Joint Modeling of Longitudinal and Time-to-Event Data with Applications in R

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Contents

What is this Course About

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

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

- Implicit outcomes
  - ▷ missing data
  - ▷ random visit times

What is this Course About (cont'd)

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

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

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

What is this Course About (cont'd)

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

Joint Modeling Techniques
for Longitudinal and Time-to-Event Data

Learning Objectives

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

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

Agenda

- **Part I:** Introduction
  - ▷ Data sets that we will use throughout the course
  - ▷ Research questions

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

Agenda (cont'd)

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

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

Agenda (cont'd)

- **Part V:** Extensions of the Basic Joint Model
  - ▷ Functional forms
  - ▷ Multivariate joint models

- **Part VI:** Dynamic Predictions
  - ▷ Individualized predictions
  - ▷ Effect of the functional forms
  - ▷ Accuracy measures

Structure of the Course & Material

- Lectures & short software practicals using the R package **JMbayes2**

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

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

References

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

* extra references of papers using joint modeling available at pp. 215–222.

References (cont'd)

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

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

References (cont'd)

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

Part I

Introduction

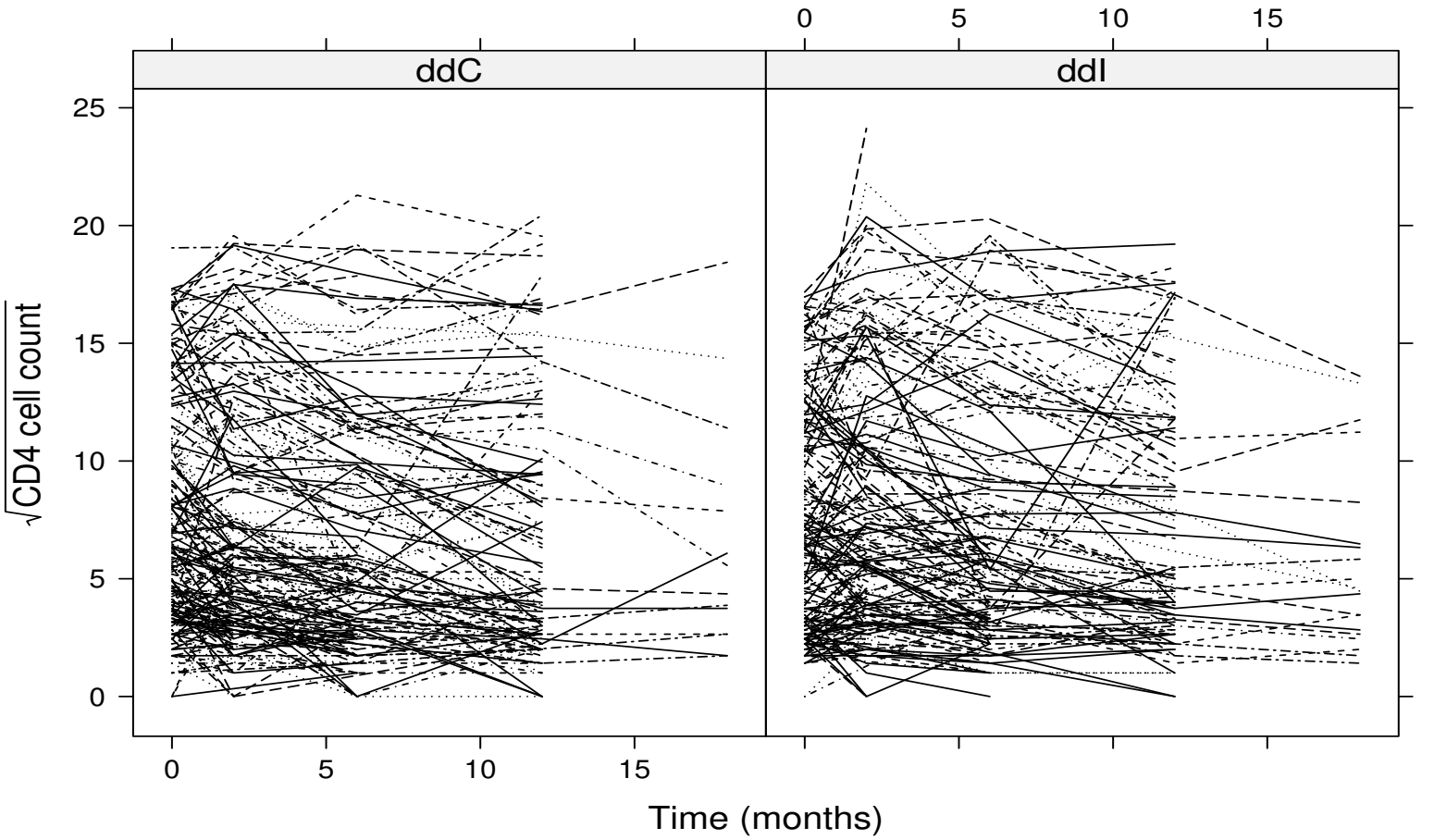
1.1 Motivating Longitudinal Studies

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

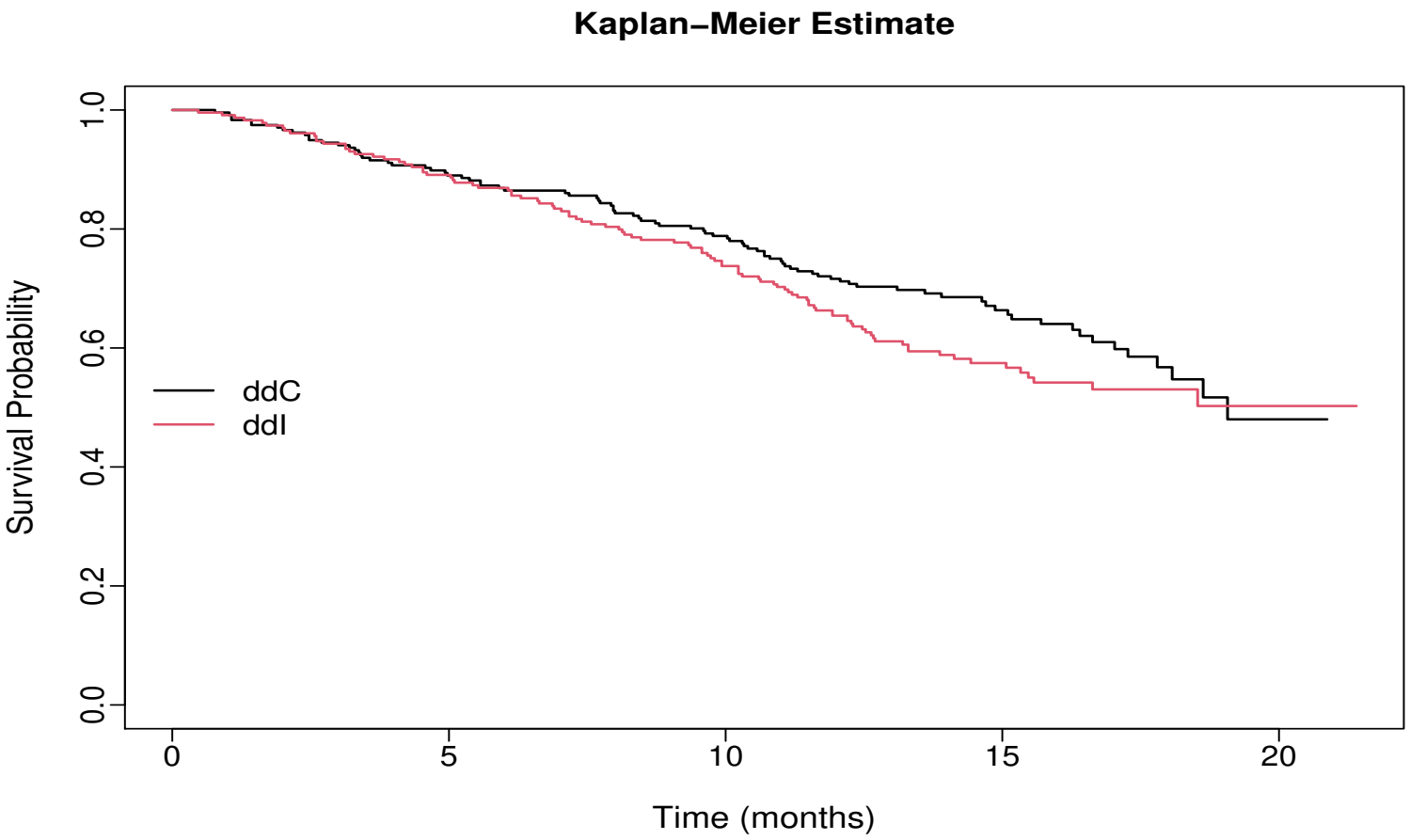
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)

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

1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)

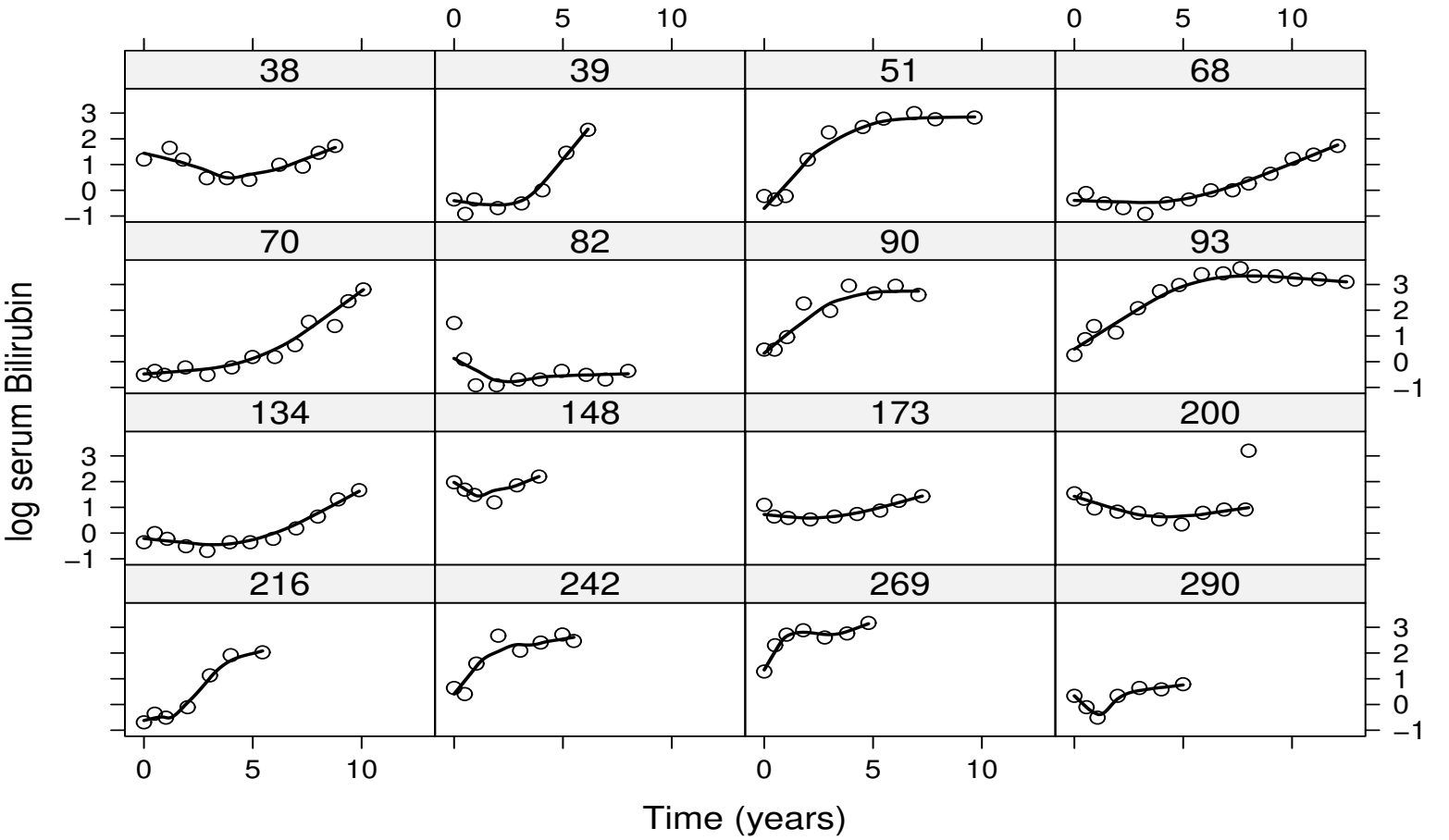
- Research Questions:
  - ▷ How strong is the association between CD4 cell count and the risk of death?
  - ▷ Is CD4 cell count a good biomarker?
    - * if treatment improves CD4 cell count, does it also improve survival?

1.1 Motivating Longitudinal Studies (cont'd)

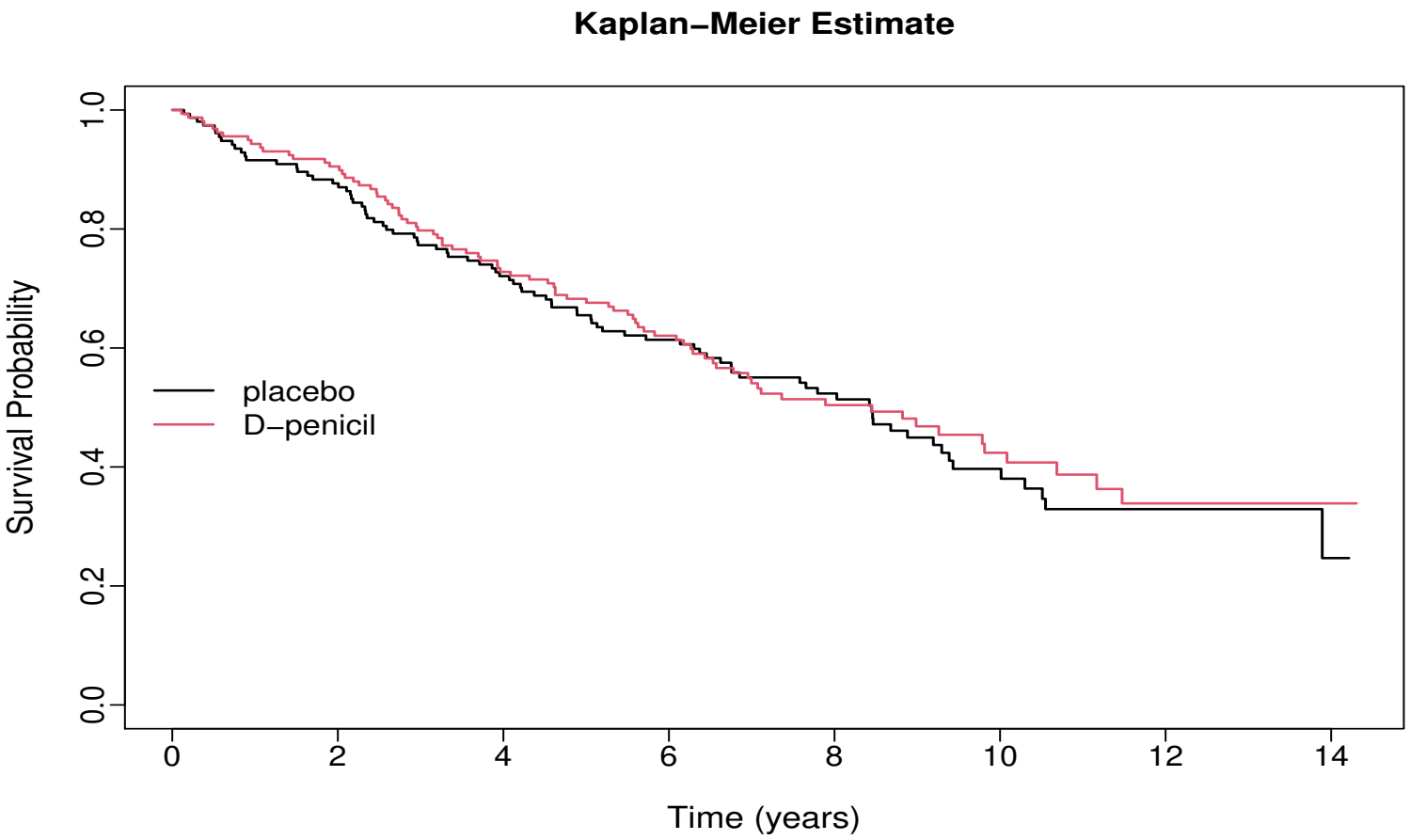
- PBC: Primary Biliary Cirrhosis:
  - ▷ a chronic, fatal but rare liver disease
  - ▷ characterized by inflammatory destruction of the small bile ducts within the liver

- Outcomes of interest:
  - ▷ time to death or liver transplantation
  - ▷ randomized treatment: 158 patients received D-penicillamine and 154 placebo
  - ▷ longitudinal bilirubin levels, cholesterol, prothrombin time (continuous)
  - ▷ longitudinal ascites, hepatomegaly, edema (categorical)

1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)

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

1.2 Research Questions

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

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

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

1.2 Research Questions (cont'd)

- Focus on multiple outcomes
  - ▷ **Complex effect estimation:** how strong is the association between the longitudinal evolution of CD4 cell counts and the hazard of death?
  - ▷ **Handling implicit outcomes:** focus on longitudinal outcomes but with dropout or random visit times

Part II

Linear Mixed-Effects Models

2.1 Linear Mixed Models

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

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.

2.1 Linear Mixed Models (cont'd)

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

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

where

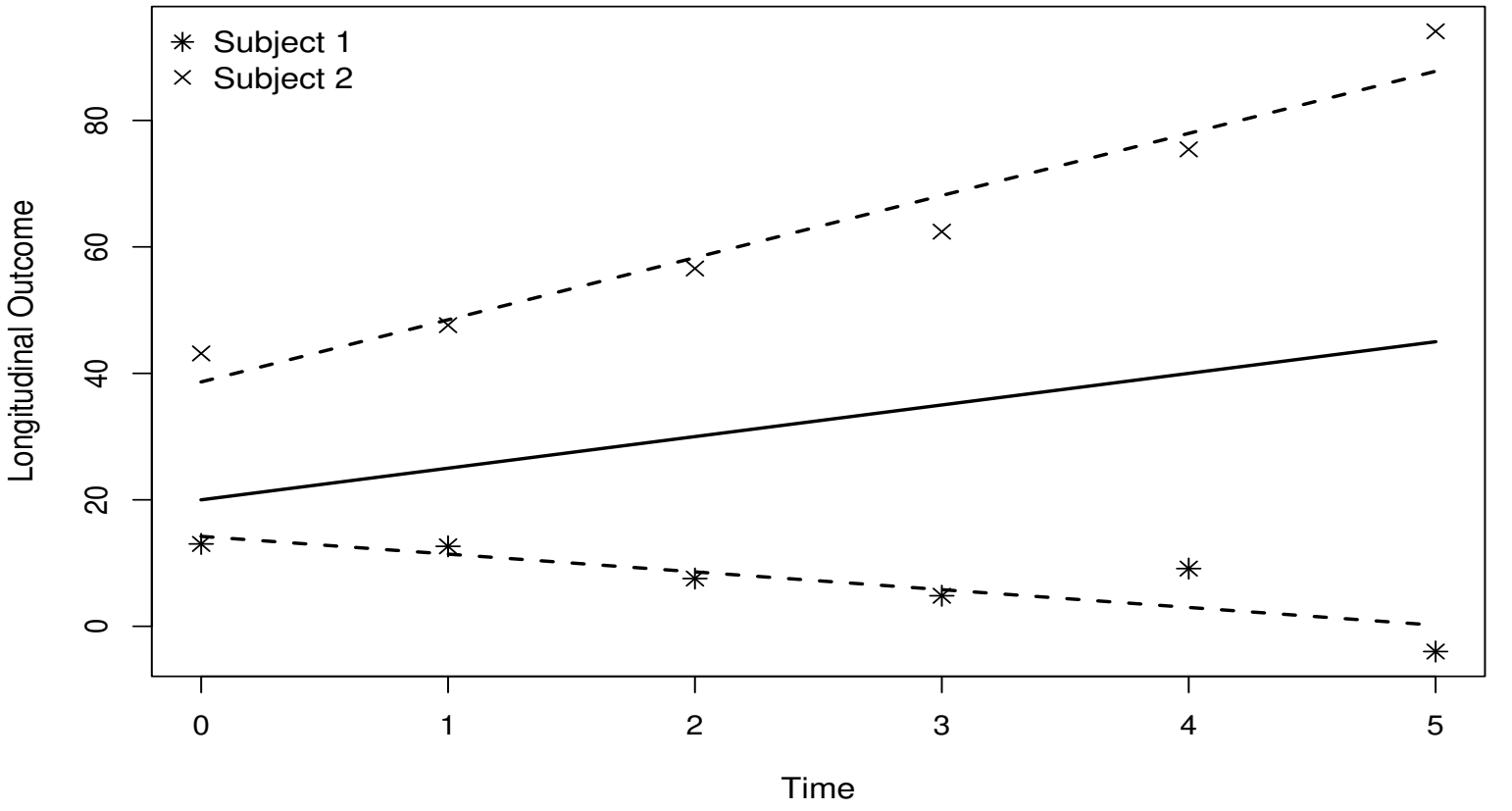
  - $\triangleright$ y_i the vector of responses for the ith subject
  - $\triangleright$ X_i design matrix describing structural component
  - $\triangleright$ V_i covariance matrix describing the correlation structure

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

2.1 Linear Mixed Models (cont'd)

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

2.1 Linear Mixed Models (cont'd)



2.1 Linear Mixed Models (cont'd)

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

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

  where

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

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

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

2.1 Linear Mixed Models (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

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

2.1 Linear Mixed Models (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
- ▷ $b_i \perp\!\!\!\perp \varepsilon_i$

2.1 Linear Mixed Models (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

2.1 Linear Mixed Models (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

2.1 Linear Mixed Models (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

2.2 Linear Mixed 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

2.2 Linear Mixed Models in R (cont'd)

R> We will only use package **nlme** because package **JMbayes2** 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

2.2 Linear Mixed 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
⋮	⋮	⋮	⋮	⋮

2.2 Linear Mixed 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)`
  ⇒ `cd4 ~ poly(time, 2)`

R> Note: the intercept term is included by default

2.2 Linear Mixed Models in R (cont'd)

R> The code used to fit the linear mixed model for the AIDS dataset (p. 21) is as follows

