

# Joint Modelling of Longitudinal and Survival Data: Tools to Evaluate Exposures and Predict Outcome Across the Lifespan

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*material based on work by Dimitris Rizopoulos*

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# What is this Course About

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- Often in follow-up studies different types of outcomes are collected
- **Explicit** outcomes
  - ▷ multiple longitudinal responses (e.g., biomarkers, blood values)
  - ▷ time-to-event(s) of particular interest (e.g., death, treatment)

# What is this Course About (cont'd)

---

- Methods for the separate analysis of such outcomes are well established in the literature
- **Longitudinal data:**
  - ▷ mixed effects models, GEE, ...
- **Survival data:**
  - ▷ Cox model, accelerated failure time models, ...

# What is this Course About (cont'd)

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

**Joint Modeling Framework  
for Longitudinal and Survival Data**



# Learning Objectives

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- **Goals:** After this workshop 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 workshop will be explanatory rather than mathematically rigorous
  - ▷ emphasis is given on applications

- **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

## Agenda (cont'd)

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- **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

## Agenda (cont'd)

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- **Part V:** Extensions of the Basic Joint Model

- ▷ Parameterizations
- ▷ Variable selection
- ▷ Time-varying effects

- **Part VI:** Dynamic Predictions

- ▷ Individualized predictions for the survival

# Structure of the Course & Material

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- Lectures & short software practicals using R package **JMbayes**

- Material (also available in

<https://github.com/ERandrinopoulou/JointModelsWorkshopCincinnati2018>):

- ▷ Course Notes (slides)
- ▷ R code in soft format (app)
- ▷ Practicals with solutions

- **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.

## References (cont'd)

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- Useful material for package **JMbayes**
  - ▷ a paper describing the current capabilities of the package is available on JSS  
<http://dx.doi.org/10.18637/jss.v072.i07>

## References (cont'd)

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- 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.



## References (cont'd)

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- 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.

# Chapter 1

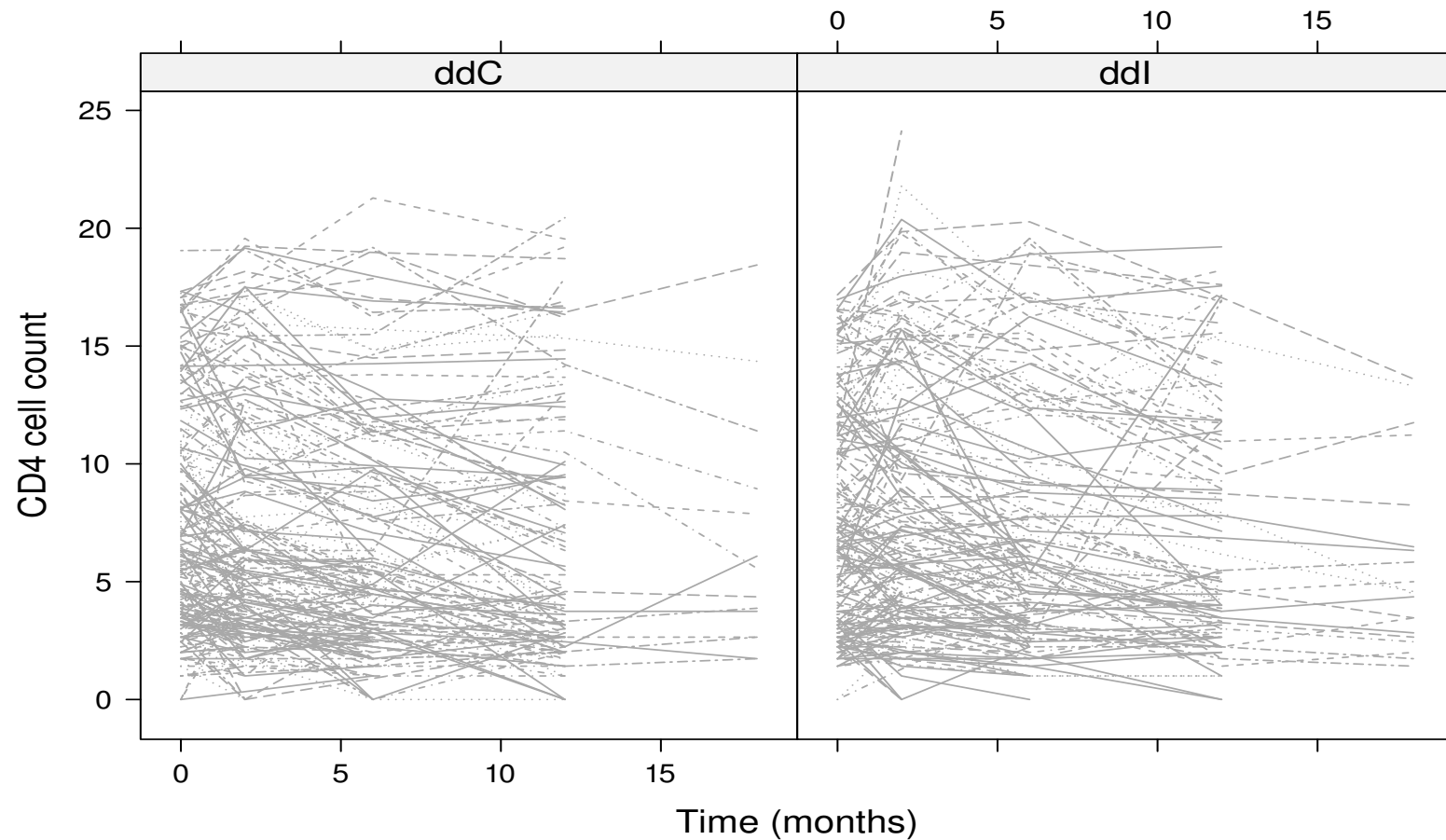
## Introduction

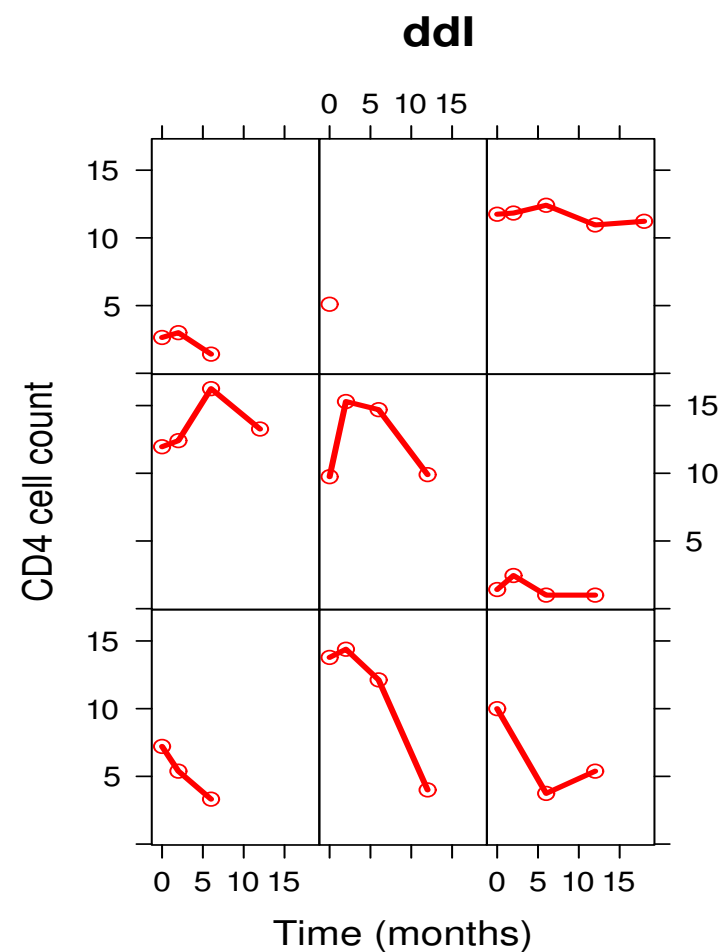
## 1.1 Motivating Studies

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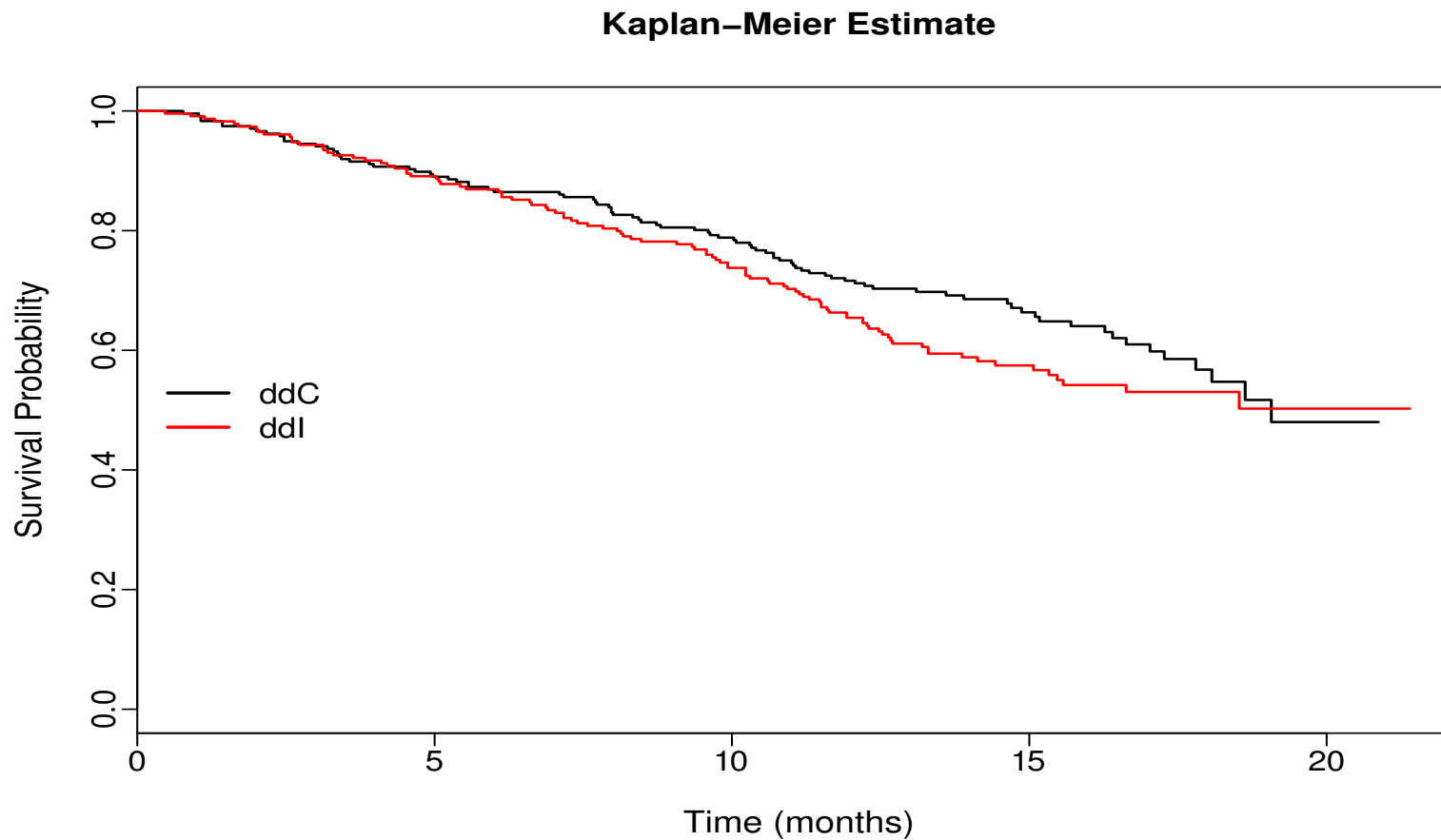
- **AIDS:** 467 HIV infected patients who had failed or were intolerant to zidovudine therapy (AZT) (Abrams et al., NEJM, 1994)
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)
  - ▷ Randomized treatment: 230 patients ddI and 237 ddC
- Outcomes of interest:
  - ▷ **time-to-death**
  - ▷ **CD4 cell count** at baseline, 2, 6, 12 and 18 months

# 1.1 Motivating Studies (cont'd)





# 1.1 Motivating Studies (cont'd)



## 1.1 Motivating 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?

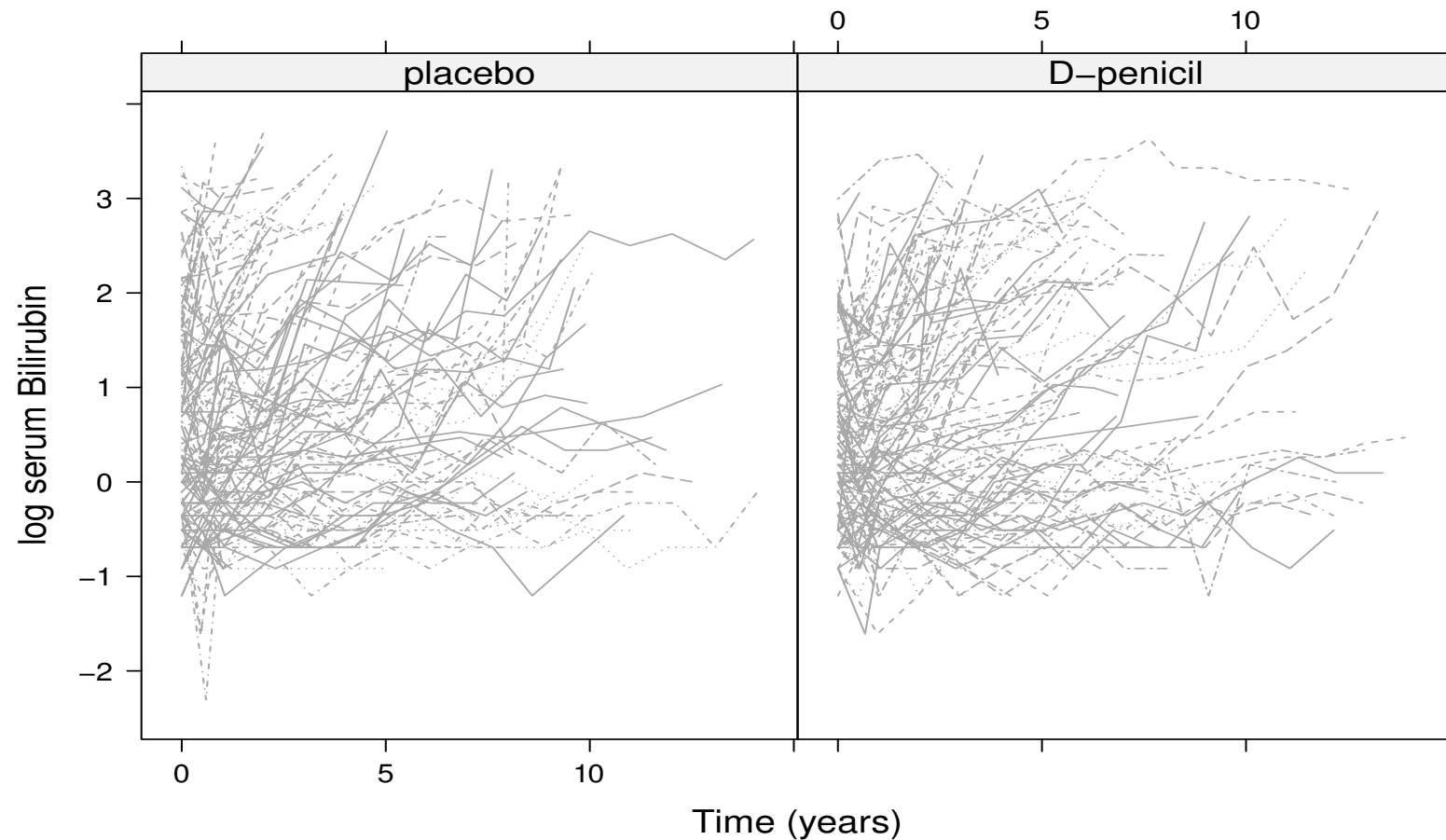
## 1.1 Motivating Studies (cont'd)

