Tutorial IV: Dynamic Predictions from Joint Models

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Joint Modeling and Beyond
Meeting and Tutorials on Joint Modeling With Survival, Longitudinal, and Missing Data
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Contents

Chapter 1

Extensions of Joint Models

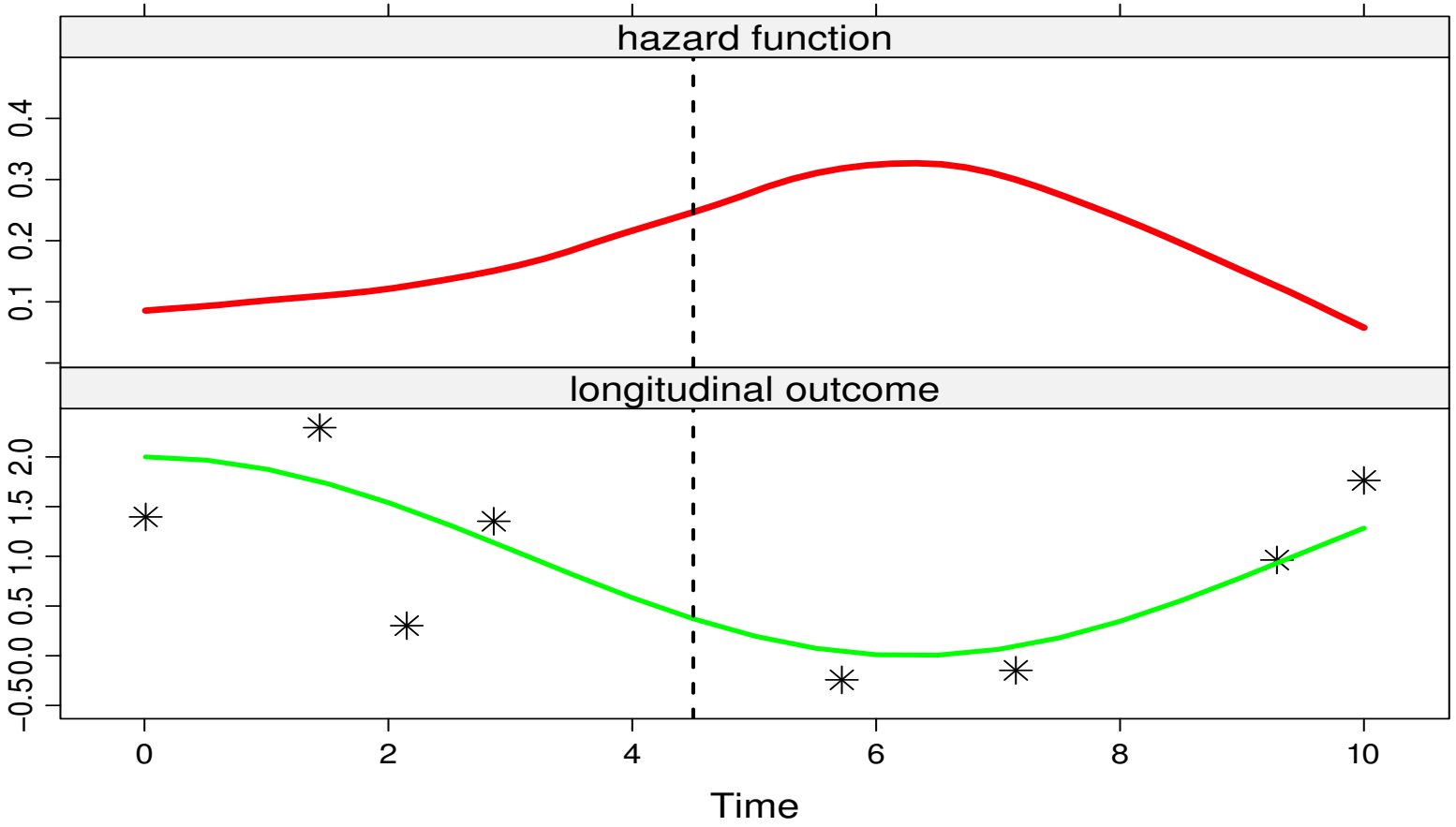
1.1 Parameterizations

- The standard joint model

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

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

1.1 Parameterizations (cont'd)



1.1 Parameterizations (cont'd)

- The standard joint model

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

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

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

1.1 Parameterizations (cont'd)

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

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

1.1 Parameterizations (cont'd)

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

- Let's see some possibilities...

1.1 Parameterizations (cont'd)

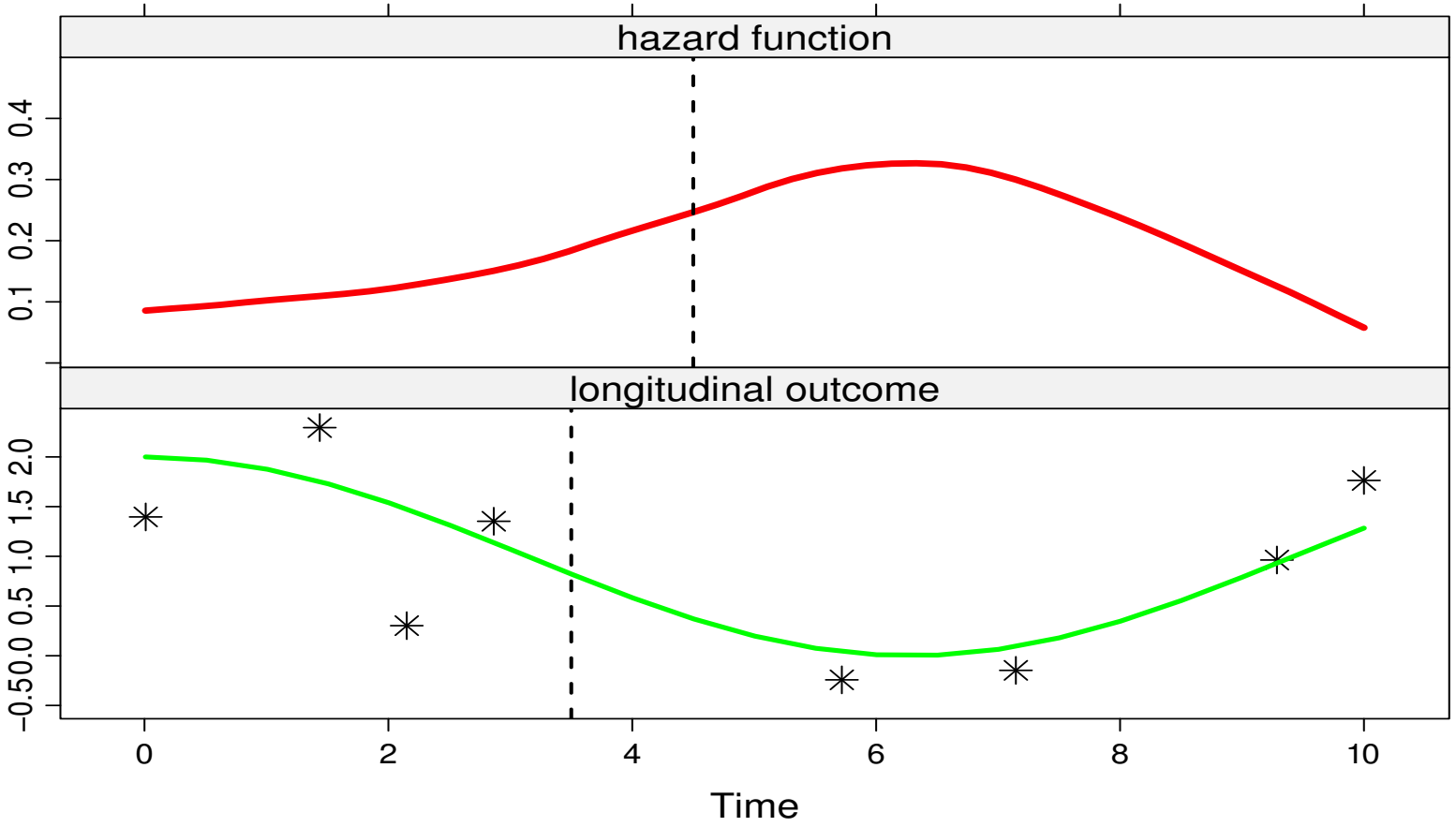
- *Lagged Effects:* The hazard for an event at t is associated with the level of the marker at a previous time point:

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

where

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

1.1 Parameterizations (cont'd)



1.1 Parameterizations (cont'd)

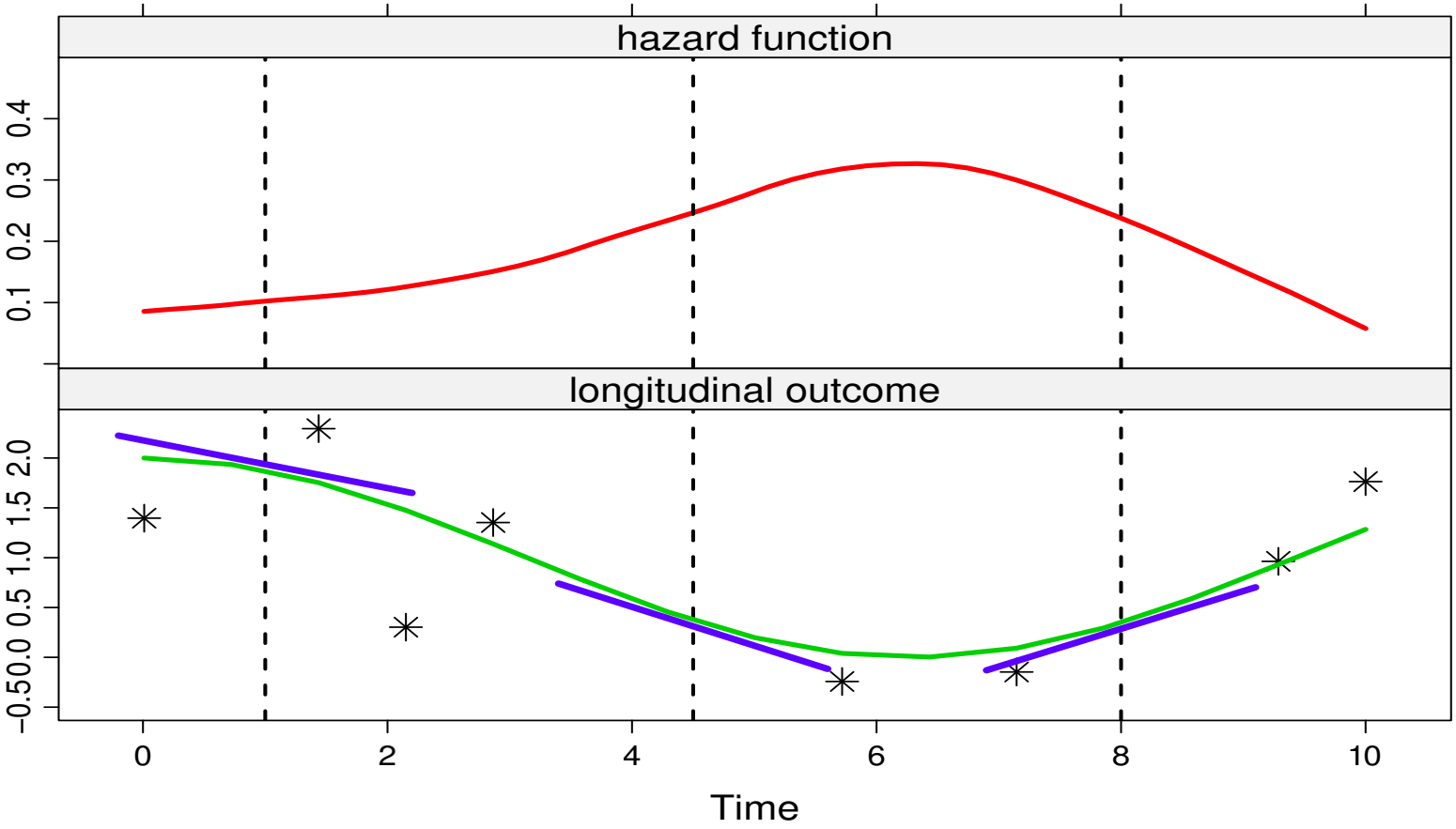
- *Time-dependent Slopes:* The hazard for an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

