Introduction to the Joint Modeling of Longitudinal and Survival Data, with Applications in R

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Contents

What is this Course About

- Often in follow-up studies different types of outcomes are collected

- Explicit outcomes
  - ▷ multiple longitudinal responses (e.g., markers, blood values)
  - ▷ time-to-event(s) of particular interest (e.g., death, relapse)

- Implicit outcomes
  - ▷ missing data (e.g., dropout, intermittent missingness)
  - ▷ random visit times

What is this Course About (cont'd)

- Methods for the separate analysis of such outcomes are well established in the literature

- Survival data:
  - ▷ Cox model, accelerated failure time models, ...

- Longitudinal data
  - ▷ mixed effects models, GEE, marginal models, ...

What is this Course About (cont'd)

Purpose of this course is to present the state of the art in

Joint Modeling Techniques
for Longitudinal and Survival Data

Learning Objectives

- **Goals:** After this course participants will be able to
  - ▷ identify settings in which a joint modeling approach is required,
  - ▷ construct and fit an appropriate joint model, and
  - ▷ correctly interpret the obtained results

- The course will be explanatory rather than mathematically rigorous
  - ▷ emphasis is given on sufficient detail in order for participants to obtain a clear view on the different joint modeling approaches, and how they should be used in practice

Agenda

- **Part I:** Introduction
  - ▷ Data sets that we will use throughout the course
  - ▷ Categorization of possible research questions

- **Part II:** (brief) Review of Linear Mixed Models
  - ▷ Features of repeated measurements data
  - ▷ Linear mixed models
  - ▷ Missing data in longitudinal studies

Agenda (cont'd)

- **Part III:** (brief) Review of Relative Risk Models
  - ▷ Features of survival data
  - ▷ Relative risk models
  - ▷ Time-dependent covariates

- **Part IV:** The Basic Joint Model
  - ▷ Definition
  - ▷ Estimation & Inference
  - ▷ Connection with the missing data framework

Agenda (cont'd)

- **Part V:** Extensions of the Basic Joint Model
  - ▷ Parameterizations
  - ▷ Latent class joint models
  - ▷ Other extensions for the longitudinal and survival submodels (briefly)

- **Part VI:** Dynamic Predictions
  - ▷ Individualized predictions for the survival and longitudinal outcomes
  - ▷ Effect of the parameterization
  - ▷ Accuracy measures (if we have the time)

Structure of the Course & Material

- Lectures & short software practicals using R package **JM** and/or **JMbayes2**

- Material (also available in http://www.drizopoulos.com/):
  - ▷ Course Notes
  - ▷ R code in soft format

- Within the course notes there are several examples of R code which are denoted by the symbol 'R> '

References

- Joint modeling sources*
  - ▷ Rizopoulos, D. (2012). *Joint Models for Longitudinal and Time-to-Event Data, with Applications in R*. Boca Raton: Chapman & Hall/CRC.
  - ▷ Fitzmaurice, G., Davidian, M., Verbeke, G. and Molenberghs, G. (2009). *Longitudinal Data Analysis*. Handbooks of Modern Statistical Methods. Boca Raton: Chapman & Hall/CRC, Chapter 15.
  - ▷ Wu, L. (2009). *Mixed Effects Models for Complex Data*. Boca Raton: Chapman & Hall/CRC, Chapter 8.
  - ▷ Ibrahim, J., Chen, M.-H. and Sinha, D. (2001). *Bayesian Survival Analysis*. New York: Springer-Verlag, Chapter 7.

* extra references of papers using joint modeling available at pp. 225–232.

References (cont'd)

- Useful material for package **JM** can be found in the web sites:
  - ▷ http://jmr.r-forge.r-project.org [R code used in the book]
  - ▷ http://www.drizopoulos.com/ → Software [additional R script files]

- Useful material for package **JMbayes2**
  - ▷ a website with several examples: https://drizopoulos.github.io/JMbayes2/

- Blog about joint modeling http://iprogn.blogspot.nl/

References (cont'd)

- Other software packages capable of fitting joint models
  - ▷ in **R**: **joineR** (by Philipson et al.), **joineRML** (by Hickey et al.), **lcmm** (by Proust-Lima et al.)
  - ▷ in **SAS**: **%JM** macro (by Garcia-Hernandez and Rizopoulos – http://www.jm-macro.com/), **%JMFit** macro (by Zhang et al.)
  - ▷ in **STATA**: **stjm** and **merlin** (by Crowther)

References (cont'd)

- Standard texts in survival analysis
  - ▷ Kalbfleisch, J. and Prentice, R. (2002). *The Statistical Analysis of Failure Time Data, 2nd Ed.*. New York: Wiley.
  - ▷ Therneau, T. and Grambsch, P. (2000). *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag.
  - ▷ Cox, D. and Oakes, D. (1984). *Analysis of Survival Data*. London: Chapman & Hall.
  - ▷ Andersen, P., Borgan, O., Gill, R. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. New York: Springer-Verlag.
  - ▷ Klein, J. and Moeschberger, M. (2003). *Survival Analysis - Techniques for Censored and Truncated Data*. New York: Springer-Verlag.

References (cont'd)

- Standard texts in longitudinal data analysis
  - ▷ Verbeke, G. and Molenberghs, G. (2000). *Linear Mixed Models for Longitudinal Data*. New York: Springer-Verlag.
  - ▷ Molenberghs, G. and Verbeke, G. (2005). *Models for Discrete Longitudinal Data*. New York: Springer-Verlag.
  - ▷ Fitzmaurice, G., Laird, N., and Ware, J. (2004). *Applied Longitudinal Analysis*. Hoboken: Wiley.
  - ▷ Diggle, P., Heagerty, P., Liang, K.-Y., and Zeger, S. (2002). *Analysis of Longitudinal Data*, 2nd edition. New York: Oxford University Press.

Part I

Introduction

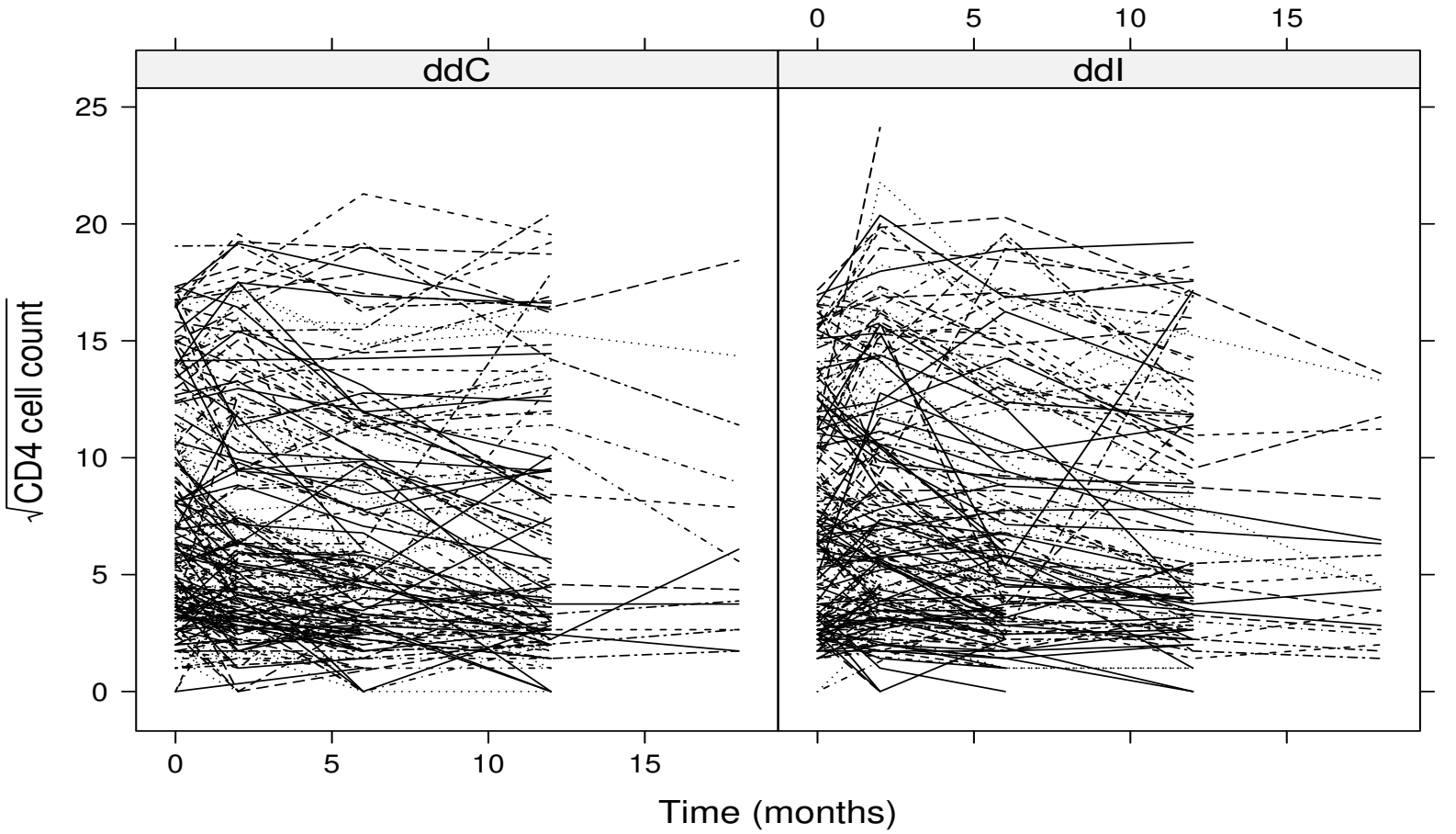
1.1 Motivating Longitudinal Studies

- AIDS: 467 HIV infected patients who had failed or were intolerant to zidovudine therapy (AZT) (Abrams et al., NEJM, 1994)

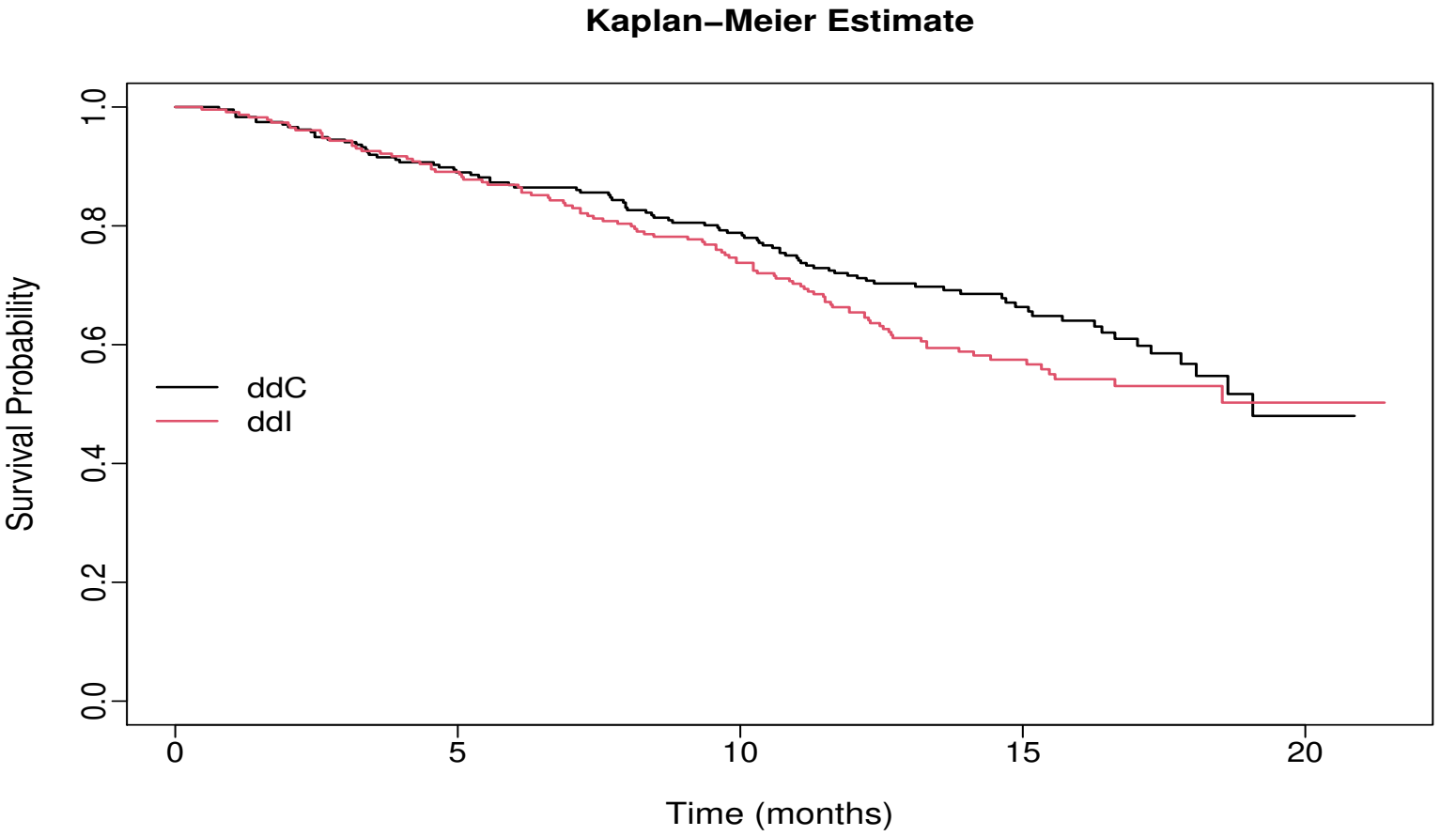
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)

- Outcomes of interest:
  - ▷ time to death
  - ▷ randomized treatment: 230 patients ddI and 237 ddC
  - ▷ CD4 cell count measurements at baseline, 2, 6, 12 and 18 months
  - ▷ prevOI: previous opportunistic infections

1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)

- Research Questions:
  - ▷ How strong is the association between CD4 cell count and the risk of death?
  - ▷ Is CD4 cell count a good biomarker?
    - * if treatment improves CD4 cell count, does it also improve survival?

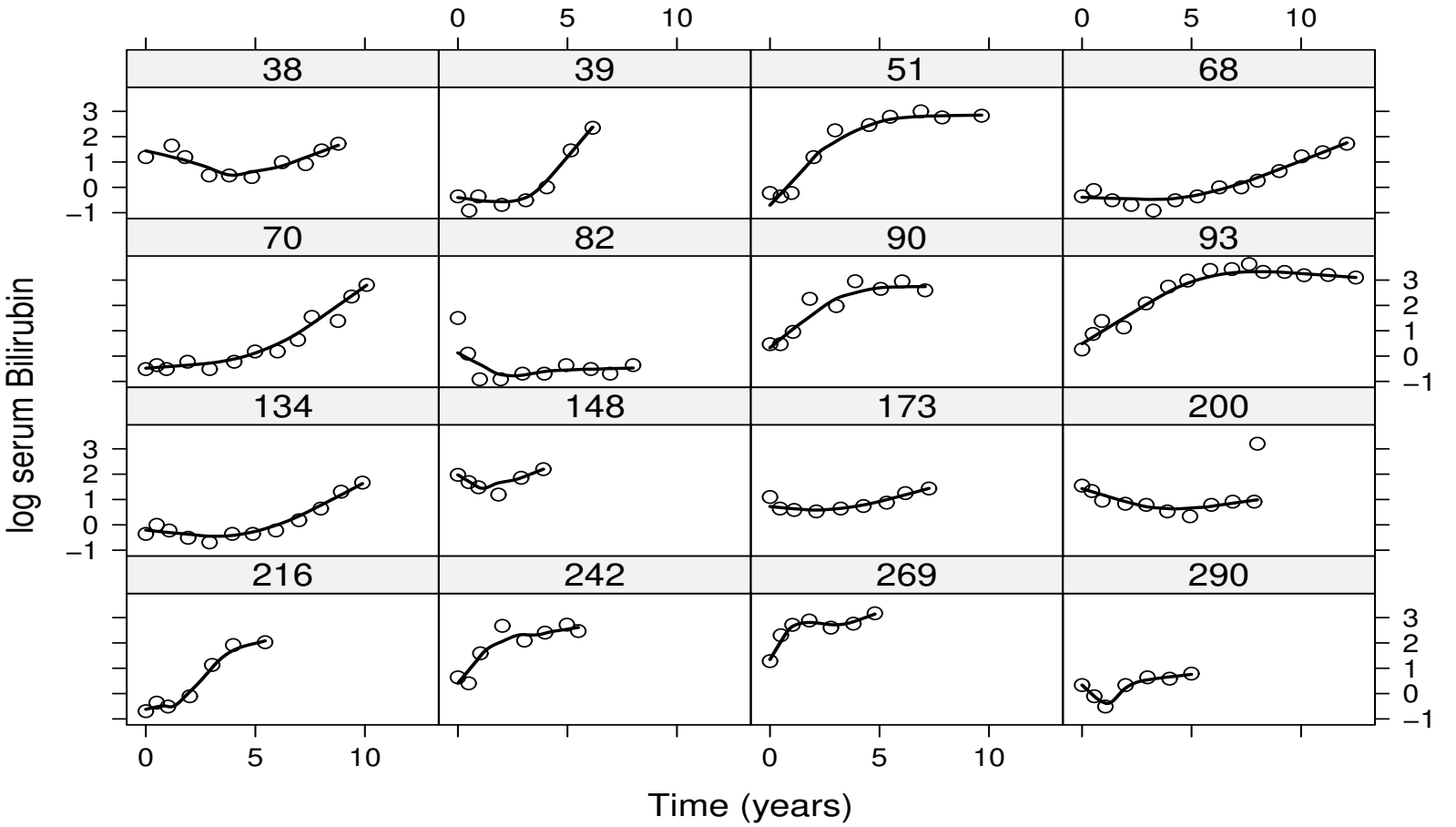
1.1 Motivating Longitudinal Studies (cont'd)

- PBC: Primary Biliary Cirrhosis:
  - ▷ a chronic, fatal but rare liver disease
  - ▷ characterized by inflammatory destruction of the small bile ducts within the liver

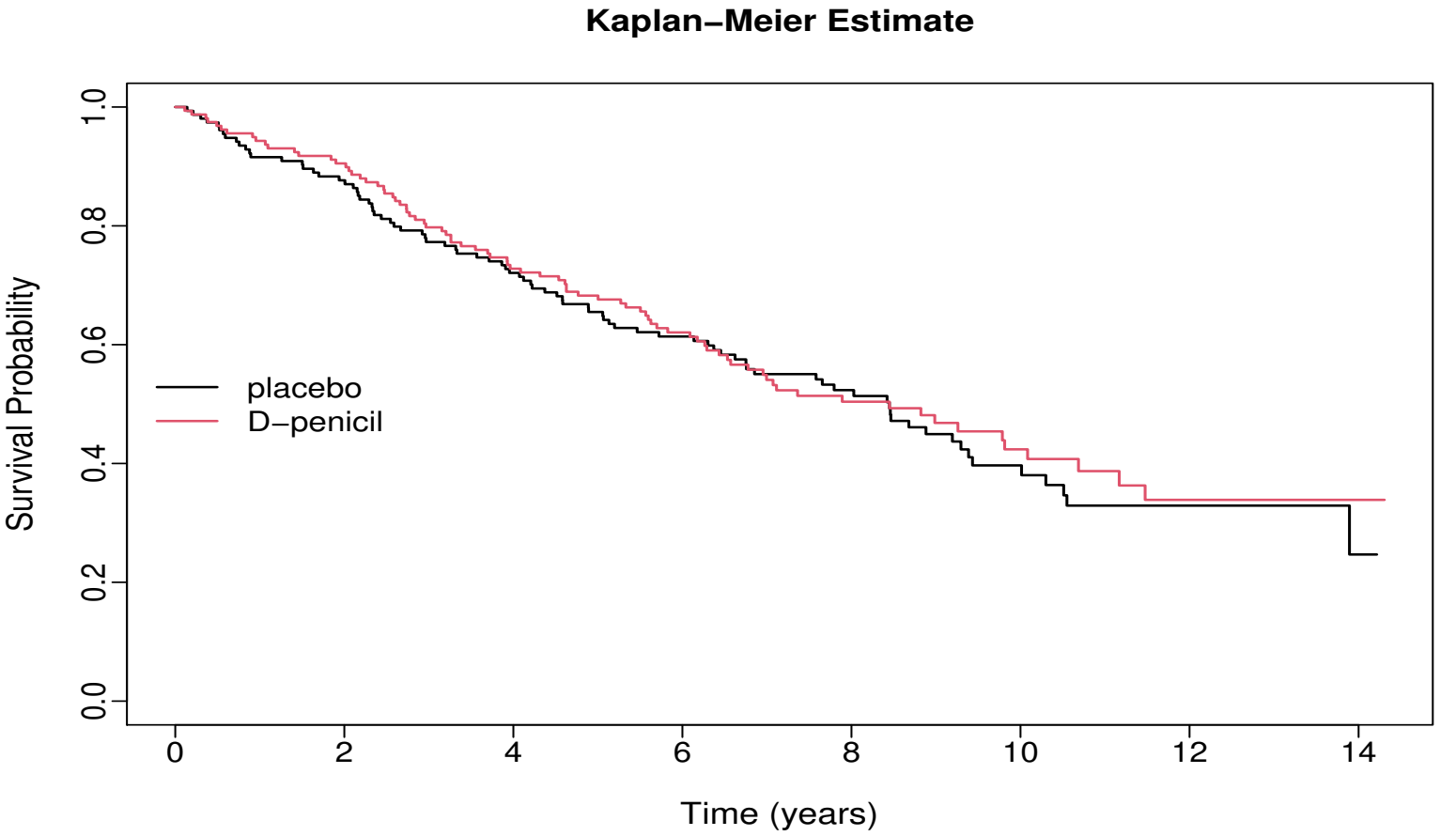
- Data collected by Mayo Clinic from 1974 to 1984 (Murtaugh et al., Hepatology, 1994)

- Outcomes of interest:
  - ▷ time to death and/or time to liver transplantation
  - ▷ randomized treatment: 158 patients received D-penicillamine and 154 placebo
  - ▷ longitudinal serum bilirubin levels

1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)

- Research Questions:
  - ▷ How strong is the association between bilirubin and the risk of death?
  - ▷ How the observed serum bilirubin levels could be utilized to provide predictions of survival probabilities?
  - ▷ Can bilirubin discriminate between patients of low and high risk?

1.2 Research Questions

- Depending on the questions of interest, different types of statistical analysis are required

- We will distinguish between two general types of analysis
  - ▷ separate analysis per outcome
  - ▷ joint analysis of outcomes

- Focus on each outcome separately
  - ▷ does treatment affect survival?
  - ▷ are the average longitudinal evolutions different between males and females?
  - ▷ ...

1.2 Research Questions (cont'd)

- Focus on multiple outcomes
  - ▷ Complex hypothesis testing: does treatment improve the average longitudinal profiles in all markers?
  - ▷ Complex effect estimation: how strong is the association between the longitudinal evolution of CD4 cell counts and the hazard of death?
  - ▷ Association structure among outcomes:
    * how the association between markers evolves over time (evolution of the association)
    * how marker-specific evolutions are related to each other (association of the evolutions)

1.2 Research Questions (cont'd)

- ▷ Prediction: can we improve prediction for the time to death by considering all markers simultaneously?

- ▷ Handling implicit outcomes: focus on a single longitudinal outcome but with dropout or random visit times

1.3 Recent Developments

- Up to now emphasis has been
  - ▷ *restricted* or *coerced* to separate analysis per outcome
  - ▷ or given to naive types of joint analysis (e.g., last observation carried forward)

- Main reasons
  - ▷ lack of appropriate statistical methodology
  - ▷ lack of efficient computational approaches & software

1.3 Recent Developments (cont'd)

- However, recently there has been an explosion in the statistics and biostatistics literature of joint modeling approaches

- Many different approaches have been proposed that
  - ▷ can handle different types of outcomes
  - ▷ can be utilized in pragmatic computing time
  - ▷ can be rather flexible
  - ▷ **most importantly:** can answer the questions of interest

1.4 Joint Models

- Let Y_1 and Y_2 two outcomes of interest measured on a number of subjects for which joint modeling is of scientific interest
  - ▷ both can be measured longitudinally
  - ▷ one longitudinal and one survival

- We have various possible approaches to construct a joint density $p(y_1, y_2)$ of $\{Y_1, Y_2\}$
  - ▷ Conditional models: $p(y_1, y_2) = p(y_1)p(y_2 \mid y_1)$
  - ▷ Copulas: $p(y_1, y_2) = c\{\mathcal{F}(y_1), \mathcal{F}(y_2)\}p(y_1)p(y_2)$

But **Random Effects Models** have (more or less) prevailed

1.4 Joint Models (cont'd)

- Random Effects Models specify

$$p(y_1, y_2) = \int p(y_1, y_2 \mid b)\, p(b)\, db$$
$$= \int p(y_1 \mid b)\, p(y_2 \mid b)\, p(b)\, db$$

  ▷ Unobserved random effects b explain the association between Y_1 and Y_2

  ▷ Conditional Independence assumption

$$Y_1 \perp\!\!\!\perp Y_2 \mid b$$

1.4 Joint Models (cont'd)

- Features:
  - ▷ Y_1 and Y_2 can be of different type
    - * one continuous and one categorical
    - * one continuous and one survival
    - * ...
  - ▷ Extensions to more than two outcomes straightforward
  - ▷ Specific association structure between Y_1 and Y_2 is assumed
  - ▷ Computationally intensive (especially in high dimensions)

Part II

Linear Mixed-Effects Models

2.1 Features of Longitudinal Data

- Repeated evaluations of the same outcome in each subject over time
  - ▷ CD4 cell count in HIV-infected patients
  - ▷ serum bilirubin in PBC patients

- Longitudinal studies allow to investigate
  1. how treatment means differ at specific time points, e.g., at the end of the study (*cross-sectional effect*)
  2. how treatment means or differences between means of treatments change over time (*longitudinal effect*)

2.1 Features of Longitudinal Data (cont'd)

Measurements on the same subject are expected to be (positively) correlated

- This implies that standard statistical tools, such as the t-test and simple linear regression that assume independent observations, are not optimal for longitudinal data analysis.

2.2 The Linear Mixed Model

- The direct approach to model correlated data $\Rightarrow$ *multivariate regression*

$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i),$$

where

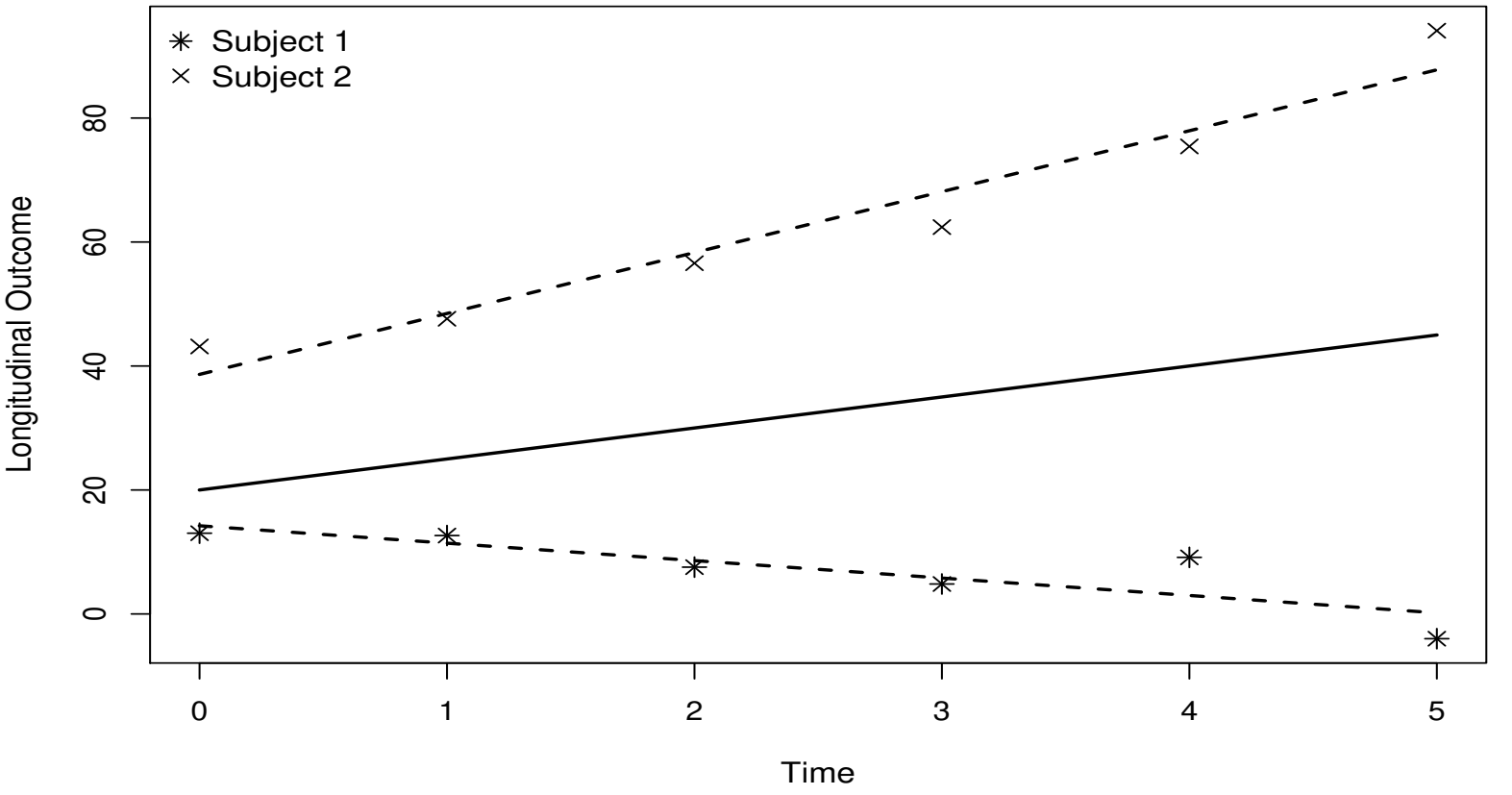
  - $\triangleright$ y_i the vector of responses for the ith subject
  - $\triangleright$ X_i design matrix describing structural component
  - $\triangleright$ V_i covariance matrix describing the correlation structure

- There are several options for modeling V_i, e.g., compound symmetry, autoregressive process, exponential spatial correlation, Gaussian spatial correlation, ...

