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

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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., 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)

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

Joint Modeling Framework
for Longitudinal and Survival Data

Learning Objectives

- **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

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

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

Agenda (cont'd)

- **Part V:** Extensions of the Basic Joint Model
  - ▷ Parameterizations
  - ▷ Variable selection
  - ▷ Time-varying effcts

- **Part VI:** Dynamic Predictions
  - ▷ Individualized predictions for the survival

Structure of the Course & Material

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

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

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.

References (cont'd)

- 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)

- 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)

- 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

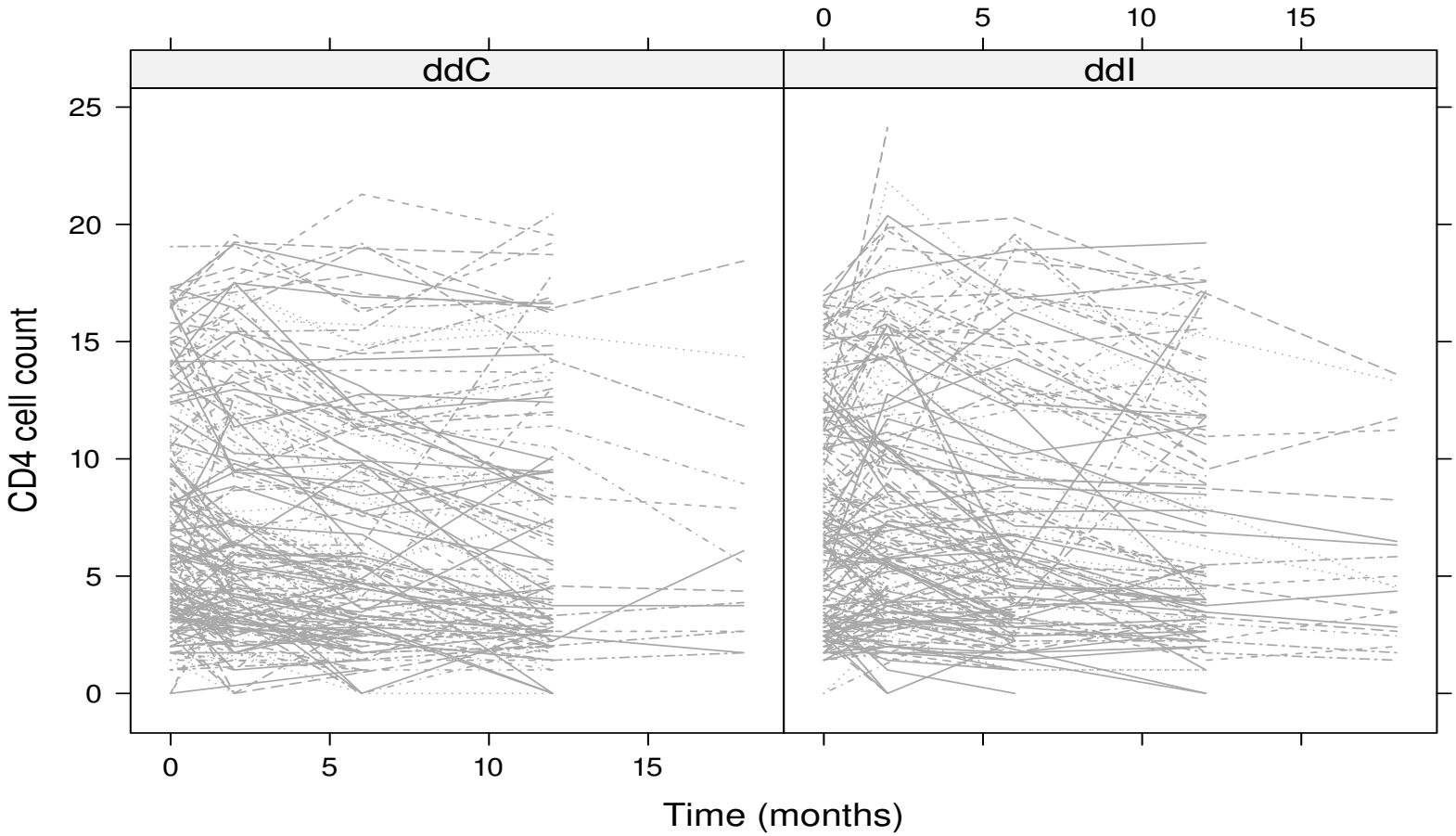
1.1 Motivating Studies

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

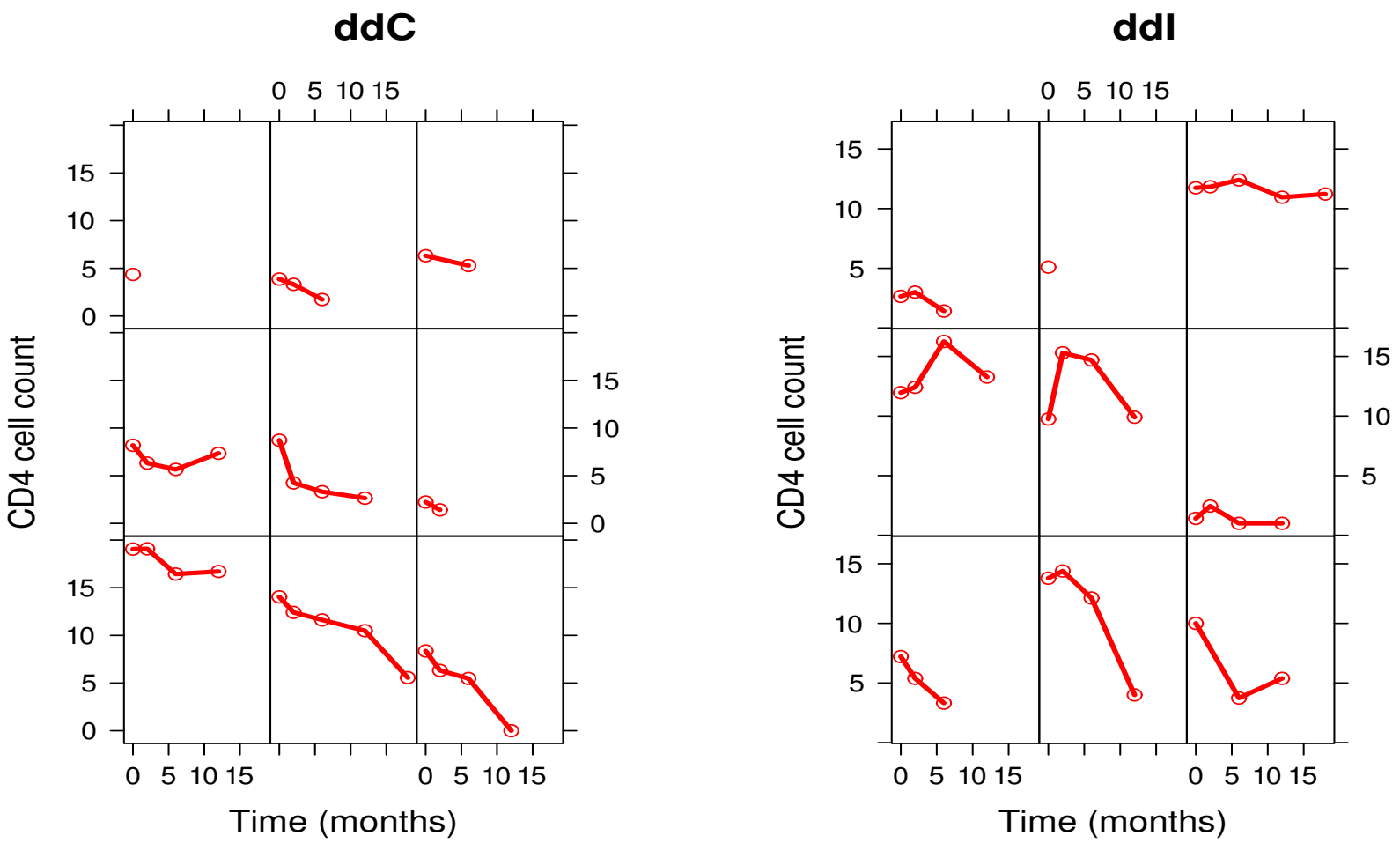
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)
  - ▷ Randomized treatment: 230 patients ddI and 237 ddC

- Outcomes of interest:
  - ▷ **time-to-death**
  - ▷ **CD4 cell count** at baseline, 2, 6, 12 and 18 months

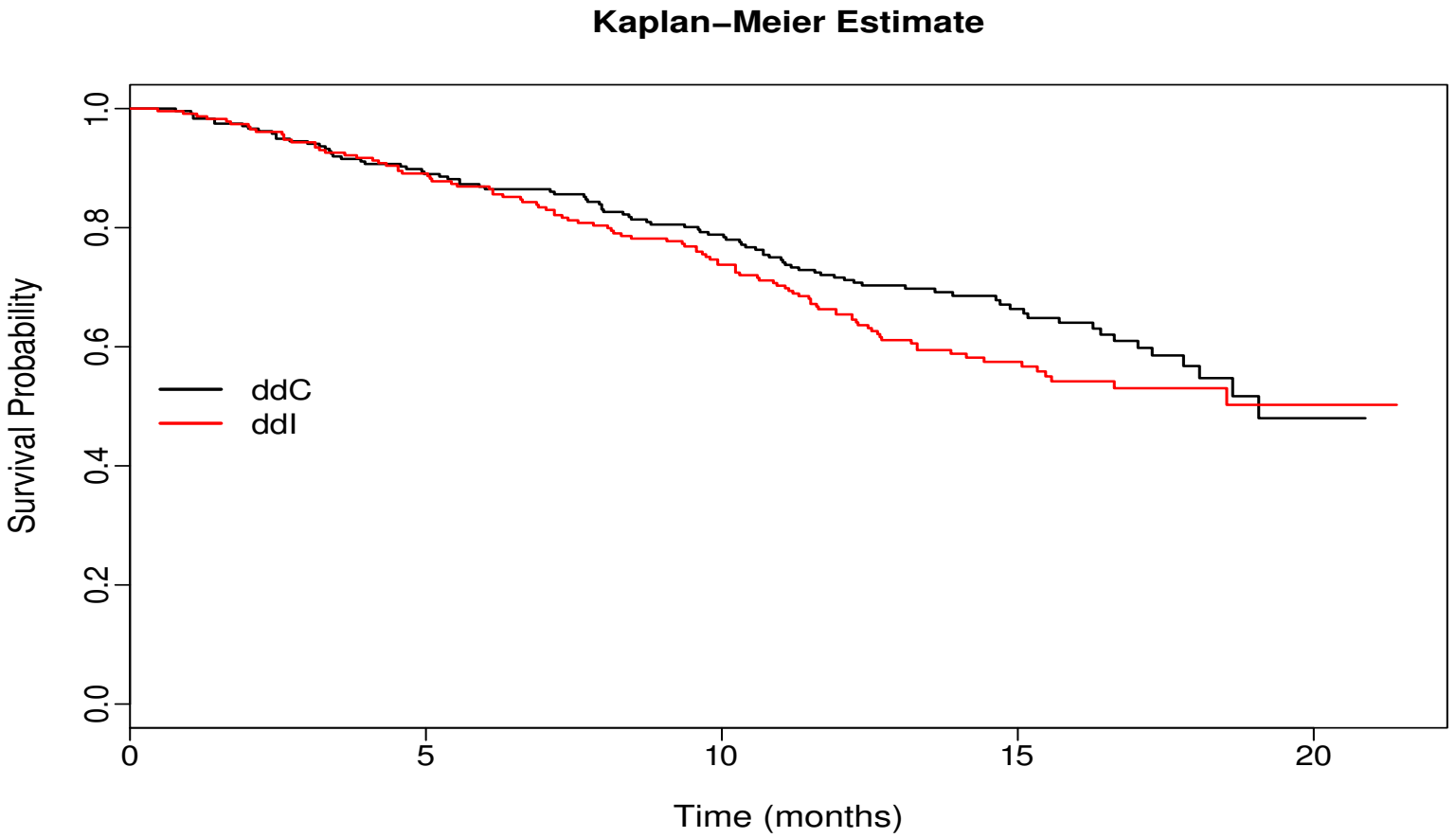
1.1 Motivating Studies (cont'd)



1.1 Motivating Studies (cont'd)



1.1 Motivating Studies (cont'd)



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?