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

where

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

1.1 Parameterizations (cont'd)



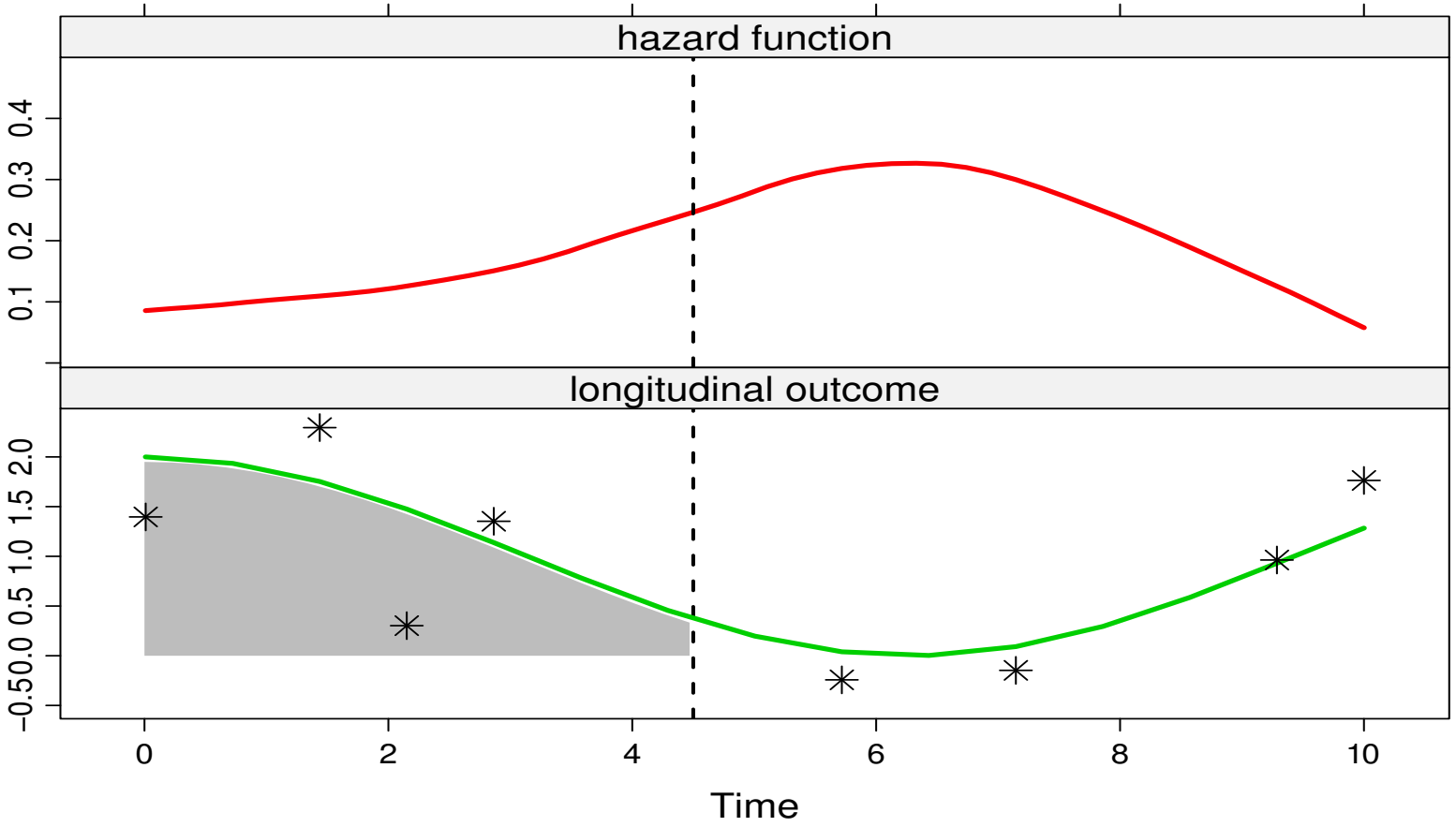
1.1 Parameterizations (cont'd)

- *Cumulative Effects:* The hazard for 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 $\mathcal{M}_i(t)$

1.1 Parameterizations (cont'd)



1.1 Parameterizations (cont'd)

- *Weighted Cumulative Effects (convolution):* The hazard for 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
  - ▷ ...

1.1 Parameterizations (cont'd)

- *Random Effects:* The hazard for 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

1.1 Parameterizations (cont'd)

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

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

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

  and the following four survival submodels

1.1 Parameterizations (cont'd)

- Model I (current value)

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

- Model II (current value + current slope)

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

where

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

1.1 Parameterizations (cont'd)

- Model III (random slope)

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

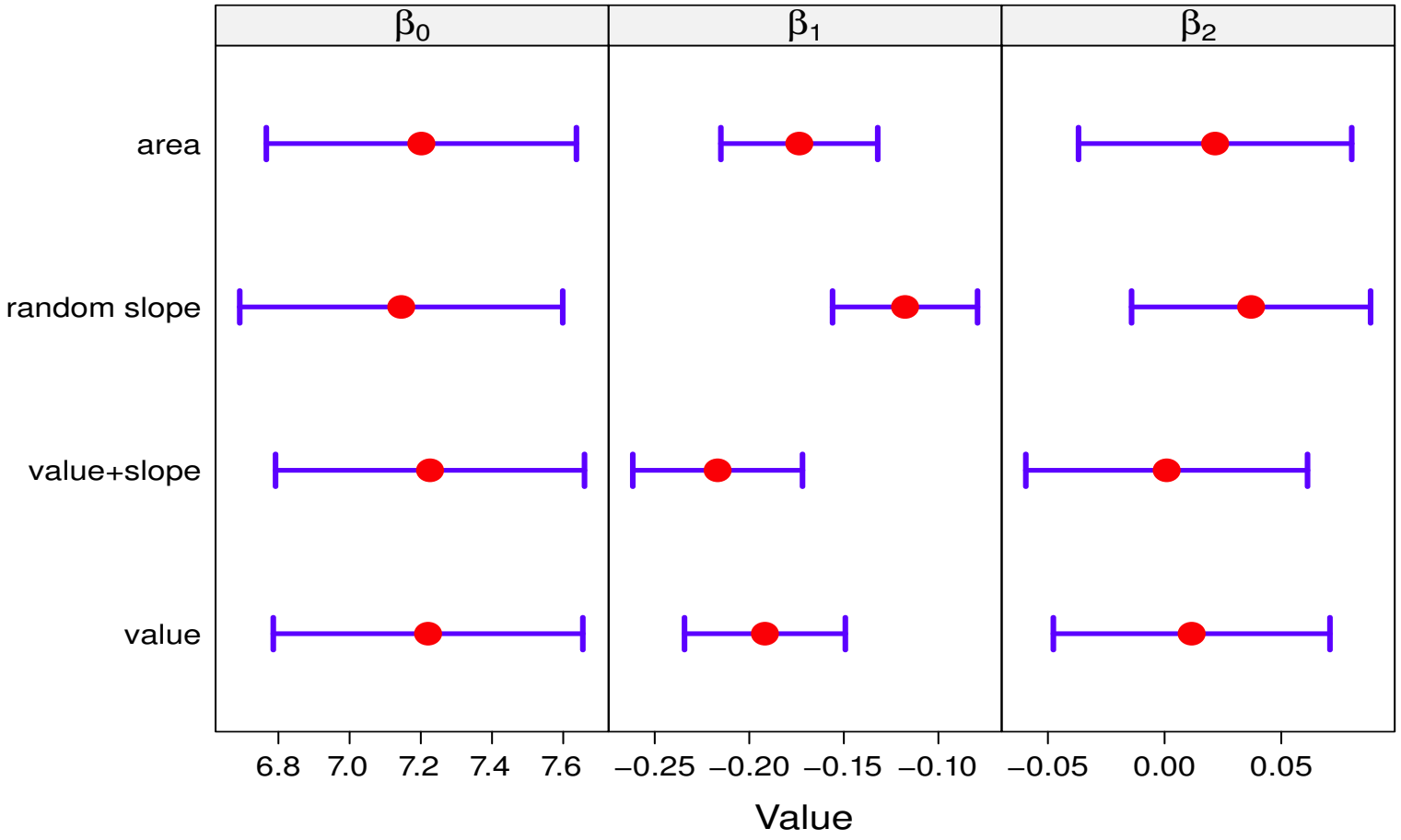
- Model IV (area)

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

where

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

1.1 Parameterizations (cont'd)



1.1 Parameterizations (cont'd)

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

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

1.2 Multiple Longitudinal Markers

- So far we have concentrated on a single continuous marker

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

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

1.2 Multiple Longitudinal Markers (cont'd)

We need to extend the basic joint model!

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

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

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

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

1.2 Multiple Longitudinal Markers (cont'd)

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

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

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

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

1.3 Multiple Failure Times

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

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

1.3 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

1.3 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

1.3 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

1.4 Extensions & Parameterizations

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

1.4 Extensions & Parameterizations (cont'd)

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

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

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

Chapter 2

Dynamic Predictions, Discrimination & Calibration

2.1 Survival Probabilities: Definitions

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

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

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

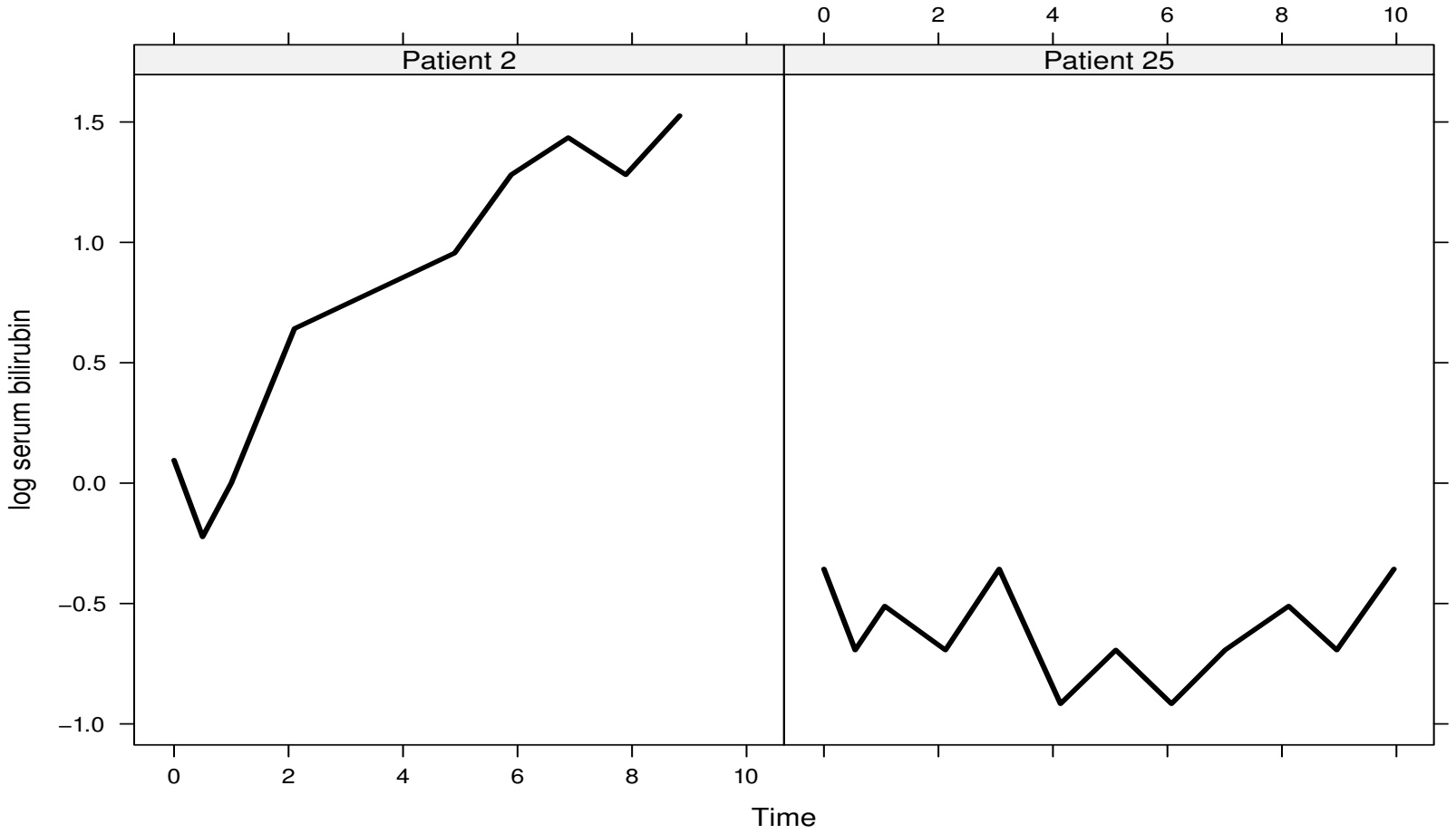
2.1 Survival Probabilities: Definitions (cont'd)