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

summary(lmeFit)
```

2.3 Missing Data Mechanisms

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

2.3 Missing Data Mechanisms (cont'd)

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

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

2.3 Missing Data Mechanisms (cont'd)

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

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

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

2.3 Missing Data Mechanisms (cont'd)

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

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

2.3 Missing Data Mechanisms (cont'd)

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

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

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

2.3 Missing Data Mechanisms (cont'd)

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

2.3 Missing Data Mechanisms (cont'd)

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

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

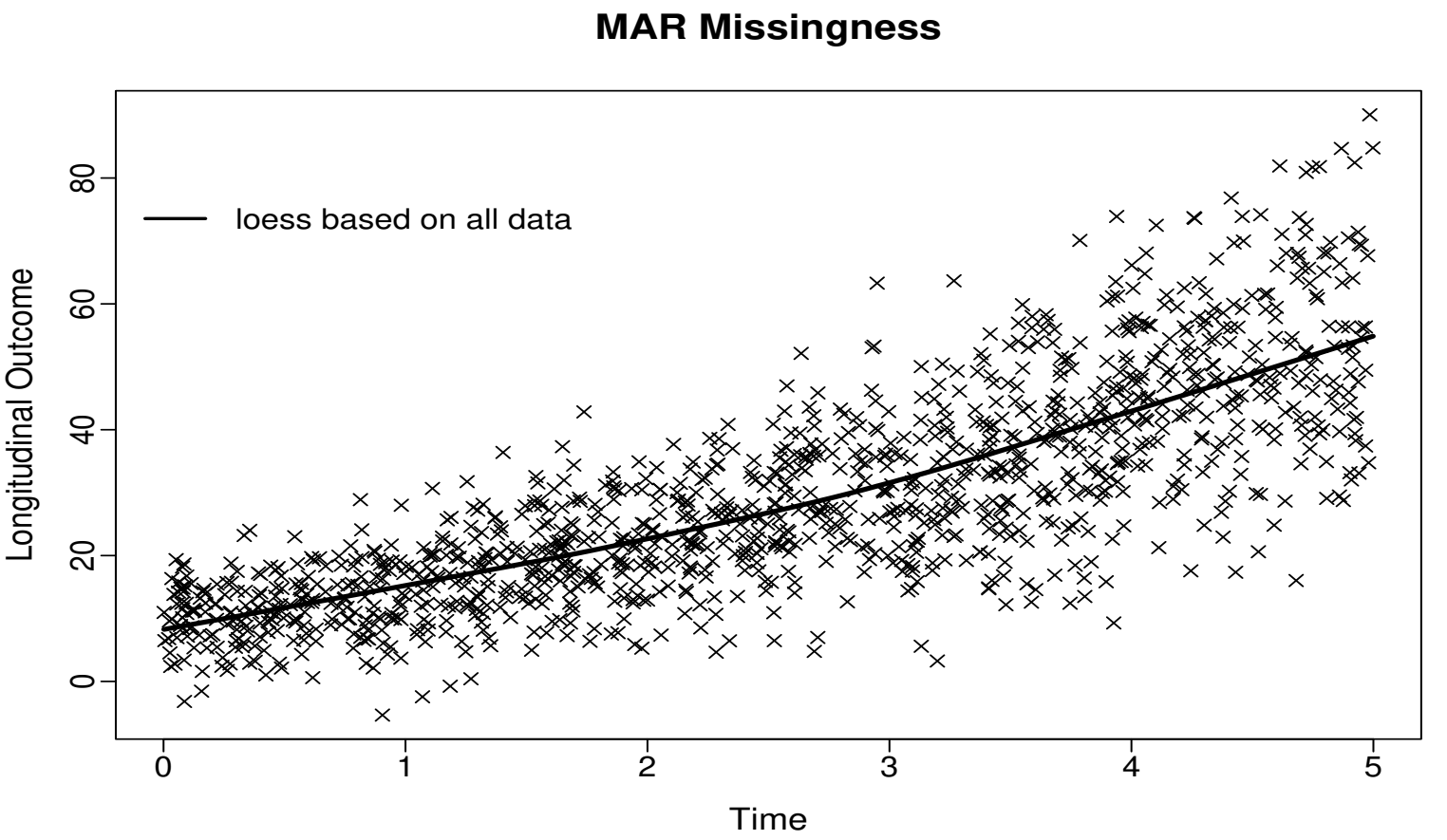
- Examples
  - ▷ study protocol requires patients whose response value exceeds a threshold to be removed from the study
  - ▷ physicians give rescue medication to patients who do not respond to treatment

2.3 Missing Data Mechanisms (cont'd)

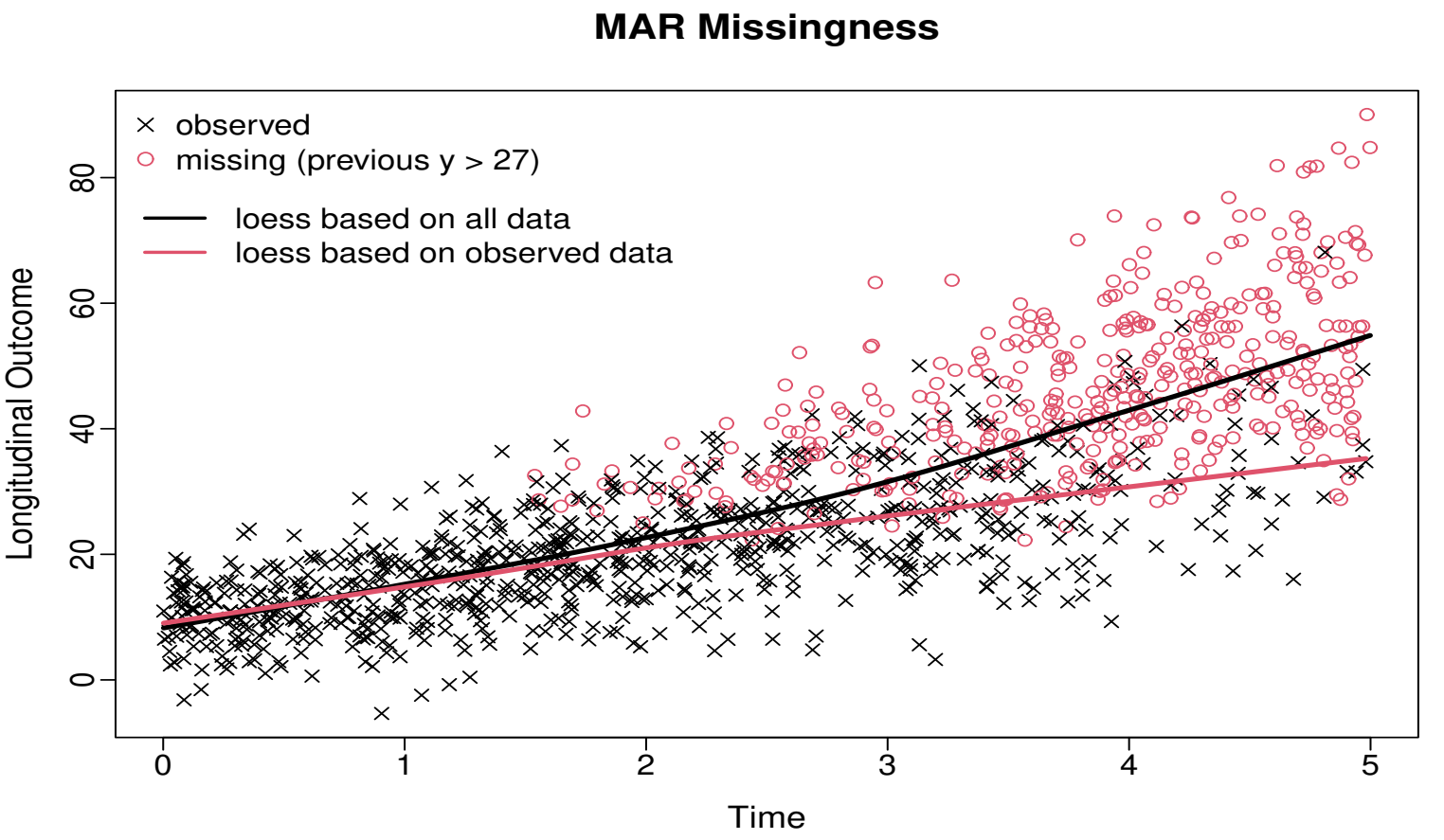
- Features of MAR:
  - ▷ The observed data cannot be considered a random sample from the target population
  - ▷ Not all statistical procedures provide valid results

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

2.3 Missing Data Mechanisms (cont'd)



2.3 Missing Data Mechanisms (cont'd)



2.3 Missing Data Mechanisms (cont'd)

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

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

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

2.3 Missing Data Mechanisms (cont'd)

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

Analysis that are valid under MAR will not be valid under MNAR

2.3 Missing Data Mechanisms (cont'd)

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

Note: We can distinguish between MCAR and MAR

Part III

Relative Risk Models

3.1 Relative Risk Models

- The 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 Relative Risk Models (cont'd)

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

Here we focus on non-informative right censoring

3.1 Relative Risk Models (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 $\{T_i, \delta_i\}$

3.1 Relative Risk Models (cont'd)

- **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

3.1 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

3.1 Relative Risk Models (cont'd)

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

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

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

3.2 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)
```

3.2 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

3.3 Time-Varying Covariates

- Often interest in the association between a time-varying 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?

3.3 Time-Varying 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 want to study time-varying covariates, a more **careful consideration** is required

3.3 Time-Varying Covariates (cont'd)

- There are two types of time-varying covariates

  (Kalbfleisch & Prentice, *The Stat. Anal. of Failure Time Data*, 2002)

  ▷ External (aka exogenous): the value of the covariate at time point t is not affected by the occurrence of an event at time point u, with $t > u$

  ▷ Internal (aka endogenous): not External

- This is a difficult concept and we will try to explain it with an example...

3.3 Time-Varying Covariates (cont'd)

- Example: Consider a study on asthma, in particular on the time until an asthma attack for a group of patients

- We have two time-varying covariates: Pollution levels & a biomarker for asthma

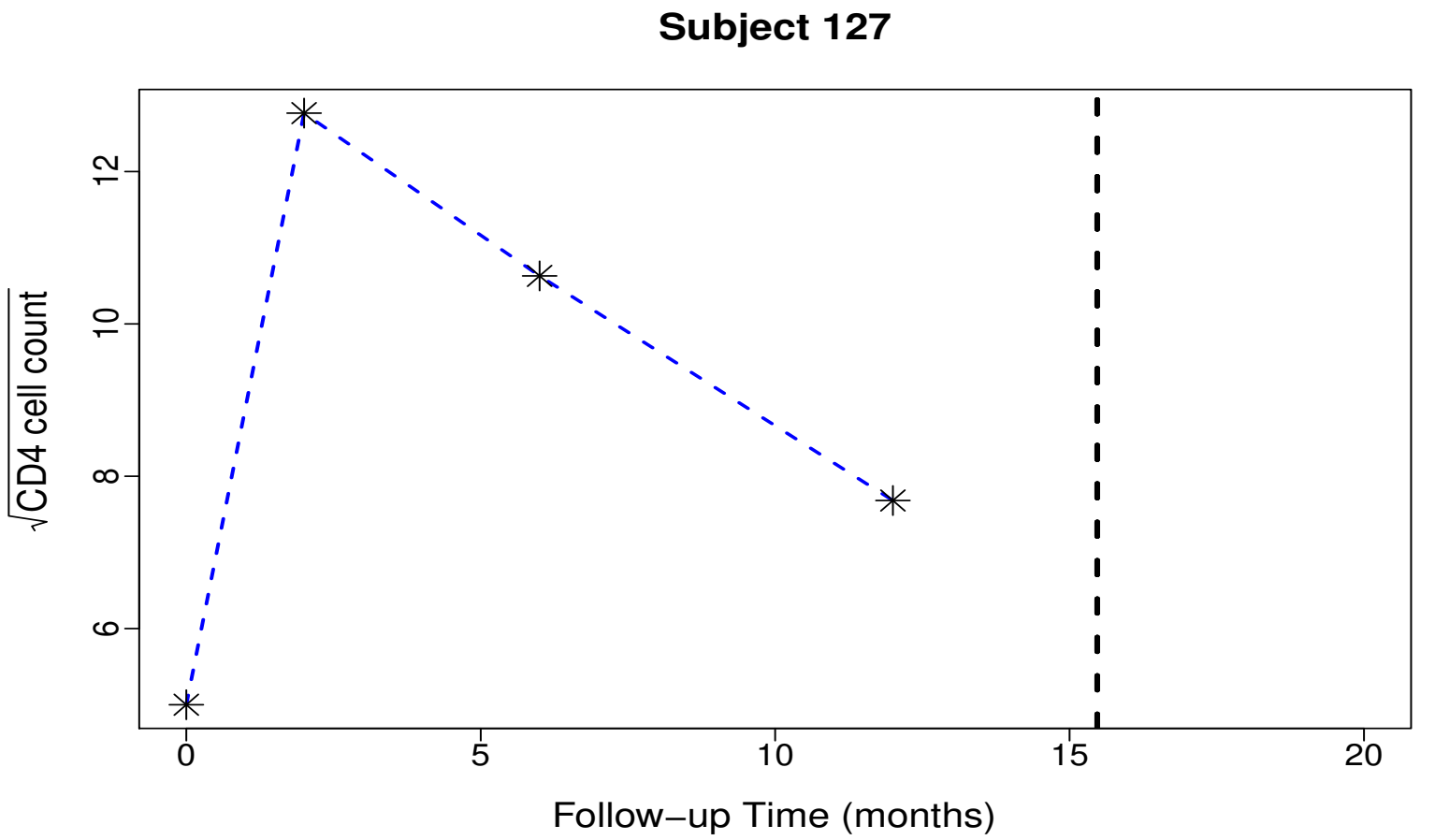
- Say a patient had an asthma attack at a particular time point u
  - ▷ Pollution levels
    - * will the pollution levels at time $t > u$ be affected by the fact that the patient had an attack at u? $\Rightarrow$ **No**
  - ▷ Biomarker
    - * will the biomarker level at time $t > u$ be affected by the fact that the patient had an attack at u? $\Rightarrow$ **Yes**

3.3 Time-Varying Covariates (cont'd)

- It is **important** to distinguish between these two types of time-varying 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

3.3 Time-Varying Covariates (cont'd)



3.3 Time-Varying Covariates (cont'd)

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

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

where

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

3.3 Time-Varying Covariates (cont'd)

- Interpretation:

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

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

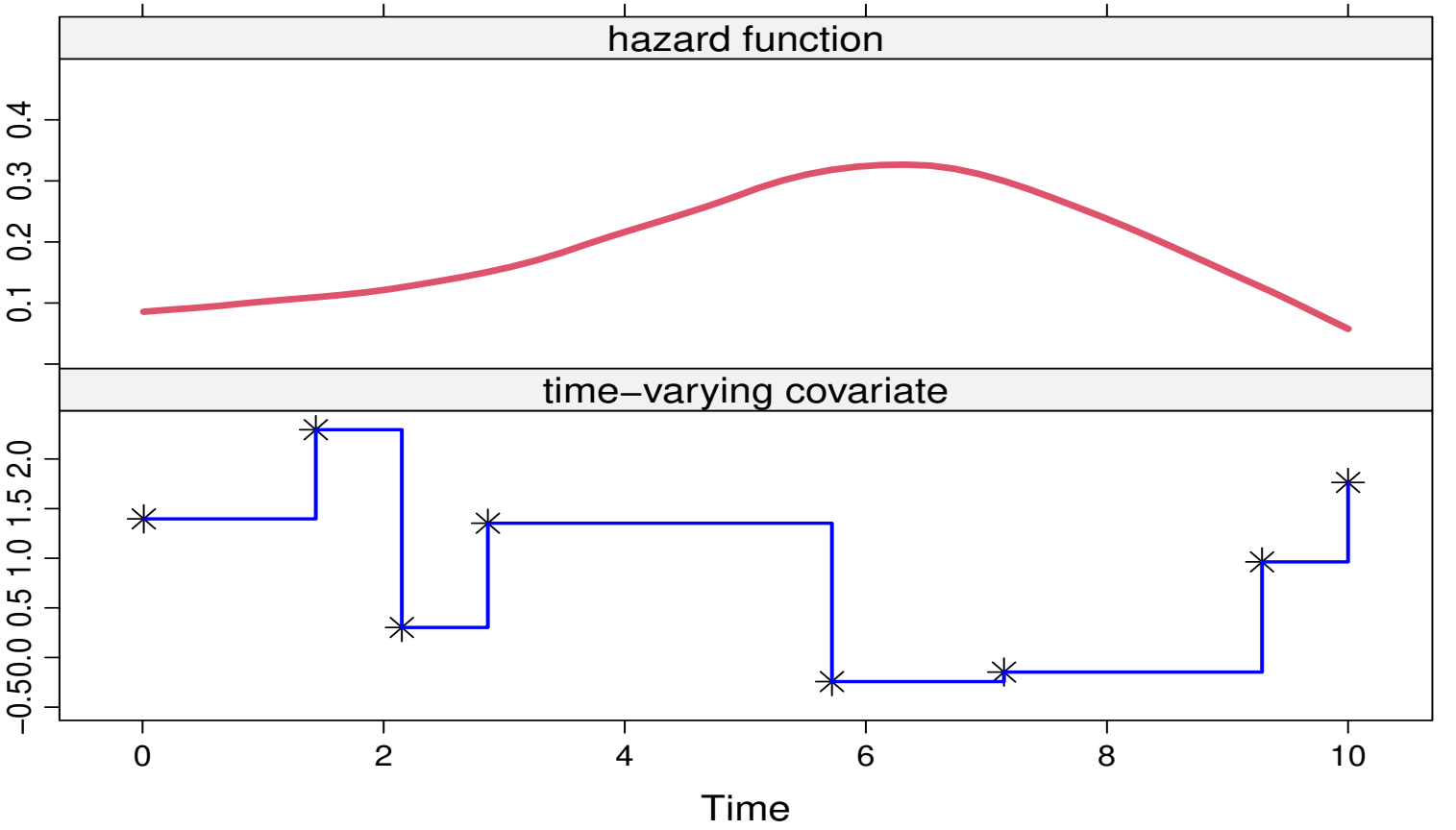
- Parameters are estimated based on the log-partial likelihood function

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

3.3 Time-Varying Covariates (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

3.3 Time-Varying Covariates (cont'd)



3.3 Time-Varying Covariates (cont'd)

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

Treating endogenous covariates as exogenous may produce spurious results!

Part IV

The Basic Joint Model

4.1 Joint Modeling Framework

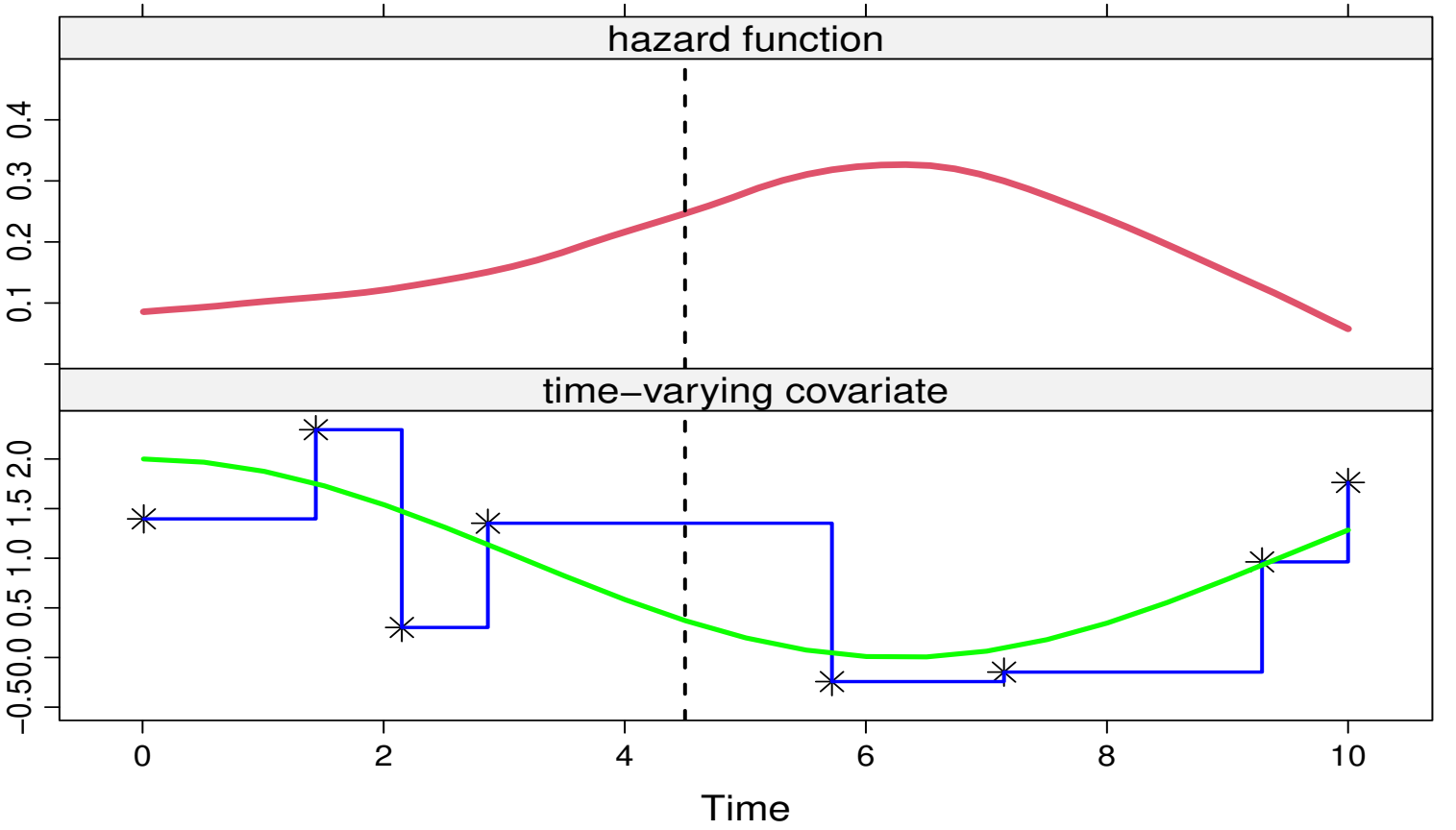
- To account for the special features of endogenous covariates a new class of models has been developed

Joint Models for Longitudinal and Time-to-Event Data

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

- Feature: covariate 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 covariate

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

4.1 Joint Modeling Framework (cont'd)

- Step 1: Let's assume that we know $m_i(t)$, i.e., the *true* & *unobserved* value of the covariate 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 association between the time-varying covariate and the risk of an event
  - w_i baseline covariates

4.1 Joint Modeling Framework (cont'd)

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

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

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

where

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

4.1 Joint Modeling Framework (cont'd)

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

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

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

  where

  ▷ b_i a vector of random effects that explains the interdependencies

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

4.1 Joint Modeling Framework (cont'd)

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

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

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

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

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

Caveat: CI is difficult to test

4.1 Joint Modeling Framework (cont'd)

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

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

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

4.1 Joint Modeling Framework (cont'd)

- Joint models require a full specification of the joint distribution
  - ▷ **we need an assumption for the baseline hazard**

- General Advice: Use a parametric but flexible model for $h_0(t)$:

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

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)

- Penalize spline coefficients for smoothness

$$p(\gamma_{h_0} \mid \tau_h) \propto \tau_h^{\rho/2} \exp\left(-\frac{\tau_h}{2}\gamma_{h_0}^\top \Delta_r^\top \Delta_r \gamma_{h_0}\right),$$

where

  - τ_h smoothing parameter
  - Δ_r denotes r-th differences penalty matrix
  - ρ rank of $\Delta_r^\top \Delta_r$

4.2 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

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

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

4.2 Bayesian Estimation (cont'd)

- No closed-form solutions for the integrals in the normalizing constant
  $\Rightarrow$ MCMC or Hamiltonian Monte Carlo

- For MCMC estimation, combination of Gibbs and Metropolis-Hastings algorithm
  - ▷ Robbins-Monro adaptive optimal scaling

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

4.2 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
  - ▷ ...

