Dynamic Risk Predictions from Joint Models with Applications in R

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ASA Risk Analysis Section

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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 Webinar 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 Webinar About (cont'd)

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

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

Learning Objectives

- After this webinar the participants will
  - ▷ be familiarized with joint modeling framework,
  - ▷ know how predictions are derived from joint models
  - ▷ know how to evaluate the accuracy of these predictions, and
  - ▷ be able to fit joint models in R and derive predictions

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. 106–113.

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:
  - ▷ https://jmr.r-forge.r-project.org [R code used in the book]
  - ▷ https://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)

Agenda

- **Part I:** 10:00 – 10:55
  - ▷ introduction to the JM framework
  - ▷ how to fit in R
  - ▷ functional forms

- **Part II:** 11:00 – 11:55
  - ▷ dynamic predictions
  - ▷ predictive accuracy measures

- **Part III:** 12:00 – 13:00
  - ▷ practical in R

Part I

Introduction

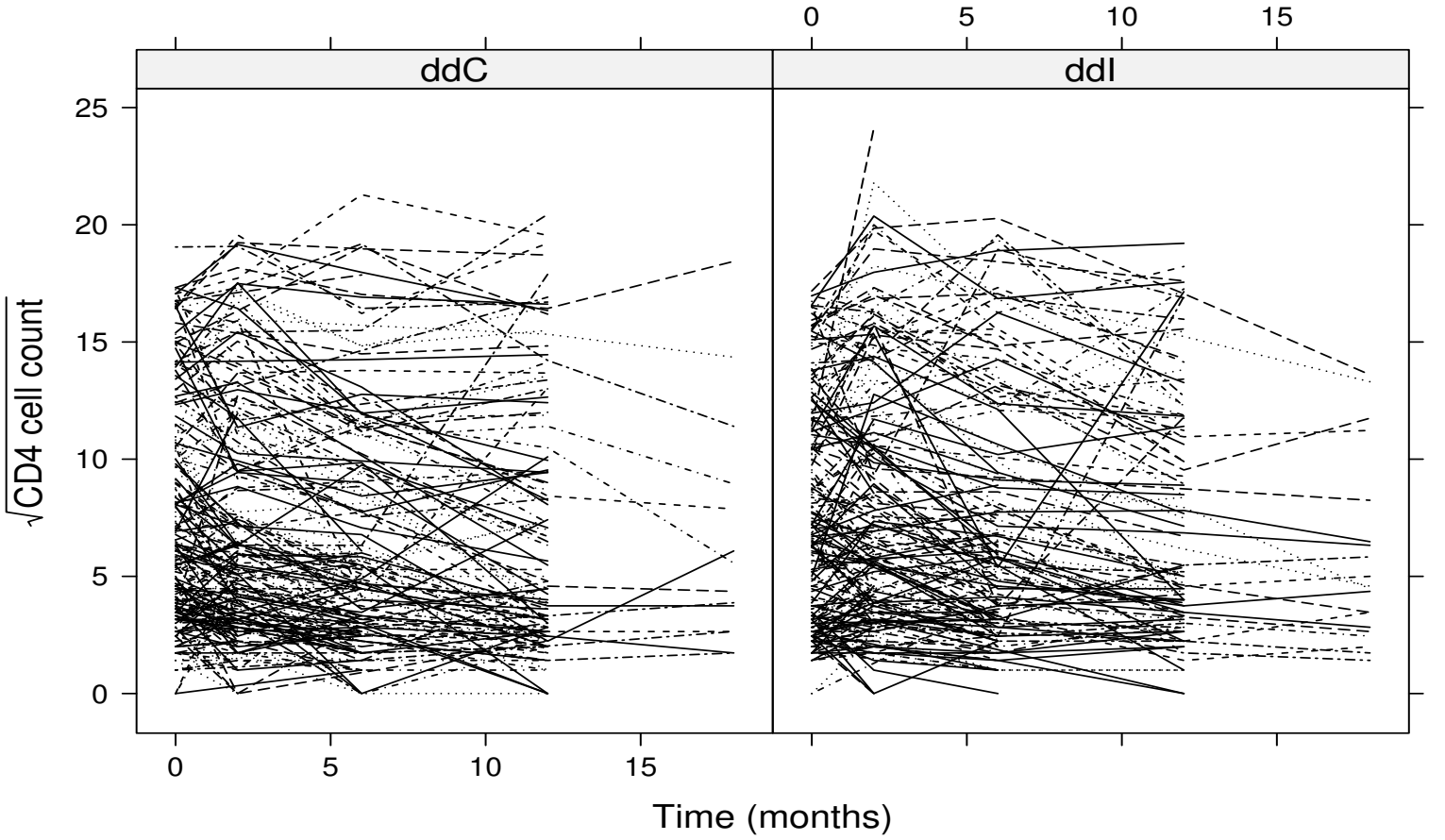
1.1 Motivating Longitudinal Studies

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

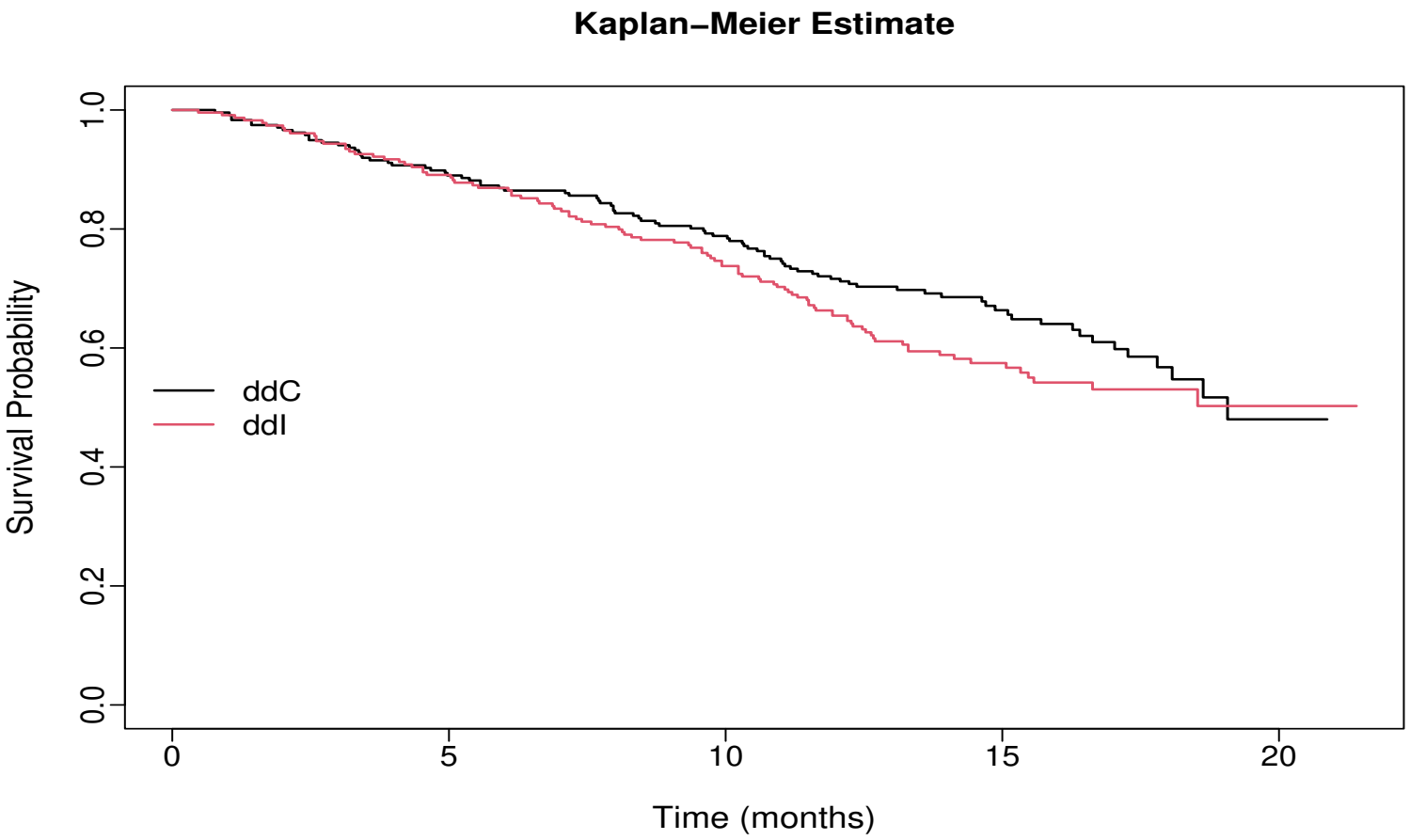
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)

- 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

1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)



1.1 Motivating Longitudinal Studies (cont'd)

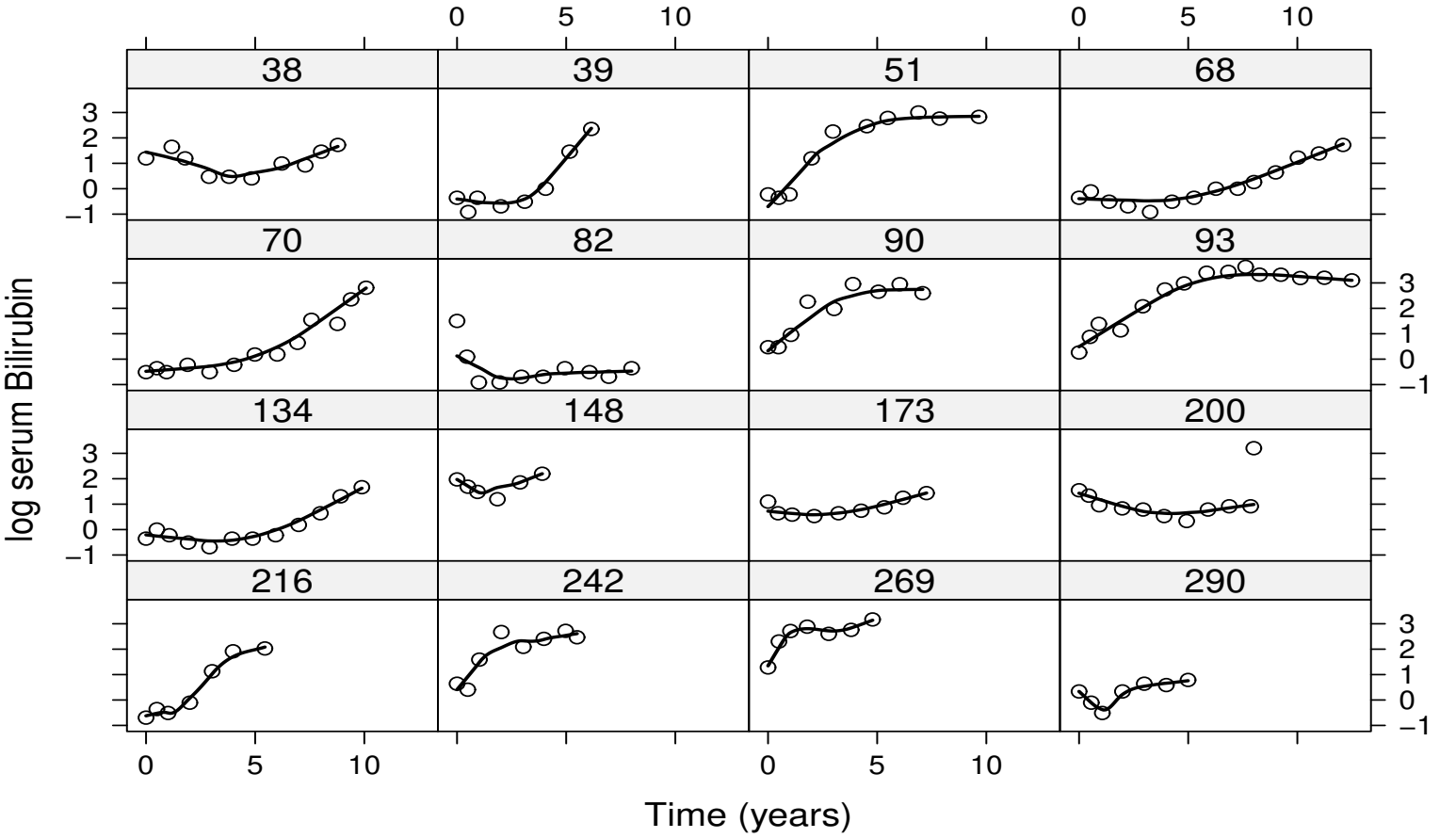
- Research Questions:
  - ▷ How strong is the association between CD4 cell count and the risk of death?
  - ▷ Is CD4 cell count a good biomarker?
    - * if treatment improves CD4 cell count, does it also improve survival?