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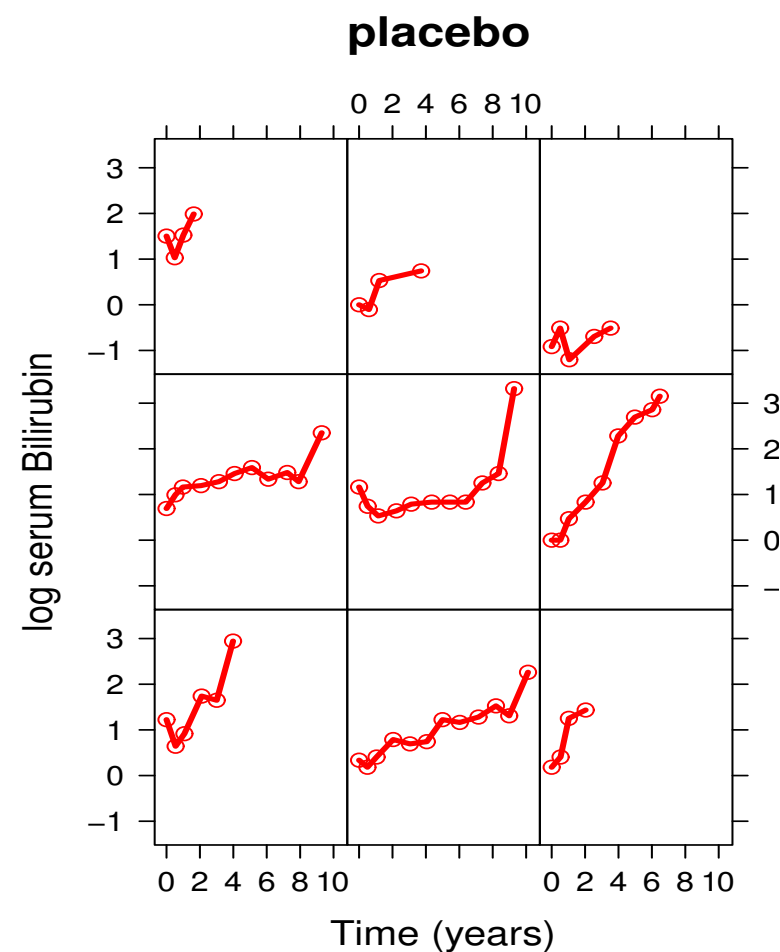
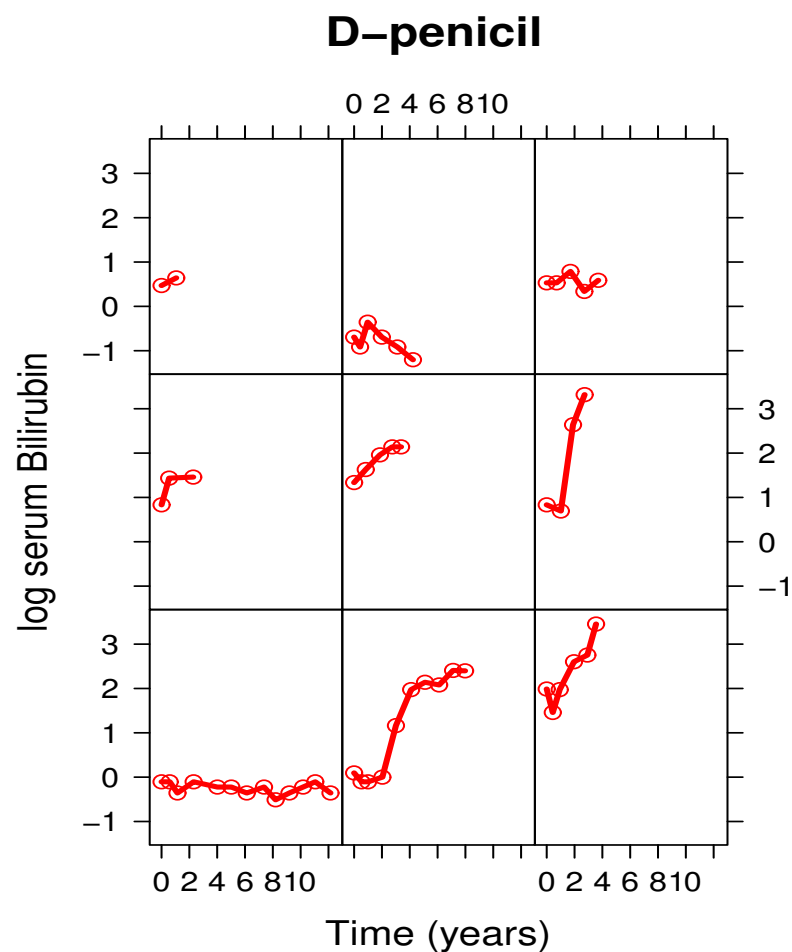
- **PBC:** 312 patients with Primary Biliary Cirrhosis which is a chronic, fatal but rare liver disease
- Data collected by Mayo Clinic from 1974 to 1984 (Murtaugh et al., Hepatology, 1994)
  - ▷ Randomized treatment: 158 patients received D-penicillamine and 154 placebo
- Outcomes of interest:
  - ▷ **time-to-death** and/or **time-to-liver transplantation**
  - ▷ **longitudinal serum bilirubin levels**
  - ▷ **longitudinal serum cholesterol levels**



# 1.1 Motivating Studies (cont'd)

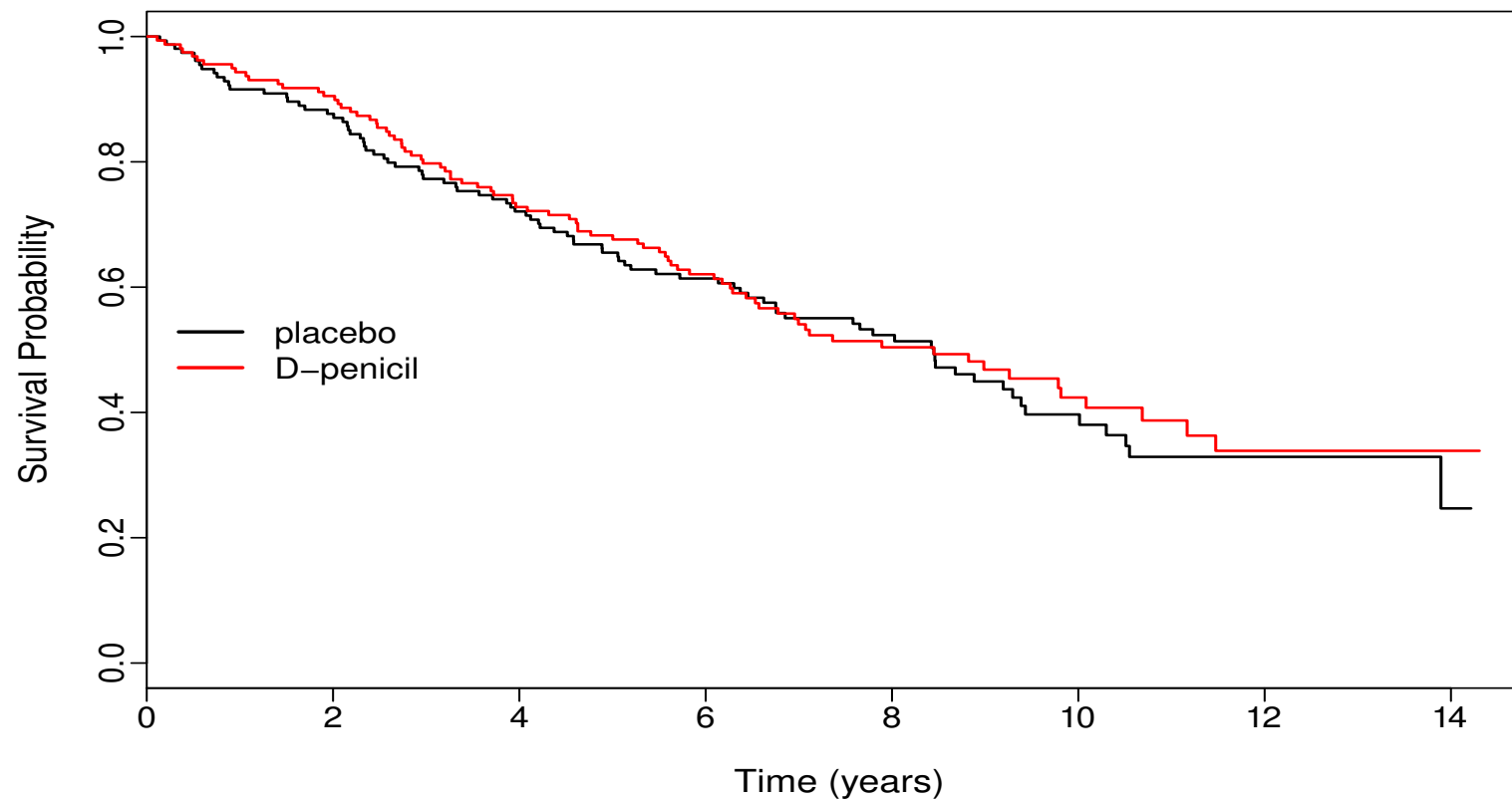


# 1.1 Motivating Studies (cont'd)



# 1.1 Motivating Studies (cont'd)

Kaplan–Meier Estimate



## 1.1 Motivating Studies (cont'd)

---

- Research Questions:
  - ▷ How strong is the association between bilirubin and cholesterol with the risk of death?
  - ▷ How could we utilize the observed serum bilirubin levels to provide predictions of survival probabilities?
  - ▷ Can bilirubin and cholesterol 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 the two treatments or between males and females?

## 1.2 Research Questions (cont'd)

---

- Focus on multiple outcomes
  - ▷ How strong is the association between the longitudinal evolution of the biomarkers and the hazard rate of death?
  - ▷ Association structures:
    - \* which feature of the biomarker(s) is associated with the hazard of death?
    - \* how marker-specific evolutions are related to each other
  - ▷ Prediction: can we improve prediction for the time to death by considering all available information simultaneously?

## 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, mean or slope of the repeated covariate, ...)
- 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



# Chapter 2

## 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 and cholesterol 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  $\Rightarrow$  *linear regression*

$$y_i(t) = x_i^\top(t)\beta + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, V_i),$$

where

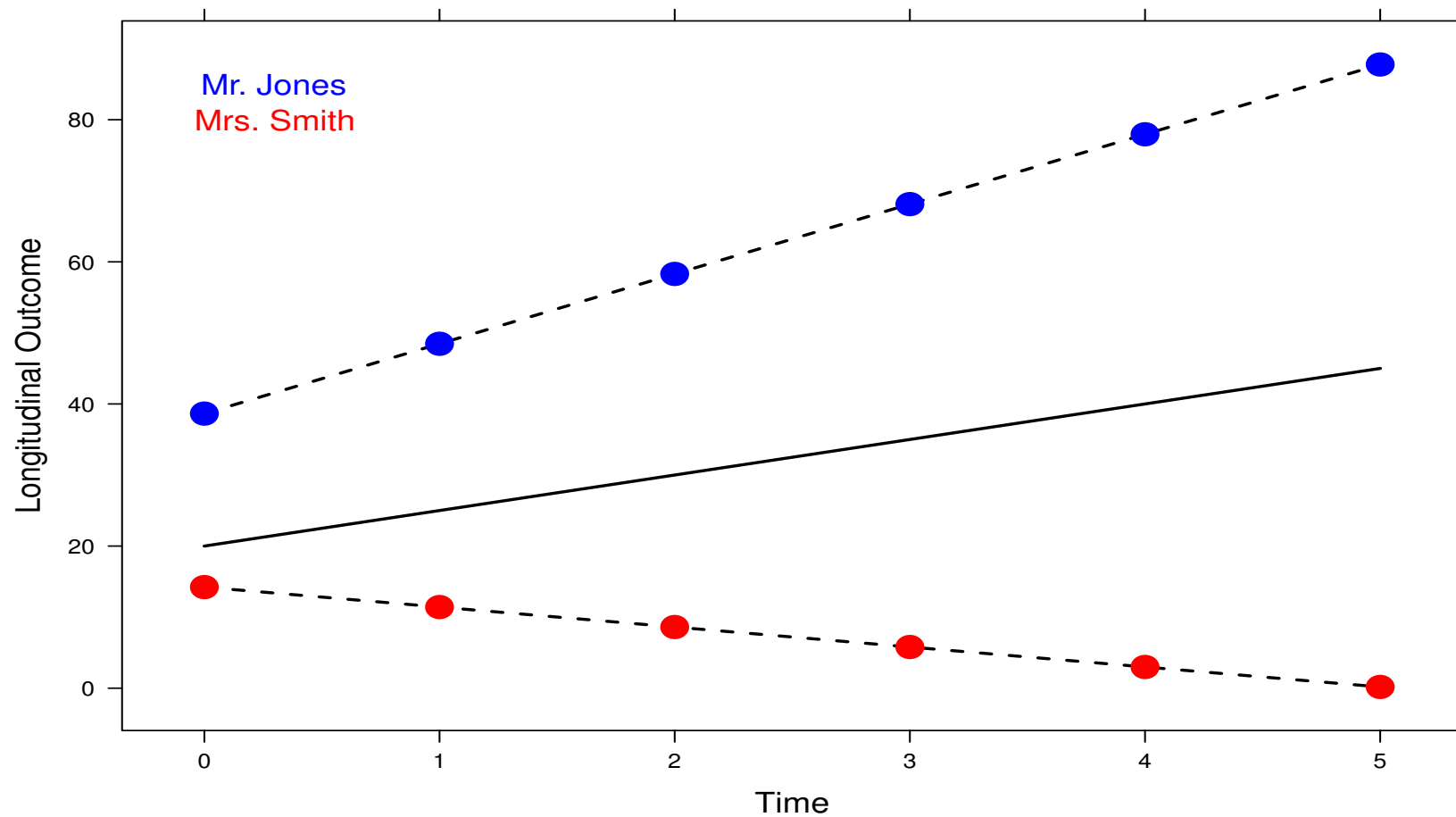
- ▷  $y_i(t)$  the vector of responses for the  $i$ th subject
  - ▷  $x_i^\top(t)$  design matrix describing structural component
  - ▷  $V_i$  covariance matrix describing the correlation structure
- There are several options for modeling  $V_i$ , e.g., compound symmetry, autoregressive process, exponential 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  $j$ th response of the  $i$ th subject
- ▷  $\tilde{\beta}_{i0}$  is the intercept and  $\tilde{\beta}_{i1}$  the slope for subject  $i$