4.2 Bayesian Estimation (cont'd)

- Model comparison: *Information Criteria for Predictive Accuracy*
  - ▷ Deviance information criterion (DIC)
  - ▷ Watanabe-Akaike information criterion (WAIC)
  - ▷ log pseudo-marginal likelihood (LPML)

- Two versions available
  - ▷ conditional on the random effects
  - ▷ marginalized over the random effects

Preferable is to work with the marginalized versions

4.3 A Comparison with the TD Cox

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

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

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

	JM	Cox
	log HR (std.err)	log HR (std.err)
Treat	0.35 (0.21)	0.31 (0.15)
$CD4^{1/2}$	−0.28 (0.04)	−0.19 (0.02)

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

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

- A unit decrease in $CD4^{1/2}$, results in a
  - ▷ **Joint Model**: 1.32-fold increase in risk (95% CI: 1.23; 1.43)
  - ▷ **Time-Dependent Cox**: 1.21-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 endogenous time-varying covariates

4.4 Joint Models in R

R> Joint models are fitted using function `jm()` from package **JMbayes2**, e.g.,

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

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

jointFit <- jm(CoxFit, lmeFit, time_var = "obstime")

summary(jointFit)
```

4.4 Joint Models in R (cont'd)

R> 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> The scale of the time variables in the mixed and Cox models need to be the same

▷ i.e., both in months, or both in years, etc.

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

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

4.4 Joint Models in R (cont'd)

R> Useful functions

- ▷ `summary()`: summarizes the fitted model
- ▷ `compare_jm()`: compares fitted models using DIC and WAIC
- ▷ `coef()`, `fixef()`, `ranef()`: extract estimated coefficients and random effects
- ▷ `traceplot()` & `ggtraceplot`: produces traceplots
- ▷ `densplot()` & `ggdensityplot()`: produces density plots
- ▷ `predict()`: calculates predictions

4.5 Connection with Missing Data

- So far we have focused on handling endogenous covariates for time-to-event outcomes

However, joint models are also used to account for missing data in longitudinal outcomes

4.5 Connection with Missing Data (cont'd)

- To show this connection more clearly
  - ▷ $T_i = \min(T_i^*, C_i)$
  - ▷ T_i^*: time to dropout due to an **"event"**
  - ▷ C_i: time to dropout due to **"censoring"**
  - ▷ y_i^o: longitudinal measurements before T_i^* or C_i
  - ▷ y_i^m: longitudinal measurements after T_i^* or C_i

4.5 Connection with Missing Data (cont'd)

- Missing data mechanism:

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

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

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

4.5 Connection with Missing Data (cont'd)

- What about censoring?
  - ▷ censoring also corresponds to dropout for the longitudinal outcome

- *Likelihood-based inferences for joint models provide valid inferences when censoring is MCAR or MAR*
  - ▷ a patient relocates to another country (MCAR)
  - ▷ a patient is excluded from the study when her longitudinal response exceeds a pre-specified threshold (MAR)

4.5 Connection with Missing Data (cont'd)

Joint models allow to distinguish between two types of dropout

- Subject drops out at time T_i and $\delta_i = 0 \Rightarrow$ **MCAR/MAR dropout**

- Subjects drops out at time T_i and $\delta_i = 1 \Rightarrow$ **MNAR dropout**

4.5 Connection with Missing Data (cont'd)

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

$$p\left(y_i^o, y_i^m, T_i^*, C_i; \theta, \psi\right) = \int p\left(y_i^o, y_i^m, T_i^*, C_i, b_i; \theta, \psi, D\right) db_i$$

4.5 Connection with Missing Data (cont'd)

- Key assumptions:
  - ▷ Conditional Independence
  - ▷ Non Informative Censoring

$$\int p\left(T_i^* \mid b_i; \psi^{T^*}\right) p\left(C_i \mid y_i^o; \psi^C\right) p\left(y_i^o, y_i^m \mid b_i; \theta\right) p\left(b_i; D\right) db_i$$

4.5 Connection with Missing Data (cont'd)

- On the subject specific level:

$$\begin{cases} \int p\left(T_i \mid b_i; \psi^{T^*}\right) p\left(y_i^o, y_i^m \mid b_i; \theta\right) p\left(b_i; D\right) db_i, & i : \text{dropout} \quad \rightarrow \quad \textbf{MNAR} \\ \int p\left(C_i \mid y_i^o; \psi^C\right) p\left(y_i^o, y_i^m \mid b_i; \theta\right) p\left(b_i; D\right) db_i, & i : \text{censored} \quad \rightarrow \quad \textbf{MAR} \end{cases}$$

4.5 Connection with Missing Data (cont'd)

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

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

  - ▷ Pattern mixture models:

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

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

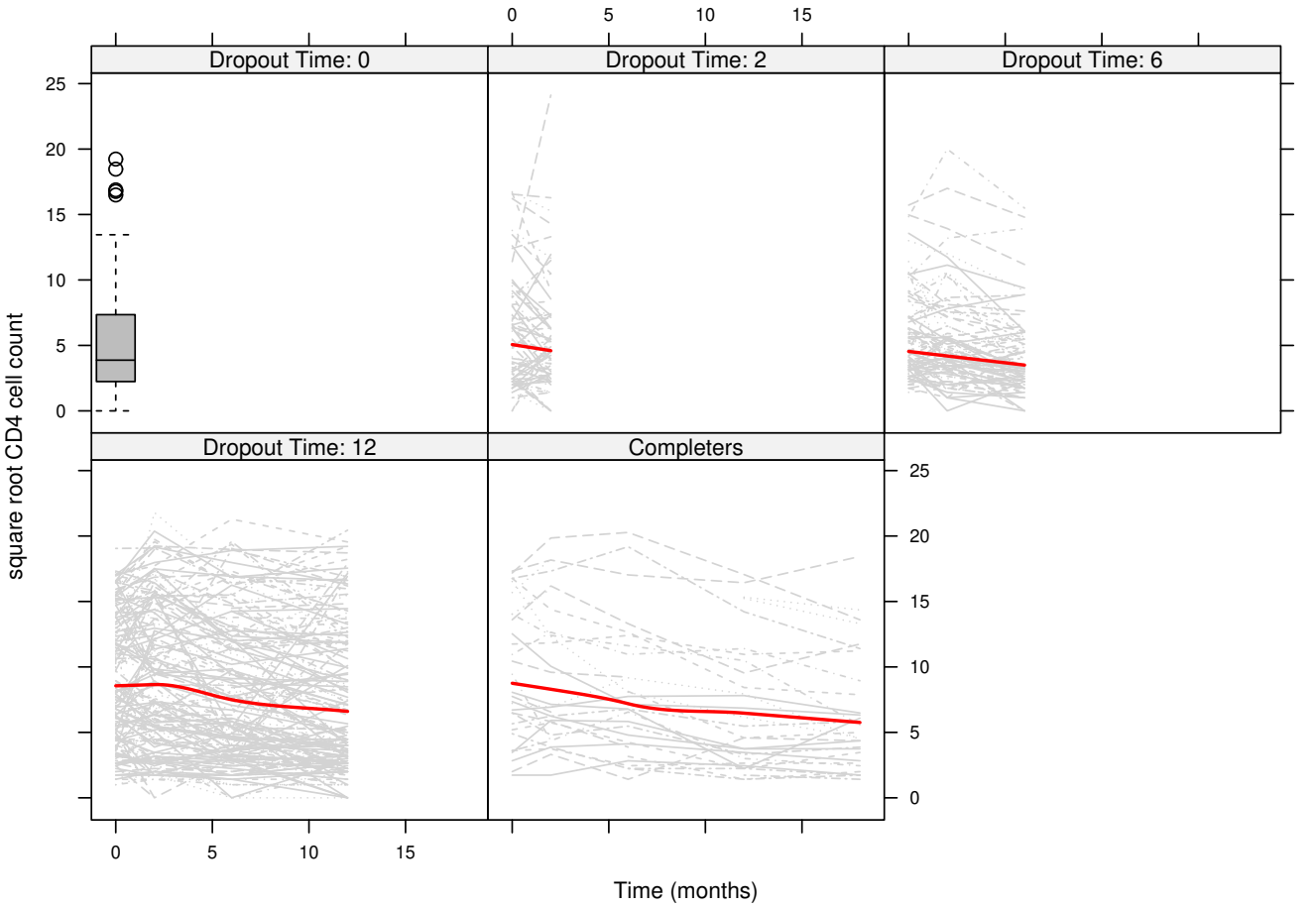
4.5 Connection with Missing Data (cont'd)

- Example: In the AIDS data set we have a considerable amount of missing data

	ddC		ddI	
Dropout Pattern	N	%	N	%
OXXXX	29	14.4%	32	15.6%
OOXXX	35	17.4%	37	18.0%
OOOXX	41	20.4%	47	22.9%
OOOOX	85	42.3%	76	37.1%
OOOOO	11	5.5%	13	6.3%
Total	201	100%	205	100%

- The sample evolutions of the $\sqrt{\text{CD4}}$ cell counts per dropout pattern have the form

4.5 Connection with Missing Data (cont'd)



4.5 Connection with Missing Data (cont'd)

- Example: In the AIDS data we want to investigate how dropout affects inferences

- A comparison between
  - ▷ linear mixed-effects model $\Rightarrow$ MAR
  - ▷ joint model dropout due to death $\Rightarrow$ MNAR
  - ▷ joint model dropout due to death or other causes $\Rightarrow$ MNAR

- MAR assumes that dropout depends only on the observed data

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

4.5 Connection with Missing Data (cont'd)

	LMM (MAR)	JM (MNAR) dropout-death	JM (MNAR) dropout-all
	value (s.e.)	value (s.e)	value (s.e)
Inter	7.19 (0.22)	7.19 (0.3)	7.19 (0.3)
Time	−0.16 (0.02)	−0.19 (0.04)	−0.17 (0.04)
Treat:Time	0.03 (0.03)	0.01 (0.05)	0.02 (0.05)

- Minimal sensitivity in parameter estimates & standard deviations

  $\Rightarrow$ **Warning:** This does not mean that this is always the case!

Part V

Extensions of Joint Models

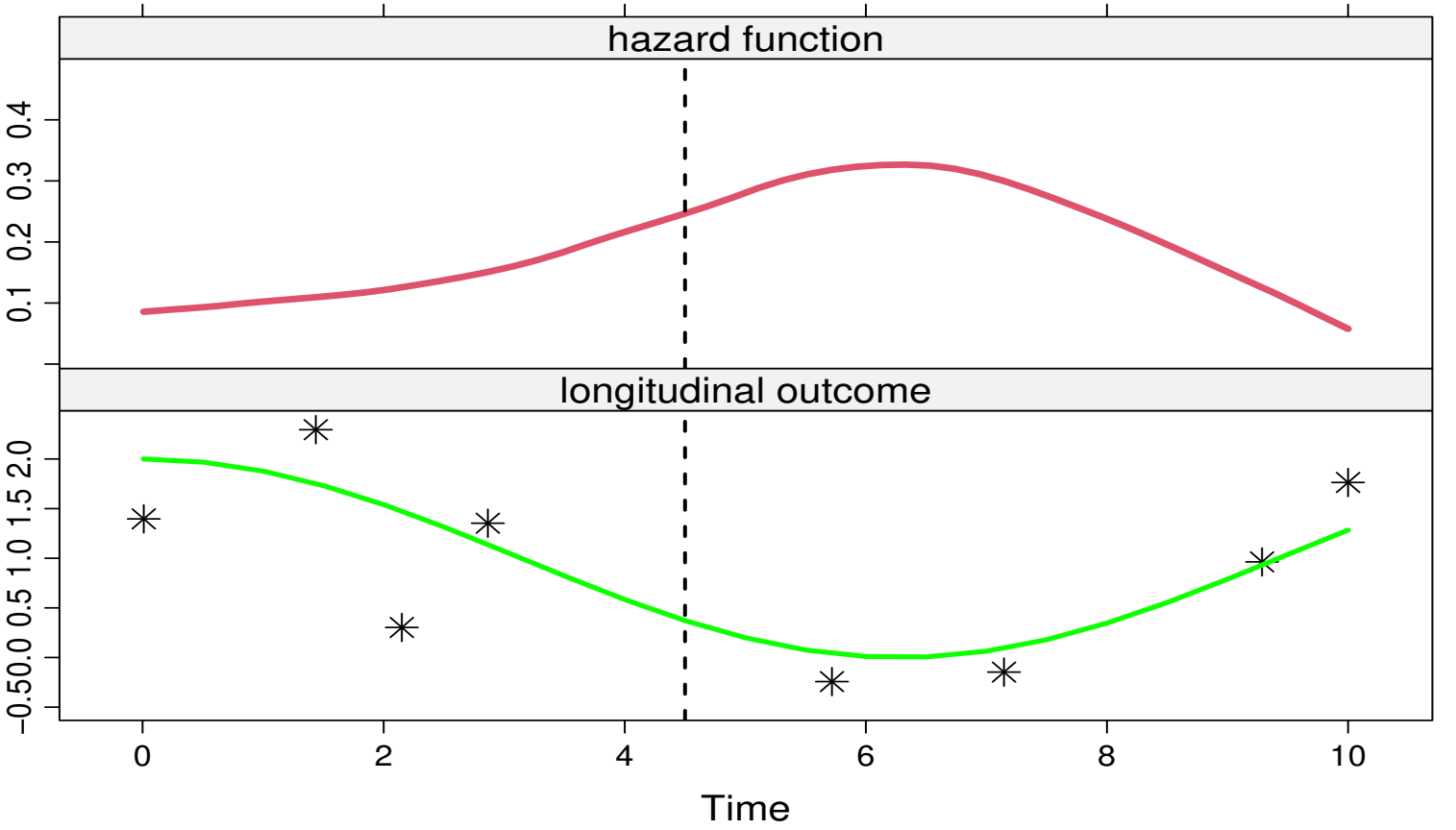
5.1 Functional Forms

- 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 Functional Forms (cont'd)



5.1 Functional Forms (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 Functional Forms (cont'd)

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

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

5.1 Functional Forms (cont'd)

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

- Let's see some possibilities...

5.1 Functional Forms (cont'd)

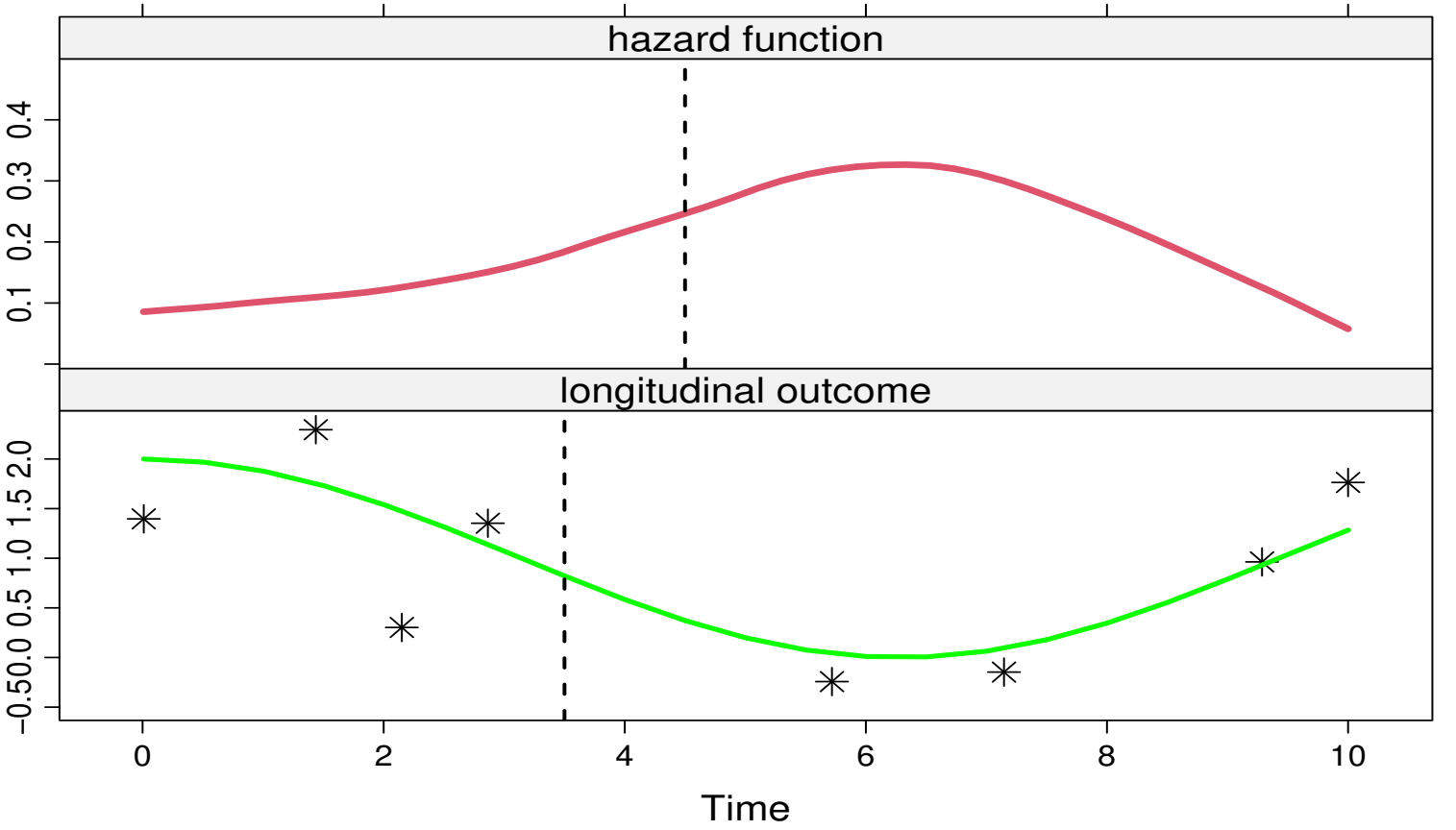
- *Lagged Effects:* The hazard of an event at t is associated with the level of the marker at a previous time point:

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

where

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

5.1 Functional Forms (cont'd)



5.1 Functional Forms (cont'd)

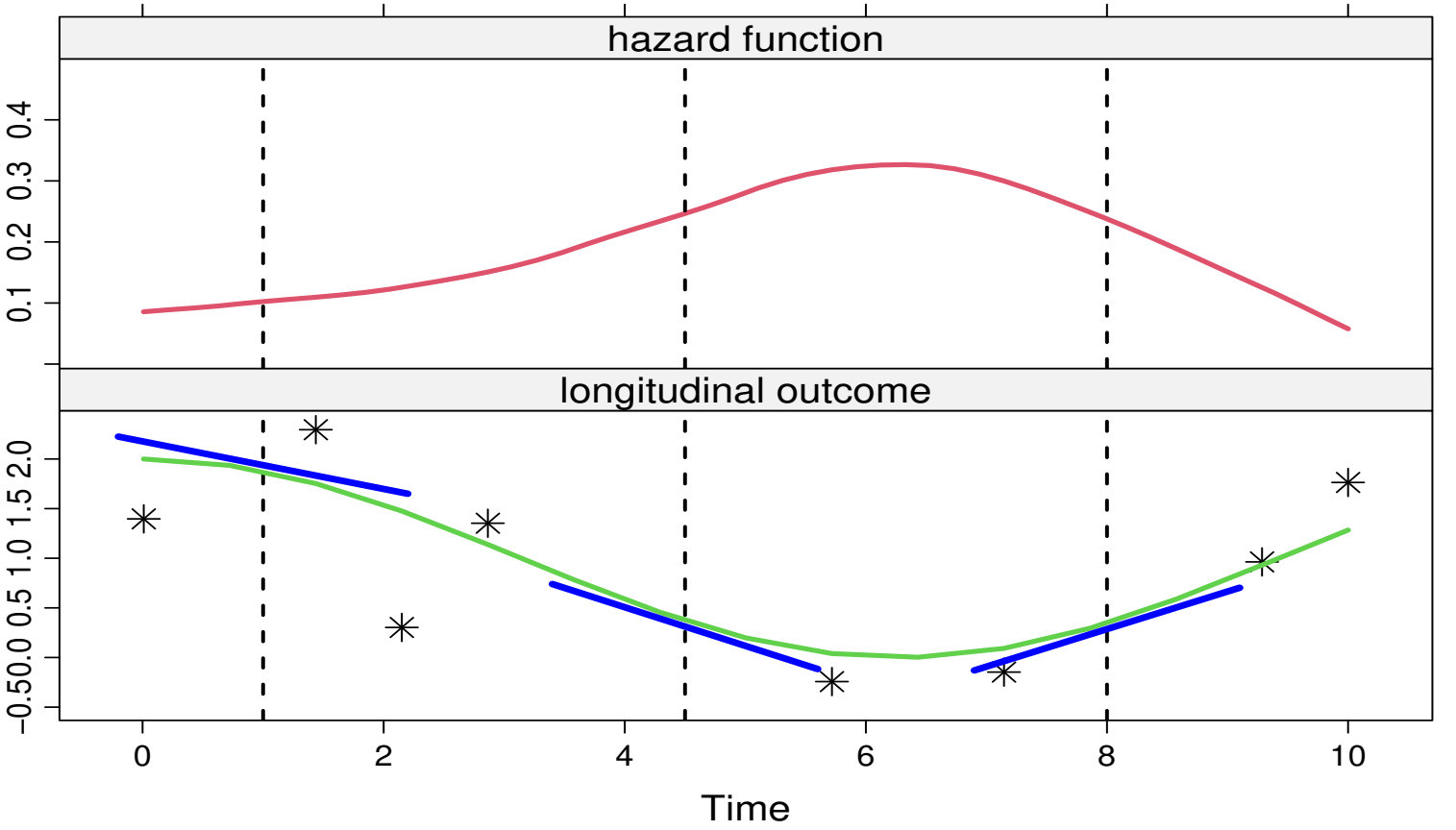
- *Time-dependent Slopes:* The hazard of an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

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

where

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

5.1 Functional Forms (cont'd)



5.1 Functional Forms (cont'd)

- The definition of the slope is

$$m_i'(t) = \lim_{\epsilon \to 0} \frac{m_i(t+\epsilon) - m_i(t)}{\epsilon}$$

  the change in the longitudinal profile *as ϵ approaches zero*

- It can be challenging to interpret
  - ▷ it is the 'current' slope

5.1 Functional Forms (cont'd)

- *Time-dependent Slopes 2:* The hazard of an event at t is associated with the change of the trajectory the last year:

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

where

$$\Delta m_i(t) = m_i(t) - m_i(t-1)$$

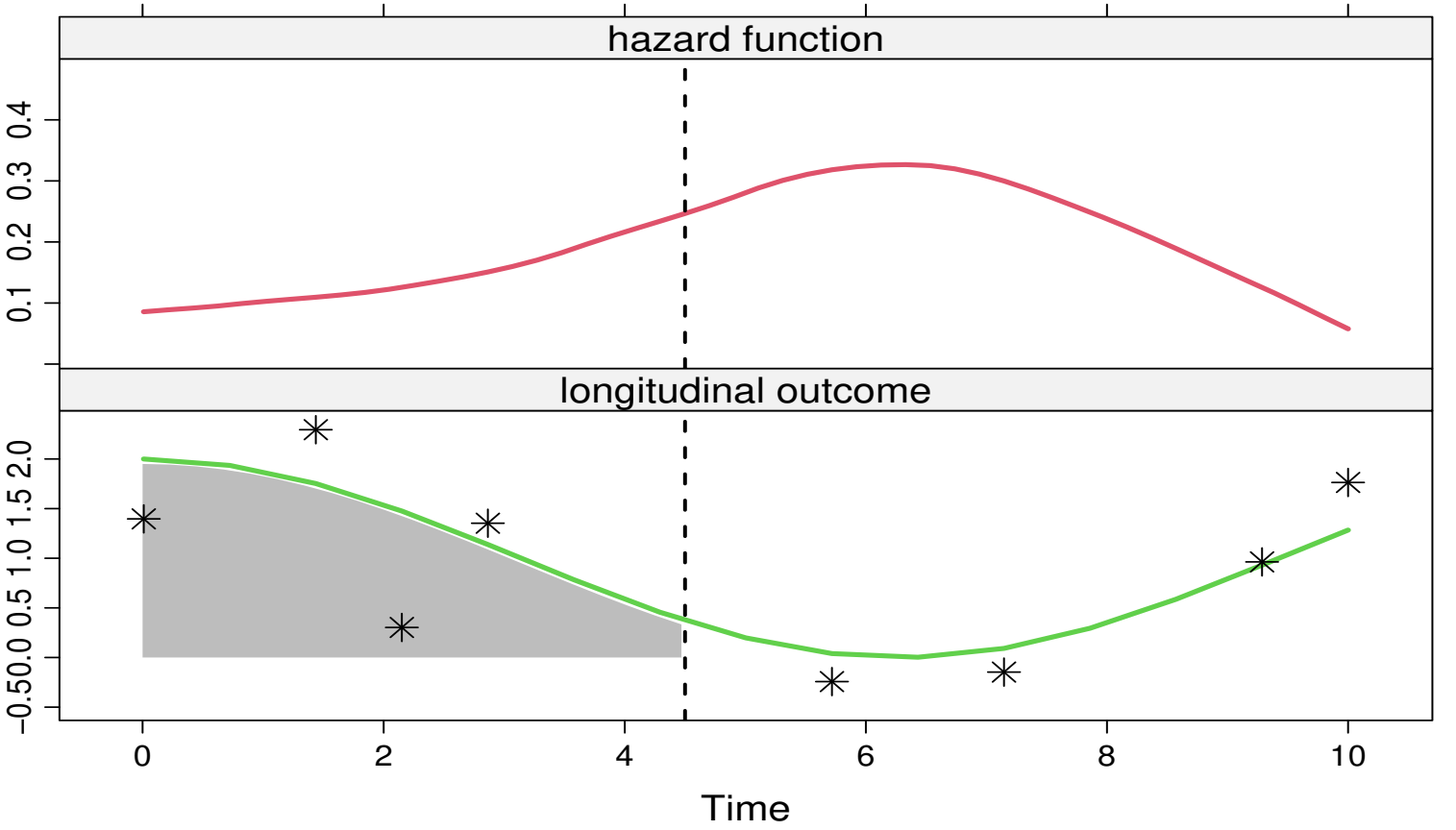
5.1 Functional Forms (cont'd)

- *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 Functional Forms (cont'd)



5.1 Functional Forms (cont'd)

- *Cumulative Effects 2:* The hazard of an event at t is associated with the whole area under the trajectory up to t:

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

- We account for the observation period

5.1 Functional Forms (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 Functional Forms (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 Functional Forms (cont'd)

- Example: Sensitivity of inferences for the longitudinal process to the choice of the functional forms 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 Functional Forms (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 slope)

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

where

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

5.1 Functional Forms (cont'd)

- Model II (current value + current slope)

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

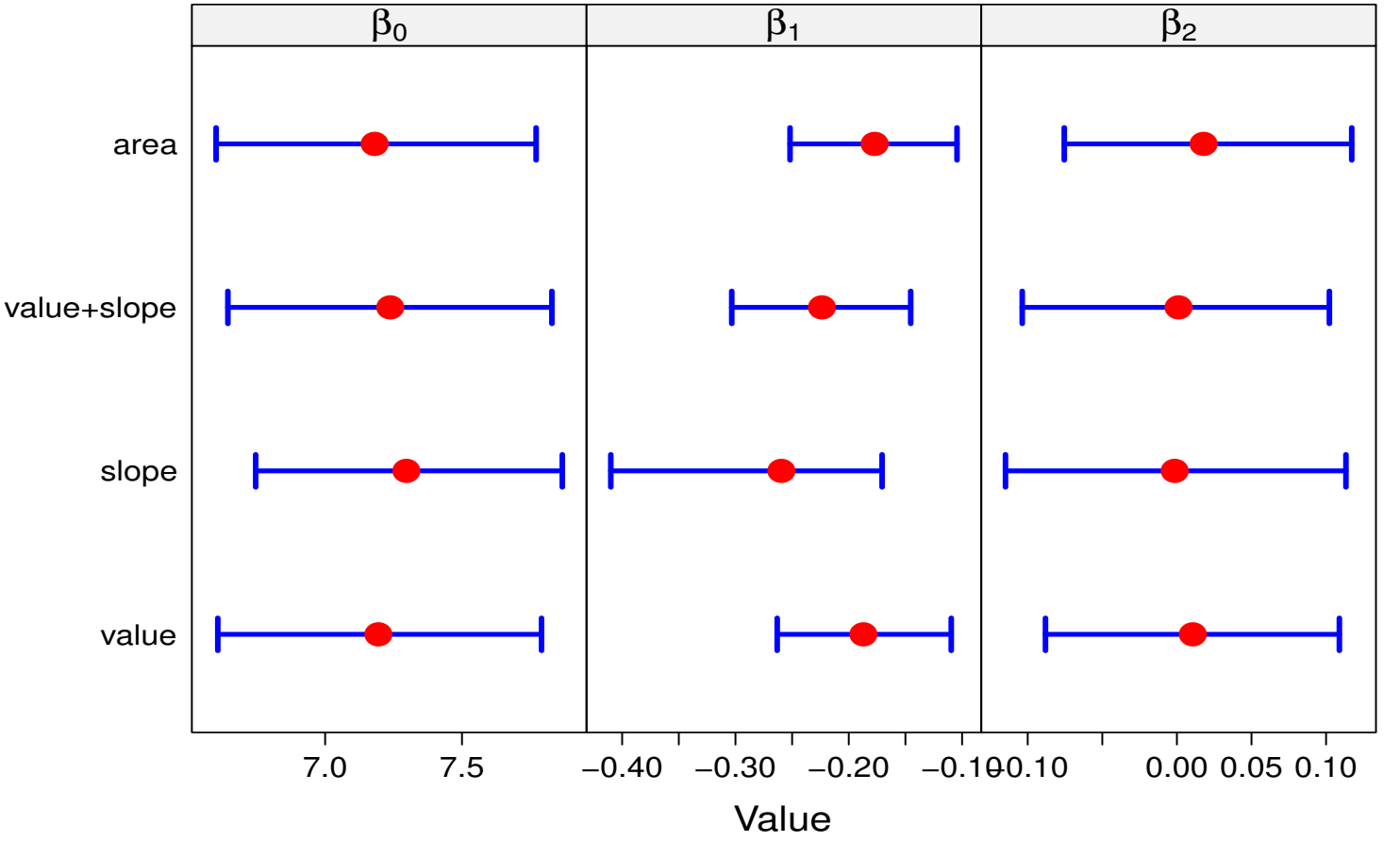
- Model IV (area)

$$h_i(t) \;=\; h_0(t)\exp\left\{\gamma \texttt{ddI}_i + \alpha_3 \frac{\int_0^t m_i(s)\; ds}{t}\right\},$$

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 Functional Forms (cont'd)



5.1 Functional Forms (cont'd)

- There are some differences between the functional forms
  - ▷ especially in the slope parameters

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

5.1 Functional Forms (cont'd)

R> In **JMbayes2** the specification of functional forms is done via the `functional_forms` argument

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

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

5.1 Functional Forms (cont'd)

R> The `area()` function calculates the *Cumulative Effects 2* functional form, where the integral is divide by the length of the period

R> The `slope()` function can be used for the *Time-dependent Slopes 2* functional form via