1.1 Motivating Longitudinal Studies (cont'd)

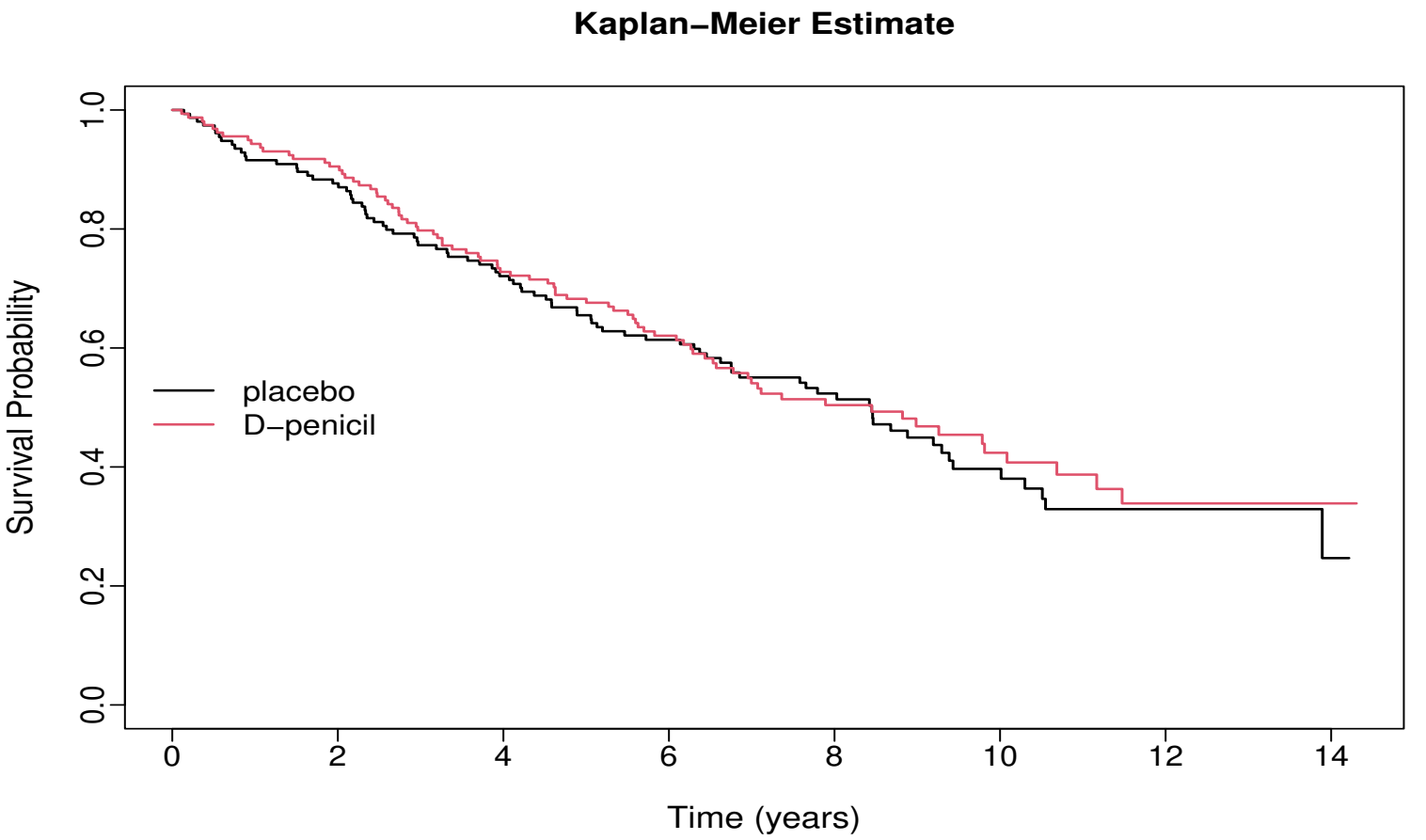
- PBC: Primary Biliary Cirrhosis:
  - ▷ a chronic, fatal but rare liver disease
  - ▷ characterized by inflammatory destruction of the small bile ducts within the liver

- 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?
    - * *endogenous* vs. exogenous time-varying covariates
  - ▷ **Handling implicit outcomes:** focus on longitudinal outcomes but with dropout or random visit times
    - * *missing not at random* vs. missing at random

Part II

The Basic Joint Model

2.1 Joint Modeling Framework

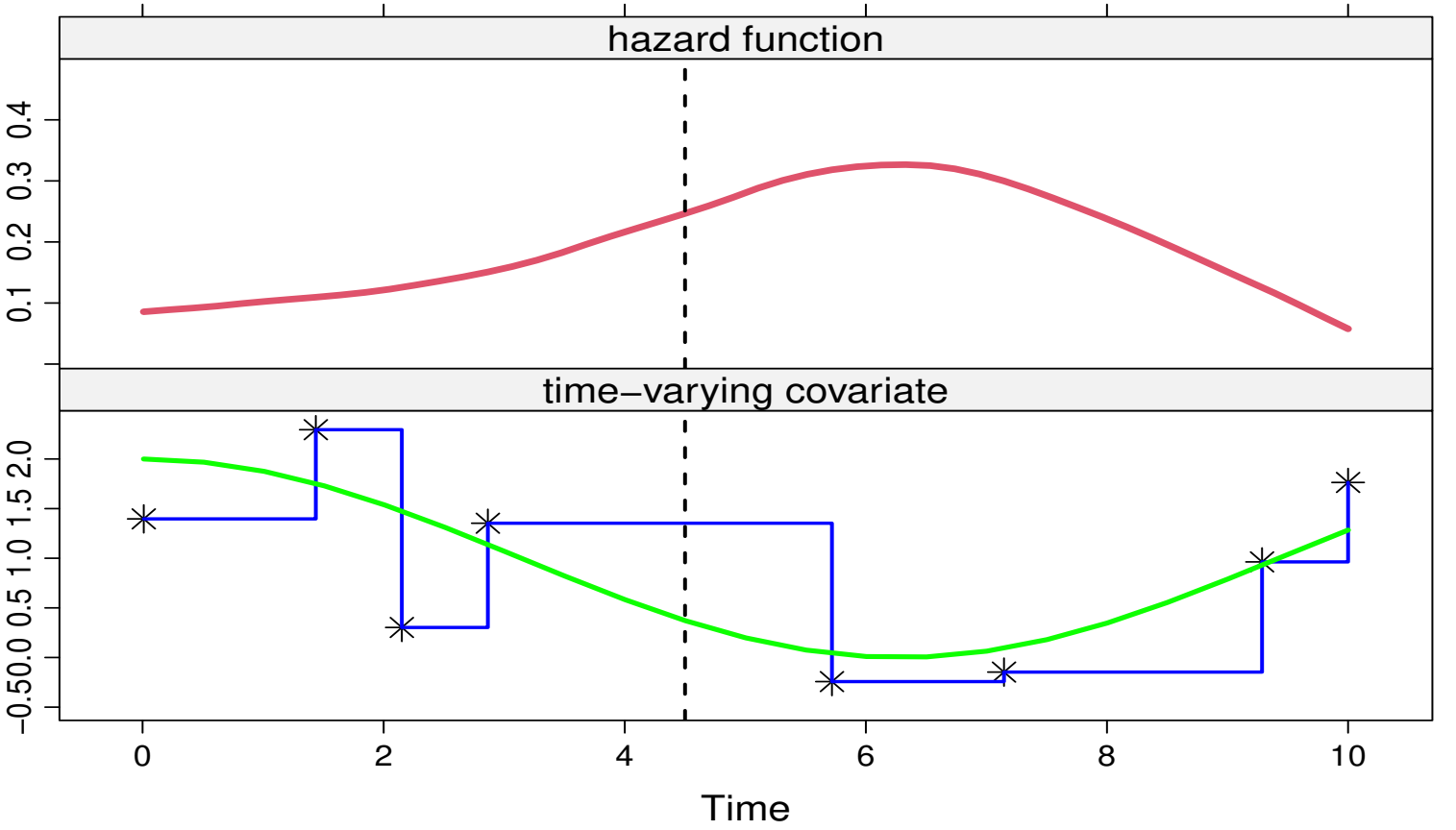
- To account for the special features of endogenous covariates a new class of models has been developed

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

2.1 Joint Modeling Framework (cont'd)



2.1 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, ...

2.1 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

2.1 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, $b_i \sim \mathcal{N}(0, D)$

2.1 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

2.1 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

2.1 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.

2.1 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

2.1 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 $\Delta_r^\top \Delta_r$

2.2 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

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

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

2.2 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)

2.3 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

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

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

	JM	Cox
	log HR (std.err)	log HR (std.err)
Treat	0.33 (0.2)	0.31 (0.15)
$CD4^{1/2}$	−0.29 (0.04)	−0.19 (0.02)

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

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

- A unit decrease in $CD4^{1/2}$, results in a
  - ▷ **Joint Model**: 1.33-fold increase in risk (95% CI: 1.24; 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