## 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

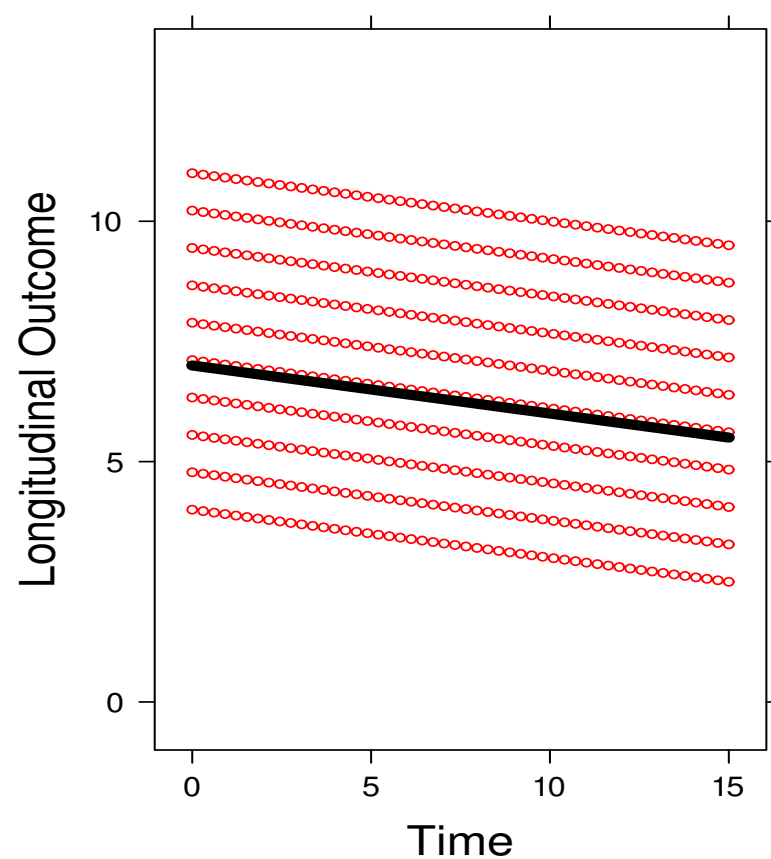
- ▷  $\beta$ s are known as the *fixed effects*
  - ▷  $b_i$ s are known as the *random effects*
- In accordance for the random effects we assume

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

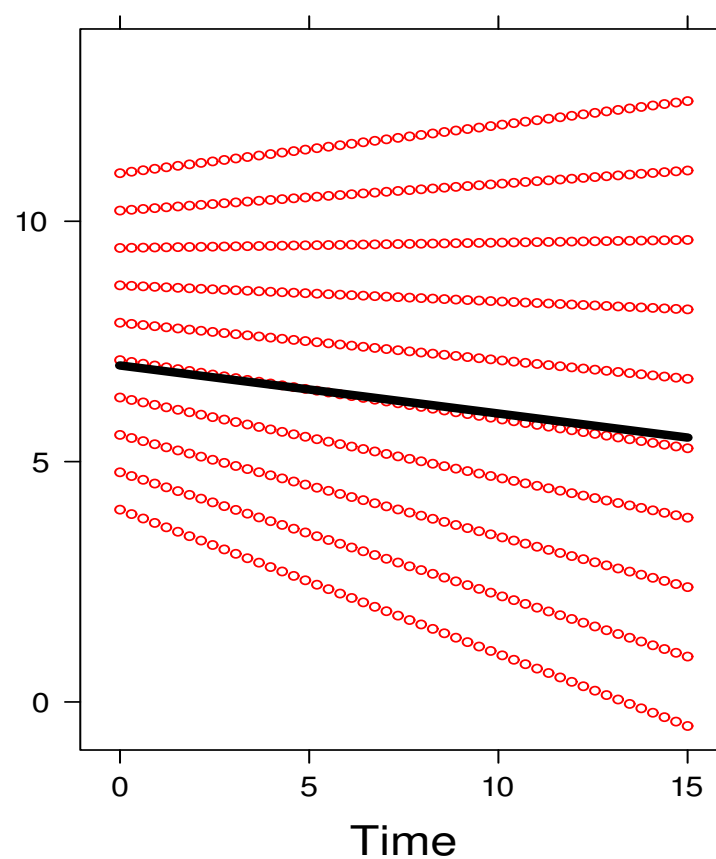


## 2.2 The Linear Mixed Model (cont'd)

**Random Intercepts**



**Random Slopes**



## 2.2 The Linear Mixed Model (cont'd)

---

- Put in a general form

$$\begin{cases} y_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2 \mathbf{I}_{n_i}), \end{cases}$$

with

- ▷  $x_i^\top(t)$  design matrix for the fixed effects  $\beta$
- ▷  $z_i^\top(t)$  design matrix for the random effects  $b_i$
- ▷  $b_i \perp\!\!\!\perp \varepsilon_i$

## 2.2 The Linear Mixed Model (cont'd)

---

- Interpretation:
  - ▷  $\beta_j$  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  $i$ th subject deviates from those in the population
- Advantageous feature: population + subject-specific predictions
  - ▷  $\beta$  describes mean response changes in the population
  - ▷  $\beta + b_i$  describes individual response trajectories

## 2.2 The Linear Mixed Model (cont'd)

---

- Estimation  $\rightarrow$  maximum likelihood (MLE)
- The log-likelihood of a linear mixed model takes the form

$$\ell(\theta) = \sum_{i=1}^n \log \int p(y_i | b_i; \theta_y) p(b_i; \theta_b) db_i,$$

where  $p(\cdot)$  the density function

## 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**)

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

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

## 2.2 The Linear Mixed Model (cont'd)

---

	Value	Std.Err.	<i>t</i> -value	<i>p</i> -value
$\beta_0$	7.189	0.222	32.359	< 0.001
$\beta_1$	-0.163	0.021	-7.855	< 0.001
$\beta_2$	0.028	0.030	0.952	0.342

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

## 2.3 Mixed-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

## 2.3 Mixed-Effects Models in R (cont'd)

---

- R>** We will only use package **nlme** because package **JMbayes** 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