```
slope(..., eps = 1, direction = "back")
```

5.2 Multiple Longitudinal Markers

- So far we have concentrated on a single continuous longitudinal outcome

- But very often we may have several outcomes 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)
  - ▷ ...

5.2 Multiple Longitudinal Markers (cont'd)

We need to extend the basic joint model!

- To handle multiple longitudinal outcomes 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

5.2 Multiple Longitudinal Markers (cont'd)

- Correlation between the longitudinal outcomes is captured by assuming a multivariate normal distribution for the random effects

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

5.2 Multiple Longitudinal Markers (cont'd)

- Two ways to include the longitudinal markers in the survival submodel
  - ▷ conditional expected value

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

  - ▷ or conditional linear predictor

$$\begin{cases} h_i(t) \;=\; h_0(t)\exp\{\gamma^\top w_i + \sum_{j=1}^{J}\alpha_j \eta_{ij}(t)\} \\ \\ \eta_{ij} \;=\; x_{ij}^\top(t)\beta_j + z_{ij}^\top(t)b_{ij} \end{cases}$$

5.2 Multiple Longitudinal Markers (cont'd)

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

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

5.2 Multiple Longitudinal Markers (cont'd)

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

5.2 Multiple Longitudinal Markers (cont'd)

- Example: Multivariate joint model for the PBC dataset
  - ▷ log(ser Bilir): linear mixed-effects model
    - * fixed effects: intercept and linear time effect
    - * random effects: intercept and linear time effect
  - ▷ spiders: mixed-effects logistic regression model
    - * fixed effects: intercept and linear time effect
    - * random effects: intercept

5.2 Multiple Longitudinal Markers (cont'd)

- time-to-death: relative risk model
  - baseline covariates: drug and age
  - Analysis I: conditional linear predictor
  - Analysis II: conditional expected value

5.2 Multiple Longitudinal Markers (cont'd)

- Analysis I: conditional linear predictor

	Value	Std.Dev.	2.5%	97.5%
D-penicil	−0.080	0.250	−0.566	0.408
Age	0.064	0.010	0.045	0.083
value(logSB)	1.306	0.136	1.055	1.583
value(spiders)	0.077	0.056	−0.032	0.188

5.2 Multiple Longitudinal Markers (cont'd)

- Analysis II: conditional expected value

	Value	Std.Dev.	2.5%	97.5%
D-penicil	−0.091	0.250	−0.577	0.399
Age	0.064	0.010	0.044	0.084
value(logSB)	1.309	0.146	1.042	1.617
expit(value(spiders))	0.572	0.387	−0.262	1.314

5.2 Multiple Longitudinal Markers (cont'd)

R> To fit a multivariate joint model in **JMbayes2** we need first to fit a series of univariate mixed models.

▷ for non-Gaussian longitudinal data we use **GLMMadaptive**

```
mixed_model(spiders ~ year, data = pbc2,
            family = binomial(), random = ~ year | id)
```

- Arguments of `mixed_model()`
  - ▷ `fixed`: formula for the response outcome and fixed effects
  - ▷ `random`: formula for random effects
  - ▷ `family`: distribution of longitudinal outcome
  - ▷ `data`: dataset

5.2 Multiple Longitudinal Markers (cont'd)

R> To fit a multivariate joint model, we use `jm()` as before but we now provide a `list()` of mixed models

- ▷ an example for the PBC dataset using serum bilirubin (continuous) and spiders (binary)

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

melrFit <- mixed_model(spiders ~ year, data = pbc2, family = binomial(),
                       random = ~ 1 | id)

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

jm(CoxFit, list(lmmFit, melrFit), time_var = "year")
```

5.2 Multiple Longitudinal Markers (cont'd)

R> The default in `jm()` is to include the conditional linear predictor $\eta_{ij}(t)$ in the survival submodel

▷ to include the conditional expected value, we can use the `functional_forms` argument, e.g.,

```
jm(CoxFit, list(lmmFit, melrFit), time_var = "year",
   functional_forms = ~ value(log(serBilir)) +
            vexpit(value(spiders)),
   n_iter = 20000L, n_burnin = 10000L)
```

5.2 Multiple Longitudinal Markers (cont'd)

R> Function `jm()` allows for various types of mixed models

- ▷ continuous: Student's t, Beta, Gamma, censored normal
- ▷ categorical: Binomial, Poisson, Negative Binomial, Beta Binomial

For more info see
https://drizopoulos.github.io/JMbayes2/
→ Articles → Non-Gaussian Mixed Models

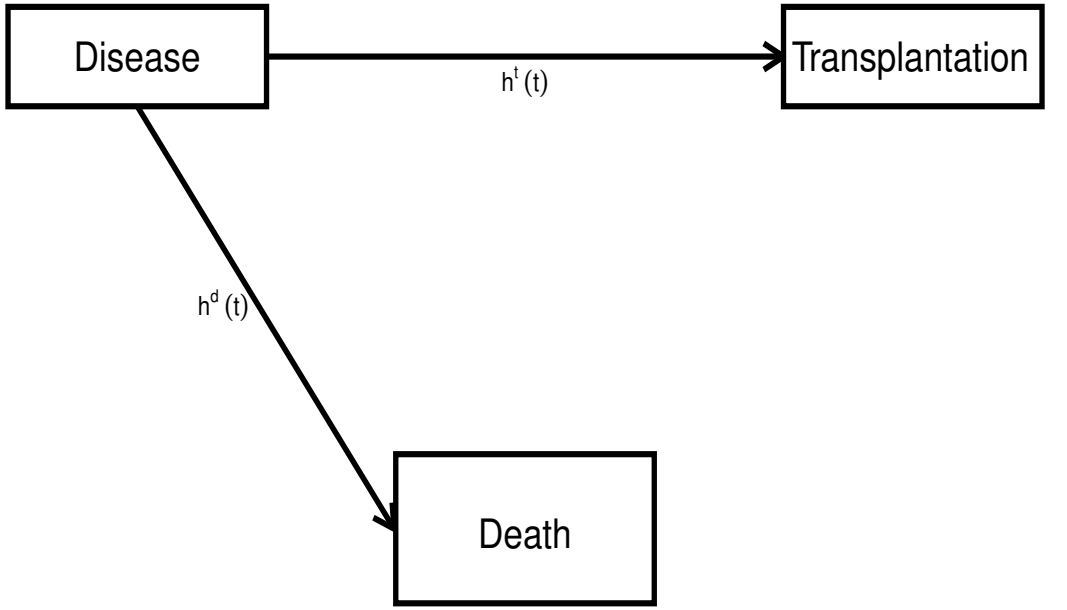
5.3 Multiple Failure Times

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

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

5.3 Multiple Failure Times (cont'd)

- Competing risks:
  - ▷ Death precludes the occurrence of transplantation
  - ▷ Transplantation modifies the risk of death



5.3 Multiple Failure Times (cont'd)

- Joint models with competing risks:

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

where

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

5.3 Multiple Failure Times (cont'd)

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

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

with

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

5.3 Multiple Failure Times (cont'd)

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

5.3 Multiple Failure Times (cont'd)

- Example: Competing risks analysis for the PBC dataset
  - ▷ log(ser Bilir): linear mixed-effects model
    - * fixed effects: intercept, drug, linear time, interaction drug with time
    - * random effects: intercept and linear time
  - ▷ time to death or transplantation: relative risk model
    - * competing risks: transplantation and death
    - * baseline covariates: drug *different* per competing risk
    - * time-varying: current value log ser Bilir *different* per competing risk

5.3 Multiple Failure Times (cont'd)

	Value	Std.Dev.	2.5%	97.5%
D-penicil	−0.396	0.565	−1.562	0.709
D-penicil:dead	0.478	0.563	−0.552	1.668
value(logSB)	1.135	0.212	0.744	1.561
value(logSB):dead	0.101	0.217	−0.331	0.543

5.3 Multiple Failure Times (cont'd)

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

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

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

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

5.3 Multiple Failure Times (cont'd)

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

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

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

5.3 Multiple Failure Times (cont'd)

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

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

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

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

5.3 Multiple Failure Times (cont'd)

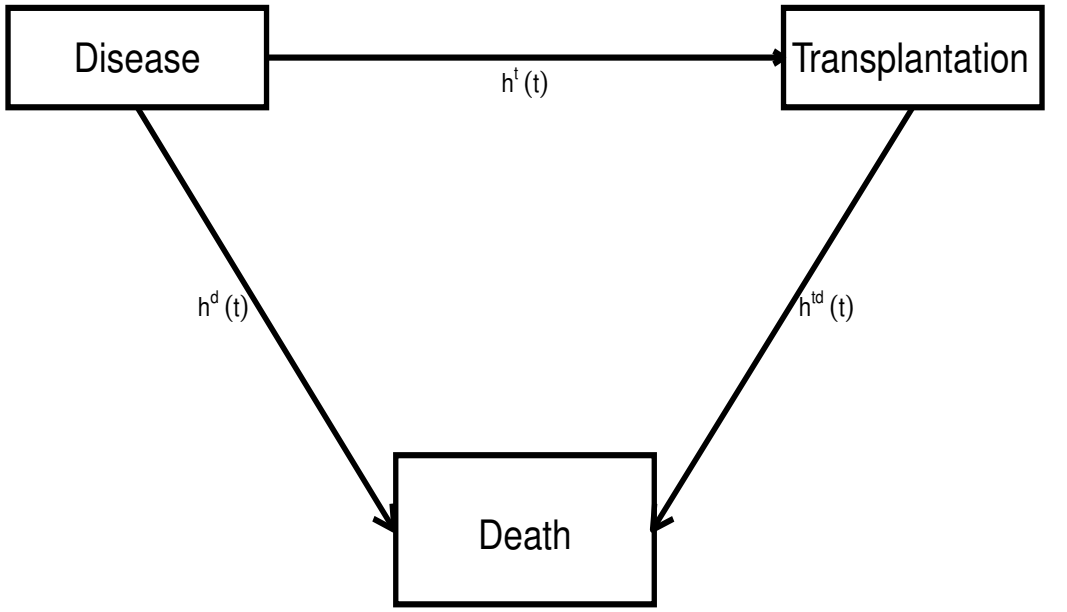
R> Then the joint model is fitted with the code

```
jm(CoxFit_CR, lmeFit_CR, time_var = "year",
   functional_forms = ~ value(log(serBilir)) * CR)
```

For more info see
https://drizopoulos.github.io/JMbayes2/
→ Articles → Competing Risks

5.3 Multiple Failure Times (cont'd)

- Multi-state models:
  - ▷ Transition between transplantation and death is of interest
  - ▷ Effect of covariates and/or biomarkers can be **different for each transition**



5.3 Multiple Failure Times (cont'd)

- Joint models with multi-state processes:

$$\begin{cases} y_i(t) &= m_i(t) + \varepsilon_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \\ h_i^d(t) &= h_0^d(t)\exp\left[w_i^{d\top}\gamma_d + \alpha^d m_i(t)\right], \\ h_i^t(t) &= h_0^t(t)\exp\left[w_i^{t\top}\gamma_t + \alpha^t m_i(t)\right], \\ h_i^{td}(t) &= h_0^{td}(t)\exp\left[w_i^{td\top}\gamma_{td} + \alpha^{td} m_i(t)\right], \end{cases}$$

where

- ▷ $h_i^d(t)$ transition intensity from disease to death
- ▷ $h_i^t(t)$ transition intensity from disease to transplantation
- ▷ $h_i^{td}(t)$ transition intensity from transplantation to death

5.3 Multiple Failure Times (cont'd)

Multi-state long-format **different** than the long format in Competing Risks

- General rule: 1 row per **possible** transition.
  - ▷ competing risks: always 2 rows per subject because **both transitions always possible** from starting state.
  - ▷ multi-state: unequal number of rows per subject because **not all transitions possible** from starting state)

5.3 Multiple Failure Times (cont'd)

For more info see
https://drizopoulos.github.io/JMbayes2/
→ Articles → Multi-State Processes

5.3 Multiple Failure Times (cont'd)

- Multiple Failure Times: recurrent events

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

5.3 Multiple Failure Times (cont'd)

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

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

with

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

5.3 Multiple Failure Times (cont'd)

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

    are independent given $\{b_i, \mathsf{v}_i\}$

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

Part VI

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

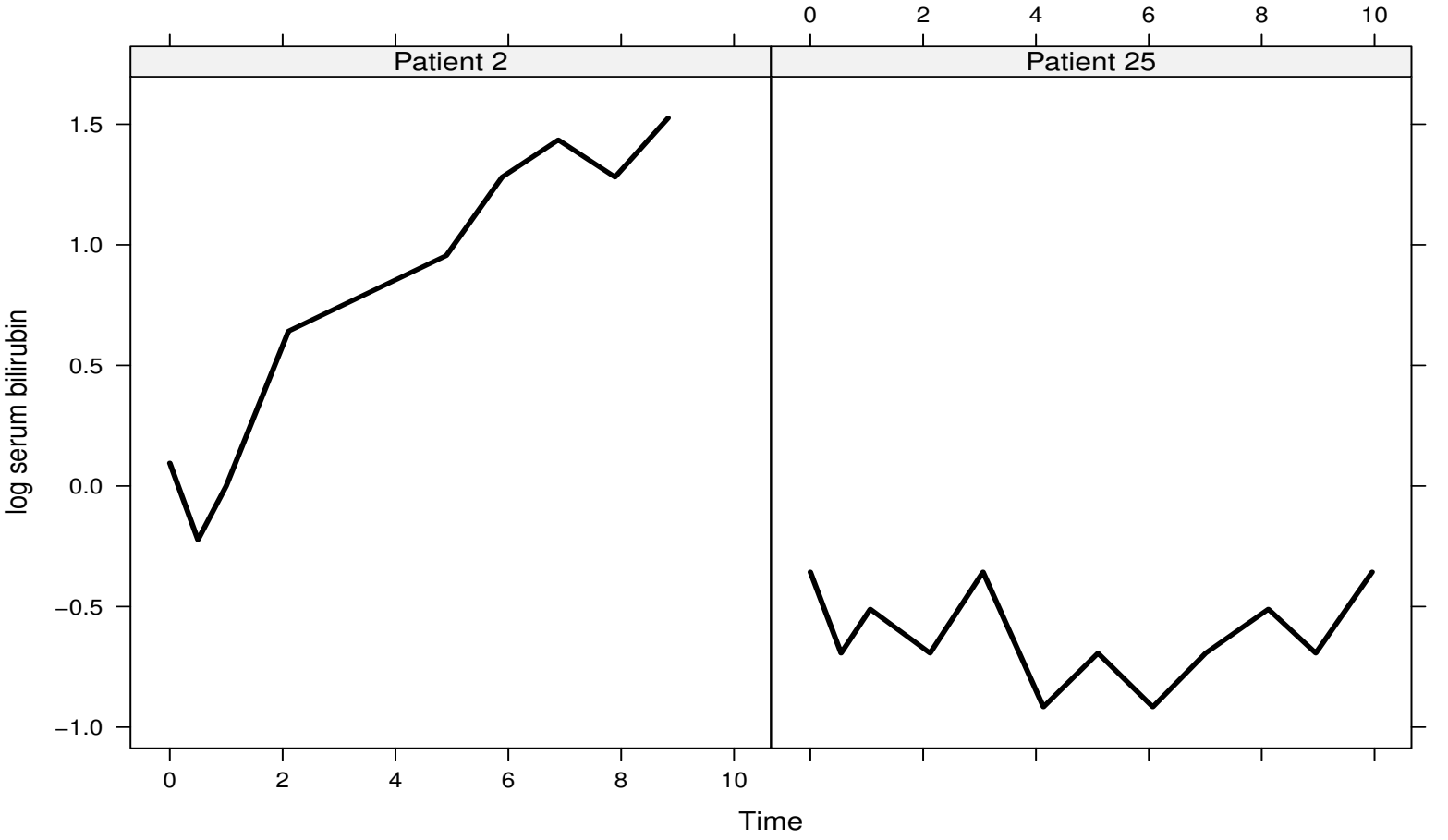
6.1 Survival Probabilities (cont'd)

- We are interested in predicting survival probabilities for a new patient j with serum bilirubin measurements up to time t

- Example: Patients 2 and 25 from the PBC dataset have 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 covariate
  - ▷ 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

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

where

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

6.1 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)

6.1 Survival Probabilities (cont'd)

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

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

- The first part of the integrand takes the form

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

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

6.1 Survival Probabilities (cont'd)

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

Step 1. draw $\theta^{(\ell)} \sim [\theta \mid \mathcal{D}_n]$

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

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

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

6.1 Survival Probabilities (cont'd)

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

- Longitudinal submodel
  - ▷ fixed effects: intercept & natural cubic splines of time with 3 d.f., sex, and interaction of the time effect with sex
  - ▷ random effects: intercept, natural cubic splines of time with 3 d.f.