2.4 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)
```

2.4 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

2.4 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

Part III

Functional Forms

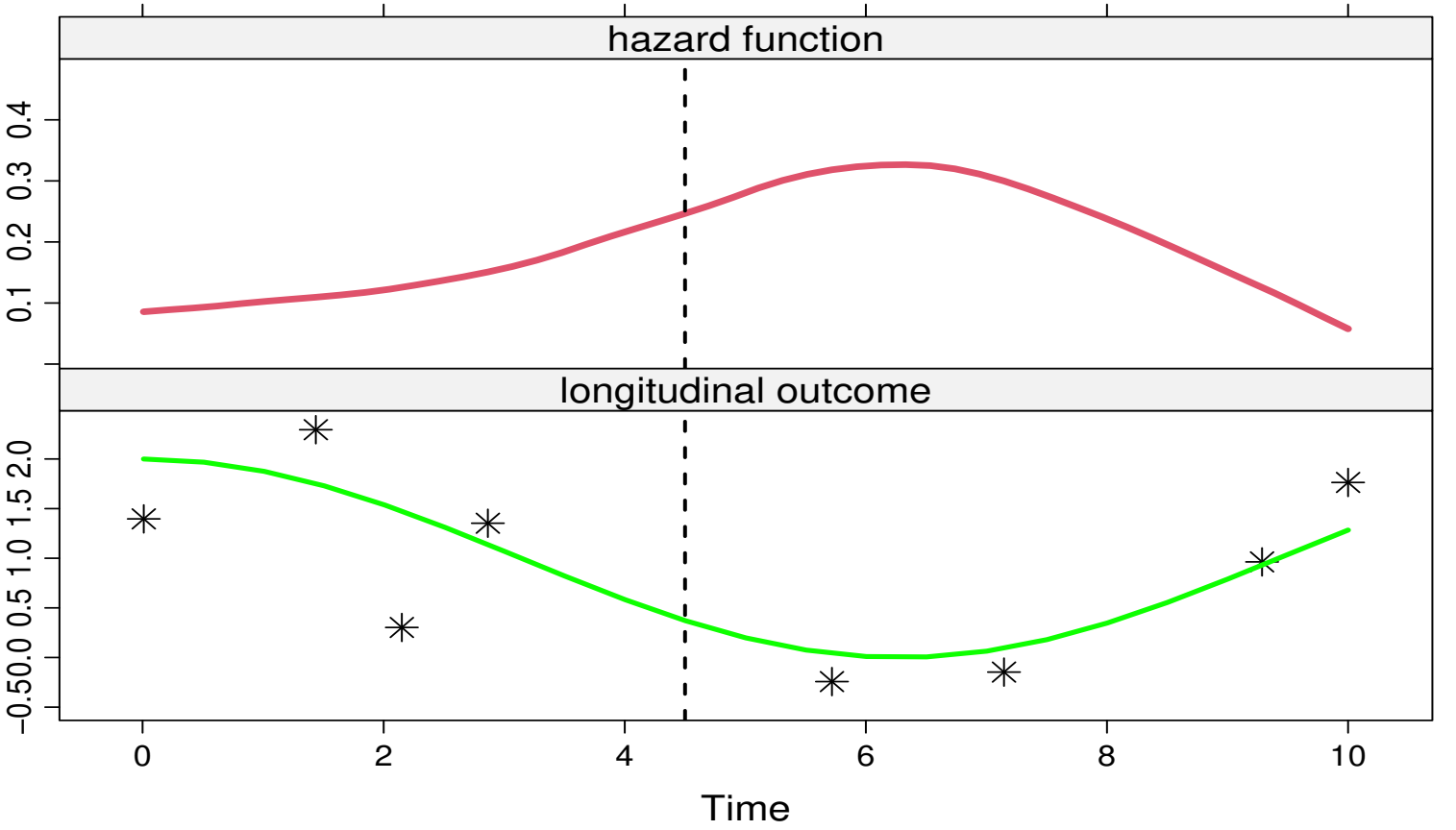
3.1 Functional Forms

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

3.1 Functional Forms (cont'd)



3.1 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?

3.1 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

3.1 Functional Forms (cont'd)

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

- Let's see some possibilities...

3.1 Functional Forms (cont'd)

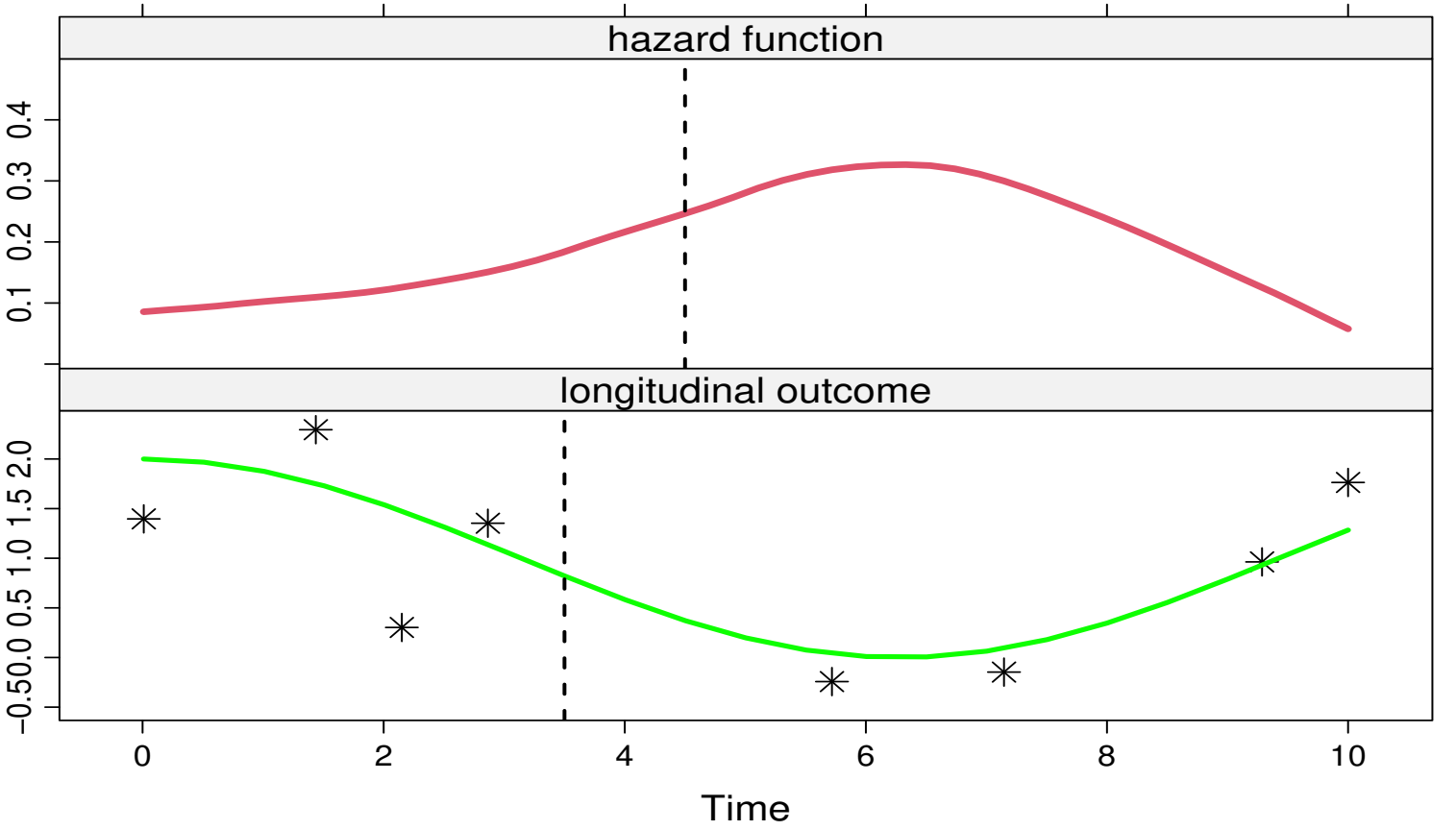
- *Lagged Effects:* The hazard of an event at t is associated with the level of the marker at a previous time point:

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

where

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

3.1 Functional Forms (cont'd)



3.1 Functional Forms (cont'd)

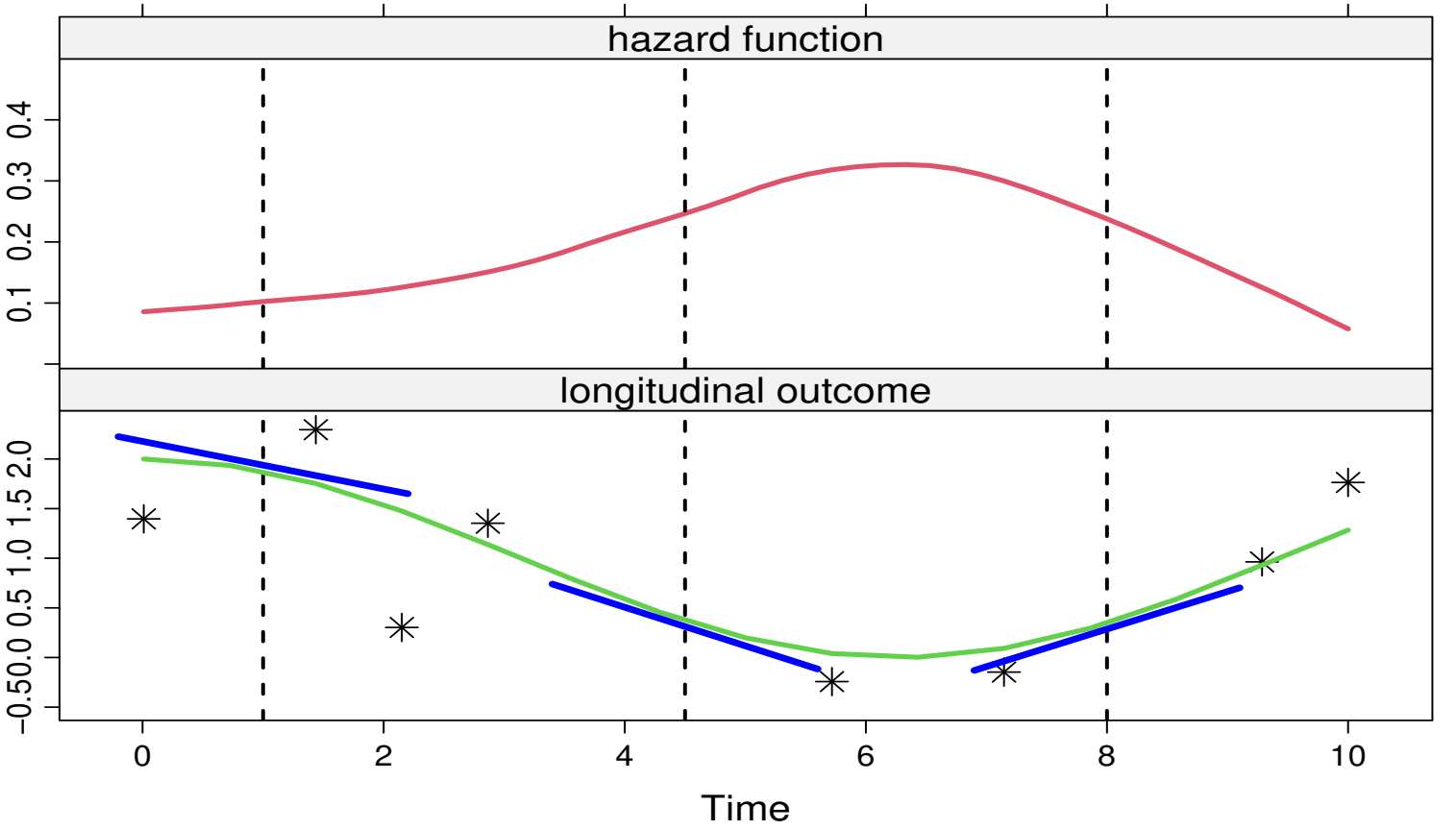
- *Time-dependent Slopes:* The hazard of an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

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

where

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

3.1 Functional Forms (cont'd)



3.1 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

3.1 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

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

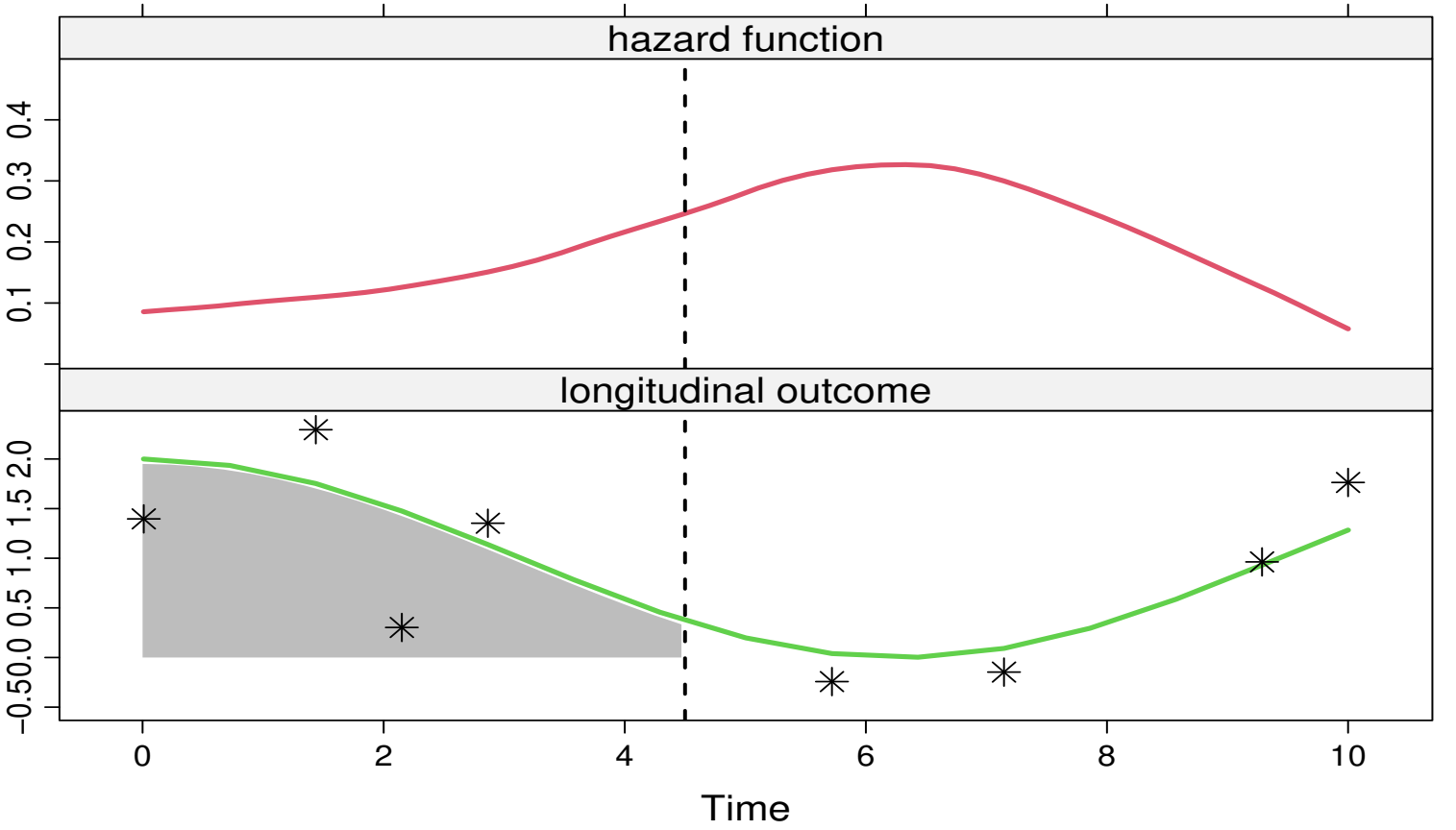
3.1 Functional Forms (cont'd)

- *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 $\mathcal{M}_i(t)$

3.1 Functional Forms (cont'd)



3.1 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

3.1 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
  - ▷ ...

3.1 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)
```