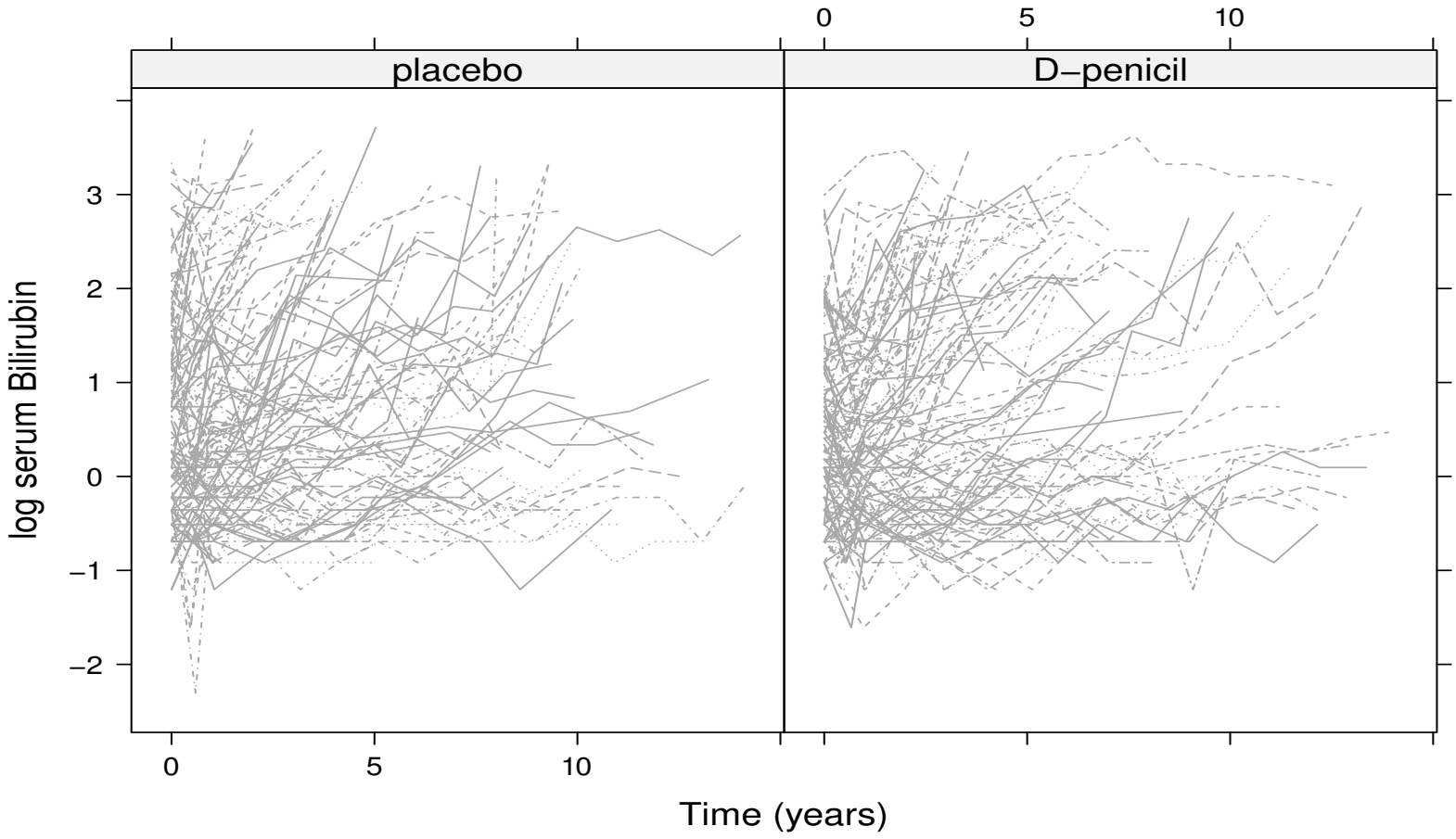
1.1 Motivating Studies (cont'd)

- 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)



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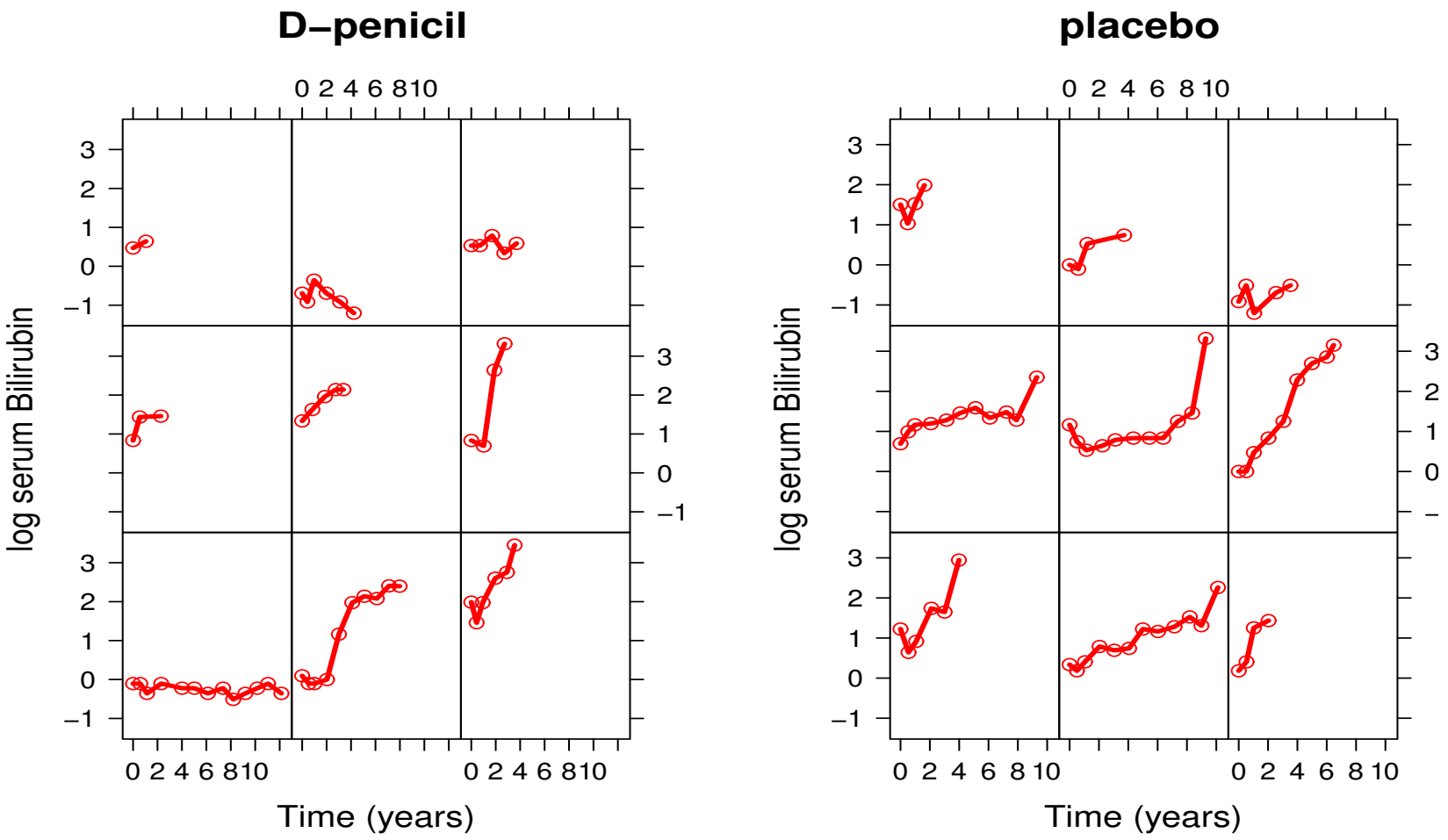

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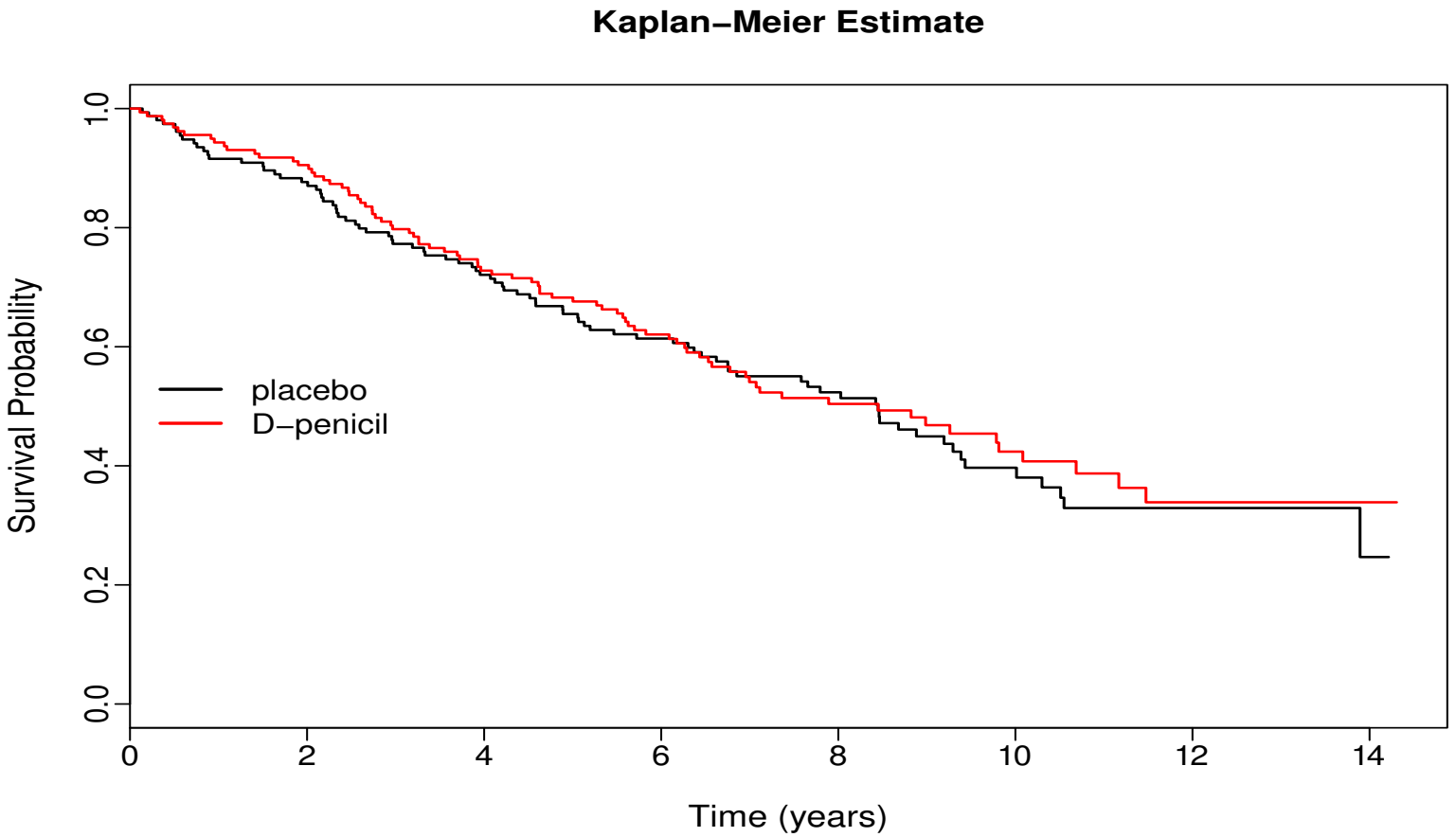


1.1 Motivating Studies (cont'd)

- Research Questions:
  - ▷ How strong is the association between bilirubin and cholesterol with the risk of death?
  - ▷ How could be utilized 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*

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

where

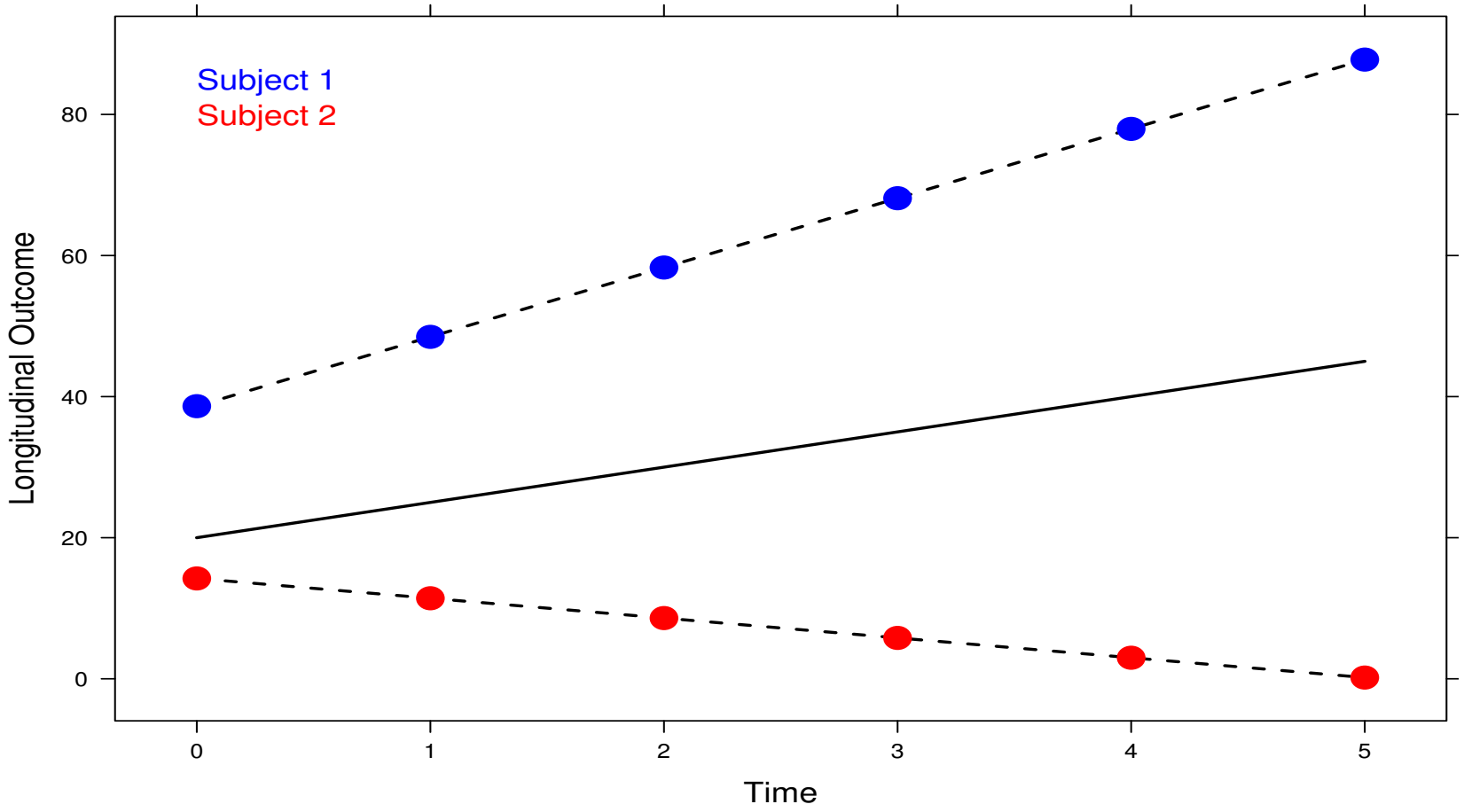
  - $\triangleright$ y_i the vector of responses for the ith subject
  - $\triangleright$ X_i design matrix describing structural component
  - $\triangleright$ V_i covariance matrix describing the correlation structure