2.2 The Linear Mixed Model (cont'd)

- **Alternative intuitive approach:** Each subject in the population has her own subject-specific mean response profile over time

2.2 The Linear Mixed Model (cont'd)



2.2 The Linear Mixed Model (cont'd)

- The evolution of each subject over time can be described by a linear model

$$y_{ij} = \tilde{\beta}_{i0} + \tilde{\beta}_{i1} t_{ij} + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2),$$

  where

  - ▷ y_{ij} the jth response of the ith subject
  - ▷ $\tilde{\beta}_{i0}$ is the intercept and $\tilde{\beta}_{i1}$ the slope for subject i

- **Assumption:** Subjects are randomly sampled from a population $\Rightarrow$ subject-specific regression coefficients are also sampled from a population of regression coefficients

$$\tilde{\beta}_i \sim \mathcal{N}(\beta, D)$$

2.2 The Linear Mixed Model (cont'd)

- We can reformulate the model as

$$y_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t_{ij} + \varepsilon_{ij},$$

  where

  - ▷ βs are known as the *fixed effects*
  - ▷ b_is are known as the *random effects*

- In accordance for the random effects we assume

$$b_i = \begin{bmatrix} b_{i0} \\ b_{i1} \end{bmatrix} \sim \mathcal{N}(0, D)$$

2.2 The Linear Mixed Model (cont'd)

- Put in a general form

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}), \end{cases}$$

with

- ▷ X design matrix for the fixed effects β
- ▷ Z design matrix for the random effects b_i
- ▷ $b_i \perp\!\!\!\perp \varepsilon_i$

2.2 The Linear Mixed Model (cont'd)

- Interpretation:
  - ▷ β_j denotes the change in the average y_i when x_j is increased by one unit
  - ▷ b_i are interpreted in terms of how a subset of the regression parameters for the ith subject deviates from those in the population

- Advantageous feature: population + subject-specific predictions
  - ▷ β describes mean response changes in the population
  - ▷ $\beta + b_i$ describes individual response trajectories

2.2 The Linear Mixed Model (cont'd)

- How do the random effects capture correlation:
  - ▷ Given the random effects, the measurements of each subject are independent (*conditional independence assumption*)

$$p(y_i \mid b_i) = \prod_{j=1}^{n_i} p(y_{ij} \mid b_i)$$

  - ▷ Marginally (integrating out the random effects), the measurements of each subject are correlated

$$p(y_i) = \int p(y_i \mid b_i)\, p(b_i)\, db_i \quad \Rightarrow \quad y_i \sim \mathcal{N}(X_i\beta,\ Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i})$$

2.2 The Linear Mixed Model (cont'd)

- Estimation
  - ▷ Fixed effects: For known marginal covariance matrix $V_i = Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$, the fixed effects are estimated using generalized least squares

$$\hat{\beta} = \left(\sum_{i=1}^{n} X_i^\top V_i^{-1} X_i \right)^{-1} \sum_{i=1}^{n} X_i^\top V_i^{-1} y_i$$

  - ▷ Variance Components: The unique parameters in V_i are estimated based on either maximum likelihood (ML) or restricted maximum likelihood (REML)
    - * REML provides unbiased estimates for the variance components in small samples

2.2 The Linear Mixed Model (cont'd)

- Example: We fit a linear mixed model for the AIDS dataset assuming
  - ▷ different average longitudinal evolutions per treatment group (fixed part)
  - ▷ random intercepts & random slopes (random part)

$$\begin{cases} y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 \{\texttt{ddI}_i \times t_{ij}\} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

- Note: We did not include a main effect for treatment due to randomization

2.2 The Linear Mixed Model (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	7.189	0.222	32.359	< 0.001
β_1	-0.163	0.021	-7.855	< 0.001
β_2	0.028	0.030	0.952	0.342

- No evidence of differences in the average longitudinal evolutions between the two treatments

2.3 Mixed Models with Correlated Errors

- We have seen two classes of models for longitudinal data, namely
  - ▷ *Marginal Models*

$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i), \quad \text{and}$$

  - ▷ *Conditional Models*

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}) \end{cases}$$

2.3 Mixed Models with Correlated Errors (cont'd)

- It is also possible to combine the two approaches and obtain a linear mixed model with correlated error terms

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \Sigma_i), \end{cases}$$

  where, as in marginal models, we can consider different forms for Σ_i

- The corresponding marginal model is of the form

$$y_i \sim \mathcal{N}(X_i\beta,\ Z_i D Z_i^\top + \Sigma_i)$$

2.3 Mixed Models with Correlated Errors (cont'd)

- Features
  - ▷ both b_i and Σ_i try to capture the correlation in the observed responses y_i
  - ▷ this model does not assume conditional independence

- Choice between the two approaches is to a large extent philosophical
  - ▷ *Random Effects*: trajectory of a subject dictated by time-independent random effects $\Rightarrow$ the shape of the trajectory is an inherent characteristic of this subject
  - ▷ *Serial Correlation*: attempts to more precisely capture features of the trajectory by allowing subject-specific trends to vary over time

2.3 Mixed Models with Correlated Errors (cont'd)

- It is evident that there is a contest for information between the two approaches
  - ▷ often in practice it is not possible to include both many random effects and a serial correlation term because of numerical problems

We will follow here the Random Effects paradigm

- For two reasons
  1. We can capture more complex correlation by considering more elaborate random effects structures
  2. It makes more sense for the joint models we will consider

2.4 Mixed-Effects Models in R

R> There are two primary packages in R for mixed models analysis:

- Package **nlme**
  - fits linear & nonlinear mixed effects models, and marginal models for normal data
  - allows for both random effects & correlated error terms
  - several options for covariances matrices and variance functions

- Package **lme4**
  - fits linear, nonlinear & generalized mixed effects models
  - uses only random effects
  - allows for nested and crossed random-effects designs

2.4 Mixed-Effects Models in R (cont'd)

R> We will only use package **nlme** because package **JM** accepts as an argument a linear mixed model fitted by **nlme**

R> The basic function to fit linear mixed models is `lme()` and has three basic arguments

- ▷ `fixed`: a formula specifying the response vector and the fixed-effects structure
- ▷ `random`: a formula specifying the random-effects structure
- ▷ `data`: a data frame containing all the variables

2.4 Mixed-Effects Models in R (cont'd)

R> The data frame that contains all variables should be in the *long format*

Subject	y	time	gender	age
1	5.1	0.0	male	45
1	6.3	1.1	male	45
2	5.9	0.1	female	38
2	6.9	0.9	female	38
2	7.1	1.2	female	38
2	7.3	1.5	female	38
⋮	⋮	⋮	⋮	⋮

2.4 Mixed-Effects Models in R (cont'd)

R> Using formulas in R

- ▷ CD4 = Time + Gender
  ⇒ `cd4 ~ time + gender`

- ▷ CD4 = Time + Gender + Time*Gender
  ⇒ `cd4 ~ time + gender + time:gender`
  ⇒ `cd4 ~ time*gender` (the same)

- ▷ CD4 = Time + Time^2
  ⇒ `cd4 ~ time + I(time^2)`

R> Note: the intercept term is included by default

2.4 Mixed-Effects Models in R (cont'd)

R> The code used to fit the linear mixed model for the AIDS dataset (p. 30) is as follows

```
lmeFit <- lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = ~ obstime | patient)

summary(lmeFit)
```

2.4 Mixed-Effects Models in R (cont'd)

R> The same fixed-effects structure but only random intercepts

```
lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = ~ 1 | patient)
```

R> The same fixed-effects structure, random intercepts & random slopes, with a diagonal covariance matrix (using the `pdDiag()` function)

```
lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = list(patient = pdDiag(form = ~ obstime)))
```

2.5 Missing Data in Longitudinal Studies

- A major challenge for the analysis of longitudinal data is the problem of missing data
  - ▷ studies are designed to collect data on every subject at a set of prespecified follow-up times
  - ▷ often subjects miss some of their planned measurements for a variety of reasons
- We can have different patterns of missing data

2.5 Missing Data in Longitudinal Studies (cont'd)

Subject	Visits				
	1	2	3	4	5
1	x	x	x	x	x
2	x	x	x	?	?
3	?	x	x	x	x
4	?	x	?	x	?

- ▷ Subject 1: Completer
- ▷ Subject 2: dropout
- ▷ Subject 3: late entry
- ▷ Subject 4: intermittent

2.5 Missing Data in Longitudinal Studies (cont'd)

- Implications of missingness:
  - ▷ we collect less data than originally planned ⇒ *loss of efficiency*
  - ▷ not all subjects have the same number of measurements ⇒ *unbalanced datasets*
  - ▷ missingness may depend on outcome ⇒ *potential bias*

- For the handling of missing data, we introduce the missing data indicator

$$r_{ij} = \begin{cases} 1 & \text{if } y_{ij} \text{ is observed} \\ 0 & \text{otherwise} \end{cases}$$

2.5 Missing Data in Longitudinal Studies (cont'd)

- We obtain a partition of the complete response vector y_i
  - ▷ observed data y_i^o, containing those y_{ij} for which $r_{ij} = 1$
  - ▷ missing data y_i^m, containing those y_{ij} for which $r_{ij} = 0$

- **For the remaining we will focus on dropout** $\Rightarrow$ notation can be simplified
  - ▷ Discrete dropout time: $r_i^d = 1 + \sum_{j=1}^{n_i} r_{ij}$ (ordinal variable)
  - ▷ **Continuous time**: T_i^* denotes the time to dropout

2.6 Missing Data Mechanisms

- To describe the probabilistic relation between the measurement and missingness processes Rubin (1976, Biometrika) has introduced three mechanisms

- *Missing Completely At Random (MCAR)*: The probability that responses are missing is unrelated to both y_i^o and y_i^m

$$p(r_i \mid y_i^o, y_i^m) = p(r_i)$$

- Examples
  - ▷ subjects go out of the study after providing a pre-determined number of measurements
  - ▷ laboratory measurements are lost due to equipment malfunction

2.6 Missing Data Mechanisms (cont'd)

- Features of MCAR:
  - ▷ The observed data y_i^o can be considered a random sample of the complete data y_i
  - ▷ We can use any statistical procedure that is valid for complete data
    - * sample averages per time point
    - * linear regression, ignoring the correlation (consistent, but not efficient)
    - * t-test at the last time point
    - * ...

2.6 Missing Data Mechanisms (cont'd)

- *Missing At Random (MAR)*: The probability that responses are missing is related to y_i^o, but is unrelated to y_i^m

$$p(r_i \mid y_i^o, y_i^m) = p(r_i \mid y_i^o)$$

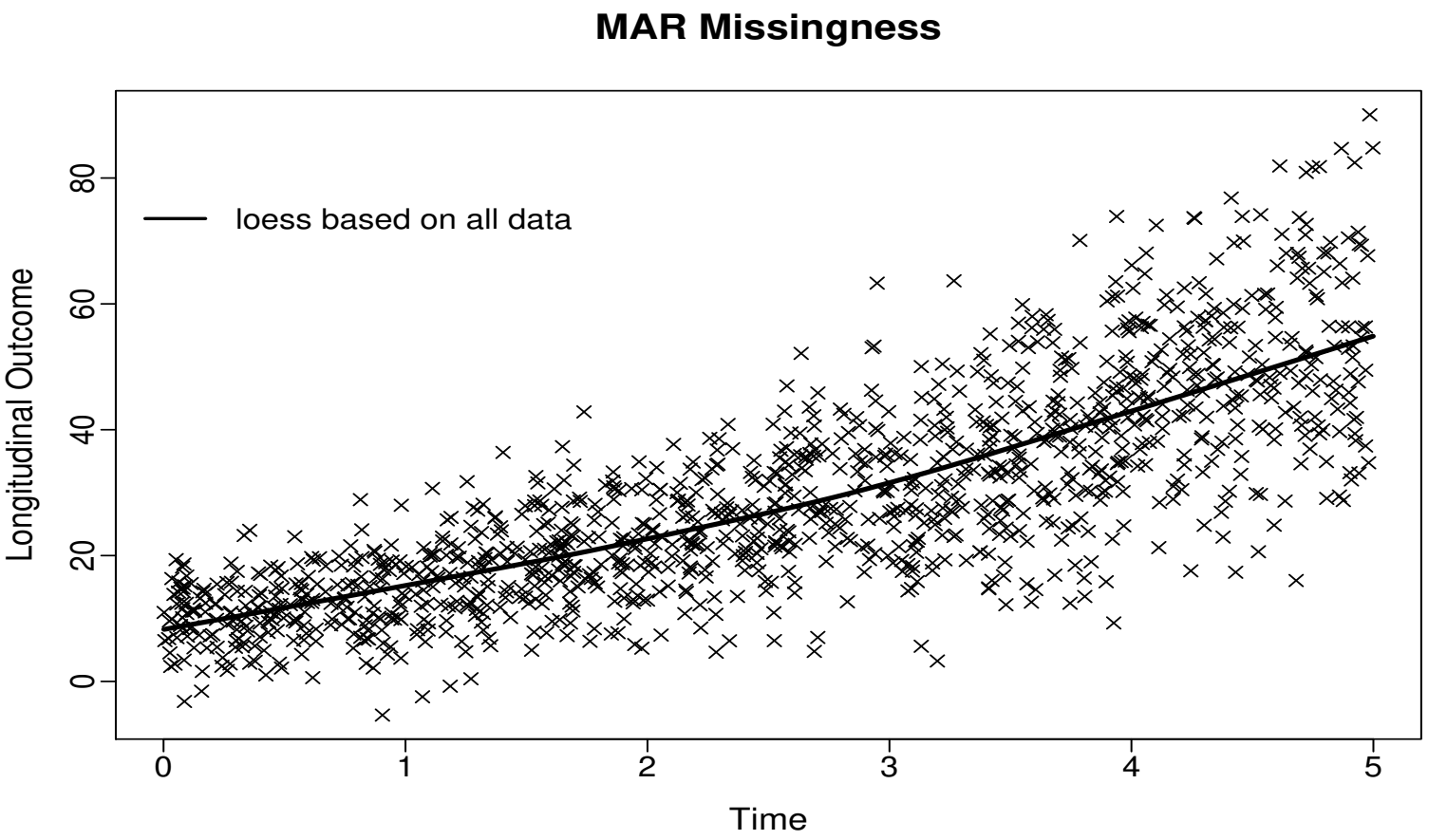
- Examples
  - ▷ study protocol requires patients whose response value exceeds a threshold to be removed from the study
  - ▷ physicians give rescue medication to patients who do not respond to treatment

2.6 Missing Data Mechanisms (cont'd)

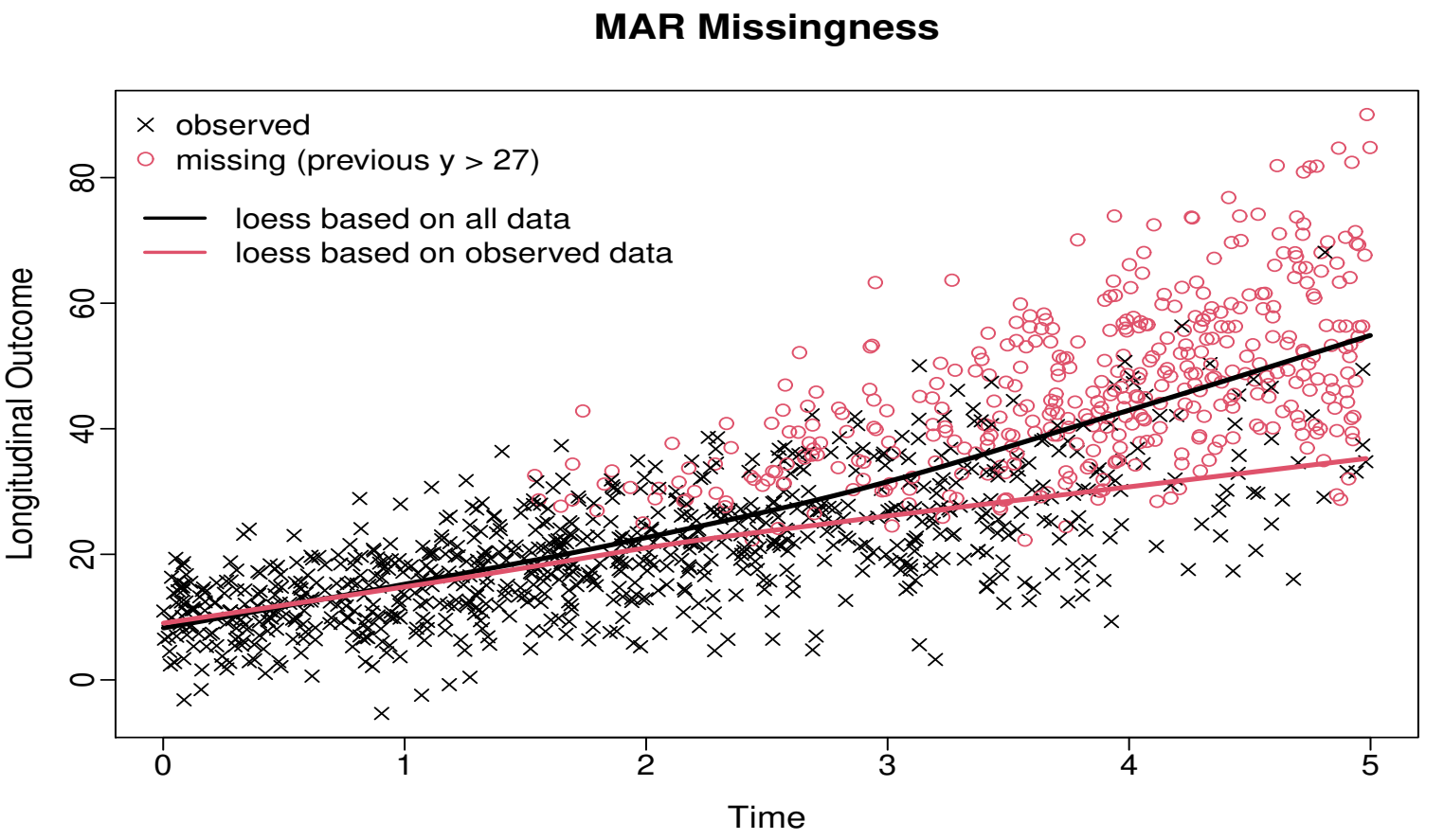
- Features of MAR:
  - ▷ The observed data cannot be considered a random sample from the target population
  - ▷ Not all statistical procedures provide valid results

Not valid under MAR	Valid under MAR
sample marginal evolutions	sample subject-specific evolutions
methods based on moments, such as GEE	likelihood based inference
mixed models with misspecified correlation structure	mixed models with correctly specified correlation structure
marginal residuals	subject-specific residuals

2.6 Missing Data Mechanisms (cont'd)



2.6 Missing Data Mechanisms (cont'd)



2.6 Missing Data Mechanisms (cont'd)

- *Missing Not At Random (MNAR)*: The probability that responses are missing is related to y_i^m, and possibly also to y_i^o

$$p(r_i \mid y_i^m) \quad \text{or} \quad p(r_i \mid y_i^o, y_i^m)$$

- Examples
  - ▷ in studies on drug addicts, people who return to drugs are less likely than others to report their status
  - ▷ in longitudinal studies for quality-of-life, patients may fail to complete the questionnaire at occasions when their quality-of-life is compromised

2.6 Missing Data Mechanisms (cont'd)

- Features of MNAR
  - ▷ The observed data cannot be considered a random sample from the target population
  - ▷ Only procedures that explicitly model the joint distribution $\{y_i^o, y_i^m, r_i\}$ provide valid inferences $\Rightarrow$ **analyses which are valid under MAR will not be valid under MNAR**

2.6 Missing Data Mechanisms (cont'd)

We cannot tell from the data at hand whether the missing data mechanism is MAR or MNAR

Note: We can distinguish between MCAR and MAR

Part III

Relative Risk Models

3.1 Features of Survival Data

- The most important characteristic that distinguishes the analysis of time-to-event outcomes from other areas in statistics is **Censoring**
  - ▷ the event time of interest is not fully observed for all subjects under study

- Implications of censoring:
  - ▷ standard tools, such as the sample average, the t-test, and linear regression **cannot** be used
  - ▷ inferences may be sensitive to misspecification of the distribution of the event times

3.1 Features of Survival Data (cont'd)

- Several types of censoring:
  - ▷ Location of the true event time wrt the censoring time: *right*, *left* & *interval*
  - ▷ Probabilistic relation between the true event time & the censoring time: *informative* & *non-informative* (similar to MNAR and MAR)

Here we focus on non-informative right censoring

- Note: Survival times may often be truncated; analysis of truncated samples requires similar calculations as censoring

3.1 Features of Survival Data (cont'd)

- Notation (i denotes the subject)
  - ▷ T_i^* 'true' time-to-event
  - ▷ C_i the censoring time (e.g., the end of the study or a random censoring time)

- Available data for each subject
  - ▷ observed event time: $T_i = \min(T_i^*, C_i)$
  - ▷ event indicator: $\delta_i = 1$ if event; $\delta_i = 0$ if censored

Our aim is to make valid inferences for T_i^* but using only $\{T_i, \delta_i\}$

3.2 Basic functions in Survival Analysis

- *Hazard function:* The instantaneous risk of an event at time t, given that the event has not occurred until t

$$h(t) = \lim_{dt \to 0} \frac{\Pr(t \leq T^* < t + dt \mid T^* \geq t)}{dt}, \quad t > 0$$

  - ▷ it is **not** a probability, i.e., $h(t) \in (0, \infty)$
  - ▷ can be interpreted as the expected number of events per individual per unit of time

3.2 Basic functions in Survival Analysis (cont'd)

- *Survival function:* The probability of being alive up to time t

$$S(t) \;=\; \Pr(T^* > t)$$

  - ▷ decreasing function of time
  - ▷ connected to the hazard via

$$S(t) \;=\; \exp\left\{ -\int_0^t h(s)\, ds \right\}$$

$\mathcal{H}(t) = \int_0^t h(s)ds$ is known as the *cumulative hazard function*

3.2 Basic functions in Survival Analysis (cont'd)

- Consistent estimates for the survival and cumulative hazard functions that account for censoring are provided by the
  - ▷ Kaplan-Meier estimator

$$\widehat{S}_{KM}(t) = \prod_{i:t_i \leq t} \frac{r_i - d_i}{r_i}$$

  - ▷ Nelson-Aalen estimator

$$\widehat{\mathcal{H}}_{NA}(t) = \sum_{i:t_i \leq t} \frac{d_i}{r_i},$$

with r_i # subjects still at risk at t_i, and d_i # events at t_i

3.3 Relative Risk Models

- **Relative Risk Models** assume a multiplicative effect of covariates on the hazard scale, i.e.,

$$h_i(t) = h_0(t) \exp(\gamma_1 w_{i1} + \gamma_2 w_{i2} + \ldots + \gamma_p w_{ip}) \Rightarrow$$

$$\log h_i(t) = \log h_0(t) + \gamma_1 w_{i1} + \gamma_2 w_{i2} + \ldots + \gamma_p w_{ip},$$

where

  - $h_i(t)$ denotes the hazard of an event for patient i at time t
  - $h_0(t)$ denotes the baseline hazard
  - $w_{i1}, \ldots, w_{ip}$ a set of covariates

3.3 Relative Risk Models (cont'd)

- The baseline hazard $h_0(t)$ represents the hazard of an event when all the covariates or all the γs are 0

- That is, $h_0(t)$ represents the instantaneous risk of experiencing the event at time t, without the influence of any covariate

- Therefore,
  - ▷ if a covariate has a beneficial effect, decreases $h_0(t) \rightarrow \boxed{\boldsymbol{\gamma < 0}}$
  - ▷ if it has a harmful effect, increases $h_0(t) \rightarrow \boxed{\boldsymbol{\gamma > 0}}$

3.3 Relative Risk Models (cont'd)

- Standard MLE can be applied based on the log-likelihood function

$$\ell(\theta) = \sum_{i=1}^{n} \delta_i \log p(T_i;\theta) + (1-\delta_i) \log S_i(T_i;\theta),$$

which also can be re-expressed in terms of the hazard function

$$\ell(\theta) = \sum_{i=1}^{n} \delta_i \log h_i(T_i;\theta) - \int_0^{T_i} h_i(s;\theta)\, ds$$

Sensitivity to distributional assumptions due to censoring

3.3 Relative Risk Models (cont'd)

- **Cox Model:** We make no assumptions for the baseline hazard function

- Parameter estimates and standard errors are based on the log partial likelihood function

$$p\ell(\gamma) = \sum_{i=1}^{n} \delta_i \Big[\gamma^\top w_i - \log\Big\{ \sum_{j:T_j \geq T_i} \exp(\gamma^\top w_j) \Big\} \Big],$$

  where only patients who had an event contribute

3.3 Relative Risk Models (cont'd)

- Example: For the PBC dataset were interested in the treatment effect while correcting for sex and age effects

$$h_i(t) = h_0(t) \exp(\gamma_1 \texttt{D-penic}_i + \gamma_2 \texttt{Female}_i + \gamma_3 \texttt{Age}_i)$$

	Value	HR	Std.Err.	z-value	p-value
γ_1	-0.138	0.871	0.156	-0.882	0.378
γ_2	-0.493	0.611	0.207	-2.379	0.017
γ_3	0.021	1.022	0.008	2.784	0.005

3.4 Relative Risk Models in R

R> The primary package in R for the analysis of survival data is the **survival** package

R> A key function in this package that is used to specify the available event time information in a sample at hand is `Surv()`

R> For right censored failure times (i.e., what we will see in this course) we need to provide the observed event times `time`, and the event indicator `status`, which equals 1 for true failure times and 0 for right censored times

```
Surv(time, status)
```

3.4 Relative Risk Models in R (cont'd)

R> Cox models are fitted using function `coxph()`. For instance, for the PBC data the following code fits the Cox model that contains the main effects of 'drug', 'sex' and 'age':

```
coxFit <- coxph(Surv(years, status2) ~ drug + sex + age,
    data = pbc2.id)

summary(coxFit)
```

R> The two main arguments are a formula specifying the design matrix of the model and a data frame containing all the variables

3.5 Time Dependent Covariates

- Often interest in the association between a time-dependent covariate and the risk of an event
  - ▷ treatment changes with time (e.g., dose)
  - ▷ time-dependent exposure (e.g., smoking, diet)
  - ▷ markers of disease or patient condition (e.g., blood pressure, PSA levels)
  - ▷ ...

- Example: In the PBC study, are the longitudinal bilirubin measurements associated with the hazard of death?