- Survival submodel
  - ▷ sex effect + *underlying* serum bilirubin level

6.1 Survival Probabilities (cont'd)

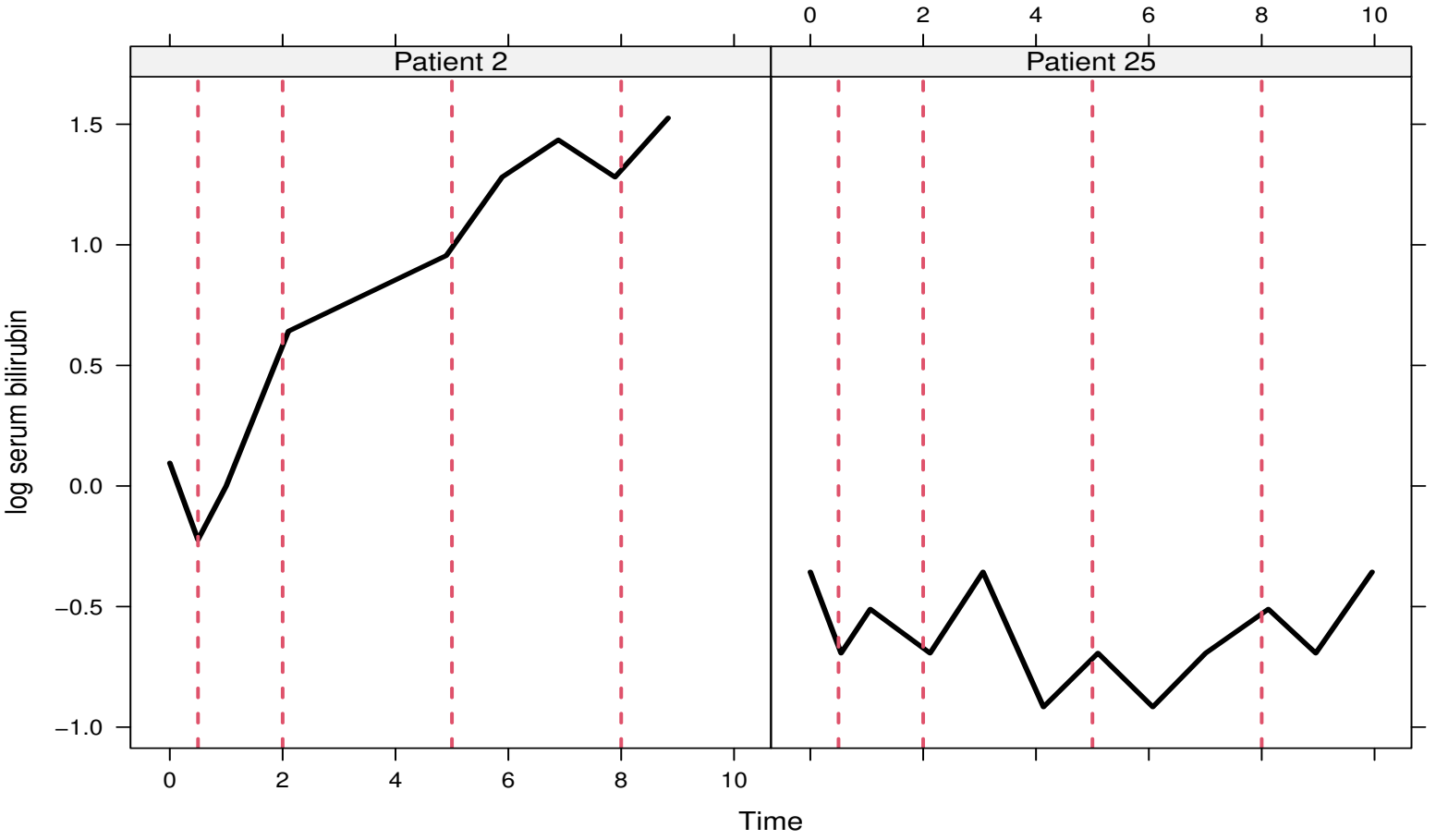
- Based on the fitted joint model we estimate $\pi_j(u \mid t)$ for Patients 2 and 25

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

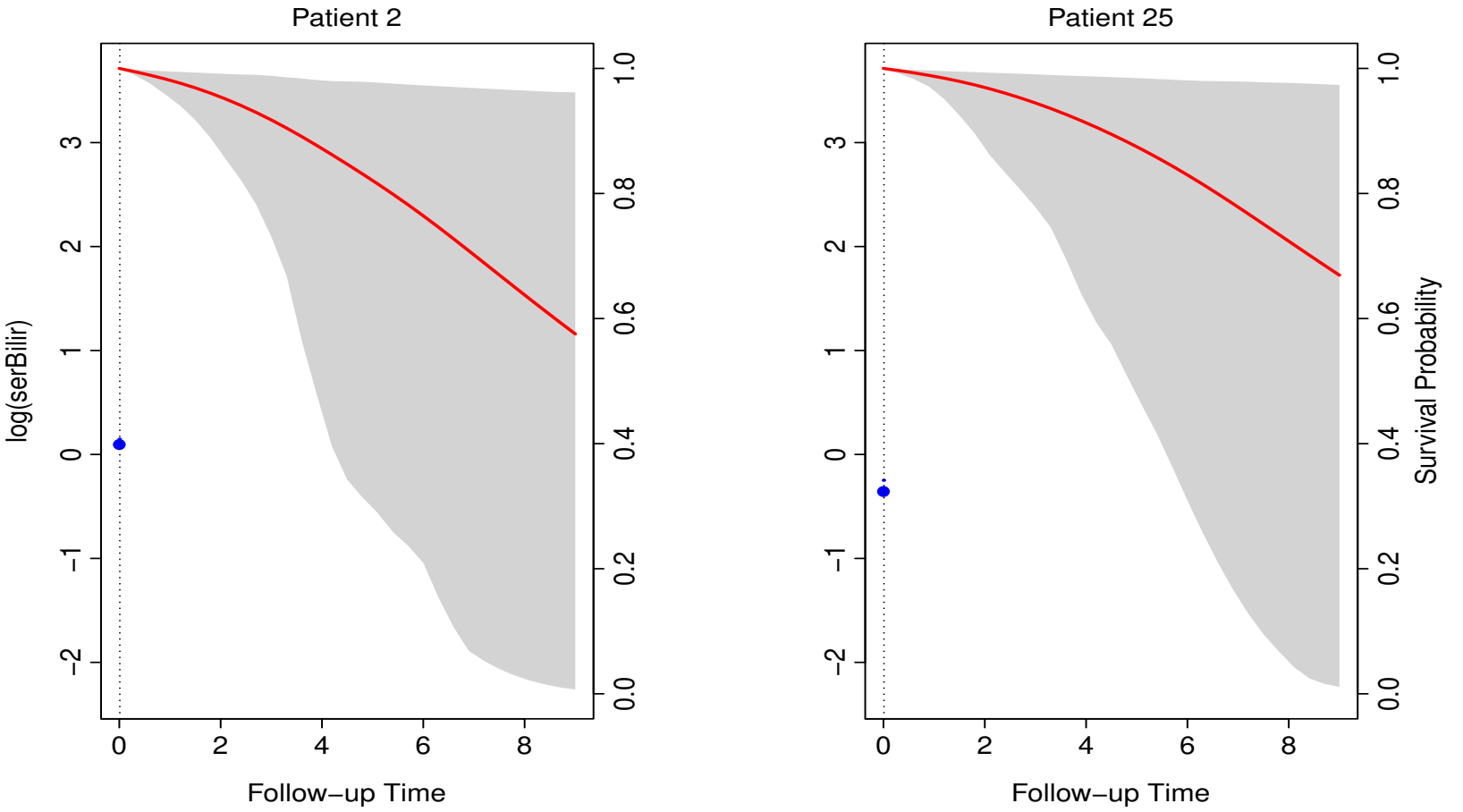
$$\hat{\pi}_j(u \mid t) = \text{mean}\{\pi_j^{(\ell)}(u \mid t), \ell = 1, \ldots, L\}$$

  and calculated a corresponding 95% pointwise CIs

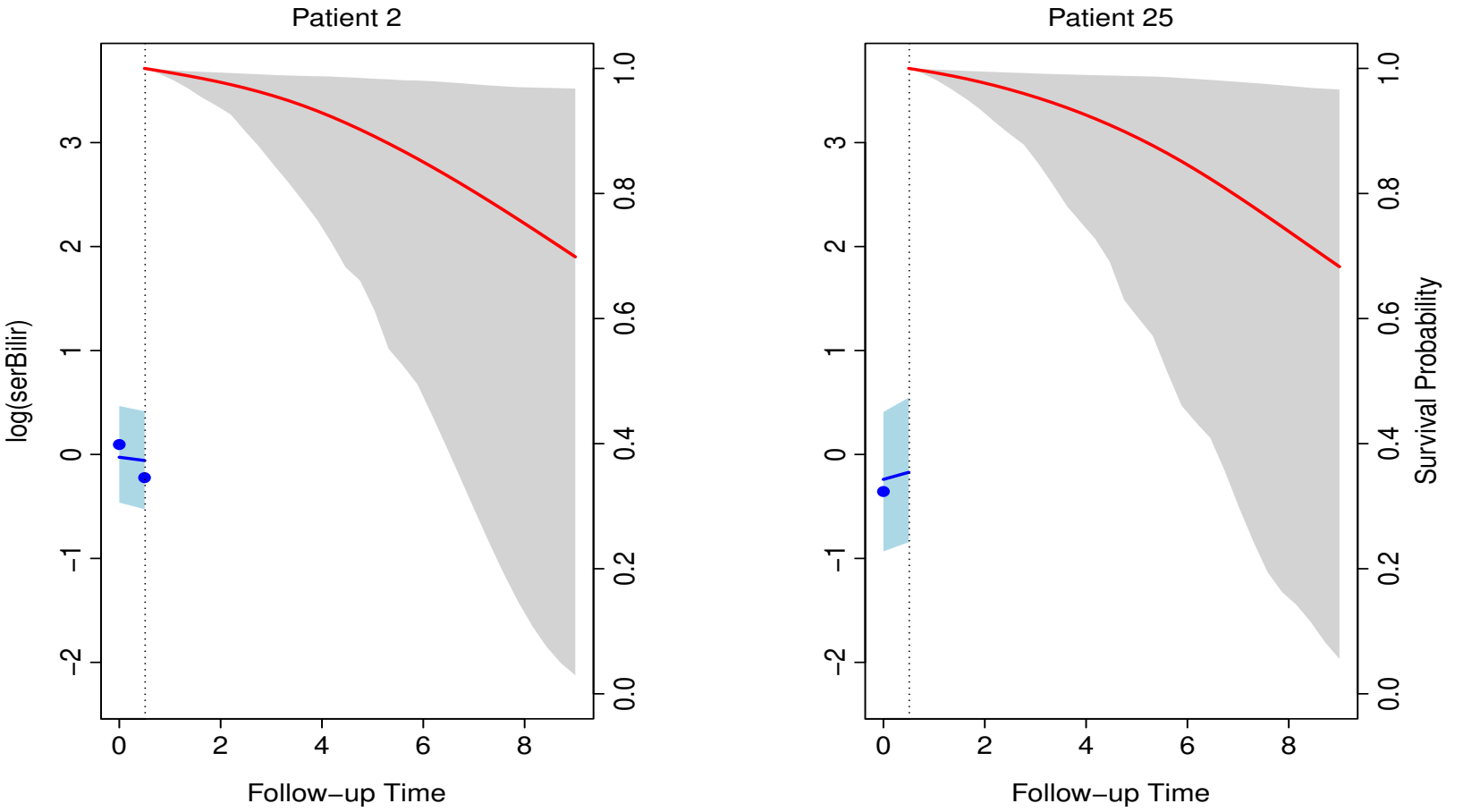
6.1 Survival Probabilities (cont'd)



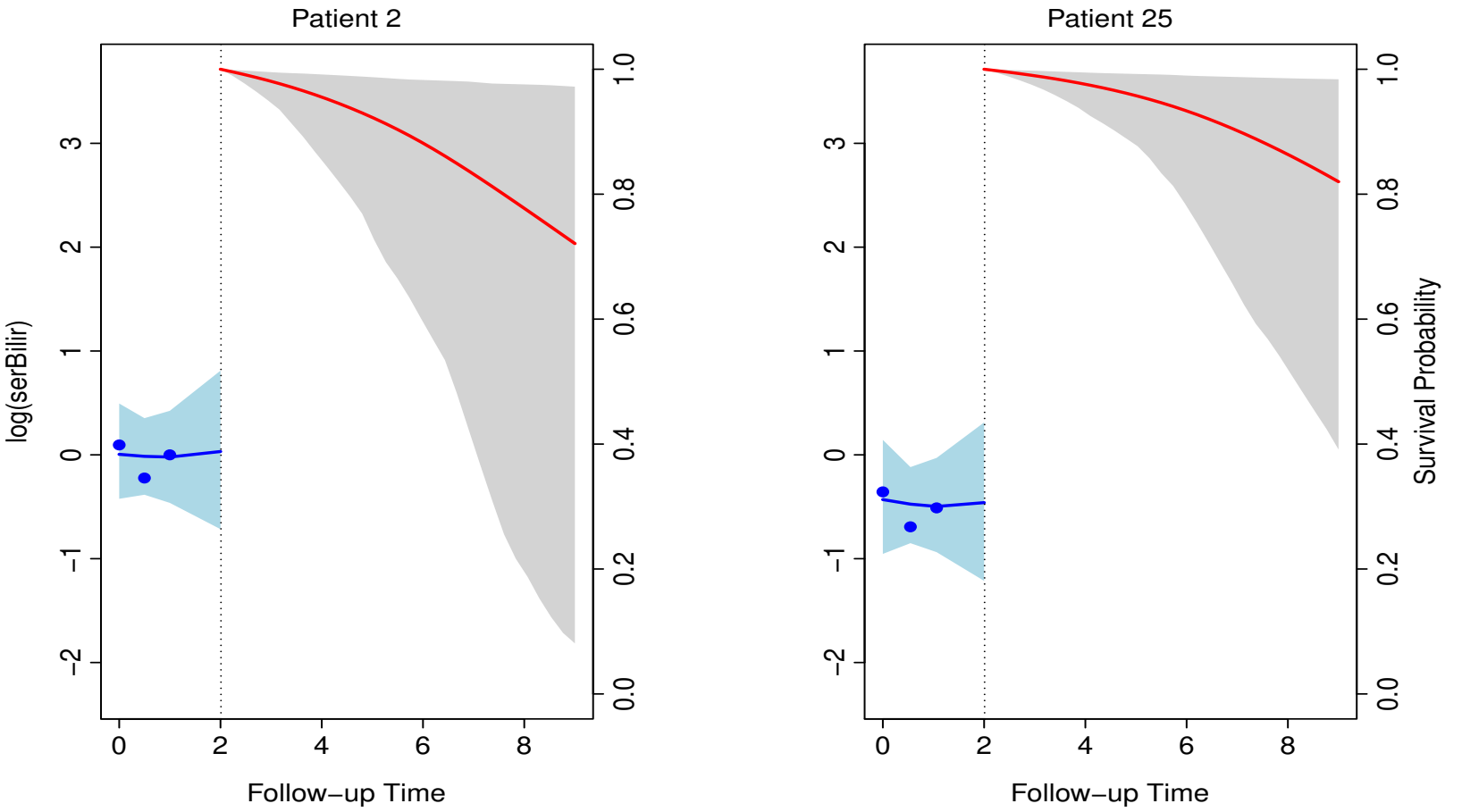
6.1 Survival Probabilities (cont'd)



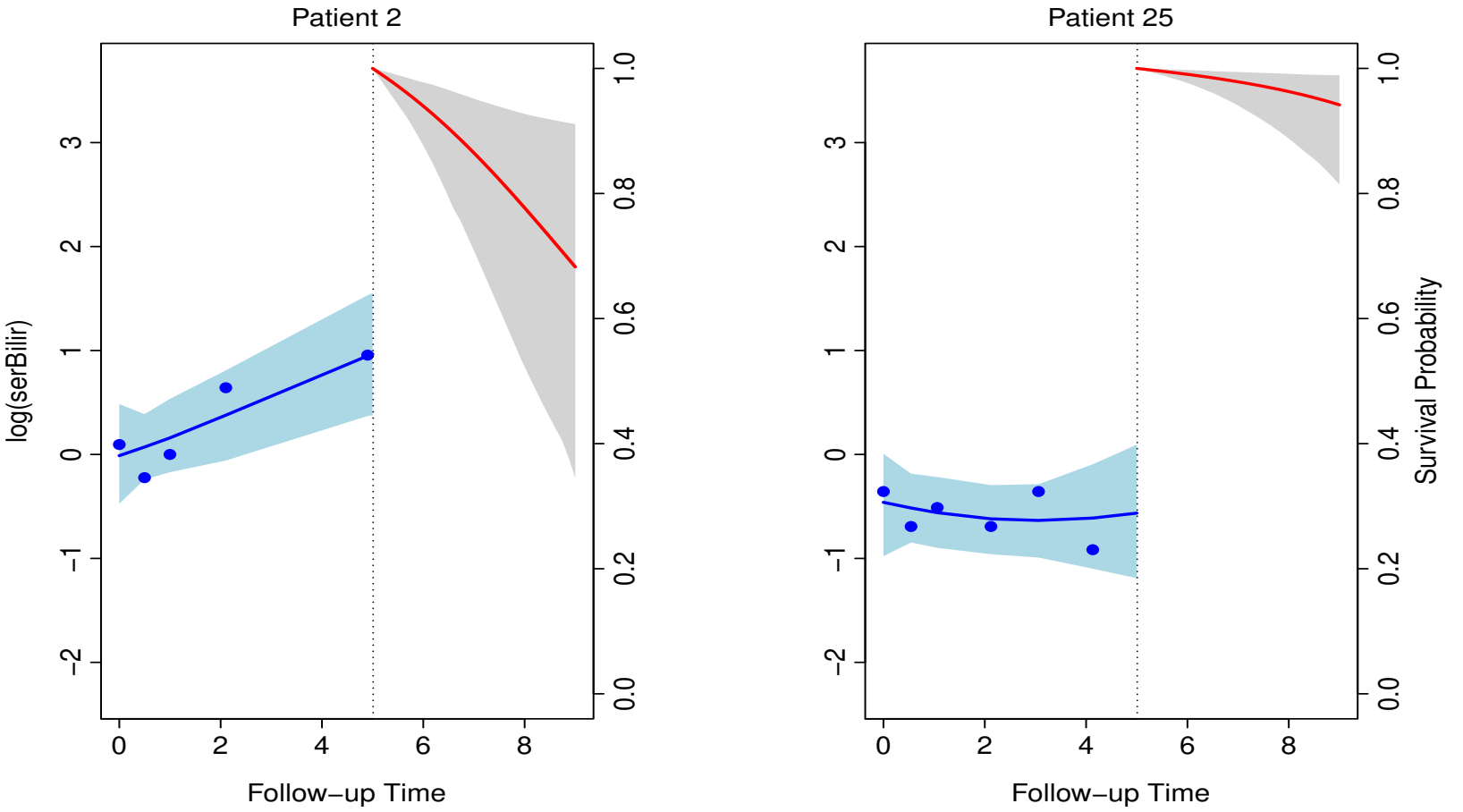
6.1 Survival Probabilities (cont'd)



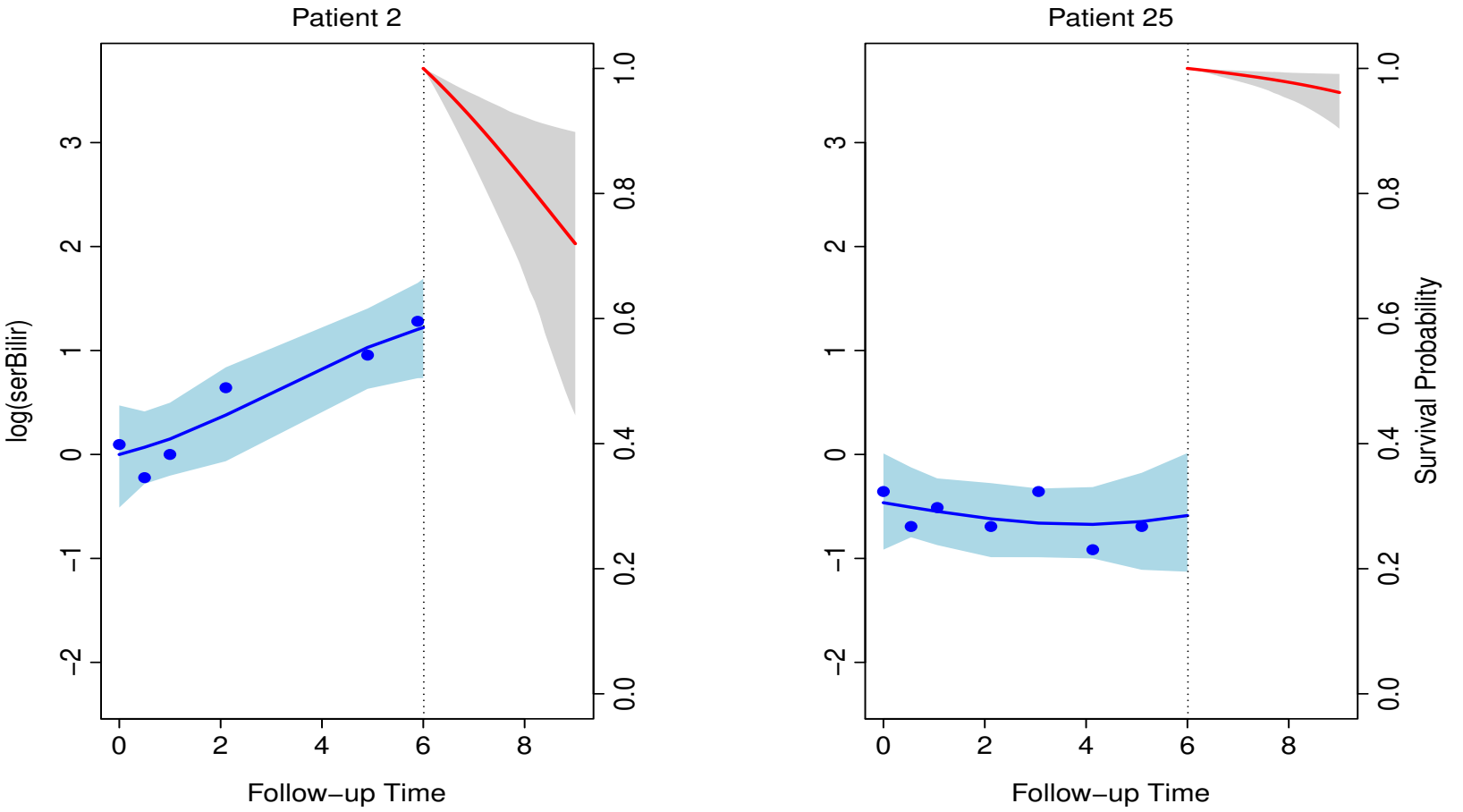
6.1 Survival Probabilities (cont'd)



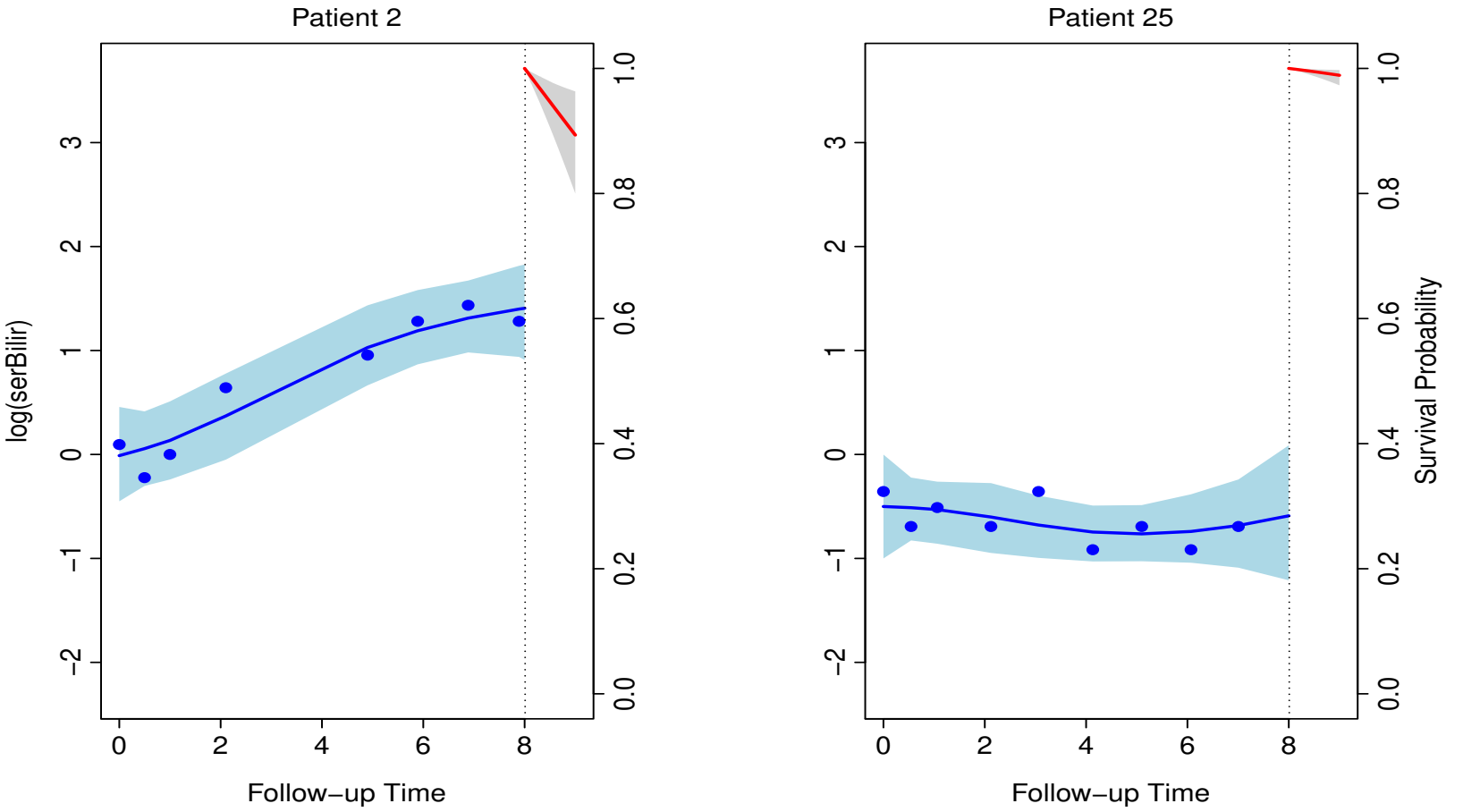
6.1 Survival Probabilities (cont'd)