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

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

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

2.1 Survival Probabilities: Definitions (cont'd)



2.1 Survival Probabilities: Definitions (cont'd)

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

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

and we are interested in

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

where

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

2.2 Survival Probabilities: Estimation

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

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

2.2 Survival Probabilities: Estimation (cont'd)

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

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

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

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

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

2.2 Survival Probabilities: Estimation (cont'd)

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

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

- We have already seen the first part of the integrand

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

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

2.2 Survival Probabilities: Estimation (cont'd)

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

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

where

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

2.2 Survival Probabilities: Estimation (cont'd)

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

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

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

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

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

2.2 Survival Probabilities: Estimation (cont'd)

- Steps 1 and 3 are straightforward

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

2.2 Survival Probabilities: Estimation (cont'd)

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

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

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

2.2 Survival Probabilities: Estimation (cont'd)

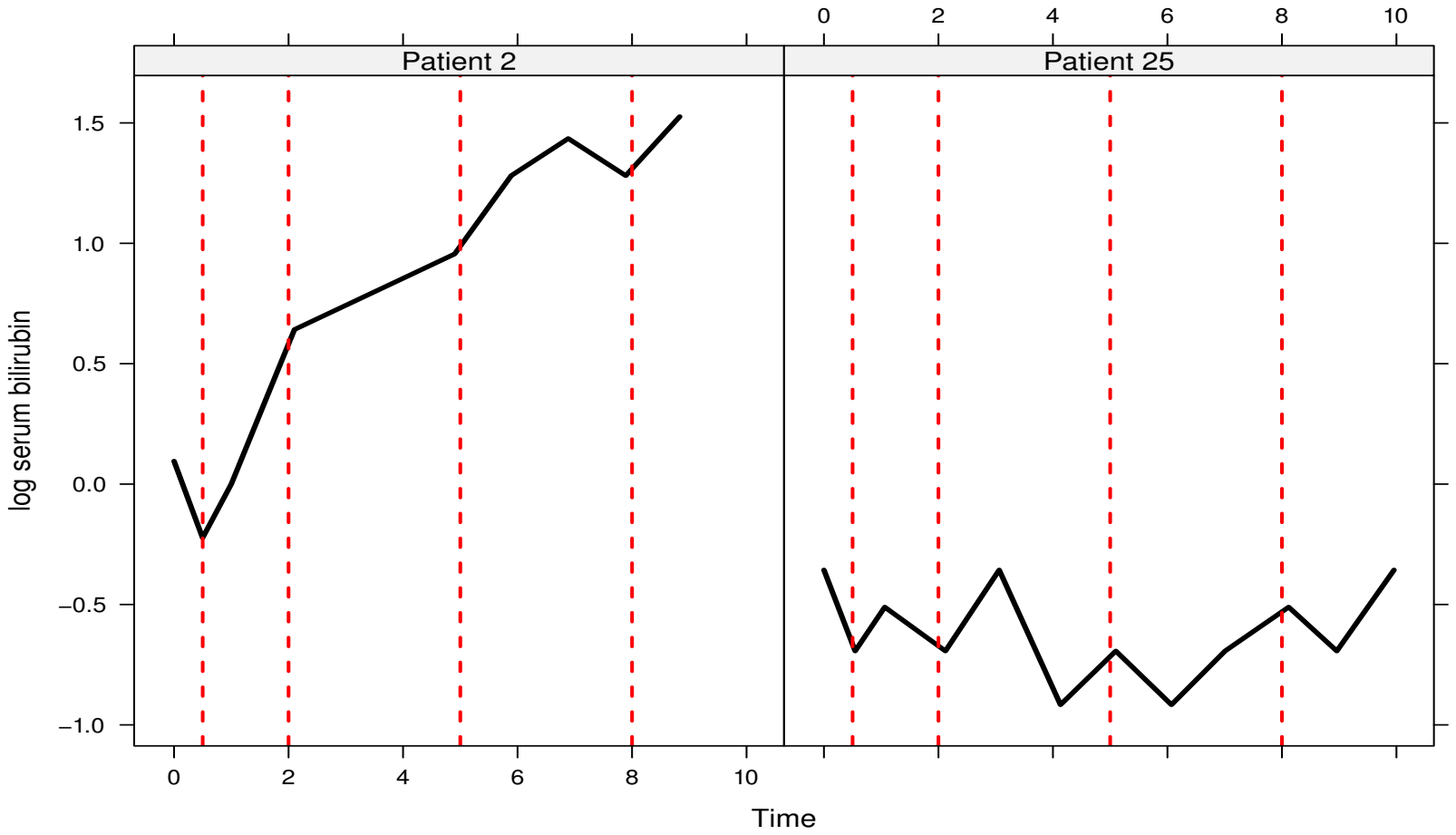
- Based on the fitted joint model we estimate $\pi_j(u \mid t)$ for Patients 2 and 25

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

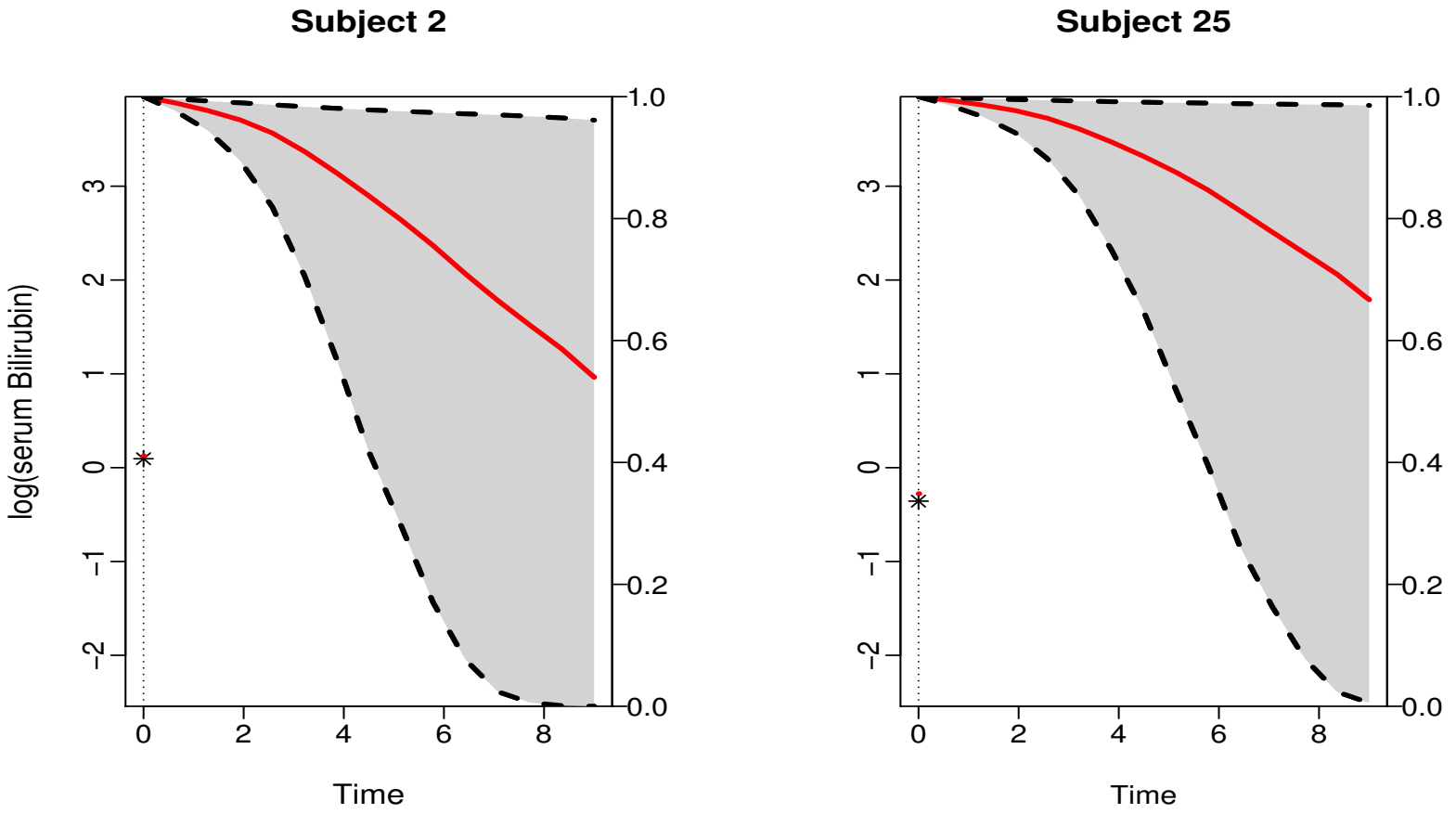
$$\hat{\pi}_j(u \mid t) = \text{median}\{\pi_j^{(\ell)}(u \mid t), \ell = 1, \ldots, L\}$$

  and calculated a corresponding 95% pointwise CIs

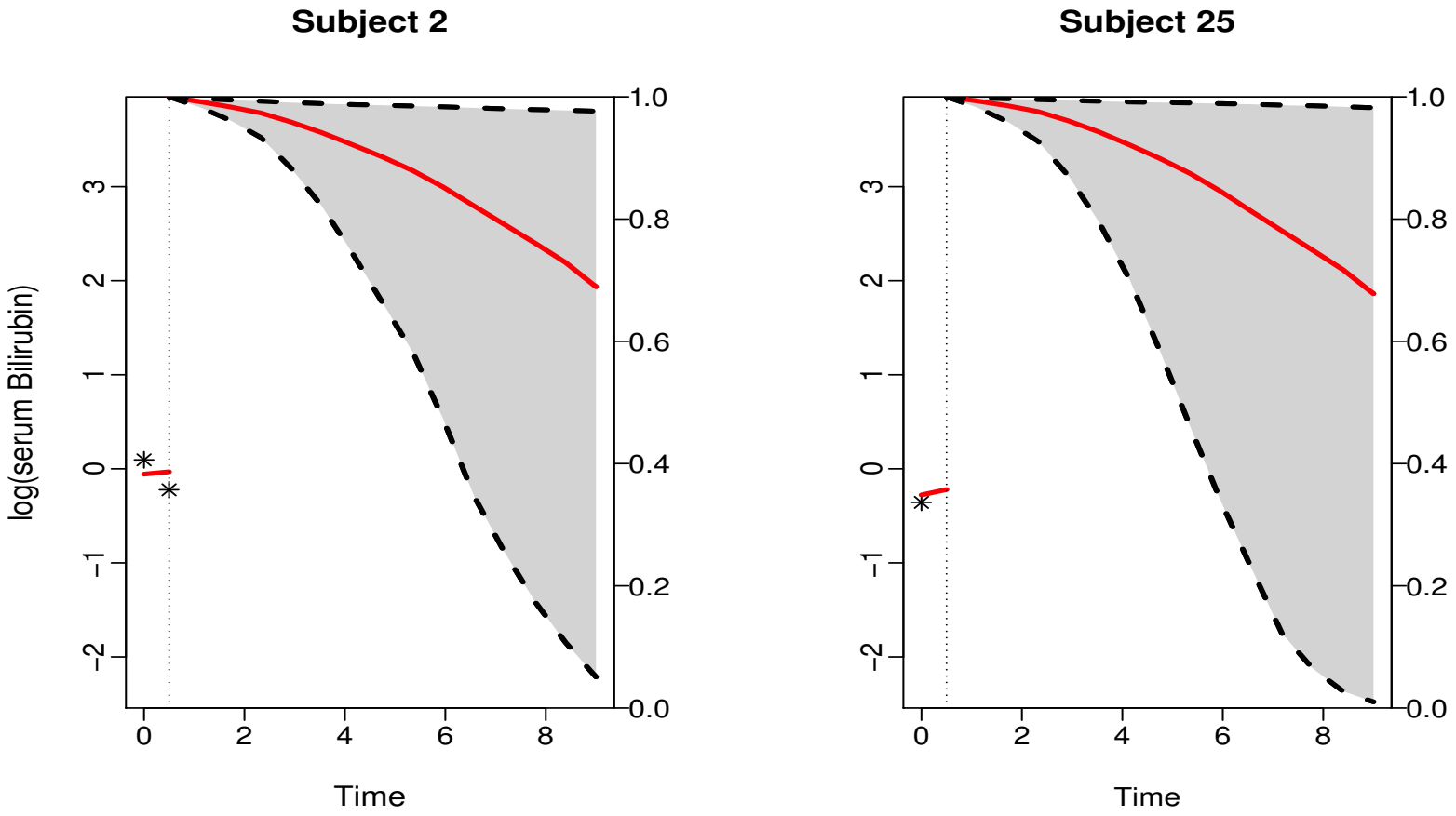
2.2 Survival Probabilities: Estimation (cont'd)