3.5 Time Dependent Covariates (cont'd)

- To answer our questions of interest we need to postulate a model that relates
  - ▷ the serum bilirubin with
  - ▷ the time-to-death

- The association between **baseline** marker levels and the risk of death can be estimated with standard statistical tools (e.g., Cox regression)

- When we move to the time-dependent setting, a more **careful consideration** is required

3.5 Time Dependent Covariates (cont'd)

- There are two types of time-dependent covariates
  (Kalbfleisch and Prentice, 2002, Section 6.3)
  - ▷ Exogenous (aka external): the future path of the covariate up to any time $t > s$ is not affected by the occurrence of an event at time point s, i.e.,

$$\Pr\{\mathcal{Y}_i(t) \mid \mathcal{Y}_i(s), T_i^* \geq s\} = \Pr\{\mathcal{Y}_i(t) \mid \mathcal{Y}_i(s), T_i^* = s\},$$

    where $0 < s \leq t$ and $\mathcal{Y}_i(t) = \{y_i(s), 0 \leq s < t\}$

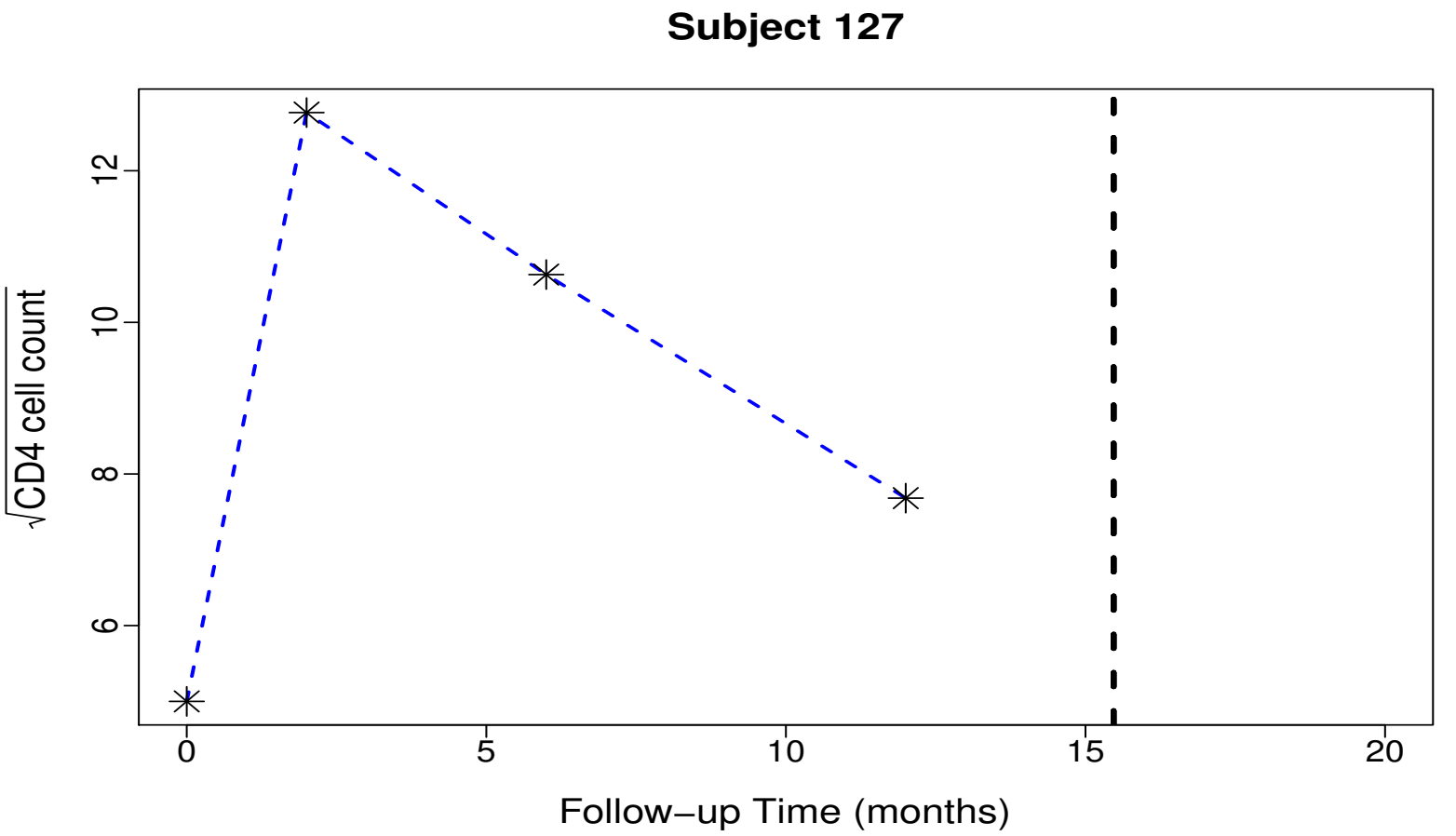
  - ▷ Endogenous (aka internal): not Exogenous

3.5 Time Dependent Covariates (cont'd)

- It is **very important** to distinguish between these two types of time-dependent covariates, because the type of covariate dictates the appropriate type of analysis

- In our motivating examples all time-varying covariates are **Biomarkers** $\Rightarrow$ These are always **endogenous** covariates
  - ▷ measured with error (i.e., biological variation)
  - ▷ the complete history is not available
  - ▷ existence directly related to failure status

3.5 Time Dependent Covariates (cont'd)



3.6 Extended Cox Model

- The Cox model presented earlier can be extended to handle time-dependent covariates using the counting process formulation

$$h_i(t \mid \mathcal{Y}_i(t), w_i) = h_0(t) R_i(t) \exp\{\gamma^\top w_i + \alpha y_i(t)\},$$

where

  - ▷ $N_i(t)$ is a counting process which counts the number of events for subject i by time t,
  - ▷ $h_i(t)$ denotes the intensity process for $N_i(t)$,
  - ▷ $R_i(t)$ denotes the at risk process ('1' if subject i still at risk at t), and
  - ▷ $y_i(t)$ denotes the value of the time-varying covariate at t

3.6 Extended Cox Model (cont'd)

- Interpretation:

$$h_i(t \mid \mathcal{Y}_i(t), w_i) = h_0(t) R_i(t) \exp\{\gamma^\top w_i + \alpha y_i(t)\}$$

$\exp(\alpha)$ denotes the relative increase in the risk of an event at time t that results from one unit increase in $y_i(t)$ at the same time point

- Parameters are estimated based on the log-partial likelihood function

$$p\ell(\gamma, \alpha) = \sum_{i=1}^{n} \int_0^\infty \Big\{ R_i(t) \exp\{\gamma^\top w_i + \alpha y_i(t)\} - \log\Big[\sum_j R_j(t) \exp\{\gamma^\top w_j + \alpha y_j(t)\}\Big] \Big\} dN_i(t)$$

3.6 Extended Cox Model (cont'd)

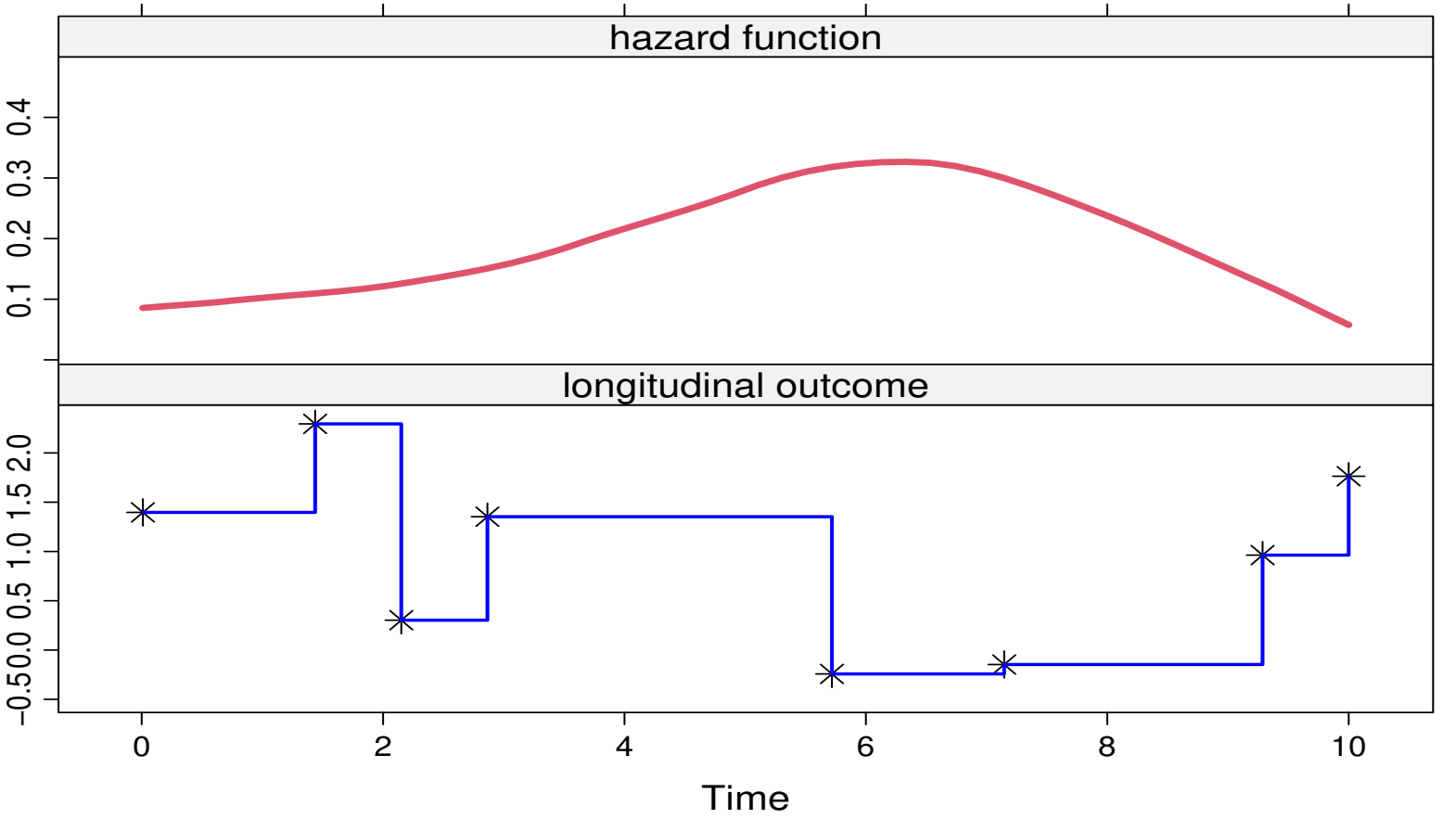
- Typically, data must be organized in the long format

Patient	Start	Stop	Event	$y_i(t)$	Age
1	0	135	1	5.5	45
2	0	65	0	2.2	38
2	65	120	0	3.1	38
2	120	155	1	4.1	38
3	0	115	0	2.5	29
3	115	202	0	2.9	29
⋮	⋮	⋮	⋮	⋮	⋮

3.6 Extended Cox Model (cont'd)

- How does the extended Cox model handle time-varying covariates?
  - ▷ assumes no measurement error
  - ▷ step-function path
  - ▷ existence of the covariate is not related to failure status

3.6 Extended Cox Model (cont'd)



3.6 Extended Cox Model (cont'd)

- Therefore, the extended Cox model is only valid for exogenous time-dependent covariates

Treating endogenous covariates as exogenous may produce spurious results!

Part IV

The Basic Joint Model

4.1 Joint Modeling Framework

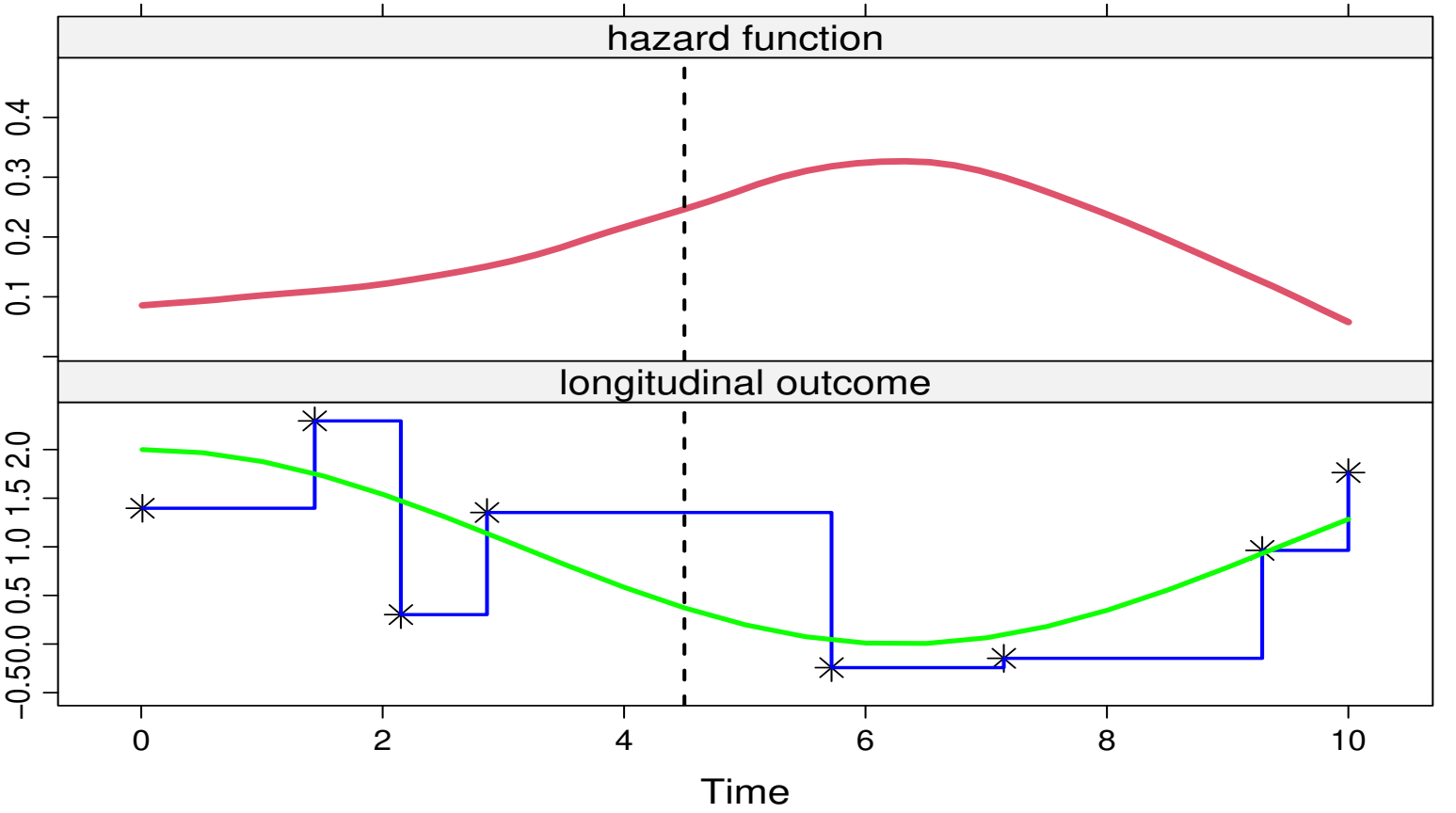
- To account for the special features of endogenous covariates a new class of models has been developed

Joint Models for Longitudinal and Time-to-Event Data

- Intuitive idea behind these models
  1. use an appropriate model to describe the evolution of the marker over time for each patient
  2. the estimated evolutions are then used in a Cox model

- Feature: Marker level's are **not** assumed constant between visits

4.1 Joint Modeling Framework (cont'd)



4.1 Joint Modeling Framework (cont'd)

- Some notation
  - ▷ T_i^*: True event time for patient i
  - ▷ T_i: Observed event time for patient i
  - ▷ δ_i: Event indicator, i.e., equals 1 for true events
  - ▷ y_i: Longitudinal responses

- We will formulate the joint model in 3 steps – in particular, ...

4.1 Joint Modeling Framework (cont'd)

- Step 1: Let's assume that we know $m_i(t)$, i.e., the *true* & *unobserved* value of the marker at time t

- Then, we can define a standard relative risk model

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha m_i(t)\},$$

where

  - $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$ longitudinal history
  - α quantifies the strength of the association between the marker and the risk of an event
  - w_i baseline covariates

4.1 Joint Modeling Framework (cont'd)

- Step 2: From the observed longitudinal response $y_i(t)$ reconstruct the covariate history for each subject

- Mixed effects model (we focus, for now, on continuous markers)

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \qquad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \end{aligned}$$

where

  - ▷ $x_i(t)$ and β: Fixed-effects part
  - ▷ $z_i(t)$ and b_i: Random-effects part, $b_i \sim \mathcal{N}(0, D)$

4.1 Joint Modeling Framework (cont'd)

- Step 3: The two processes are associated $\Rightarrow$ define a model for their joint distribution

- Joint Models for such joint distributions are of the following form
  (Tsiatis & Davidian, Stat. Sinica, 2004)

$$p(y_i, T_i, \delta_i) = \int p(y_i \mid b_i) \left\{ h(T_i \mid b_i)^{\delta_i} S(T_i \mid b_i) \right\} p(b_i)\, db_i,$$

  where

  ▷ b_i a vector of random effects that explains the interdependencies

  ▷ $p(\cdot)$ density function; $S(\cdot)$ survival function

4.1 Joint Modeling Framework (cont'd)

- Key assumption: **Full Conditional Independence** $\Rightarrow$ random effects explain all interdependencies

  ▷ the longitudinal outcome is independent of the time-to-event outcome

  ▷ the repeated measurements in the longitudinal outcome are independent of each other

$$p(y_i, T_i, \delta_i \mid b_i) = p(y_i \mid b_i)\, p(T_i, \delta_i \mid b_i)$$

$$p(y_i \mid b_i) = \prod_j p(y_{ij} \mid b_i)$$

Caveat: CI is difficult to be tested

4.1 Joint Modeling Framework (cont'd)

- The censoring and visiting* processes are assumed non-informative:

- Decision to withdraw from the study or appear for the next visit
  - ▷ **may depend** on observed past history (baseline covariates + observed longitudinal responses)
  - ▷ **no additional dependence** on underlying, latent subject characteristics associated with prognosis

*The visiting process is defined as the mechanism (stochastic or deterministic) that generates the time points at which longitudinal measurements are collected.

4.1 Joint Modeling Framework (cont'd)

- The survival function, which is a part of the likelihood of the model, depends on the whole longitudinal history

$$S_i(t \mid b_i) = \exp\left(- \int_0^t h_0(s) \exp\{\gamma^\top w_i + \alpha m_i(s)\} \, ds \right)$$

- Therefore, care in the definition of the design matrices of the mixed model
  - ▷ when subjects have nonlinear profiles $\Rightarrow$
  - ▷ use splines or polynomials to model them flexibly

4.1 Joint Modeling Framework (cont'd)

- Random-effects distribution
  - ▷ in mixed models it is customary to assume normality (see p. 85);
  - ▷ however, in joint models this distribution plays a more prominent role because the random effects explain all associations (see p. 87);
  - ▷ nevertheless, robustness, especially as n_i increases (see Rizopoulos et al., 2008, Biometrika)

4.1 Joint Modeling Framework (cont'd)

- Assumptions for the baseline hazard function $h_0(t)$
  - ▷ parametric $\Rightarrow$ possibly restrictive
  - ▷ unspecified $\Rightarrow$ within JM framework underestimates standard errors
- It is advisable to use parametric but flexible models for $h_0(t)$
  - ▷ splines

$$\log h_0(t) = \gamma_{h_0,0} + \sum_{q=1}^{Q} \gamma_{h_0,q} B_q(t, v),$$

where

* $B_q(t, v)$ denotes the q-th basis function of a B-spline with knots $v_1, \ldots, v_Q$
* γ_{h_0} a vector of spline coefficients

4.1 Joint Modeling Framework (cont'd)

- It is advisable to use parametric but flexible models for $h_0(t)$
  - ▷ step-functions: piecewise-constant baseline hazard often works satisfactorily

$$h_0(t) = \sum_{q=1}^{Q} \xi_q I(v_{q-1} < t \leq v_q),$$

where $0 = v_0 < v_1 < \cdots < v_Q$ denotes a split of the time scale

4.2 Estimation

- Mainly maximum likelihood but also Bayesian approaches

- The log-likelihood contribution for subject i:

$$\ell_i(\theta) \;=\; \log \int \left\{ \prod_{j=1}^{n_i} p(y_{ij} \mid b_i; \theta) \right\} \Big\{ h(T_i \mid b_i; \theta)^{\delta_i} \; S_i(T_i \mid b_i; \theta) \Big\} p(b_i; \theta) \; db_i,$$

where

$$S_i(t \mid b_i; \theta) \;=\; \exp\left(- \int_0^t h_0(s; \theta) \exp\{\gamma^\top w_i + \alpha m_i(s)\} \; ds \right)$$

4.2 Estimation (cont'd)

- Both integrals do not have, in general, a closed-form solution $\Rightarrow$ need to be approximated numerically

- Standard numerical integration algorithms
  - ▷ Gaussian quadrature
  - ▷ Monte Carlo
  - ▷ ...

- More difficult is the integral with respect to b_i because it can be of high dimension
  - ▷ Laplace approximations
  - ▷ pseudo-adaptive Gaussian quadrature rules

4.2 Estimation (cont'd)

- To maximize the approximated log-likelihood

$$\ell(\theta) = \sum_{i=1}^{n} \log \int p(y_i \mid b_i; \theta) \left\{ h(T_i \mid b_i; \theta)^{\delta_i} \, S_i(T_i \mid b_i; \theta) \right\} p(b_i; \theta) \, db_i,$$

  we need to employ an optimization algorithm

- Standard choices
  - ▷ EM (treating b_i as missing data)
  - ▷ Newton-type
  - ▷ hybrids (start with EM and continue with quasi-Newton)

4.2 Estimation (cont'd)

- Standard errors: Standard asymptotic MLE

$$\hat{\text{var}}(\hat{\theta}) = \left\{ -\sum_{i=1}^{n} \frac{\partial^2 \log p(y_i, T_i, \delta_i; \theta)}{\partial \theta^\top \partial \theta}\Big|_{\theta=\hat{\theta}} \right\}^{-1}$$

- Standard asymptotic tests + information criteria
  - ▷ likelihood ratio test
  - ▷ score test
  - ▷ Wald test
  - ▷ AIC, BIC, ...

4.2 Estimation (cont'd)

- Based on a fitted joint model, estimates for the random effects are based on the posterior distribution:

$$p(b_i \mid T_i, \delta_i, y_i; \theta) = \frac{p(T_i, \delta_i \mid b_i; \theta)\, p(y_i \mid b_i; \theta)\, p(b_i; \theta)}{p(T_i, \delta_i, y_i; \theta)}$$

$$\propto p(T_i, \delta_i \mid b_i; \theta)\, p(y_i \mid b_i; \theta)\, p(b_i; \theta),$$

in which θ is replaced by its MLE $\hat{\theta}$

4.2 Estimation (cont'd)

- Measures of location

$$\begin{cases} \bar{b}_i = \int b_i \, p(b_i \mid T_i, \delta_i, y_i; \hat{\theta}) \, db_i \\ \\ \hat{b}_i = \text{argmax}_b \{\log p(b \mid T_i, \delta_i, y_i; \hat{\theta})\} \end{cases}$$

- Measures of dispersion

$$\begin{cases} \text{var}(b_i) = \int (b_i - \bar{b}_i)(b_i - \bar{b}_i)^\top \, p(b_i \mid T_i, \delta_i, y_i; \hat{\theta}) \, db_i \\ \\ H_i = \left\{ -\frac{\partial^2 \log p(b|T_i, \delta_i, y_i; \hat{\theta})}{\partial b^\top \partial b} \Big|_{b=\hat{b}_i} \right\}^{-1} \end{cases}$$

4.3 Bayesian Estimation

- Bayesian estimation
  - ▷ under the Bayesian paradigm both θ and $\{b_i, i = 1, \ldots, n\}$ are regarded as parameters

- Inference is based on the full posterior distribution

$$p(\theta, b \mid T, \delta, y) = \frac{\prod_i p(T_i, \delta_i \mid b_i; \theta)\, p(y_i \mid b_i; \theta)\, p(b_i; \theta)\, p(\theta)}{\prod_i p(T_i, \delta_i, y_i)}$$

$$\propto \prod_{i=1}^{n} \Big\{ p(T_i, \delta_i \mid b_i; \theta)\, p(y_i \mid b_i; \theta)\, p(b_i; \theta) \Big\}\, p(\theta)$$

4.3 Bayesian Estimation (cont'd)

- No closed-form solutions for the integrals in the normalizing constant $\Rightarrow$ **MCMC**

- For the standard joint model we have define thus far, the majority of the parameters can be updated using Gibbs sampling (or slice sampling)
  - ▷ when no close-form posterior conditionals are available, we can use the Metropolis-Hastings algorithm

- To gain in efficiency, we can do block-updating for many of the parameters, i.e.,
  - ▷ fixed effects β
  - ▷ random effects b_i
  - ▷ baseline covariates in the survival submodel γ

4.3 Bayesian Estimation (cont'd)

- Good proposal distributions can be obtained from the separate fits of the two submodels

- Not directly programmable in WinBUGS, INLA, etc., due to the integral in the definition of the survival function

$$S_i(t \mid b_i; \theta) = \exp\left(- \int_0^t h_0(s; \theta) \exp\{\gamma^\top w_i + \alpha m_i(s)\} \, ds \right)$$

extra steps required...

4.3 Bayesian Estimation (cont'd)

- Inference then proceeds in the usual manner from the MCMC output, e.g.,
  - ▷ posterior means, variances, and standard errors
  - ▷ credible intervals
  - ▷ Bayes factors
  - ▷ DIC, CPO
  - ▷ ...

4.4 A Comparison with the TD Cox

- Example: To illustrate the virtues of joint modeling, we compare it with the standard time-dependent Cox model for the AIDS data

$$\begin{cases} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 t + \beta_2 \{t \times \texttt{ddI}_i\} + b_{i0} + b_{i1} t + \varepsilon_i(t), \qquad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \\ \\ h_i(t) &= h_0(t) \exp\{\gamma \texttt{ddI}_i + \alpha m_i(t)\}, \end{cases}$$

where

▷ $h_0(t)$ is assumed piecewise-constant

4.4 A Comparison with the TD Cox (cont'd)

	JM	Cox
	log HR (std.err)	log HR (std.err)
Treat	0.33 (0.16)	0.31 (0.15)
$CD4^{1/2}$	−0.29 (0.04)	−0.19 (0.02)

- Clearly, there is a considerable effect of ignoring the measurement error, especially for the CD4 cell counts

4.4 A Comparison with the TD Cox (cont'd)

- A unit decrease in $CD4^{1/2}$, results in a
  - ▷ **Joint Model**: 1.3-fold increase in risk (95% CI: 1.24; 1.43)
  - ▷ **Time-Dependent Cox**: 1.2-fold increase in risk (95% CI: 1.16; 1.27)

- Which one to believe?
  - ▷ a lot of theoretical and simulation work has shown that the Cox model underestimates the true association size of markers

4.5 Joint Models in R

R> Joint models are fitted using function `jointModel()` from package **JM**. This function accepts as main arguments a linear mixed model and a Cox PH model based on which it fits the corresponding joint model

```
lmeFit <- lme(CD4 ~ obstime + obstime:drug,
    random = ~ obstime | patient, data = aids)

coxFit <- coxph(Surv(Time, death) ~ drug, data = aids.id, x = TRUE)

jointFit <- jointModel(lmeFit, coxFit, timeVar = "obstime",
    method = "piecewise-PH-aGH")

summary(jointFit)
```

4.5 Joint Models in R (cont'd)

R> As before, the data frame given in `lme()` should be in the long format, while the data frame given to `coxph()` should have one line per subject*

▷ the ordering of the subjects needs to be the same

R> In the call to `coxph()` you need to set `x = TRUE` (or `model = TRUE`) such that the design matrix used in the Cox model is returned in the object fit

R> Argument `timeVar` specifies the time variable in the linear mixed model

* Unless you want to include exogenous time-varying covariates or handle competing risks

4.5 Joint Models in R (cont'd)

R> Argument `method` specifies the type of relative risk model and the type of numerical integration algorithm – the syntax is as follows:

`<baseline hazard>-<parameterization>-<numerical integration>`

Available options are:

- `"piecewise-PH-GH"`: PH model with piecewise-constant baseline hazard
- `"spline-PH-GH"`: PH model with B-spline-approximated log baseline hazard
- `"weibull-PH-GH"`: PH model with Weibull baseline hazard
- `"weibull-AFT-GH"`: AFT model with Weibull baseline hazard
- `"Cox-PH-GH"`: PH model with unspecified baseline hazard

`GH` stands for standard Gauss-Hermite; using `aGH` invokes the pseudo-adaptive Gauss-Hermite rule

4.5 Joint Models in R (cont'd)

R> Joint models under the Bayesian approach are fitted using function `jm()` from package **JMbayes2**. This function works in a similar manner as function `jointModel()`, e.g.,

```
lmeFit <- lme(CD4 ~ obstime + obstime:drug,
    random = ~ obstime | patient, data = aids)

coxFit <- coxph(Surv(Time, death) ~ drug, data = aids.id)

jointFitBayes <- jm(coxFit, lmeFit, time_var = "obstime")

summary(jointFitBayes)
```

4.5 Joint Models in R (cont'd)

R> **JMbayes2** is more flexible:

- ▷ directly implements the MCMC
- ▷ allows for multiple longitudinal outcomes (continuous & categorical)
- ▷ allows for general transformation functions
- ▷ penalized B-splines for the baseline hazard function
- ▷ multi-state models & competing risks
- ▷ recurrent events (soon available)
- ▷ ...