3.1 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")
```

Part IV

Dynamic Predictions

4.1 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

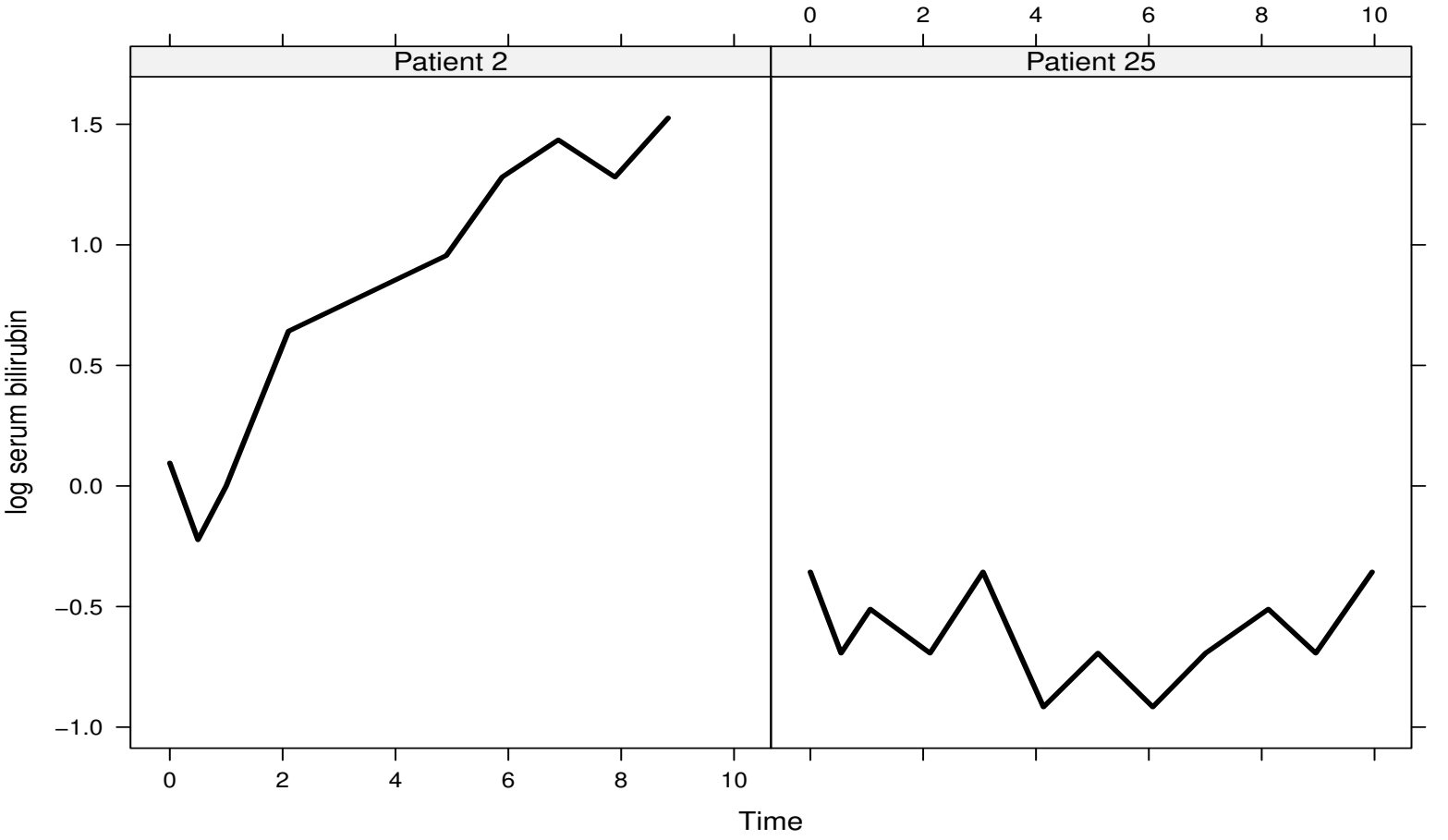
4.1 Survival Probabilities (cont'd)

- 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

4.1 Survival Probabilities (cont'd)



4.1 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

4.1 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)

4.1 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

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

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

4.1 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

4.1 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

4.1 Survival Probabilities (cont'd)

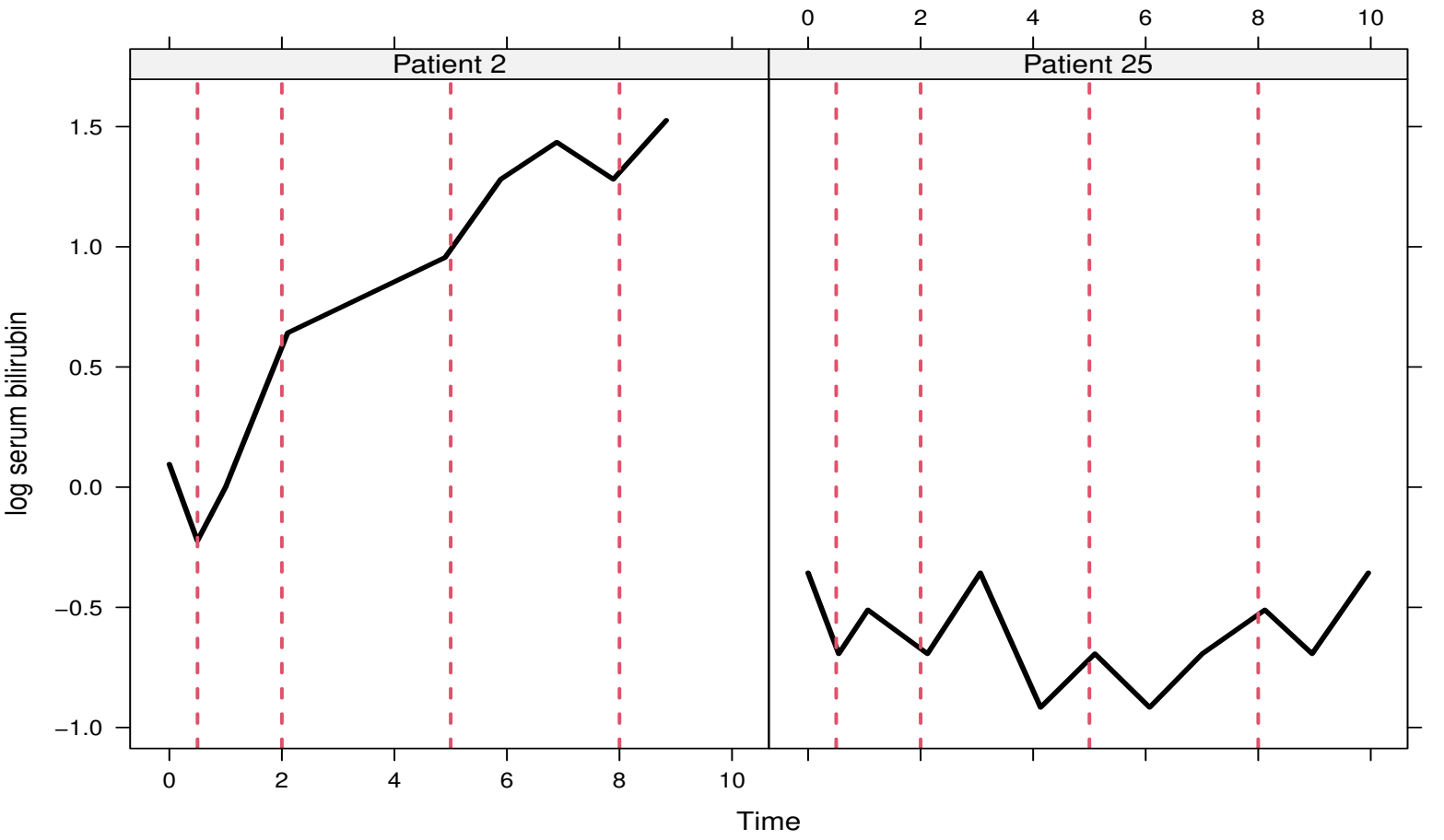
