: sleep deprivation study

Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study

GREGORY BELENKY, NANCY J. WESENSTEN, DAVID R. THORNE,
MARIA L. THOMAS, HELEN C. SING, DANIEL P. REDMOND,
MICHAEL B. RUSSO and THOMAS J. BALKIN
Division of Neuropsychiatry, Walter Reed Army Institute of Research, Silver Spring, MD, USA

SUMMARY Daytime performance changes were examined during chronic sleep restriction or augmentation and following subsequent recovery sleep. Sixty-six normal volunteers spent either 3 ($n = 18$), 5 ($n= 16$), 7 ($n = 16$), or 9 h ($n = 16$) daily time in bed (TIB) for 7 days (restriction/augmentation) followed by 3 days with 8 h daily TIB (recovery). In the 3-h group, speed (mean and fastest 10% of responses) on the psychomotor vigilance task (PVT) declined, and PVT lapses (reaction times greater than 500 ms) increased steadily across the 7 days of sleep restriction. In the 7- and 5-h groups speed initially declined, then appeared to stabilize at a reduced level; lapses were increased only in the 5-h group. In the 9-h group, speed and lapses remained at baseline levels. During recovery, PVT speed in the 7- and 5-h groups (and lapses in the 5-h group) remained at the stable, but reduced levels seen during the last days of the experimental phase, with no evidence of recovery. Speed and lapses in the 3-h group recovered rapidly following the first night of recovery sleep; however, recovery was incomplete with speed and lapses stabilizing at a level comparable with the 7- and 5-h groups. Performance in the 9-h group remained at baseline levels during the recovery phase. These results suggest that the brain adapts to chronic sleep restriction. In mild to moderate sleep restriction this adaptation is sufficient to stabilize performance, although at a reduced level. These adaptive changes are hypothesized to restrict brain operational capacity and to persist for several days after normal sleep duration is

Worked example: sleep deprivation study

- ▶ Step 0: data inspection
    - ▶ Load the lme4 package

        library(lme4)

    - ▶ load the sleepstudy data set

        data(sleepstudy)

    - ▶ Explore the data:
        1. How many observations?
        2. How many variables/What is their name?
        3. How many subjects are followed-up?
        4. How many observations per subject?

► Step 0: data inspection
  ► Load the `lme4` package

                    library(lme4)

  ► load the `sleepstudy` data set

                    data(sleepstudy)

 ► Explore the data:
    1. `dim(sleepstudy)`: 180 observations
    2. `colnames(sleepstudy)`: 3 covariates: `Reaction`: reaction
       time (ms), `Days`: day of the measure, `Subject`: subject ID
    3. `length(unique(sleepstudy$Subject))`: 18 subjects
    4. `table(sleepstudy$Subject)`: each participant was
       followed-up for 10 days

                    ⇒ balanced design

- ▶ Step 1: data visualisation
  - ▶ Crude representation of the data
    ```
    plot(sleepstudy$Days,sleepstudy$Reaction)
    ```
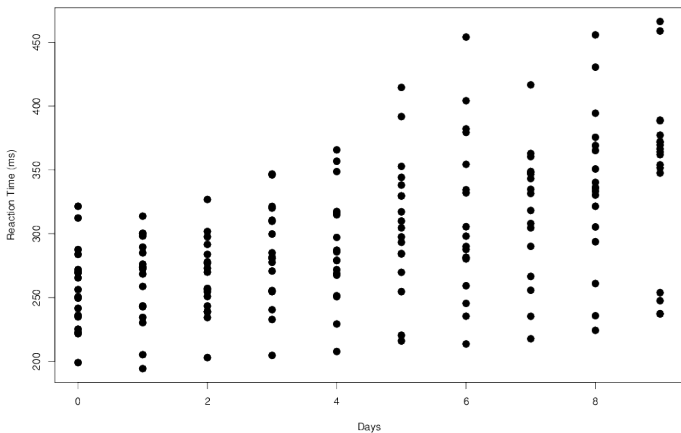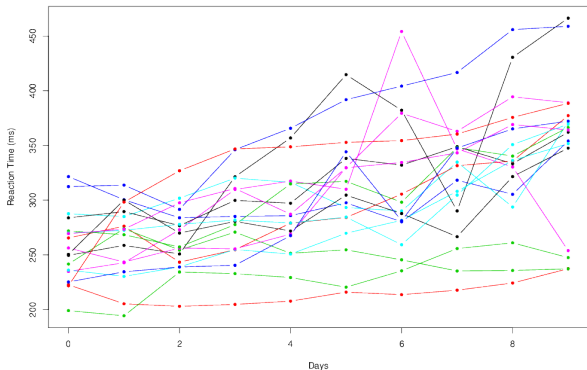