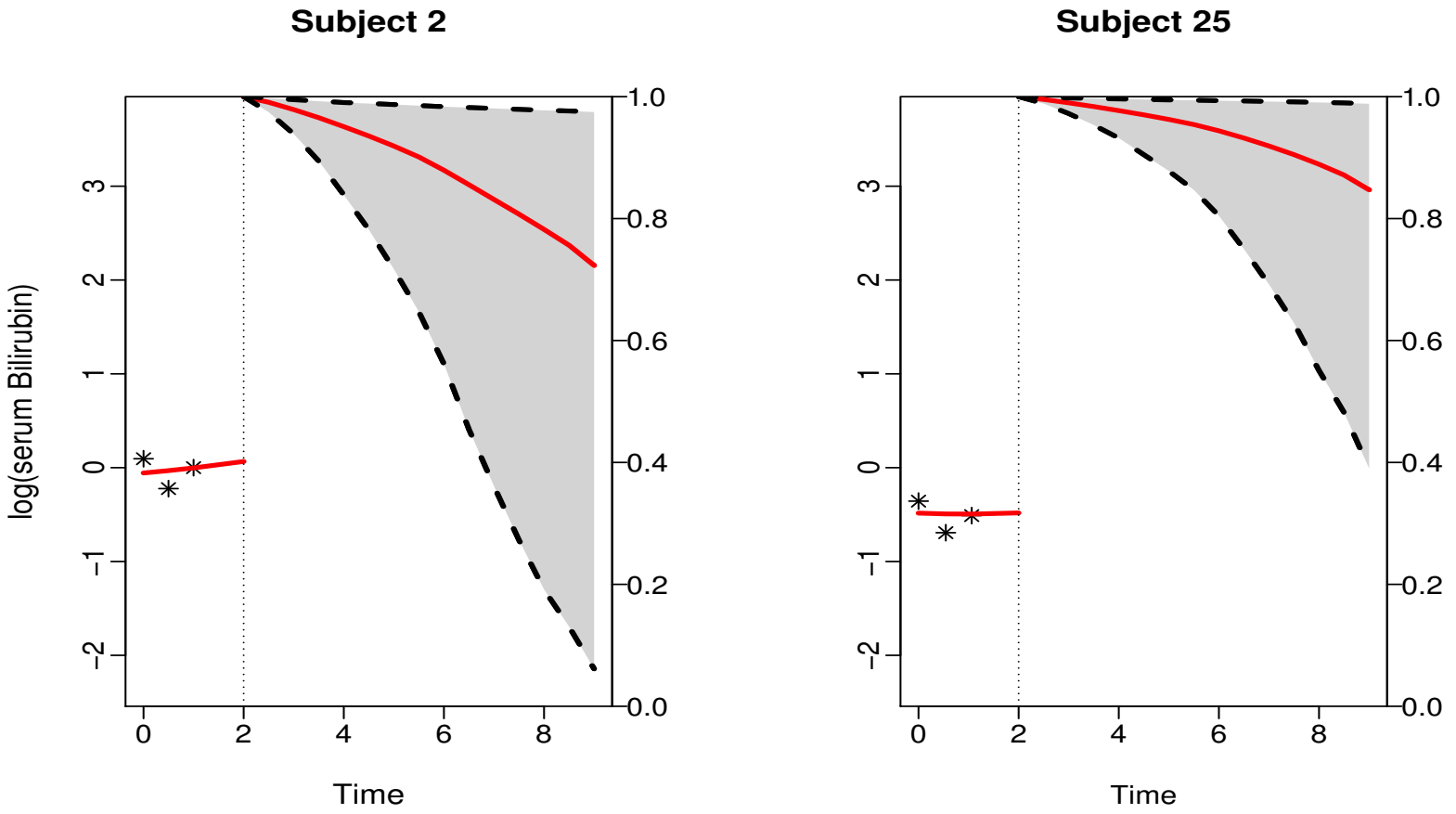
2.2 Survival Probabilities: Estimation (cont'd)



2.2 Survival Probabilities: Estimation (cont'd)



2.2 Survival Probabilities: Estimation (cont'd)



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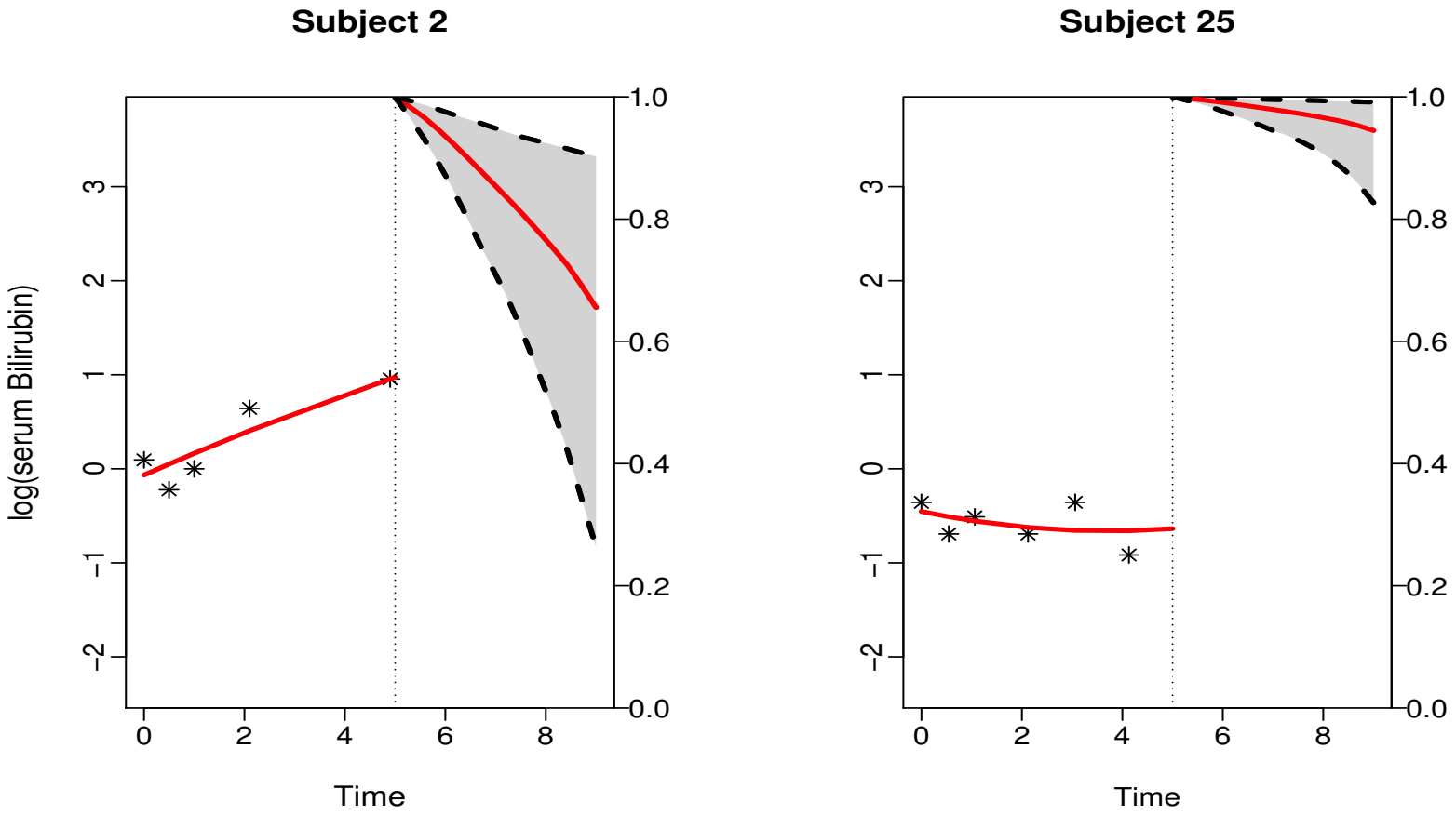
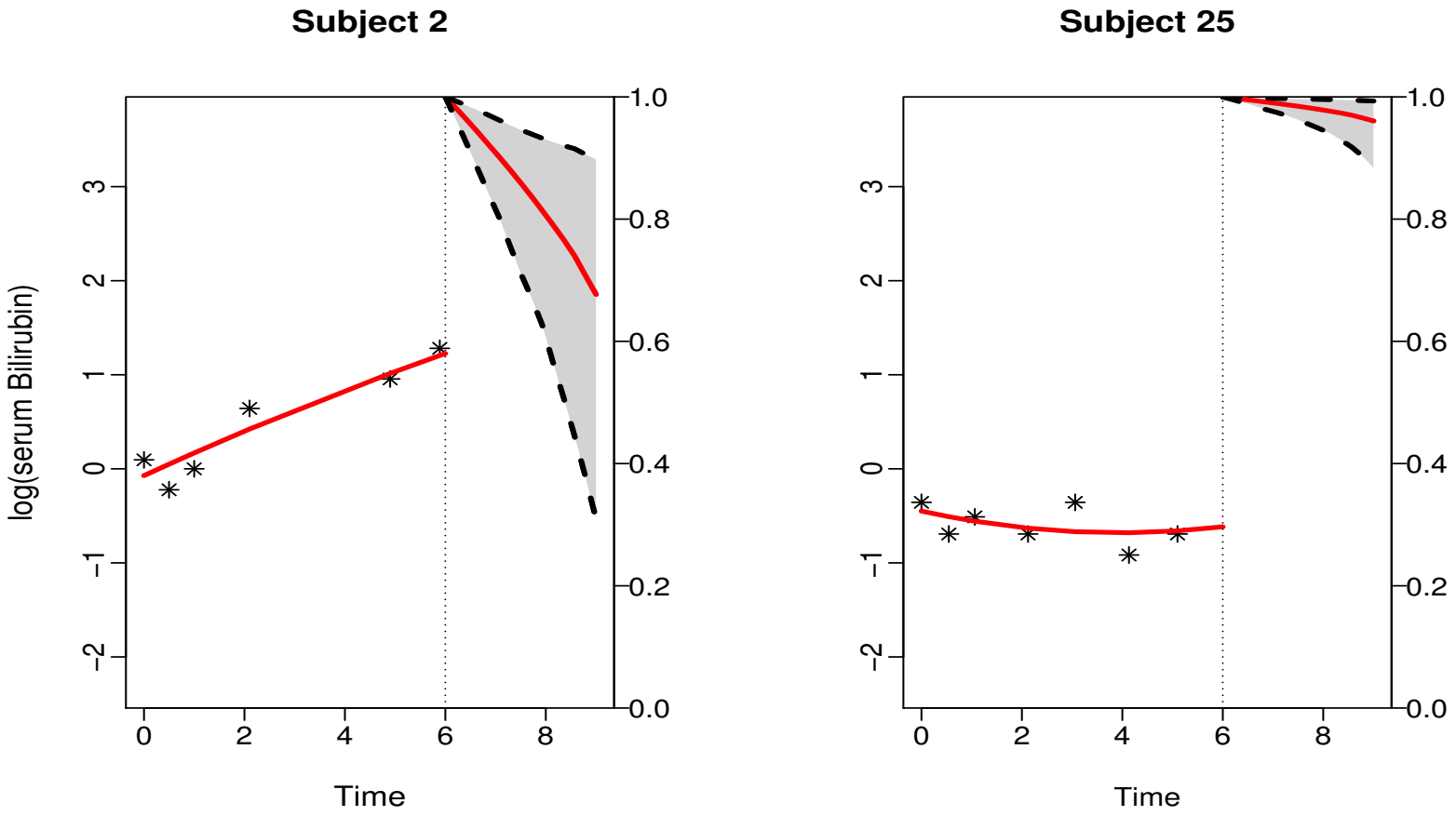
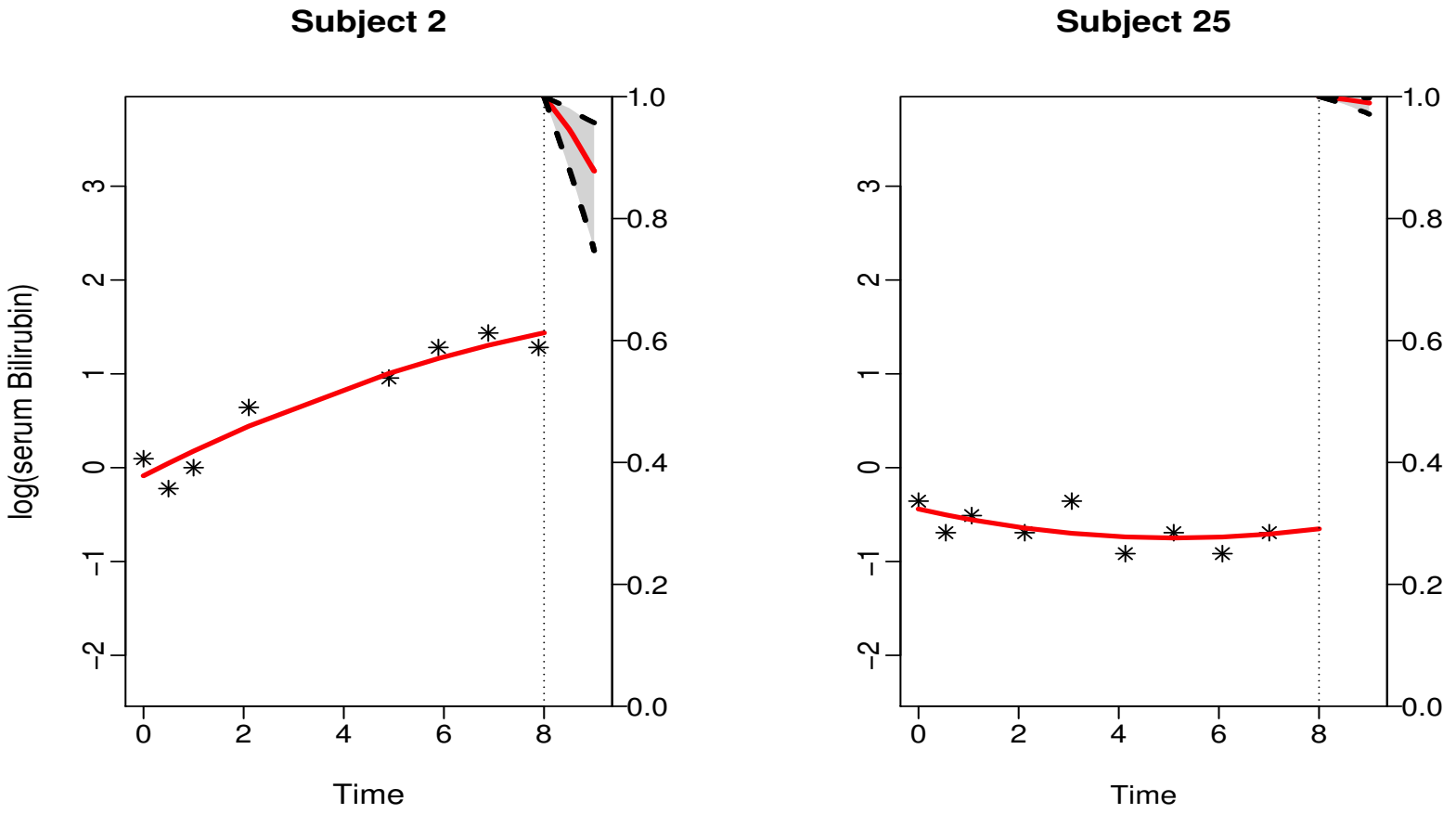