- Based on the fitted joint model we estimate $\pi_j(u \mid t)$ for Patients 2 and 25

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

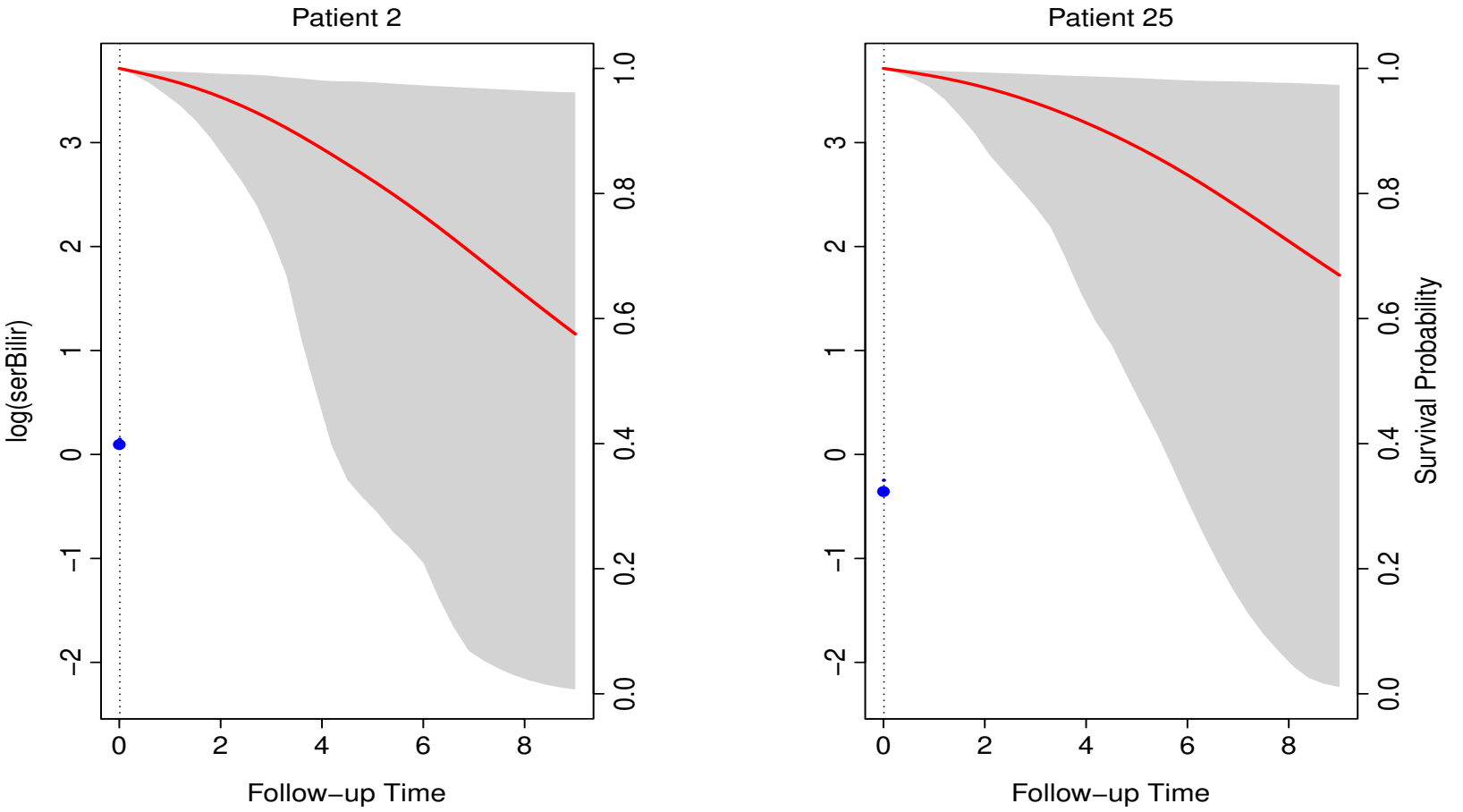
$$\hat{\pi}_j(u \mid t) = \text{mean}\{\pi_j^{(\ell)}(u \mid t), \ell = 1, \ldots, L\}$$

  and calculated a corresponding 95% pointwise CIs

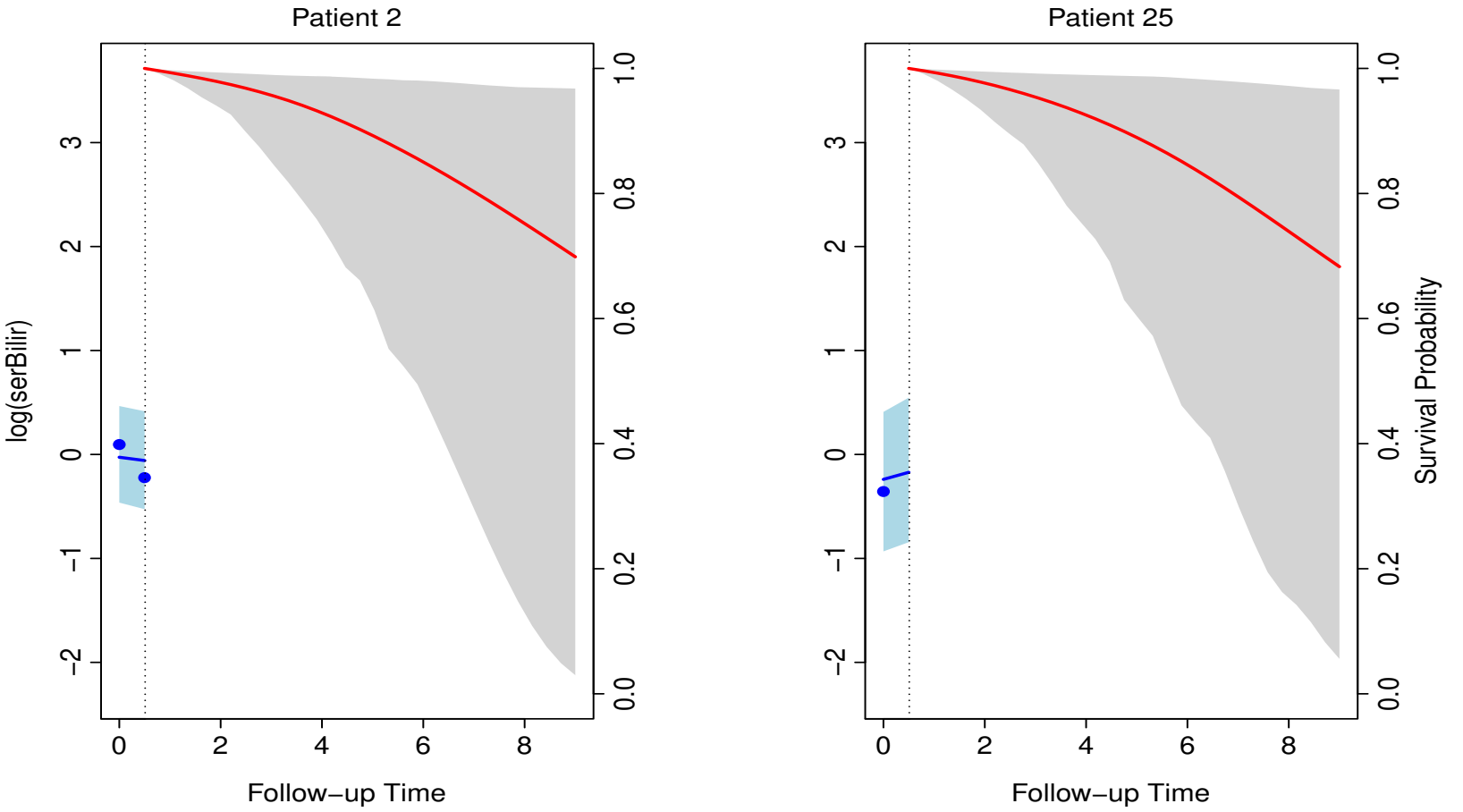
4.1 Survival Probabilities (cont'd)



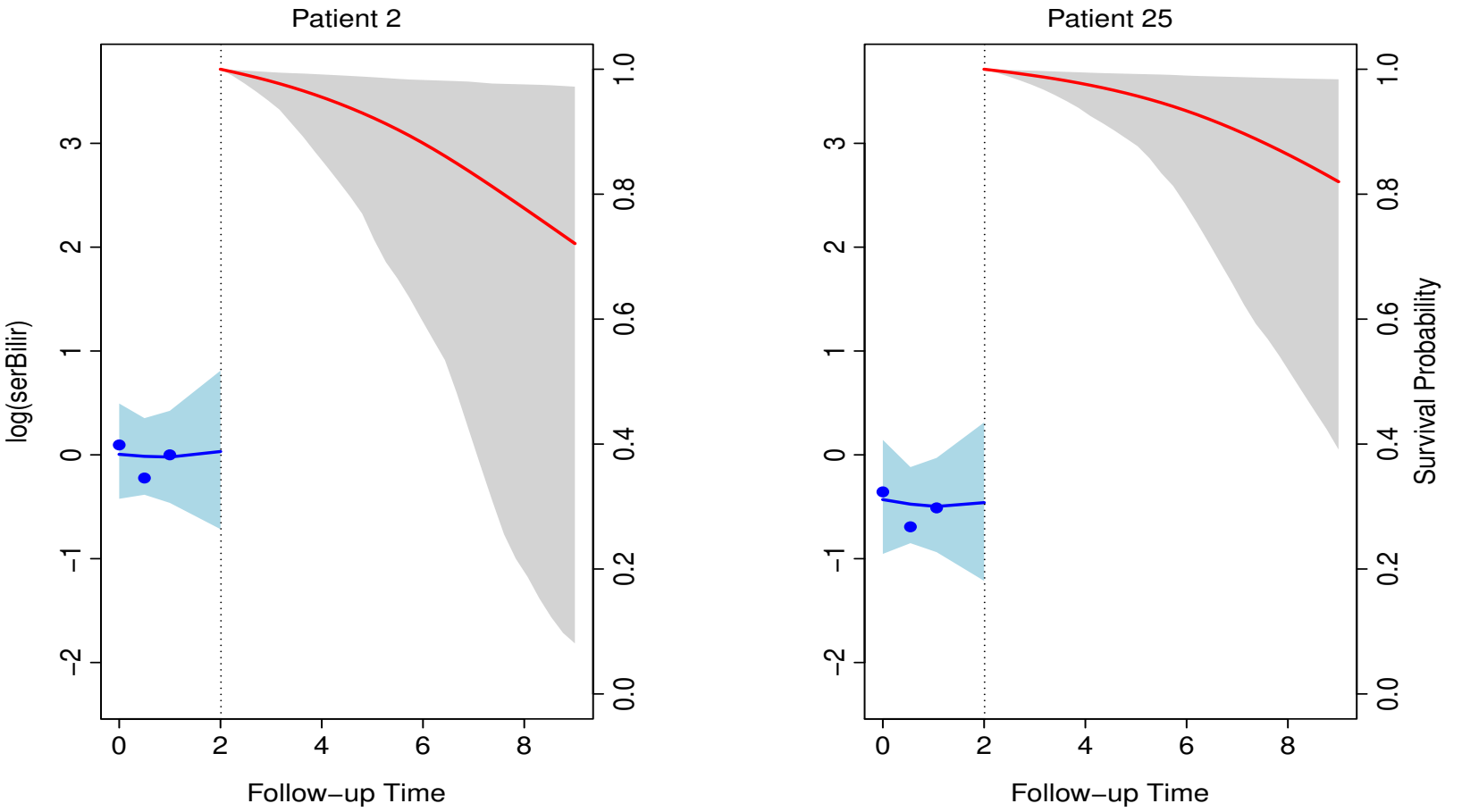
4.1 Survival Probabilities (cont'd)



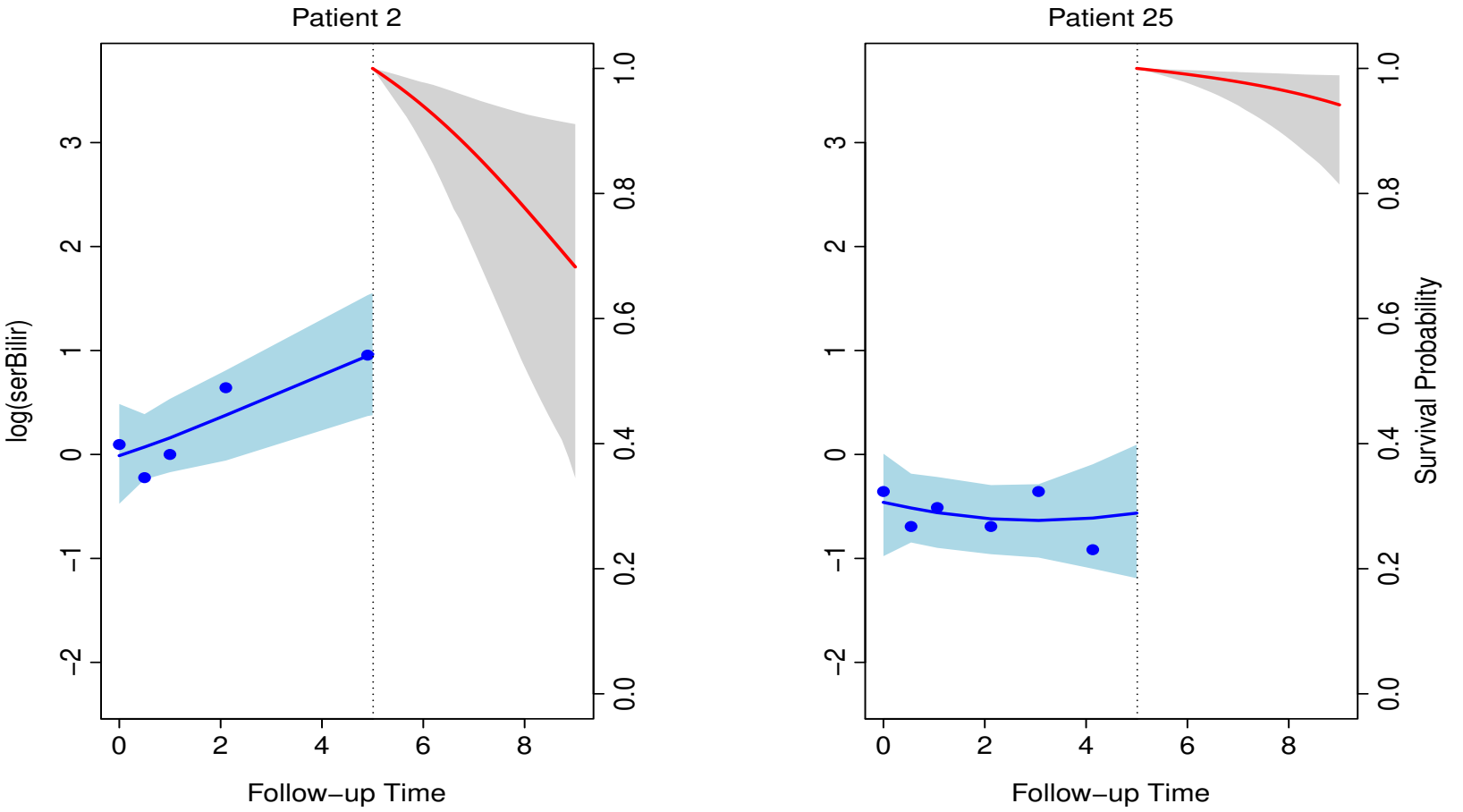
4.1 Survival Probabilities (cont'd)



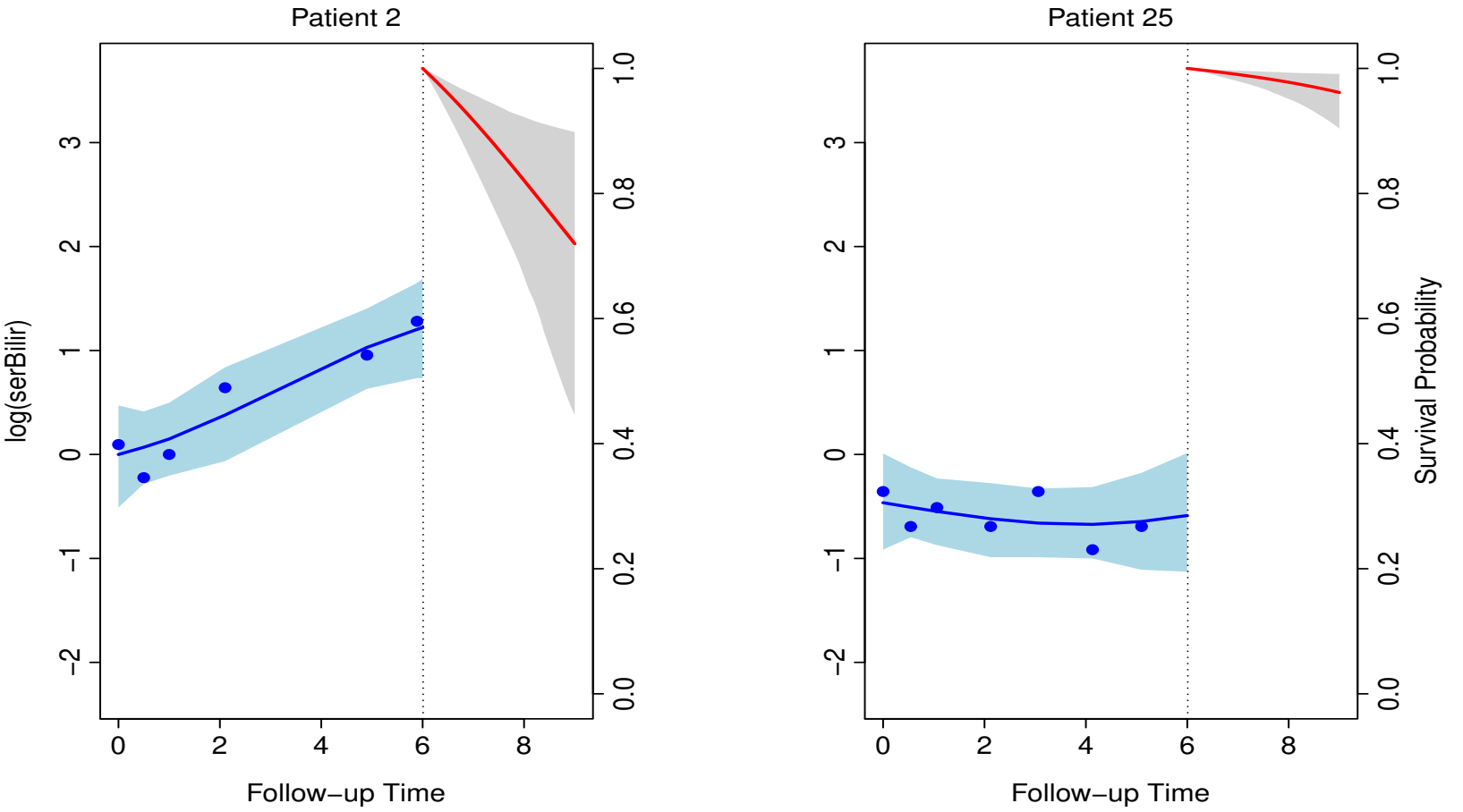
4.1 Survival Probabilities (cont'd)



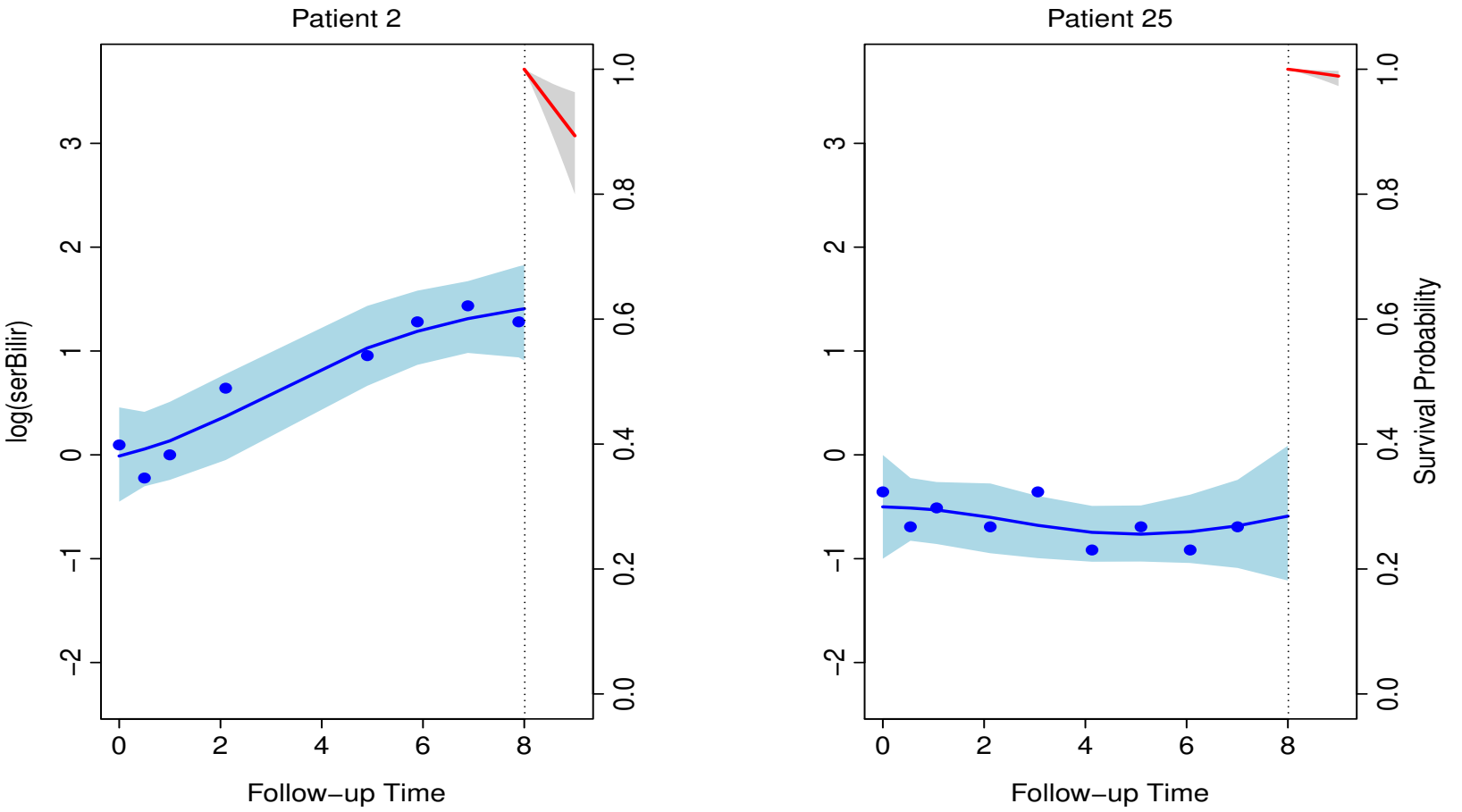
4.1 Survival Probabilities (cont'd)



4.1 Survival Probabilities (cont'd)



4.1 Survival Probabilities (cont'd)



4.1 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)
```