## 2.3 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
⋮	⋮	⋮	⋮	⋮

## 2.3 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<sup>2</sup>

⇒ `cd4 ~ time + I(time^2)`

R> Note: the intercept term is included by default

## 2.3 Mixed-Effects Models in R (cont'd)

---

**R>** The code used to fit the linear mixed model for the AIDS dataset (p. 28) is as follows

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

```
summary(lmeFit)
```

## 2.3 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)))
```

# Chapter 3

## 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*

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 Relative Risk Models

---

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

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

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

where

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

## 3.2 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

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

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

**Sensitivity to distributional assumptions due to censoring**

## 3.2 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

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

where only patients who had an event contribute

## 3.2 Relative Risk Models (cont'd)

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

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

	Value	HR	Std.Err.	z-value	p-value
$\gamma_1$	-0.138	0.871	0.156	-0.882	0.378
$\gamma_2$	-0.493	0.611	0.207	-2.379	0.017
$\gamma_3$	0.021	1.022	0.008	2.784	0.005

### 3.3 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)`

### 3.3 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

## 3.4 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?

## 3.4 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



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

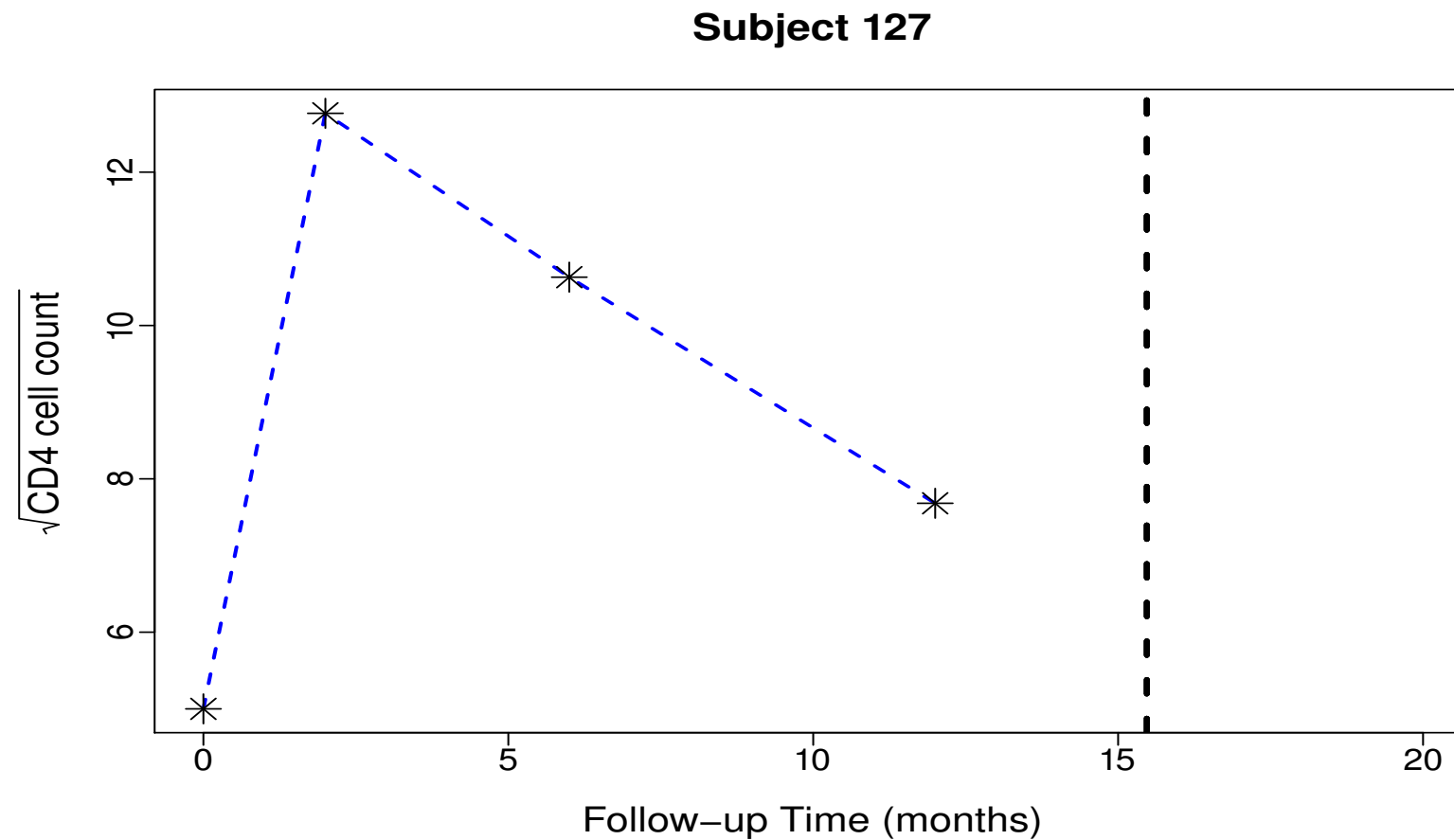
- ▷ Endogenous (aka internal): not Exogenous

## 3.4 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

## 3.4 Time Dependent Covariates (cont'd)



## 3.5 Extended Cox Model

---

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

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

where

- ▷  $y_i(t)$  denotes the value of the time-varying covariate at  $t$

## 3.5 Extended Cox Model (cont'd)

---

- Interpretation:

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

$\exp(\alpha)$  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

## 3.5 Extended Cox Model (cont'd)

---

- Typically, data must be organized in the long format

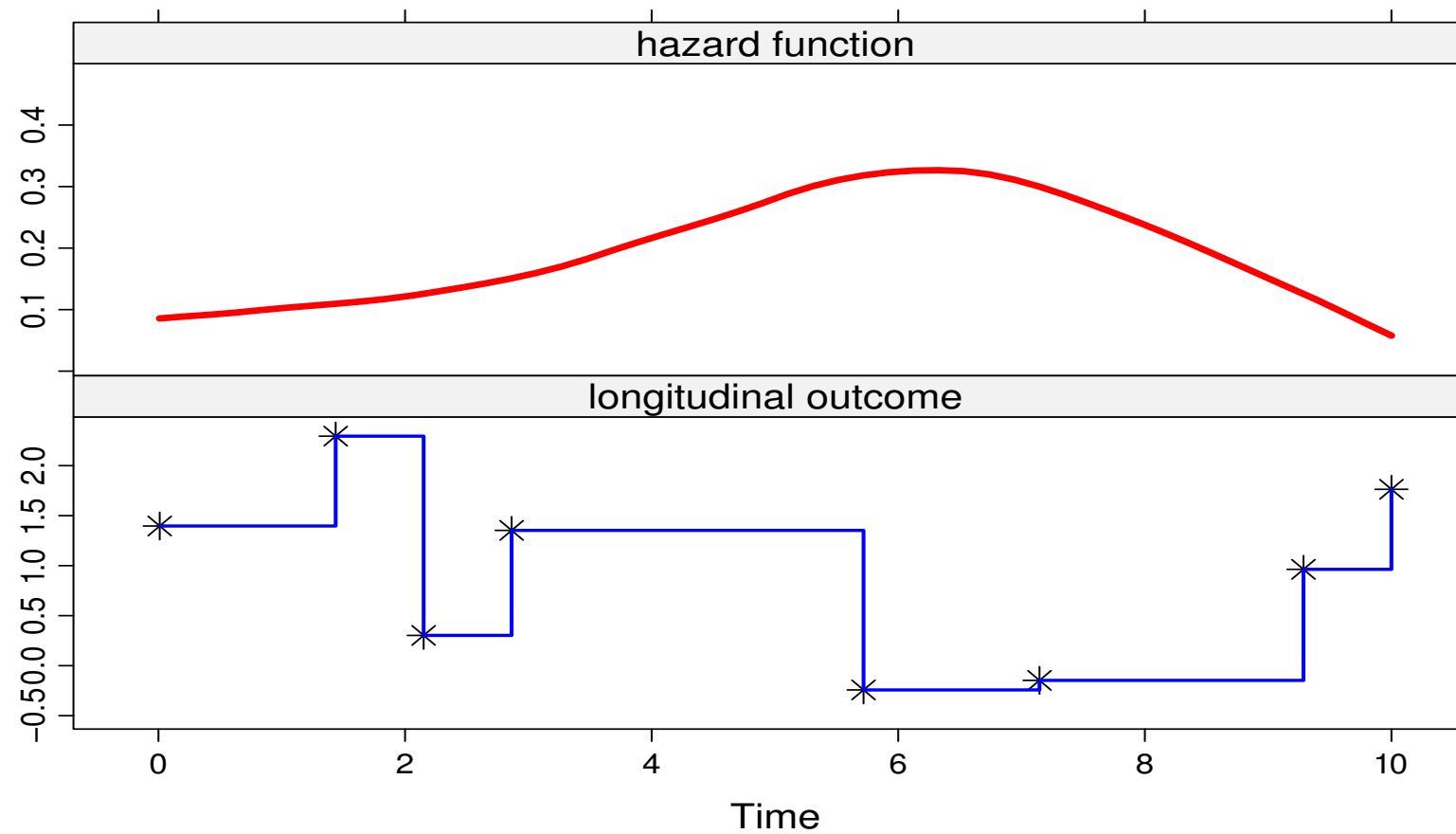
Patient	Start	Stop	Event	$y_i(t)$	Age
1	0	135	1	5.5	45
2	0	65	0	2.2	38
2	65	120	0	3.1	38
2	120	155	1	4.1	38
3	0	115	0	2.5	29
3	115	202	0	2.9	29
⋮	⋮	⋮	⋮	⋮	⋮

## 3.5 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

## 3.5 Extended Cox Model (cont'd)





## 3.5 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!**

## 3.5 Extended Cox Model (cont'd)

---

**Quiz 1: Is treatment an endogenous or an exogenous time-dependent variable?**

# Chapter 4

## The Basic Joint Model

## 4.1 Joint Modeling Framework

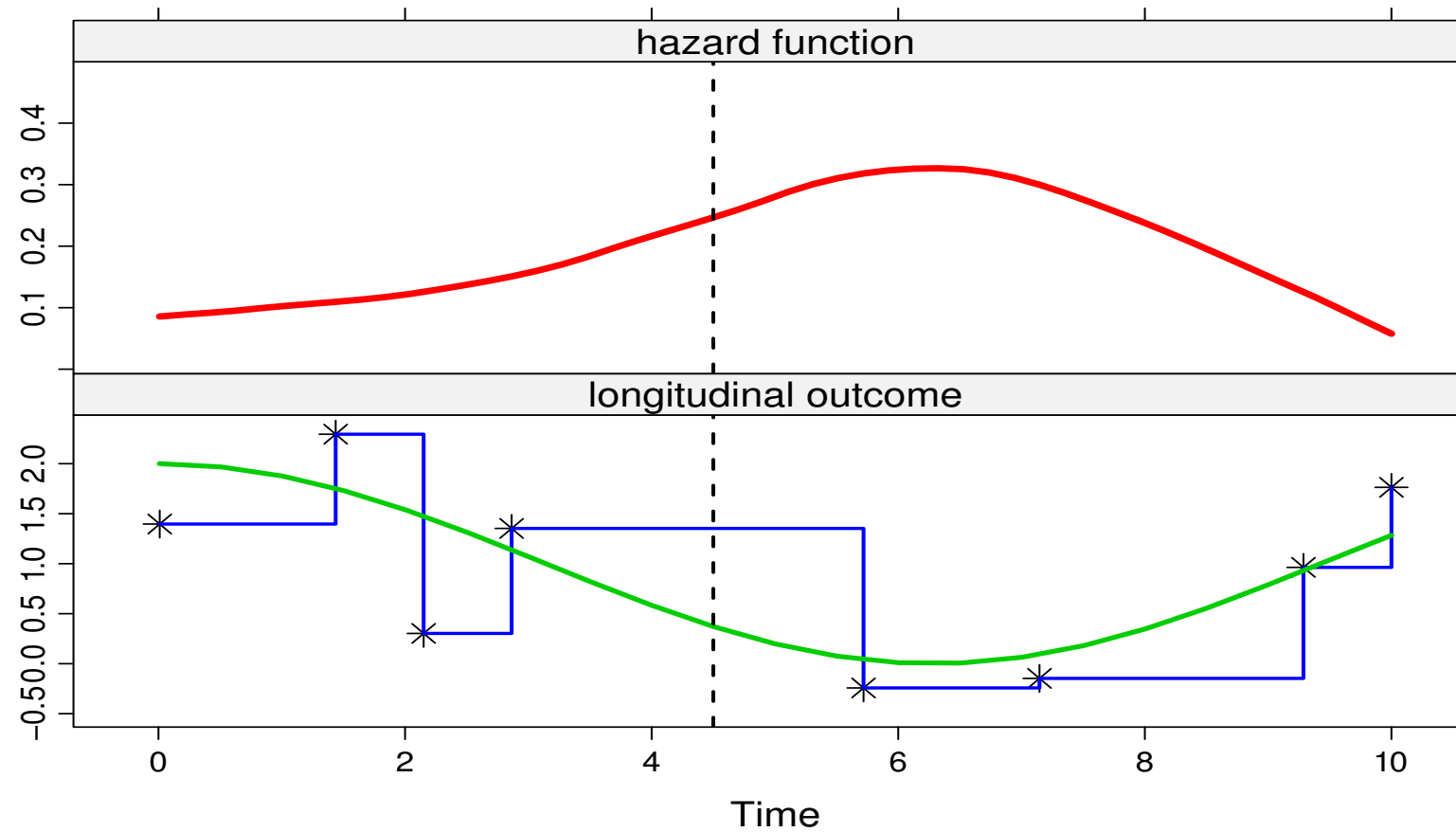
---

- 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 levels 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  $i$
  - ▷  $\delta_i$ : 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:** From the observed longitudinal response  $y_i(t)$  reconstruct the covariate history for each subject
- Then, we can define a mixed effects model (we focus, for now, on continuous markers)

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

where

- ▷  $x_i(t)$  and  $\beta$ : 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 2: 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
- ▷  $\alpha$  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 3:** The two processes are associated  $\Rightarrow$  define a model for their joint distribution
- Joint Models (JM) for such joint distributions are of the following form  
(Tsiatis & Davidian, Stat. Sinica, 2004)

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

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

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

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

## 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)

---

- 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  $v_1, \dots, v_Q$
- \*  $\gamma_{h_0}$  a vector of spline coefficients

## 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.

## 4.2 Estimation

---

- Mainly maximum likelihood but also Bayesian approaches
- The log-likelihood contribution for subject  $i$ :

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

where

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

## 4.3 Introduction to Bayesian\*

---

- Bayes theorem

$$p(B | A) = \frac{p(A | B) * p(B)}{p(A)}$$

## 4.3 Introduction to Bayesian\* (cont'd)

---

- Bayes theorem

$$p(\text{hypothesis} \mid \text{data}) = \frac{p(\text{data} \mid \text{hypothesis}) * p(\text{hypothesis})}{p(\text{data})}$$

where hypothesis is typically something unobserved or unknown. It's what you want to learn about using the data.

For regression models, the "hypothesis" is a parameter (intercept, slopes or error terms).

Bayes theorem tells you the probability of the hypothesis given the data.



## 4.3 Introduction to Bayesian\* (cont'd)

---

- How plausible is some hypothesis given the data?

$$p(\text{hypothesis} \mid \text{data}) = \frac{p(\text{data} \mid \text{hypothesis}) * p(\text{hypothesis})}{p(\text{data})}$$
$$\propto p(\text{data} \mid \text{hypothesis}) * p(\text{hypothesis})$$

- Renaming...

$$\text{posterior} \propto \text{data} * \text{prior}$$

Bayes' theorem provides a systematic way to update our knowledge as we encounter new data.

## 4.3 Introduction to Bayesian\* (cont'd)

Quiz 2: What do you see in the following picture? Are you a Bayesian or not?



## 4.4 Bayesian Estimation

---

- Bayesian estimation
  - ▷ under the Bayesian paradigm both  $\theta$  and  $b_i \{i = 1, \dots, n\}$  are regarded as parameters
- Inference is based on the full posterior distribution

$$p(\theta, b \mid T, \delta, y) = \frac{\prod_i p(T_i, \delta_i \mid b_i; \theta) p(y_i \mid b_i; \theta) p(b_i; \theta) p(\theta)}{\prod_i p(T_i, \delta_i, y_i)}$$
$$\propto \prod_{i=1}^n \left\{ p(T_i, \delta_i \mid b_i; \theta) p(y_i \mid b_i; \theta) p(b_i; \theta) \right\} p(\theta)$$

## 4.4 Bayesian Estimation (cont'd)

---

- For the standard joint model we have defined thus far, the majority of the parameters can be updated using Gibbs sampling (or slice sampling)  $\Rightarrow$  **MCMC**
  - ▷ when no close-form posterior conditionals are available, we can use the Metropolis-Hastings algorithm
- Good proposal distributions can be obtained from the separate fits of the two submodels

## 4.4 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
  - ▷ ...

## 4.5 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

$$\left\{ \begin{array}{l} y_i(t) = m_i(t) + \varepsilon_i(t) \\ \quad = \beta_0 + \beta_1 t + \beta_2 \{t \times \text{ddI}_i\} + b_{i0} + b_{i1} t + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \\ \\ h_i(t) = h_0(t) \exp\{\gamma \text{ddI}_i + \alpha m_i(t)\}, \end{array} \right.$$

where

▷  $h_0(t)$  is assumed P-splines

## 4.5 Comparison with the TD Cox (cont'd)

	JMbayes	Cox
	log HR (std.err)	log HR (std.err)
Treat	0.342 (0.008)	0.309 (0.147)
CD4 <sup>1/2</sup>	−0.297 (0.002)	−0.193 (0.024)

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

## 4.5 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; 1.47)
  - ▷ **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



## 4.6 Joint Models in R

---

**R>** Joint models are fitted using function `jointModelBayes()` from package **JMbayes**. 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 <- jointModelBayes(lmeFit, coxFit, timeVar = "obstime",  
                           baseHaz = c("P-splines"))
```

```
summary(jointFit)
```

## 4.6 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

## 4.6 Joint Models in R (cont'd)

---

R> Argument `baseHaz` specifies the type of relative risk model

Available options are:

- ▷ `"regression-splines"`: B-spline basis function
- ▷ `"P-splines"`: B-spline basis function with penalties (P-splines)

## 4.6 Joint Models in R (cont'd)

---

**R>** details about **JMbayes**:

- ▷ directly implements the MCMC
- ▷ allows for categorical longitudinal data as well
- ▷ allows for general transformation functions
- ▷ penalized B-splines for the baseline hazard function
- ▷ ...

## 4.6 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 Joint Models in R (cont'd)

---

**Quiz 3: What is the interpretation of the parameters in the survival submodel from the output of the basic joint model (app)?**

# Chapter 5

## Extensions of Joint Models

## 5.1 Parameterizations

---

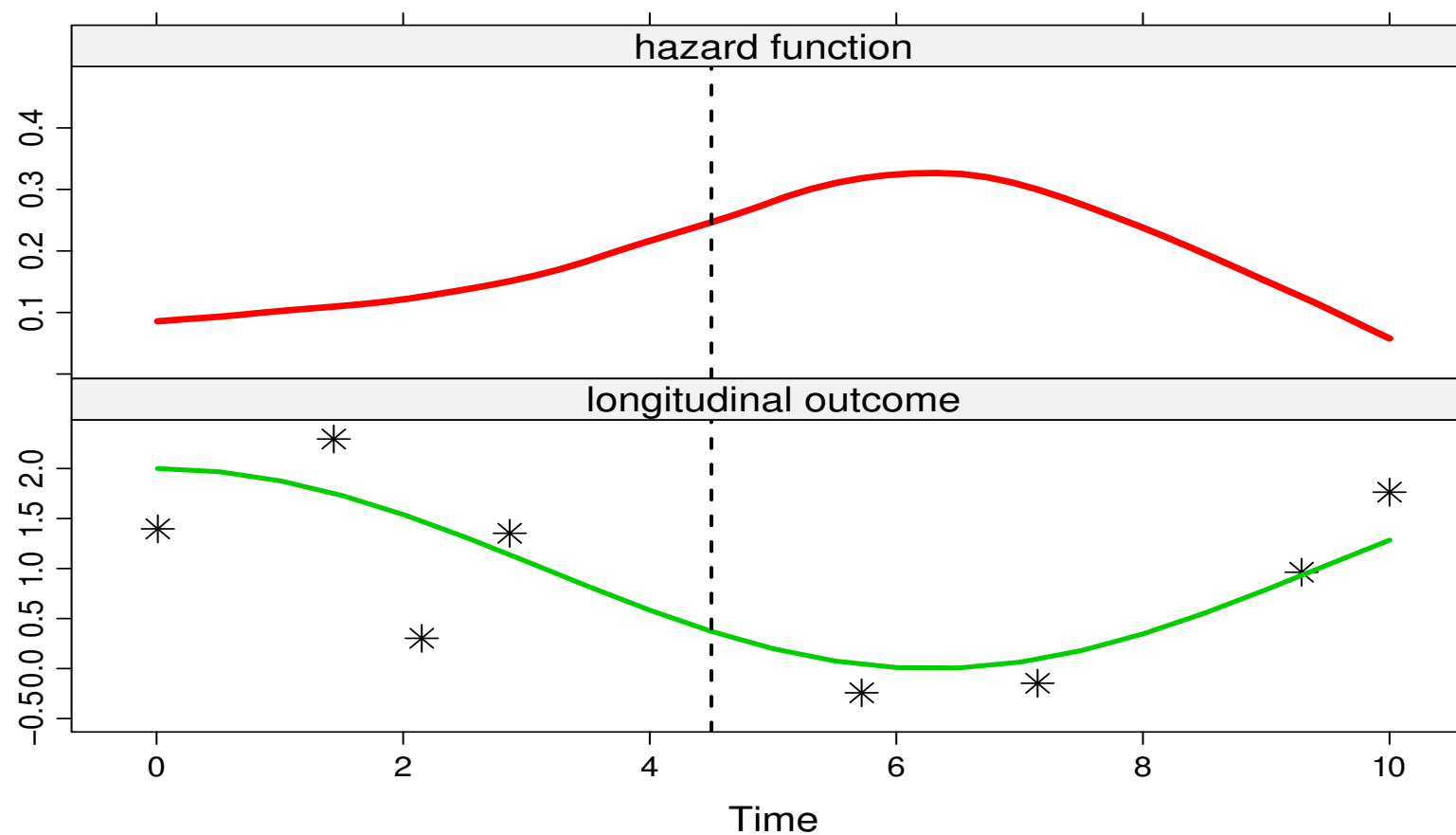
- The standard joint model

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

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

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

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., patients 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)