4.5 Joint Models in R (cont'd)

R> In both packages methods are available for the majority of the standard generic functions + extras

- ▷ `summary()`, `anova()`, `vcov()`, `logLik()`
- ▷ `coef()`, `fixef()`, `ranef()`
- ▷ `fitted()`, `residuals()`
- ▷ `plot()`
- ▷ `xtable()` (you need to load package **xtable** first)

4.6 Connection with Missing Data

- So far we have attacked the problem from the survival point of view

- However, often, we may be also interested on the longitudinal outcome

- **Issue:** When patients experience the event, they dropout from the study
  - ▷ a direct connection with the missing data field

Dropout must be taken into account when deriving inferences for the longitudinal outcome

4.6 Connection with Missing Data (cont'd)

- To show this connection more clearly
  - ▷ T_i^*: true time-to-event
  - ▷ y_i^o: longitudinal measurements before T_i^*
  - ▷ y_i^m: longitudinal measurements after T_i^*

- **Important to realize** that the model we postulate for the longitudinal responses is for the complete vector $\{y_i^o, y_i^m\}$
  - ▷ implicit assumptions about missingness

4.6 Connection with Missing Data (cont'd)

- Missing data mechanism:

$$p(T_i^* \mid y_i^o, y_i^m) = \int p(T_i^* \mid b_i)\, p(b_i \mid y_i^o, y_i^m)\, db_i$$

still depends on y_i^m, which corresponds to nonrandom dropout

Intuitive interpretation: Patients who dropout show different longitudinal evolutions than patients who do not

4.6 Connection with Missing Data (cont'd)

- Implications of nonrandom dropout
  - ▷ observed data do not constitute a random sample from the target population

- This feature complicates the validation of the joint model's assumptions using standard residual plots
  - ▷ what is the problem: Residual plots may show systematic behavior due to dropout and not because of model misfit

4.6 Connection with Missing Data (cont'd)

- What about censoring?
  - ▷ censoring also corresponds to a discontinuation of the data collection process for the longitudinal outcome

- Likelihood-based inferences for joint models provide valid inferences when censoring is MAR
  - ▷ a patient relocates to another country (MCAR)
  - ▷ a patient is excluded from the study when her longitudinal response exceeds a prespecified threshold (MAR)
  - ▷ censoring depends on random effects (MNAR)

4.6 Connection with Missing Data (cont'd)

- Joint models belong to the class of *Shared Parameter Models*

$$p(y_i^o, y_i^m, T_i^*) = \int p(y_i^o, y_i^m \mid b_i)\, p(T_i^* \mid b_i)\, p(b_i) db_i$$

the association between the longitudinal and missingness processes is explained by the *shared* random effects b_i

4.6 Connection with Missing Data (cont'd)

- The other two well-known frameworks for MNAR data are
  - ▷ Selection models

$$p(y_i^o, y_i^m, T_i^*) = p(y_i^o, y_i^m)\, p(T_i^* \mid y_i^o, y_i^m)$$

  - ▷ Pattern mixture models:

$$p(y_i^o, y_i^m, T_i^*) = p(y_i^o, y_i^m \mid T_i^*)\, p(T_i^*)$$

- These two model families are primarily applied with discrete dropout times and cannot be easily extended to continuous time

4.6 Connection with Missing Data (cont'd)

- A nice feature of joint models / shared parameter models is that they can 'automatically' handle intermittent missing data – the observed data likelihood contributions take the form:

$$
\begin{aligned}
p(y_i^o, T_i^*) &= \int p(y_i^o, y_i^m, T_i^*)\, dy_i^m \\
&= \int \int p(y_i^o, y_i^m \mid b_i)\, p(T_i^* \mid b_i)\, p(b_i)\, db_i dy_i^m \\
&= \int \left\{ \int p(y_i^o, y_i^m \mid b_i)\, dy_i^m \right\} p(T_i^* \mid b_i)\, p(b_i)\, db_i \\
&= \int p(y_i^o \mid b_i)\, p(T_i^* \mid b_i)\, p(b_i)\, db_i
\end{aligned}
$$

This is not the case for selection and pattern mixture models!

4.6 Connection with Missing Data (cont'd)

- Example: In the AIDS data the association parameter α was highly significant, suggesting nonrandom dropout

- A comparison between
  - ▷ linear mixed-effects model $\Rightarrow$ MAR
  - ▷ joint model $\Rightarrow$ MNAR

  is warranted

- MAR assumes that missingness depends only on the observed data

$$p(T_i^* \mid y_i^o, y_i^m) = p(T_i^* \mid y_i^o)$$

4.6 Connection with Missing Data (cont'd)

	LMM (MAR)	JM (MNAR)
	value (s.e.)	value (s.e)
Inter	7.19 (0.22)	7.22 (0.22)
Time	−0.16 (0.02)	−0.19 (0.02)
Treat:Time	0.03 (0.03)	0.01 (0.03)

- Minimal sensitivity in parameter estimates & standard errors

  ⇒ **Warning:** This does not mean that this is always the case!

Part V

Extensions of Joint Models

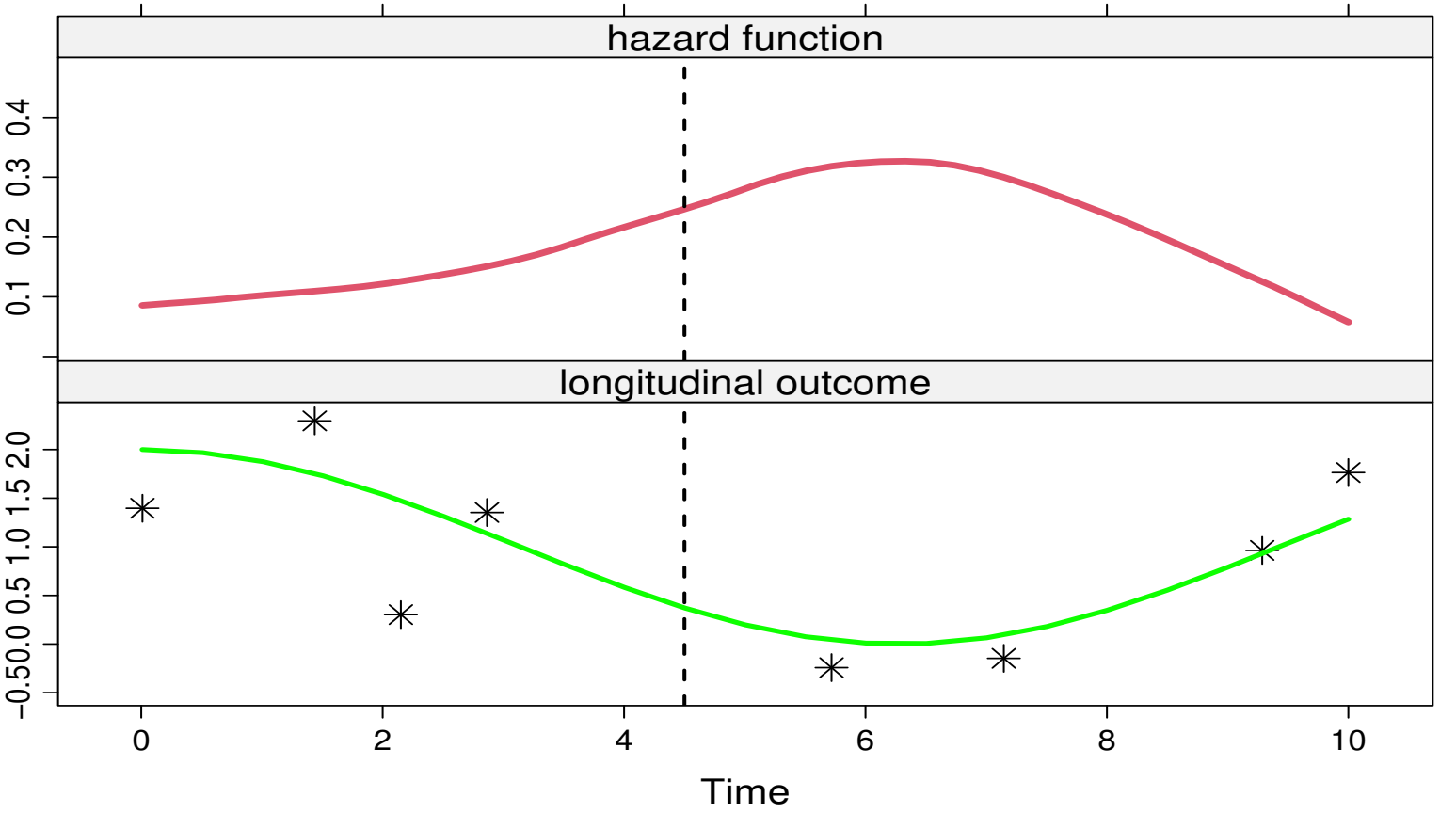
5.1 Parameterizations

- The standard joint model

$$\begin{cases} h_i(t \mid \mathcal{M}_i(t)) &= h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}, \\ \\ y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \end{cases}$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

5.1 Parameterizations (cont'd)



5.1 Parameterizations (cont'd)

- The standard joint model

$$\begin{cases} h_i(t \mid \mathcal{M}_i(t)) &= h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}, \\ \\ y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \end{cases}$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

Is this the only option? Is this the most optimal choice?

5.1 Parameterizations (cont'd)

- Note: Inappropriate modeling of time-dependent covariates may result in surprising results

- Example: Cavender et al. (1992, J. Am. Coll. Cardiol.) conducted an analysis to test the effect of cigarette smoking on survival of patients who underwent coronary artery surgery
  - ▷ the estimated effect of current cigarette smoking was positive on survival although not significant (i.e., patient who smoked had higher probability of survival)
  - ▷ most of those who had died were smokers but many stopped smoking at the last follow-up before their death

5.1 Parameterizations (cont'd)

We need to carefully consider the functional form of time-dependent covariates

- Let's see some possibilities...

5.1 Parameterizations (cont'd)

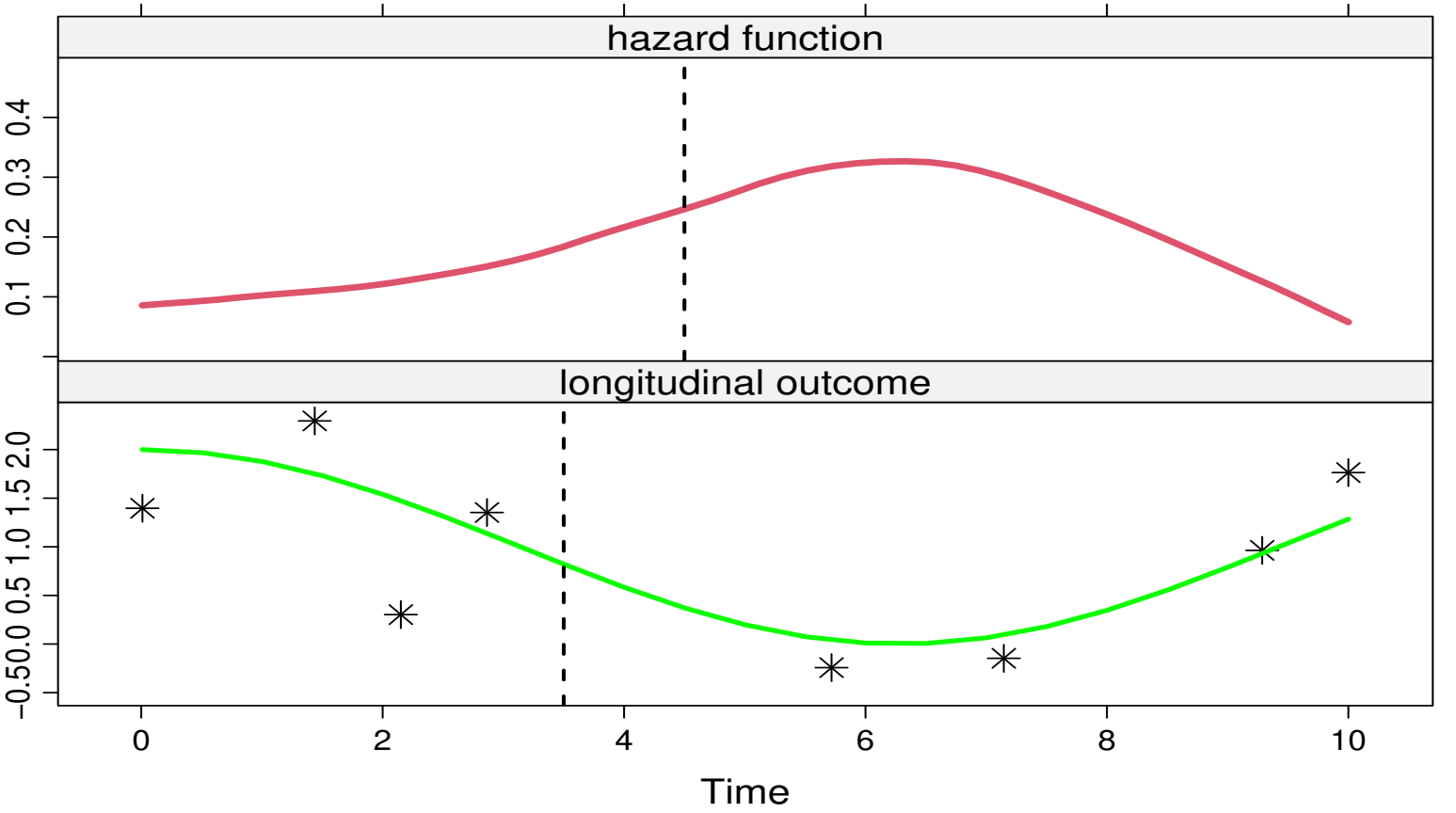
- *Lagged Effects:* The hazard of an event at t is associated with the level of the marker at a previous time point:

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha m_i(t_+^c)\},$$

where

$$t_+^c = \max(t - c, 0)$$

5.1 Parameterizations (cont'd)



5.1 Parameterizations (cont'd)

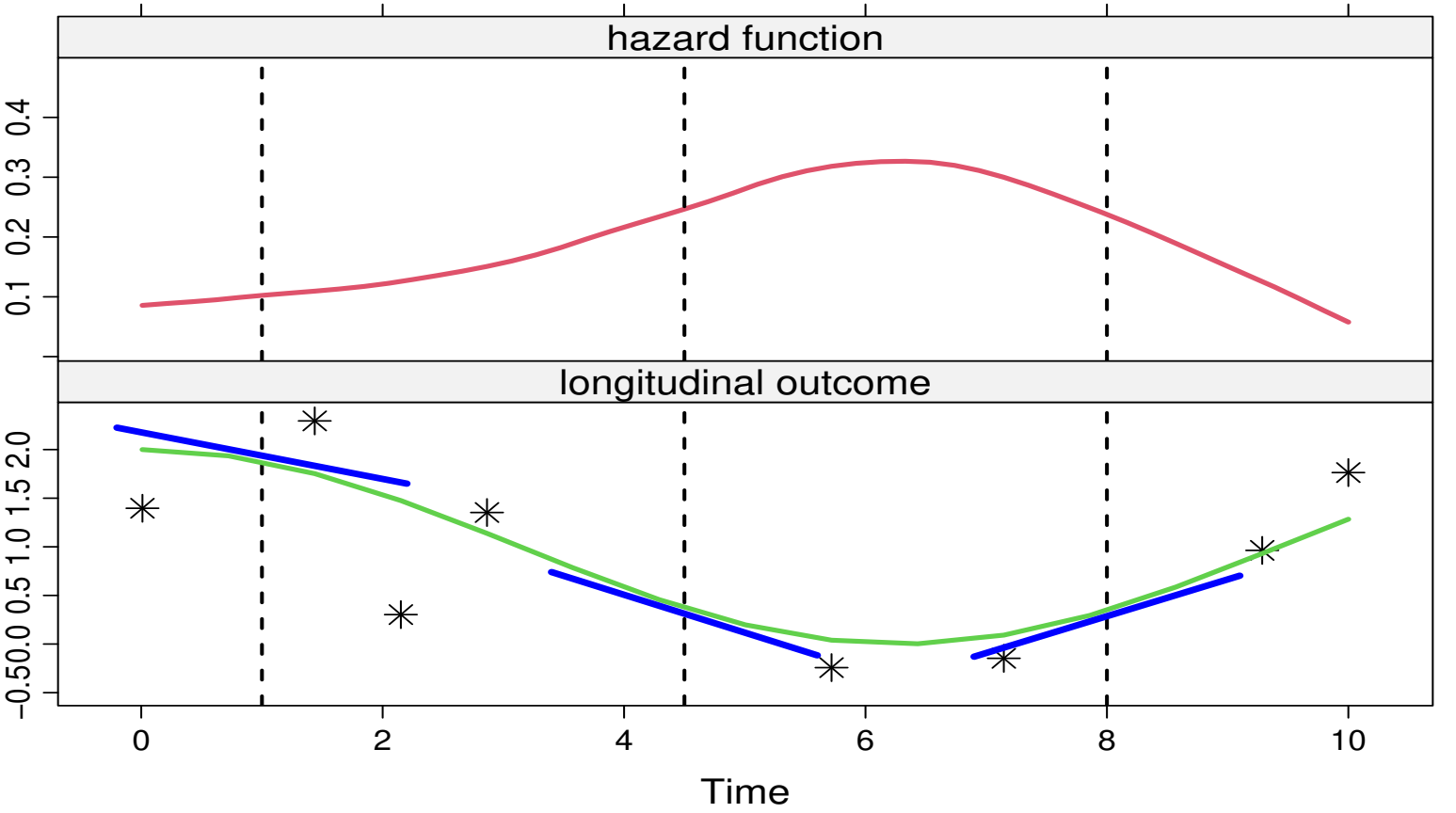
- *Time-dependent Slopes:* The hazard of an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

where

$$m_i'(t) = \frac{d}{dt}\{x_i^\top(t)\beta + z_i^\top(t) b_i\}$$

5.1 Parameterizations (cont'd)



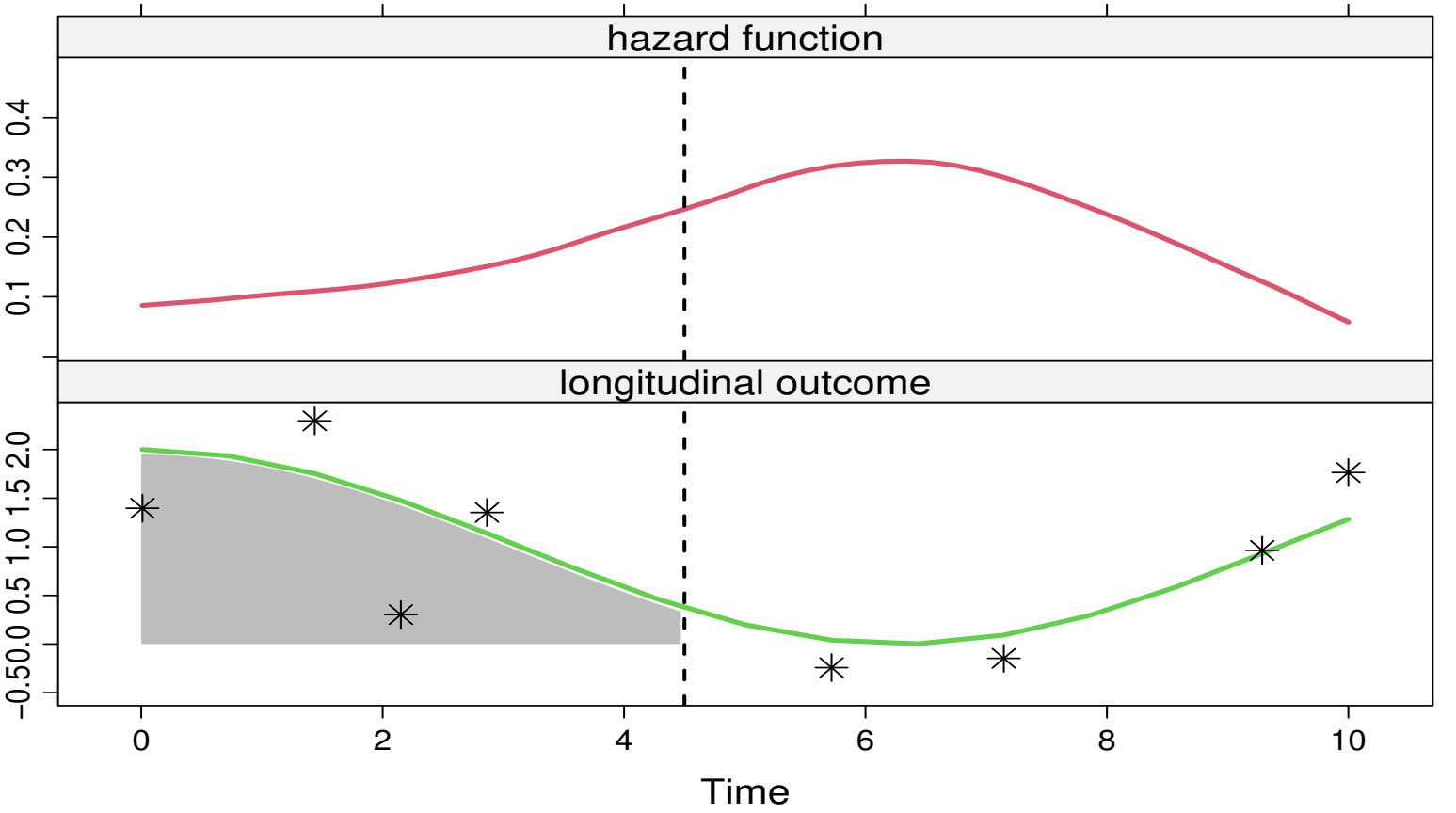
5.1 Parameterizations (cont'd)

- *Cumulative Effects:* The hazard of an event at t is associated with the whole area under the trajectory up to t:

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\left\{\gamma^\top w_i + \alpha \int_0^t m_i(s)\, ds\right\}$$

- Area under the longitudinal trajectory taken as a summary of $\mathcal{M}_i(t)$

5.1 Parameterizations (cont'd)



5.1 Parameterizations (cont'd)

- *Weighted Cumulative Effects (convolution):* The hazard of an event at t is associated with the area under the weighted trajectory up to t:

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\Big\{\gamma^\top w_i + \alpha \int_0^t \varpi(t-s) m_i(s)\, ds\Big\},$$

where $\varpi(\cdot)$ an appropriately chosen weight function, e.g.,

  - ▷ Gaussian density
  - ▷ Student's-t density
  - ▷ ...

5.1 Parameterizations (cont'd)

- *Random Effects:* The hazard of an event at t is associated only with the random effects of the longitudinal model:

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp(\gamma^\top w_i + \alpha^\top b_i)$$

- Features:
  - ▷ avoids numerical integration for the survival function
  - ▷ interpretation of α more difficult, especially in high-dimensional random-effects settings

5.1 Parameterizations (cont'd)

- Example: Sensitivity of inferences for the longitudinal process to the choice of the parameterization for the AIDS data

- We use the same mixed model as before, i.e.,

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 t + \beta_2 \{t \times \texttt{ddI}_i\} + b_{i0} + b_{i1} t + \varepsilon_i(t) \end{aligned}$$

  and the following four survival submodels

5.1 Parameterizations (cont'd)

- Model I (current value)

$$h_i(t) \;=\; h_0(t)\exp\{\gamma \texttt{ddI}_i + \alpha_1 m_i(t)\}$$

- Model II (current value + current slope)

$$h_i(t) \;=\; h_0(t)\exp\{\gamma \texttt{ddI}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

where

▷ $m_i'(t) = \beta_1 + \beta_2 \texttt{ddI}_i + b_{i1}$

5.1 Parameterizations (cont'd)

- Model III (random slope)

$$h_i(t) \;=\; h_0(t)\exp\{\gamma \texttt{ddI}_i + \alpha_3 b_{i1}\}$$

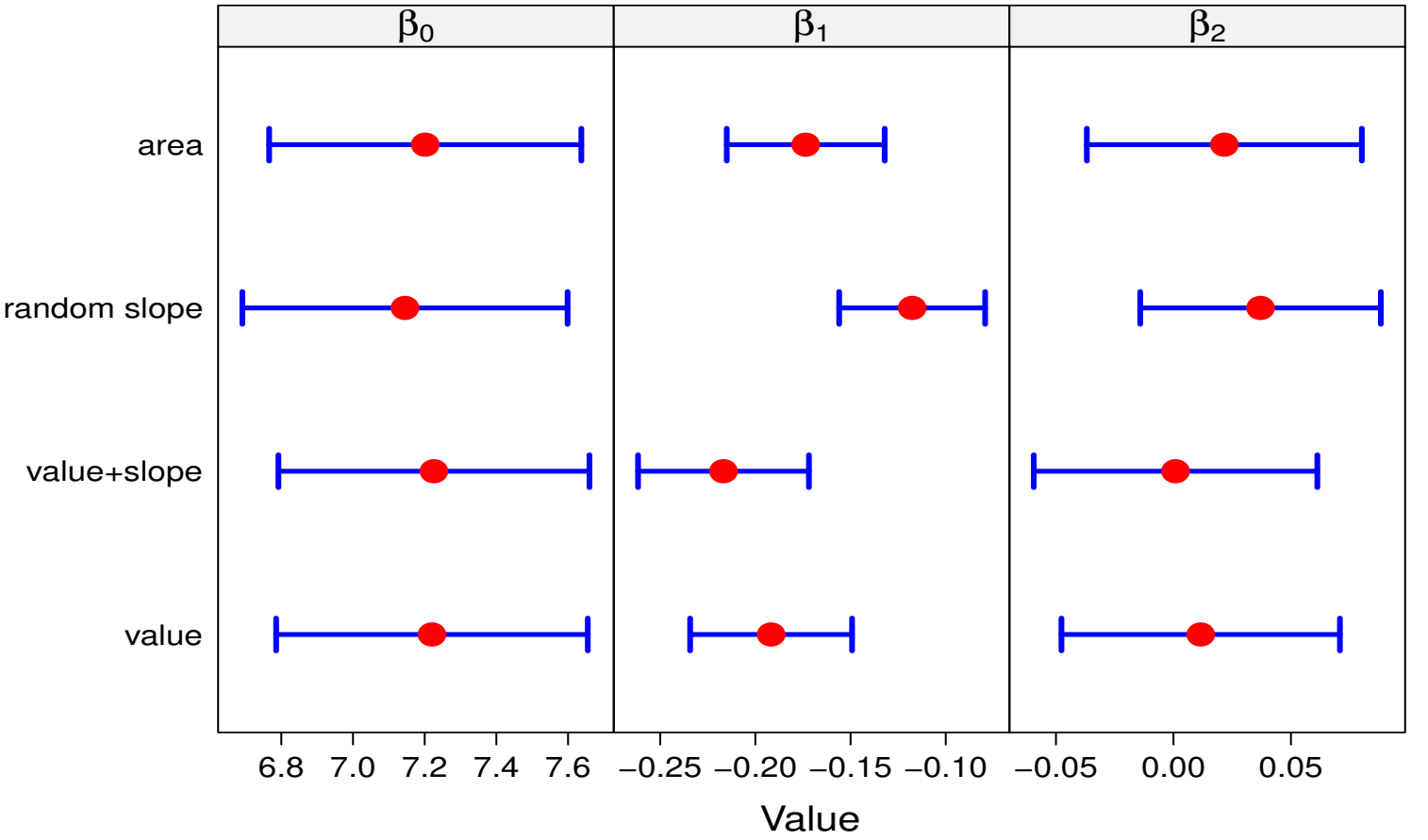
- Model IV (area)

$$h_i(t) \;=\; h_0(t)\exp\Big\{\gamma \texttt{ddI}_i + \alpha_4 \int_0^t m_i(s)\; ds\Big\},$$

where

▷ $\int_0^t m_i(s)\; ds = \beta_0 t + \frac{\beta_1}{2}t^2 + \frac{\beta_2}{2}\{t^2 \times \texttt{ddI}_i\} + b_{i0}t + \frac{b_{i1}}{2}t^2$

5.1 Parameterizations (cont'd)



5.1 Parameterizations (cont'd)

- There are noticeable differences between the parameterizations
  - ▷ especially in the slope parameters

- Therefore, a sensitivity analysis should not stop at the standard joint model parameterization but also consider alternative association structures

5.1 Parameterizations (cont'd)

R> Lagged effects can be fitted using the `lag` argument of `jointModel()`. For example, the following code fits a joint model for the PBC dataset with

- ▷ random intercepts and random slopes for log serum bilirubin, and
- ▷ a relative risk model with piecewise-constant baseline hazard and the *true* effect at the previous year

```
lmeFit <- lme(log(serBilir) ~ year, random = ~ year | id, data = pbc2)

coxFit <- coxph(Surv(years, status2) ~ 1, data = pbc2.id, x = TRUE)

jointFit <- jointModel(lmeFit, coxFit, timeVar = "year",
    method = "piecewise-PH-aGH", lag = 1)

summary(jointFit)
```

5.1 Parameterizations (cont'd)

R> For the time-dependent slopes and cumulative effects parameterizations, arguments `parameterization` and `derivForm` of `jointModel()` should be used

- ▷ the first one just specifies whether we want to include a single or two terms involving $m_i(t)$ in the linear predictor of the survival submodel, options are
  - * `parameterization = "value"`
  - * `parameterization = "slope"`
  - * `parameterization = "both"`

- ▷ the second one requires a few extra steps to specify – we will see an example in the practical

5.1 Parameterizations (cont'd)

R> In the newer **JMbayes2** the specification of functional forms is easier

▷ e.g., the following codes includes the area and slope in the linear predictor, and the interaction of the former with sex

```
jmFit <- jm(CoxFit, lmeFit, time_var = "time",
            functional_forms = ~ value(y) + area(y):sex)
```

5.2 Latent Class Joint Models

- In many settings it may not be reasonable to assume that the population under study is homogeneous

- Heterogeneity attributed to factors we have recorded
  - ▷ stratified analysis

- Heterogeneity attributed to factors we have **not** recorded
  - ▷ mixture models (aka latent class models)

