Introduction to mixed model and missing data issues in longitudinal studies

Hélène Jacqmin-Gadda

INSERM, U897, Bordeaux, France

Inserm workshop, St Raphael

Outline of the talk I

Longitudinal data : definition

Definition :

Variables measured at several times on the same subjects

Examples :

- repeated measures of biological markers (CD4, HIV RNA) in HIV patients
- repeated measures of neuropsychological tests to study cognitive aging
- Repeated events : dental caries, absences from school or job, ...

Longitudinal data analysis

Objective :

- Describe change of the variable with time
- Identify factors associated with change

Problem : Intra-subject correlation

Example : HIV clinical trial

X_i=1 if treatment A,

X_i=0 if treatment B

Criterion : Change over time of CD4

Repeated measures of CD4 over the follow-up period.

$t = 0$ at initiation of treatment.

Y_{ij} = CD4 measure for subject i at time t_{ij}, $i = 1, ..., N$, $j = 1, ..., n_i$.

Analysis assuming independence

$Y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij} + \epsilon_{ij}$
with $\epsilon_{ij} \sim \mathcal{N}(O, \sigma^2)$ and $\epsilon_{ij} \perp \epsilon_{ij'}$

Intra-subject correlation

$\rightarrow$ $\hat{Var}(\hat{\beta})$ biased

$\rightarrow$ Tests for β biased

For time-independent covariate :

- $var(\hat{\beta}_2)$ under-estimated
- Tests for $H_0 : \beta_2 = 0$ anti-conservative (p value too small)

Linear mixed model with random intercept

$$Y_{ij} = (\beta_0 + \gamma_{0i}) + \beta_1 t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij} + \epsilon_{ij}$$

with $\gamma_{0i} \sim \mathcal{N}(O, \sigma_0^2)$, and $\epsilon_{ij} \sim \mathcal{N}(O, \sigma^2)$ and $\epsilon_{ij} \perp \epsilon_{ij'}$

- γ_{0i} are random variables
- Only one additional parameter : σ_0^2

Linear mixed model with random intercept (2)

- Population (marginal) mean :

$$E(Y_{ij}) = \beta_0 + \beta_1 t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij}$$

- Subject-specific (conditional) mean :

$$E(Y_{ij}|\gamma_{0i}) = (\beta_0 + \gamma_{0i}) + \beta_1 t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij}$$

- Assume common correlation between all the repeated measures

Linear mixed model with random intercept and slope

$$Y_{ij} = (\beta_0 + \gamma_{0i}) + (\beta_1 + \gamma_{1i})t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij} + \epsilon_{ij},$$

$$\gamma_{0i} \sim \mathcal{N}(O, \sigma_0^2),\ \gamma_{1i} \sim \mathcal{N}(O, \sigma_1^2),\ \epsilon_{ij} \sim \mathcal{N}(O, \sigma^2),\ \epsilon_{ij} \perp \epsilon_{ij'}$$

- Population (marginal) mean :

$$E(Y_{ij}) = \beta_0 + \beta_1 t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij}$$

- Subject-specific (conditional) mean :

$$E(Y_{ij}|\gamma_i) = (\beta_0 + \gamma_{0i}) + (\beta_1 + \gamma_{1i})t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij}$$

- The correlation between repeated measures depend on measurement times

Linear mixed model : general formulation

$$Y_{ij} = X_{ij}^T \beta + Z_{ij}^T \gamma_i + \epsilon_{ij}$$

$$\gamma_i \sim \mathcal{N}(0, B) \text{ and } \epsilon_i \sim \mathcal{N}(0, R_i).$$

X_{ij} : vector of explanatory variables
β : vector of fixed effects
Z_{ij} : sub-vector of X_{ij} (including functions of time)
γ_i : vector of random effects.

Population (marginal) mean : $E(Y_{ij}) = X_{ij}^T \beta$
Subject-specific (conditional) mean : $E(Y_{ij}|\gamma_i) = X_{ij}^T \beta + Z_{ij}^T \gamma_i$

Linear mixed model : example

Linear mixed model with AR Gaussian error

$$Y_{ij} = (\beta_0 + \gamma_{0i}) + (\beta_1 + \gamma_{1i})t_{ij} + \beta_2 X_i + \beta_3 X_i t_{ij} + w_{ij} + e_{ij}$$

with $\gamma_i^t = (\gamma_{0i}, \gamma_{1i}) \sim \mathcal{N}(\mathbf{0}, B)$,

$e_{ij} \sim \mathcal{N}(O, \sigma^2)$, $e_{ij} \perp e_{ij'}$,

$w_{ij} \sim \mathcal{N}(O, \sigma_w^2)$ and $Corr(w_{ij}, w_{ij'}) = exp(-\delta|t_{ij} - t_{ij'}|)$