---

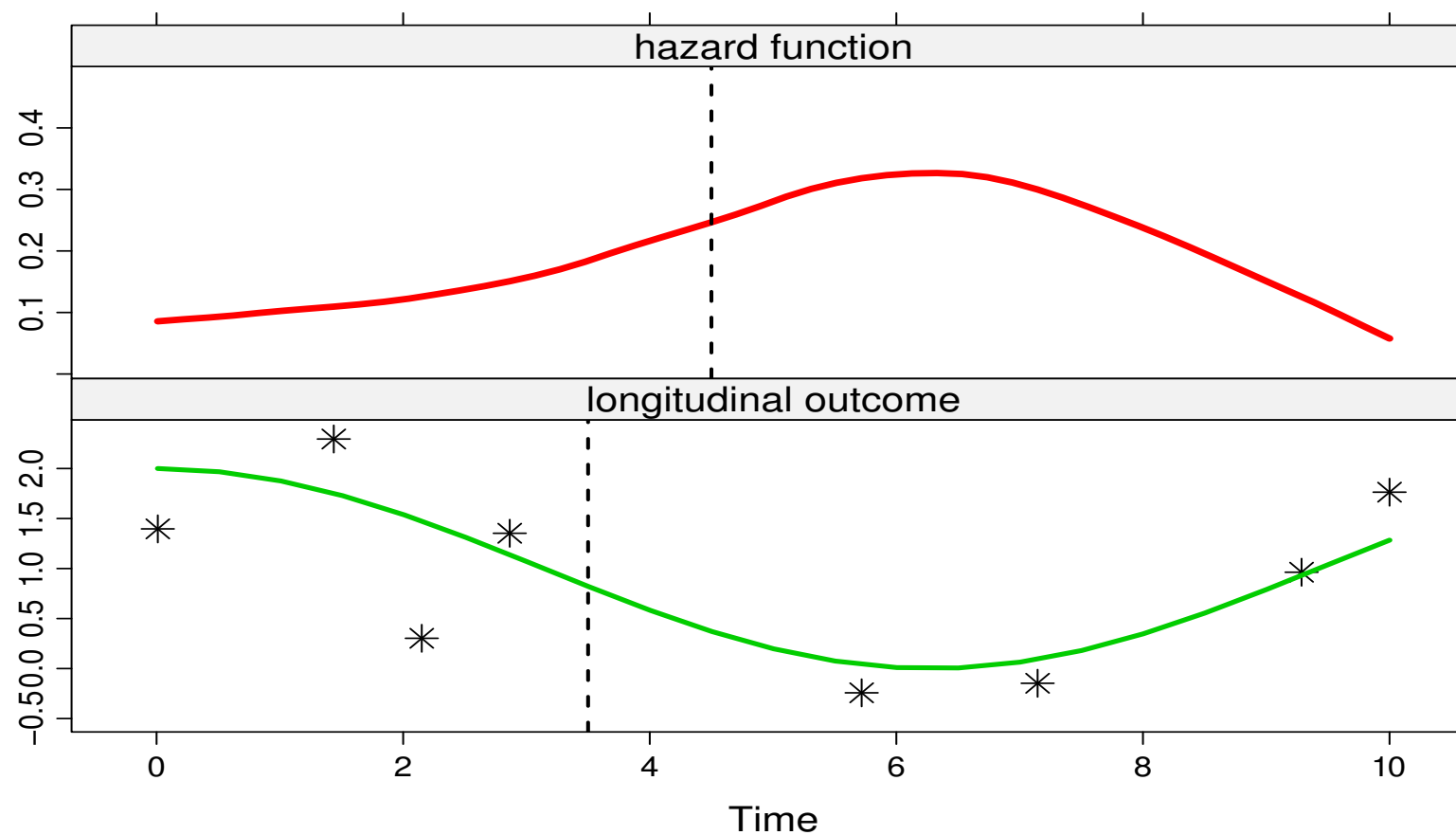
- *Lagged Effects*: The hazard of an event at  $t$  is associated with the level of the marker at a previous time point:

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

where

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

## 5.1 Parameterizations (cont'd)



## 5.1 Parameterizations (cont'd)

---

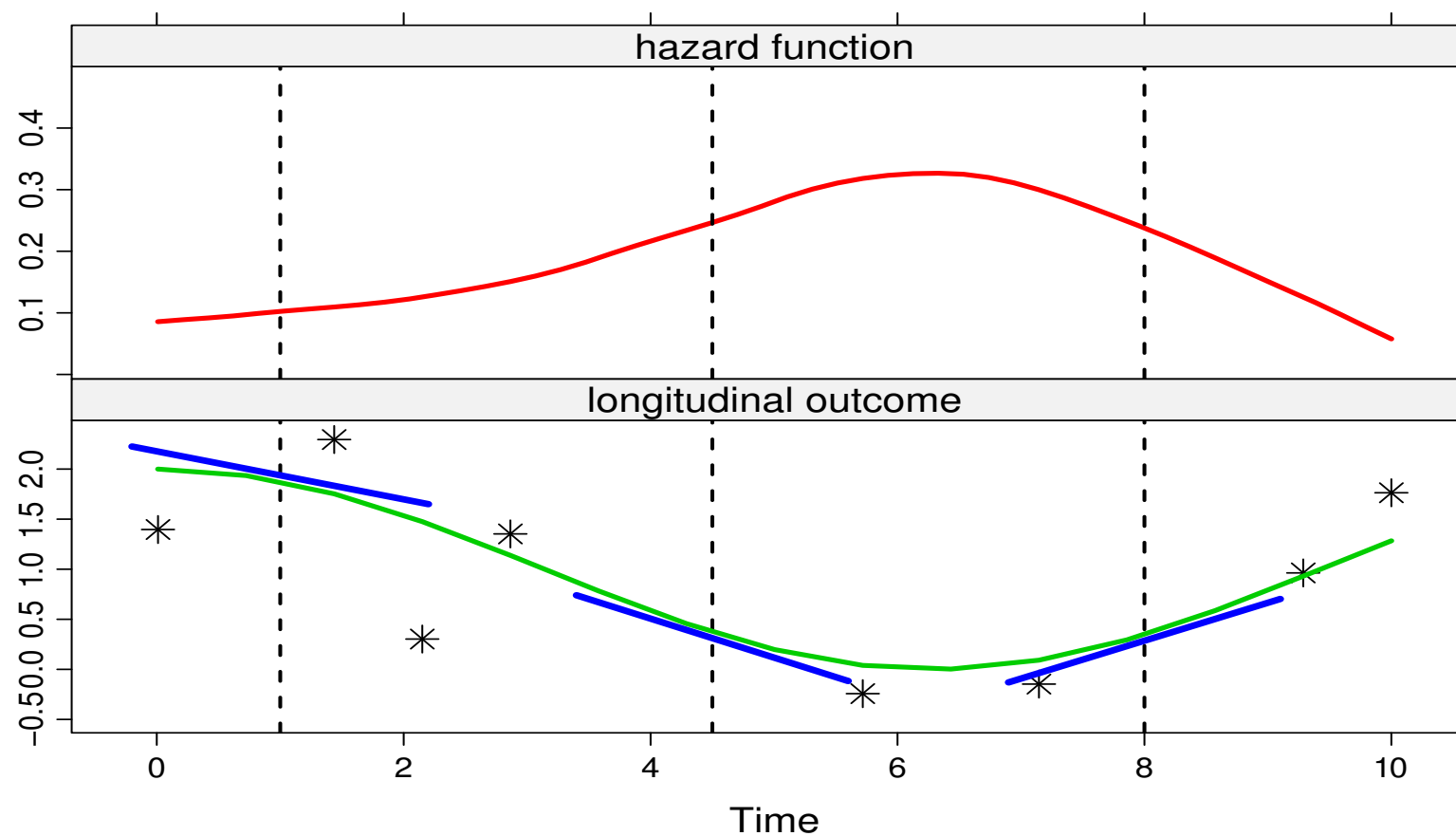
- *Time-dependent Slopes*: The hazard of an event at  $t$  is associated with both the current value and the slope of the trajectory at  $t$  (Ye et al., 2008, Biometrics):

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

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)

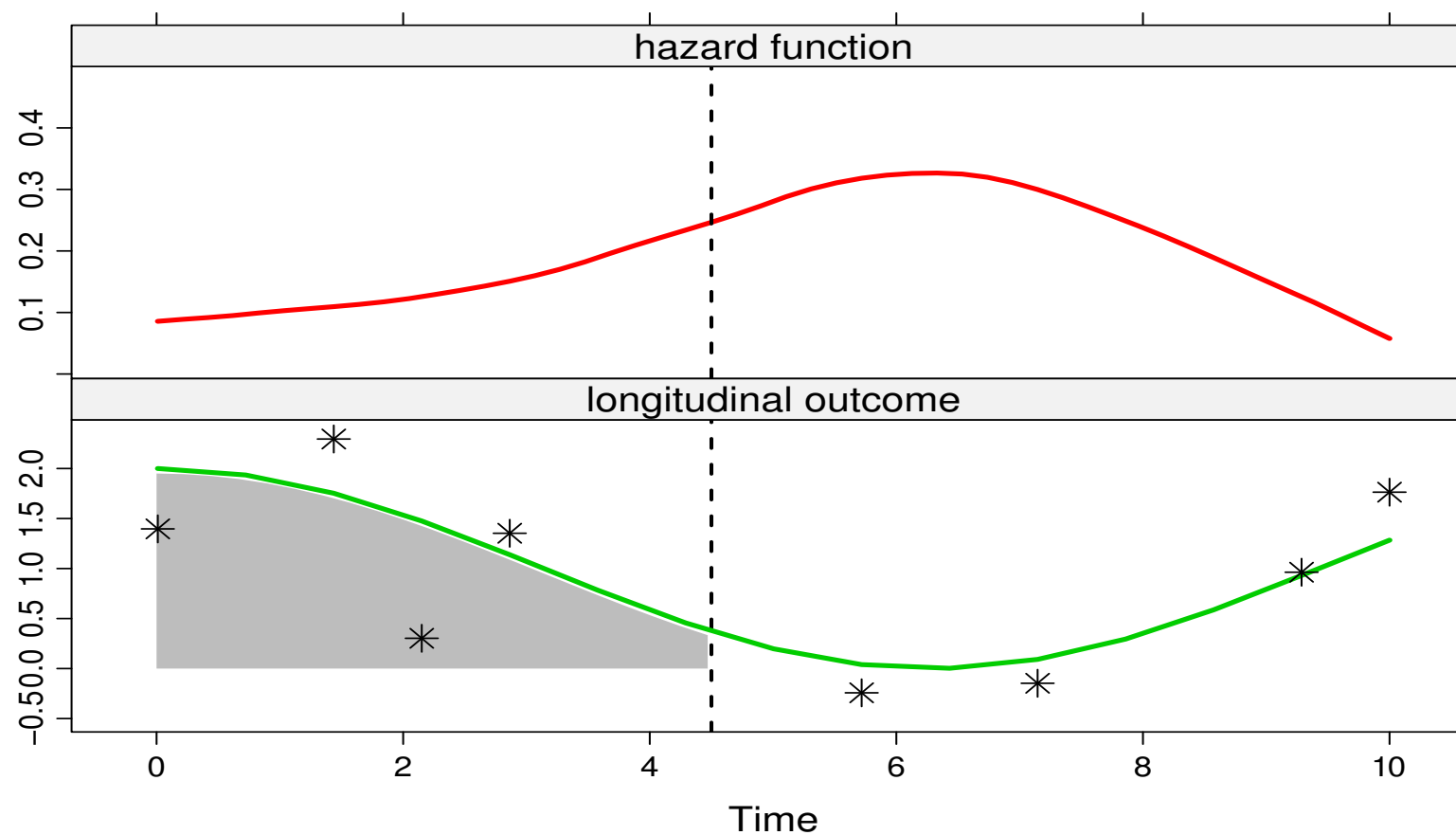
---

- *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  $t$ :

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

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  $\alpha$  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.,

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

and the following four survival submodels

## 5.1 Parameterizations (cont'd)

---

- Model I (current value)

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

- Model II (current value + current slope)

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

where

$$\triangleright m'_i(t) = \beta_1 + \beta_2 \text{ddI}_i + b_{i1}$$

## 5.1 Parameterizations (cont'd)

---

- Model III (random slope)

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

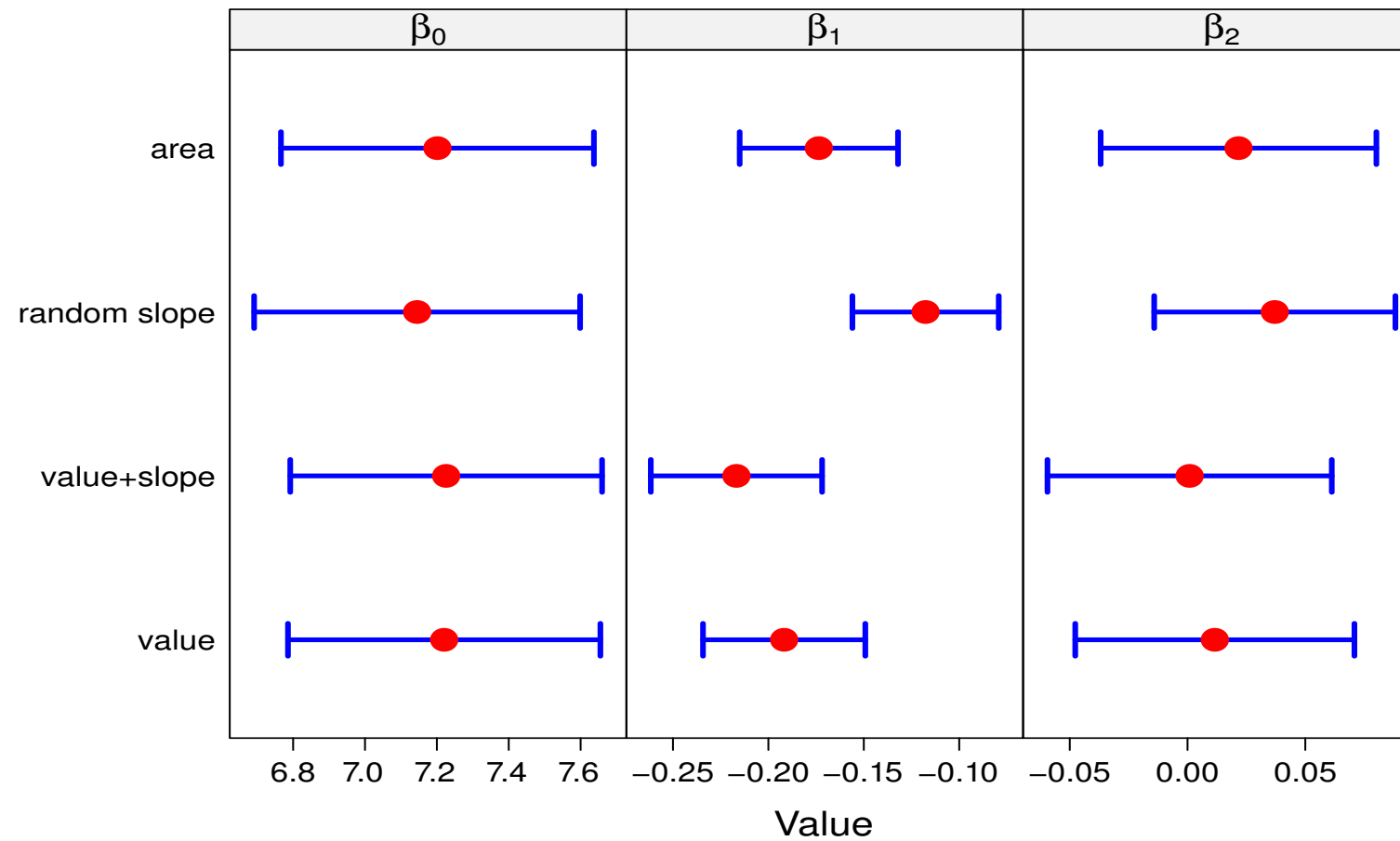
- Model IV (area)

$$h_i(t) = h_0(t) \exp\left\{\gamma \text{ddI}_i + \alpha_4 \int_0^t m_i(s) ds\right\},$$

where

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

## 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

## 5.2 Parameterizations in R

---

- R>** Lagged effects can be fitted using the `lag` argument of `jointModelBayes()`. 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 P-splines 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 <- jointModelBayes(lmeFit, coxFit, timeVar = "year",  
  baseHaz = "P-splines", lag = 1)
```