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

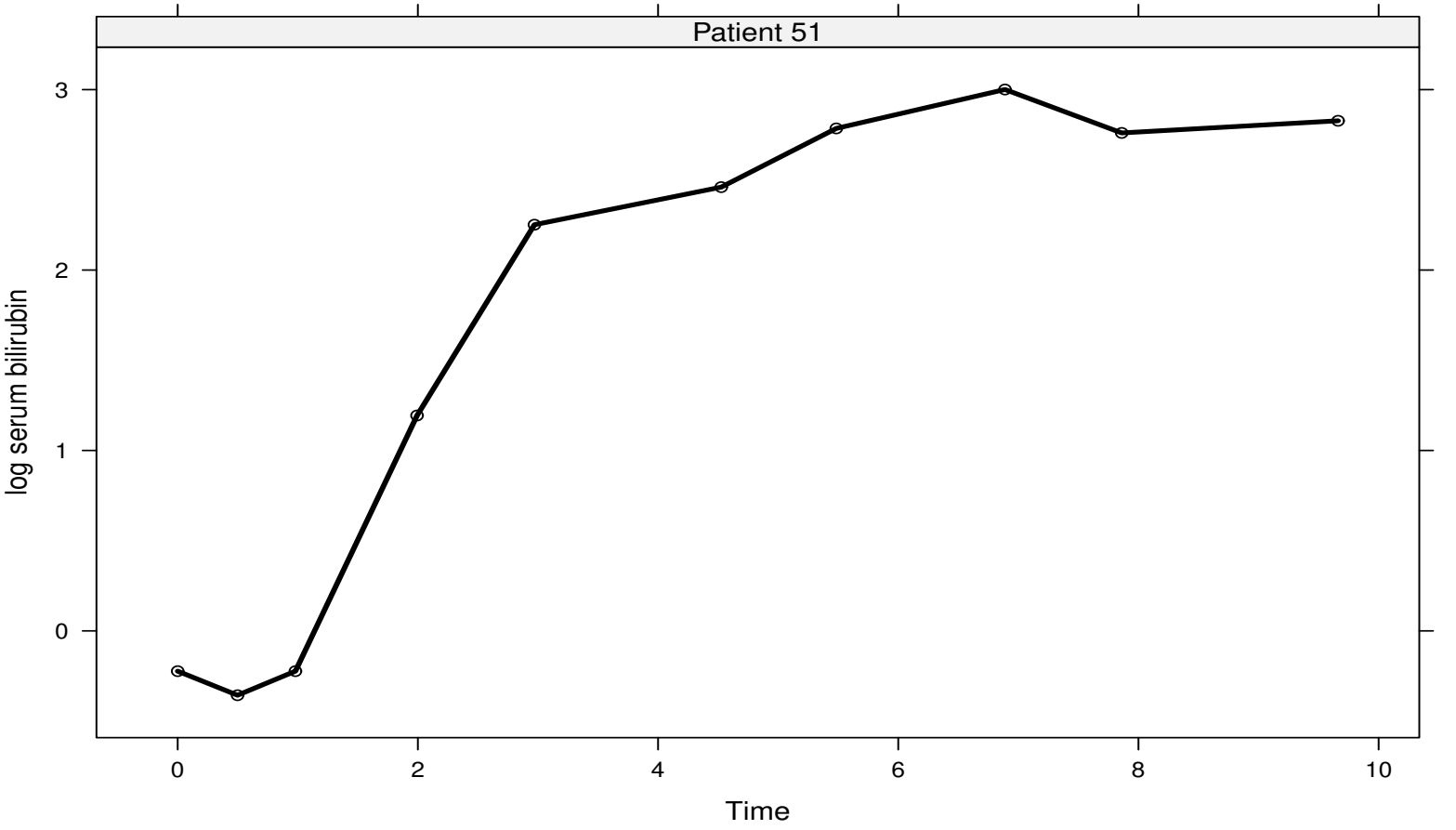
4.2 Functional Forms (cont'd)

- 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

4.2 Functional Forms (cont'd)



4.2 Functional Forms (cont'd)

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

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

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

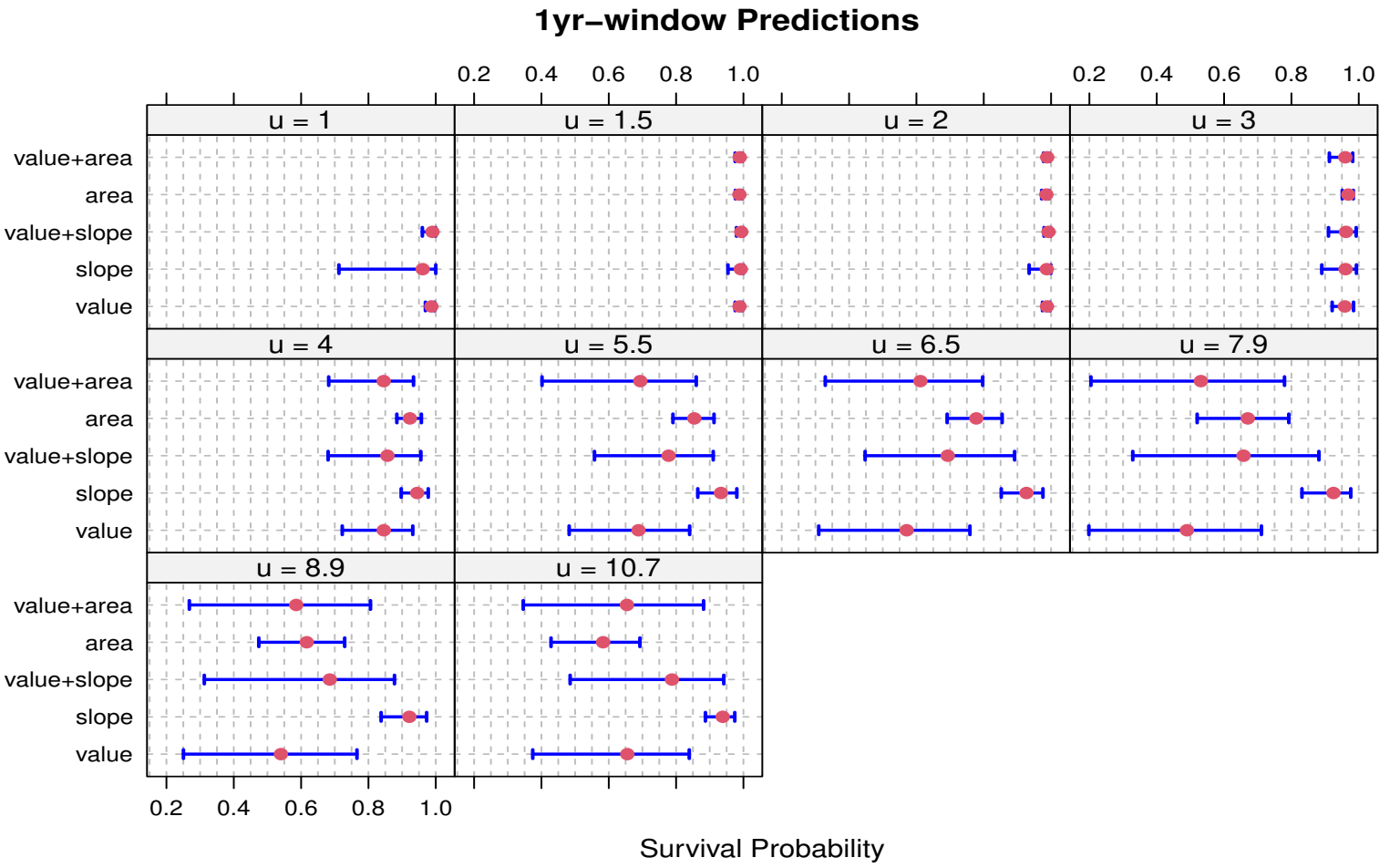
$$h_i(t) = h_0(t)\exp\{\gamma \texttt{D-pnc}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\}$$