⇒ general increase of reaction time with sleeping deprivation
⇒ however large variability withing each day

- Step 1: data visualisation
  - Accounting for intra-individual correlation: plotting trajectories
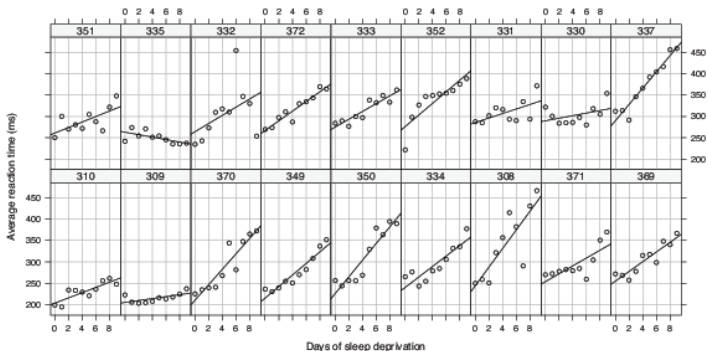

⇒ accounting for the intra-individual correlation reinforces the trend
⇒ need to account for an individual effect

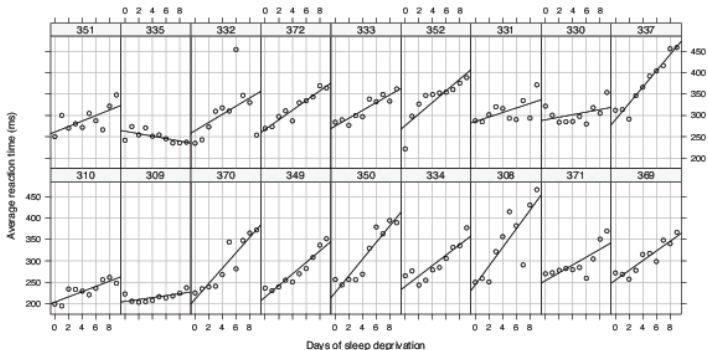▶ Step 2: Model formulation

   ▶ Investigating individual trajectories

⇒ how interpret this plot?

- ▶ Step 2: Model formulation
  - ▶ Investigating individual trajectories

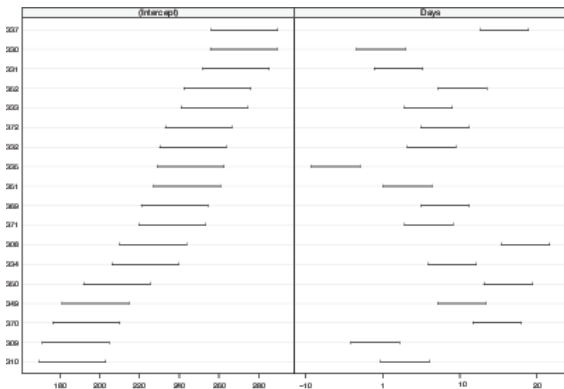 - ▶ variable reaction time at enrollment (from 200 to 300 ms)
  - ▶ variable increase with days of sleep deprivation (*e.g.* ind 309 *vs.* ind 308)

    ⇒ need for both random intercept and slope

- ▶ Step 2: Model formulation
  - ▶ Do intercept and slope correlate with individual?