5.2 Latent Class Joint Models (cont'd)

- Latent class joint model: We assume that the association between the longitudinal and event time processes is explained by some latent population heterogeneity

- Let G sub-populations, and $c_i = 1, \ldots, G$ the *latent* sub-population indicator of the ith subject in the sample

- Conditional independence:

$$p(T_i, \delta_i, y_i \mid c_i = g, b_i; \theta) = p(T_i, \delta_i \mid c_i = g; \theta)\, p(y_i \mid c_i = g, b_i; \theta)$$

$$p(y_i \mid c_i = g, b_i; \theta) = \prod_j p(y_{ij} \mid c_i = g, b_i; \theta)$$

5.2 Latent Class Joint Models (cont'd)

$$\begin{cases} h_i(t \mid c_i = g) & = h_{0g}(t) \exp(\gamma_g^\top w_i), \\ \{y_i(t) \mid c_i = g\} & = x_i^\top(t)\beta_g + z_i^\top(t) b_{ig} + \varepsilon_i(t), \quad b_{ig} \sim \mathcal{N}(\mu_g, \sigma_g^2 D), \\ \Pr(c_i = g) & = \exp(\lambda_g^\top u_i) \Big/ \sum_{l=1}^{G} \exp(\lambda_l^\top u_i) \end{cases}$$

- The latent class joint models consists of three parts:
  - ▷ stratified relative risk model
  - ▷ heterogeneity linear mixed model
  - ▷ multinomial model for class membership

5.2 Latent Class Joint Models (cont'd)

- Features:
  - ▷ avoids numerical integration
  - ▷ local maxima
  - ▷ requires multiple fits to find the optimal number of classes (typically chosen using information criteria)
  - ▷ no association parameter $\Rightarrow$ no straightforward interpretation

5.2 Latent Class Joint Models (cont'd)

- Example: Latent class joint model analysis of the AIDS dataset
  - ▷ longitudinal submodel: random intercepts and random slopes with class-specific fixed effects
  - ▷ survival submodel: class-specific baseline risk & treatment effects
  - ▷ class membership submodel: treatment effect

- We fitted the models with 2, 3, 4, and 5 classes

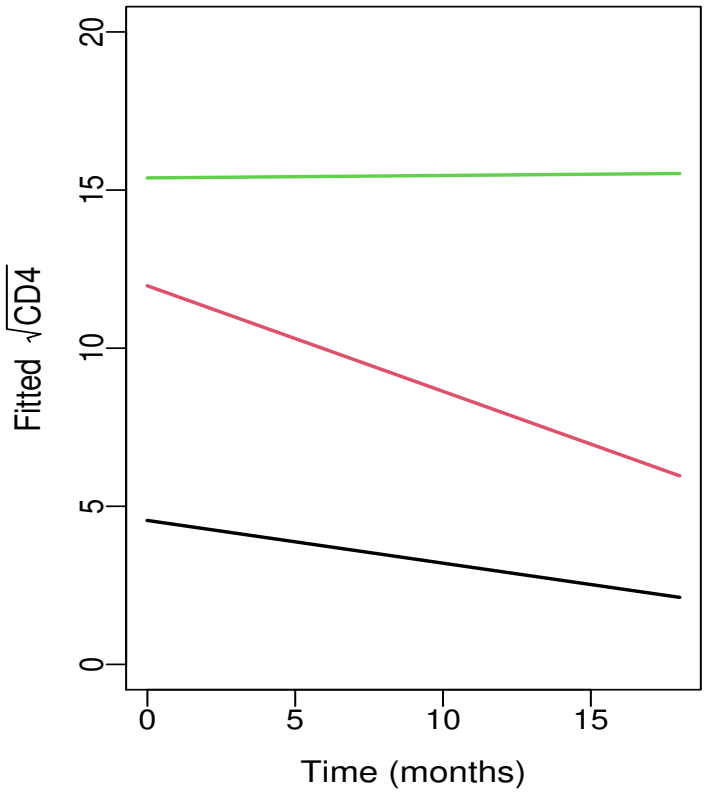
5.2 Latent Class Joint Models (cont'd)

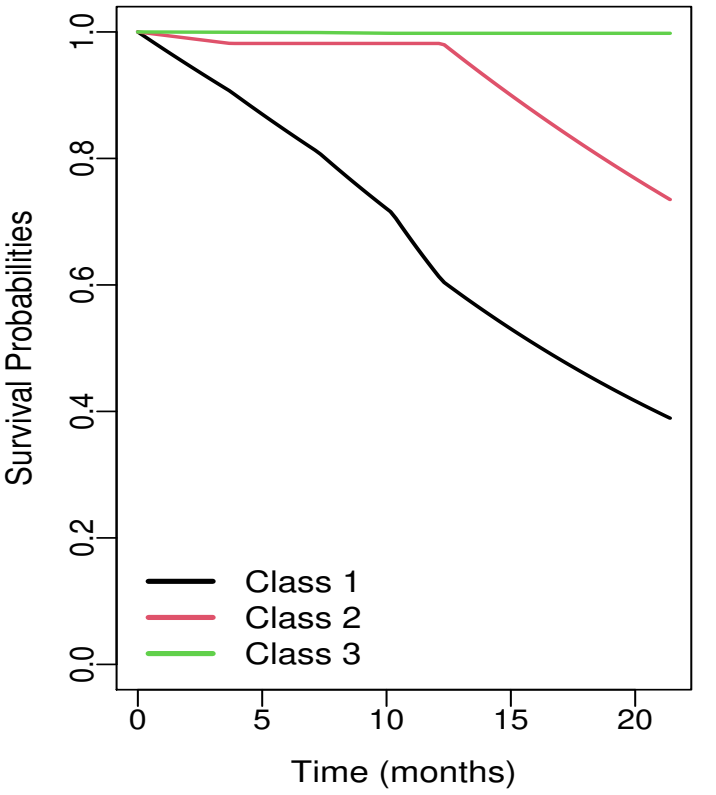
# Classes	logLik	AIC	BIC
2	−4258.74	8565.48	8665.00
3	−4223.03	8516.06	**8661.18**
4	−4198.63	**8489.26**	8679.99
5	−4192.98	8499.96	8736.30

- AIC favors the 4-class model, whereas BIC chooses the 3-class solution

- Empirical studies suggest that the BIC more often finds the correct number of latent subgroups

5.2 Latent Class Joint Models (cont'd)





5.2 Latent Class Joint Models (cont'd)

R> Latent class joint models can be fitted in R using function `Jointlcmm()` from package **lcmm**

```
lcjmFit.aids <- Jointlcmm(fixed = CD4 ~ obstime + drug,
    mixture = ~ obstime + drug, random = ~ obstime,
    classmb = ~ drug, subject = "patient", ng = 3, data = aids,
    survival = Surv(Time, death) ~ mixture(drug),
    hazard = "6-quant-piecewise", hazardtype = "Specific")

summary(lcjmFit.aids)
```

5.3 Multiple Longitudinal Markers

- So far we have concentrated on a single continuous marker

- But very often we may have several markers we wish to study, some of which could be categorical

- Example: In the PBC dataset we have used serum bilirubin as the most important marker, but during follow-up several other markers have been recorded
  - ▷ serum cholesterol (continuous)
  - ▷ edema (3 categories)
  - ▷ ascites (2 categories)
  - ▷ ...

5.3 Multiple Longitudinal Markers (cont'd)

We need to extend the basic joint model!

- To handle multiple longitudinal markers of different types we use Generalized Linear Mixed Models

  ▷ We assume $Y_{i1}, \ldots, Y_{iJ}$ for each subject, each one having a distribution in the exponential family, with expected value

$$m_{ij}(t) \;=\; E(y_{ij}(t) \mid b_{ij}) = g_j^{-1}\{x_{ij}^{\top}(t)\beta_j + z_{ij}^{\top}(t)b_{ij}\},$$

  with $g(\cdot)$ denoting a link function

5.3 Multiple Longitudinal Markers (cont'd)

▷ Correlation between the outcomes is built by assuming a multivariate normal distribution for the random effects

$$b_i = (b_{i1}^\top, \ldots, b_{iJ}^\top)^\top \sim \mathcal{N}(0, D)$$

- The expected value of each longitudinal marker is incorporated in the linear predictor of the survival submodel

$$h_i(t) \;=\; h_0(t) \exp\{\gamma^\top w_i + \sum_{j=1}^{J} \alpha_j m_{ij}(t)\}$$

5.3 Multiple Longitudinal Markers (cont'd)

- **Full Conditional Independence**: Given the random effects
  - ▷ the repeated measurements in each outcome are independent,
  - ▷ the longitudinal outcomes are independent of each other, and
  - ▷ longitudinal outcomes are independent of the time-to-event outcome

$$
\begin{aligned}
p(y_{ij} \mid b_{ij}) &= \prod_{k=1}^{n_{ij}} p(y_{ij,k} \mid b_{ij}) \\
p(y_i \mid b_i) &= \prod_{j} p(y_{ij} \mid b_{ij}) \\
p(y_i, T_i, \delta_i \mid b_i) &= \prod_{j} p(y_{ij} \mid b_{ij})\, p(T_i, \delta_i \mid b_i)
\end{aligned}
$$

5.3 Multiple Longitudinal Markers (cont'd)

- Features of multivariate joint models
  - ▷ using CI is straightforward to extend joint models to multiple longitudinal outcomes of different types
  - ▷ computationally much more intensive due to requirement for high dimensional numerical integrations with respect to the random effects

5.3 Multiple Longitudinal Markers (cont'd)

R> An example for the PBC dataset using serum bilirubin (continuous) and spiders (binary)

```
lmmFit <- lme(log(serBilir) ~ year, data = pbc2, random = ~ year | id)

melrFit <- mixed_model(spiders ~ year, data = pbc2, family = binomial(),
                       random = ~ year | id)

CoxFit <- coxph(Surv(years, status2) ~ drug + age, data = pbc2.id)

multJMFit <- jm(CoxFit, list(lmmFit, melrFit), time_var = "year")
summary(multJMFit)
```

5.3 Multiple Longitudinal Markers (cont'd)

R> Function `jm()` also allows for

- ▷ right, left, interval censored data
- ▷ left truncated data
- ▷ exogenous time-varying covariates

More info and vignettes in
https://drizopoulos.github.io/JMbayes2/

5.4 Multiple Failure Times

- Often multiple failure times are recorded
  - ▷ competing risks
  - ▷ recurrent events

- Example: In the PBC dataset ⇒ competing risks
  - ▷ Some patients received a liver transplantation
  - ▷ So far we have used the composite event, i.e. death or transplantation whatever comes first
  - ▷ When interest only is on one type of event, the other should be considered as a competing risk

5.4 Multiple Failure Times (cont'd)

- Joint models with competing risks:

$$\begin{cases} y_i(t) = m_i(t) + \varepsilon_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \\ h_i^d(t) = h_0^d(t)\exp\{\gamma_d^\top w_i + \alpha_d m_i(t)\}, \\ h_i^{tr}(t) = h_0^{tr}(t)\exp\{\gamma_{tr}^\top w_i + \alpha_{tr} m_i(t)\}, \end{cases}$$

where

- ▷ $h_i^d(t)$ hazard function for death
- ▷ $h_i^{tr}(t)$ hazard function for transplantation

5.4 Multiple Failure Times (cont'd)

- In the estimation, the only difference is in the construction of the likelihood part for the event process

$$p(T_i, \delta_i \mid b_i; \theta) = \prod_{k=1}^{K} \Big[h_{0k}(T_i) \exp\{\gamma_k^\top w_i + \alpha_k m_i(T_i)\} \Big]^{I(\delta_i = k)} \times \exp\left(- \sum_{k=1}^{K} \int_0^{T_i} h_{0k}(s) \exp\big\{ \gamma_k^\top w_i + \alpha_k m_i(s) \big\} \, ds \right),$$

with

- $T_i = \min(T_{i1}^*, \ldots, T_{iK}^*, C_i)$, with C_i denoting the censoring time
- $\delta_i \in \{0, 1, \ldots, K\}$, with 0 corresponding to censoring

5.4 Multiple Failure Times (cont'd)

- This is different than in standard Cox models
  - ▷ i.e., we **cannot** fit a cause-specific hazard joint model by treating events from other causes as censored

5.4 Multiple Failure Times (cont'd)

R> Function jm() can fit joint models with competing risks and multi-state processes; an example with competing risks

- ▷ first, the survival data have to be prepared in the competing risks long format using function crLong(), e.g.,

```
pbc2.id[pbc2.id$id %in% c(1,2,5), c("id", "years", "status")]
```

```
  id     years       status
1  1  1.095170         dead
2  2 14.152338        alive
5  5  4.120578 transplanted
```

5.4 Multiple Failure Times (cont'd)

```
pbc2.idCR <- crLong(pbc2.id, statusVar = "status",
    censLevel = "alive", nameStrata = "CR")
```

```
pbc2.idCR[pbc2.idCR$id %in% c(1,2,5),
        c("id", "years", "status", "CR", "status2")]
```

	id	years	status	CR	status2
1	1	1.095170	dead	dead	1
1.1	1	1.095170	dead	transplanted	0
2	2	14.152338	alive	dead	0
2.1	2	14.152338	alive	transplanted	0
5	5	4.120578	transplanted	dead	0
5.1	5	4.120578	transplanted	transplanted	1

5.4 Multiple Failure Times (cont'd)

R> To fit the joint model, we first fit the linear mixed and relative risk models as before

▷ for the latter we use the data in the competing risks long and put the event-type variable as strata

```
lmeFit.CR <- lme(log(serBilir) ~ drug * year, data = pbc2,
    random = ~ year | id)

coxFit.CR <- coxph(Surv(years, status2) ~ drug * strata(CR),
    data = pbc2.idCR)
```

5.4 Multiple Failure Times (cont'd)

R> Then the joint model is fitted with the code

```
jointFit.CR <- jm(coxFit.CR, lmeFit.CR, time_var = "year",
                  functional_forms = ~ value(log(serBilir)):CR)

summary(jointFit.CR)
```

5.4 Multiple Failure Times (cont'd)

- Multiple Failure Times: recurrent events

- Example: In the PBC dataset $\Rightarrow$ recurrent events
  - ▷ Patients showed irregular visiting patterns
  - ▷ So far, when we fitted the joint model we assumed that the visiting process is non-informative
  - ▷ If this assumption is violated, we should also model this process in order to obtain valid inferences

5.4 Multiple Failure Times (cont'd)

- Joint model with recurrent (visiting process) & terminal events

$$\begin{cases} y_i(t) &= m_i(t) + \varepsilon_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \\ r_i(t) &= r_0(t)\exp\{\gamma_r^\top w_{ri} + \alpha_r m_i(t) + \mathsf{v}_i\}, \\ h_i(t) &= h_0(t)\exp\{\gamma_h^\top w_{hi} + \alpha_h m_i(t) + \zeta \mathsf{v}_i\}, \end{cases}$$

with

- ▷ $r_i(t)$ hazard function for the recurrent events
- ▷ $h_i(t)$ hazard function for the terminal event
- ▷ v_i frailty term accounting for the correlation in the recurrent events

5.4 Multiple Failure Times (cont'd)

- Conditional independence assumptions augmented
  - ▷ recurrent events are independent given v_i
  - ▷ longitudinal measurements are independent giver b_i
  - ▷ all three processes, namely
    * longitudinal process,
    * recurrent events process, and
    * terminating event process

    are independent given $\{b_i, v_i\}$

- We need to postulate a distribution for the frailty terms
  - ▷ typical choice is the Gamma because it's conjugate

5.5 Extensions & Parameterizations

- Note: In the previous extensions of joint models, i.e.,
  - ▷ multiple longitudinal markers
  - ▷ multiple failure times

  we used the default parameterization that includes the current value term $m_i(t)$ in the linear predictor of the survival submodel(s)

> Nonetheless, all the other parameterizations we have seen earlier are also applicable

5.5 Extensions & Parameterizations (cont'd)

- For example in the case of multiple longitudinal outcomes

$$g_j\left[E\{y_{ij}(t) \mid b_{ij}\}\right] = m_{ij}(t) = x_{ij}^{\top}(t)\beta_j + z_{ij}^{\top}(t)b_{ij}$$

$$h_i(t) = h_0(t)\exp\left\{\gamma^{\top}w_i + \sum_{j=1}^{J}\sum_{l=1}^{L} f_{jl}(\mathcal{H}_{ij}(t), \alpha_{jl})\right\}$$

5.5 Extensions & Parameterizations (cont'd)

- In this case we face a challenging model selection problem

- Different possible solutions
  - ▷ lasso
  - ▷ ridge
  - ▷ horseshoe
  - ▷ ...

5.5 Extensions & Parameterizations (cont'd)

R> Function `jm()` also allows to consider multiple parameterizations per outcome

R> It also implements a global-local ridge-type prior for the association parameters

$$\alpha_{jl} \sim \mathcal{N}(0, \tau\psi_{jl})$$

$$\tau^{-1} \sim Gamma(0.1, 0.1)$$

$$\psi_{jl}^{-1} \sim Gamma(1, 0.01)$$

Part VI

Dynamic Predictions, Discrimination & Calibration

6.1 Survival Probabilities: Definitions

- Nowadays there is great interest for prognostic models and their application to personalized medicine

- Examples are numerous
  - ▷ cancer research, cardiovascular diseases, HIV research, ...

Physicians are interested in accurate prognostic tools that will inform them about the future prospect of a patient in order to adjust medical care

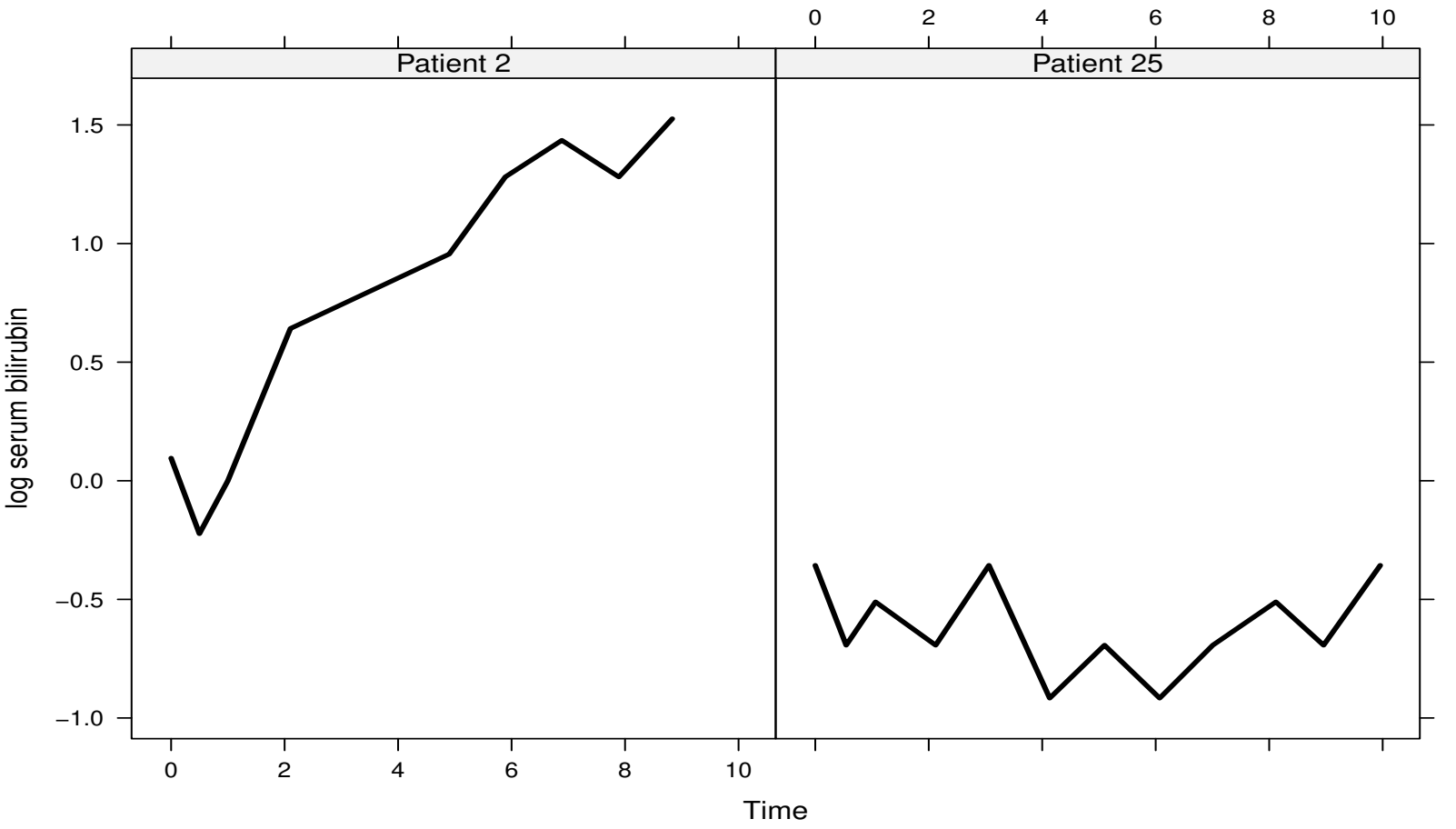
6.1 Survival Probabilities: Definitions (cont'd)

- We are interested in predicting survival probabilities for a new patient j that has provided a set of serum bilirubin measurements up to a specific time point t

- Example: We consider Patients 2 and 25 from the PBC dataset that have provided us with 9 and 12 serum bilirubin measurements, respectively
  - ▷ **Dynamic Prediction** survival probabilities are dynamically updated as additional longitudinal information is recorded

- We need to account for the endogenous nature of the marker
  - ▷ providing measurements up to time point $t \Rightarrow$ the patient was still alive at time t

6.1 Survival Probabilities: Definitions (cont'd)



6.1 Survival Probabilities: Definitions (cont'd)

- More formally, for a new subject j we have available measurements up to time point t

$$\mathcal{Y}_j(t) = \{y_j(s), 0 \leq s \leq t\}$$

and we are interested in

$$\pi_j(u \mid t) = \mathsf{Pr}\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\},$$

where

▷ where $u > t$, and

▷ $\mathcal{D}_n$ denotes the sample on which the joint model was fitted

6.2 Survival Probabilities: Estimation

- We assume that the joint model has been fitted to the data at hand

- Based on the fitted model we can estimate the conditional survival probabilities
  (Rizopoulos, 2011, Biometrics)

6.2 Survival Probabilities: Estimation (cont'd)

- $\pi_j(u \mid t)$ can be rewritten as

$$\pi_j(u \mid t) = \int \frac{S_j\{u \mid \mathcal{M}_j(u, b_j, \theta); \theta\}}{S_j\{t \mid \mathcal{M}_j(t, b_j, \theta); \theta\}} p(b_j \mid T_j^* > t, \mathcal{Y}_j(t); \theta)\, db_j$$

- A naive estimator for $\pi_j(u \mid t)$ can be constructed by plugging-in the MLEs and the Empirical Bayes estimates

$$\tilde{\pi}_j(u \mid t) = \frac{S_j\{u \mid \mathcal{M}_j(u, \hat{b}_j, \hat{\theta}); \hat{\theta}\}}{S_j\{t \mid \mathcal{M}_j(t, \hat{b}_j, \hat{\theta}); \hat{\theta}\}}$$

  - ▷ this works relatively well in practice, but
  - ▷ standard errors are difficult to compute

6.2 Survival Probabilities: Estimation (cont'd)

- It is convenient to proceed using a Bayesian formulation of the problem $\Rightarrow$ $\pi_j(u \mid t)$ can be written as

$$\Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\} = \int \Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t); \theta\}\, p(\theta \mid \mathcal{D}_n)\, d\theta$$

- We have already seen the first part of the integrand

$$\Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t); \theta\} =$$

$$= \int \frac{S_j\{u \mid \mathcal{M}_j(u, b_j, \theta); \theta\}}{S_j\{t \mid \mathcal{M}_j(t, b_j, \theta); \theta\}}\, p(b_j \mid T_j^* > t, \mathcal{Y}_j(t); \theta)\, db_j$$

6.2 Survival Probabilities: Estimation (cont'd)

- Provided that the sample size is sufficiently large, we can approximate the posterior of the parameters by

$$\{\theta \mid \mathcal{D}_n\} \sim \mathcal{N}(\hat{\theta}, \hat{\mathcal{H}}),$$

where

  - ▷ $\hat{\theta}$ are the MLEs, and
  - ▷ $\hat{\mathcal{H}}$ their asymptotic covariance matrix

6.2 Survival Probabilities: Estimation (cont'd)

- A Monte Carlo estimate of $\pi_j(u \mid t)$ can be obtained using the following simulation scheme:

Step 1. draw $\theta^{(\ell)} \sim \mathcal{N}(\hat{\theta}, \hat{\mathcal{H}})$

Step 2. draw $b_j^{(\ell)} \sim \{b_j \mid T_j^* > t, \mathcal{Y}_j(t), \theta^{(\ell)}\}$

Step 3. compute $\pi_j^{(\ell)}(u \mid t) = S_j\{u \mid \mathcal{M}_j(u, b_j^{(\ell)}, \theta^{(\ell)}); \theta^{(\ell)}\} \Big/ S_j\{t \mid \mathcal{M}_j(t, b_j^{(\ell)}, \theta^{(\ell)}); \theta^{(\ell)}\}$

- Repeat Steps 1–3, $\ell = 1, \ldots, L$ times, where L denotes the number of Monte Carlo samples

6.2 Survival Probabilities: Estimation (cont'd)

- Steps 1 and 3 are straightforward

- In Step 2 we need to sample from $\{b_j \mid T_j^* > t, \mathcal{Y}_j(t), \theta^{(\ell)}\}$, which is nonstandard
  - ▷ as n_i increases, this posterior converges to a multivariate normal distribution (Rizopoulos et al., Biometrika, 2008)
  - ▷ we use a Metropolis-Hastings algorithm with multivariate t proposals

6.2 Survival Probabilities: Estimation (cont'd)

- Example: Dynamic predictions of survival probabilities for Patients 2 & 25 from the PBC dataset: We fit the joint model

- Longitudinal submodel
  - ▷ fixed effects: Linear & quadratic time, treatment and their interaction
  - ▷ random effects: Intercept, linear & quadratic time effects

- Survival submodel
  - ▷ treatment effect + *underlying* serum bilirubin level
  - ▷ piecewise-constant baseline hazard in 7 intervals

6.2 Survival Probabilities: Estimation (cont'd)

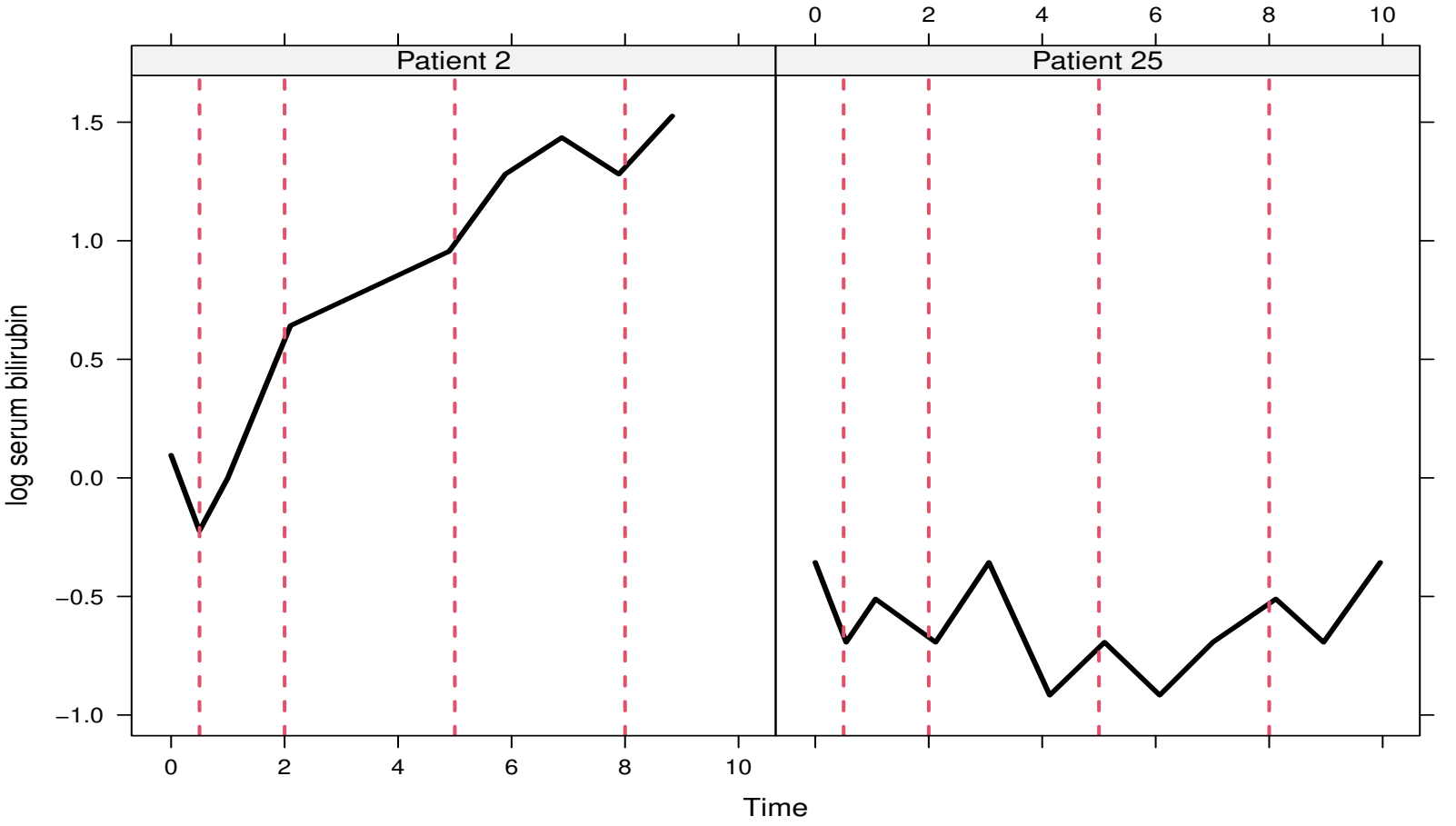
- Based on the fitted joint model we estimate $\pi_j(u \mid t)$ for Patients 2 and 25