Linear mixed model : Estimation

- Maximum likelihood estimator
- $Y_i = (Y_{i1}, ..., Y_{ij}, ..., Y_{in_i})^T$ multivariate Gaussian with
  - mean $X_i\beta$
  - and covariance matrix $V_i = Z_i B Z_i^T + R_i$
- Softwares : SAS Proc mixed, R lme, stata

Generalized linear mixed model

$Y_{ij} \sim$ exponential family of distribution and

$$g(E(Y_{ij}|\gamma_i)) = X_{ij}^T\beta + Z_{ij}^T\gamma_i \text{ with } \gamma_i \sim \mathcal{N}(O, B).$$

- Example : Logistic mixed model

$$logit(Pr(Y_{ij} = 1|\gamma_i)) = X_{ij}^T\beta + Z_{ij}^T\gamma_i \text{ with } \gamma_i \sim \mathcal{N}(0, B).$$

- Maximum likelihood estimation : Numerical integration
- Softwares : SAS Proc nlmixed, R nlme, stata

Typology of missing data in longitudinal studies

Notation :

$Y_i = (Y_{obs,i}, Y_{mis,i})$
with $Y_{obs,i}$ the observed part of Y_i and $Y_{mis,i}$ the missing part,

$R_{ij} = 1$ if Y_{ij} is observed and $R_{ij} = 0$ if Y_{ij} is missing
$R_i = (R_{i1}, ..., R_{ij}, ..., R_{in_i})'$

X_i explanatory variables completely observed

Typology of missing data (2)

Monotone missing data = dropout : $P(R_{ij} = 0 | R_{ij-1} = 0) = 1$
R_i may be summarized by the time to dropout T_i
and an indicator for dropout δ_i

Intermittent missing data : $P(R_{ij} = 0 | R_{ij-1} = 0) < 1$

Typology of missing data (3)

Missing Completely at random (MCAR) :

$P(R_{ij} = 1)$ is constant

The observed sample is representative of the whole sample.

$\rightarrow$ Loss of precision, no bias

Covariate-dependent missingness process :

$P(R_{ij} = 1) = f(X_i)$

$\rightarrow$ Loss of precision, no bias if analyses are adjusted on X_i

Typology of missing data (4)

Missing at random (MAR) : $P(R_{ij} = 1) = f(Y_{obs,i}, X_i)$

Example : Probability of dropout depends on past observed values

$\rightarrow$ Loss of precision, no bias with appropriate statistical methods

Informatives or MNAR : $P(R_{ij} = 1) = f(Y_{mis,i}, Y_{obs,i}, X_i)$

Example : Probability that Y be observed depends on current Y value

$\rightarrow$ Loss of precision, biases

$\rightarrow$ Sensitivity analyses

Exploring incomplete data

- Describe missing data frequency
- Cross classify missing data patterns with covariates
- Compare mean evolution for available data and complete cases
- Compare mean evolution until time t given observation status at time $t+1$
- Logistic regression for $P(R_{ij}=1)$ given covariates and $Y_{ik}, k<j$
- Cox regression for time to dropout given covariates

$\rightarrow$ Impossible to distinguish MAR from MNAR

An example : Paquid data set

The Paquid Cohort in Gironde

- 2792 subjects of 65 years and older at baseline
- Living at home at the beginning of the study (1988) in Gironde (France)
- Seen at home at 1, 3, 5, 8, and 10 years after the baseline visit
- Cognitive measure : Digit Symbol Substitution Test of Wechsler (attention, limited time to 90s)