6.1 Survival Probabilities (cont'd)



6.1 Survival Probabilities (cont'd)



6.1 Survival Probabilities (cont'd)

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

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

sfit

plot(sfit)
```

6.2 Longitudinal Outcomes Prediction

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

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

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

and we are interested in

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

6.2 Longitudinal Outcomes Prediction (cont'd)

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

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

- With the first part of the integrand given by:

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

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

6.2 Longitudinal Outcomes Prediction (cont'd)

- A similar Monte Carlo simulation scheme:

Step 1. draw $\theta^{(\ell)} \sim [\theta \mid \mathcal{D}_n]$

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

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

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

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

6.2 Longitudinal Outcomes Prediction (cont'd)

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

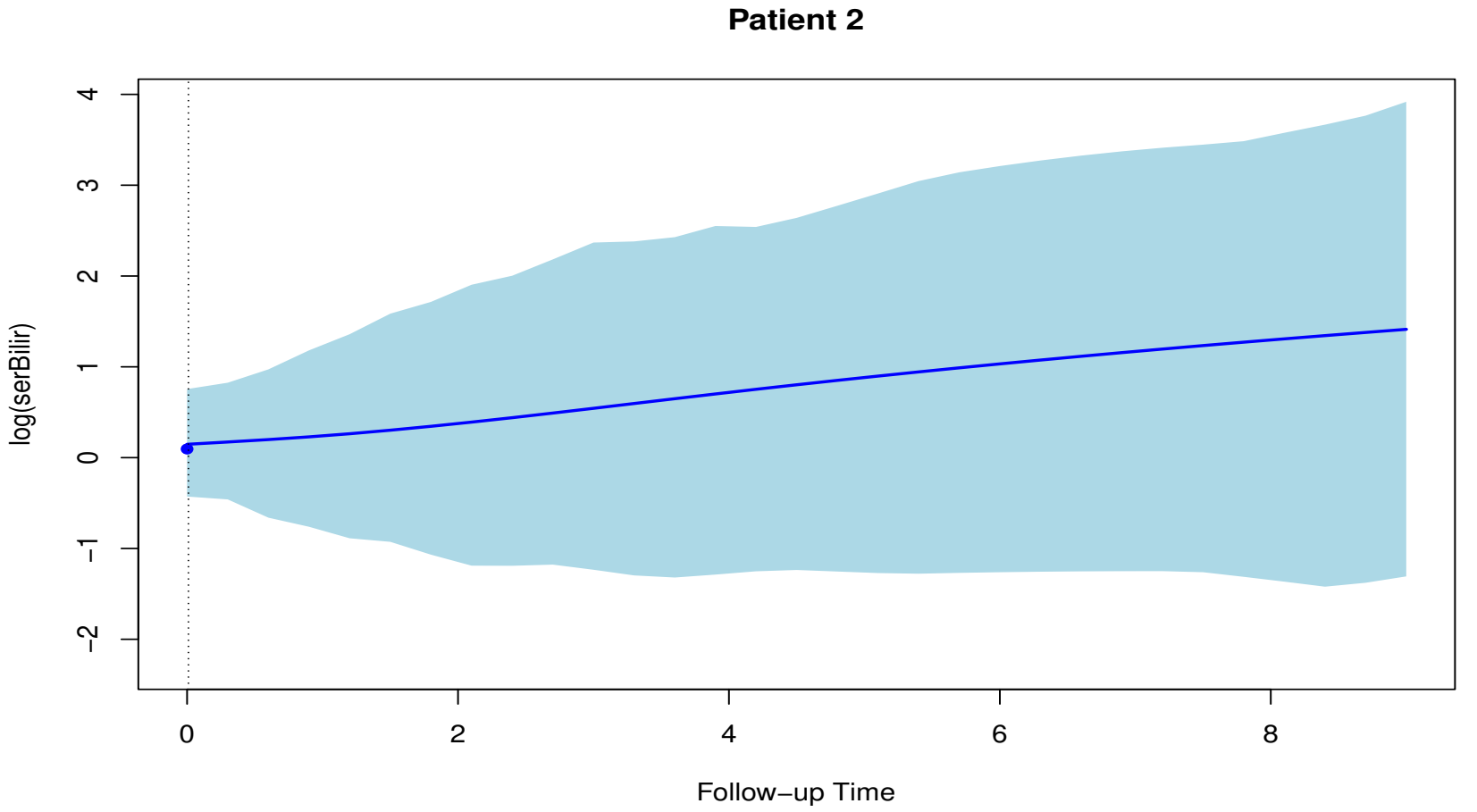
- Longitudinal submodel
  - ▷ fixed effects: intercept & natural cubic splines of time with 3 d.f., sex, and interaction of the time effect with sex
  - ▷ random effects: intercept, natural cubic splines of time with 3 d.f.

- Survival submodel
  - ▷ sex effect + *underlying* serum bilirubin level

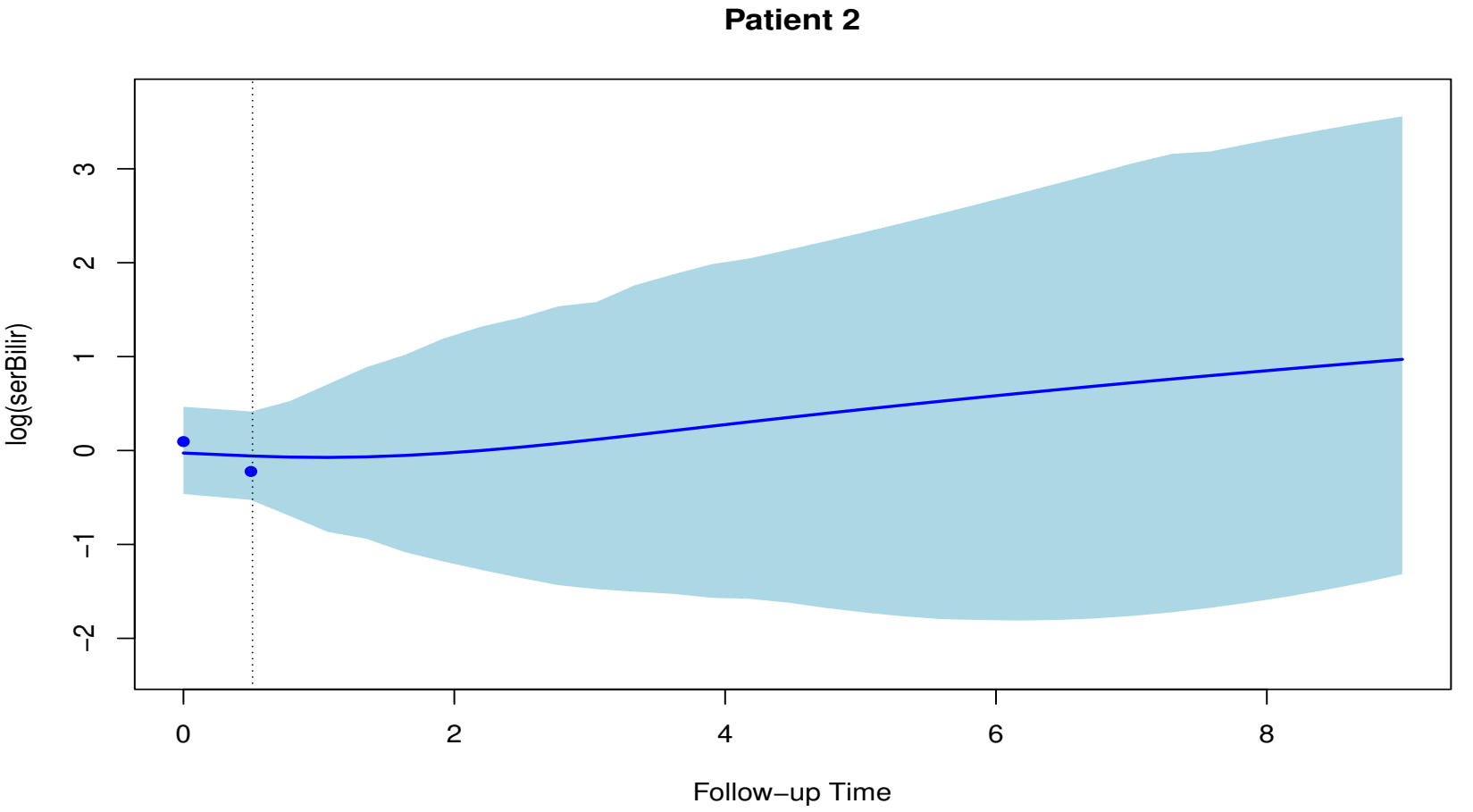
6.2 Longitudinal Outcomes Prediction (cont'd)

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

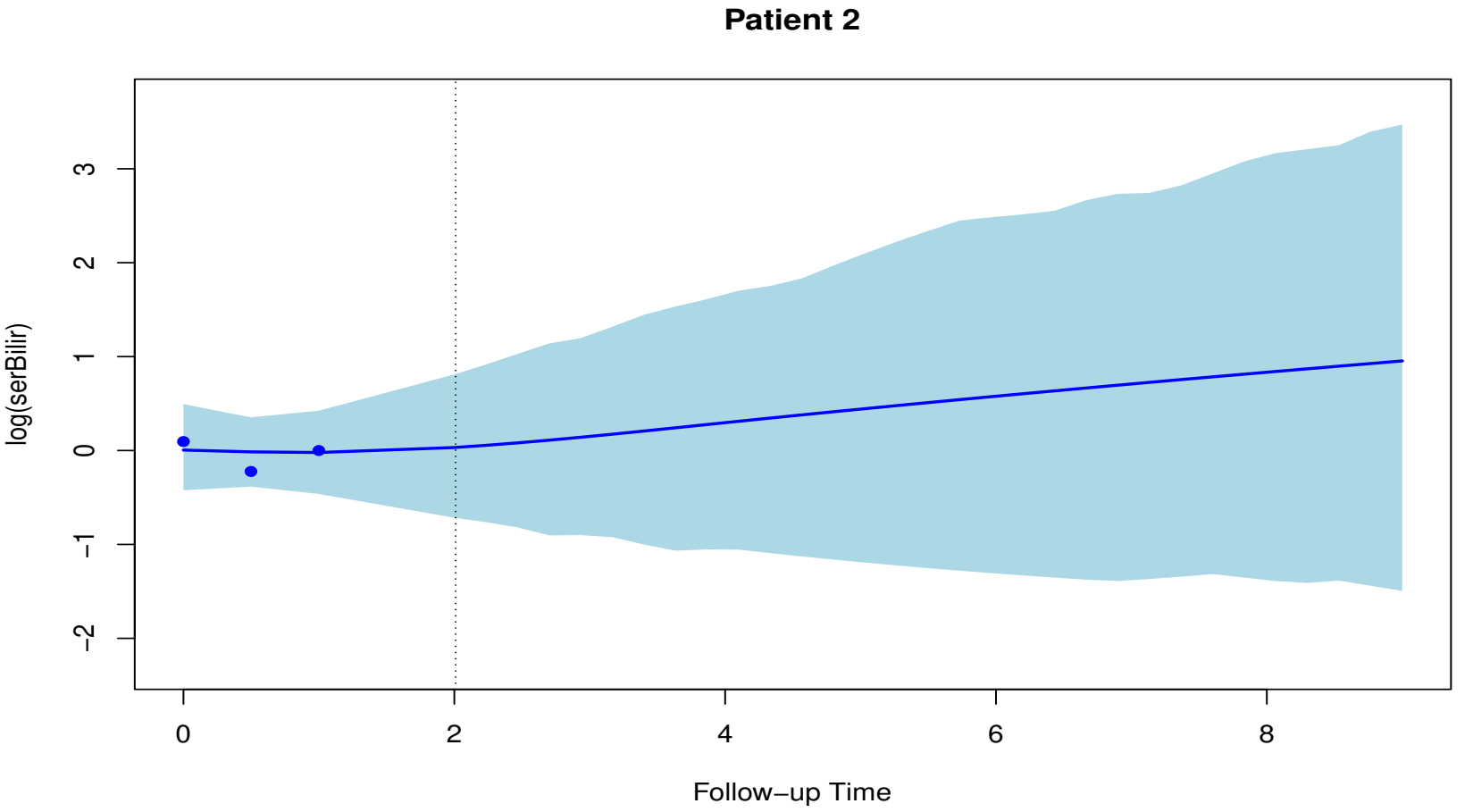
6.2 Longitudinal Outcomes Prediction (cont'd)



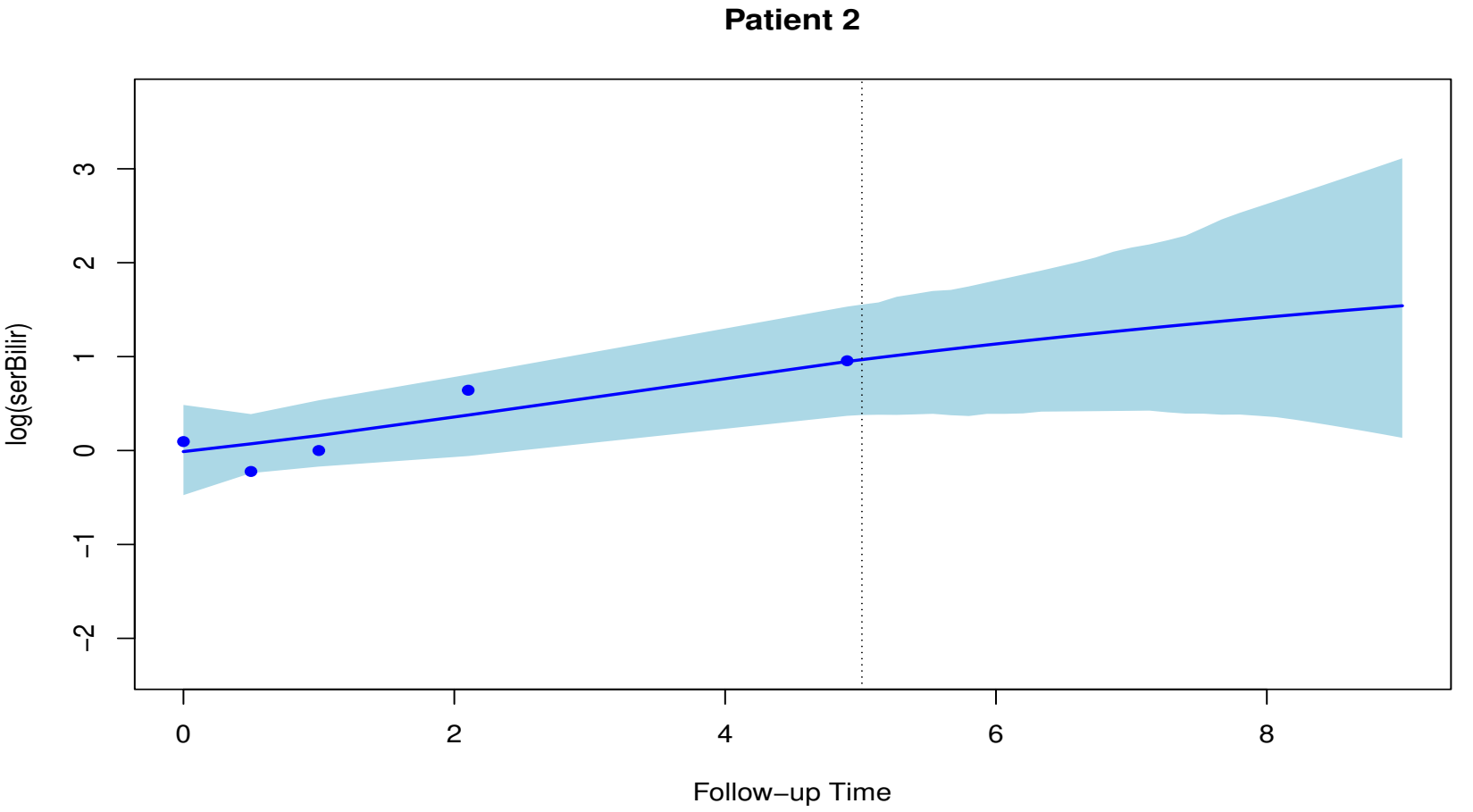
6.2 Longitudinal Outcomes Prediction (cont'd)



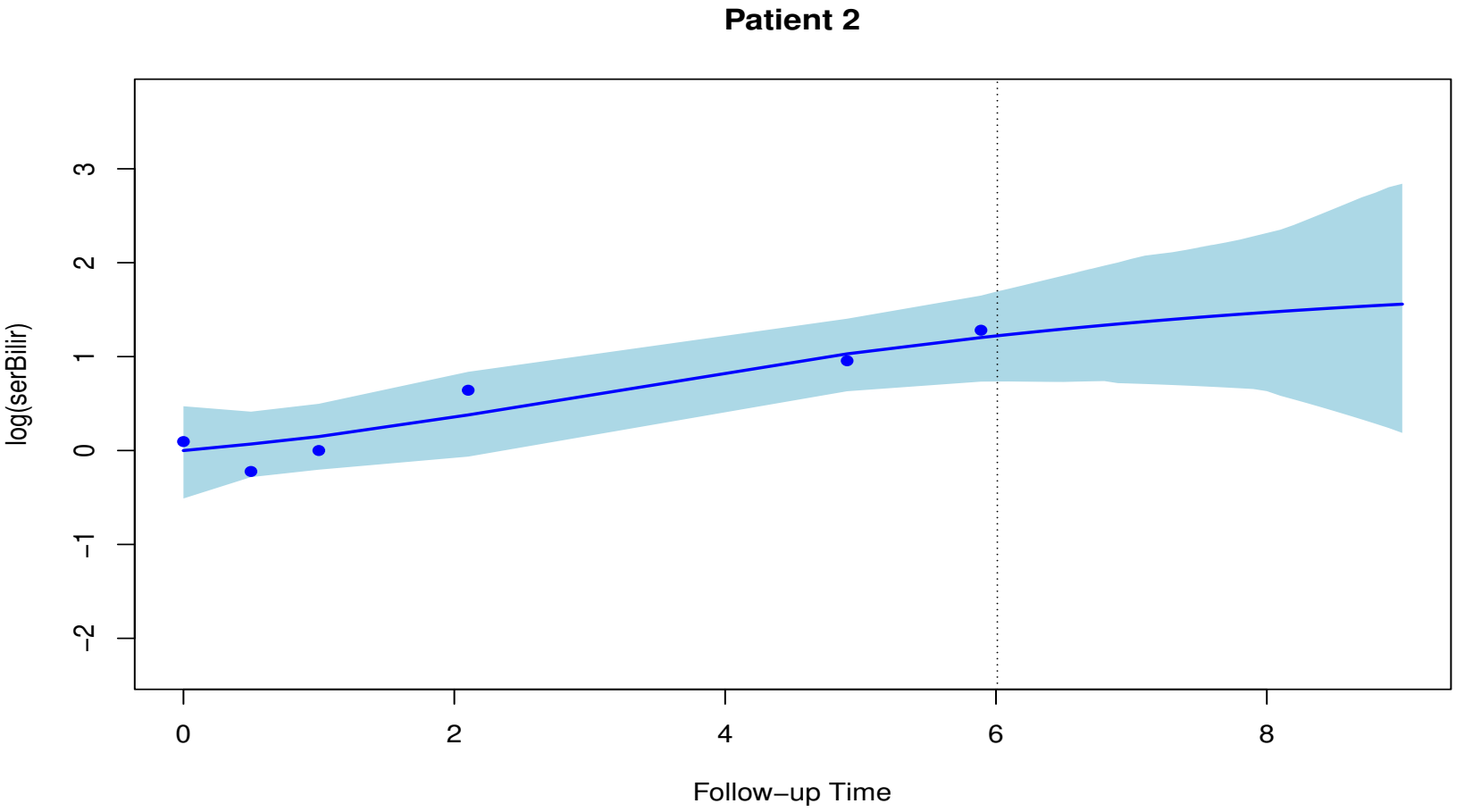
6.2 Longitudinal Outcomes Prediction (cont'd)



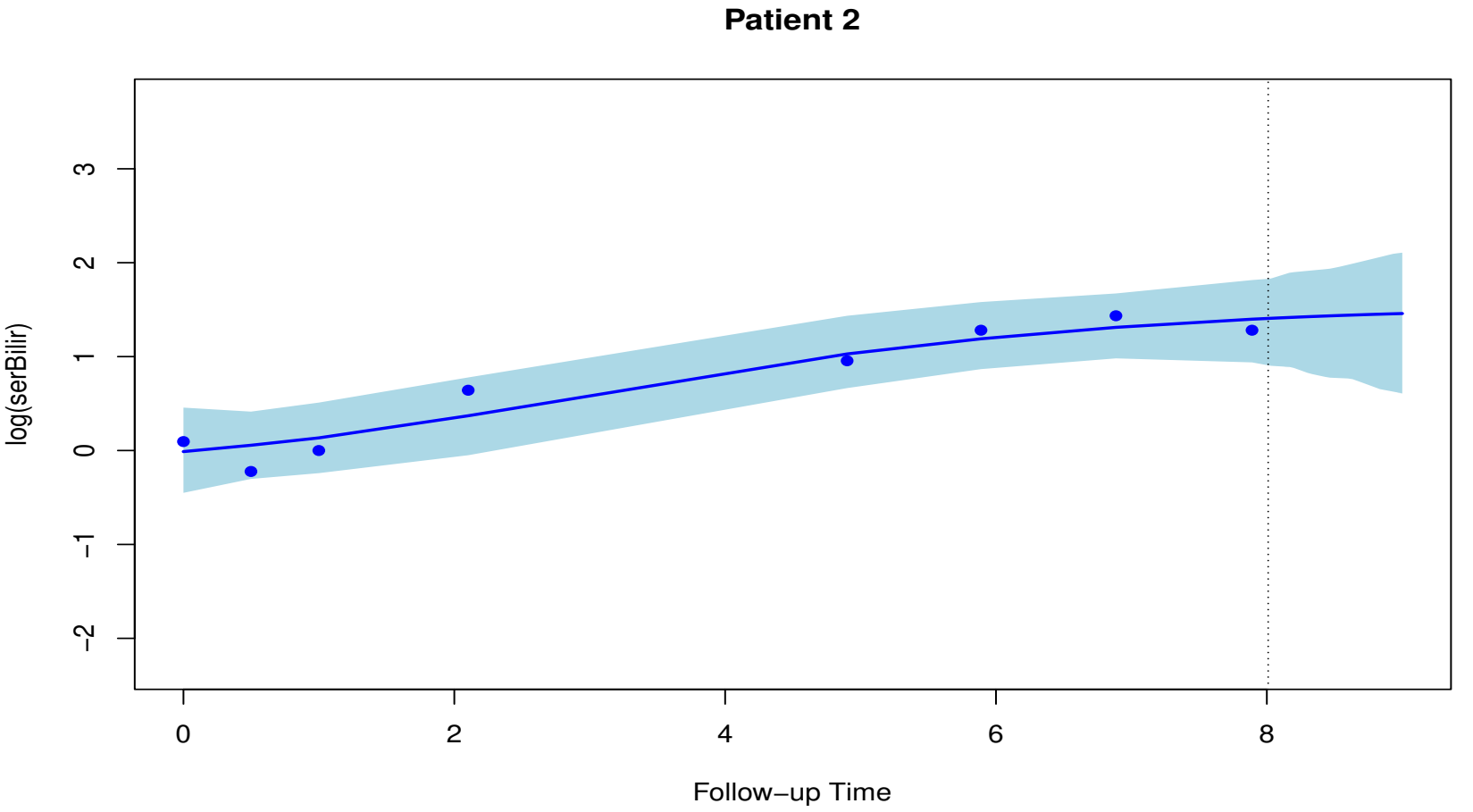
6.2 Longitudinal Outcomes Prediction (cont'd)



6.2 Longitudinal Outcomes Prediction (cont'd)



6.2 Longitudinal Outcomes Prediction (cont'd)



6.2 Longitudinal Outcomes Prediction (cont'd)

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