- We use 500 Monte Carlo samples, and we took as estimate

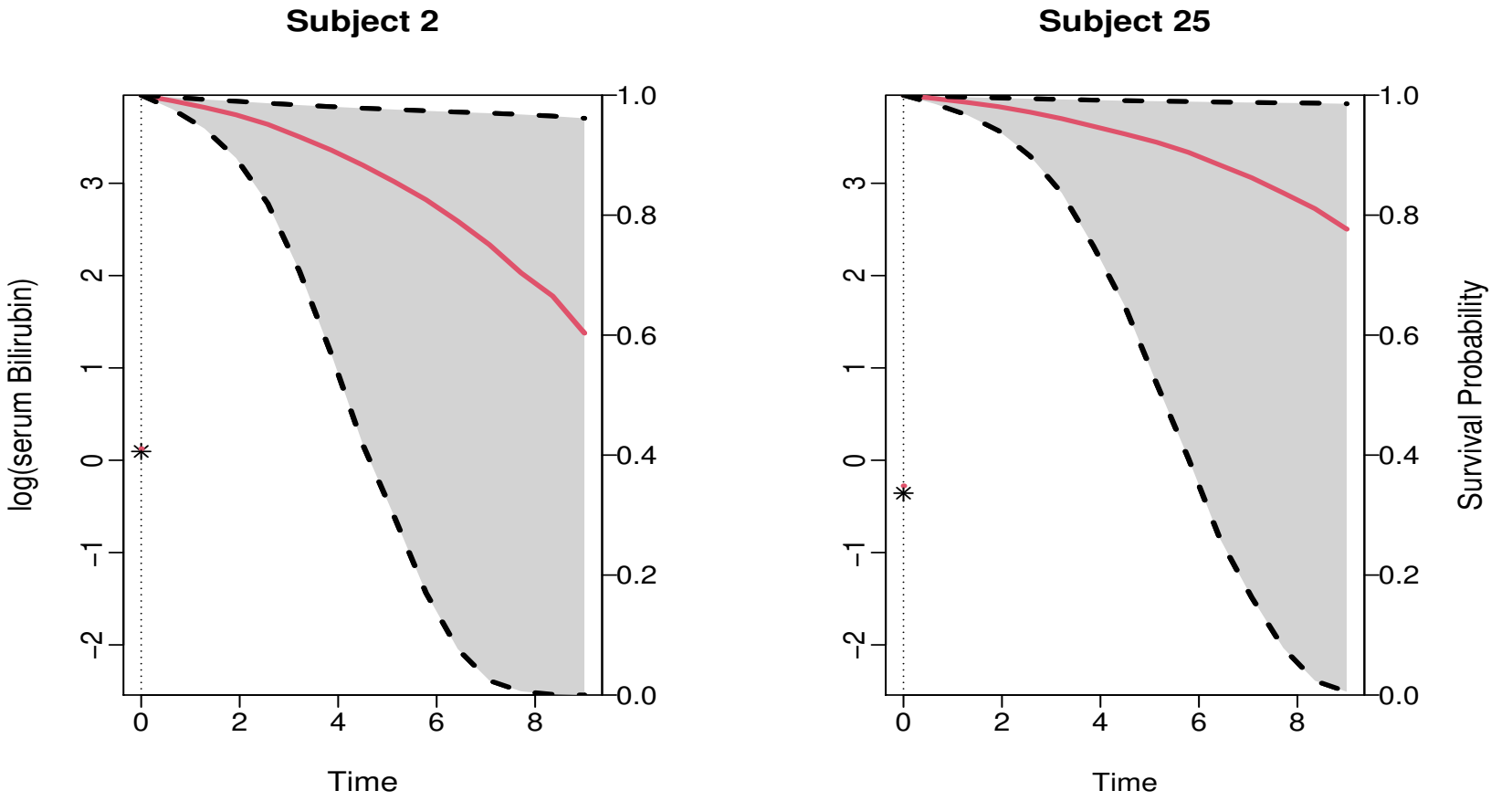
$$\hat{\pi}_j(u \mid t) = \text{mean}\{\pi_j^{(\ell)}(u \mid t), \ell = 1, \ldots, L\}$$

  and calculated a corresponding 95% pointwise CIs

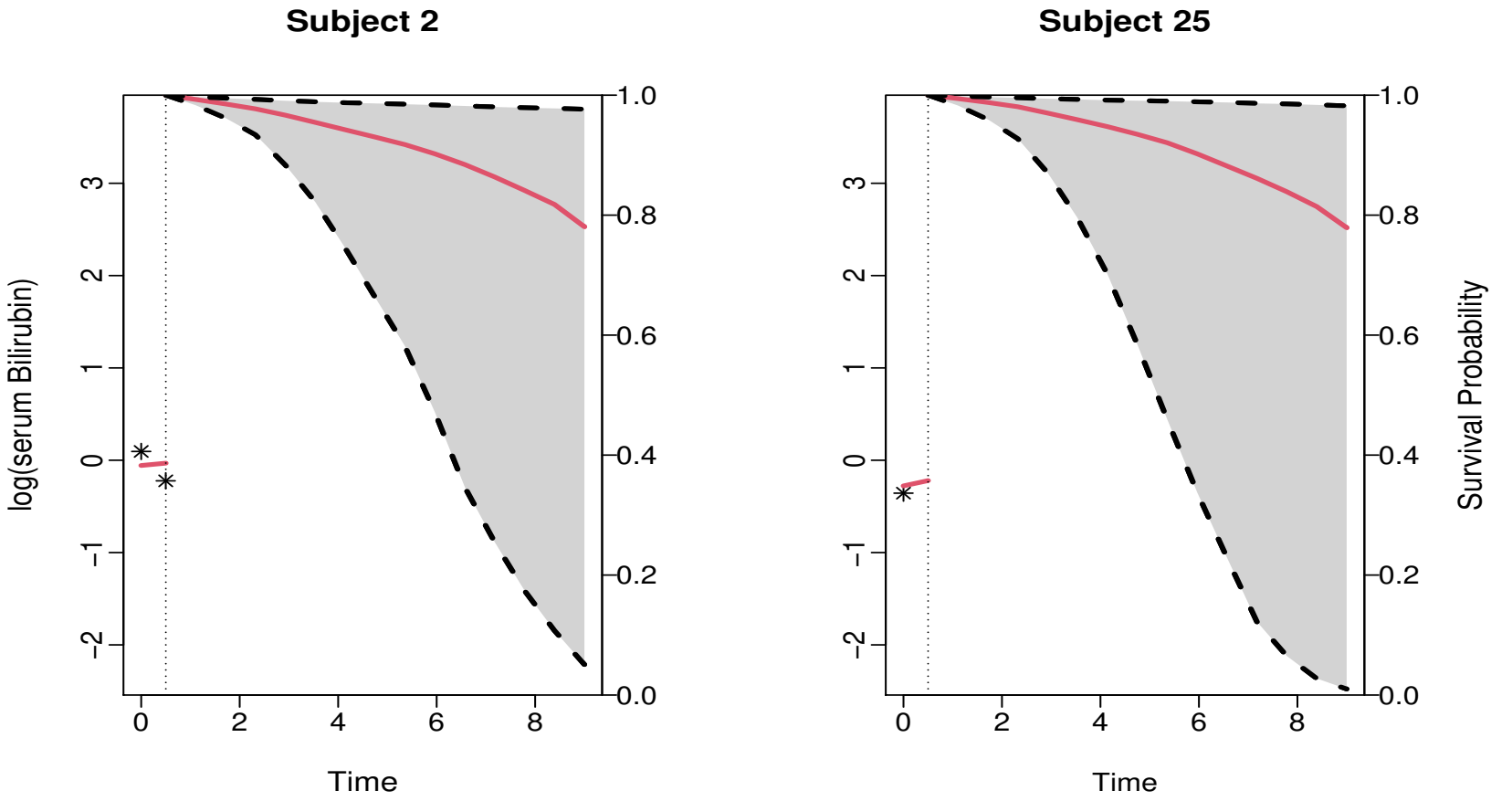
6.2 Survival Probabilities: Estimation (cont'd)



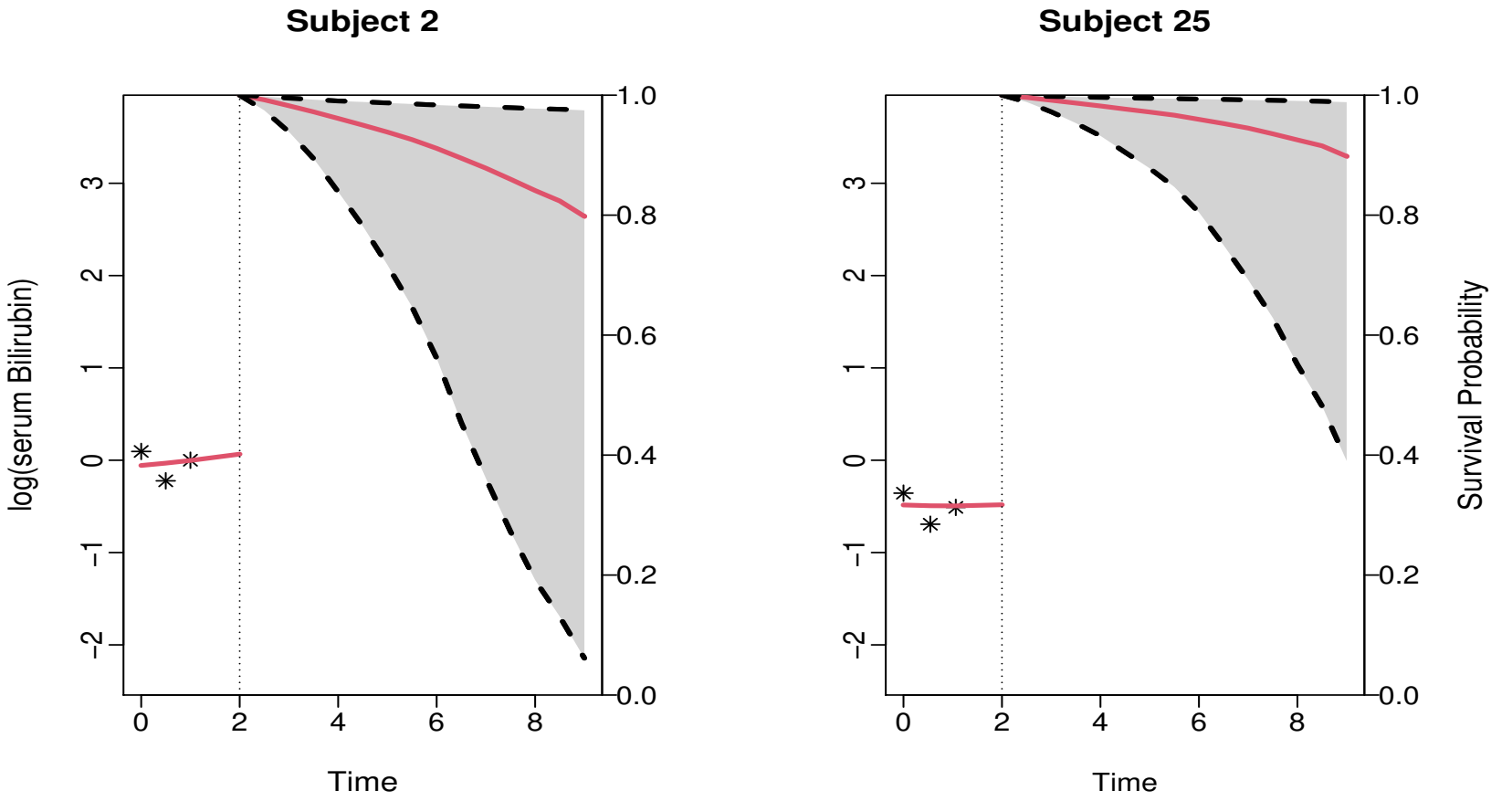
6.2 Survival Probabilities: Estimation (cont'd)



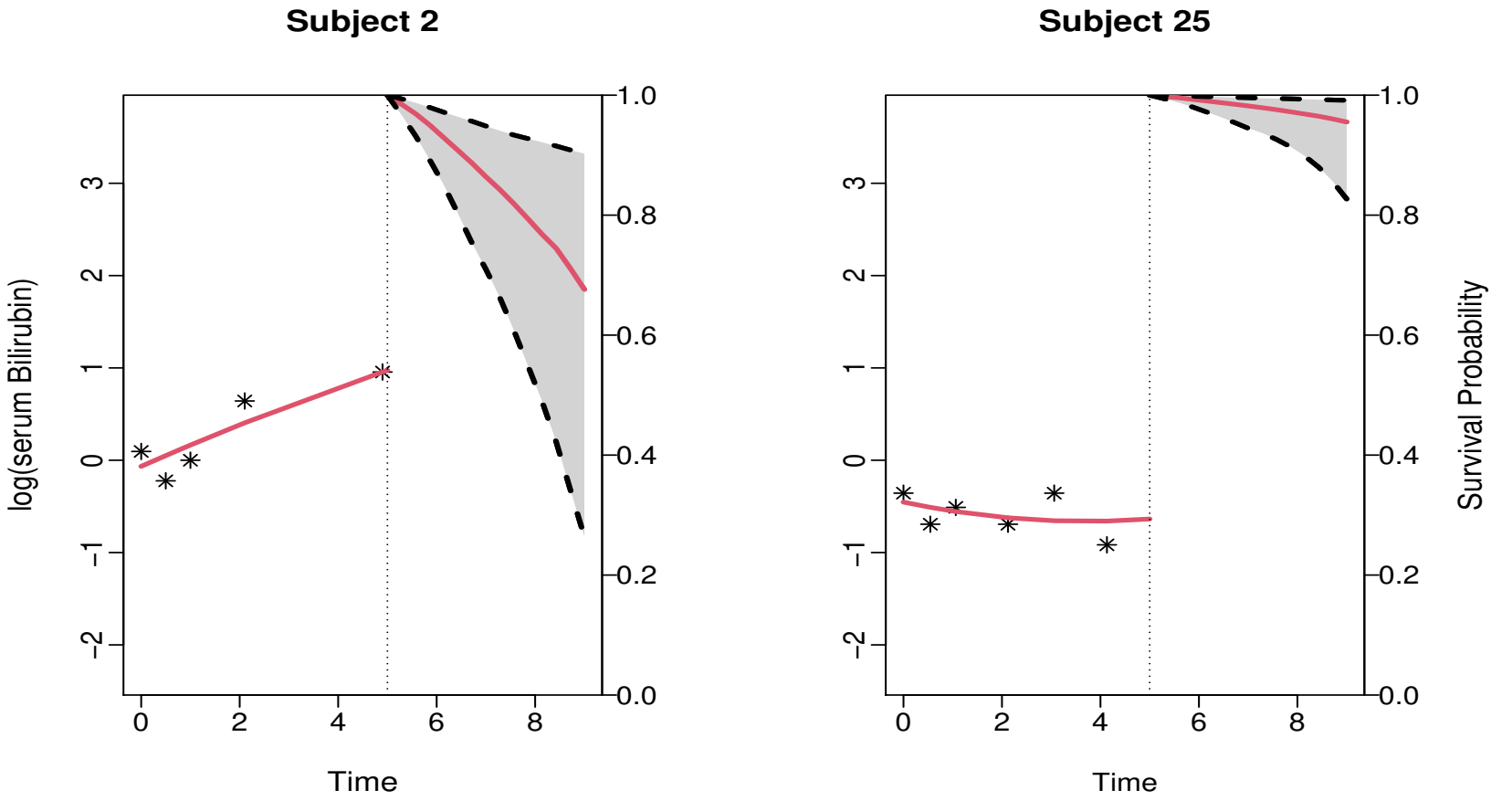
6.2 Survival Probabilities: Estimation (cont'd)



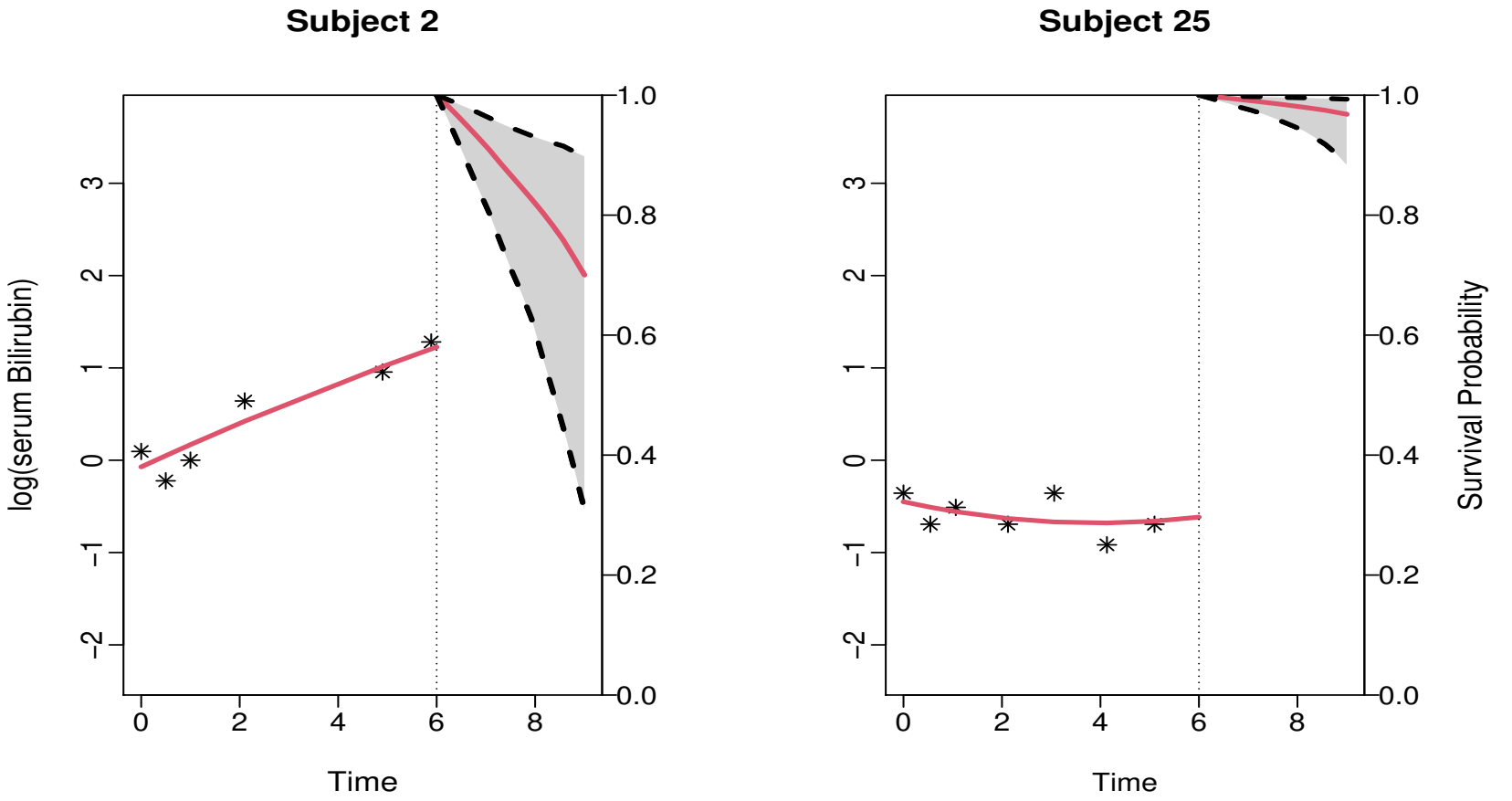
6.2 Survival Probabilities: Estimation (cont'd)



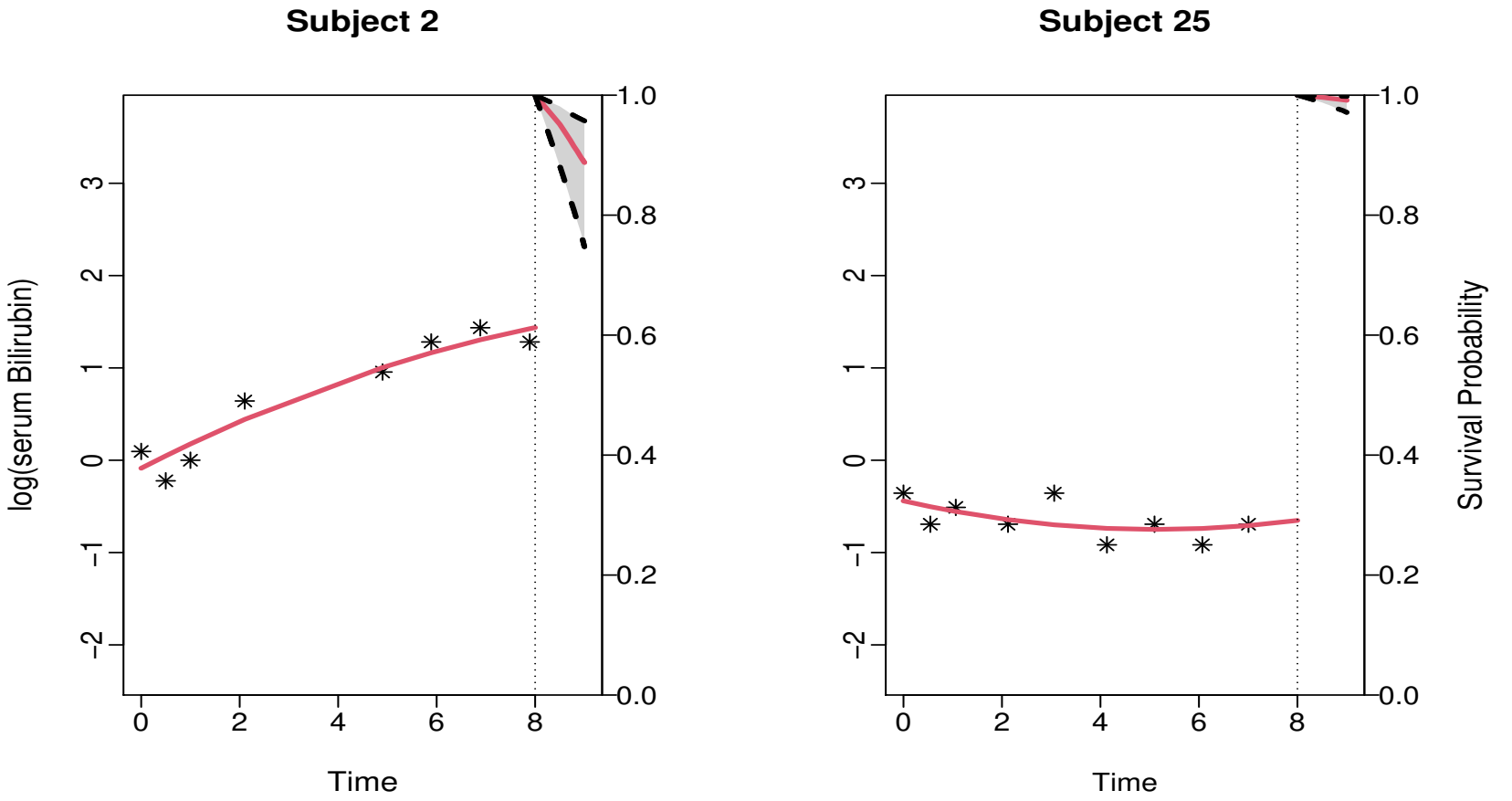
6.2 Survival Probabilities: Estimation (cont'd)



6.2 Survival Probabilities: Estimation (cont'd)



6.2 Survival Probabilities: Estimation (cont'd)



6.2 Survival Probabilities: Estimation (cont'd)

R> In package **JM**, individualized predictions of survival probabilities are computed by function `survfitJM()` – for example, for Patient 2 from the PBC dataset we have

```
sfit <- survfitJM(jointFit, newdata = pbc2[pbc2$id == "2", ])

sfit

plot(sfit)
plot(sfit, include.y = TRUE)
```

6.2 Survival Probabilities: Estimation (cont'd)

R> In package **JMbayes2**, individualized predictions of survival probabilities are computed by function `predict()` – for example, for Patient 2 from the PBC dataset we have

```
sfit <- predict(jointFit, newdata = pbc2[pbc2$id == "2", ],
                process = "event", return_newdata = TRUE)

sfit

plot(sfit)
```

6.3 Longitudinal Responses: Definitions

- In some occasions it may be also of interest to predict the longitudinal outcome

- We can proceed in the same manner as for the survival probabilities: We have available measurements up to time point t

$$\mathcal{Y}_j(t) = \{y_j(s), 0 \leq s \leq t\}$$

and we are interested in

$$\omega_j(u \mid t) = E\big\{y_j(u) \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\big\}, \quad u > t$$

6.3 Longitudinal Responses: Definitions (cont'd)

- To estimate $\omega_j(u \mid t)$ we can follow a similar approach as for $\pi_j(u \mid t)$ – Namely, $\omega_j(u \mid t)$ is written as:

$$E\{y_j(u) \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\} = \int E\{y_j(u) \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n; \theta\}\, p(\theta \mid \mathcal{D}_n)\, d\theta$$

- With the first part of the integrand given by:

$$E\{y_j(u) \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n; \theta\} =$$

$$= \int \{x_j^\top(u)\beta + z_j^\top(u) b_j\}\, p(b_j \mid T_j^* > t, \mathcal{Y}_j(t); \theta)\, db_j$$

6.3 Longitudinal Responses: Estimation (cont'd)

- A similar Monte Carlo simulation scheme:

Step 1. draw $\theta^{(\ell)} \sim \mathcal{N}(\hat{\theta}, \hat{\mathcal{H}})$

Step 2. draw $b_j^{(\ell)} \sim \{b_j \mid T_j^* > t, \mathcal{Y}_j(t), \theta^{(\ell)}\}$

Step 3. compute $\omega_j^{(\ell)}(u \mid t) = x_j^\top(u)\beta^{(\ell)} + z_j^\top(u)b_j^{(\ell)}$

- Note: Prediction intervals can be easily computed by replacing Step 3 with a draw from:

$$\omega_j^{(\ell)}(u \mid t) \sim \mathcal{N}\Big\{x_j^\top(u)\beta^{(\ell)} + z_j^\top(u)b_j^{(\ell)}, \quad [\sigma^2]^{(\ell)}\Big\}$$

6.3 Longitudinal Responses: Estimation (cont'd)

- Example: Dynamic predictions of serum bilirubin for Patients 2 & 25 from the PBC dataset: We fit the joint model

- Longitudinal submodel
  - ▷ fixed effects: Linear & quadratic time, treatment and their interaction
  - ▷ random effects: Intercept, linear & quadratic time effects

- Survival submodel
  - ▷ treatment effect + *underlying* serum bilirubin level
  - ▷ piecewise-constant baseline hazard in 7 intervals

6.3 Longitudinal Responses: Estimation (cont'd)

- Based on the fitted joint model we estimate $\omega_j(u \mid t)$ for Patients 2 and 25