  - ▶ no clear relationship between intercept and slope
    - ⇒ random intercept and slope are assumed independent

- ▶ Step 3: Run the model
  - ▶ Define the model in R include a random intercept and slope:
    ```
    Mymodel <- lmer(Reaction ~ Days + (Days|Subject),
                         sleepstudy)
    ```
  - ▶ What are the fixed effect estimates? Interpret them.
  - ▶ What do the random effect estimates represent?
  - ▶ What is the correlation between the random intercept and slope?
  - ▶ How would the RE estimates look like if there was not individual differences?

Syntax : Response $\sim$ Fixed effects covariates $+$ (Random effects covariate | Identifiers)

Intercept included by default $(1+$ Cov | Identifiers)
$\leftrightarrow$ (Cov | Identifiers)

- ▶ Step 3: Run the model
  - ▶ Define the model in R include a random intercept and slope:
    ```
    Mymodel <- lmer(Reaction~Days + (Days|Subject),
                    sleepstudy)
    ```
  - ▶ What are the fixed effect estimates? Interpret them.

    ```
    summary(Mymodel)
    ```

    Estimates suggest an average Reaction time a enrollment of
    251.4 ms, and an increase of 10.5 ms/day of sleep deprivation.
  - ▶ What do the random effect estimates represent?

    ```
    ranef(Mymodel)
    ```

    REs measure the individual deviation from the average (*i*)-
    reaction time at enrollment (intercept), and (*ii*)- reaction time
    increase with $\#$ days of sleep deprivation (slope).
    Ind 309 has a better reaction time at enrolment and was less
    affected by sleep deprivation, while Ind 337 was slower at
    enrollment and more affected by sleep deprivation.

▶ Step 3: Run the model

  ▶ Define the model in R include a random intercept and slope:

    Mymodel <- lmer(Reaction∼Days + (Days|Subject),
                    sleepstudy)

  ▶ What is the correlation between the random intercept and slope?
    Results confirmed low correlation between random slope and intercept ($< 7\%$)

  ▶ How would the RE estimates look like if there was not individual differences?
    If there was no intra-individual correlation within the data, then the random effect estimates would support a limited deviation from the overall intercept and slope

$$\Rightarrow \text{small RE estimates}$$
$$\Rightarrow \text{small variance of the RE}$$

Advantages of Linear mixed models

- LMM uses all the information is used (*i.e.* not only summary statistics analysis)
- Number and times of measurement may vary over subjects (individual varying times)
- Correct inference with variances accounting for correlation
- Flexible modelling of intra-subject correlation
- Robust to misspecification of random-effect distribution
- Marginal interpretation & subject-specific interpretation
  - ⇒ enables to assess overall *vs*. individual patterns
- Robust to missing at random data

Limitations/Extensions of Linear mixed models

- Limited to univariate outcome

    $\Rightarrow$ use of multivariate linear mixed models (MLMM)

- Limited to continuous outcome

    $\Rightarrow$ use of generalised linear mixed models (GLMM)

  $\Rightarrow$ accommodate categorical, binary, count, and survival outcome(s)

- Limited to homogeneous population

  $\Rightarrow$ LMM cannot accommodate mean trajectories depending on a factor (heterogeneous population)

    $\Rightarrow$ (LCMM)

Principle of LCMM

- Motivating example: PSA trajectories after radiation therapy
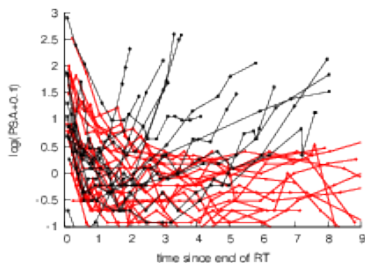
- Aim: explain individual trajectories accounting for class-specific features
- Methodological framework: 2 levels (*i.e.* sub-models) are defined
    1. One model for class membership probability
    2. One model for each class-specific trajectories

Conclusion

Mixed models:

- ► Easy to run - available in most statistical software
- ► Results are easy to interpret and enable to assess the relative importance of general *vs*. individual-specific contribution to the observed variability
- ► Existing extensions enable the analysis of most of the outcomes