2.2 Survival Probabilities: Estimation (cont'd)



2.2 Survival Probabilities: Estimation (cont'd)



2.2 Survival Probabilities: Estimation (cont'd)

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

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

sfit

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

2.3 Dynamic Predictions using Landmarking

- Dynamic predictions of survival probabilities can be also derived using a landmark approach

- How this works?
  - ▷ choose a landmark point t, e.g., for the future patient of interest the last time point she was alive
  - ▷ from the original dataset keep only the patients who were at risk at the landmark
  - ▷ fit a Cox model to this dataset including the last available value of the biomarker as baseline covariate

$$h_i(u-t) \;=\; h_0(u-t)\exp\{\gamma^\top w_i + \alpha\tilde{y}_i(t)\}, \quad u > t$$

2.3 Dyn. Predictions using Landmarking (cont'd)

▷ for the new patient compute her survival probability at u using the fitted Cox model and the Breslow estimator

$$\hat{\pi}_j^{LM}(u \mid t) = \exp\Big[-\widehat{H}_0(u)\exp\{\hat{\gamma}^\top w_j + \hat{\alpha}\tilde{y}_j(t)\}\Big],$$

where

$$\widehat{H}_0(u) = \sum_{i \in \mathcal{R}(t)} \frac{I(T_i \leq u)\delta_i}{\sum_{\ell \in \mathcal{R}(u)} \exp\{\hat{\gamma}^\top w_\ell + \hat{\alpha}\tilde{y}_\ell(t)\}},$$

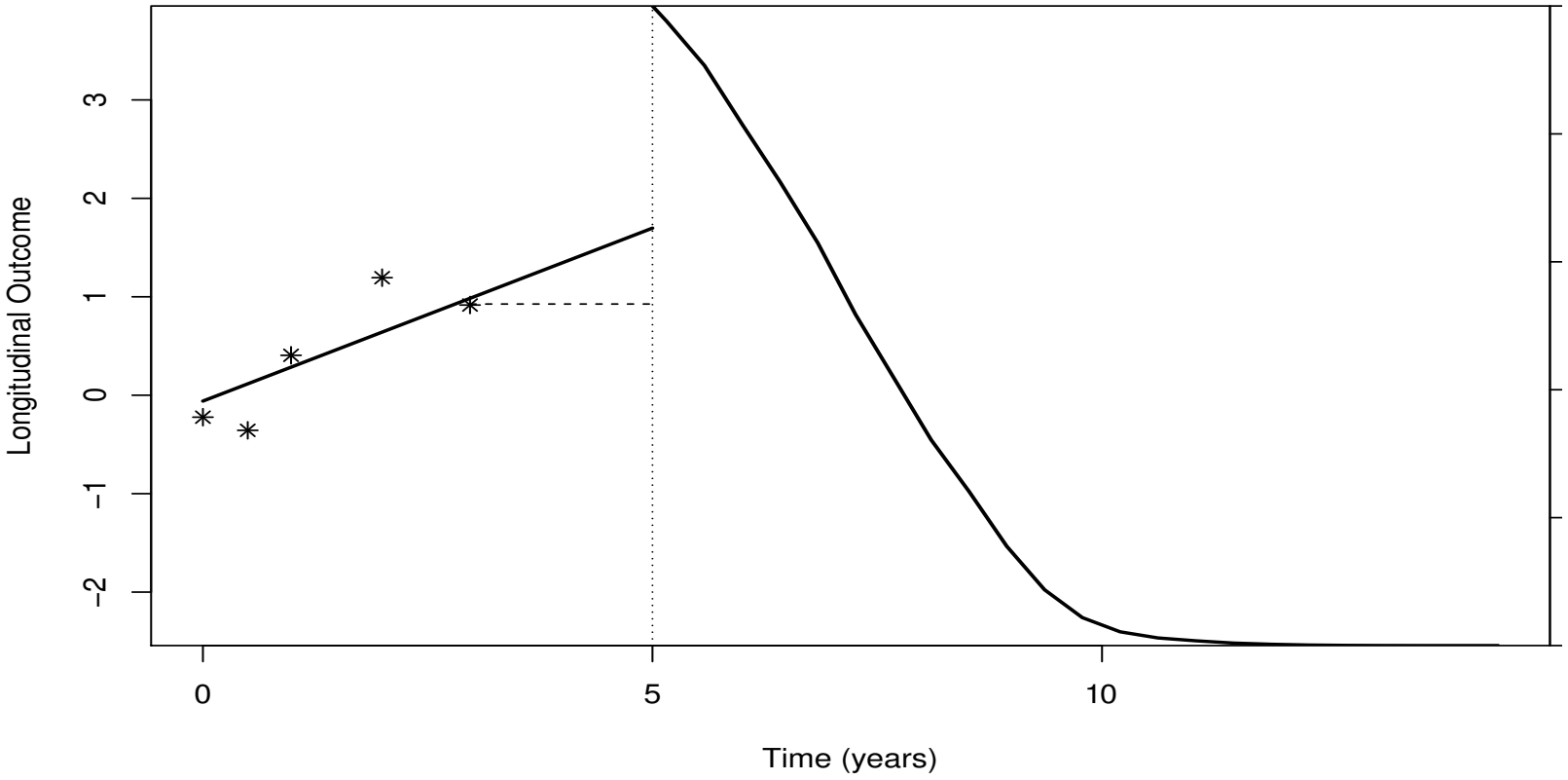
and $\mathcal{R}(t) = \{i : T_i > t\}$

2.3 Dyn. Predictions using Landmarking (cont'd)

- Sometimes landmarking works, **but not always!**

- Main differences between landmarking and joint modeling
  - ▷ **Extrapolation:**
    - * both require the level of the marker at t
    - * landmarking extrapolates the last biomarker value (Last Value Carried Forward approach)
    - * joint modeling builds the subject-specific profile which extrapolates up to t
    - * from a biological point of view the joint modeling approach seems more logical than landmarking

2.3 Dyn. Predictions using Landmarking (cont'd)



2.3 Dyn. Predictions using Landmarking (cont'd)

- Main differences between landmarking and joint modeling
  - ▷ **Implicit processes:**

Landmarking	Joint Modeling
* MCAR missing data long. process	* MAR missing data long. process
* non-informative visiting process	* visiting process allowed to depend on long. history
* non-informative censoring	* censoring allowed to depend on long. history

2.4 Longitudinal Responses: Definitions

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

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

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

and we are interested in

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

2.4 Longitudinal Responses: Definitions (cont'd)

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

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

- With the first part of the integrand given by:

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

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

2.4 Longitudinal Responses: Estimation (cont'd)

- A similar Monte Carlo simulation scheme:

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

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

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

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

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

2.4 Longitudinal Responses: Estimation (cont'd)

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

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

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

2.4 Longitudinal Responses: Estimation (cont'd)

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

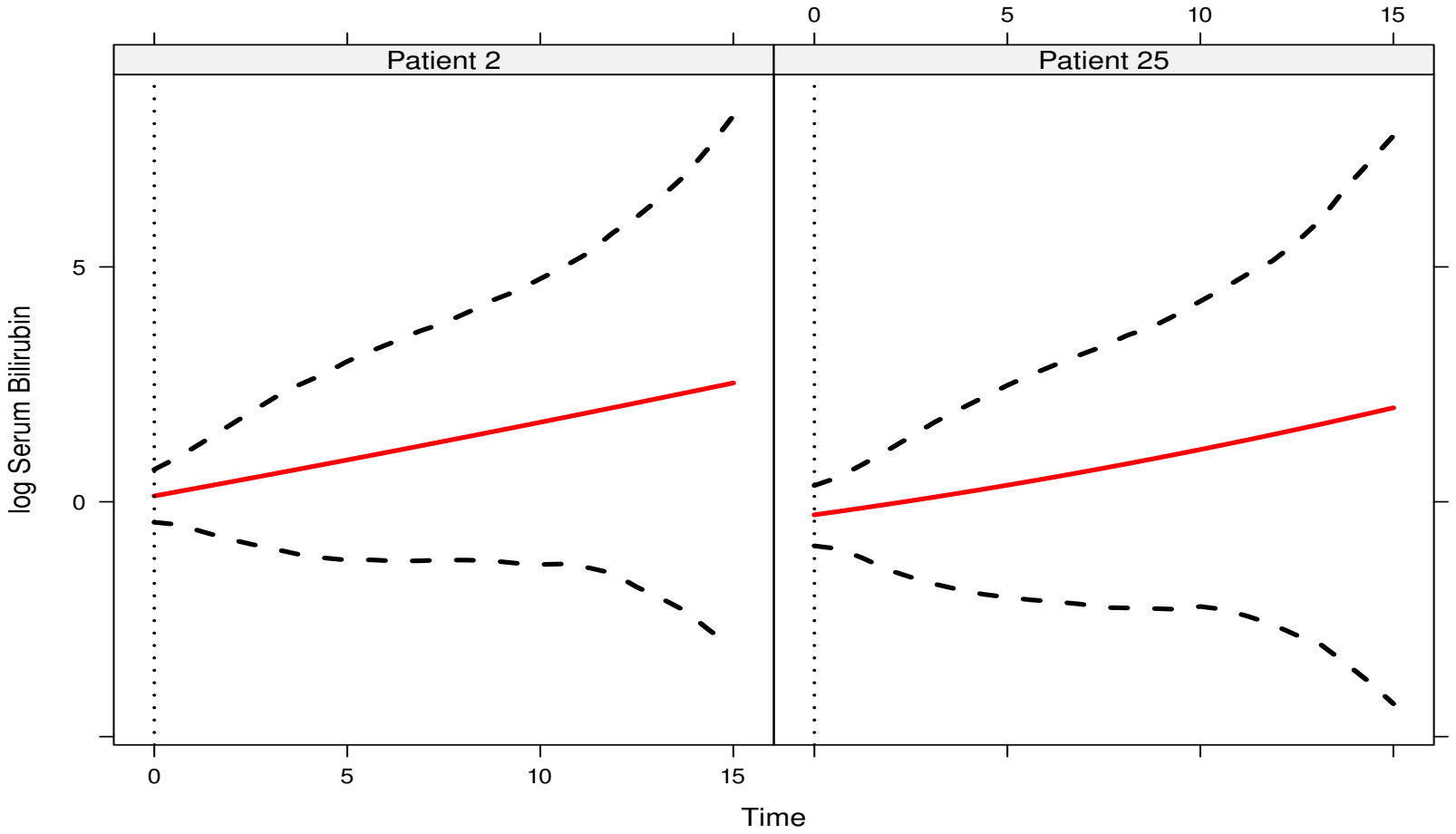
- Point estimates

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

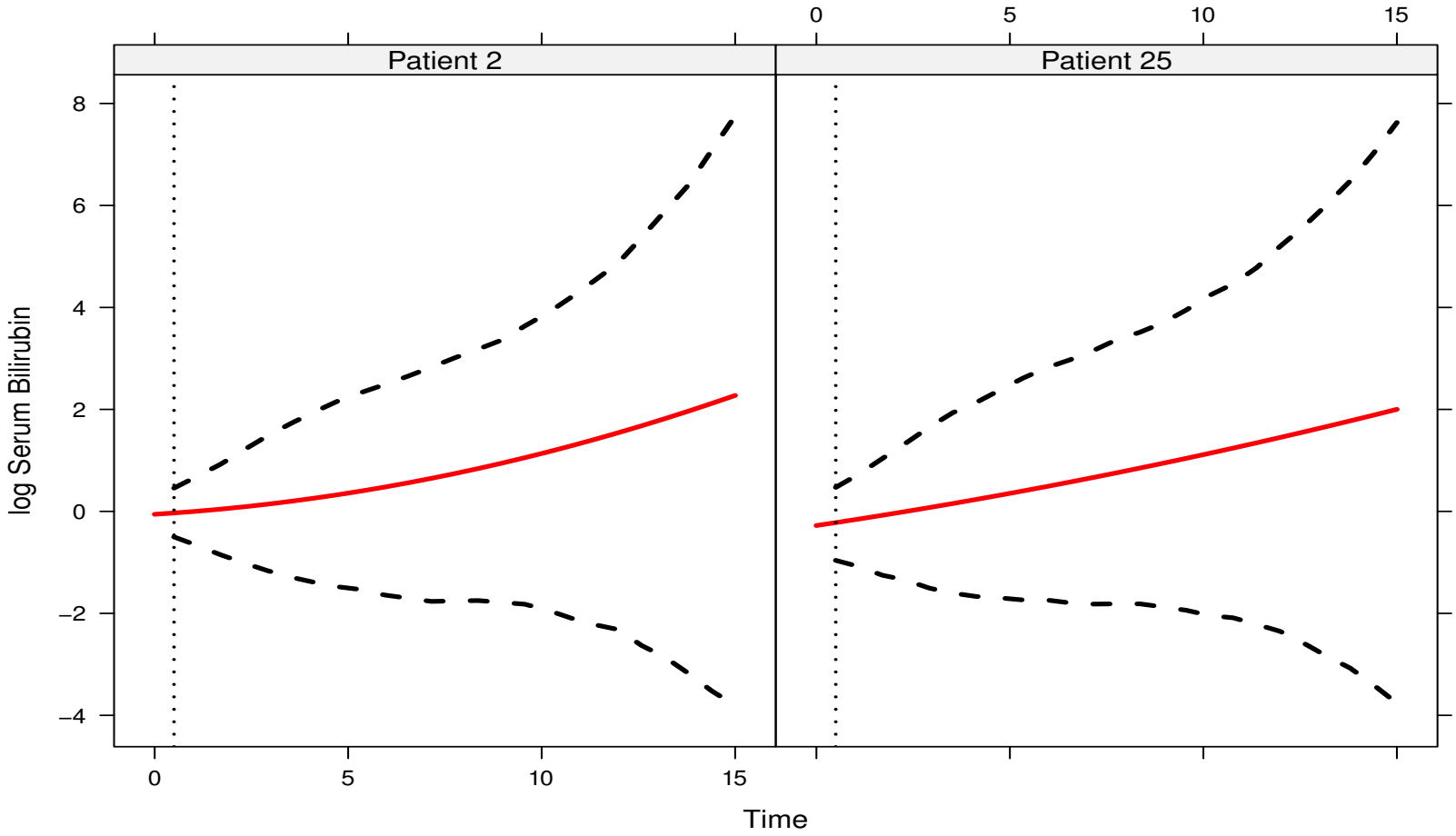
  where $\hat{\beta}$: MLEs & $\hat{b}_j$: empirical Bayes estimates

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

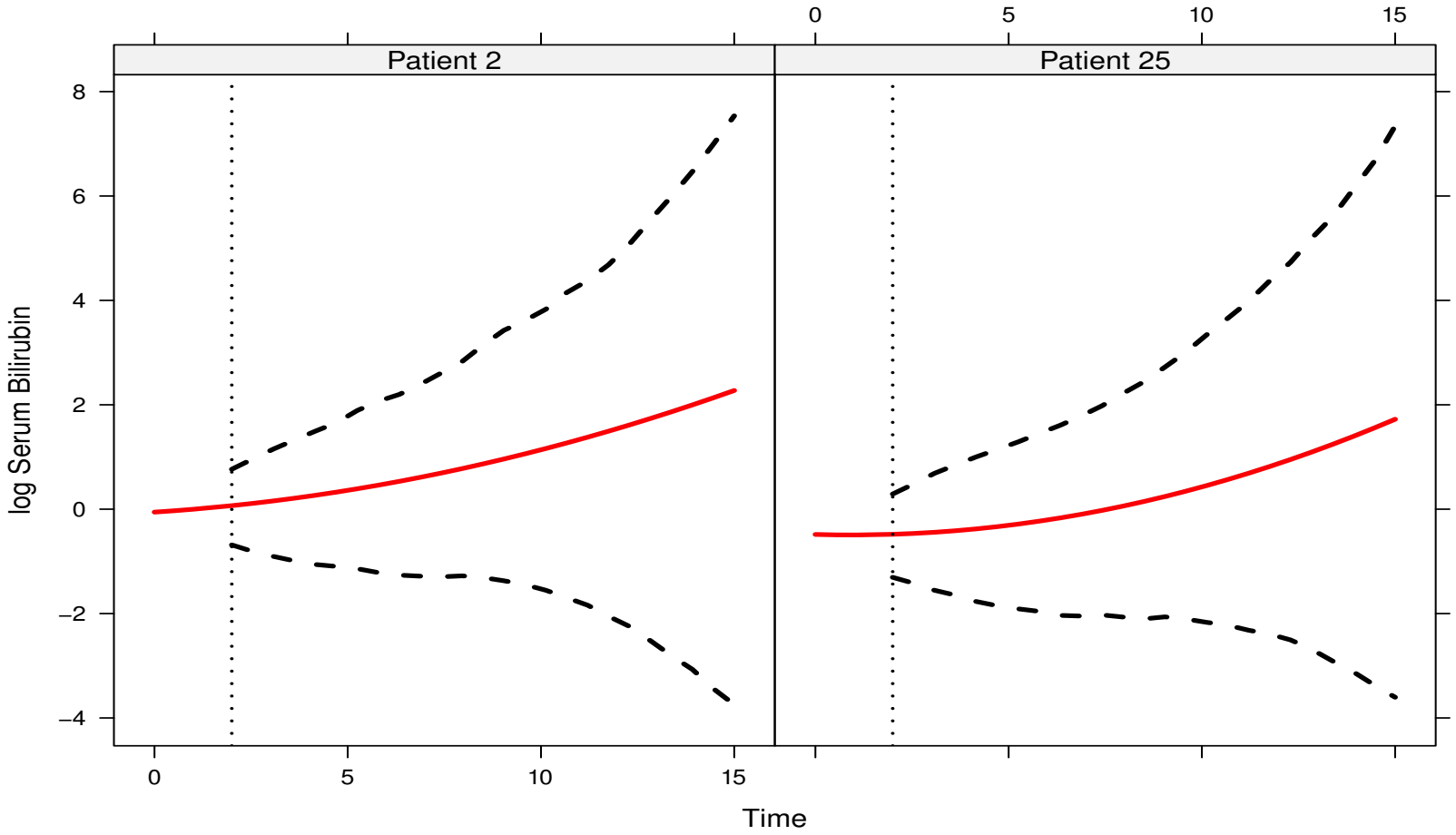
2.4 Longitudinal Responses: Estimation (cont'd)



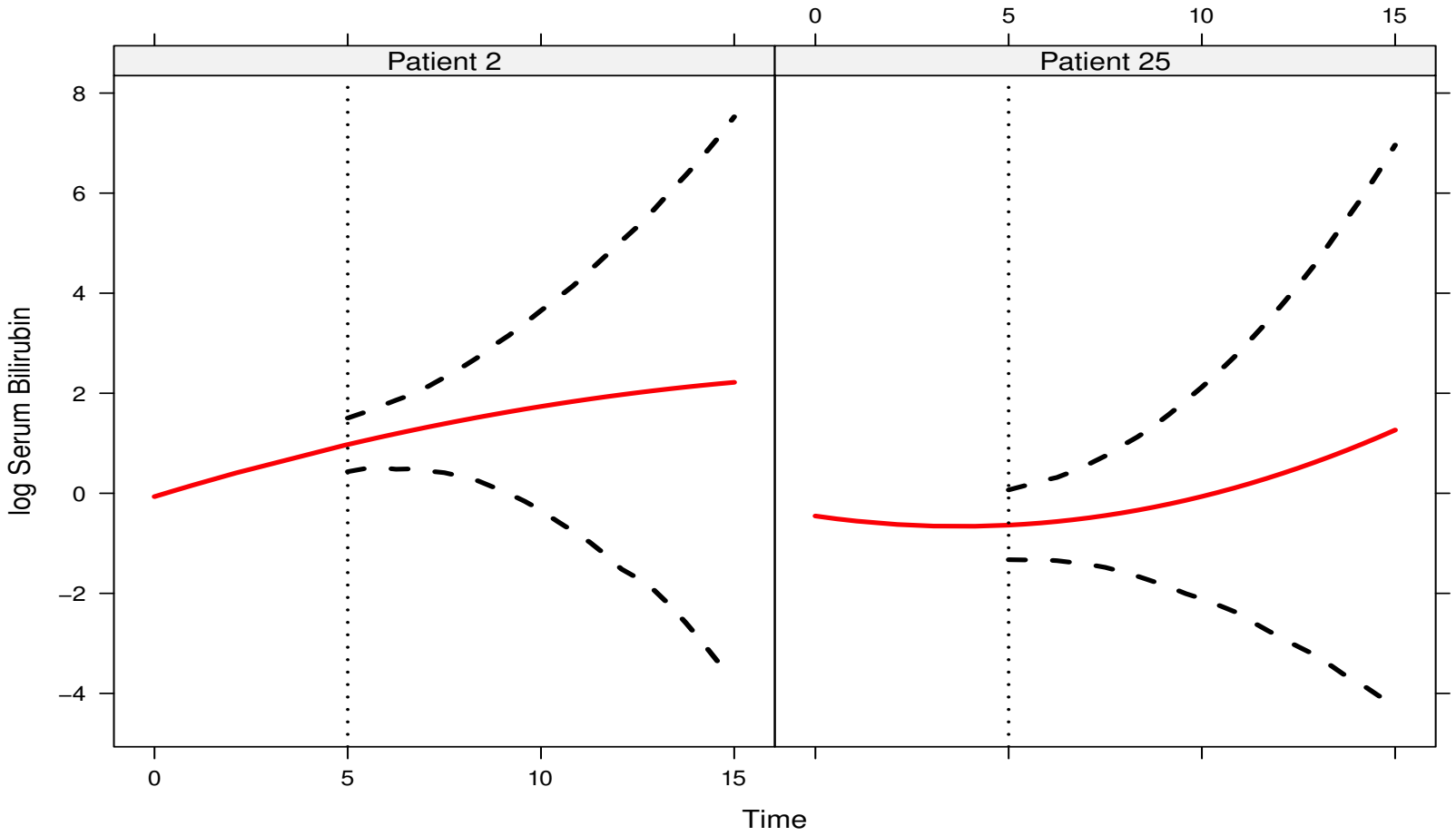
2.4 Longitudinal Responses: Estimation (cont'd)