```
summary(jointFit)
```

## 5.2 Parameterizations in R (cont'd)

---

**R>** For the time-dependent slopes and cumulative effects parameterizations, arguments `param` and `extraForm` of `jointModelBayes()` should be used

▷ Options are

- \* `param = "td-value"`
- \* `param = "td-extra"`
- \* `param = "td-both"`
- \* `param = "shared-betasRE"`
- \* `param = "shared-RE"`

## 5.2 Parameterizations in R (cont'd)

---

**R>** Include also the slope of the longitudinal biomarker

```
dform = list(fixed = ~ 1, random = ~ 1,  
             indFixed = 2, indRandom = 2)
```

```
jointFit2 <- jointModelBayes(lmeFit, coxFit, timeVar = "year",  
                             param = "td-both", extraForm = dform, baseHaz = "P-splines")
```

```
summary(jointFit2)
```

## 5.3 Multiple Biomarkers

---

- 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 Biomarkers (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  $Y_{i1}, \dots, Y_{iJ}$  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 Biomarkers (cont'd)

---

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

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

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

$$h_i\{t \mid \mathcal{M}_i(t)\} = h_0(t) \exp\left\{\gamma^\top w_i + \sum_{j=1}^J \alpha_j m_{ij}(t)\right\},$$

where  $\mathcal{M}_i(t) = \{m_{ij}(s), 0 \leq s < t, 1 \leq j \leq J\}$

## 5.4 Multiple Biomarkers in R

---

**R>** Joint models for multiple longitudinal outcomes can be fitted with function `mvJointModelBayes()` from package **JMbayes**

- The use of this function mimics the one of `jointModelBayes()` but with some small differences, namely
  - ▷ we fit a *multivariate* mixed model using `mvglmr()`,
  - ▷ following we fit a Cox model using `coxph()`, and
  - ▷ and we give the resulting objects as input in `mvJointModelBayes()`



## 5.4 Multiple Biomarkers in R (cont'd)

---

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

```
multMixedFit <- mvglmer(list(log(serBilir) ~ year + (year | id),  
                             spiders ~ year + (1 | id)), data = pbc2,  
                        families = list(gaussian, binomial))
```

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

```
multJMFit <- mvJointModelBayes(multMixedFit, coxFit, timeVar = "year")  
summary(multJMFit)
```

## 5.4 Multiple Biomarkers in R (cont'd)

---

- R> Function `mvJointModelBayes()` also allows for
- ▷ right, left, interval censored data
  - ▷ left truncated data
  - ▷ exogenous time-varying covariates

## 5.5 Variable Selection

---

- Note: In the previous extension of joint models,

- ▷ multiple longitudinal markers

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 Variable Selection (cont'd)

---

- For example in the case of multiple longitudinal outcomes

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

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

where  $\mathcal{M}_i(t) = \{m_{ij}(s), 0 \leq s < t, 1 \leq j \leq J\}$

## 5.5 Variable Selection (cont'd)

---

- In this case we face a challenging model selection problem
- Different possible solutions
  - ▷ lasso
  - ▷ ridge
  - ▷ horseshoe
  - ▷ ...

## 5.6 Variable Selection in R

---

R> Function `mvJointModelBayes()` also allows to consider multiple parameterization per outcome in a similar manner as `jointModelBayes()` does

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

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

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

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

## 5.6 Variable Selection in R (cont'd)

---

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

```
Forms <- list("log(serBilir)" = "value",  
             "log(serBilir)" = list(fixed = ~ 1, random = ~ 1,  
                                   indFixed = 2, indRandom = 2, name = "slope"),  
             "spiders" = list(fixed = ~ 0 + year + I(year^2/2), random = ~ 0 + year,  
                              indFixed = 1:2, indRandom = 1, name = "area"))
```

```
multJMFit2 <- update(multJMFit, Formulas = Forms)  
summary(multJMFit2)
```

```
Ints <- list("log(serBilir)" = ~ drug, "log(serBilir)_slope" = ~ drug,  
            "spiders_area" = ~ drug)  
multJMFit3 <- update(multJMFit2, Interactions = Ints,  
                    priors = list(shrink_alphas = TRUE))  
summary(multJMFit3)
```

## 5.7 Time-Varying Association

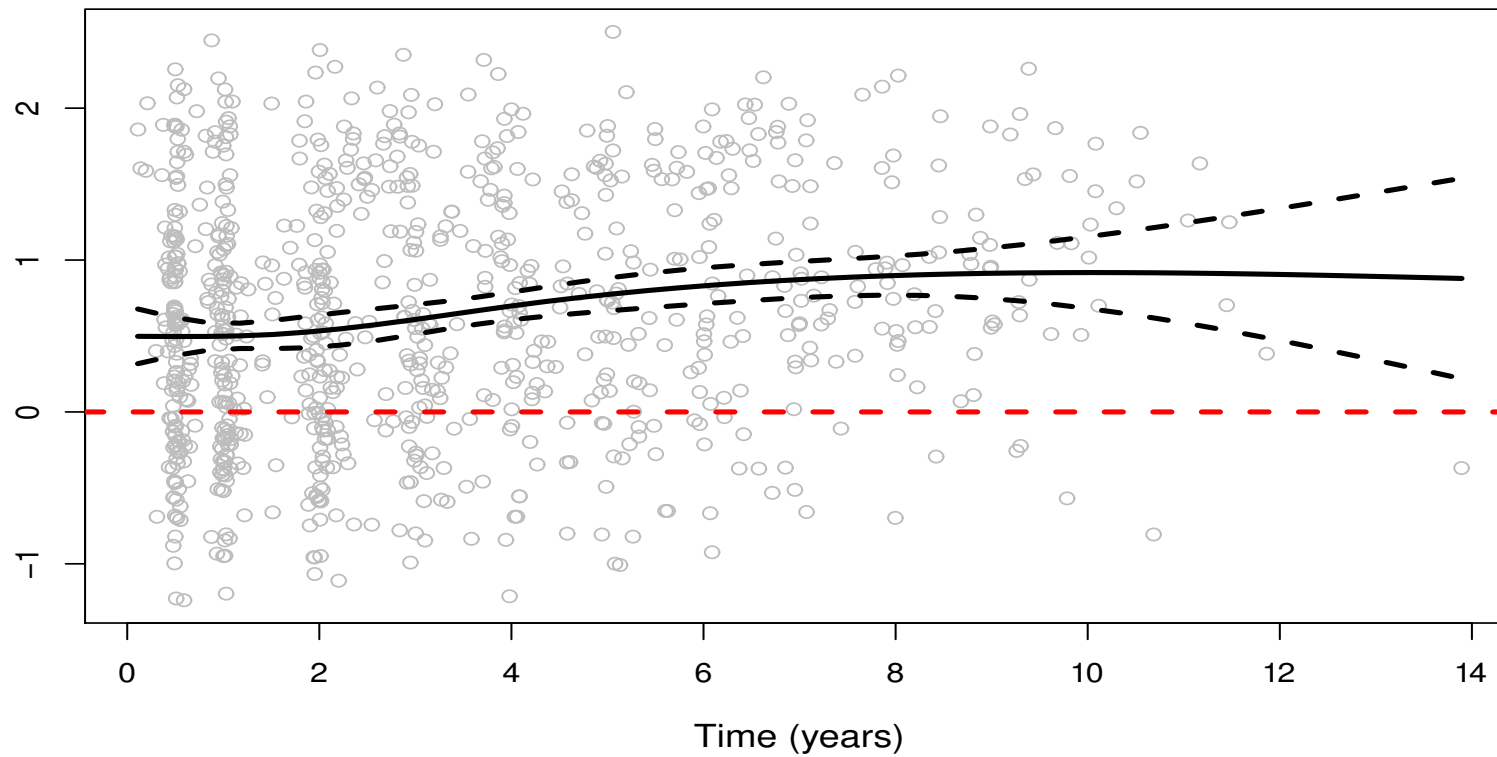
---

- Standard joint models assume a constant regression coefficient for the effect of the covariates.
  - ▷ when treatment is initiated, the strength of the association between the longitudinal and survival outcomes may also change



## 5.7 Time-Varying Association (cont'd)

Time-varying coefficient for log Serum Bilirubin



## 5.7 Time-Varying Association (cont'd)

---

**A time-varying coefficient joint model**

## 5.7 Time-Varying Association (cont'd)

---

Specifically,

$$h_i\{t \mid \mathcal{M}_i(t)\} = h_0(t) \exp[\gamma^\top w_i + \sum_{j=1}^J \sum_{l=1}^L f_{j\ell}\{m_{ij}(t), \lambda_{j\ell}(t)\}],$$

where

- $w_i$  is a vector of baseline covariates with a corresponding vector of regression coefficients  $\gamma$
- $f_{j\ell}\{m_{ij}(t), \lambda_{j\ell}(t)\}$  is the outcome ( $j = 1, \dots, J$ ) and the form of association ( $\ell = 1, \dots, L$ ) between the longitudinal and the survival outcomes

## 5.7 Time-Varying Association (cont'd)

---

- We consider estimation of the function  $\lambda_{j\ell}(t)$  using the regression P-spline method, where

$$\lambda_{j\ell}(t) = \sum_{u=1}^U \alpha_u B_u(t, \nu),$$

where

- $\alpha_u$  is a set of parameters that capture the strength of association between the longitudinal and survival outcomes
  - $B_u(t, \nu)$  denotes the  $q$ -th basis function of a B-spline with knots  $\nu_1, \dots, \nu_Q$
- The idea behind the P-spline method is to assume a high number of knots and penalize the coefficients to tackle the problem of the large number of parameters.

## 5.8 Time-Varying Association in R

---

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

```
Ints_tveffect <- list("log(serBilir)_value" = ~ 0 + tve(years, df = 8))
JMFit_tveffect <- mvJointModelBayes(multMixedFit, coxFit, timeVar = "year",
                                   Interactions = Ints_tveffect)