- 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

2.2 The Linear Mixed Model (cont'd)

- We can reformulate the model as

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

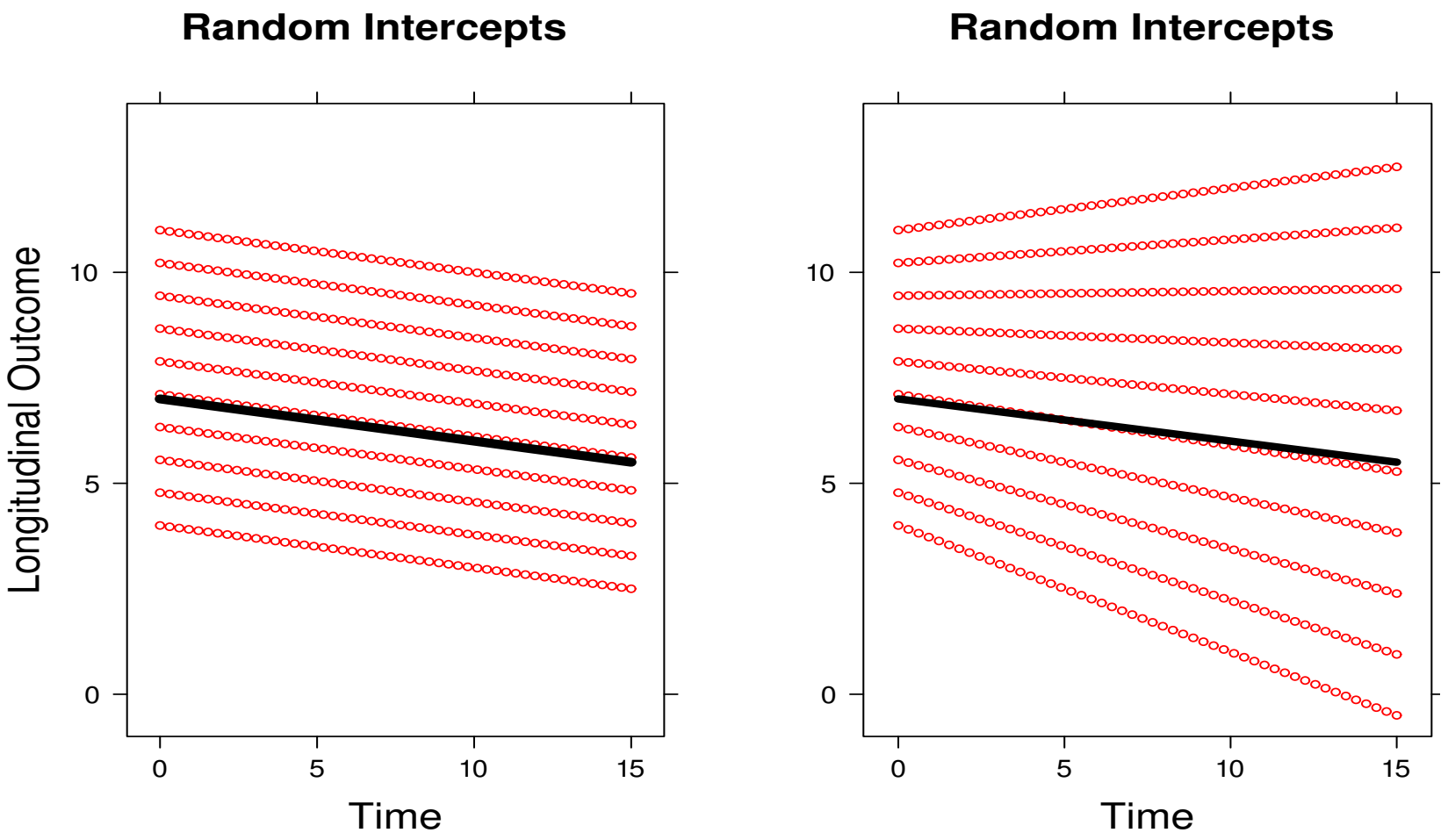
where

  - ▷ 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)



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)

- Estimation $\rightarrow$ maximum likelihood (MLE)

- The log-likelihood of a linear mixed model takes the form

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

where $p(.)$ 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)

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

- 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-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^2
  ⇒ `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.,

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

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

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

3.2 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 $p(.)$ density function; $S(.)$ 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

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

  where only patients who had an event contribute

3.2 Relative Risk Models (cont'd)

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

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

	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

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

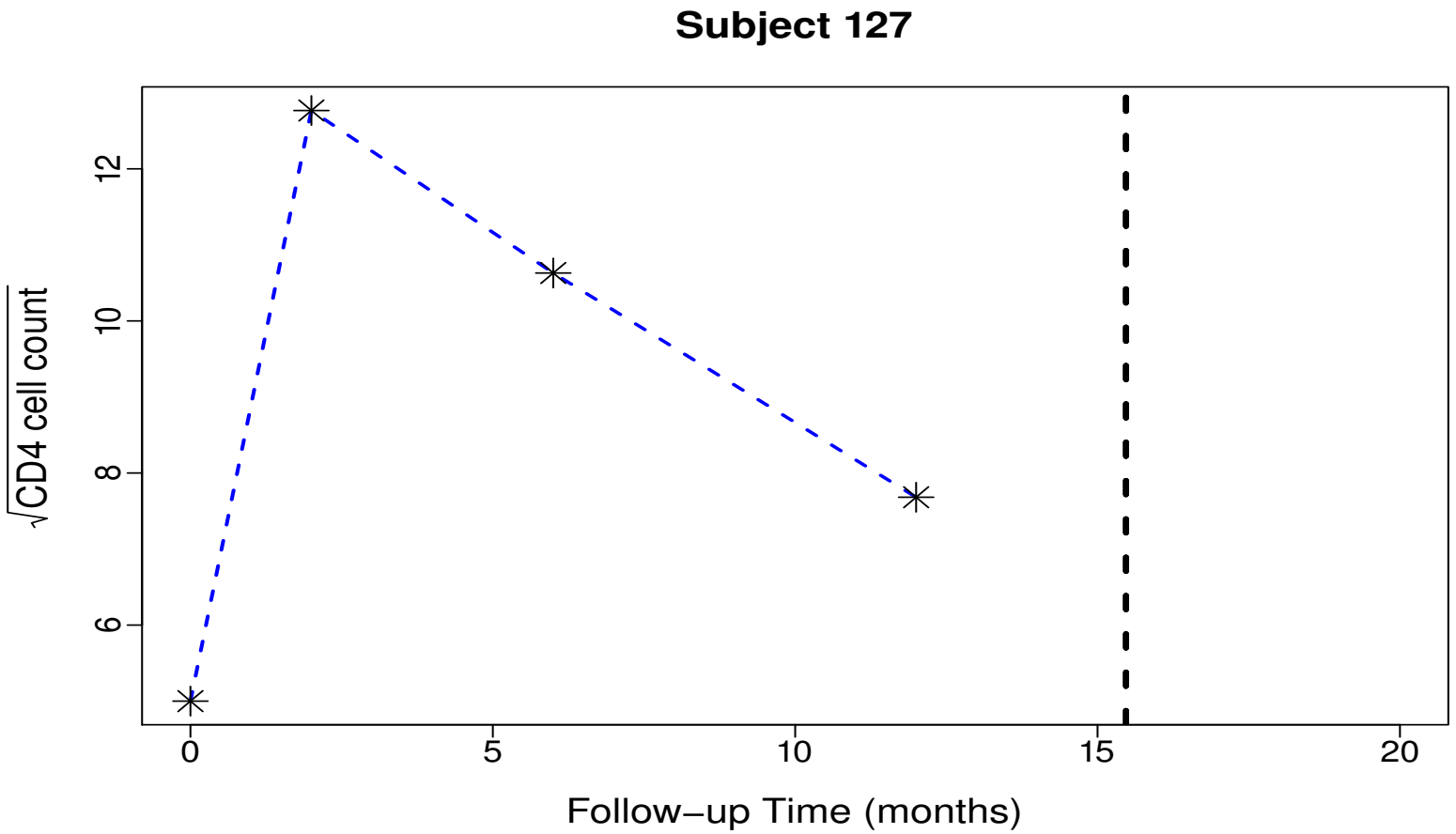
  - ▷ Endogenous (aka internal): not Exogenous

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)

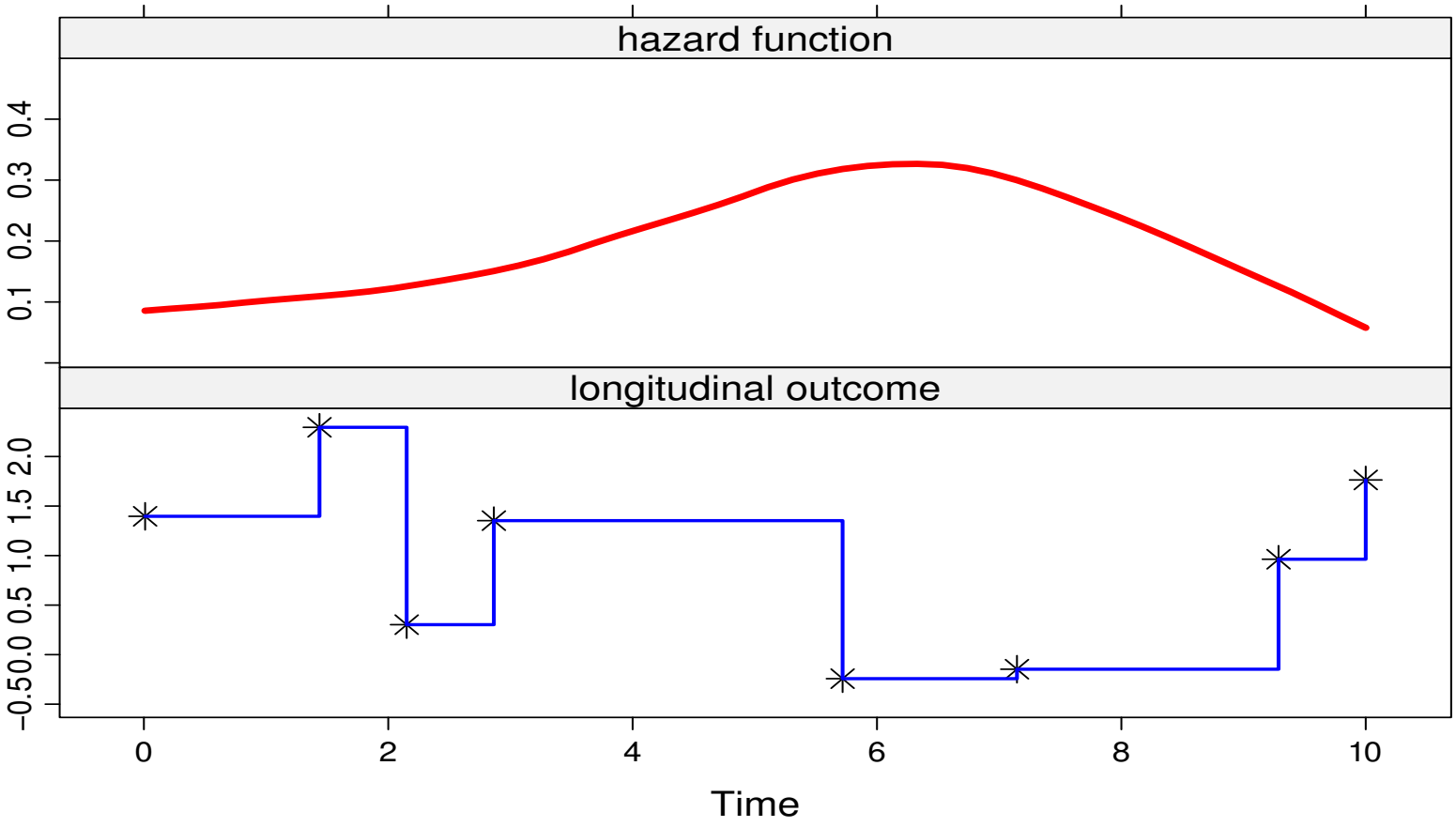
- Typically, data must be organized in the long format

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!

Chapter 4

The Basic Joint Model

4.1 Joint Modeling Framework

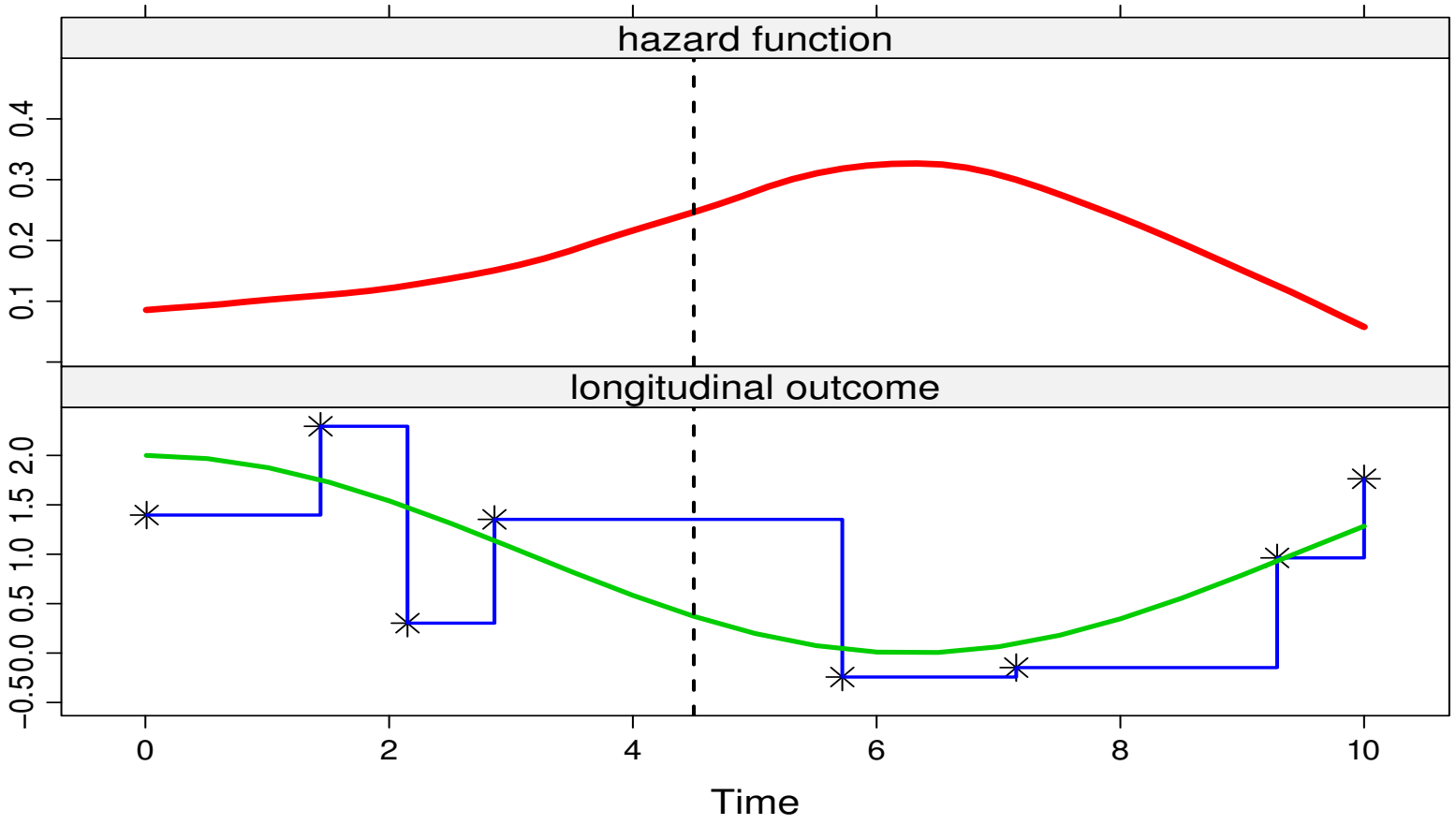
- To account for the special features of endogenous covariates a new class of models has been developed

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 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: 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)

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

where

  - $\triangleright$ $x_i(t)$ and β: Fixed-effects part
  - $\triangleright$ $z_i(t)$ 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
  - ▷ 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 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)

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

  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

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

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

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 $v_1, \ldots, v_Q$
* 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

4.1 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

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

4.3 Introduction to Bayesian* (cont'd)

- Bayes theorem

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

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?