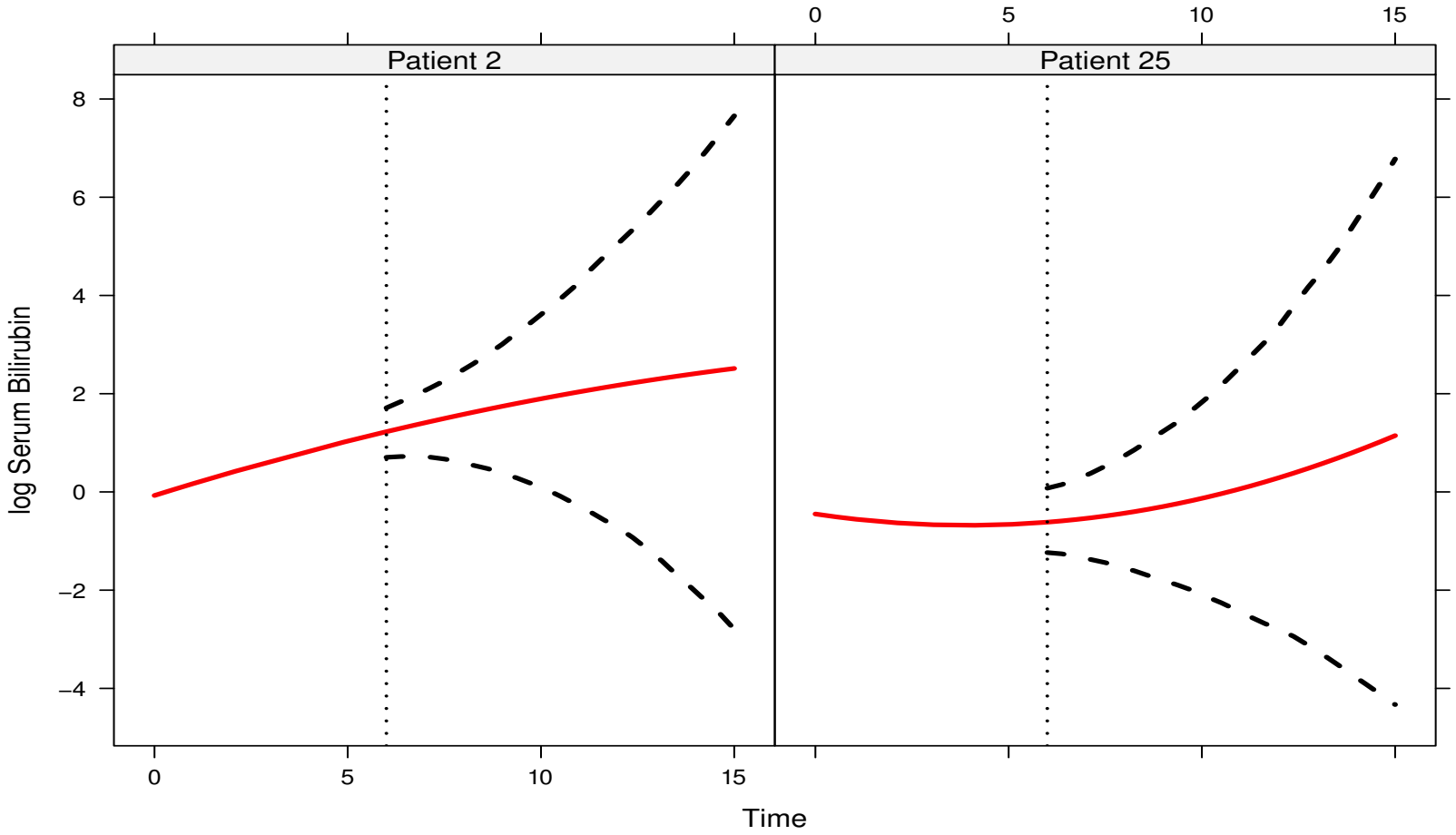
2.4 Longitudinal Responses: Estimation (cont'd)



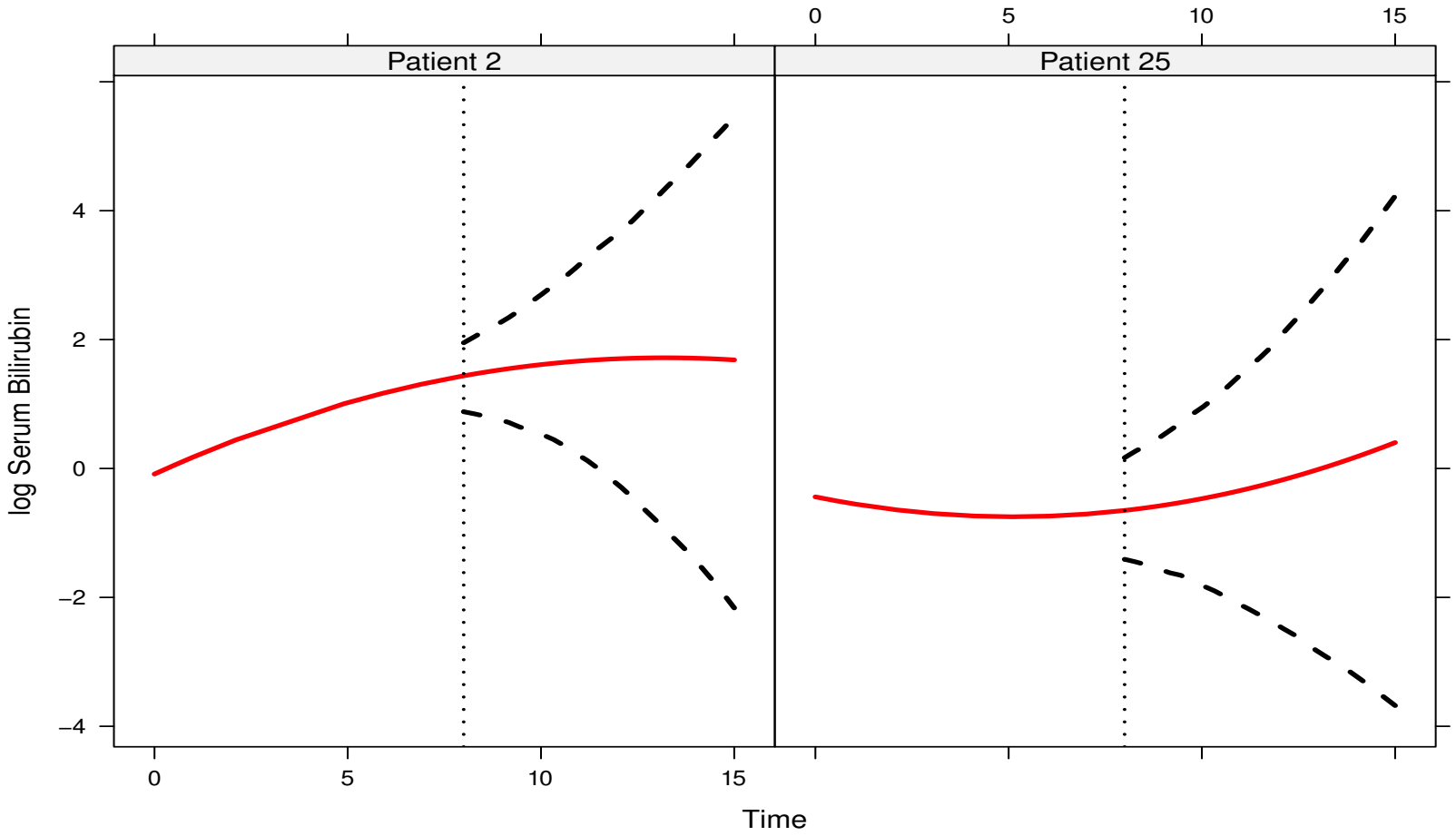
2.4 Longitudinal Responses: Estimation (cont'd)



2.4 Longitudinal Responses: Estimation (cont'd)



2.4 Longitudinal Responses: Estimation (cont'd)



2.4 Longitudinal Responses: Estimation (cont'd)

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

```
lfit <- predict(jointFit, newdata = pbc2[pbc2$id == "2", ],
    type = "Subject", interval = "conf", returnData = TRUE)

lfit

xyplot(pred + low + upp ~ year, data = lfit, type = "l",
    lty = c(1,2,2), col = c(2,1,1), lwd = 2)
```