4.2 Functional Forms (cont'd)

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

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

4.2 Functional Forms (cont'd)



4.2 Functional Forms (cont'd)

The chosen functional form can influence the derived predictions

4.2 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'

4.3 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

4.3 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

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

4.3 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

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

4.3 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)

4.3 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

4.3 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

4.3 Discrimination (cont'd)

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

4.3 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

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

4.3 Discrimination (cont'd)

- And specificity as

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

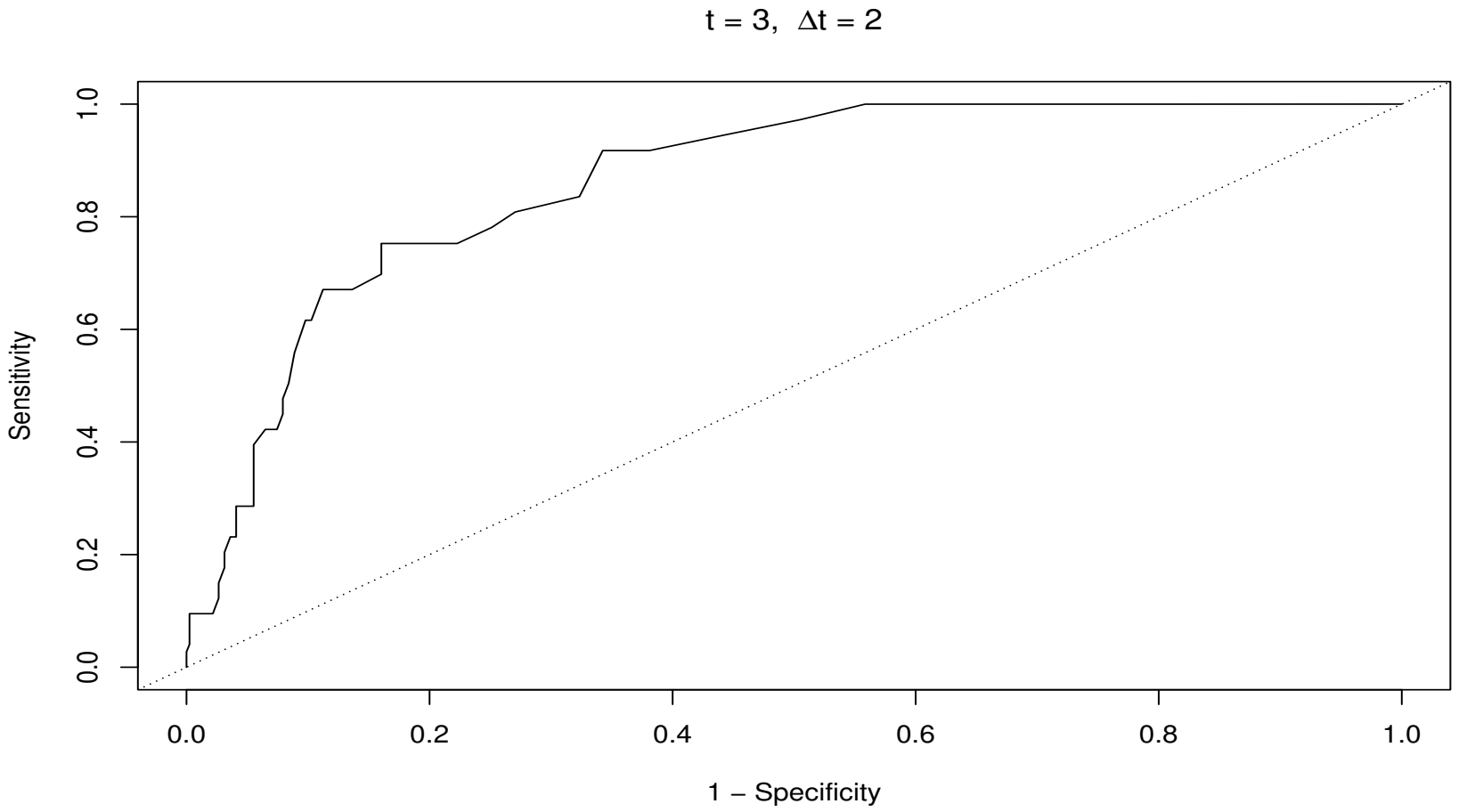
where

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

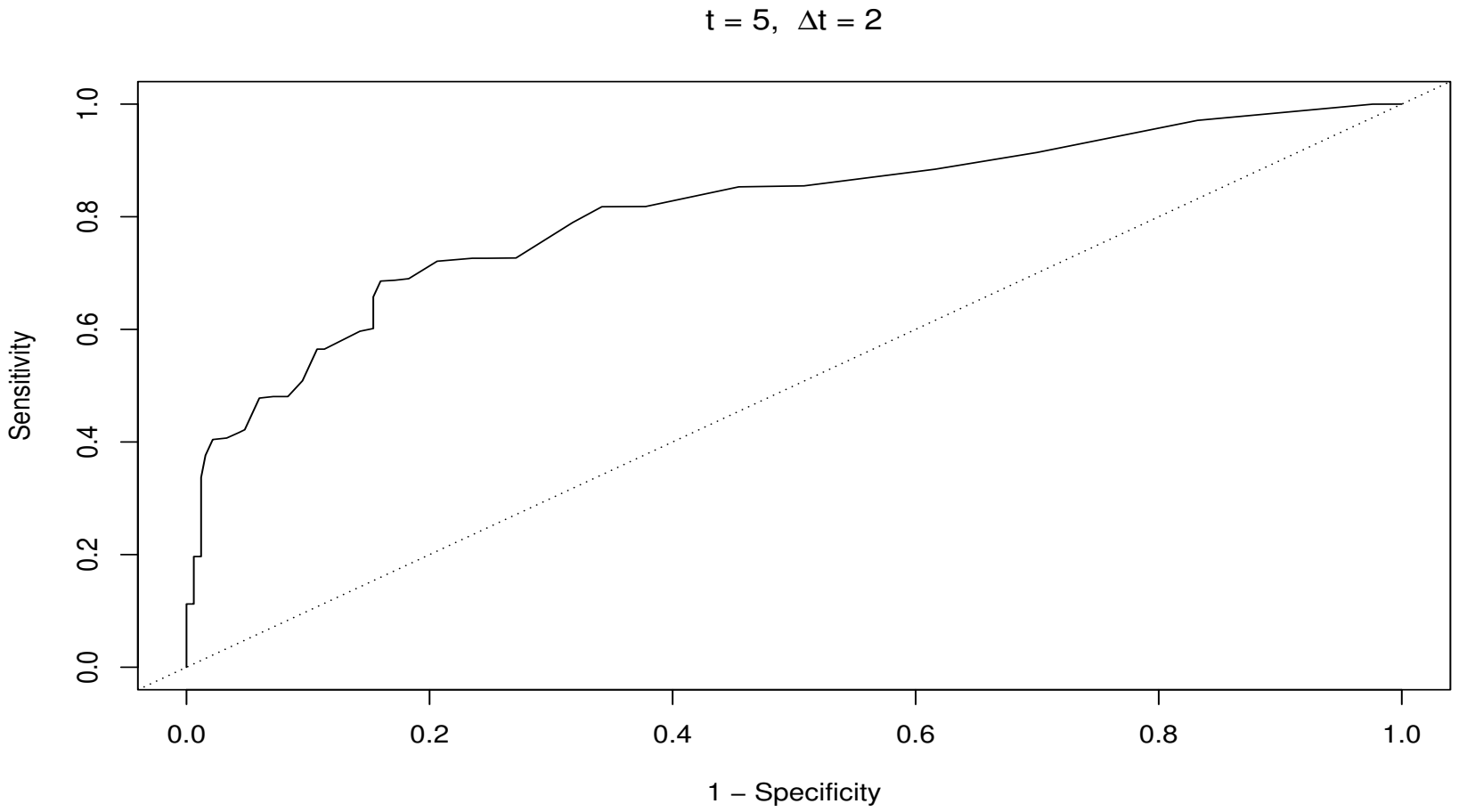
4.3 Discrimination (cont'd)

- 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 $\Delta t = 2$

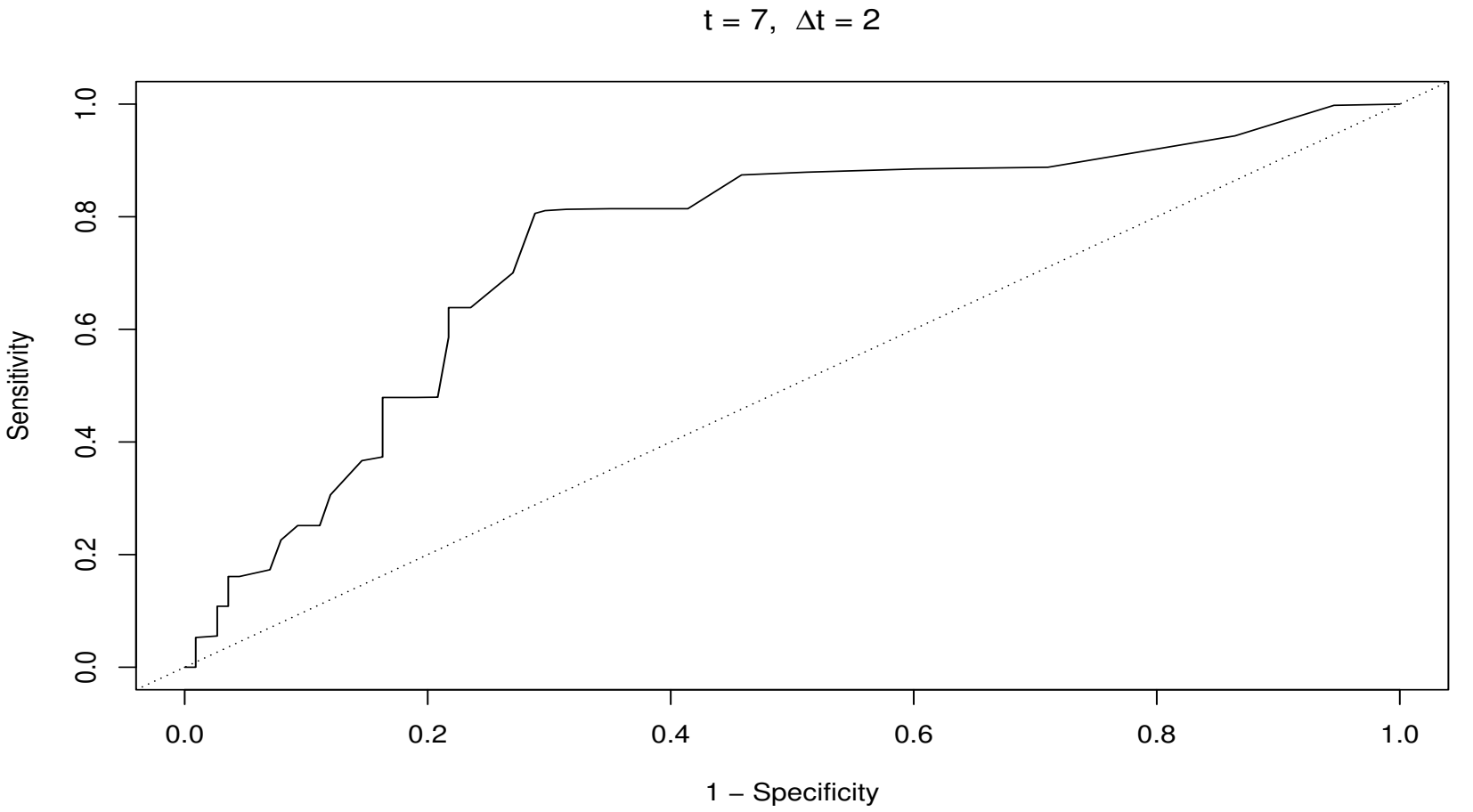
4.3 Discrimination (cont'd)