```
gfit <- predict(jointFit, newdata = pbc2[pbc2$id == "2", ],
                times = seq(7, 12, length.out = 51),
                return_newdata = TRUE)

gfit

plot(gfit)
```

6.3 Functional Forms

- All previous predictions were based on the standard joint model

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

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

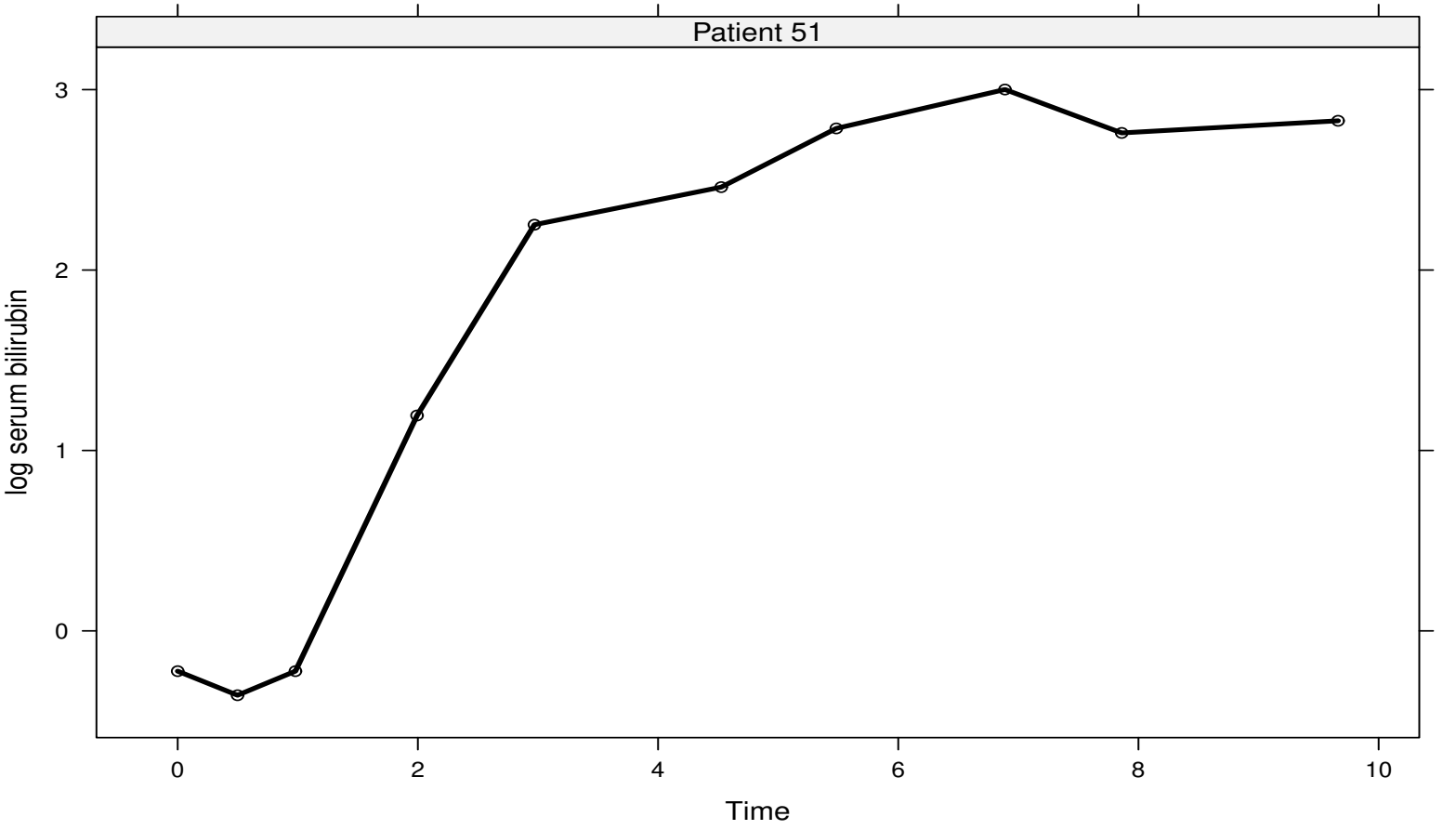
6.3 Functional Forms (cont'd)

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

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

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

6.3 Functional Forms (cont'd)



6.3 Functional Forms (cont'd)

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

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

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

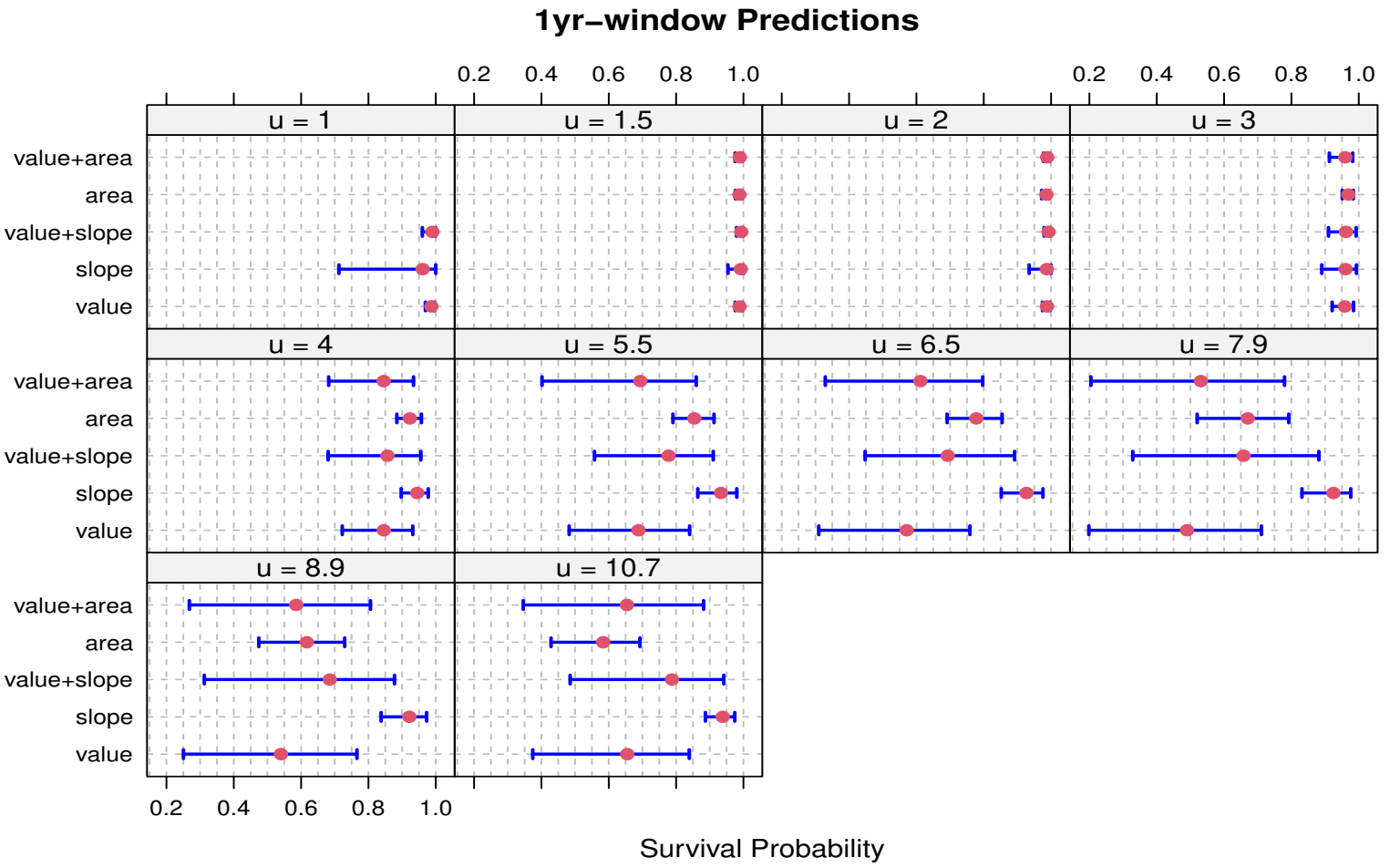
$$h_i(t) = h_0(t) \exp\{\gamma \texttt{D-pnc}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\}$$

6.3 Functional Forms (cont'd)

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

$$h_i(t) = h_0(t) \exp\left\{ \gamma \texttt{D-pnc}_i + \alpha_1 m_i(t) + \alpha_3 \frac{\int_0^t m_i(s)ds}{t} \right\},$$

6.3 Functional Forms (cont'd)



6.3 Functional Forms (cont'd)

The chosen functional form can influence the derived predictions

6.3 Functional Forms (cont'd)

- We compare the models using the information criteria

	DIC	WAIC	LPML
value + slope	5322.683	22104.998	−5535.420
area	5346.029	23268.436	−5560.009
slope	5645.578	29600.396	−7353.621
value + area	5388.139	29840.361	−9110.958
value	5439.294	30513.206	−7230.238

- The value + slope model seems to be the 'best' – we will continue with this model

6.4 Discrimination

- We have seen how to calculate predictions of conditional survival probabilities
  - ▷ however, to use these predictions in practice we need to evaluate their accuracy

- Predictive accuracy measures
  - ▷ Discrimination: sensitivity, specificity, ROC and AUC
  - ▷ Calibration: comparison between predicted and observed probabilities
  - ▷ Overall: combination of discrimination and calibration

6.4 Discrimination (cont'd)

- To assess the discriminative power of the model, we assume the following setting
  - ▷ using the available longitudinal data up to time t,
  - ▷ we are interested in events occurring in a medically-relevant interval $(t, t + \Delta t]$

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

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

6.4 Discrimination (cont'd)

- Following, we can define sensitivity

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

specificity

$$\mathsf{SP}_t^{\Delta t}(c) = \Pr\big\{\pi_j(t + \Delta t \mid t) > c \mid T_j^* > t + \Delta t\big\},$$

and the corresponding AUC

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

6.4 Discrimination (cont'd)

- To estimate the sensitivity, specificity and the AUC, *we need to account for censoring*

- Two main approaches
  - ▷ model-based weights
  - ▷ inverse probability of censoring weighting (IPCW)
    (using Kaplan-Meier or other non-parametric estimators)

6.4 Discrimination (cont'd)

- IPCW
  - ▷ *Advantage:* it provides unbiased estimates even when the model is misspecified
  - ▷ *Disadvantage:* it requires that the model for the weights is correct
    - * in settings where joint models are used, challenging because censoring may depend on the longitudinal outcomes in a complex manner

6.4 Discrimination (cont'd)

- Model-based Weights
  - ▷ *Advantage:* it allows censoring to depend on the longitudinal history (in any possible manner)
  - ▷ *Disadvantage:* it requires that the model is well calibrated

6.4 Discrimination (cont'd)

Because censoring often depends on the longitudinal history,
we opt for model-based weights

6.4 Discrimination (cont'd)

- For the $\mathcal{R}(t)$ subjects at risk at time t (i.e., $T_i > t$), sensitivity is estimated as

$$\widehat{\mathsf{SN}}_t^{\Delta t}(c) = \frac{\sum_{i:T_i \geq t} I\{\hat{\pi}_i(t + \Delta t \mid t) \leq c\} \times \Omega_i}{\sum_{i:T_i \geq t} \Omega_i},$$

where

$$\Omega_i = \begin{cases} 1, & \text{if } T_i \leq t + \Delta t \text{ and } \delta_i = 1 \\ 1 - \hat{\pi}_i(t + \Delta t \mid T_i), & \text{if } T_i \leq t + \Delta t \text{ and } \delta_i = 0 \end{cases}$$

6.4 Discrimination (cont'd)

- And specificity as

$$\widehat{\mathsf{SP}}_t^{\Delta t}(c) = \frac{\sum_{i:T_i \geq t} I\{\hat{\pi}_i(t + \Delta t \mid t) > c\} \times \Phi_i}{\sum_{i:T_i \geq t} \Phi_i},$$

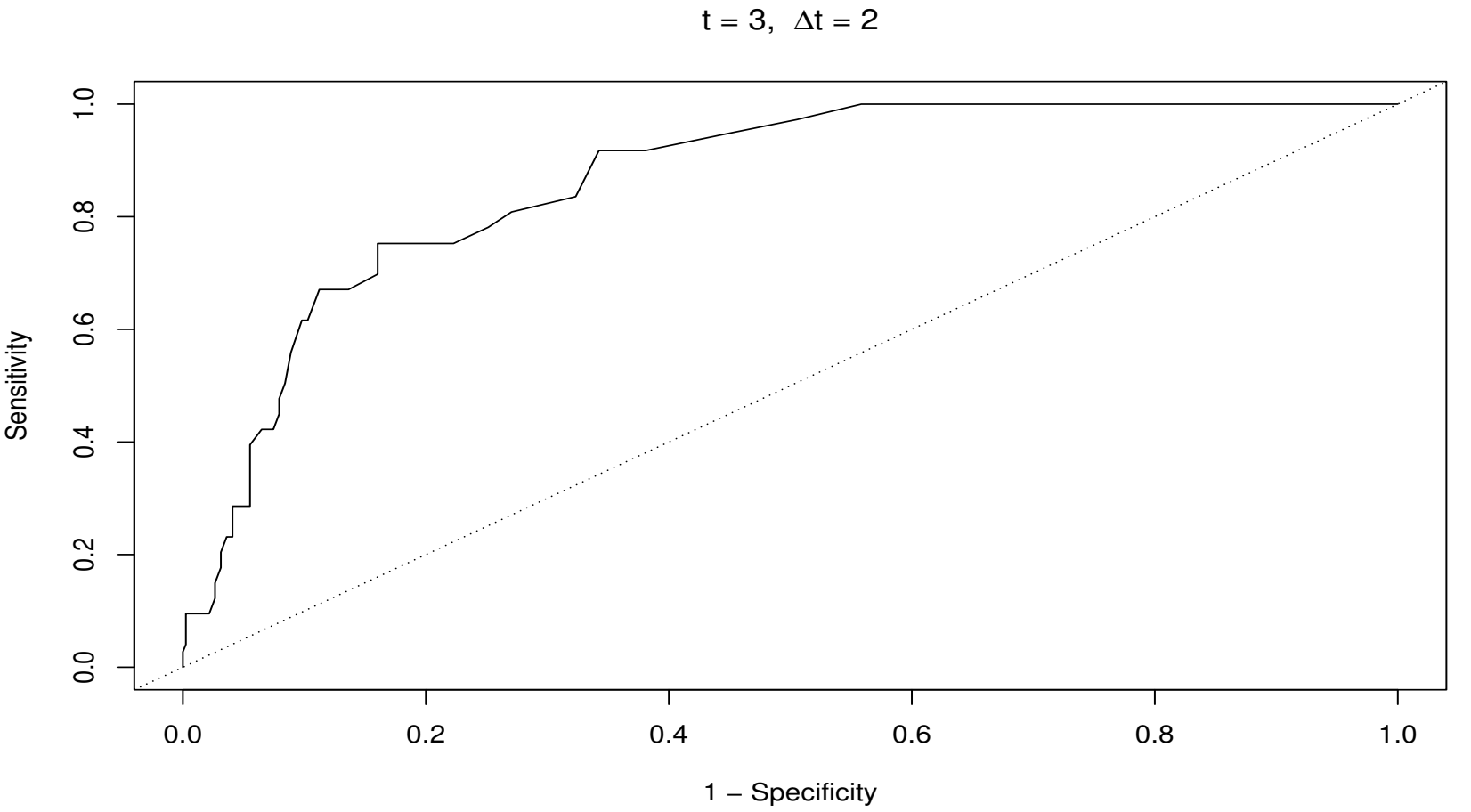
where

$$\Phi_i = \begin{cases} 1, & \text{if } T_i > t + \Delta t \\ \hat{\pi}_i(t + \Delta t \mid T_i), & \text{if } T_i \leq t + \Delta t \text{ and } \delta_i = 0 \end{cases}$$

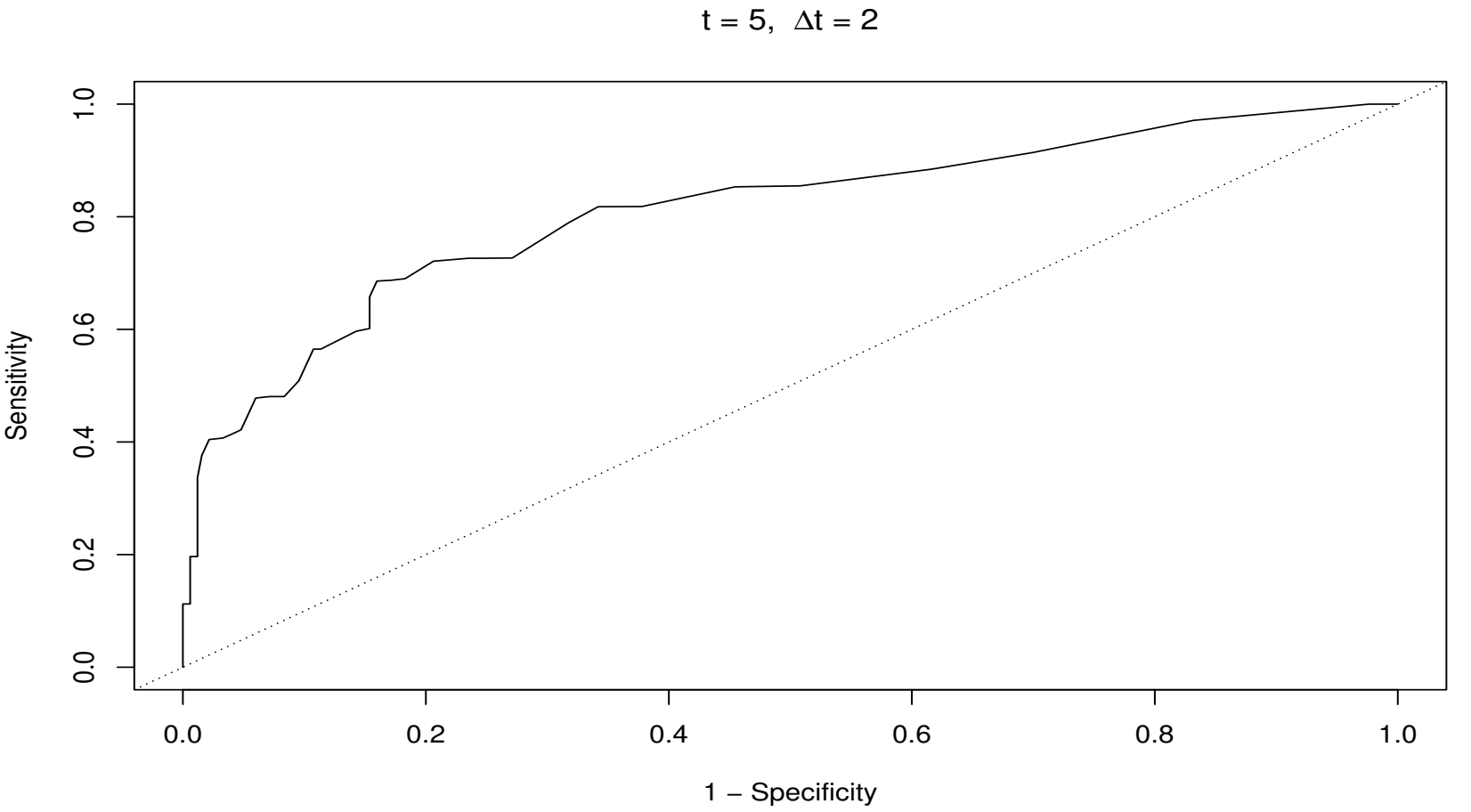
6.4 Discrimination (cont'd)

- Example: For the joint model fitted to the PBC dataset we have seen earlier
  - ▷ we estimate dynamic sensitivity, specificity and the ROC curve
  - ▷ at follow-up times $t = 3, 5,$ and 7
  - ▷ for $\Delta t = 2$

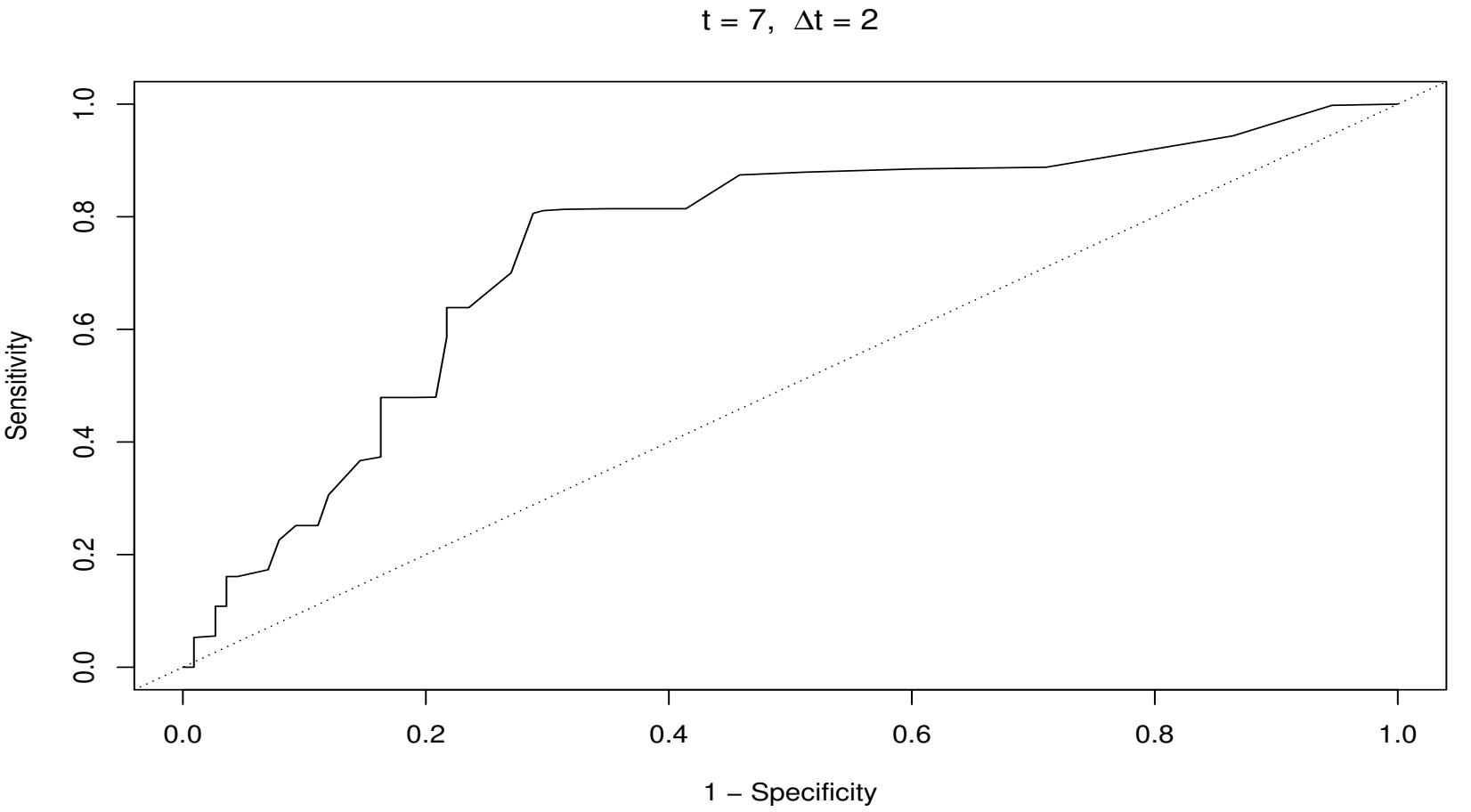
6.4 Discrimination (cont'd)



6.4 Discrimination (cont'd)



6.4 Discrimination (cont'd)



6.4 Discrimination (cont'd)

- The corresponding AUCs are

Time	AUC
t = 3	0.86
t = 5	0.81
t = 7	0.75

6.4 Discrimination (cont'd)

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