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

- 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)

4.4 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

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

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

4.4 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

- 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

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

where

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

4.5 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

4.5 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; 1.43)
  - ▷ **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

4.6 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 penatlies (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)

Chapter 5

Extensions of Joint Models

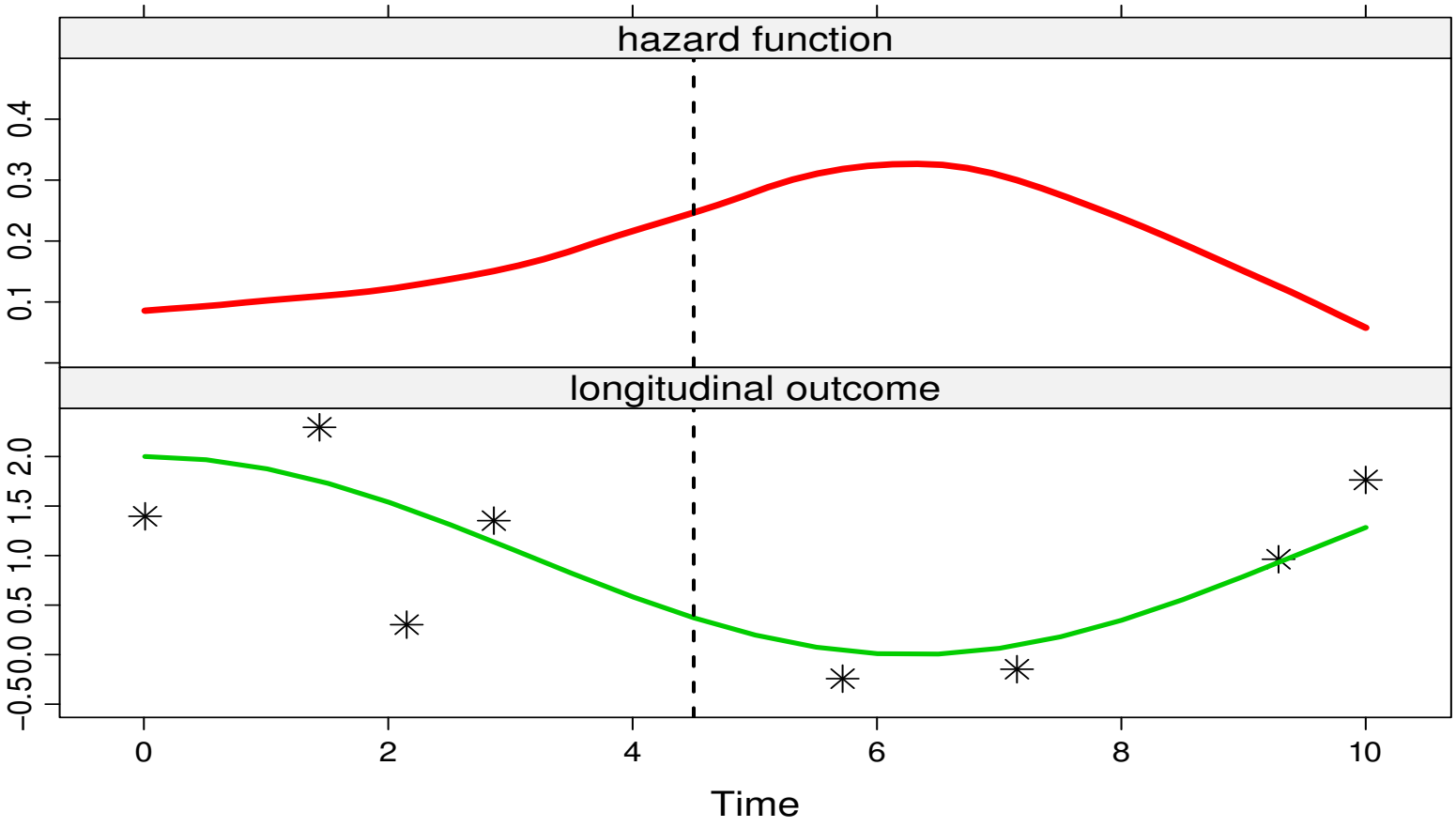
5.1 Parameterizations

- 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., 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)

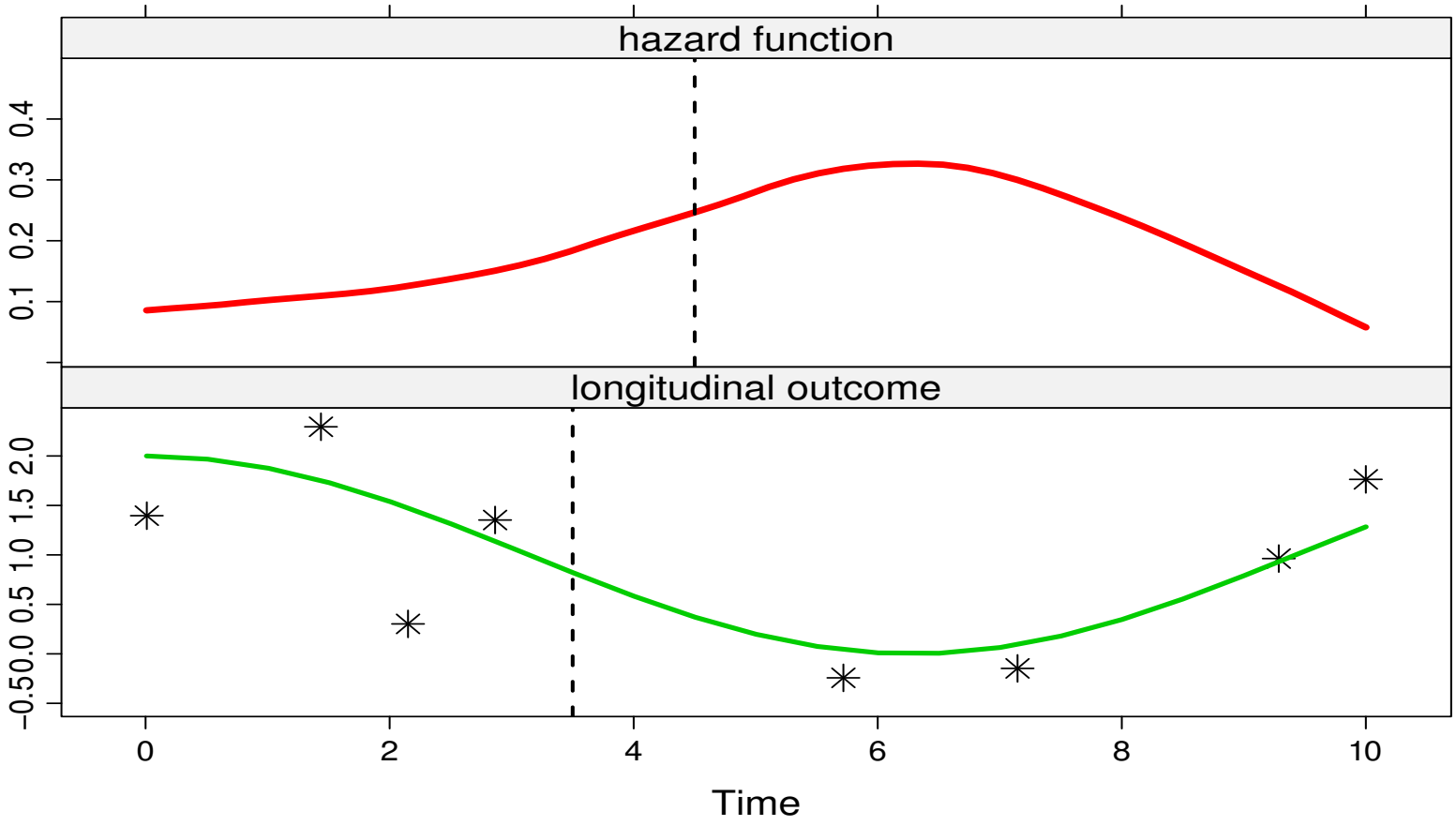
- *Lagged Effects:* The hazard of an event at t is associated with the level of the marker at a previous time point:

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

where

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

5.1 Parameterizations (cont'd)



5.1 Parameterizations (cont'd)

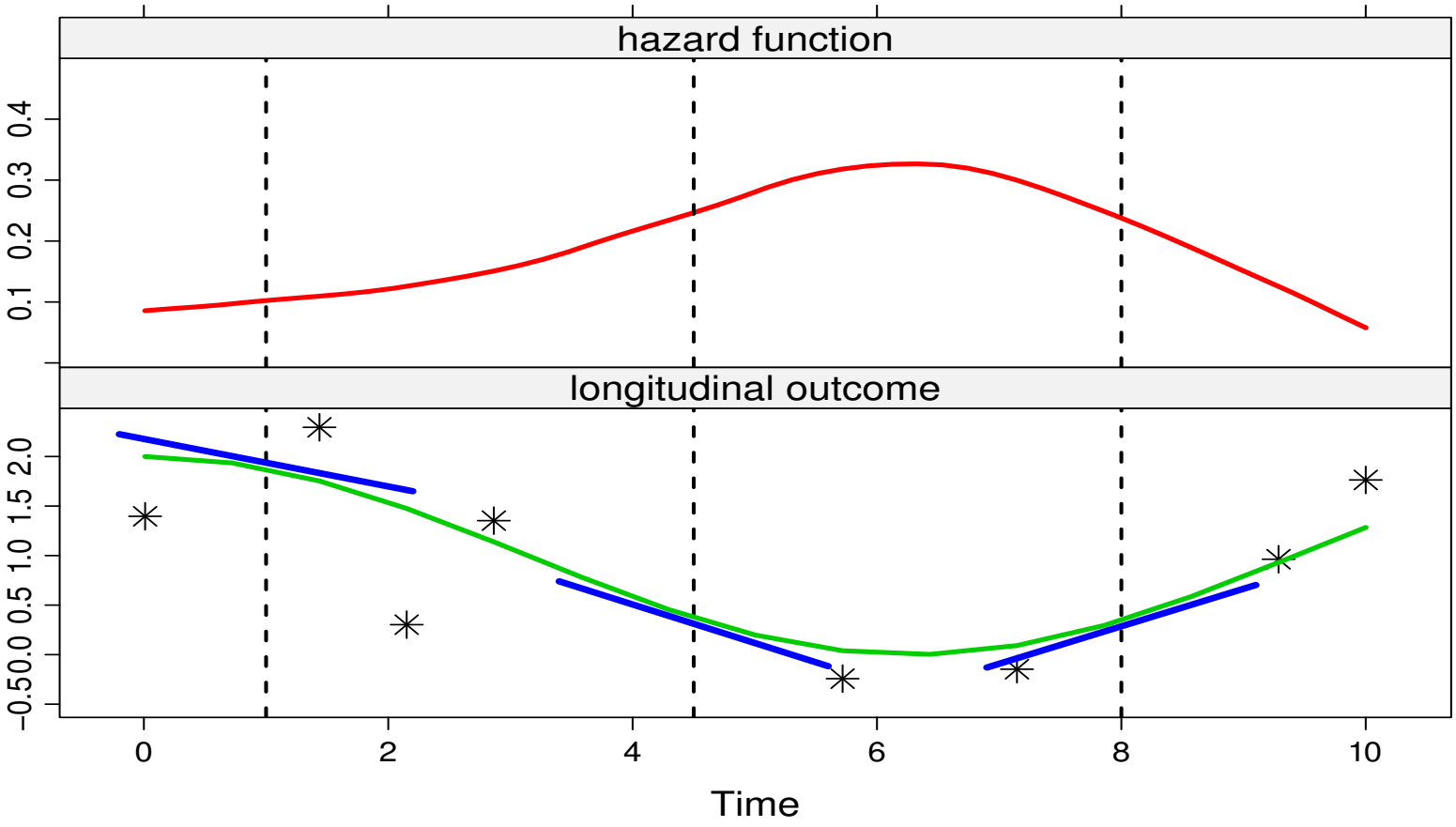
- *Time-dependent Slopes:* The hazard of an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