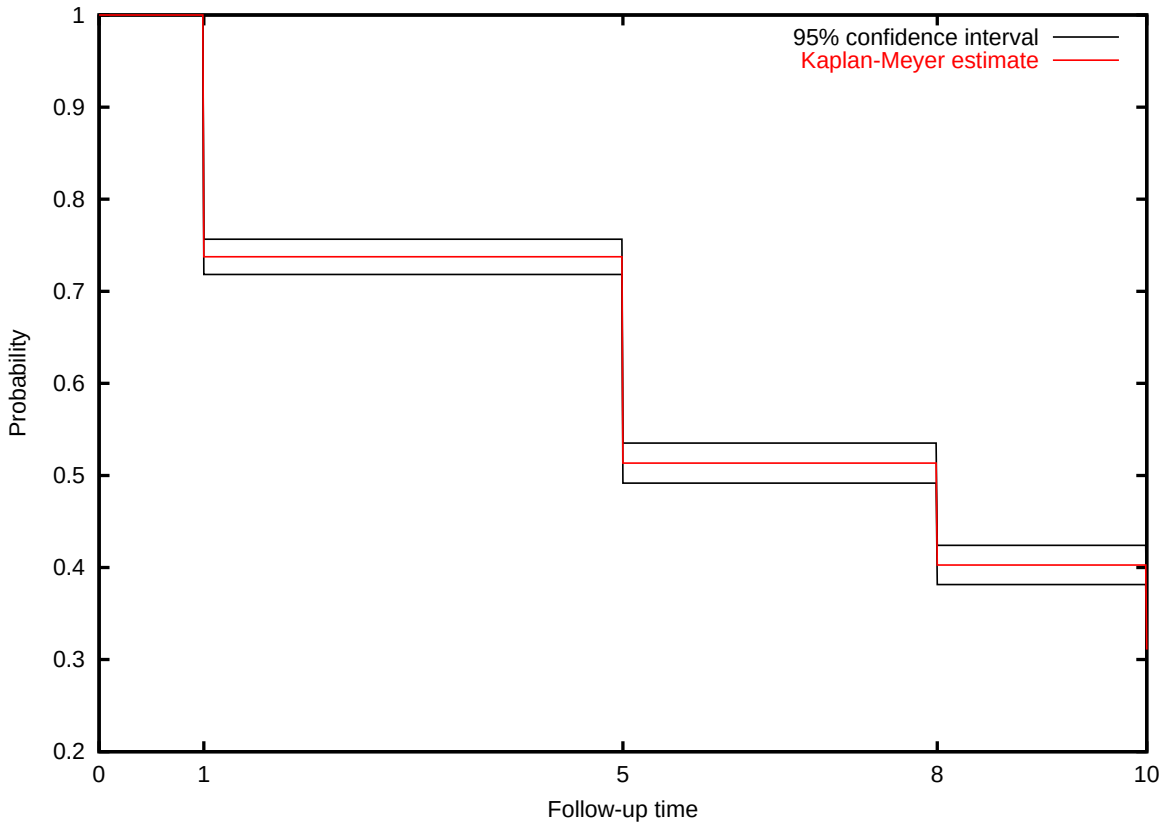
Sample :

- 2026 subjects
- without diagnosis of dementia between T0 and T10
- with the test completed at least once (at T0)