plot(JMFit_tveffect, which = "tv_effect")
```

# Chapter 6

## Dynamic Predictions

## 6.1 Survival Probabilities

---

- 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**

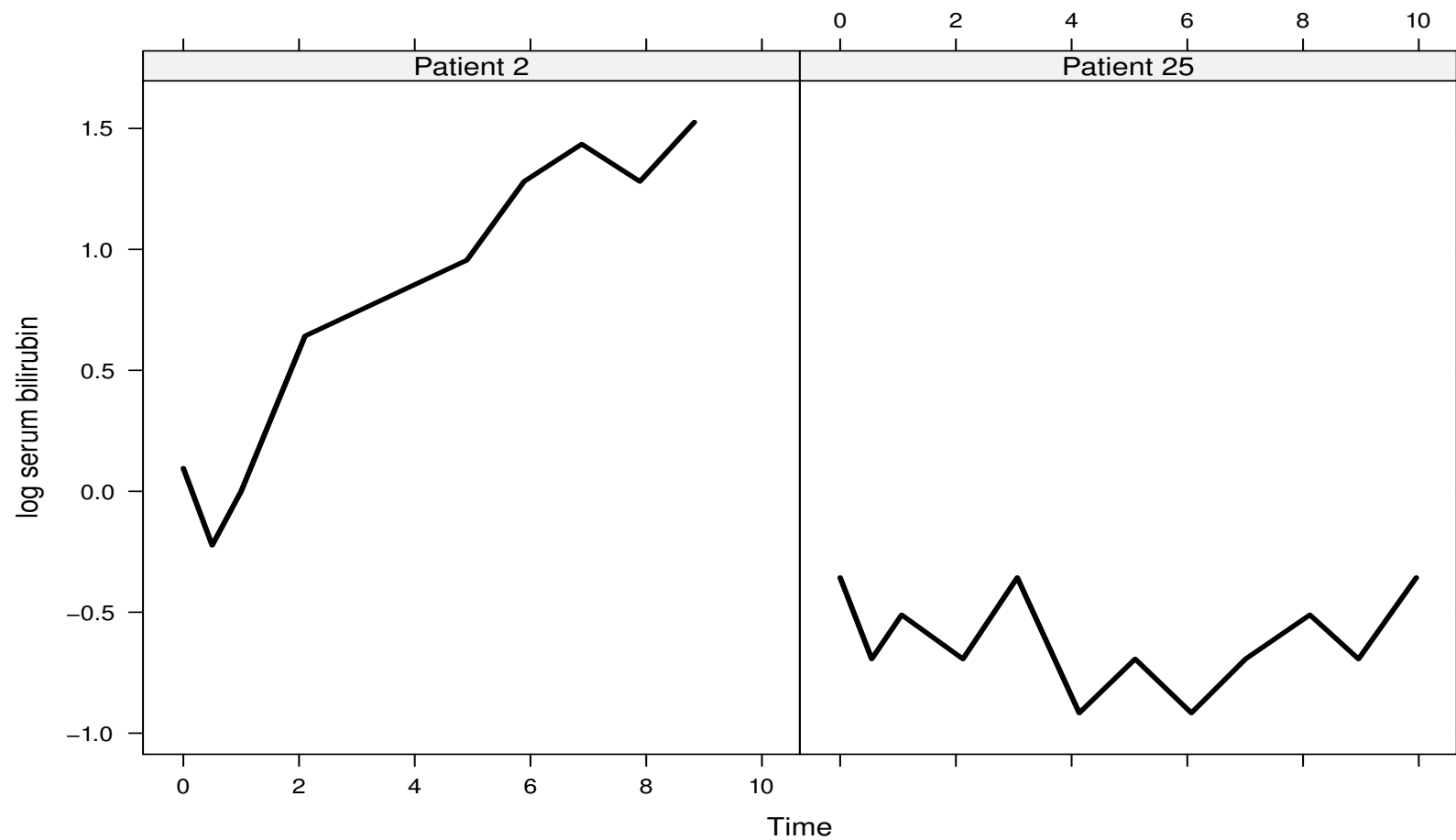
## 6.1 Survival Probabilities (cont'd)

---

- 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 (cont'd)



## 6.1 Survival Probabilities (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

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

where

- ▷ where  $u > t$ , and
- ▷  $\mathcal{D}_n$  denotes the sample on which the joint model was fitted

## 6.1 Survival Probabilities (cont'd)

---

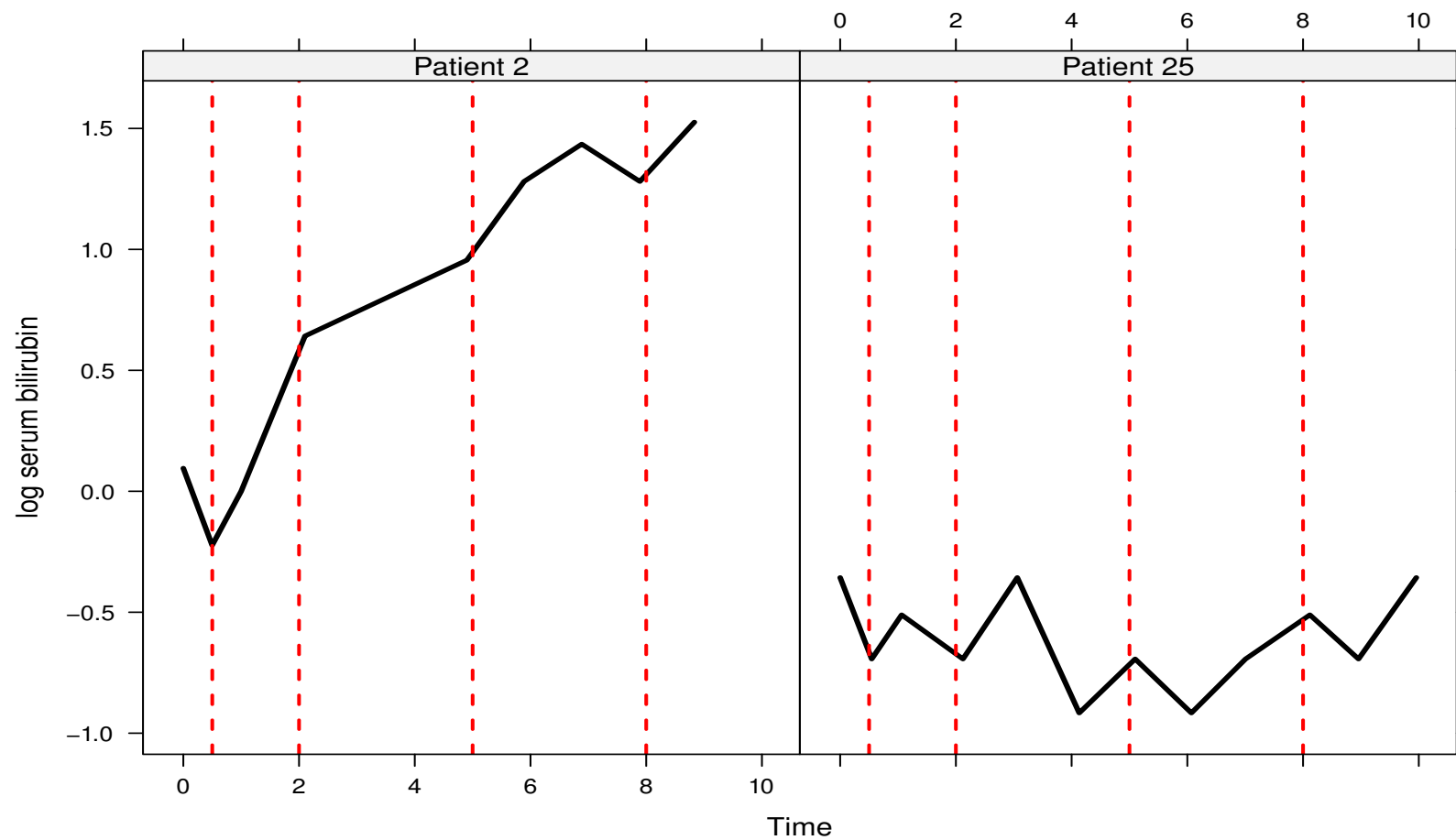
- We assume that the joint model has been fitted to the data at hand
- Based on the fitted model we can estimate the conditional survival probabilities  
(Rizopoulos, 2011, Biometrics)

## 6.2 Dynamic Predictions in R

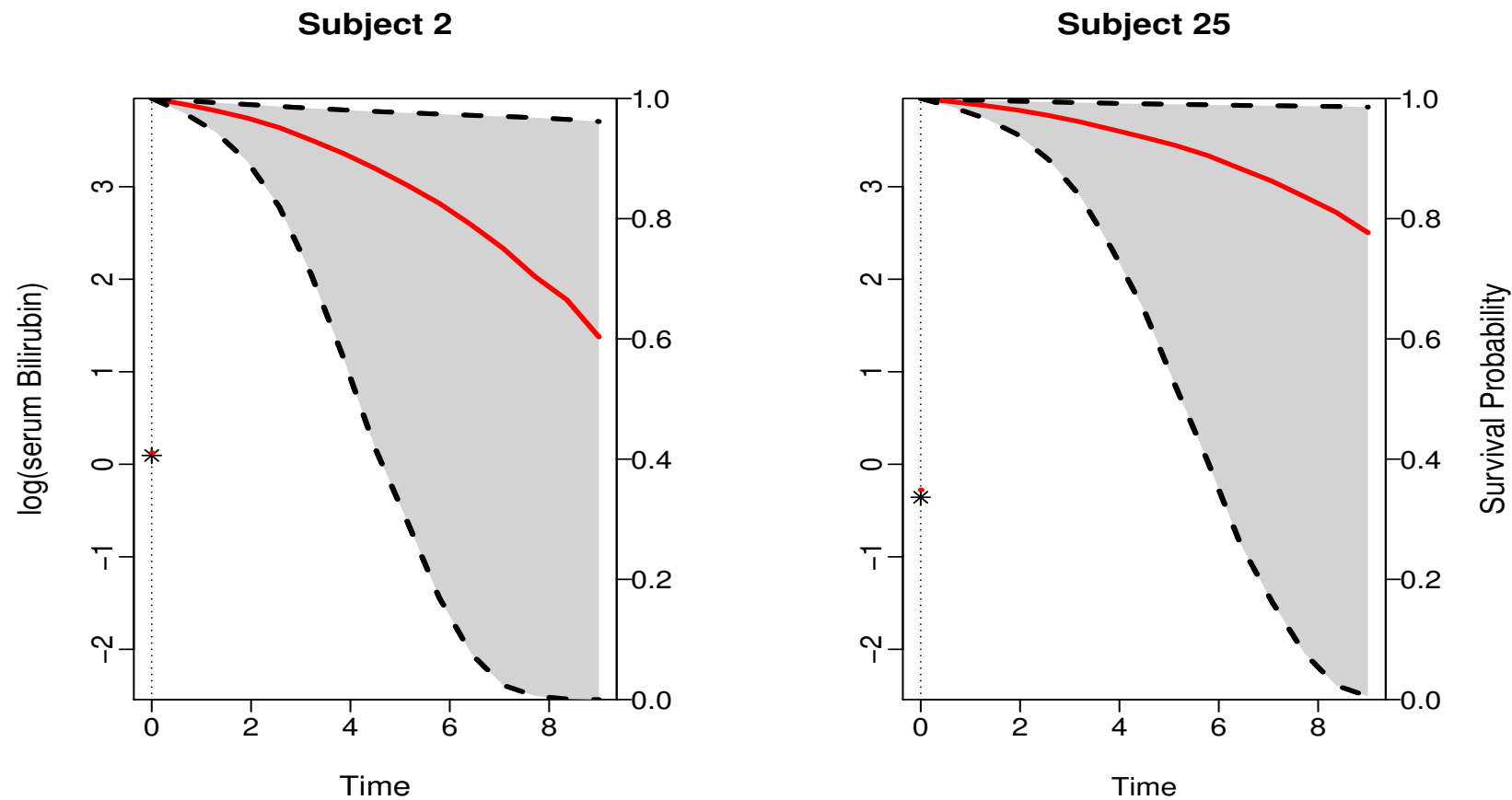
---

- Example: Dynamic predictions of survival probabilities for Patients 2 and 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
  - ▷ P-splines

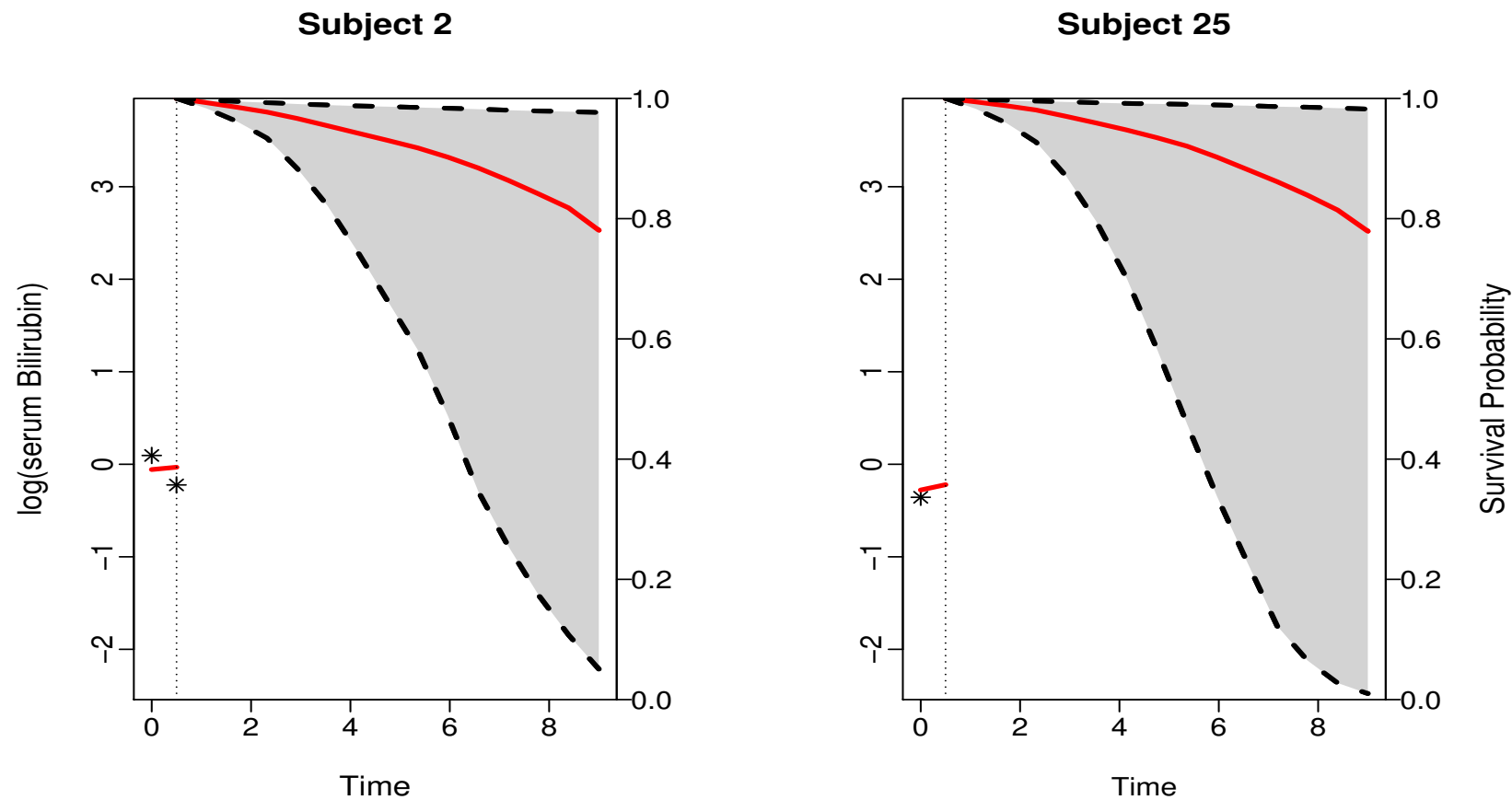
## 6.2 Dynamic Predictions in R (cont'd)



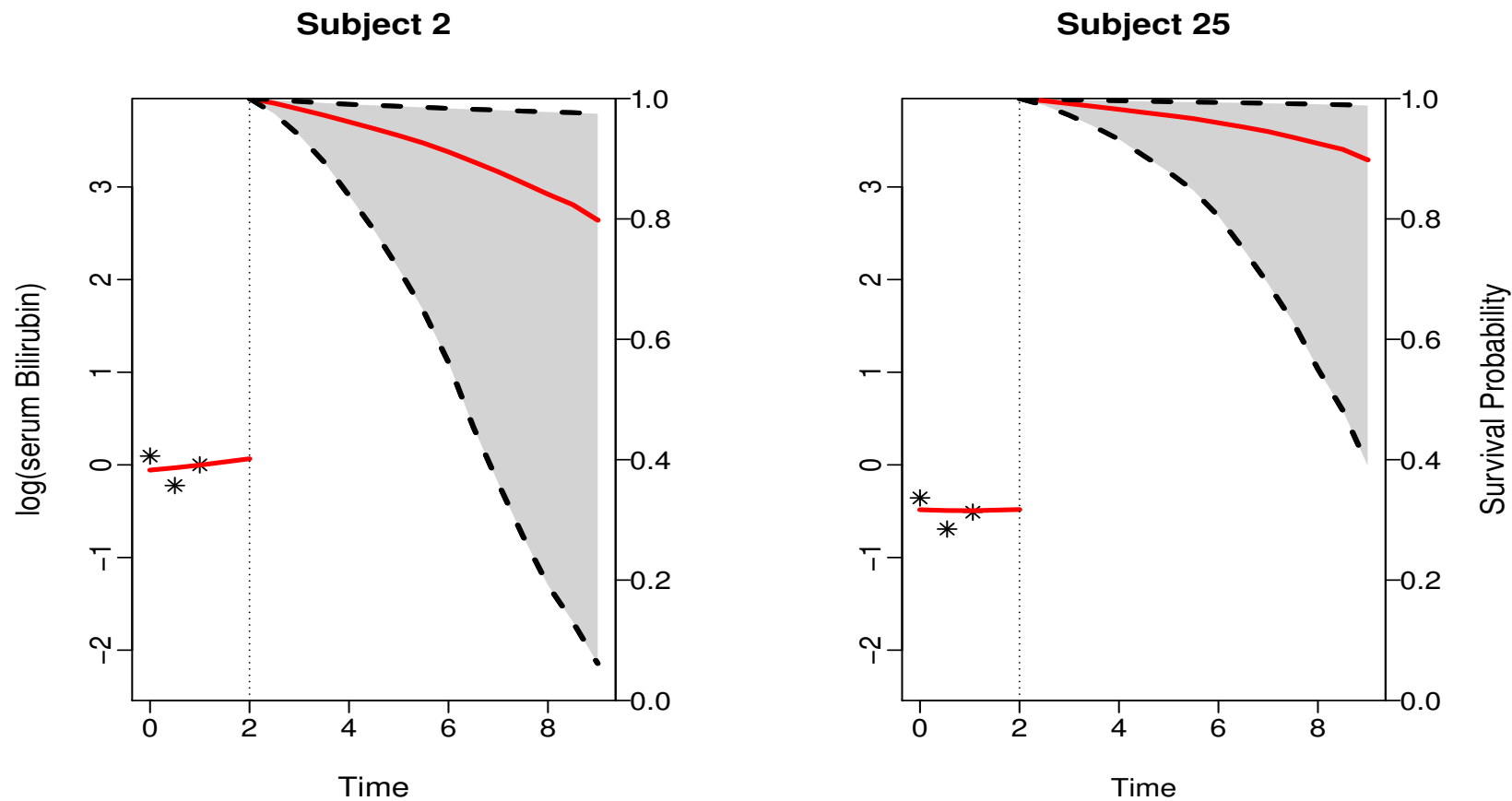
## 6.2 Dynamic Predictions in R (cont'd)



## 6.2 Dynamic Predictions in R (cont'd)

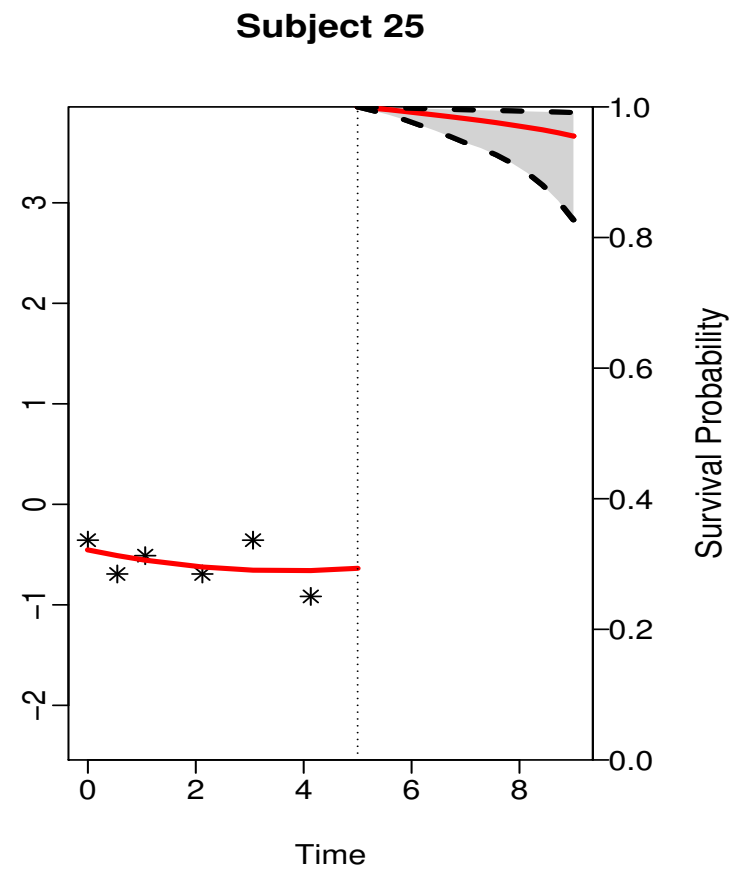
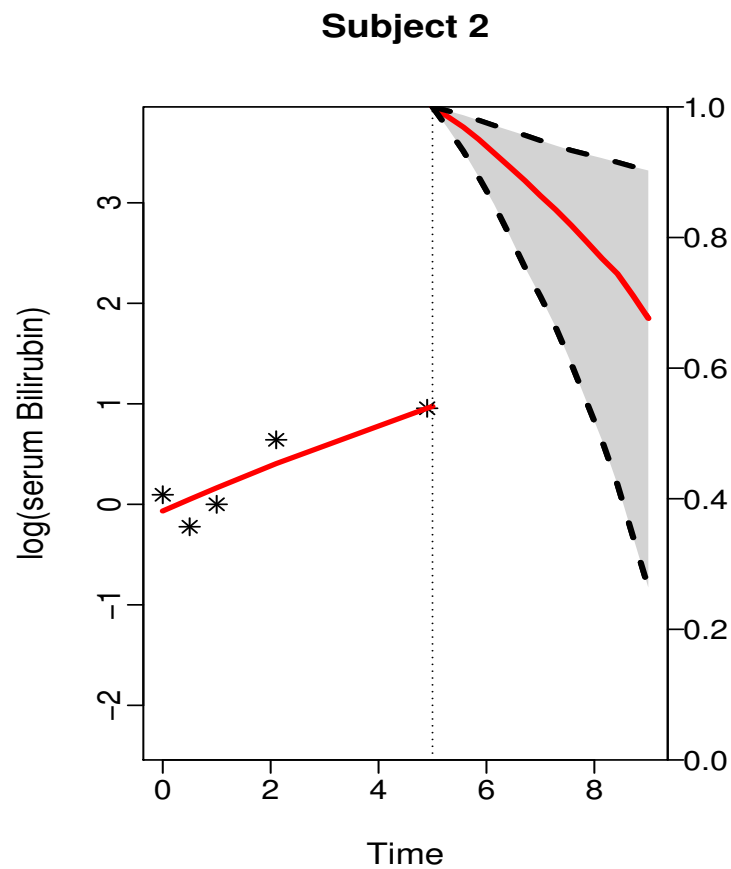


## 6.2 Dynamic Predictions in R (cont'd)



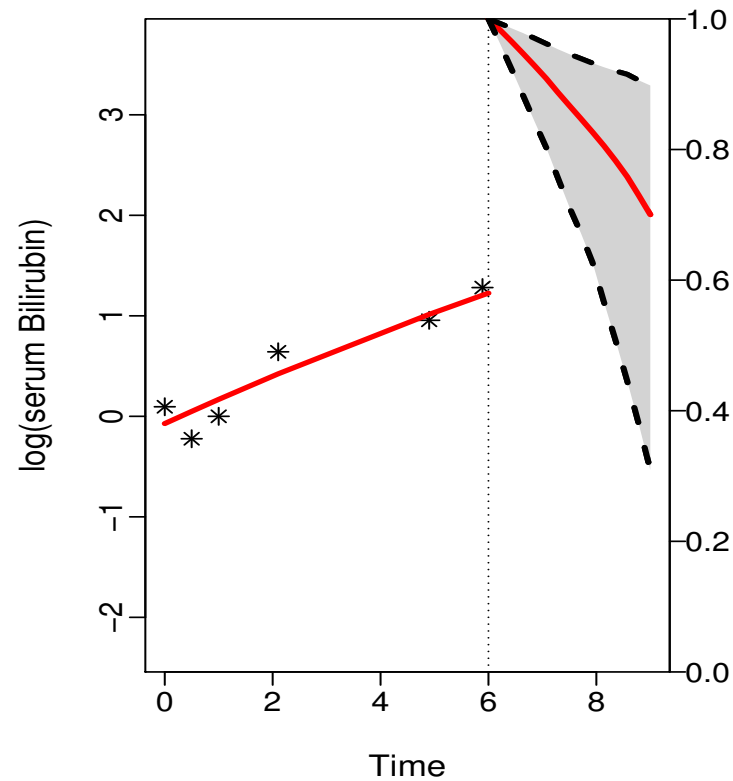


## 6.2 Dynamic Predictions in R (cont'd)

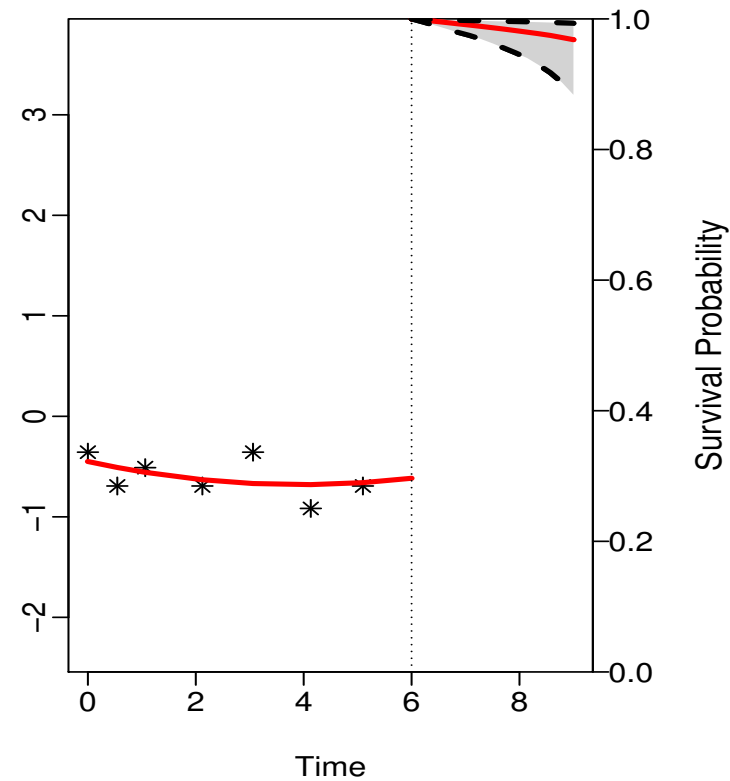