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

where

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

5.1 Parameterizations (cont'd)



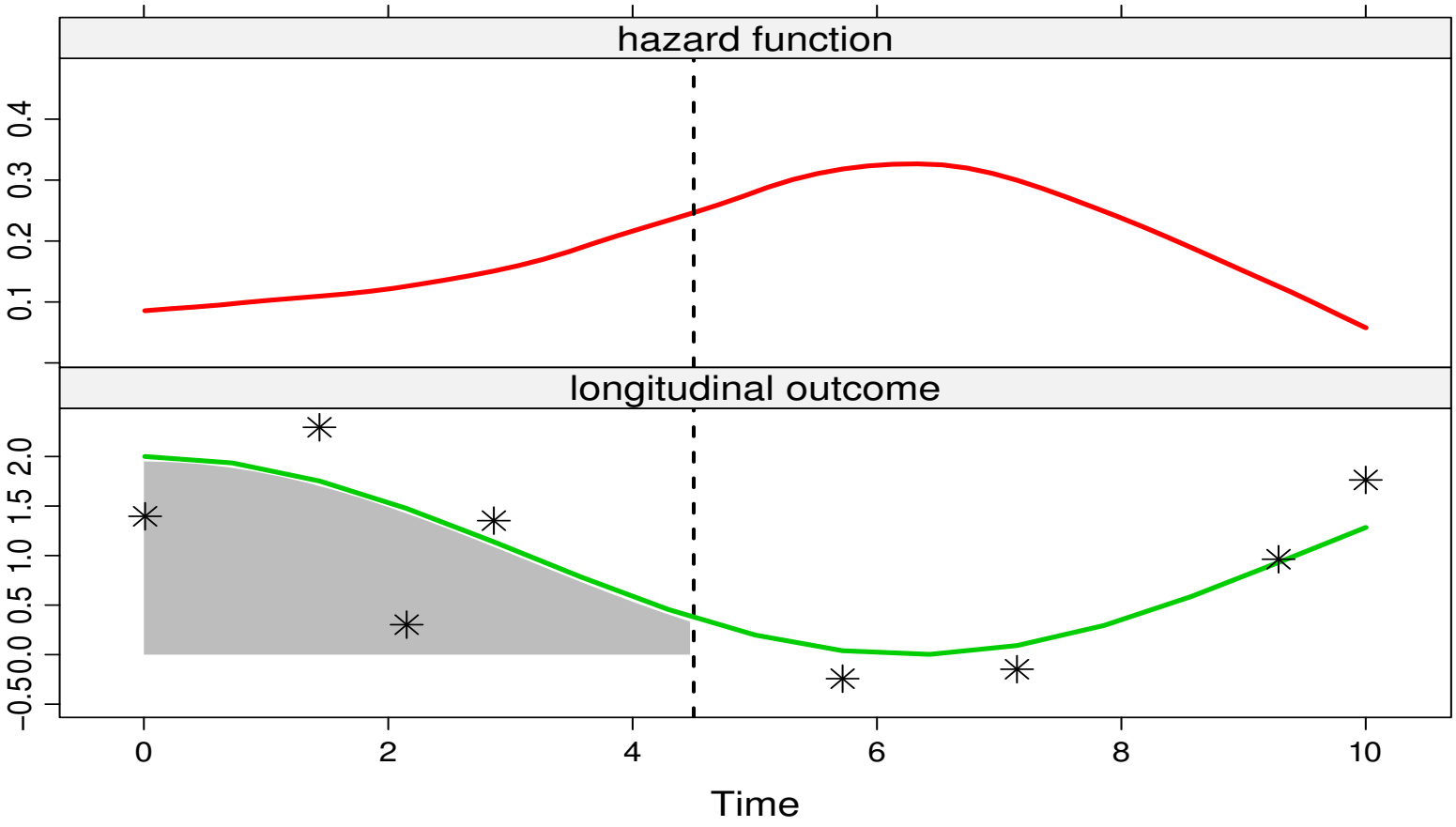
5.1 Parameterizations (cont'd)

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

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

- 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)

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

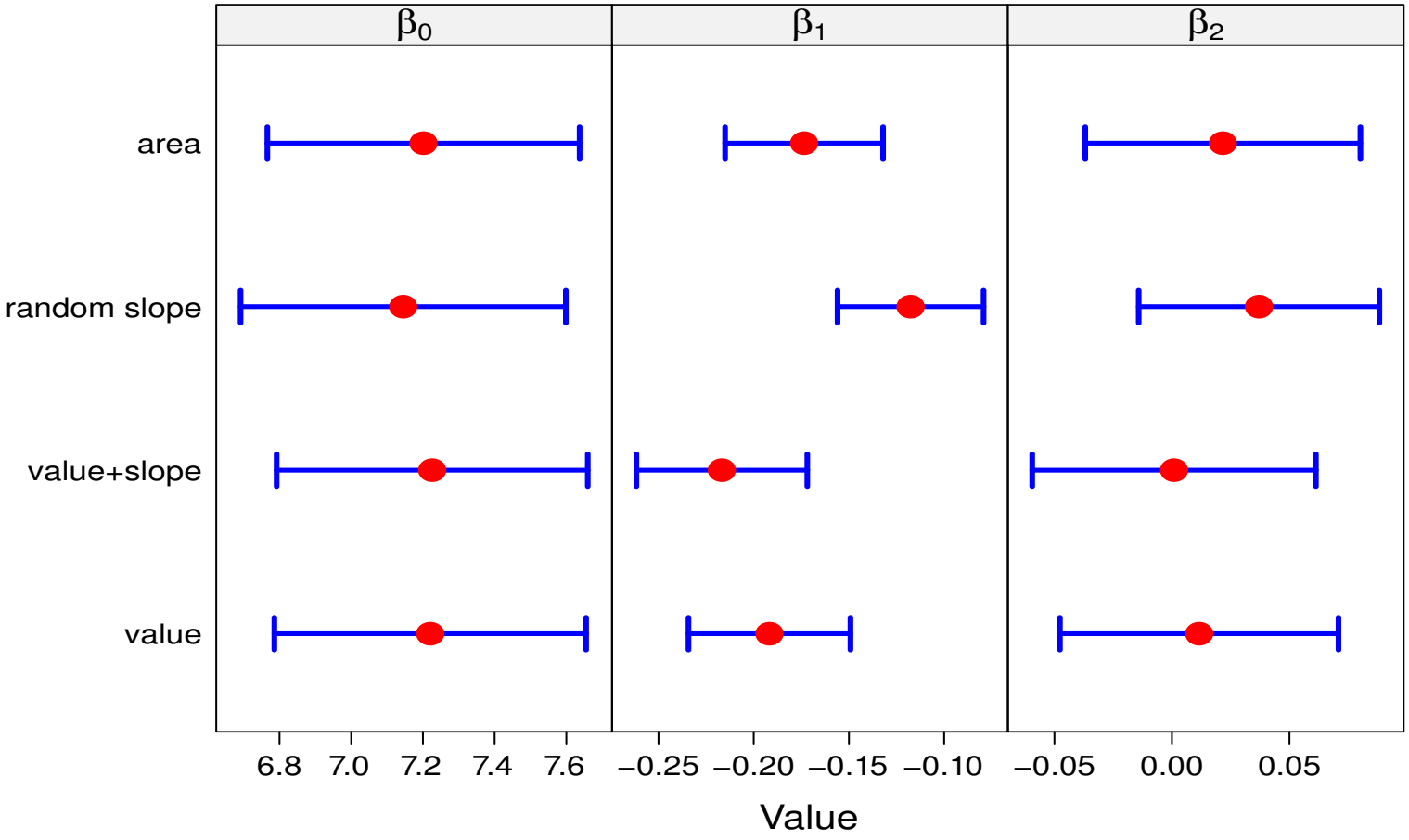
- Model IV (area)

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

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

5.2 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 $Y_{i1}, \ldots, Y_{iJ}$ 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 Biomarkers (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

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

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 `mvglmer()`,
  - ▷ 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

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

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

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 manned as `jointModelBayes()` does