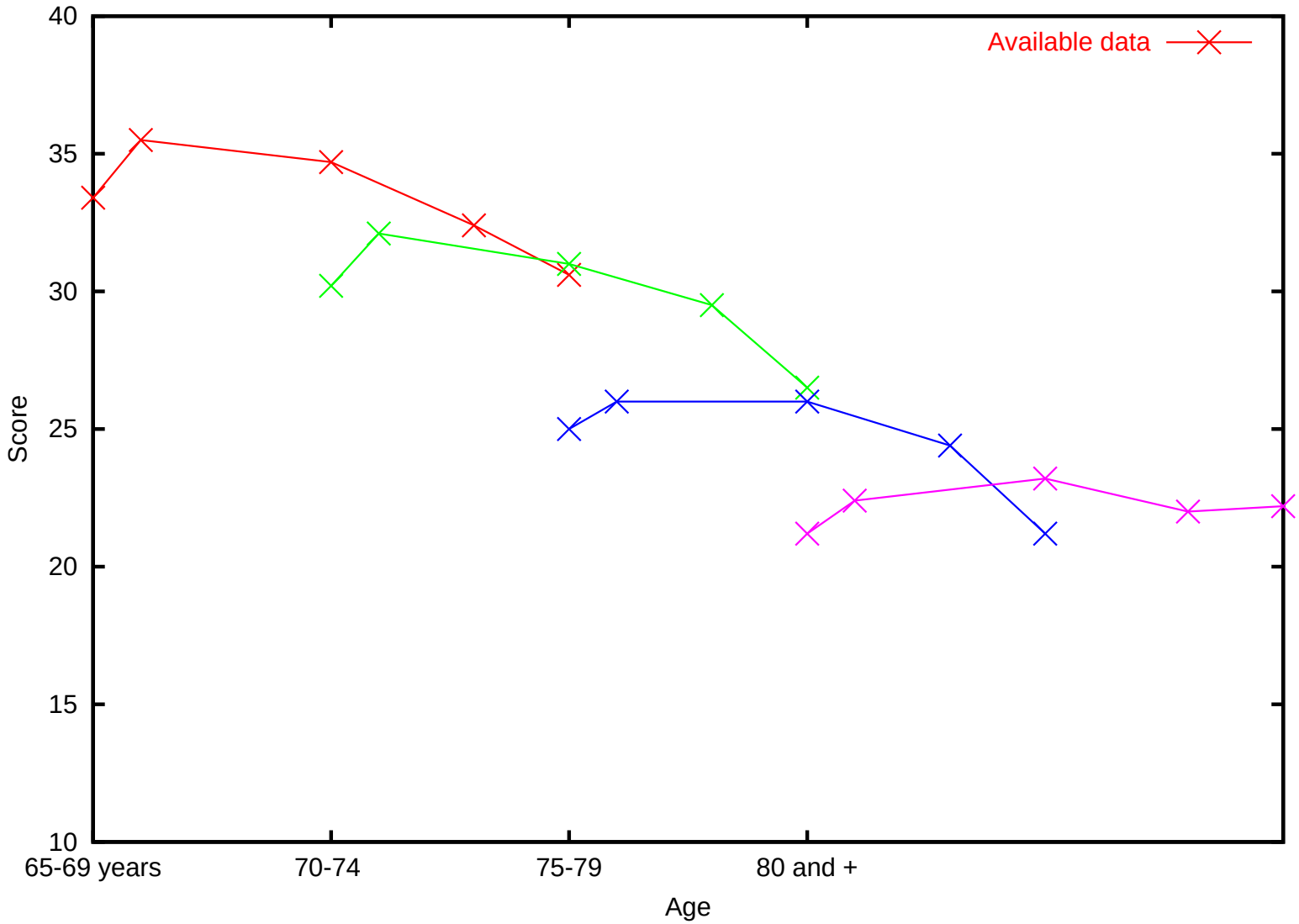
Description of dropout : Kaplan-Meyer

Dropout time (=event) : first visit with missing score

Probability to be in the cohort



Observed means of the DSST score given time



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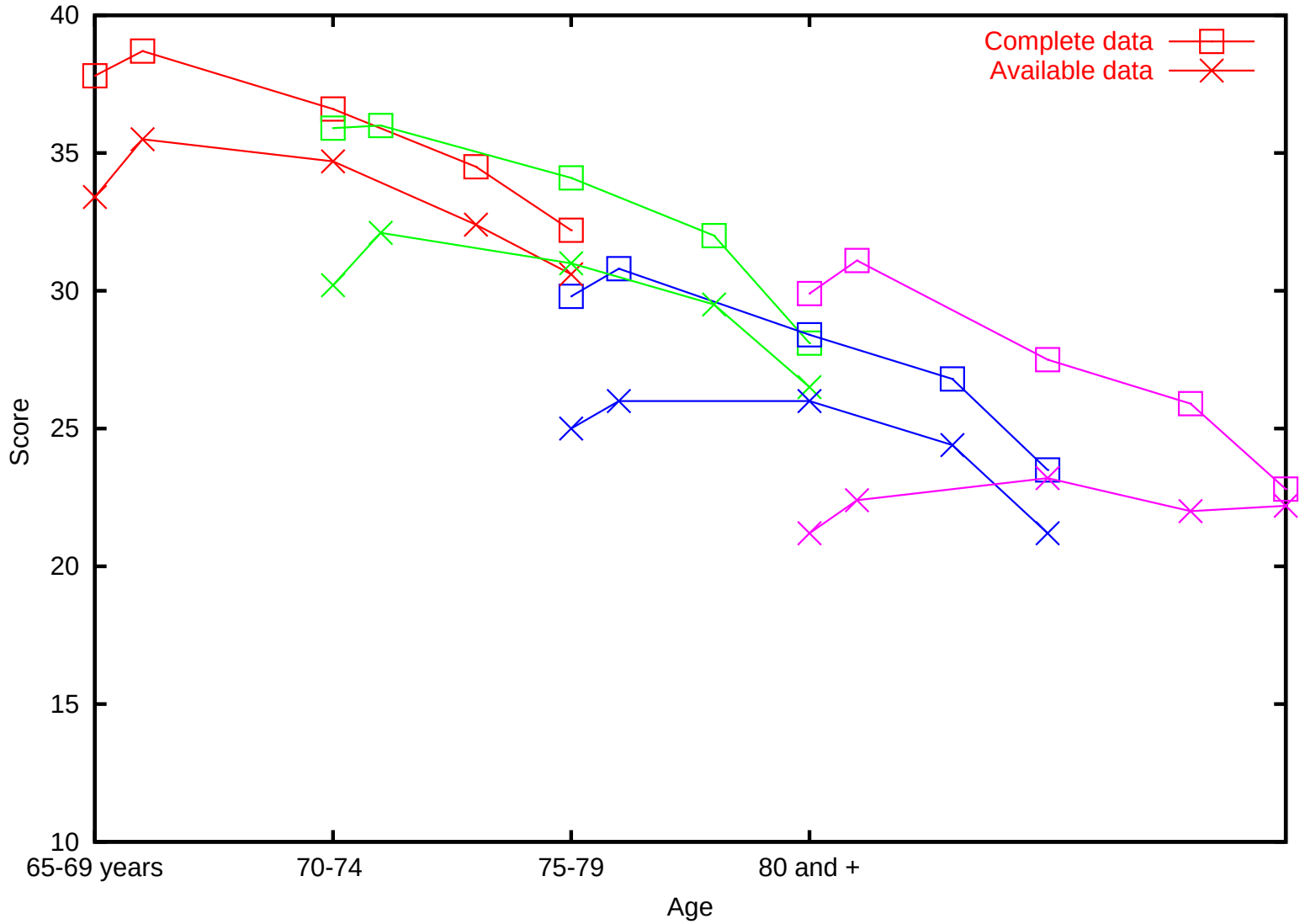