4.3 Discrimination (cont'd)



4.3 Discrimination (cont'd)



4.3 Discrimination (cont'd)

- The corresponding AUCs are

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

4.3 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)
```

4.4 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

4.4 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.,
     $\log[-\log\{\hat{\pi}_i(t + \Delta t \mid t)\}]$

4.4 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

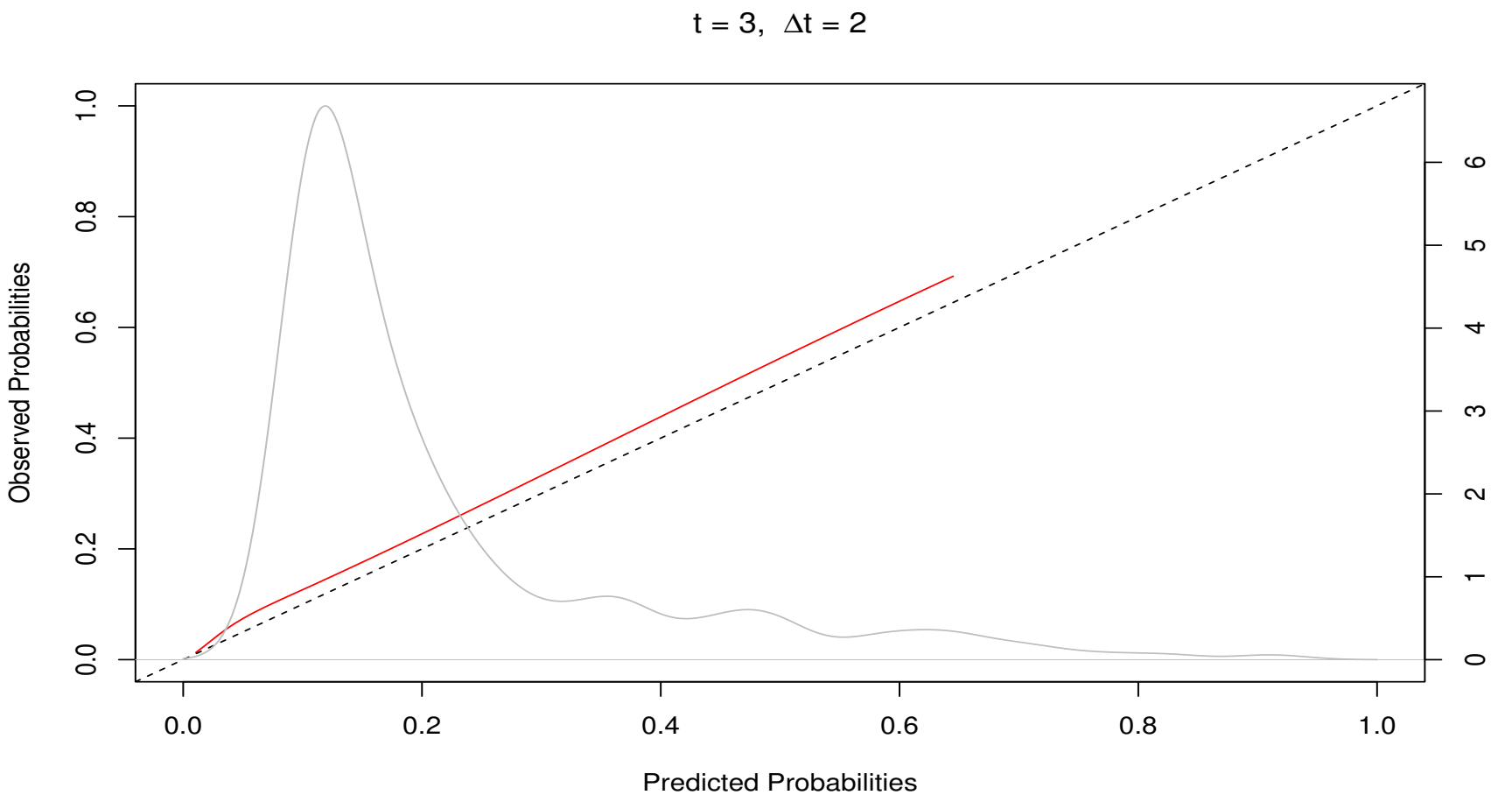
4.4 Calibration (cont'd)

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

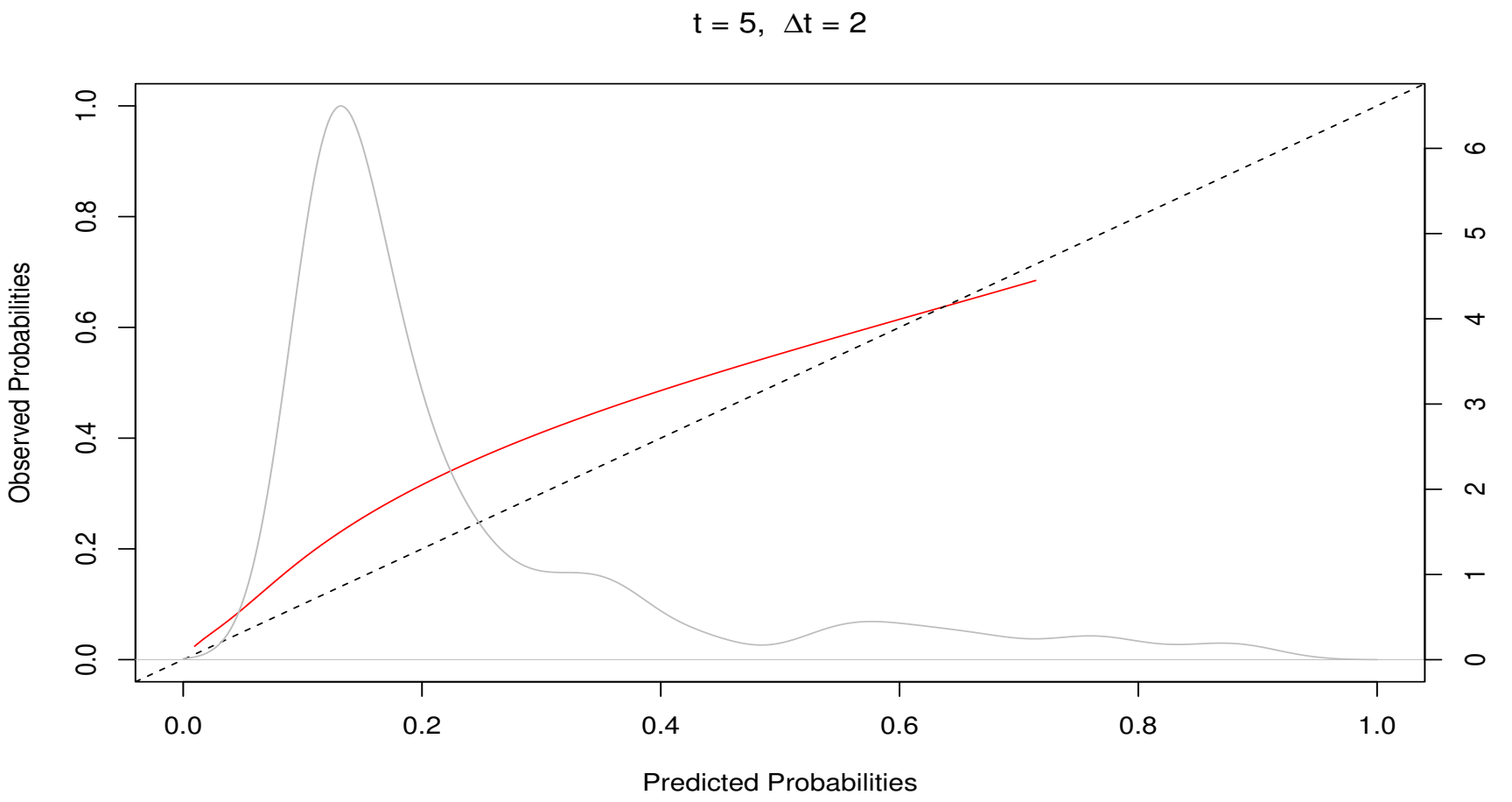
4.4 Calibration (cont'd)

- 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 $\Delta t = 2$

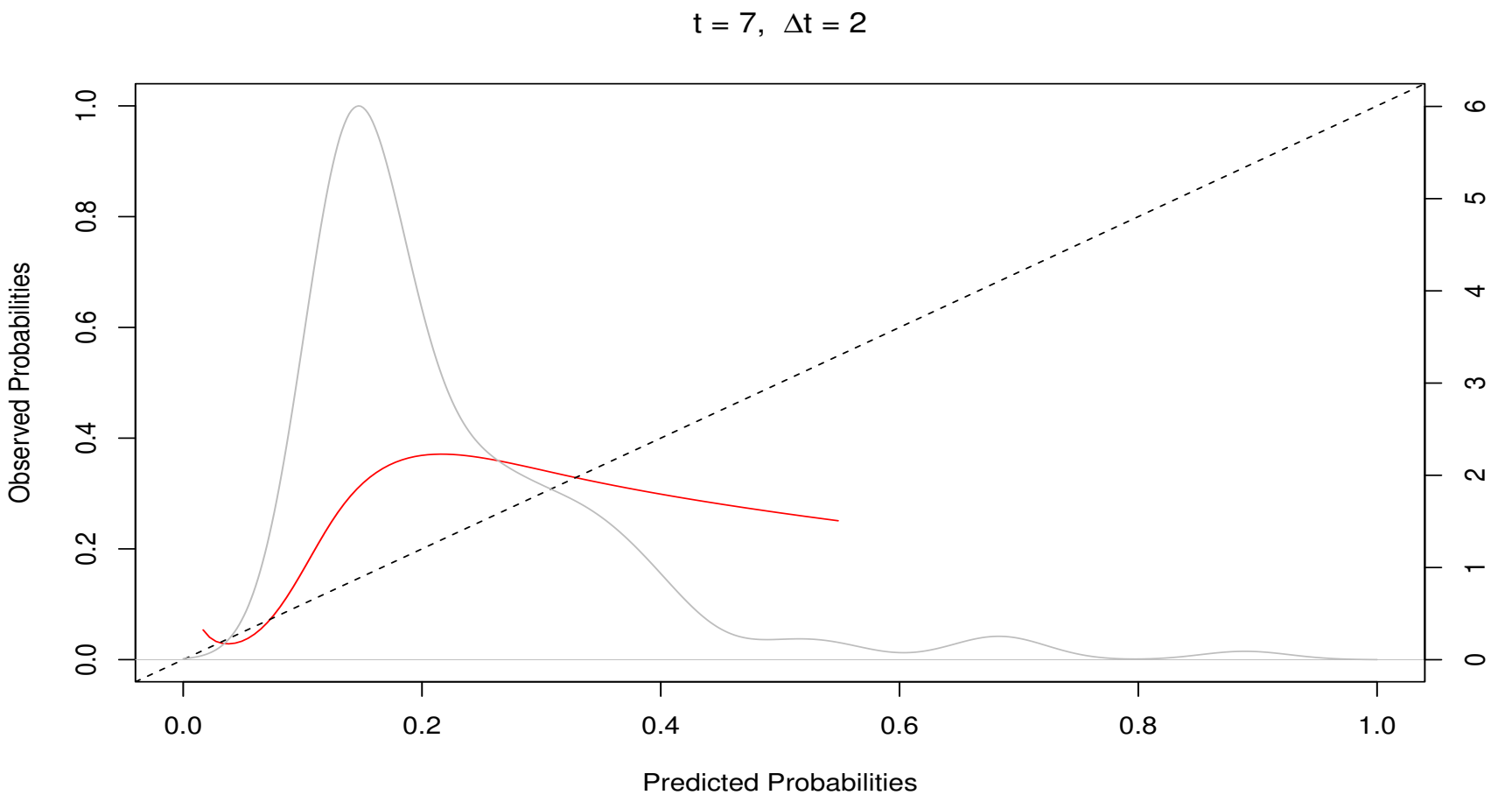
4.4 Calibration (cont'd)



4.4 Calibration (cont'd)



4.4 Calibration (cont'd)



4.4 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)
```

4.5 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*

4.5 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

4.5 Prediction Error (cont'd)

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

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

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

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

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

4.5 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

4.5 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 $\Delta t = 2$

4.5 Prediction Error (cont'd)

- The estimated Brier scores are

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

4.5 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
```

4.6 Validation

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

4.6 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**)

4.6 Validation (cont'd)

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

4.6 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 V

Closing

5.1 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

5.1 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

5.1 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 VI

Practicals

6.1 R Practical: 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:

6.1 R Practical: 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

6.1 R Practical: 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

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

6.1 R Practical: 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
```

6.1 R Practical: 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. 61)

- T4: Combine the predictions in one plot
  - ▷ say `Spred` are the survival predictions, and `Lpred` the longitudinal ones
  - ▷ use `plot(Lpred, Spred)`

6.1 R Practical: Dynamic Predictions (cont'd)

- T5: 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

6.1 R Practical: Dynamic Predictions (cont'd)

- T6: Calculate the ROC and the corresponding AUC under the postulated model at year 3 and with a 1-year window (see p. 82)

- T7: Do the calibration plot for the same period (see p. 89)

- T8: Calculate the prediction error for the same period (see p. 96)