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

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

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

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

5.6 Variable Selection in R (cont'd)

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

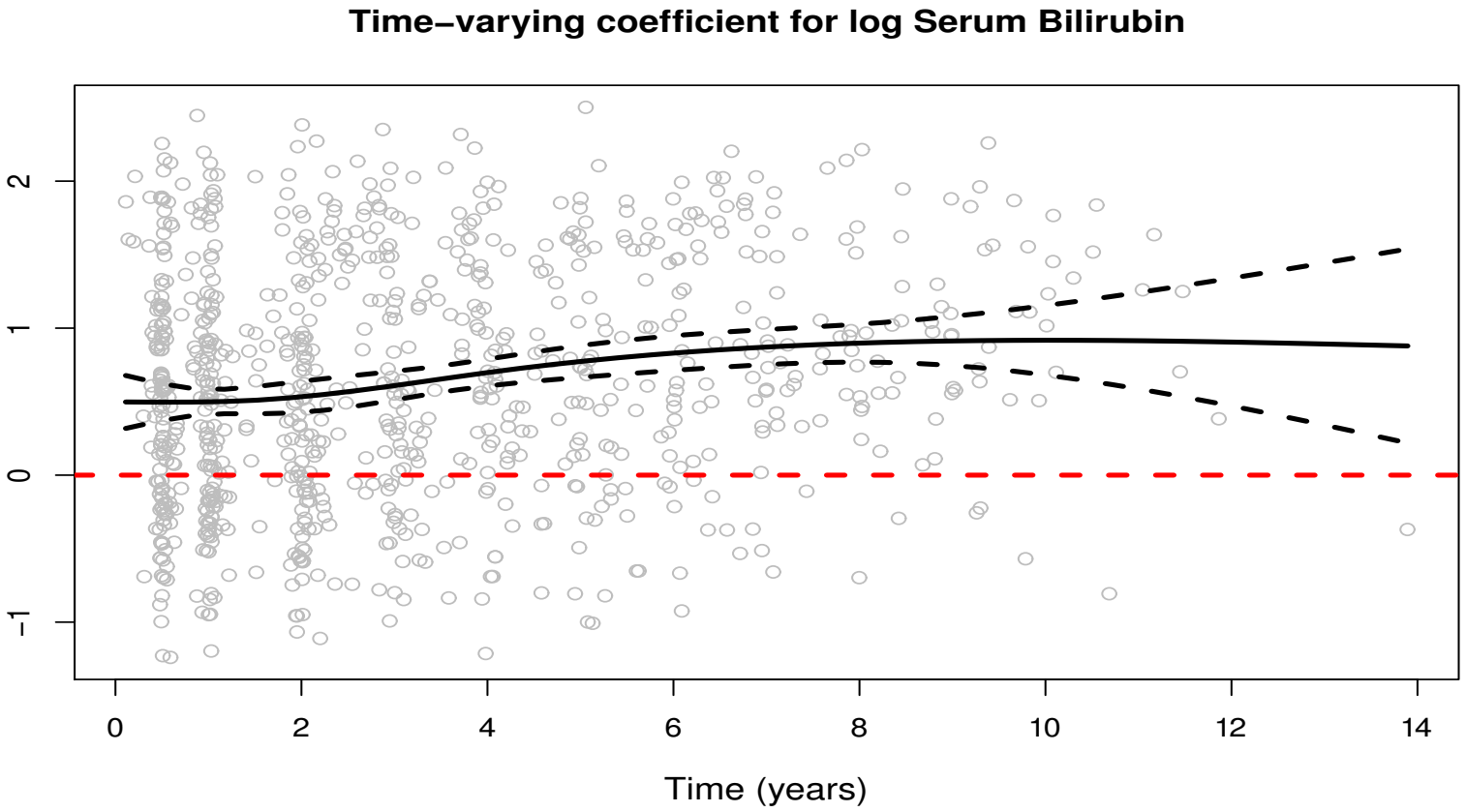
```
Forms <- list("log(serBilir)" = "value",
              "log(serBilir)" = list(fixed = ~ 1, random = ~ 1,
                                     indFixed = 2, indRandom = 2, name = "slope"),
              "spiders" = list(fixed = ~ 0 + year + I(year^2/2), random = ~ 0 + year,
                      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



5.7 Time-Varying Association (cont'd)

A time-varying coefficient joint model (VCJM)

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 γ
- $f_{j\ell}\{m_{ij}(t), \lambda_{j\ell}(t)\}$ is the outcome (j = 1, . . . , J) and the form of association ($\ell = 1$, . . . , 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

  - α_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 $\nu_1, \ldots, \nu_Q$

- 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 or 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

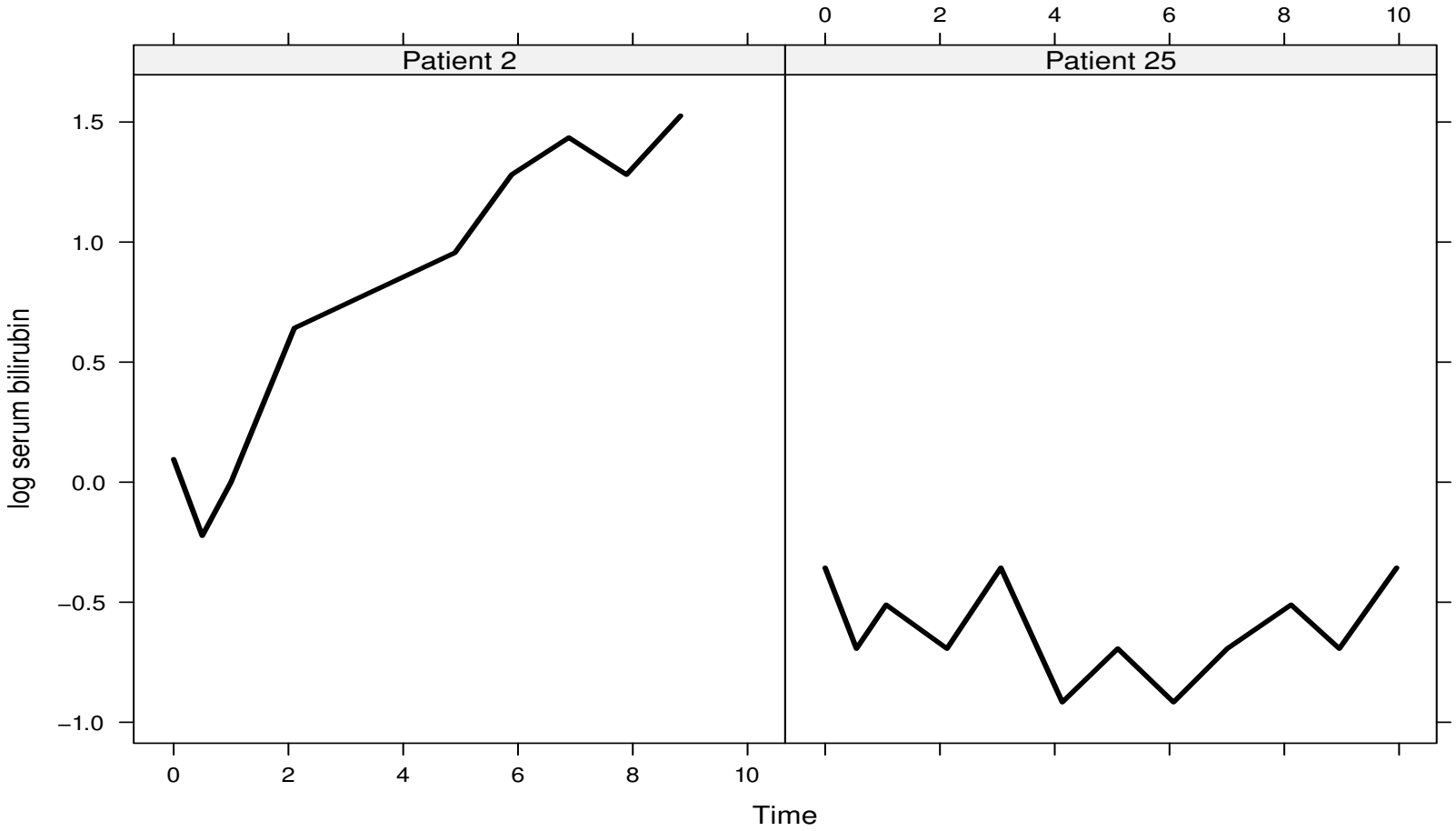
6.1 Survival Probabilities (cont'd)

- 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)

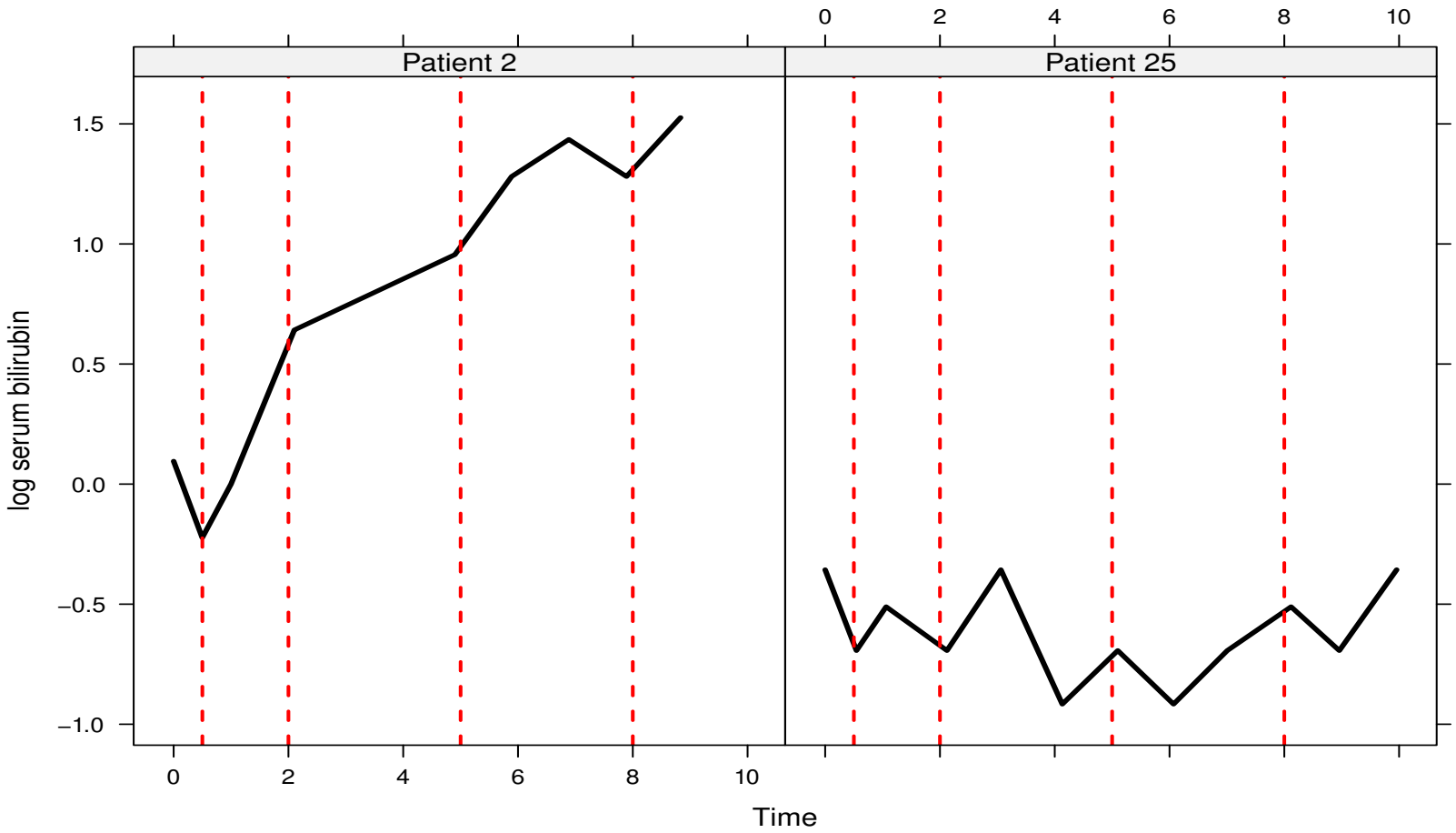
6.2 Dynamic Predictions in R

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

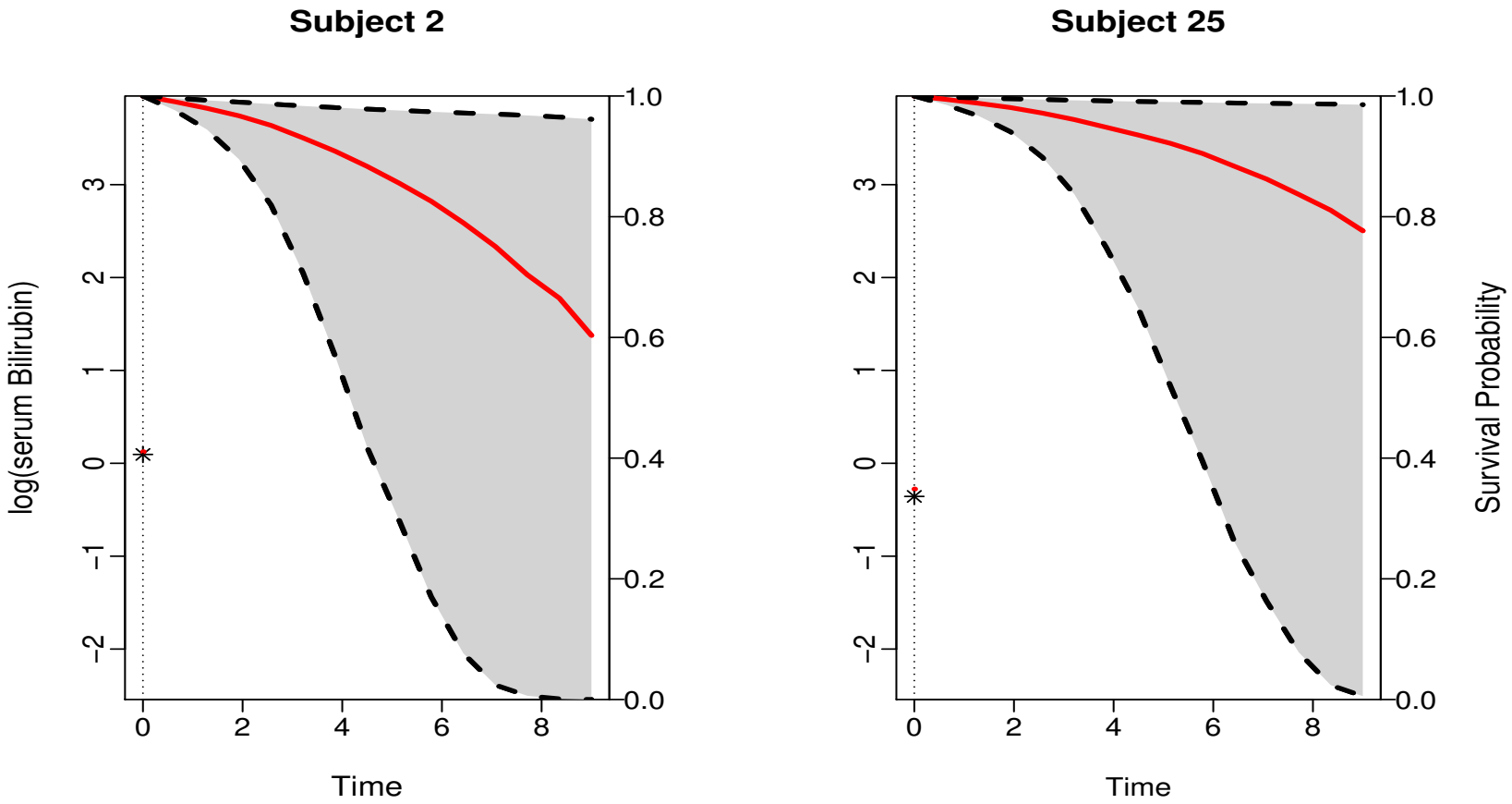
- Longitudinal submodel
  - ▷ fixed effects: Linear & quadratic time, treatment and their interaction
  - ▷ random effects: Intercept, linear & quadratic time effects

- Survival submodel
  - ▷ treatment effect + *underlying* serum bilirubin level
  - ▷ P-splines

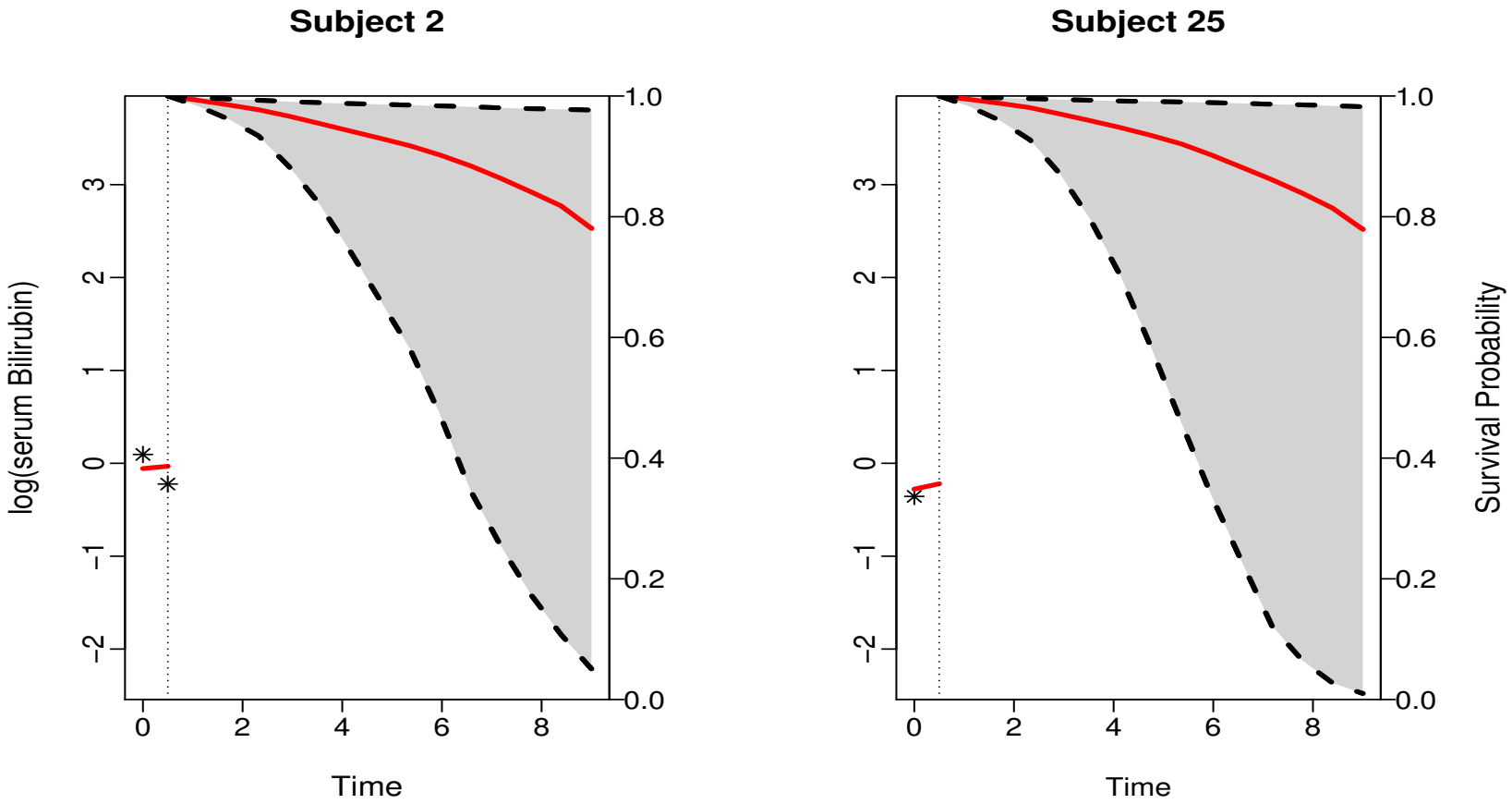
6.2 Dynamic Predictions in R (cont'd)



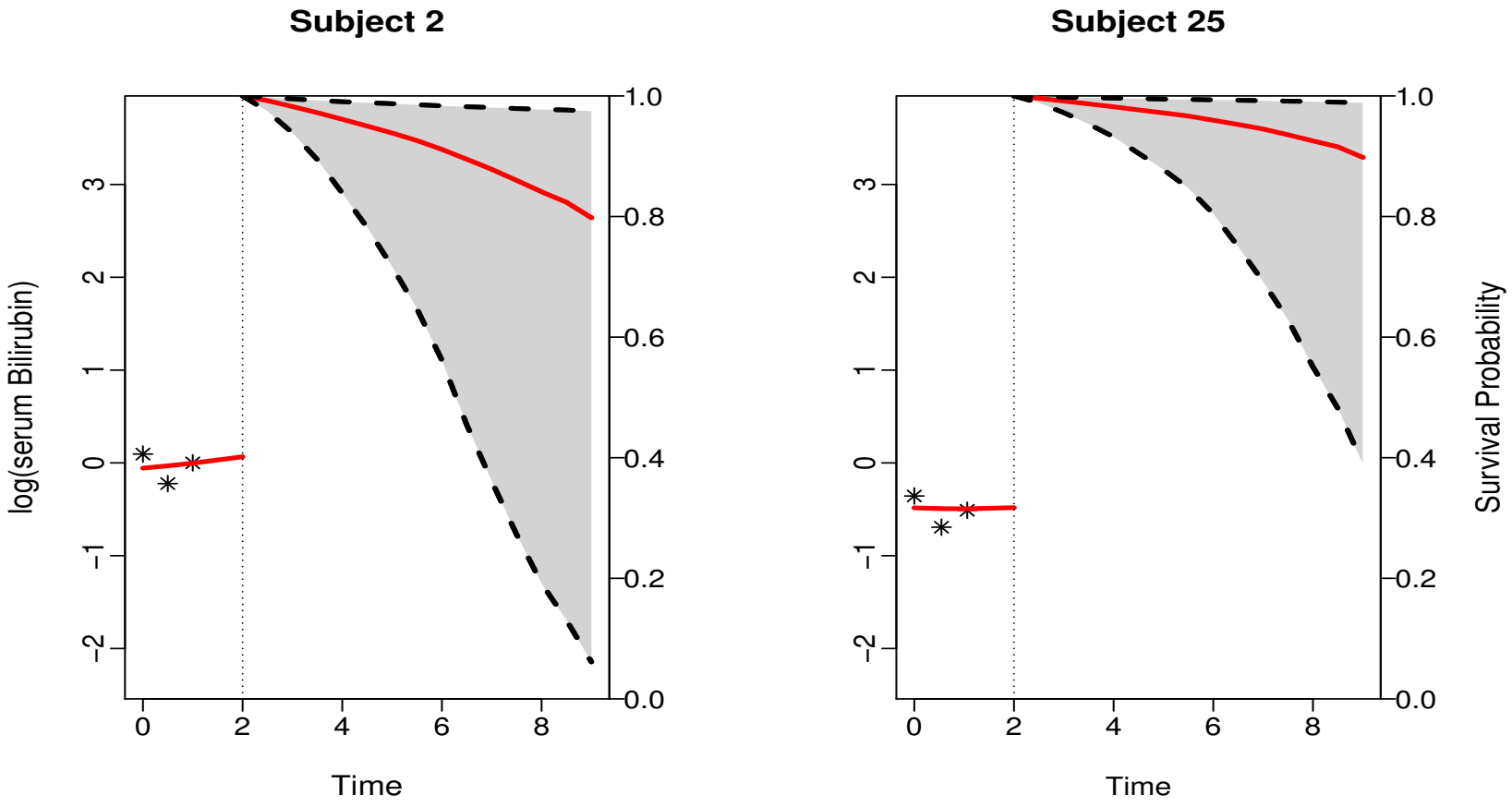
6.2 Dynamic Predictions in R (cont'd)



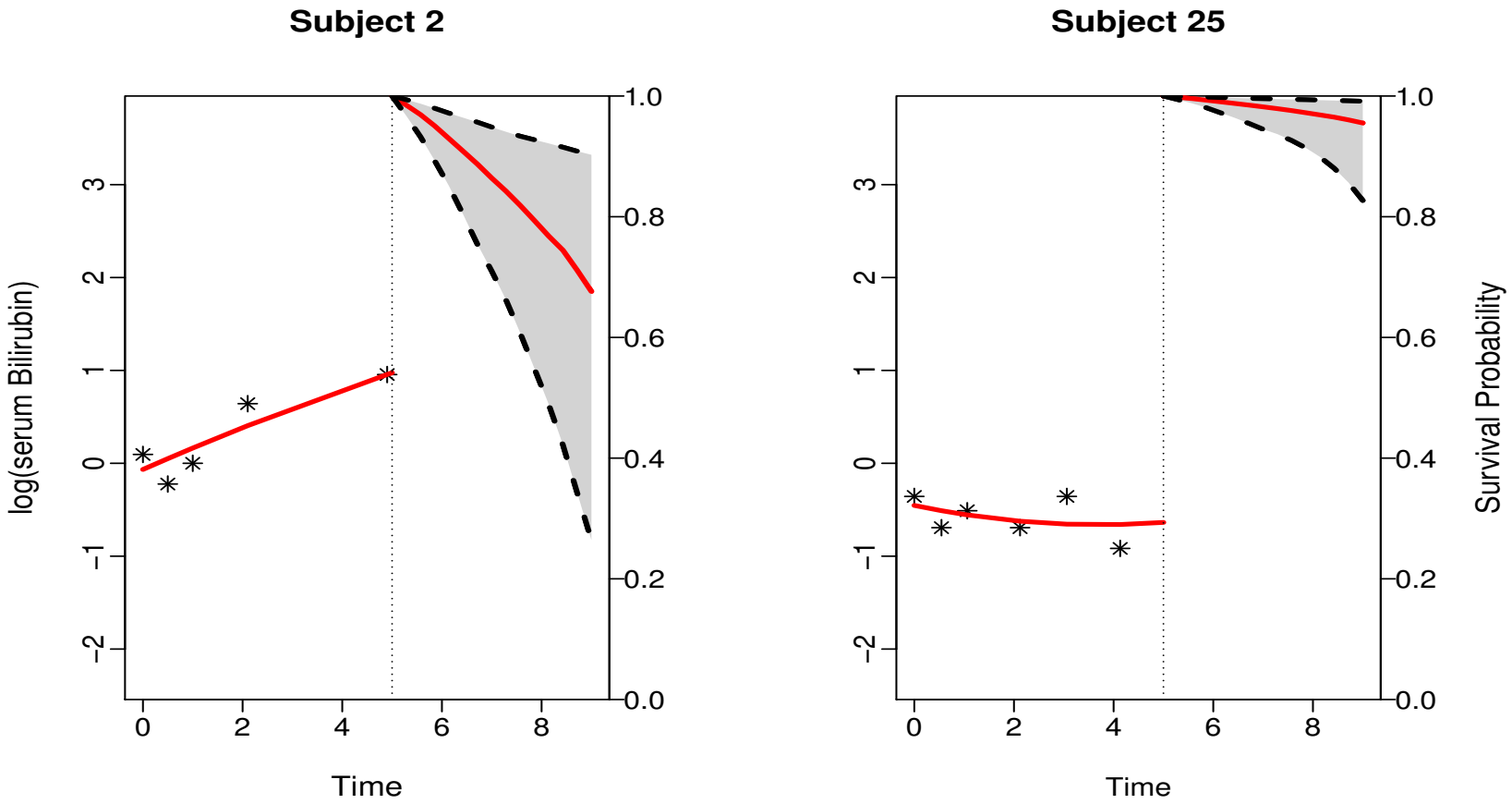
6.2 Dynamic Predictions in R (cont'd)



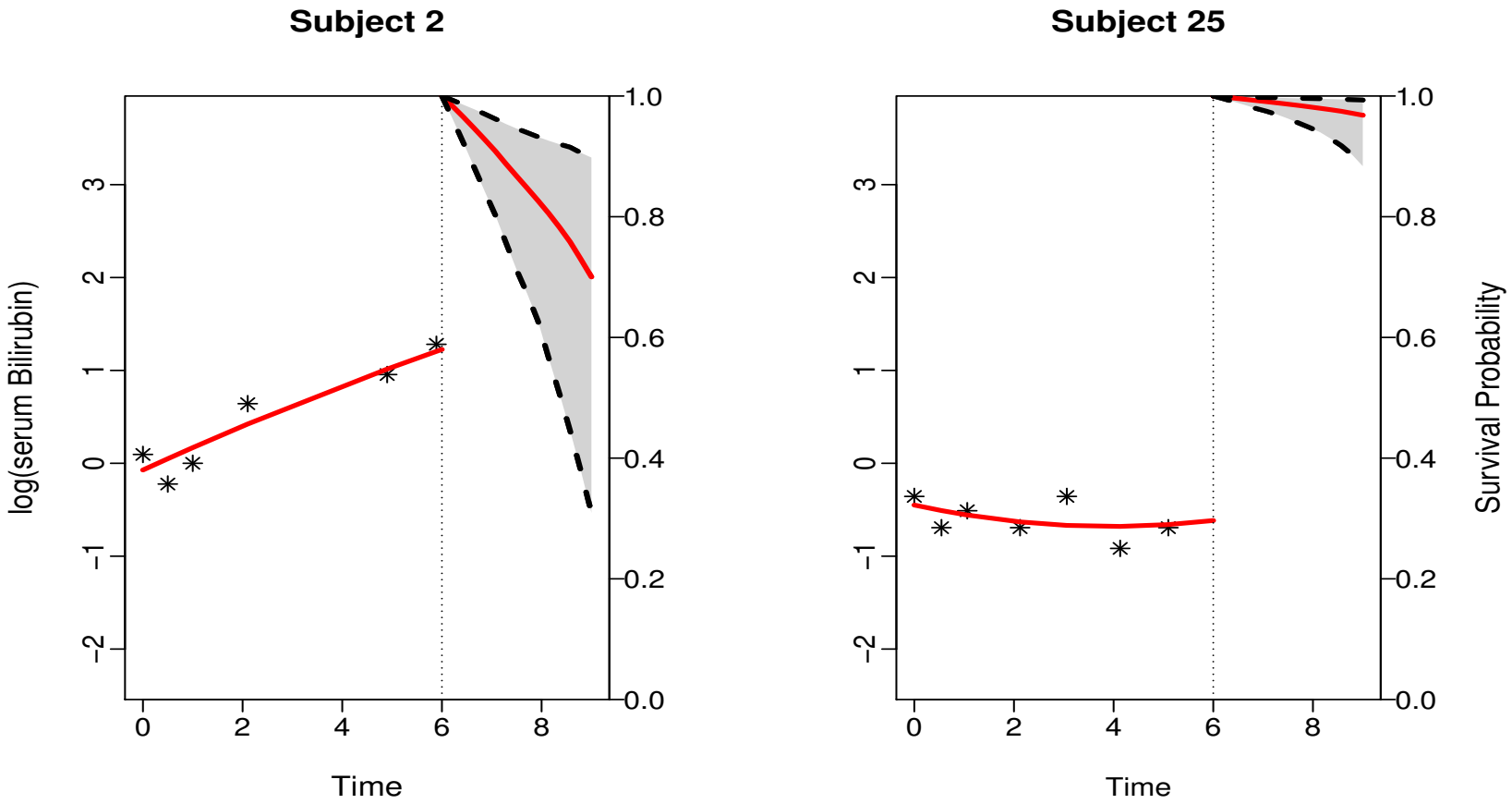
6.2 Dynamic Predictions in R (cont'd)



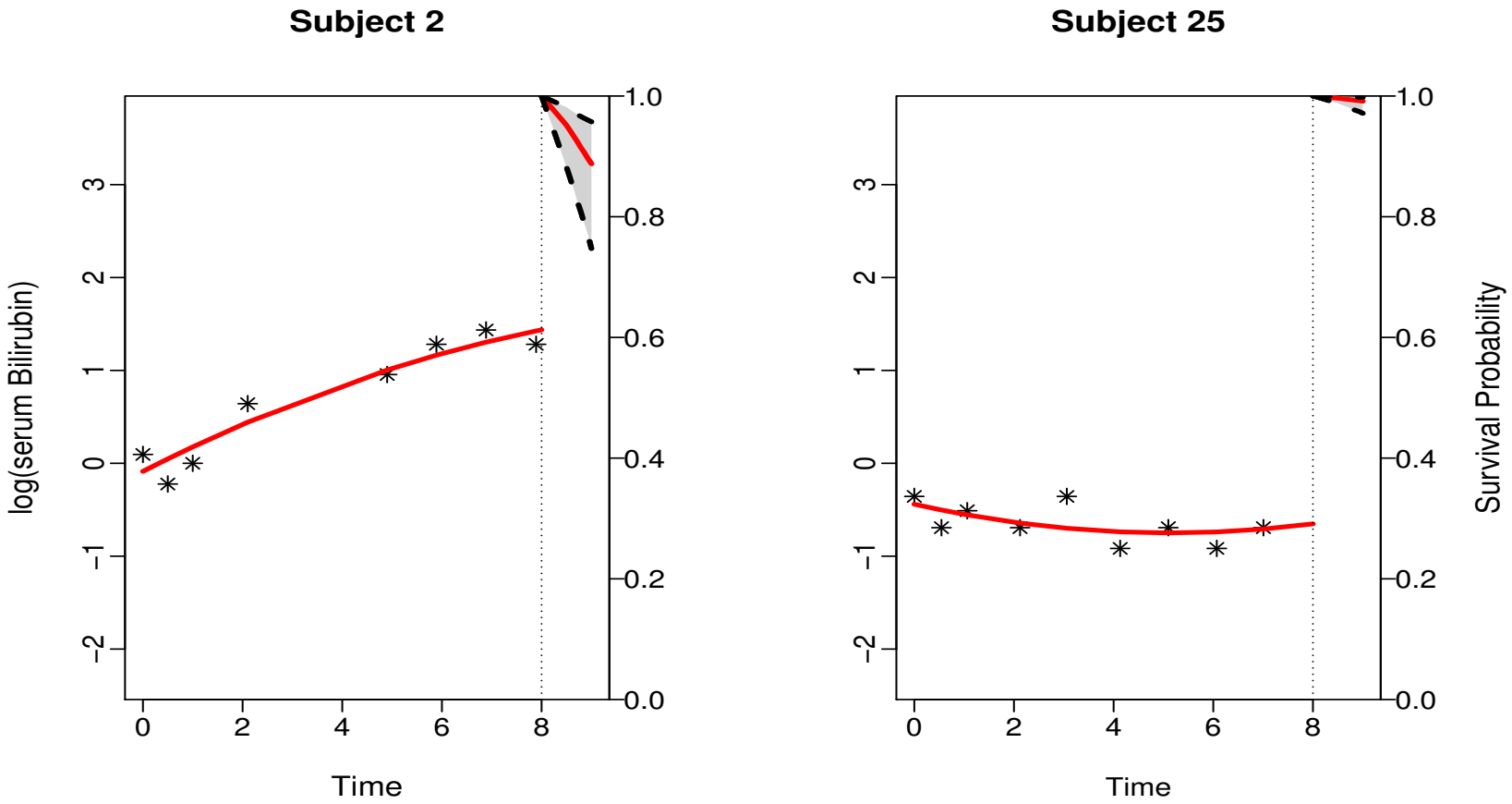
6.2 Dynamic Predictions in R (cont'd)



6.2 Dynamic Predictions in R (cont'd)



6.2 Dynamic Predictions in R (cont'd)



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 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 / 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!

7.2 Additional References

- Andrinopoulou, E.R., Eilers, P.H.C., Takkenberg, J.J.M. and Rizopoulos, D. (2017). Improved dynamic predictions from joint models of longitudinal and survival data with time-varying effects using P-splines. *Biometrics*, to appear.

- Andrinopoulou, E.R., Rizopoulos, D., Takkenberg, J.J.M. and Lesaffre, E. (2017). Combined dynamic predictions using joint models of two longitudinal outcomes and competing risk data. *Statistical Methods in Medical Research*, to appear.

- Andrinopoulou, E.R., Rizopoulos, D., Takkenberg, J.J.M. and Lesaffre, E. (2014). Joint modeling of two longitudinal outcomes and competing risk data. *Statistics in Medicine* **33**, 3167–3178.

- Brown, E. and Ibrahim, J. (2003). A Bayesian semiparametric joint hierarchical model for longitudinal and survival data. *Biometrics* **59**, 221–228.

- Brown, E. Ibrahim, J. and DeGruttola, V. (2005). A flexible B-spline model for multiple longitudinal biomarkers and survival. *Biometrics* **61**, 64–73.

- Chi, Y.-Y. and Ibrahim, J. (2006). Joint models for multivariate longitudinal and multivariate survival data. *Biometrics* **62**, 432–445.

7.2 Additional References (cont'd)

- DeGruttola, V. and Tu, X. (1994). Modeling progression of CD-4 lymphocyte count and its relationship to survival time. *Biometrics* **50**, 1003–1014.

- Elashoff, R., Li, G. and Li, N. (2008). A joint model for longitudinal measurements and survival data in the presence of multiple failure types. *Biometrics* **64**, 762–771.

- Faucett, C. and Thomas, D. (1996). Simultaneously modelling censored survival data and repeatedly measured covariates: A Gibbs sampling approach. *Statistics in Medicine* **15**, 1663–1685.

- Garcia-Hernandez, A. and Rizopoulos, D. (2017). %JM: A SAS macro to fit jointly generalized mixed models for longitudinal data and time-to-event responses. *Journal of Statistical Software*, to appear.

- Gerds, T. and Schumacher, M. (2006). Consistent estimation of the expected Brier score in general survival models with right-censored event times. *Biometrical Journal* **48**, 1029–1040.

- Heagerty, P. and Zheng, Y. (2005). Survival model predictive accuracy and ROC curves. *Biometrics* **61**, 92–105.

- Henderson, R., Diggle, P. and Dobson, A. (2000). Joint modelling of longitudinal measurements and event time data. *Biostatistics* **1**, 465–480.

7.2 Additional References (cont'd)

- Henderson, R., Diggle, P. and Dobson, A. (2002). Identification and efficacy of longitudinal markers for survival. *Biostatistics* **3**, 33–50.