Logistic regression model for dropout in the first 5 years

Covariates	OR	95% CI of the OR
T3	0.02	0.003 - 0.10
T5	0.01	0.001 - 0.09
age	1.01	0.99 - 1.02
age $\times$ T3	1.05	1.03 - 1.08
age $\times$ T5	1.06	1.03 - 1.09
previous MMSE score	0.91	0.88 - 0.93
men	0.86	0.75 - 0.99
Education (vs university level)		
No education	1.88	1.15 - 3.07
no diploma	2.02	1.39 - 2.93
CEP	1.67	1.17 - 2.40
high school level	1.39	0.96 - 2.00

Methods for MCAR or MAR data

- Complete case analysis (loss of precision, require MCAR)
- Imputation (require MCAR or MAR)
- Maximum likelihood using available data (require MAR)

Maximum likelihood for MAR data (1)

Objective : Estimate θ from the distribution $f(Y|\theta)$
Likelihood of the observed data : Y_{obs}, R

$$f(Y_{obs}, R|\theta, \psi) = \int f(Y_{obs}, Y_{mis}|\theta) f(R|Y_{obs}, Y_{mis}, \psi) dY_{mis}$$

Maximum likelihood for MAR data (2)

If the data are MAR :

$$\begin{aligned} f(Y_{obs}, R|\theta, \psi) &= \int f(Y_{obs}, Y_{mis}|\theta) f(R|Y_{obs}, \psi) dY_{mis} \\ &= f(R|Y_{obs}, \psi) \int f(Y_{obs}, Y_{mis}|\theta) dY_{mis} \\ &= f(R|Y_{obs}, \psi) f(Y_{obs}|\theta) \end{aligned}$$

Log-likelihood :

$$l(\theta, \psi|Y_{obs}, R) = l(\theta|Y_{obs}) + l(\psi|R, Y_{obs})$$

If ψ and θ are distinct :
$\rightarrow$ the missing data are ignorable
$\rightarrow$ θ is estimated by maximisation of $l(\theta|Y_{obs})$ using only available reponses.