2.4 Longitudinal Responses: Estimation (cont'd)

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

```
library(shiny)

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

2.5 Importance of the Parameterization

- All previous predictions were based on the standard joint model

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

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

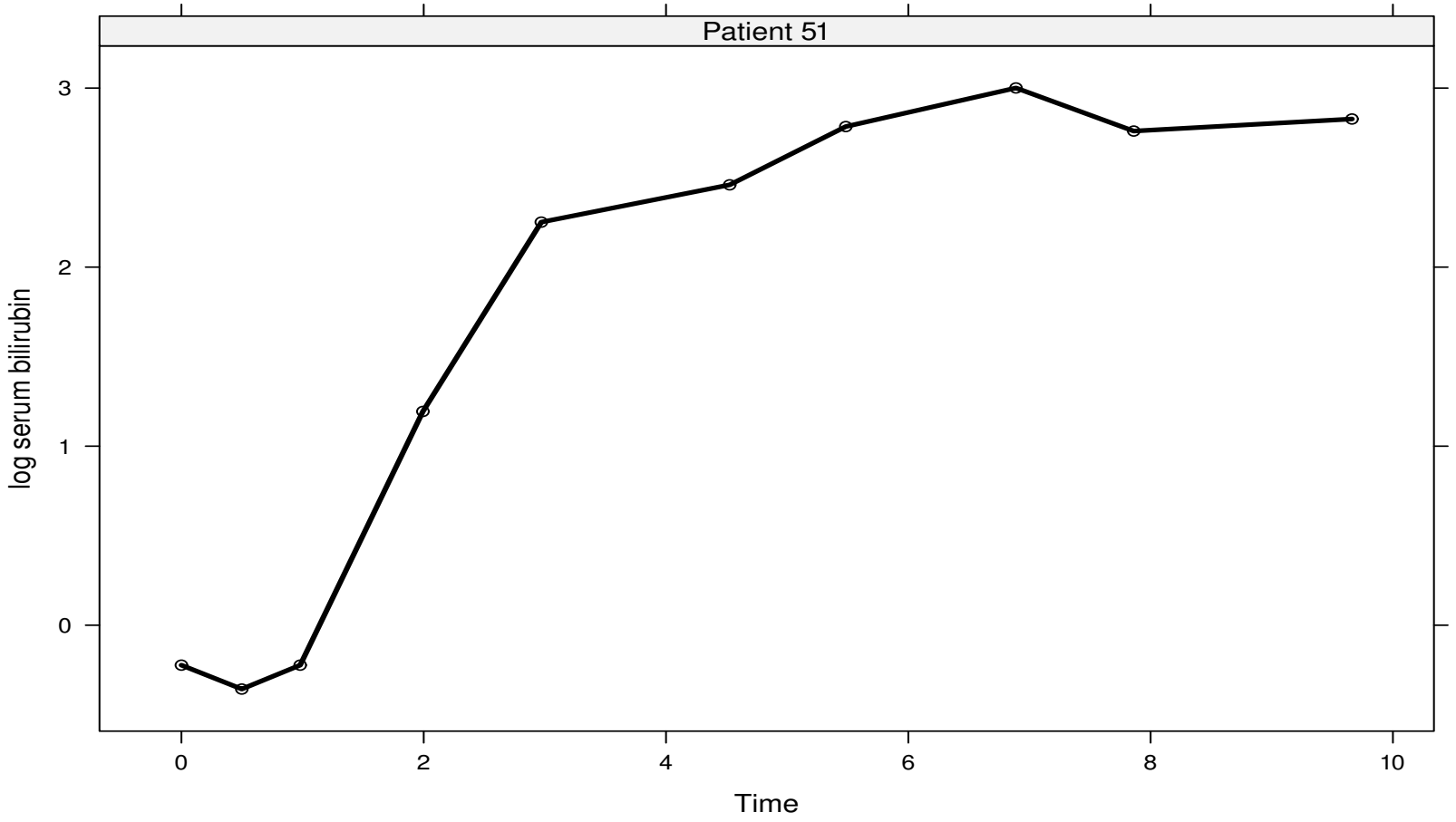
2.5 Importance of the Parameterization (cont'd)

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

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

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

2.5 Importance of the Parameterization (cont'd)



2.5 Importance of the Parameterization (cont'd)

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

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

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

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

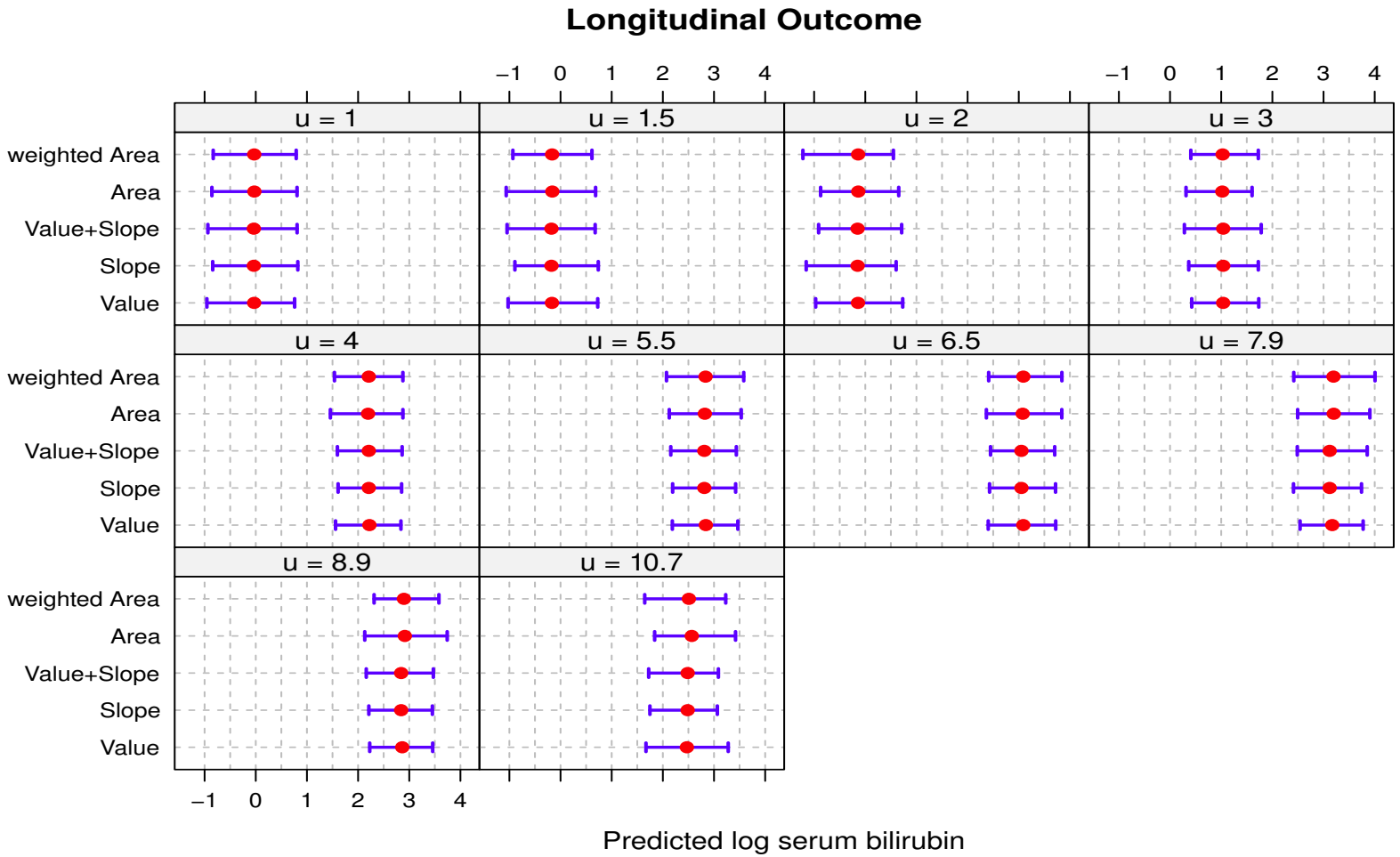
2.5 Importance of the Parameterization (cont'd)

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

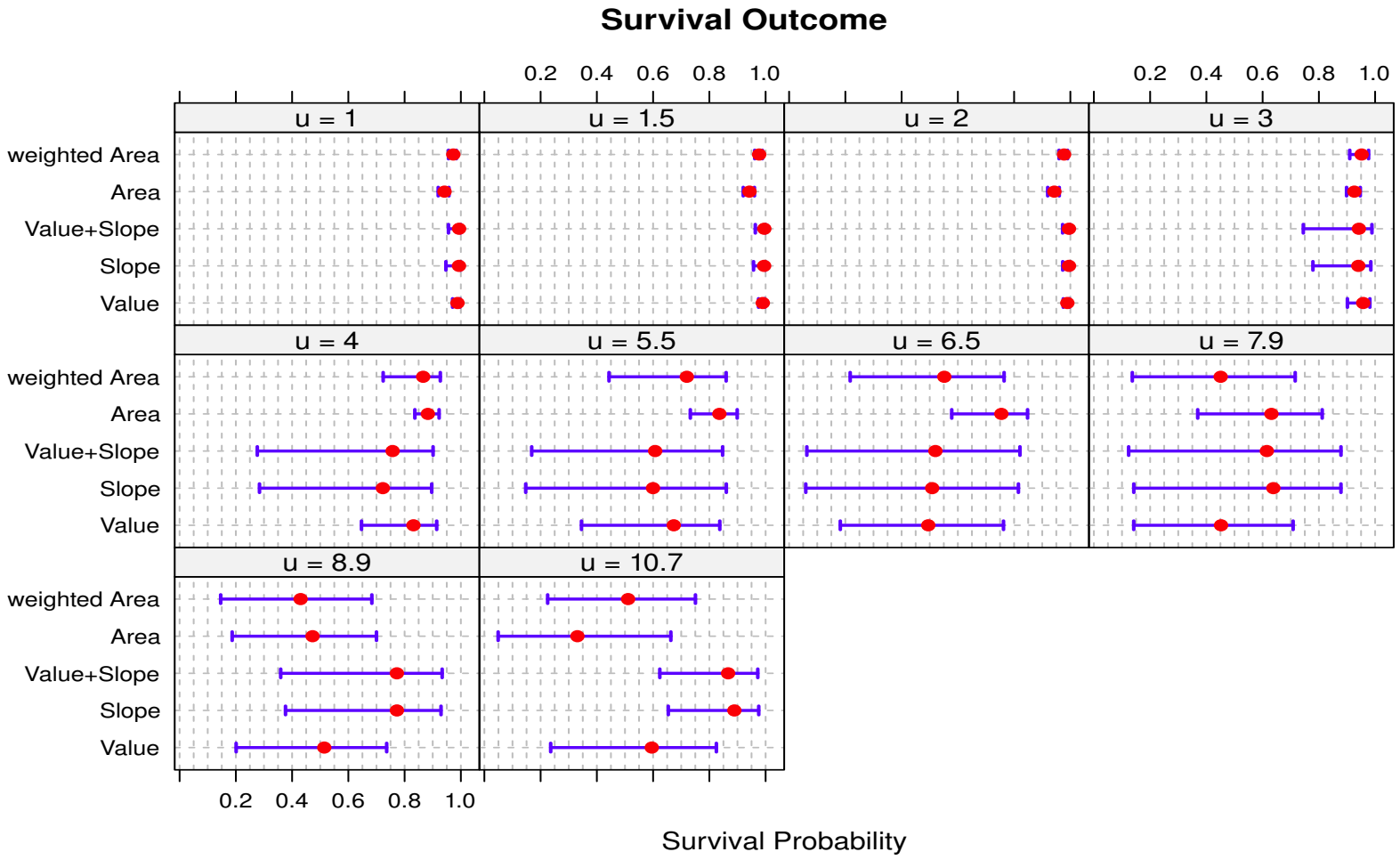
$$h_i(t) = h_0(t) \exp\Big\{\gamma \texttt{D-pnc}_i + \alpha_4 \int_0^t \phi(t-s) m_i(s)ds\Big\},$$

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

2.5 Importance of the Parameterization (cont'd)



2.5 Importance of the Parameterization (cont'd)



2.5 Importance of the Parameterization (cont'd)

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

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

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

2.6 Model Discrimination

- Often clinical interest lies in the predictive performance of a marker
  - ▷ this could be useful in medical practice if the marker alone offers good enough discrimination

- Hence, often we are also interested in the discriminative capability of the *whole* model incorporating the baseline covariates as well
  - ▷ especially when no single prognostic factor can accurately enough discriminate between patients

2.6 Model Discrimination (cont'd)

- We assume the following setting
  - ▷ using the available longitudinal data up to time t, $\mathcal{Y}_j(t) = \{y_j(s), 0 \leq s \leq t\}$
  - ▷ we are interested in events in the medically relevant interval $(t, t + \Delta t]$

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

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

2.6 Model Discrimination (cont'd)

- Following, we can define sensitivity

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

specificity

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

and the corresponding AUC

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

2.6 Model Discrimination (cont'd)

- Estimation of $\text{AUC}(t, \Delta t)$ can be based on similar arguments as Harrell's C index

$$\widehat{\text{AUC}}(t, \Delta t) = \widehat{\text{AUC}}_1(t, \Delta t) + \widehat{\text{AUC}}_2(t, \Delta t)$$

where

$$\widehat{\text{AUC}}_1(t, \Delta t) = \frac{\sum_{i=1}^{n} \sum_{j=1; j \neq i}^{n} I\{\hat{\pi}_i(t + \Delta t \mid t) < \hat{\pi}_j(t + \Delta t \mid t)\} \times I\{\Omega_{ij}^{(1)}(t)\}}{\sum_{i=1}^{n} \sum_{j=1; j \neq i}^{n} I\{\Omega_{ij}^{(1)}(t)\}},$$

with

$$\Omega_{ij}^{(1)}(t) \; = \; \left[\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 1\}\right] \cap \{T_j > t + \Delta t\}$$

2.6 Model Discrimination (cont'd)

- And

$$\widehat{\text{AUC}}_2(t, \Delta t) = \frac{\sum_{i=1}^{n} \sum_{j=1; j \neq i}^{n} I\{\hat{\pi}_i(t + \Delta t \mid t) < \hat{\pi}_j(t + \Delta t \mid t)\} \times I\{\Omega_{ij}^{(2)}(t)\} \times \widehat{K}}{\sum_{i=1}^{n} \sum_{j=1; j \neq i}^{n} I\{\Omega_{ij}^{(2)}(t)\} \times \widehat{K}},$$

with

$$\Omega_{ij}^{(2)}(t) \;=\; \left[\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 0\}\right] \cap \{T_j > t + \Delta t\}$$

and

$$\widehat{K} = 1 - \hat{\pi}_i(t + \Delta t \mid T_i)$$

2.6 Model Discrimination (cont'd)

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

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

2.7 Calibration

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

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

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

2.7 Calibration (cont'd)

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

- The expected error of prediction has the form

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

  where

  - $N_i(t) = I(T_i^* > t)$ is the event status at time t
  - $L(\cdot)$ denotes a loss function, such as the absolute or square loss

2.7 Calibration (cont'd)

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

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

  where

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

2.7 Calibration (cont'd)

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

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

2.8 Landmarking vs JM: An Example

- We have earlier seen that the landmark approach also provides estimates of dynamic survival probabilities $\pi_j(u \mid t)$
  - ▷ we make here a comparison here with joint modeling for the PBC dataset

- Joint models:
  - ▷ Longitudinal process:

$$\begin{aligned} y_i(t) \;=\; & \beta_1 \texttt{Plcb}_i + \beta_2 \texttt{D-penc}_i + \beta_3\{B_1(t,\lambda) \times \texttt{Plcb}_i\} + \beta_4\{B_1(t,\lambda) \times \texttt{D-penc}_i\} \\ & + \beta_5\{B_2(t,\lambda) \times \texttt{Plcb}_i\} + \beta_6\{B_2(t,\lambda) \times \texttt{D-penc}_i\} \\ & + \beta_7\{B_3(t,\lambda) \times \texttt{Plcb}_i\} + \beta_8\{B_3(t,\lambda) \times \texttt{D-penc}_i\} \\ & + b_{i0} + b_{i1}B_1(t,\lambda) + b_{i2}B_2(t,\lambda) + b_{i3}B_3(t,\lambda) + \varepsilon_i(t), \end{aligned}$$

2.8 Landmarking vs JM: An Example (cont'd)

- Joint models:
  - ▷ Survival process:

$$M_1: \quad h_i(t) = h_0(t)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 m_i(t)\Big\},$$

$$M_2: \quad h_i(t) = h_0(t)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\Big\},$$

$$M_3: \quad h_i(t) = h_0(t)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 \int_0^t m_i(s)ds\Big\},$$

$$M_4: \quad h_i(t) = h_0(t)\exp\big(\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 b_{i0} + \alpha_2 b_{i1} + \alpha_3 b_{i2} + \alpha_4 b_{i3}\big),$$

2.8 Landmarking vs JM: An Example (cont'd)

- We focus on the interval $[t = 7, u = 9]$ and we fit a series of Cox models to the patients at risk at $t = 7$ with corresponding association structures to the previous joint models, i.e.,

$$M_5: \quad h_i(u-7) = h_0(u-7)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 \tilde{y}_i(7)\Big\},$$

$$M_6: \quad h_i(u-7) = h_0(u-7)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 \tilde{y}_i(7) + \alpha_2 \tilde{y}'_i(7)\Big\},$$

$$M_7: \quad h_i(u-7) = h_0(u-7)\exp\Big\{\gamma_1 \texttt{D-penc}_i + \gamma_2 \texttt{Age}_i + \gamma_3 \texttt{Female}_i + \alpha_1 \sum_{s=0}^{7} y_i(s)\Delta s\Big\},$$

2.8 Landmarking vs JM: An Example (cont'd)

where

- ▷ $\tilde{y}_i'(7)$ denotes the slope defined from the last two available measurements of each patient
- ▷ $\sum_{s=0}^{7} y_i(s)\Delta s$ denotes the area under the step function defined from the observed square root aortic gradient measurements up to 7 years

- We evaluate both discrimination and calibration
  - ▷ calibration: $\widehat{\text{PE}}(9|7)$ and $\widehat{\text{IPE}}(9|7)$ using the absolute loss function
  - ▷ discrimination: $\widehat{\text{AUC}}(9|7)$ and $\widehat{\text{C}}_{dyn}^{\Delta t=2}$ based on the interval $[0, 10]$ years

2.8 Landmarking vs JM: An Example (cont'd)

	$\widehat{\text{PE}}(9\|7)$	$\widehat{\text{IPE}}(9\|7)$	$\widehat{\text{AUC}}(9\|7)$	$\widehat{\text{C}}_{dyn}^{\Delta t=2}$
M_1: JM value	0.201	0.118	0.787	0.854
M_2: JM value+slope	0.197	0.114	0.793	0.855
M_3: JM area	0.191	0.112	0.758	0.839
M_4: JM shared RE	0.191	0.108	0.807	0.840
M_5 : Cox_{LM} value	0.229	0.127	0.702	0.841
M_6 : Cox_{LM} value+slope	0.227	0.126	0.710	0.825
M_7 : Cox_{LM} area	0.226	0.125	0.697	0.827

- For this particular dataset and comparing the same parameterization we observe that joint modeling is better in terms of both calibration and discrimination

2.9 Validation

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

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

The End of Tutorial IV!

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