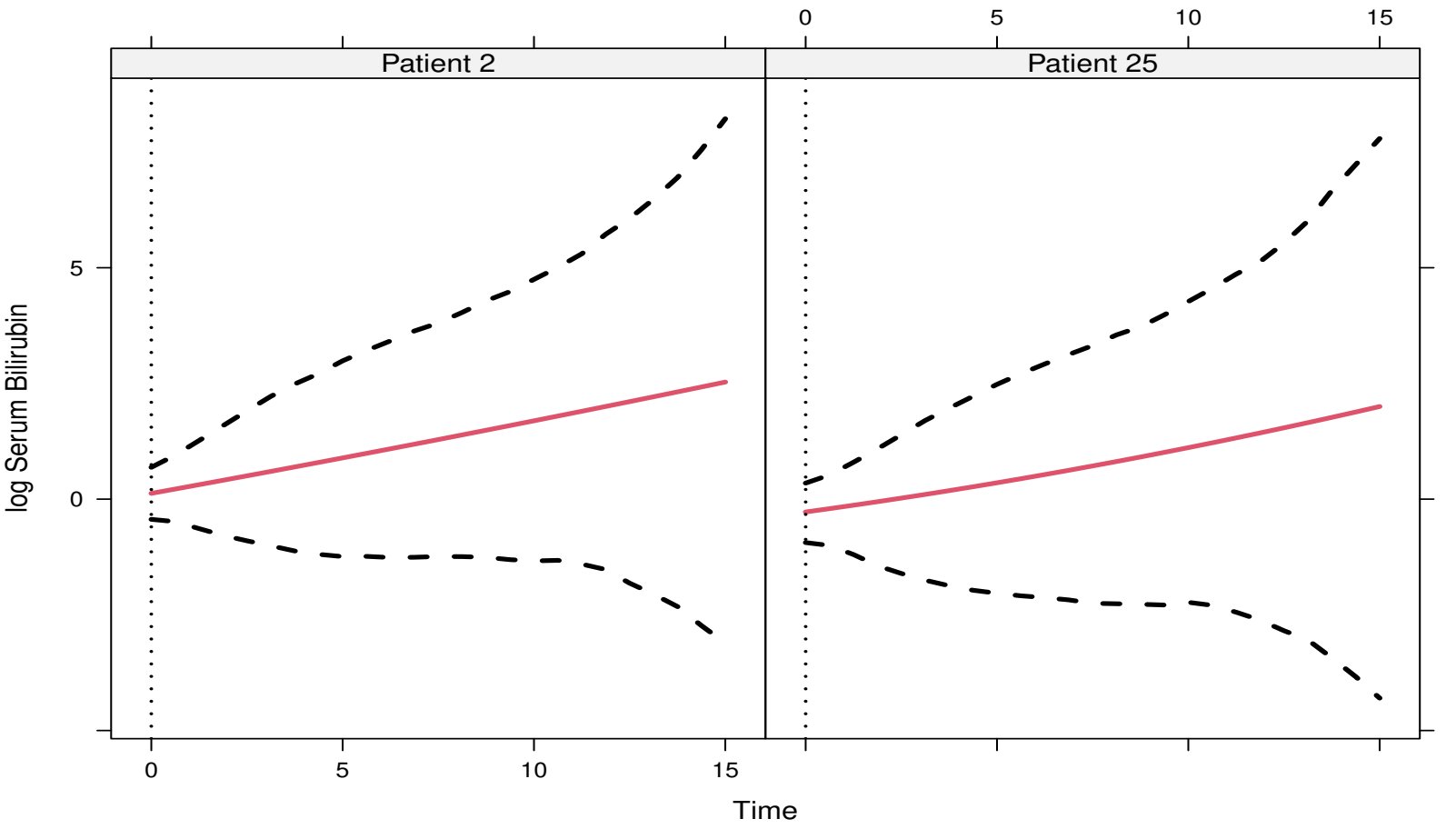
- Point estimates

$$\hat{\omega}_j(u \mid t) = x_j^\top(u)\hat{\beta} + z_j^\top(u)\hat{b}_j,$$

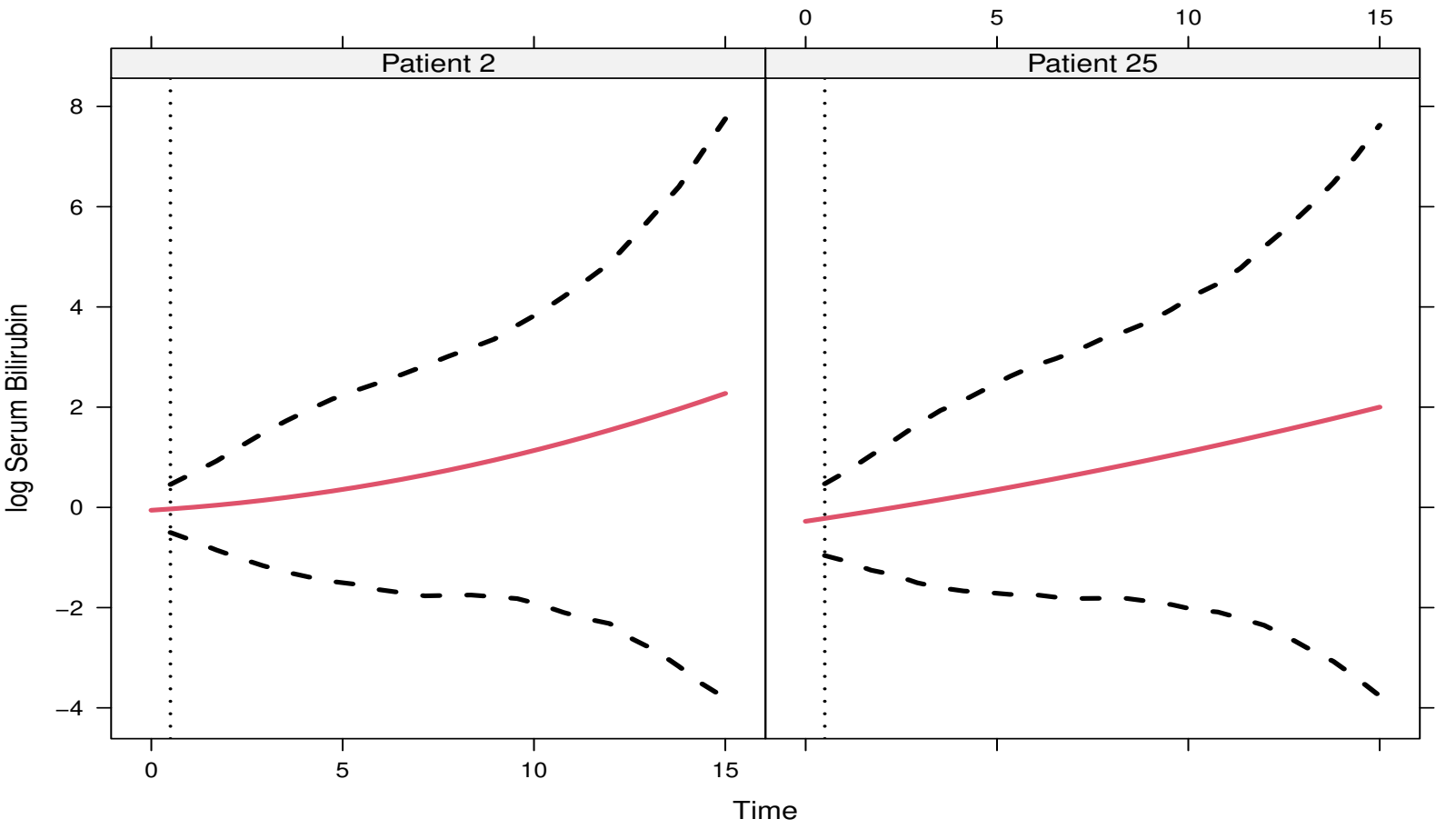
  where $\hat{\beta}$: MLEs & $\hat{b}_j$: empirical Bayes estimates

- 95% pointwise CIs
  - ▷ simulation scheme: 2.5% and 97.5% percentiles of 500 Monte Carlo samples of $\omega_j^{(\ell)}(u \mid t)$

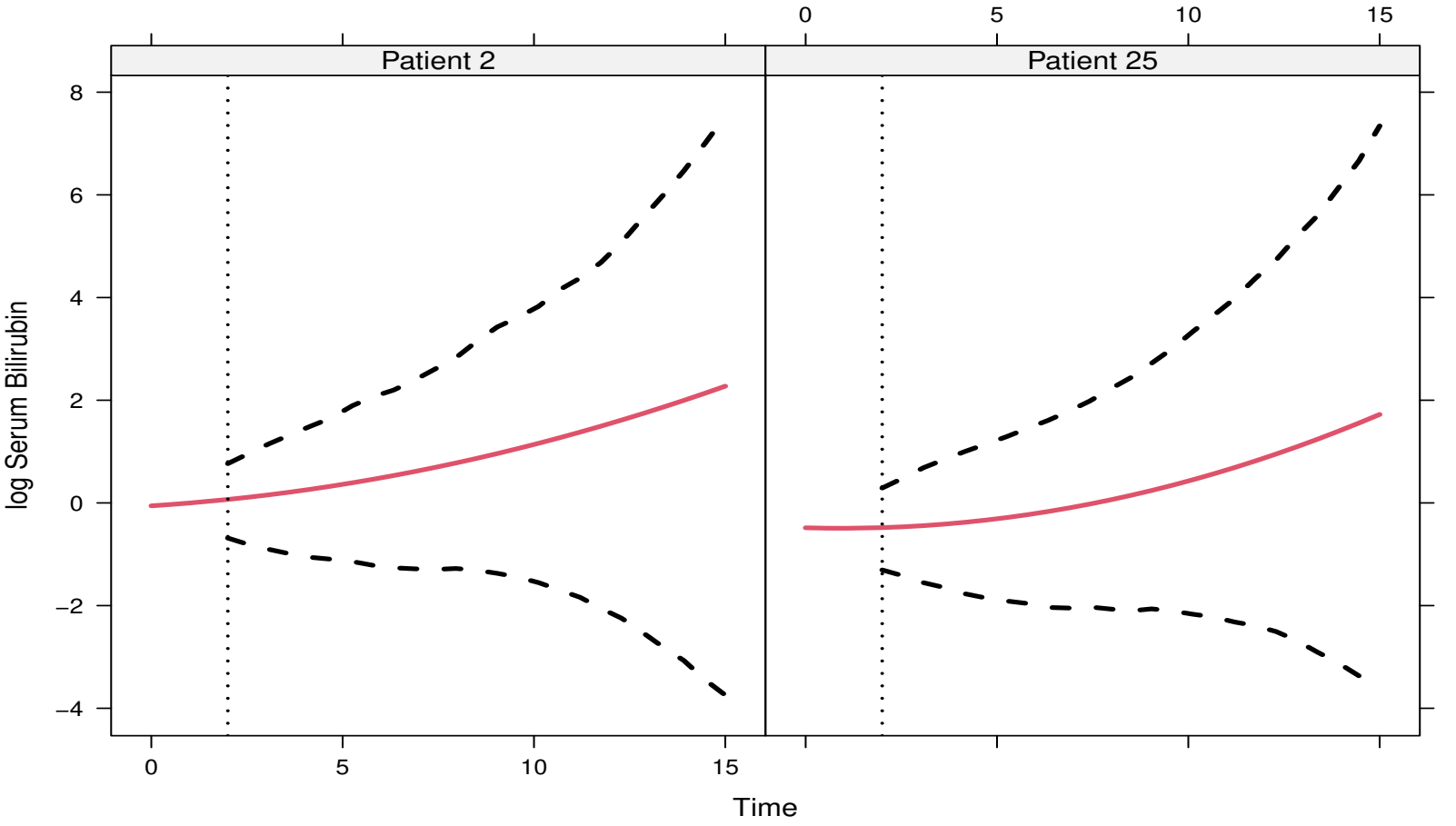
6.3 Longitudinal Responses: Estimation (cont'd)



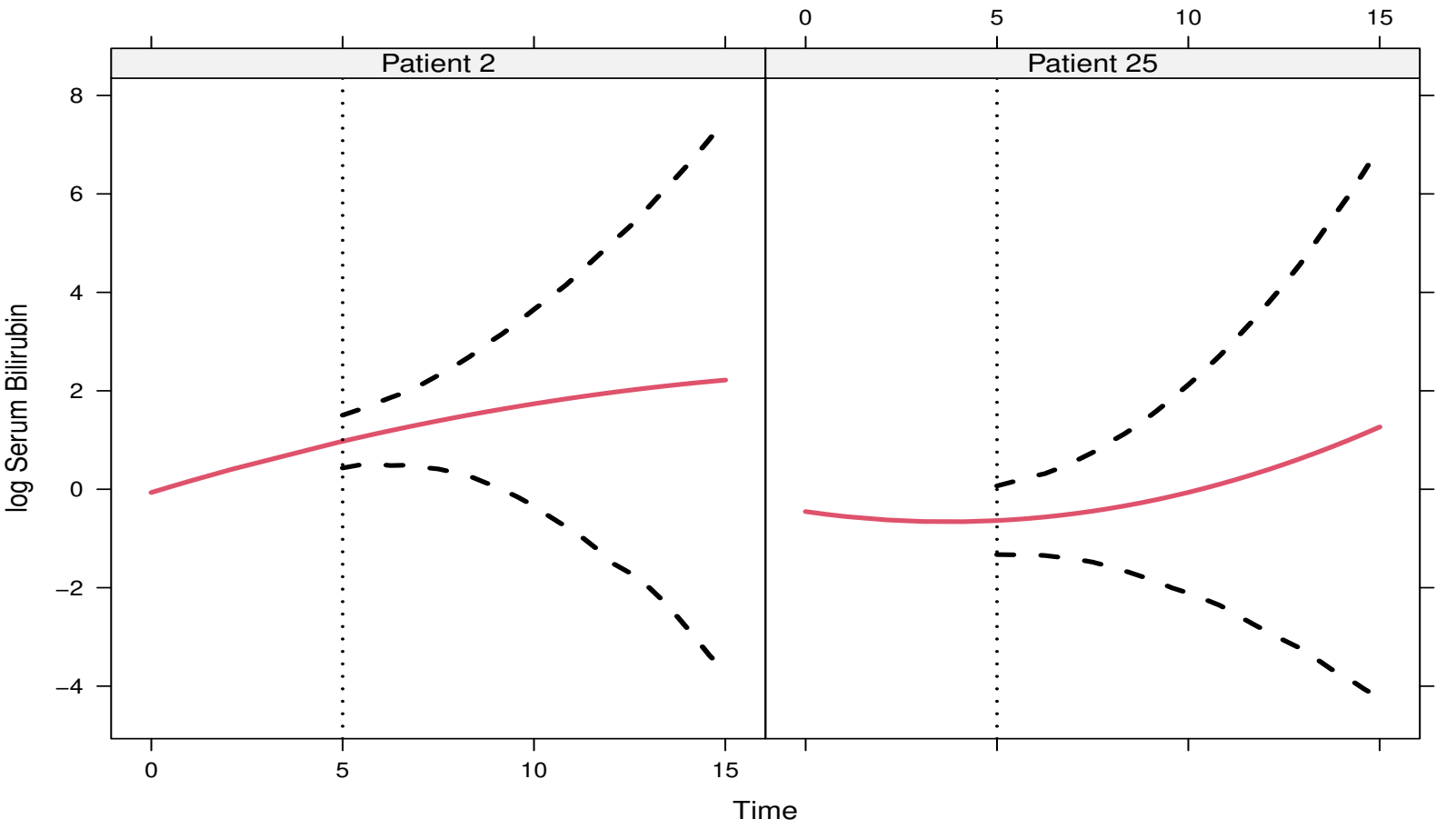
6.3 Longitudinal Responses: Estimation (cont'd)



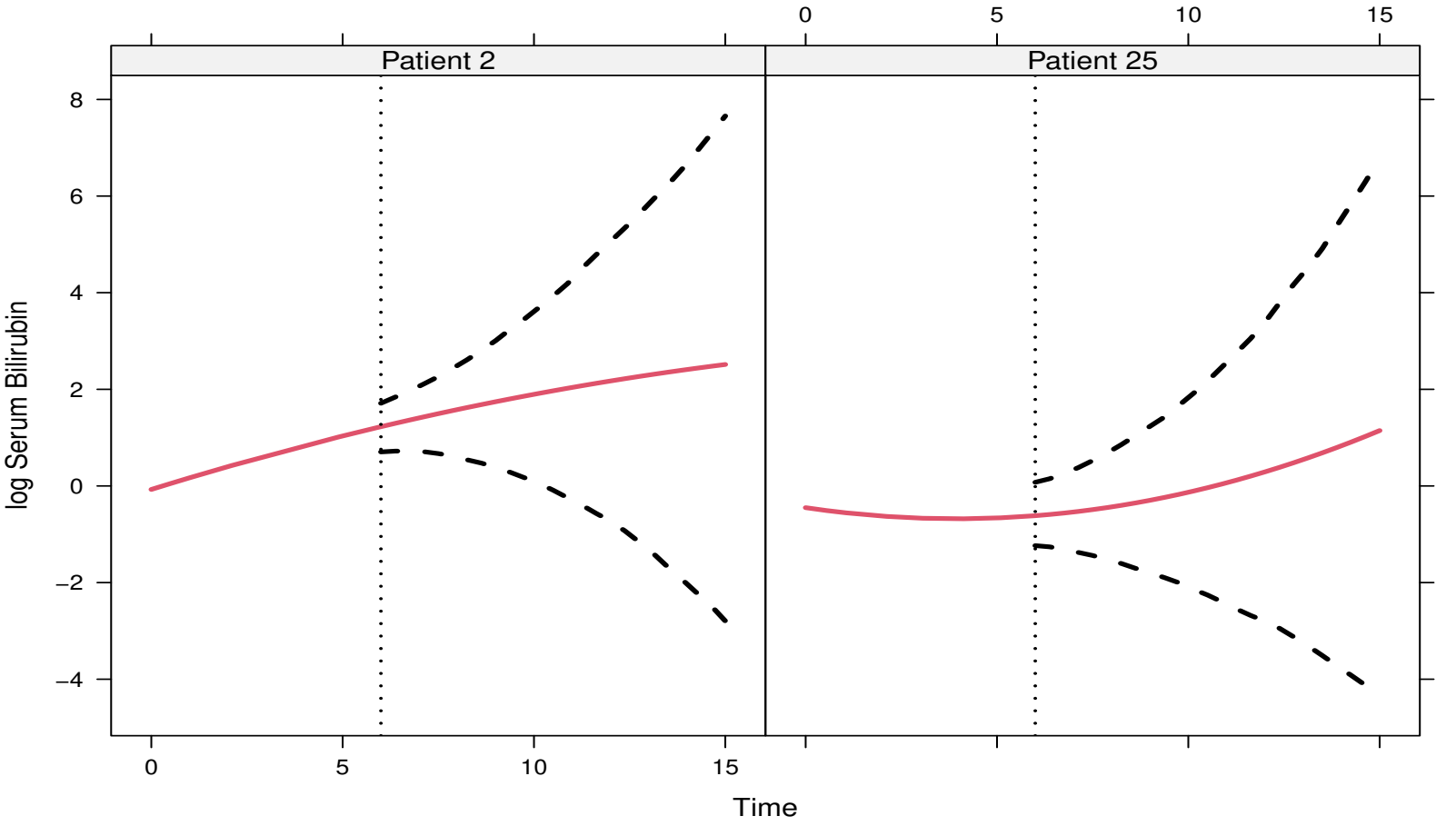
6.3 Longitudinal Responses: Estimation (cont'd)



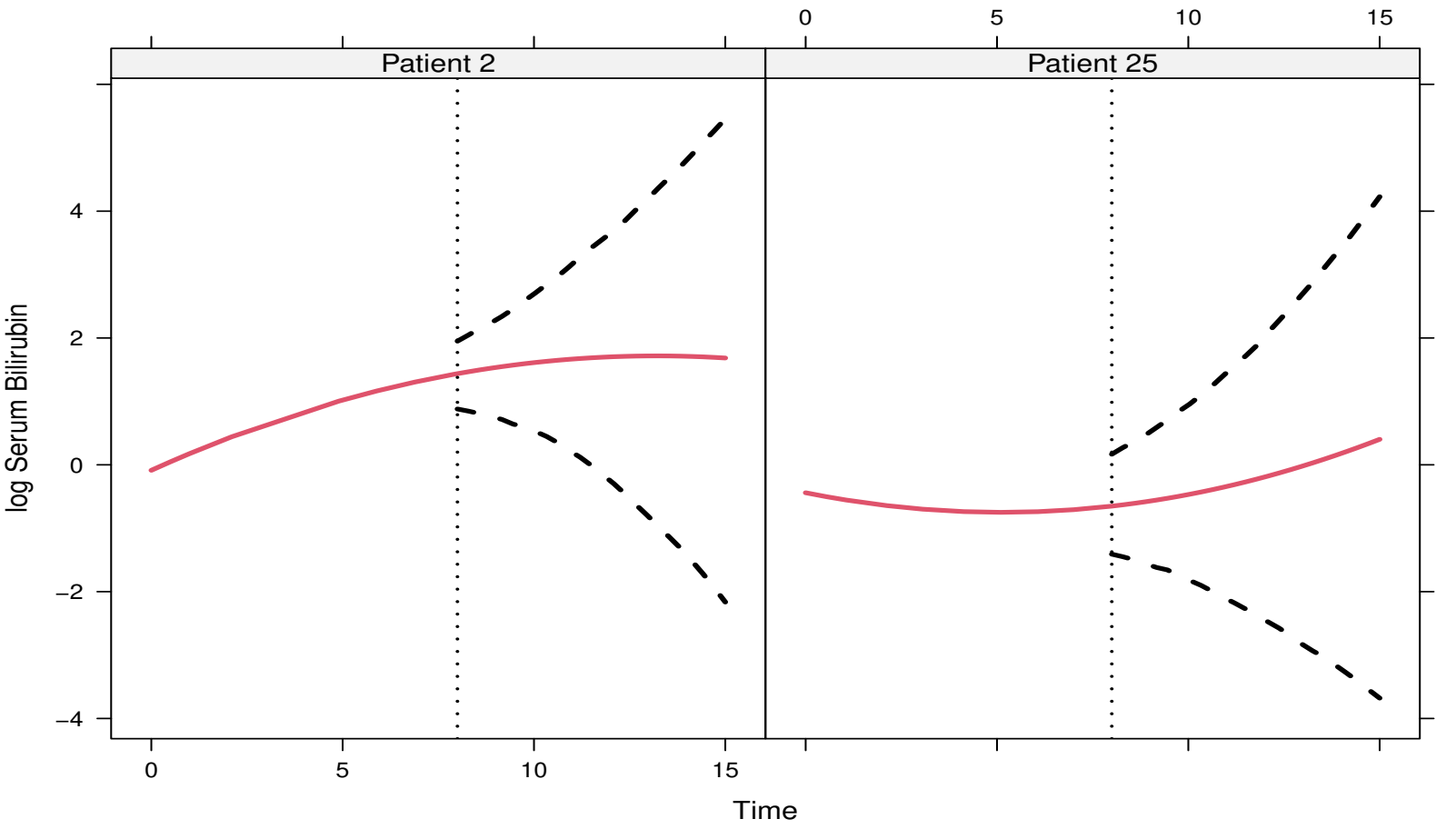
6.3 Longitudinal Responses: Estimation (cont'd)



6.3 Longitudinal Responses: Estimation (cont'd)



6.3 Longitudinal Responses: Estimation (cont'd)



6.3 Longitudinal Responses: Estimation (cont'd)

R> Individualized predictions for the longitudinal outcome are computed by function `predict()` – for example, for Patient 2 from the PBC dataset we have function

```
# in JM
lfit <- predict(jointFit, newdata = pbc2[pbc2$id == "2", ],
                type = "Subject", interval = "conf",
                returnData = TRUE)
# in JMbayes2
gfit <- predict(jointFit, newdata = pbc2[pbc2$id == "2", ],
                times = seq(7, 12, length.out = 51),
                return_newdata = TRUE)
```

6.3 Longitudinal Responses: Estimation (cont'd)

R> Web interface using the **shiny** package

```
library(shiny)

runApp(file.path(.Library, "JMbayes/demo"))
```

6.4 Importance of the Parameterization

- All previous predictions were based on the standard joint model

$$\begin{cases} h_i(t \mid \mathcal{M}_i(t)) &= h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}, \\ \\ y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \end{cases}$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

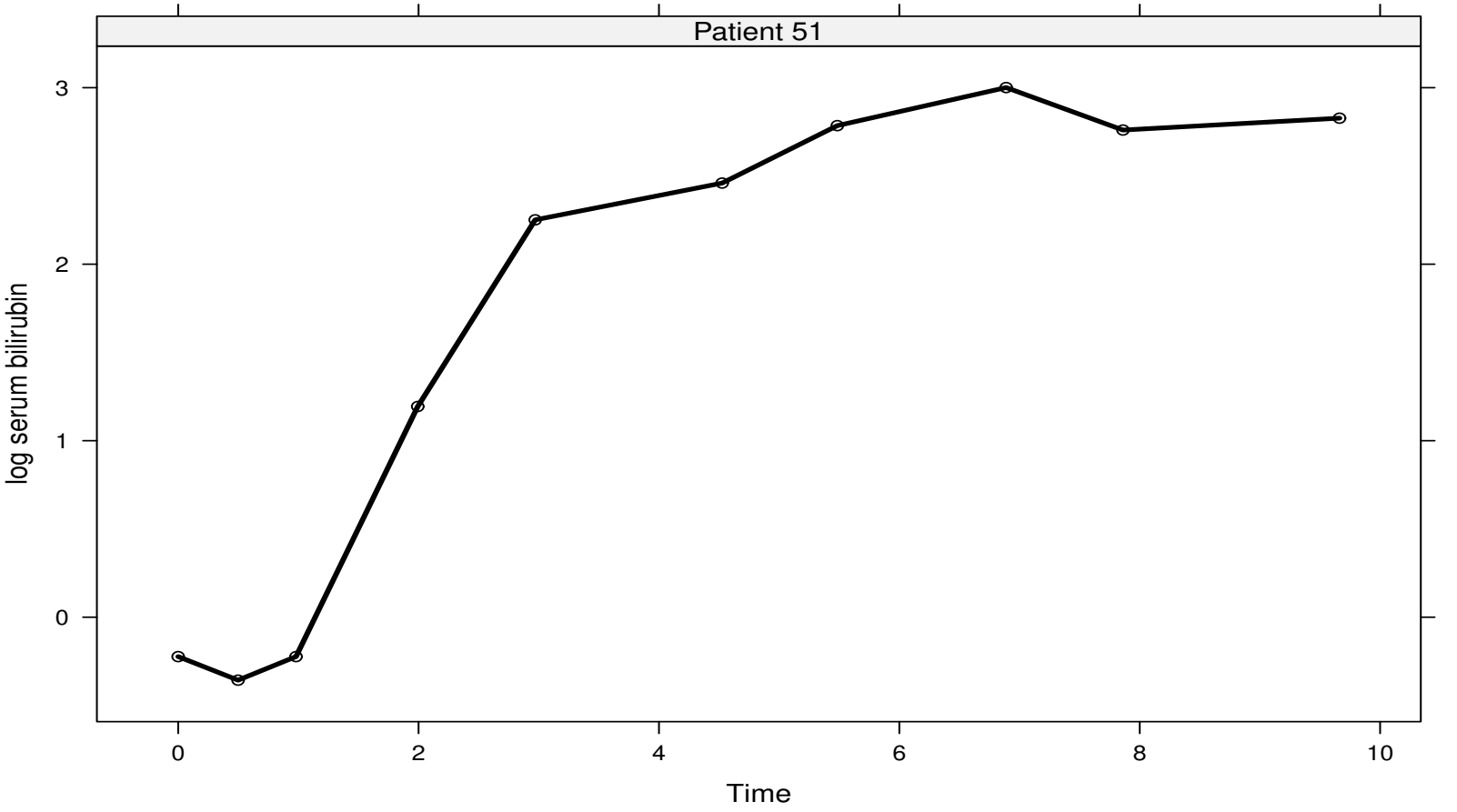
6.4 Importance of the Parameterization (cont'd)

- We have seen earlier that there are several alternative parameterizations (see Section 5.1)

- Relevant questions:
  - ▷ Does the assumed parameterization affect predictions?
  - ▷ Which parameterization is the most optimal?