Example : MAR analysis of Paquid data

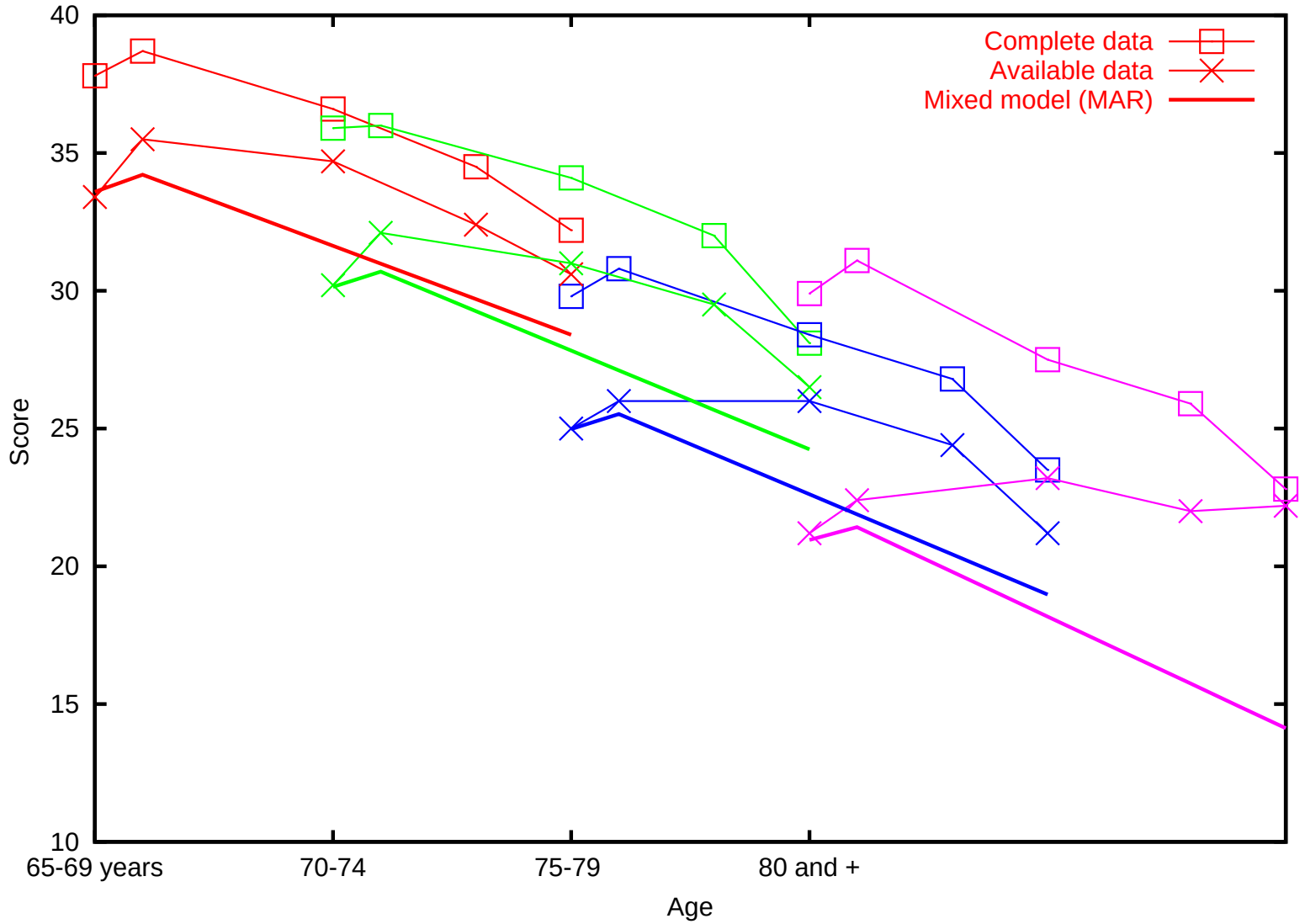
Mixed effect model

Y_{ij} test score for subject i at time t_{ij}

$$Y_{ij} = (\beta_0 + age_i'\gamma_0 + \alpha_{0i}) + (\beta_1 + age_i'\gamma_1 + \alpha_{1i}) \times t_{ij} + \beta_3 I_{\{t_{ij}=0\}} + e_{ij}$$

with
$\alpha_i = (\alpha_{0i}\alpha_{1i})^T \sim N(0, G)$, $e_{ij} \sim N\left(0, \sigma_e^2\right)$
age_i vector of indicators for baseline age classes (70-74, 75-79, 80 years and older , ref= 65-69)
$I_{\{t_{ij}=0\}}$ indicator of the baseline visit

Observed and predicted means of the score given time



Conclusion

Advantages of mixed models

- use all the available information (repeated measures)
- Flexibly handle intra-subject correlation (unbiased inference)
- Any number and times of measurements
- Robust to missing at random data
- Available in most softwares

Limits of mixed models

- Assume homogeneous population
  $\longrightarrow$ extended models included latent classes(mixture)
- As the MAR assumption is uncheckable, complete the study by a sensitivity analysis
  $\longrightarrow$ extended models for MNAR data

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