```
roc <- tvROC(jointFit, newdata = pbc2, Tstart = 5, Dt = 2)

roc

plot(roc)

tvAUC(roc)
```

6.5 Calibration

- Another relevant measure for quantifying predictive ability is *calibration*, i.e.,
  - ▷ how well can the joint model accurately predict future events

- Typically, calibration is assessed via graphical calibration curves
  - ▷ a plot of observed vs predicted cumulative risk probabilities
  - ▷ we have good calibration when the points are distributed along the main diagonal

6.5 Calibration (cont'd)

- In the context of survival analysis, the construction of these curves is complicated by censoring

- To account for censoring, we follow the recent approach of Austin et al. (SiM, 2020)

  1. we select a follow-up time t and a medically relevant interval Δt
     we only consider the subjects at risk at time t

  2. we calculate risk probabilities $\{1 - \hat{\pi}_i(t + \Delta t \mid t)\}$ from the joint model

  3. we transform these probabilities using the cloglog link, i.e.,
     $\log[-\log\{\hat{\pi}_i(t + \Delta t \mid t)\}]$

6.5 Calibration (cont'd)

4. we fit a Cox model with predictor a natural cubic spline with 3 d.f. for the transformed probabilities

5. we set as the *predicted probabilities* a regular sequence between $\min\{1 - \hat{\pi}_i(t + \Delta t \mid t)\}$ and $\max\{1 - \hat{\pi}_i(t + \Delta t \mid t)\}$

6. we calculate the *observed probabilities*: cumulative risk probabilities from the Cox model for getting the event before $t + \Delta t$ with input variable the predicted probabilities regular sequence

7. we create the curve of the observed vs predicted probabilities

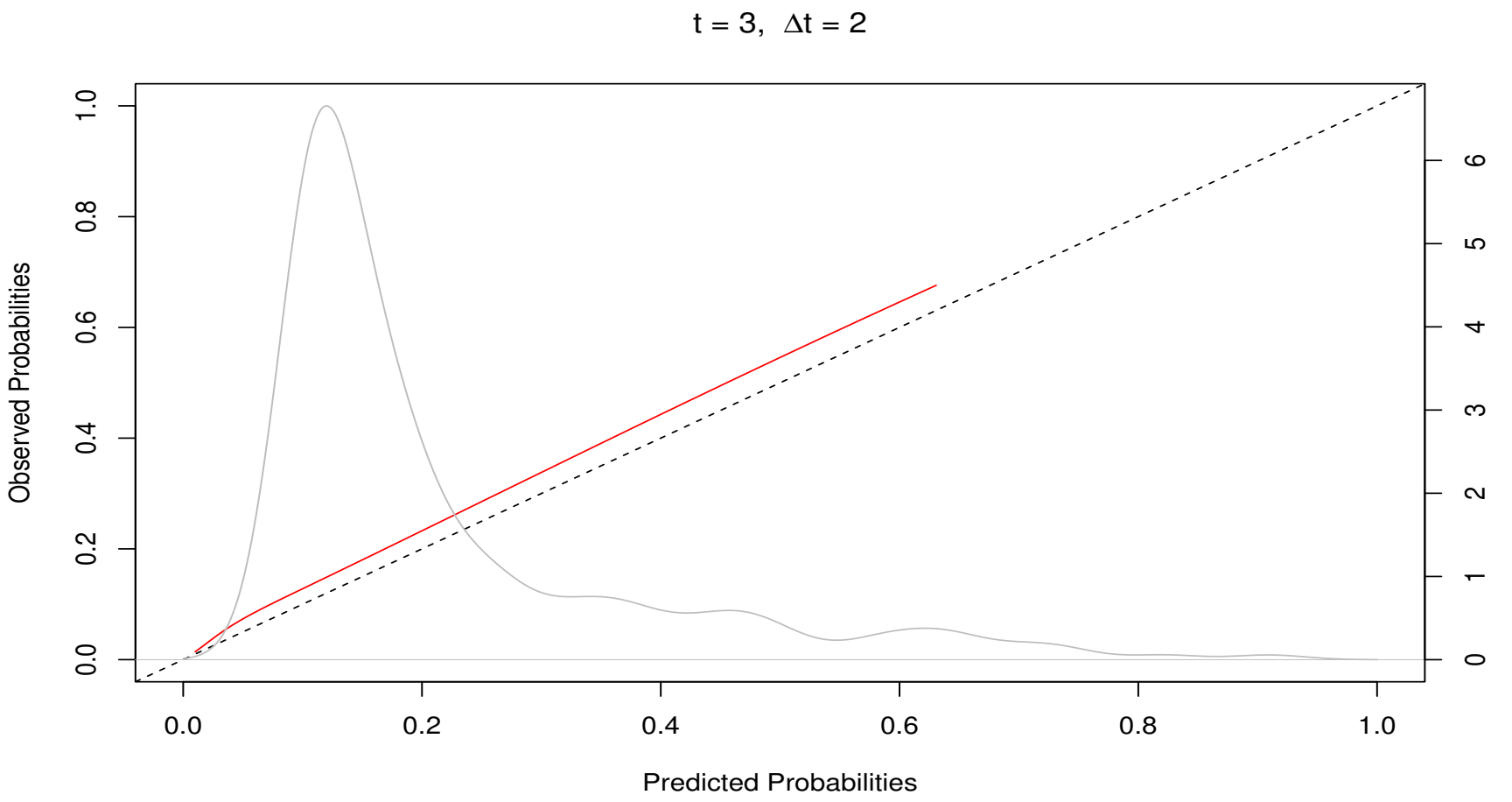
6.5 Calibration (cont'd)

- Note: we account for censoring via the Cox model
  - ▷ censoring is **not** allowed to depend on the longitudinal history

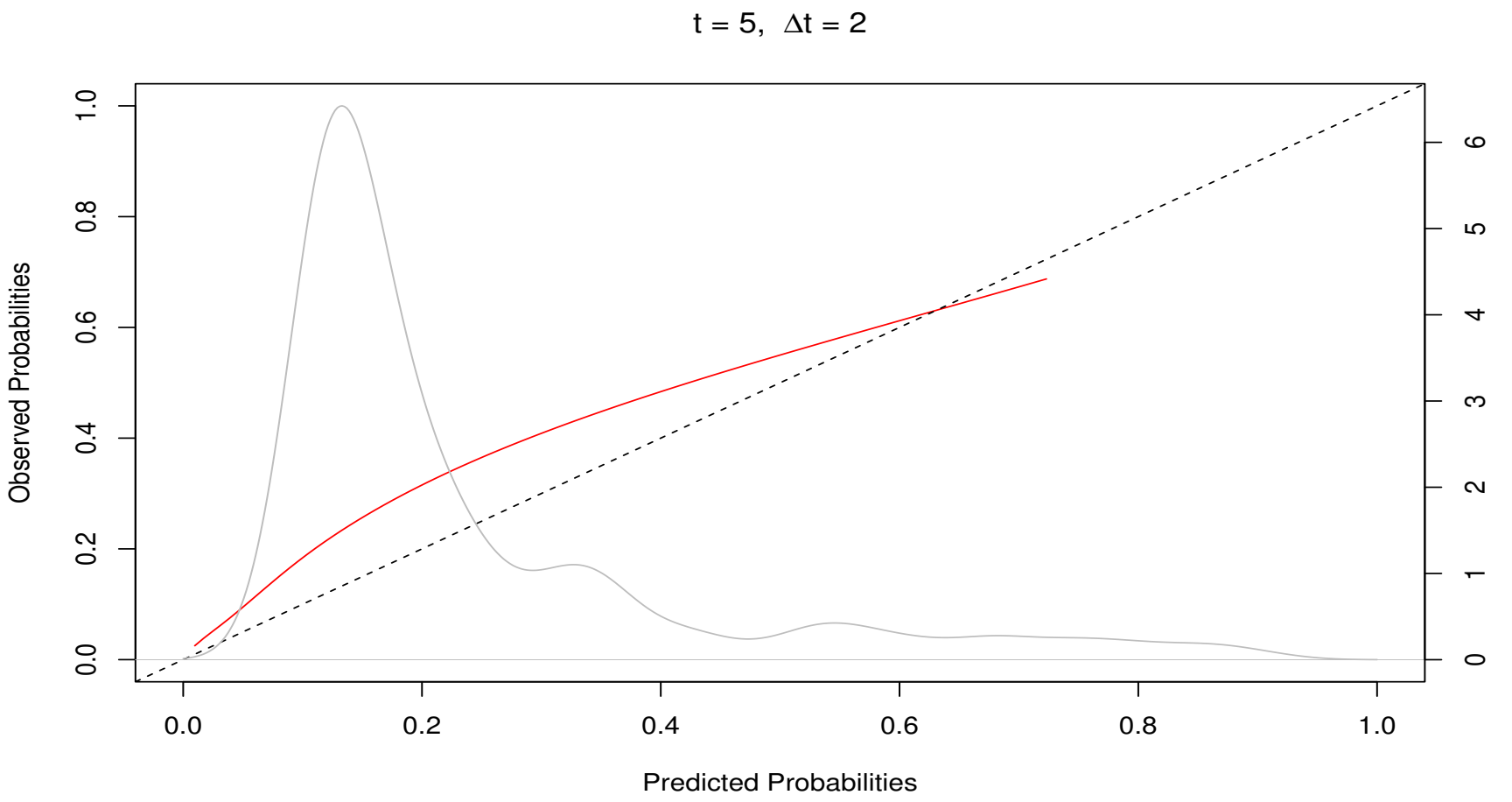
6.5 Calibration (cont'd)

- Example: For the joint model fitted to the PBC dataset we have seen earlier
  - ▷ we estimate dynamic calibration curves
  - ▷ at follow-up times $t = 3, 5,$ and 7
  - ▷ for $\Delta t = 2$

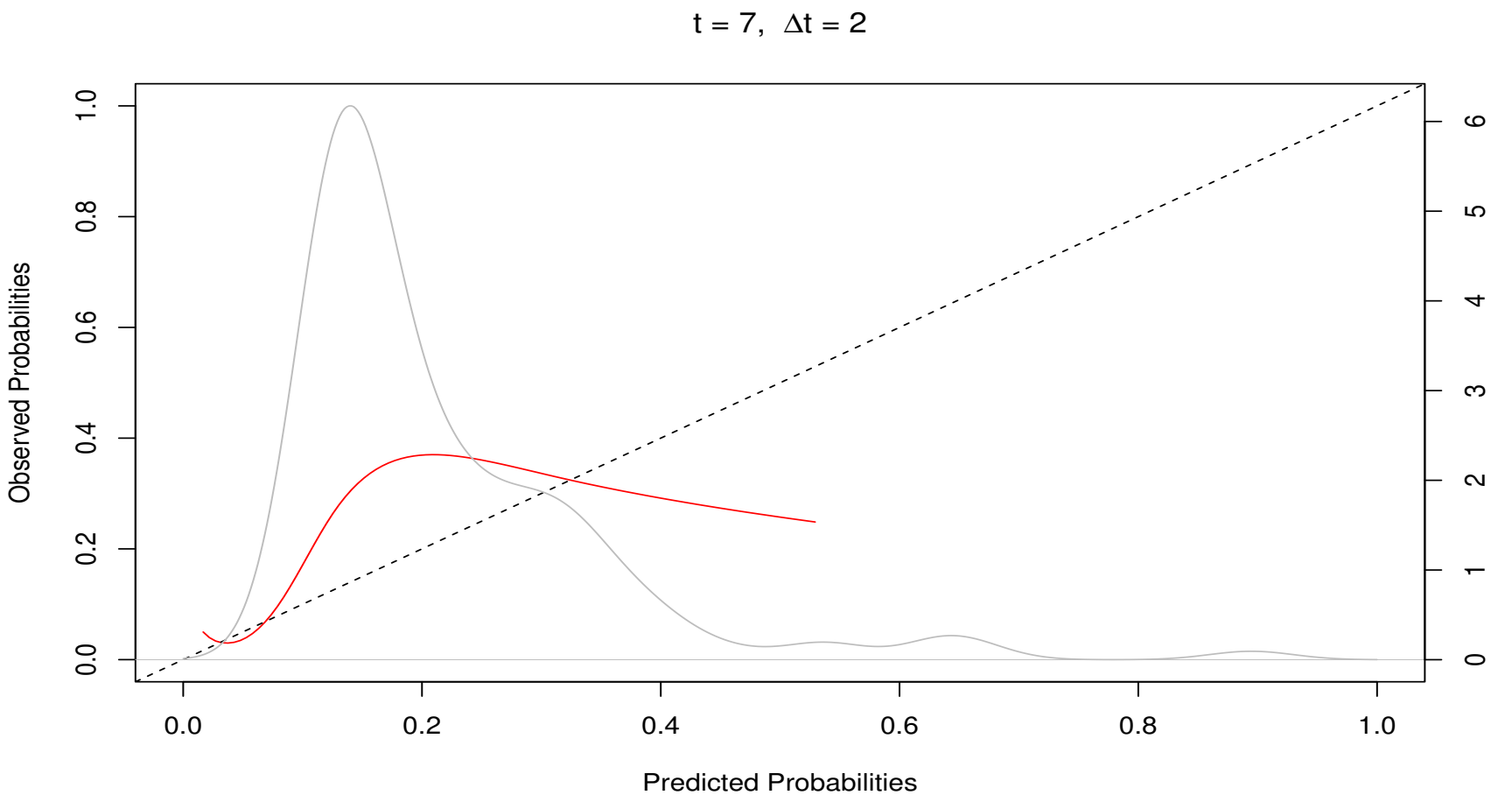
6.5 Calibration (cont'd)



6.5 Calibration (cont'd)



6.5 Calibration (cont'd)



6.5 Calibration (cont'd)

R> For a fitted joint model, we calculate the calibration plot with the syntax

```
calibration_plot(jointFit, newdata = pbc2, Tstart = 3, Dt = 2)
```

6.6 Prediction Error

- We have covered *discrimination* and *calibration* separately

- In standard survival analysis there are measures that combine the two concepts into one metric
  - ▷ the most-well know measure that achieves that is the *Brier score*

6.6 Prediction Error (cont'd)

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

- The expected quadratic error of prediction (Brier score) has the form

$$\text{PE}(t + \Delta t \mid t) = E\big[\{N_i(t + \Delta t) - \pi_i(t + \Delta t \mid t)\}^2\big]$$

  where

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

6.6 Prediction Error (cont'd)

- An estimator for $\text{PE}(t + \Delta t \mid t)$ that *accounts for censoring*

$$\widehat{\text{PE}}(t + \Delta t \mid t) = \{\mathcal{R}(t)\}^{-1} \sum_{i:T_i \geq t} I(T_i > u)\{1 - \hat{\pi}_i(t + \Delta t \mid t)\}^2$$

$$+ \delta_i I(T_i < t + \Delta t)\{0 - \hat{\pi}_i(t + \Delta t \mid t)\}^2$$

$$+ (1 - \delta_i) I(T_i < t + \Delta t) \Big[\hat{\pi}_i(t + \Delta t \mid T_i)\{1 - \hat{\pi}_i(t + \Delta t \mid t)\}^2$$

$$+ \{1 - \hat{\pi}_i(t + \Delta t \mid T_i)\}\{0 - \hat{\pi}_i(t + \Delta t \mid t)\}^2\Big]$$

6.6 Prediction Error (cont'd)

where

- ▷ $\mathcal{R}(t)$ denotes the number of subjects at risk at t
- ▷ **red part**: subjects still event-free at $t + \Delta t$
- ▷ **blue part**: subjects who had the event before $t + \Delta t$
- ▷ **green part**: subject censored before $t + \Delta t$

- The weights used to account for censoring are model-based
  - ▷ censoring is allowed to depend on the longitudinal history in any possible manner
  - ▷ the model needs to be well specified

6.6 Prediction Error (cont'd)

- Example: For the joint model fitted to the PBC dataset we have seen earlier
  - ▷ we estimate the dynamic Brier score
  - ▷ at follow-up times $t = 3, 5,$ and 7
  - ▷ for $\Delta t = 2$

6.6 Prediction Error (cont'd)

- The estimated Brier scores are

Time	Brier Score
$t = 3$	0.10
$t = 5$	0.11
$t = 7$	0.12

6.6 Prediction Error (cont'd)

R> For a fitted joint model, we calculate the time-varying Brier score with the syntax

```
predErr <- tvBrier(jointFit, newdata = pbc2, Tstart = 5, Dt = 2)

predErr
```

6.7 Validation

To obtain an objective assessment of the model's predictive capability,
we need to validate the predictive accuracy measures

6.7 Validation (cont'd)

- *Internal* validation of the predictive accuracy measures can be achieved with standard re-sampling techniques
  - ▷ cross-validation (leave-one-out or better 10-fold)
  - ▷ Bootstrap

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

6.7 Validation (cont'd)

- For *external* validation we calculate the predictive accuracy measures in a dataset from another cohort
  - ▷ perhaps after re-calibration

6.7 Validation (cont'd)

R> Functions `tvROC()`, `tvAUC()`, `calibration_plot()` and `tvBrier()` facilitate this via their `newdata` argument

- ▷ in `newdata` you can provide a dataset other than the one used to fit the model

Part VII

Closing

7.1 Concluding Remarks

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

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

7.1 Concluding Remarks (cont'd)

- **Where to pay attention when defining joint models?**
  - ▷ model flexibly the subject-specific evolutions for the longitudinal outcome
  - ▷ consider how to model the association structure between the two processes
    $\Rightarrow$ Functional Forms

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

7.1 Concluding Remarks (cont'd)

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

The End!

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Part VIII

Practicals

8.1 Practical 1: A Simple Joint Model

- We will fit a simple joint model to the PBC dataset
- Start R and load package **JMbayes2**, using `library("JMbayes2")`
- The longitudinal (long format) and survival information for the PBC patients can be found in data frames `pbc2` and `pbc2.id`
  - ▷ the variables that we will need are:

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

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

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

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

- T1: Fit the linear mixed effects model for log serum bilirubin using function `lme()`, assuming simple linear evolutions over time for each subject, i.e., a simple random-intercepts and random-slopes structure and different average evolutions per treatment group (see pp. 24–??)

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

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

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

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

- T3: Fit the Cox PH model using `coxph()` that includes only treatment as baseline covariate (see pp. 48–49)

- We want to fit the joint model

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

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

- T4: Fit this joint model based on the fitted linear mixed and Cox models using function `jm()` (see pp. 79–81)

- T5: Use the `summary()` method to obtain a detailed output of the fitted joint model – interpret the results
  - ▷ extract the `Survival` component from the result of `summary()` to calculate hazard ratios, i.e.,
  - ▷ `exp(summary(fitted_model)$Survival[c(1,3,4)])`

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

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

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

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

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

- To fit this model we need to define the `functional_forms` argument of `jm()`.
  - ▷ this argument accepts a formula with the functional form of the longitudinal outcomes, e.g.,
  - ▷ `functional_forms = ~ value(log(serBilir)) * drug`

- T6: Define this argument and fit the corresponding joint model. Use the `summary()` method to obtained a detailed output and interpret the results

- T7: Use `compare_jm()` to compare the fitted models

8.2 Practical 2: Functional Forms

- Start R and load package **JMbayes2**, using `library("JMbayes2")`

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

8.2 Practical 2: Functional Forms (cont'd)

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

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ m_i(t) &= (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})N(t)_1 + (\beta_2 + b_{i2})N(t)_2 + (\beta_3 + b_{i3})N(t)_3 \end{aligned}$$

where $N(t)_k$ denote the basis for a natural spline with three degrees of freedom

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

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

8.2 Practical 2: Functional Forms (cont'd)

- T1: Fit the linear mixed effects model for log serum bilirubin using function `lme()`
  (see pp. 24–??)

  ▷ to define the natural cubic splines use function `ns()`

  ▷ set d.f. to 3 and the boundary knots to the range of event times, i.e.,
  `ns(year, 3, B = c(0, 14.4))`

  ▷ use the splines in both the fixed- and random-effects parts

  ▷ use `optim()` for the optimization, i.e.,
  `lme(..., control = lmeControl(opt = "optim"))`

8.2 Practical 2: Functional Forms (cont'd)

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

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

- T3: Fit the null Cox PH model using `coxph()` that does not include any covariates (see pp. 48–49)

- T4: Fit the corresponding joint model based on the fitted linear mixed and Cox models using function `jm()` (see pp. 79–81)

8.2 Practical 2: Functional Forms (cont'd)

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

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

- Because $m_i(t)$ contains splines, the calculation of $m_i'(t)$ is done using numerical derivatives

8.2 Practical 2: Functional Forms (cont'd)

- T5: Fit the corresponding joint model using the `functional_forms` argument

  ▷ the term `value(log(serBilir))` includes the current value

  ▷ the term `slope(log(serBilir))` includes the current slope

  ▷ increase the number of MCMC iterations to 8500 and the burn-in to 3500

  ▷ use `summary()` and interpret the results

```
jm(..., n_iter = 8500L, n_burnin = 3500L,
   functional_forms = ~ value(log(serBilir)) + slope(log(serBilir))
```

8.2 Practical 2: Functional Forms (cont'd)

- T6: Instead of the current slope, include how much log serum bilirubin changed the last year of follow-up
  - ▷ use `slope(log(serBilir), direction = "back", eps = 1)` in the `functional_forms` argument
  - ▷ use `summary()` to interpret the results

- T7: Fit the joint model with the Cumulative Effects 2 functional form
  - ▷ use the `area()` function in the `functional_forms` argument
  - ▷ use `summary()` to interpret the results

8.3 Practical 3: Dynamic Predictions

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

- Start R and load package **JMbayes2**, using `library("JMbayes2")`

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

8.3 Practical 3: Dynamic Predictions (cont'd)

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

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

8.3 Practical 3: Dynamic Predictions (cont'd)

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

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

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

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

8.3 Practical 3: Dynamic Predictions (cont'd)

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

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

- T2: Extract the data of Patient 155 using the code and drop the survival information

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

8.3 Practical 3: Dynamic Predictions (cont'd)

- T3: Using the first measurement of Patient 155, and the fitted joint model calculate his conditional survival probabilities using function `predict()` and plot it using the `plot` method (see p. 163)

- T4: Similarly, produce predictions for future longitudinal responses of Patient 155 using the `predict()` (see p. 170)

- T5: Combine the predictions in one plot
  - ▷ say `Spred` are the survival predictions, and `Lpred` the longitudinal ones
  - ▷ use `plot(Lpred, Spred)`

8.3 Practical 3: Dynamic Predictions (cont'd)

- T6: Repeat the same procedure by including each time the next measurement of Patient 155 and see how his survival probabilities evolve dynamically over time as extra prothrombin measurements are recorded

  ▷ first using only the first measurement,

  ▷ and following update the predictions after each new longitudinal measurement has been recorded

  ▷ use a `for` loop to achieve this

8.3 Practical 3: Dynamic Predictions (cont'd)

- T7: Calculate the ROC and the corresponding AUC under the postulated model at year 3 and with a 1-year window (see p. 191)

- T8: Do the calibration plot for the same period (see p. 198)

- T9: Calculate the prediction error for the same period (see p. 205)