## 6.2 Dynamic Predictions in R (cont'd)

Subject 2

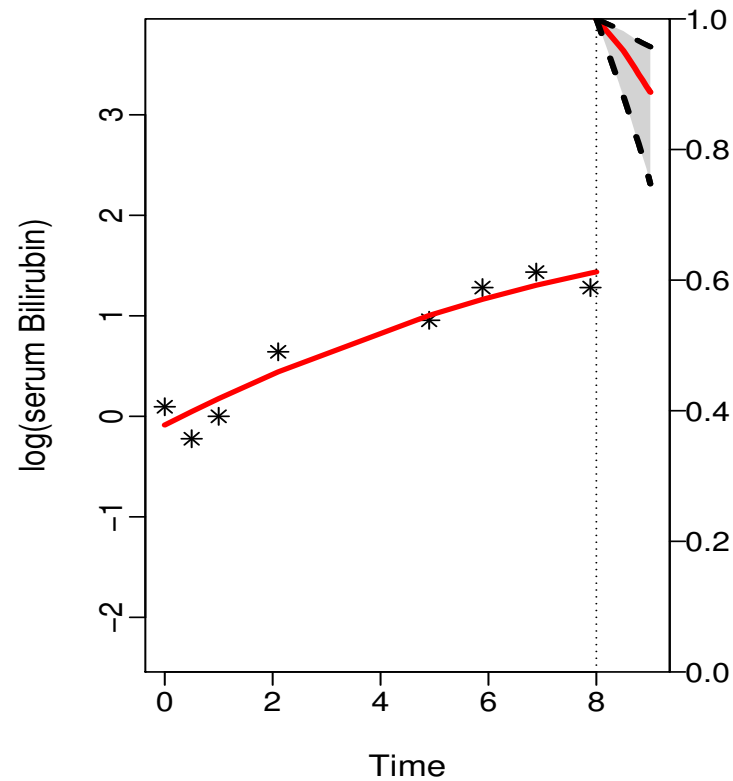


Subject 25

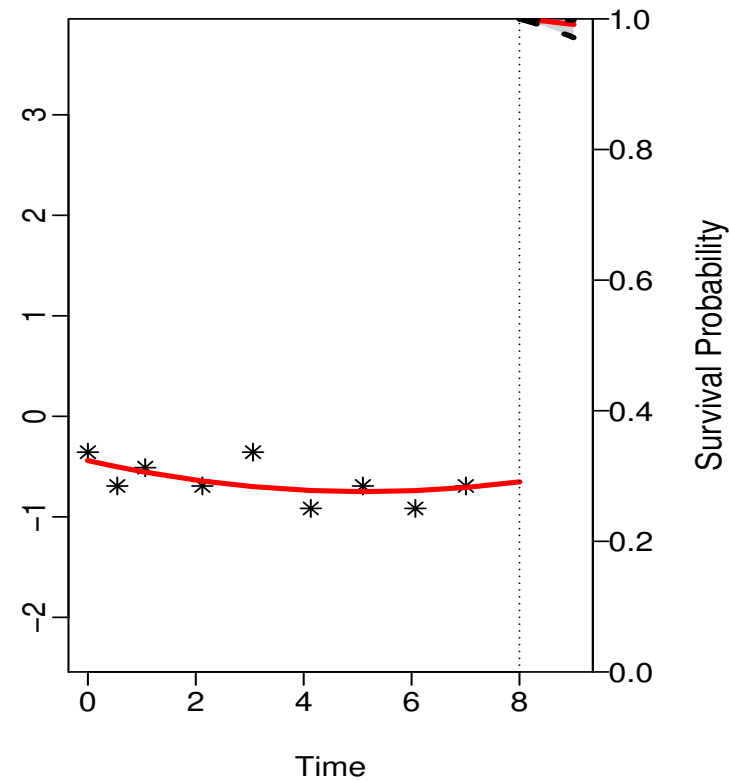


## 6.2 Dynamic Predictions in R (cont'd)

Subject 2



Subject 25



## 6.2 Dynamic Predictions in R (cont'd)

---

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

```
lmeFit <- lme(log(serBilir) ~ year*drug + I(year^2)*drug,  
             random = ~ year + year^2 | id, data = pbc2)
```

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

```
jointFit <- jointModelBayes(lmeFit, coxFit, timeVar = "year",  
                           baseHaz = "P-splines")
```

```
sfit <- survfitJM(jointFit, newdata = pbc2[pbc2$id %in% c(2, 25), ])
```

```
plot(sfit)
```

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

# Chapter 7

## Closing

## 7.1 Concluding Remarks

---

- **When we need joint models for longitudinal and survival outcomes?**
  - ▷ to investigate the association between the longitudinal and the survival outcome
  - ▷ 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  
⇒ Parameterization
- **Extensions**
  - ▷ under the full conditional independence assumption we can easily extend the basic joint model
  - ▷ multiple longitudinal outcomes / different association parameters / time-varying effects
  - ▷ 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**

- ▷ assessment of predictive performance
- ▷ diagnostics for joint models using residuals
- ▷ ...



**The End!**

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