- Example: We compare predictions for the longitudinal and survival outcomes under different parameterizations for Patient 51 from the PBC study

6.4 Importance of the Parameterization (cont'd)



6.4 Importance of the Parameterization (cont'd)

- Predictions based on five joint models for the PBC dataset
  - ▷ the same longitudinal submodel as before, and
  - ▷ relative risk submodels:

$$h_i(t) = h_0(t)\exp\{\gamma \texttt{D-pnc}_i + \alpha_1 m_i(t)\},$$

$$h_i(t) = h_0(t)\exp\{\gamma \texttt{D-pnc}_i + \alpha_2 m_i'(t)\},$$

$$h_i(t) = h_0(t)\exp\{\gamma \texttt{D-pnc}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

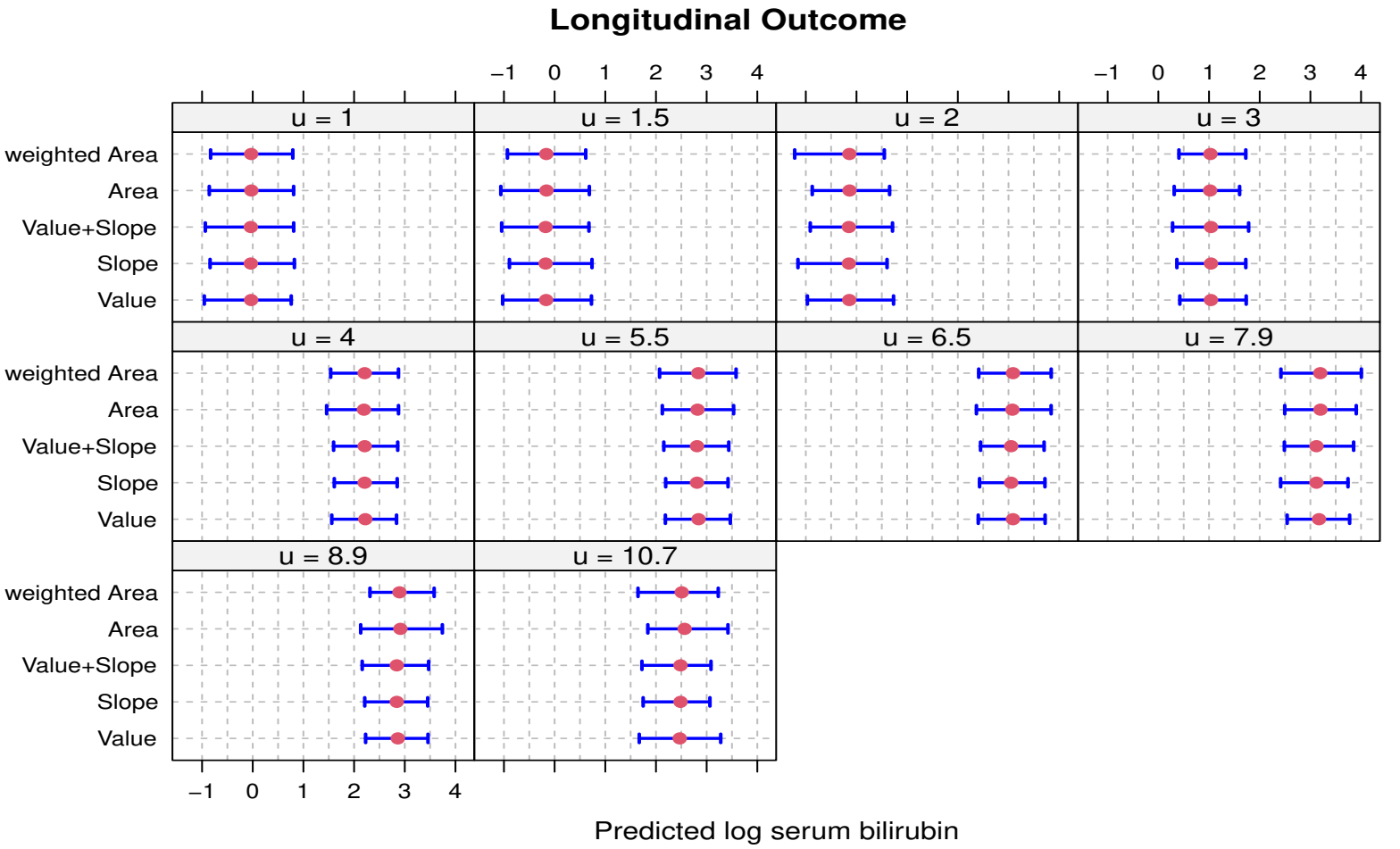
6.4 Importance of the Parameterization (cont'd)

$$h_i(t) = h_0(t) \exp\Big\{\gamma \texttt{D-pnc}_i + \alpha_3 \int_0^t m_i(s)ds\Big\},$$

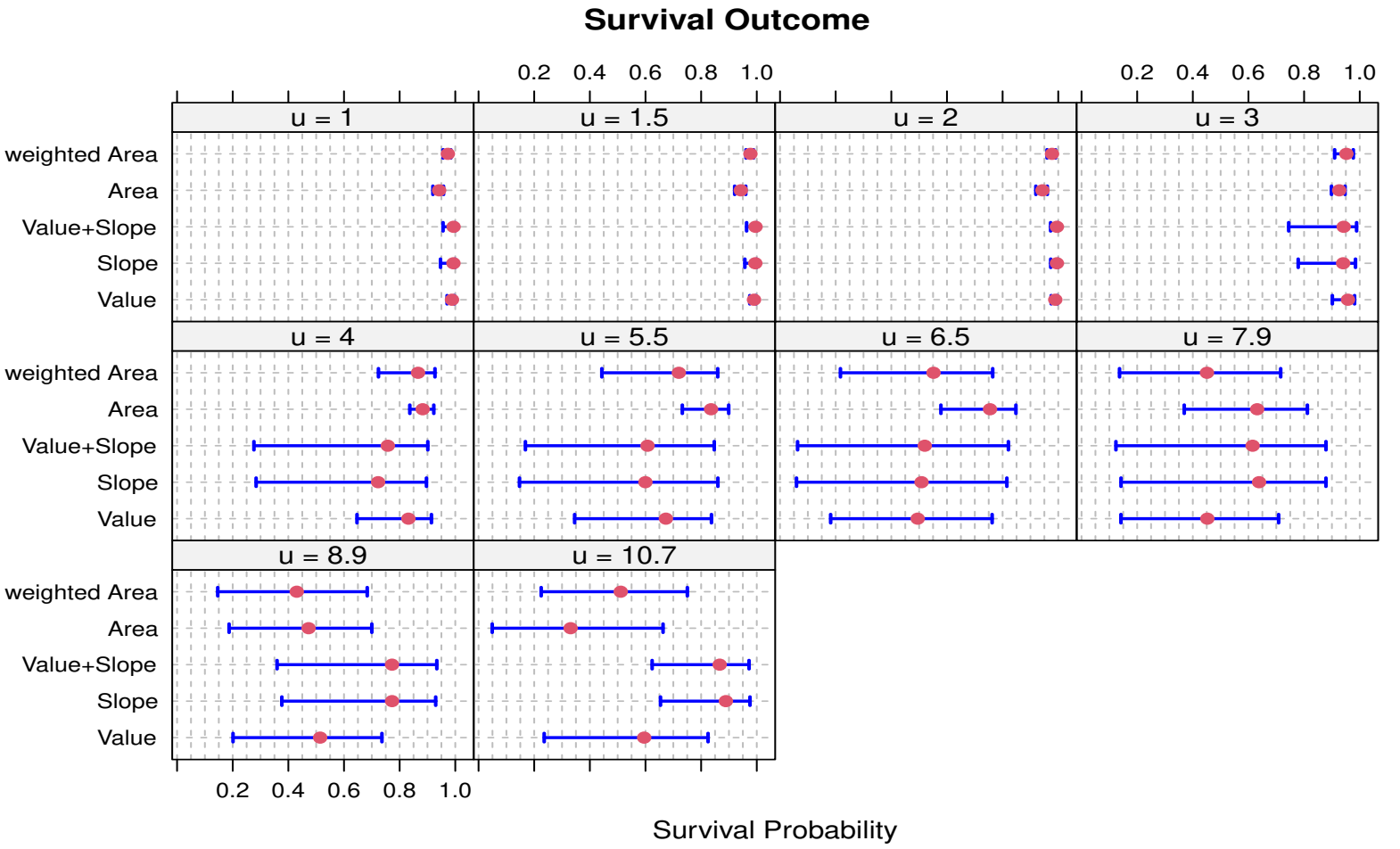
$$h_i(t) = h_0(t) \exp\Big\{\gamma \texttt{D-pnc}_i + \alpha_4 \int_0^t \phi(t-s) m_i(s)ds\Big\},$$

where $\phi(\cdot)$ standard normal pdf

6.4 Importance of the Parameterization (cont'd)



6.4 Importance of the Parameterization (cont'd)



6.4 Importance of the Parameterization (cont'd)

- The chosen parameterization can influence the derived predictions
  - ▷ especially for the survival outcome

- My current work: How to optimally choose parameterization?
  - ▷ per subject (personalized medicine)

- Quite promising results from the Bayesian approach using Bayesian Model Averaging techniques
  - ▷ it can be done with package **JMbayes**,
  - ▷ it falls a bit outside the scope of this course, but
  - ▷ I can provide information if interested...

6.5 Discrimination

- Often clinical interest lies in the predictive performance of a model
  - ▷ how good is a model in discriminating between patients of low and high risk of dying

- We develop and estimate prospective accuracy measures based on ROC methodology within the joint modeling framework

6.5 Discrimination (cont'd)

- We assume the following setting
  - ▷ using the available longitudinal data up to time t,
  - ▷ we are interested in events in the medically relevant interval $(t, t + \Delta t]$

- Based on the fitted joint model and for a particular threshold value $c \in [0, 1]$, we can term a subject as a **case** if

$$\pi_j(t + \Delta t \mid t) \leq c$$

6.5 Discrimination (cont'd)

- Following, we can define sensitivity

$$\Pr\{\pi_j(t + \Delta t \mid t) \leq c \mid T_j^* \in (t, t + \Delta t]\},$$

specificity

$$\Pr\{\pi_j(t + \Delta t \mid t) > c \mid T_j^* > t + \Delta t\},$$

and the corresponding AUC

$$\begin{aligned}&\text{AUC}(t, \Delta t)\\ &= \Pr\left[\pi_i(t + \Delta t \mid t) < \pi_j(t + \Delta t \mid t) \mid \{T_i^* \in (t, t + \Delta t]\} \cap \{T_j^* > t + \Delta t\}\right]\end{aligned}$$

6.5 Discrimination (cont'd)

- Estimation of AUC$(t, \Delta t)$ can be based on
  - ▷ similar arguments as Harrell's C index, or
  - ▷ inverse probability of censoring weighting

6.5 Model Discrimination (cont'd)

R> For a joint model fitted in **JM**, $\widehat{\text{AUC}}(t, \Delta t)$ is calculated by function `aucJM()` – for the PBC dataset

```
# AUC(t = 7, Delta t = 2)
aucJM(jointFit, newdata = pbc2, Tstart = 7, Dt = 2)
```

6.5 Model Discrimination (cont'd)

R> For a fitted joint model with **JMbayes2**, we calculate the ROC curve and the corresponding AUC

```
roc <- tvROC(jointFit, newdata = pbc2, Tstart = t0, Dt = 2)

roc

tvAUC(roc)
```

6.6 Prediction Error

- We have extensively covered *discrimination*, i.e.,
  - ▷ how well can the longitudinal biomarker(s) discriminate between subject of low and high risk of the event

- Another relevant measure for quantifying predictive ability is *calibration*, i.e.,
  - ▷ how well can the longitudinal biomarker(s) accurately predict future events

- In standard survival analysis and on the latter front there has been a lot of work on extensions of the Brier score (see Gerds and Schumacher, (2006) and references therein)

6.6 Prediction Error (cont'd)

- In the joint modeling framework we need to take into account the dynamic nature of the longitudinal marker

- The expected error of prediction has the form

$$\text{PE}(u \mid t) = E\big[L\{N_i(u) - \pi_i(u \mid t)\}\big]$$

  where

  ▷ $N_i(t) = I(T_i^* > t)$ is the event status at time t

  ▷ $L(\cdot)$ denotes a loss function, such as the absolute or square loss

6.6 Prediction Error (cont'd)

- An estimator for $\text{PE}(u \mid t)$ that accounts for censoring has been proposed by Henderson et al. (2002)

$$\widehat{\text{PE}}(u \mid t) = \{\mathcal{R}(t)\}^{-1} \sum_{i:T_i \geq t} I(T_i > u) L\{1 - \hat{\pi}_i(u \mid t)\} + \delta_i I(T_i < u) L\{0 - \hat{\pi}_i(u \mid t)\}$$
$$+(1 - \delta_i) I(T_i < u) \Big[\hat{\pi}_i(u \mid T_i) L\{1 - \hat{\pi}_i(u \mid t)\} + \{1 - \hat{\pi}_i(u \mid T_i)\} L\{0 - \hat{\pi}_i(u \mid t)\}\Big]$$

where

  - ▷ $\mathcal{R}(t)$ denotes the number of subjects at risk at t
  - ▷ **red part**: subjects still alive at u
  - ▷ **blue part**: subjects who died before u
  - ▷ **green part**: subject censored before u

6.6 Prediction Error (cont'd)

- $\mathsf{PE}(u \mid t)$ uses the longitudinal information up to time t and focuses on accuracy at single time point u
  - ▷ alternatively, we could summarize the error of prediction in a specific interval of interest, say $[t, u]$

- A weighted average of $\widehat{\mathsf{PE}}(u \mid t)$ that accounts for the reduction in the number of events due to censoring:

$$\widehat{\mathsf{IPE}}(u \mid t) = \frac{\sum_{i:t \leq T_i \leq u} \delta_i \{\widehat{S}_C(t)/\widehat{S}_C(T_i)\} \widehat{\mathsf{PE}}(u \mid t)}{\sum_{i:t \leq T_i \leq u} \delta_i \{\widehat{S}_C(t)/\widehat{S}_C(T_i)\}}$$

where

- ▷ $\widehat{S}_C(\cdot)$ denotes the Kaplan-Meier estimator of the censoring time distribution

6.6 Prediction Error (cont'd)

- Both $\widehat{\mathsf{IPE}}(u \mid t)$ and $\widehat{\mathsf{PE}}(u \mid t)$ can be used to provide a measure of explained variation between nested models

- Say model M_1 is nested in model M_2, we can compute how much the extra structure in M_2 improves accuracy by

$$R^2_{PE}(u \mid t; M_1, M_2) = 1 - \widehat{\mathsf{PE}}_{M_2}(u \mid t) \Big/ \widehat{\mathsf{PE}}_{M_1}(u \mid t)$$

or

$$R^2_{IPE}(u \mid t; M_1, M_2) = 1 - \widehat{\mathsf{IPE}}_{M_2}(u \mid t) \Big/ \widehat{\mathsf{IPE}}_{M_1}(u \mid t)$$

6.6 Prediction Error (cont'd)

R> For a fitted joint model $\widehat{\text{PE}}(u \mid t)$ and $\widehat{\text{IPE}}(u \mid t)$ are calculated by function `prederrJM()` – for the PBC dataset

```
# PE(u = 9 | t = 7)
prederrJM(jointFit, newdata = pbc2, Tstart = 7, Thoriz = 9)


# IPE(u = 9 | t = 7)
prederrJM(jointFit, newdata = pbc2, Tstart = 7, Thoriz = 9,
          interval = TRUE)
```

6.7 Validation

- Validation of both discrimination and calibration measures can be achieved with standard re-sampling techniques
  - ▷ cross-validation (leave-one-out or better 10-fold)
  - ▷ Bootstrap

- In general time consuming because it requires fitting the joint model many times
  - ▷ take advantage of parallel computing (e.g., using package **parallel**)

Part VII

Closing

7.1 Concluding Remarks

- **When we need joint models for longitudinal and survival outcomes?**
  - ▷ to handle endogenous time-varying covariates in a survival analysis context
  - ▷ to account for nonrandom dropout in a longitudinal data analysis context

- **How joint models work?**
  - ▷ a mixed model for the longitudinal outcome
  - ▷ a relative risk model for the event process
  - ▷ explain interrelationships with shared random effects

7.1 Concluding Remarks (cont'd)

- **Where to pay attention when defining joint models?**
  - ▷ model flexibly the subject-specific evolutions for the longitudinal outcome
  - ▷ use parametric but flexible models for the baseline hazard function
  - ▷ consider how to model the association structure between the two processes
    $\Rightarrow$ Parameterization

- **Extensions**
  - ▷ under the full conditional independence assumption we can easily extend the basic joint model
  - ▷ multiple longitudinal outcomes and/or multiple failure times
  - ▷ though more computationally intensive

7.1 Concluding Remarks (cont'd)

- **Individualized predictions**
  - ▷ joint models can provide subject-specific predictions for the longitudinal and survival outcomes
  - ▷ these are dynamically updated as extra information is recorded for the subjects
  - ▷ $\Rightarrow$ joint models constitute an excellent tool for personalized medicine

- **What we did not cover**
  - ▷ diagnostics for joint models using residuals
  - ▷ ...

The End!

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Part VIII

Practicals

8.1 Practical 1: A Simple Joint Model

- We will fit a simple joint model to the PBC dataset
- Start R and load package **JM**, using `library(JM)`
- The longitudinal (long format) and survival information for the PBC patients can be found in data frames `pbc2` and `pbc2.id`. The variables that we will need are:

8.1 Practical 1: A Simple Joint Model (cont'd)

- `pbc2`
  - `id`: patient id number
  - `serBilir`: serum bilirubin
  - `year`: follow-up times in years

- `pbc2.id`
  - `years`: observed event times in years
  - `status`: 'alive', 'transplanted', 'dead'
  - `drug`: treatment indicator

8.1 Practical 1: A Simple Joint Model (cont'd)

- T1: Fit the linear mixed effects model for log serum bilirubin using function `lme()`, assuming simple linear evolutions over time for each subject, i.e., a simple random-intercepts and random-slopes structure and different average evolutions per treatment group (see pp. 37–41)

$$y_i(t) = \beta_0 + \beta_1 t + \beta_2 \{\texttt{D-penic}_i \times t\} + b_{i0} + b_{i1} t + \varepsilon_i(t)$$

- T2: Create the indicator for the composite event (i.e., 'alive' = 0, 'transplanted' or 'dead' = 1) using the code

```
pbc2.id$status2 <- as.numeric(pbc2.id$status != "alive")
```

8.1 Practical 1: A Simple Joint Model (cont'd)

- T3: Fit the Cox PH model using `coxph()` that includes only treatment as baseline covariate, remember to set `x = TRUE` (see pp. 67–68)

- We want to fit the joint model

$$\begin{cases} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 t + \beta_2 \{\texttt{D-penic}_i \times t\} + b_{i0} + b_{i1} t + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \\ \\ h_i(t) &= h_0(t) \exp\{\gamma \texttt{D-penic}_i + \alpha m_i(t)\}, \end{cases}$$

8.1 Practical 1: A Simple Joint Model (cont'd)

- T4: Fit this joint model based on the fitted linear mixed and Cox models using function `jointModel()` (see pp. 106–108)

  ▷ with piecewise-constant baseline hazard & the (pseudo) adaptive GH rule

- T5: Use the `summary()` method to obtain a detailed output of the fitted joint model – interpret the results

- T6: Produce 95% confidence intervals for the parameters in the longitudinal submodel, and for the hazard ratios in the survival submodel using function `confint()` (the `parm` argument of `confint()` can take as values `"all"` (default), `"Longitudinal"` and `"Event"`)

8.1 Practical 1: A Simple Joint Model (cont'd)

- This model assumes that the strength of the association between the level of serum bilirubin and the risk for the composite event is the same in the the two treatment groups

- To relax this additivity assumption we will add the interaction effect between serum bilirubin and treatment

$$\begin{cases} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 t + \beta_2 \{\texttt{D-penic}_i \times t\} + b_{i0} + b_{i1} t + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \\ \\ h_i(t) &= h_0(t) \exp\big[\gamma \texttt{D-penic}_i + \alpha_1 m_i(t) + \alpha_2 \{\texttt{D-penic}_i \times m_i(t)\}\big], \end{cases}$$

8.1 Practical 1: A Simple Joint Model (cont'd)

- To fit this model with package **JM** we need to define the `interFact` argument of `jointModel()`. This should be a named `list` with two elements:
  - ▷ `value`: a formula with the factors for which we wish to calculate the interaction terms
  - ▷ `data`: the data frame used to fit the Cox model

- T7: Define this list and fit the corresponding joint model. Use the `summary()` method to obtained a detailed output and interpret the results

8.1 Practical 1: A Simple Joint Model (cont'd)

- Based on the fitted joint model we can test for three treatment effects, namely
  - ▷ in the longitudinal process:

$$H_0 : \beta_2 = 0$$

  - ▷ in the survival process:

$$H_0 : \gamma = \alpha_2 = 0$$

  - ▷ in the joint process:

$$H_0 : \beta_2 = \gamma = \alpha_2 = 0$$

8.1 Practical 1: A Simple Joint Model (cont'd)

- We would like test these hypotheses using likelihood ratio tests

- T8: Fit the three joint models under the corresponding H_0, and use function `anova()` to perform the LRTs (this function accepts as a first argument the joint model under the null, and as second the joint model under the alternative)

8.2 Practical 2: Challenging `jointModel()`

- T1: Download the workspace `DataPract2.RData` from `http://jmr.r-forge.r-project.org/DataPract2.RData` and load it to R (File → Load Workspace...)

- In this workspace there are the two datasets
  - `dataLong`
    - `patnr`: patient id number
    - `lnY`: longitudinal response variable
    - `obstime`: follow-up time
    - `age`: the age of the patients
    - `gender`: the gender of the patients

8.2 Practical 2: Challenging `jointModel()` (cont'd)

and

- `dataSurv`
  - `eventTime`: observed event times
  - `event`: 0 censored, 1 event
  - `age`: the age of the patients
  - `gender`: the gender of the patients

8.2 Practical 2: Challenging `jointModel()` (cont'd)

- We will fit a joint model in which
  - ▷ longitudinal submodel: linear subject-specific random slopes

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ m_i(t) &= (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + \beta_2 \texttt{age}_i + \beta_3 \texttt{gender}_i \end{aligned}$$

  - ▷ survival submodel: age, gender & the *true* effect of lnY

$$h_i(t) = h_0(t) \exp\{\gamma_1 \texttt{age}_i + \gamma_2 \texttt{gender}_i + \alpha m_i(t)\}$$

$h_0(t)$ taken piecewise-constant

8.2 Practical 2: Challenging `jointModel()` (cont'd)

- T2: Fit the linear mixed effects model for lnY using function `lme()`, controlling for age and gender, and assuming a diagonal matrix for the random effects (see pp. 37–41)

- T3: Fit the Cox PH model using `coxph()` that includes Age and Gender (see pp. 67–68)

- T4: Fit the corresponding joint model based on the fitted linear mixed and Cox models using function `jointModel()` (see pp. 106–108)

  ▷ with piecewise-constant baseline hazard & the (pseudo) adaptive GH rule

  ⇒ What do you observe?

8.2 Practical 2: Challenging `jointModel()` (cont'd)

- T5: Refit the joint model setting `verbose = TRUE`. This will print the parameter values during the optimization ⇒ What do you observe?

- T6: Refit the joint model by appropriately adjusting the `init` argument (check the help page of `jointModel()` for the syntax)

8.3 Practical 3: Using `derivForm`

- We will fit a joint model for the PBC dataset
  - ▷ longitudinal submodel: linear and quadratic subject-specific random slopes for log serum bilirubin

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ m_i(t) &= (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + (\beta_2 + b_{i2})t^2 \end{aligned}$$

  - ▷ survival submodel: *true* effect of log serum bilirubin

$$h_i(t) = h_0(t) \exp\{\alpha m_i(t)\}$$

$h_0(t)$ taken piecewise-constant

8.3 Practical 3: Using `derivForm` (cont'd)

- Start R and load package **JM**, using `library(JM)`

- The longitudinal (long format) and survival information for the PBC patients can be found in data frames `pbc2` and `pbc2.id`. The variables that we will need are:
  - ▷ `pbc2`
    - * `id`: patient id number
    - * `serBilir`: serum bilirubin
    - * `year`: follow-up times in years
  - ▷ `pbc2.id`
    - * `years`: observed event times in years
    - * `status`: 'alive', 'transplanted', 'dead'

8.3 Practical 3: Using `derivForm` (cont'd)

- T1: Fit the linear mixed effects model for log serum bilirubin using function `lme()` and assuming linear and quadratic evolutions over time for each subject, and a diagonal matrix for the random effects (see pp. 37–41), i.e.,

$$y_i(t) = m_i(t) + \varepsilon_i(t)$$

$$m_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + (\beta_2 + b_{i2})t^2$$

- T2: Create the indicator for the composite event (i.e., 'alive' = 0, 'transplanted' or 'dead' = 1) using the code

```
pbc2.id$status2 <- as.numeric(pbc2.id$status != "alive")
```

8.3 Practical 3: Using `derivForm` (cont'd)

- T3: Fit the null Cox PH model using `coxph()` that does not include any covariates, remember to set `x = TRUE` (see pp. 67–68)

- T4: Fit the corresponding joint model based on the fitted linear mixed and Cox models using function `jointModel()` (see pp. 106–108)

  ▷ with piecewise-constant baseline hazard & the (pseudo) adaptive GH rule

- We want to extend the previous joint model and include the current value and the time-dependent slope term, i.e.,

$$h_i(t) = h_0(t) \exp\{\alpha_1 m_i(t) + \alpha_2 m_i'(t)\}$$

8.3 Practical 3: Using `derivForm` (cont'd)

- The derivative of $m_i(t)$ with respect to time is

$$m_i'(t) = \frac{dm_i(t)}{dt} = (\beta_1 + b_{i1}) + 2(\beta_2 + b_{i2})t$$

- To fit this joint model we need to specify the `derivForm` argument, which is a `list` with four elements
  - ▷ `fixed`: a formula describing the fixed part of $m_i'(t)$
  - ▷ `random`: a formula describing the random part of $m_i'(t)$
  - ▷ `indFixed`: index denoting which β of $m_i(t)$ are involved in the calculation of $m_i'(t)$
  - ▷ `indRandom`: index denoting which b_i of $m_i(t)$ are involved in the calculation of $m_i'(t)$

8.3 Practical 3: Using `derivForm` (cont'd)

- Rewriting $m_i(t)$ and $m_i'(t)$ to split in a fixed and random part

$$m_i(t) = (\beta_0 + \beta_1 t + \beta_2 t^2) + (b_{i0} + b_{i1} t + b_{i2} t^2)$$

$$m_i'(t) = (\beta_1 + 2\beta_2 t) + (b_{i1} + 2 b_{i2} t)$$

Thus, the `list` to supply to `derivForm` will have the form

```
dForm <- list(
    fixed = ~ I(2*year),
    random = ~ I(2*year),
    indFixed = c(2,3),
    indRandom = c(2,3)
)
```

8.3 Practical 3: Using `derivForm` (cont'd)

- T5: Fit the joint model that includes both $m_i(t)$ and $m_i'(t)$ (see pp. 141–142)
  - ▷ you will need to set `parameterization = "both"`, and
  - ▷ for argument `derivForm` use the `dForm` list we defined above

8.3 Practical 3: Using `derivForm` (cont'd)

- We would like again to fit the joint model that includes both $m_i(t)$ and $m_i'(t)$, but now we would like to model the subject-specific longitudinal profiles more flexibly using regression splines

- T6: Re-fit the linear mixed model using natural cubic splines with 3 d.f. To do this you need to use function `ns()` from package **splines** (which is automatically loaded when you load **JM**)

  ▷ assume again a diagonal covariance matrix for the random effects

8.3 Practical 3: Using `derivForm` (cont'd)

- To fit the joint models, we again require to appropriately define the `derivForm` argument
  - ▷ Problem: How can I calculate the derivative of natural cubic spline
  - ▷ Solution: Theoretically a bit difficult, but we can do it easily in practice numerically (i.e., using numerical derivatives). This is already implemented in function `dns()`

T7: Using `dns()` define the list with the R formulas and index vector for the fixed and random effects, respectively, and fit the joint model

8.4 Practical 4: Dynamic Predictions

- We will work with the Liver Cirrhosis dataset
  - ▷ a placebo-controlled randomized trial on 488 liver cirrhosis patients

- Start R and load package **JM**, using `library(JM)`

- The longitudinal (long format) and survival information for the liver cirrhosis patients can be found in data frames `prothro` and `prothros`, respectively. The variables that we will need are:

8.4 Practical 4: Dynamic Predictions (cont'd)

- `prothro`
  - `id`: patient id number
  - `pro`: prothrobin measurements
  - `time`: follow-up times in years
  - `treat`: randomized treatment

- `prothros`
  - `Time`: observed event times in years
  - `death`: event indicator with 0 = 'alive', and 1 = 'dead'
  - `treat`: randomized treatment

8.4 Practical 4: Dynamic Predictions (cont'd)

- We will fit the following joint model to the Liver Cirrhosis dataset
  - ▷ longitudinal submodel: linear subject-specific random slopes for prothrobin levels allowing for different average evolutions in the two treatment groups

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ m_i(t) &= \beta_0 + \beta_1 t + \beta_2 \{\texttt{Trt}_i \times t\} + b_{i0} + b_{i1} t \end{aligned}$$

  - ▷ survival submodel: treatment effect & *true* effect of prothrobin

$$h_i(t) = h_0(t) \exp\{\gamma \texttt{Trt}_i + \alpha m_i(t)\}$$

$h_0(t)$ taken piecewise-constant

8.4 Practical 4: Dynamic Predictions (cont'd)

- T1: Fit the linear mixed model using `lme()`, the Cox model using `coxph()`, and the corresponding joint model using `jointModel()`

- We are interested in producing predictions of survival probabilities for Patient 155

- T2: Extract the data of Patient 155 using the code

```
dataP155 <- prothro[prothro$id == 155, ]
```

8.4 Practical 4: Dynamic Predictions (cont'd)

- T3: Using the first measurement of Patient 155, and the fitted joint model calculate his conditional survival probabilities using function `survfitJM()` and plot it using the `plot` method (see p. 190)

- T4: Repeat the same procedure by including each time the next measurement of Patient 155 and see how his survival probabilities evolve dynamically over time as extra prothrobin measurements are recorded

  ▷ check arguments `conf.int` and `fill.area` of the `plot()` method for including the 95% confidence intervals

8.4 Practical 4: Dynamic Predictions (cont'd)

- T5: Similarly, produce predictions for future longitudinal responses of Patient 155 using the `predict()` method for fitted joint models (see p. 197)
  - ▷ first using only the first measurement,
  - ▷ and following update the predictions after each new longitudinal measurement has been recorded

- T6: Calculate the AUC under the postulated model at year 2 and with a half a year window (see p. 211)

- T7: Do the same for the prediction error (see p. 218)