- Hsieh, F., Tseng, Y.-K. and Wang, J.-L. (2006). Joint modeling of survival and longitudinal data: Likelihood approach revisited. *Biometrics* **62**, 1037–1043.

- Lin, H., Turnbull, B., McCulloch, C. and Slate, E. (2002). Latent class models for joint analysis of longitudinal biomarker and event process: Application to longitudinal prostate-specific antigen readings and prostate cancer. *Journal of the American Statistical Association* **97**, 53–65.

- Liu, L. and Huang, X. (2009). Joint analysis of correlated repeated measures and recurrent events processes in the presence of death, with application to a study on acquired immune deficiency syndrome. *Journal of the Royal Statistical Society, Series C* **58**, 65–81.

- Mauff, K., Steyerberg, E.W., Nijpels, G., van der Heijden, A. and Rizopoulos, D. (2017). Extension of the association structure in joint models to include weighted cumulative effects. *Statistics in Medicine*, to appear.

- Proust-Lima, C., Joly, P., Dartigues, J. and Jacqmin-Gadda, H. (2009). Joint modelling of multivariate longitudinal outcomes and a time-to-event: A nonlinear latent class approach. *Computational Statistics and Data Analysis* **53**, 1142–1154.

7.2 Additional References (cont'd)

- Proust-Lima, C. and Taylor, J. (2009). Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: A joint modeling approach. *Biostatistics* **10**, 535–549.

- Rizopoulos, D. (2016). The R package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *Journal of Statistical Software* **72**(7), 1–45.

- Rizopoulos, D. (2012). Fast fitting of joint models for longitudinal and event time data using a pseudo-adaptive Gaussian quadrature rule. *Computational Statistics and Data Analysis* **56**, 491–501.

- Rizopoulos, D. (2011). Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics* **67**, 819–829.

- Rizopoulos, D. (2010). JM: An R package for the joint modelling of longitudinal and time-to-event data. *Journal of Statistical Software* **35** (9), 1–33.

- Rizopoulos, D. and Ghosh, P. (2011). A Bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event. *Statistics in Medicine* **30**, 1366–1380.

7.2 Additional References (cont'd)

- Rizopoulos, D., Hatfield, L.A., Carlin, B.P. and Takkenberg, J.J.M. (2014). Combining dynamic predictions from joint models for longitudinal and time-to-event data using Bayesian model averaging. *Journal of the American Statistical Association* **109**, 1385–1397.

- Rizopoulos, D. and Lesaffre, E. (2014). Introduction to the special issue on joint modelling techniques. *Statistical Methods in Medical Research* **23**, 3–10.

- Rizopoulos, D., Molenberghs, G. and Lesaffre, E. (2017). Dynamic Predictions with Time-Dependent Covariates in Survival Analysis using Joint Modeling and Landmarking. *Biometrical Journal*, to appear.

- Rizopoulos, D., Taylor, J.M.G., van Rosmalen, J., Steyerberg, E.W. and Takkenberg, J.J.M. (2016). Personalized screening intervals for biomarkers using joint models for longitudinal and survival data. *Biostatistics* **17**, 149–164.

- Rizopoulos, D., Verbeke, G. and Lesaffre, E. (2009). Fully exponential Laplace approximation for the joint modelling of survival and longitudinal data. *Journal of the Royal Statistical Society, Series B* **71**, 637–654.

- Rizopoulos, D., Verbeke, G., Lesaffre, E. and Vanrenterghem, Y. (2008). A two-part joint model for the analysis of survival and longitudinal binary data with excess zeros. *Biometrics* **64**, 611–619.

7.2 Additional References (cont'd)

- Rizopoulos, D., Verbeke, G. and Molenberghs, G. (2010). Multiple-imputation-based residuals and diagnostic plots for joint models of longitudinal and survival outcomes. *Biometrics* **66**, 20–29.

- Rizopoulos, D., Verbeke, G. and Molenberghs, G. (2008). Shared parameter models under random effects misspecification. *Biometrika* **95**, 63–74.

- Song, X., Davidian, M. and Tsiatis, A. (2002). A semiparametric likelihood approach to joint modeling of longitudinal and time-to-event data. *Biometrics* **58**, 742–753.

- Taylor, J., Park, Y., Ankerst, D., Proust-Lima, C., Williams, S., Kestin, L., Bae, K., Pickles, T., and Sandler, H. (2013). Real-time individual predictions of prostate cancer recurrence using joint models. *Biometrics*, **69**, 206–213.

- Tseng, Y.-K., Hsieh, F. and Wang, J.-L. (2005). Joint modelling of accelerated failure time and longitudinal data. *Biometrika* **92**, 587–603.

- Tsiatis, A. and Davidian, M. (2001). A semiparametric estimator for the proportional hazards model with longitudinal covariates measured with error. *Biometrika* **88**, 447–458.

7.2 Additional References (cont'd)

- Tsiatis, A. and Davidian, M. (2004). Joint modeling of longitudinal and time-to-event data: An overview. *Statistica Sinica* **14**, 809–834.

- Tsiatis, A., DeGruttola, V., and Wulfsohn, M. (1995). Modeling the relationship of survival to longitudinal data measured with error: Applications to survival and CD4 counts in patients with AIDS. *Journal of the American Statistical Association* **90**, 27–37.

- Viviani, S., Alfó, M. and Rizopoulos, D. (2014). Generalized linear mixed joint model for longitudinal and survival outcomes. *Statistics and Computing*, **24**, 417–427.

- Viviani, S., Rizopoulos, D. and Alfó, M. (2014). Local sensitivity of shared parameter models to nonignorability of dropout. *Statistical Modelling* **14**, 205–228.

- Wang, Y. and Taylor, J. (2001). Jointly modeling longitudinal and event time data with application to acquired immunodeficiency syndrome. *Journal of the American Statistical Association* **96**, 895–905.

- Wu, M. and Bailey, K. (1988). Analysing changes in the presence of informative right censoring caused by death and withdrawal. *Statistics in Medicine* **7**, 337–346.

7.2 Additional References (cont'd)

- Wu, M. and Bailey, K. (1989). Estimation and comparison of changes in the presence of informative right censoring: conditional linear model. *Biometrics* **45**, 939–955.

- Wu, M. and Carroll, R. (1988). Estimation and comparison of changes in the presence of informative right censoring by modeling the censoring process. *Biometrics* **44**, 175–188.

- Wulfsohn, M. and Tsiatis, A. (1997). A joint model for survival and longitudinal data measured with error. *Biometrics* **53**, 330–339.

- Xu, C., Baines, P. and Wang, J.-L. (2014). Standard error estimation using the EM algorithm for the joint modeling of survival and longitudinal data. *Biostatistics*, to appear.

- Xu, J. and Zeger, S. (2001). Joint analysis of longitudinal data comprising repeated measures and times to events. *Applied Statistics* **50**, 375–387.

- Ye, W., Lin, X., and Taylor, J. (2008). Semiparametric modeling of longitudinal measurements and time-to-event data a two stage regression calibration approach. *Biometrics* **64**, 1238–1246.

7.2 Additional References (cont'd)

- Yu, M., Law, N., Taylor, J., and Sandler, H. (2004). Joint longitudinal-survival-cure models and their application to prostate cancer. *Statistica Sinica* **14**, 835–862.

- Yu, M., Taylor, J. and Sandler, H. (2008). Individualized prediction in prostate cancer studies using a joint longitudinal-survival-cure model. *Journal of the American Statistical Association* **108**, 178–187.

- Zeng, D. and Cai, J. (2005). Asymptotic results for maximum likelihood estimators in joint analysis of repeated measurements and survival time. *The Annals of Statistics* **33**, 2132–2163.

- Zheng, Y. and Heagerty, P. (2007). Prospective accuracy for longitudinal markers. *Biometrics* **63**, 332–341.

7.3 Medical Papers

- Andrinopoulou, E.R., Rizopoulos, D., Jin, R., Bogers, A., Lesaffre, E. and Takkenberg, J. (2012). An introduction to mixed models and joint modeling: Analysis of valve function over time. *Annals of Thoracic Surgery* **93**, 1765–1772.

- Andrinopoulou, E.R., Rizopoulos, D., Geleijnse, M., Lesaffre, E., Bogers, A. and Takkenberg, J. (2015). Dynamic prediction of outcome for patients with severe aortic stenosis: Application of joint models for longitudinal and time-to-event data. *BMC Cardiovascular Disorders*, to appear.

- Daher Abdi, D.Z., Essig, M., Rizopoulos, D., Le Meur, Y., Premaud, A., Woillard, J.-B., Rerolle, J.-P., Marquet, P. and Rousseau, A. (2013). Impact of longitudinal exposure to mycophenolic acid on acute rejection in renal-transplant recipients using a joint modeling approach. *Pharmacological Research* **72**, 52–60.

- Ibrahim, J., Chu, H. and Chen, L.-M. (2010). Basic concepts and methods for joint models of longitudinal and survival data. *Journal of Clinical Oncology* **28**, 2796–2801.

- Nunez, J., Nunez, E., Rizopoulos, D., Minana, G., Bodi, V., Bondanza, L., Husser, O., Merlos, P., Santas, E., Pascual-Figal, D.,; Chorro, F. and Sanchis, J. (2014). Red blood cell distribution width is longitudinally associated with mortality and incident anemia in heart failure patients. *Circulation Journal* **78**, 410—418.

- Rizopoulos, D. and Takkenberg, J. (2014). Tools & Techniques: Dealing with time-varying covariates in survival analysis - joint models versus Cox models. *EuroIntervention* **10**, 285–288.

7.3 Medical Papers (cont'd)

- Thabut, G., Christie, J., Mal, H., Fournier, M., Brugiere, O., Leseche, G., Castier, Y. and Rizopoulos, D. (2013). Survival benefit of lung transplant for cystic fibrosis since lung-allocation-score implementation. *American Journal of Respiratory and Critical Care Medicine* **187**, 1335–1340.

- van der Linde, D., Roos-Hesselink, J., Rizopoulos, D., Heuvelman, H., Budts, W., van Dijk, A., Witsenburg, M., Yap, S., Bogers, A., Oxenius, A., Silversides, C., Oechslin, E. and Takkenberg, J. (2013). Surgical outcome of discrete subaortic stenosis in adults: A multicenter study. *Circulation* **127**, 1184–1191.

- van der Linde, D., Takkenberg, J., Rizopoulos, D., Heuvelman, H., Budts, W., van Dijk, A., Witsenburg, M., Yap, S., Bogers, A., Oxenius, A., Silversides, C., Oechslin, E. and Roos-Hesselink, J. (2013). Natural history of discrete subaortic stenosis in adults: A multicenter study. *European Heart Journal* **34**, 1548–1556.