Modern use of Shared Parameter Models for Dropout

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Joint Conference on Biometrics & Biopharmaceutical Statistics

August 30th, 2017

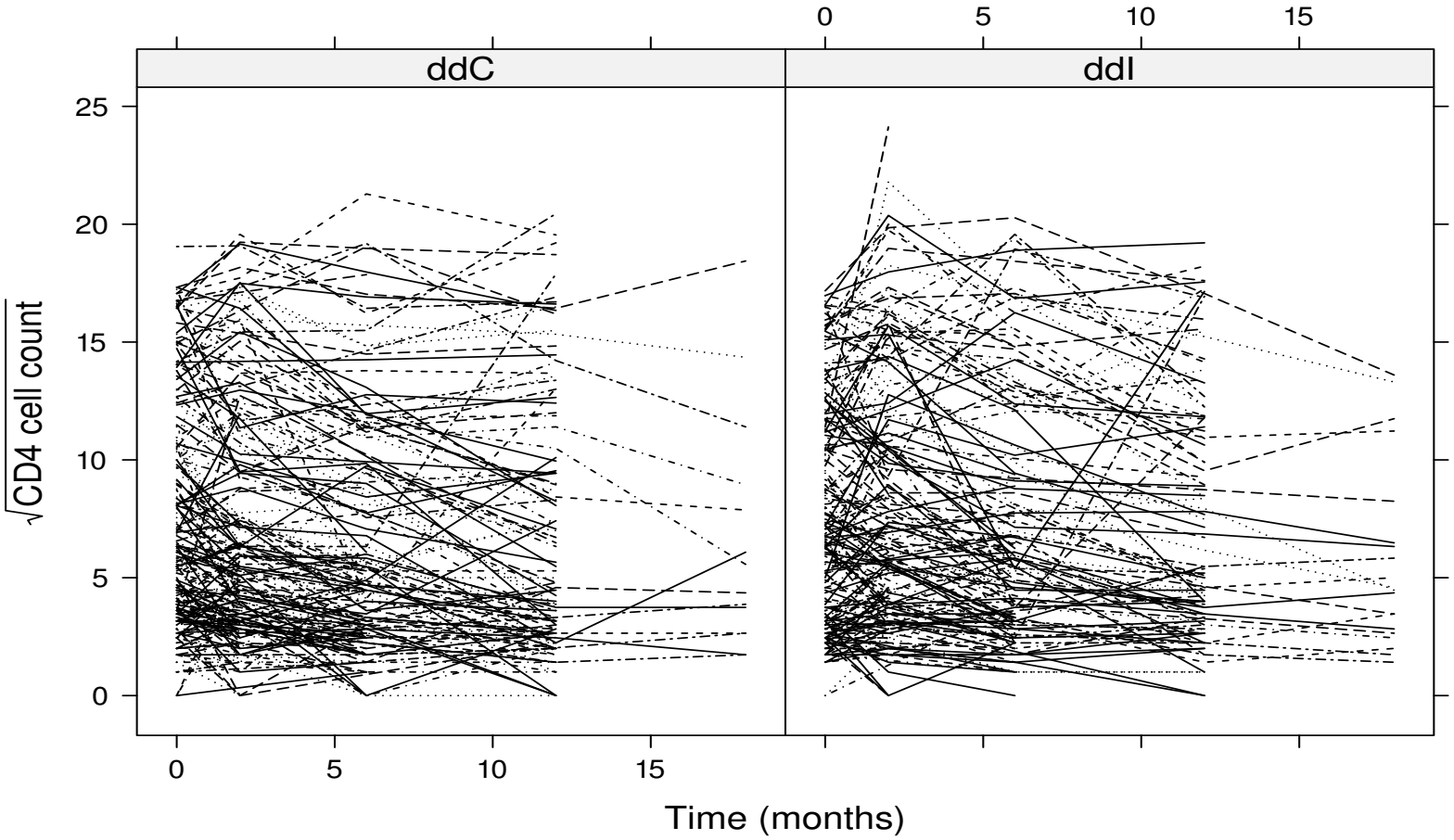
1.1 Motivating Case Study

- 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 Case Study (cont'd)



1.1 Motivating Case Study (cont'd)

- Research Question:
  - ▷ Investigate the longitudinal evolutions of CD4 cell count correcting for dropout

1.2 Goals

- **Goals** of this talk:
  - ▷ introduce joint models
  - ▷ link with missing data
  - ▷ sensitivity analysis

2.1 Missing Data in Longitudinal Studies

- 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 pre-specified follow-up times
  - ▷ often subjects miss some of their planned measurements for a variety of reasons

2.1 Missing Data in Longitudinal Studies (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

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

2.1 Missing Data in Longitudinal Studies (cont'd)

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

- **For the remaining we will focus on dropout** $\Rightarrow$ notation can be simplified
  - ▷ Discrete dropout time: $r_i^d = 1 + \sum_{j=1}^{n_i} r_{ij}$ (ordinal variable)
  - ▷ **Continuous time**: T_i^* denotes the time to dropout

2.2 Missing Data Mechanisms

- To describe the probabilistic relation between the measurement and missingness processes Rubin (1976, Biometrika) has introduced three mechanisms
  - ▷ Missing Completely At Random (MCAR)
  - ▷ Missing At Random (MAR)
  - ▷ Missing Not At Random (MNAR)

We focus on MNAR settings

2.2 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 $\Rightarrow$ **analyses which are valid under MAR will not be valid under MNAR**

2.2 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

3.1 Joint Modeling Framework

- To account for possible MNAR dropout, we need to postulate a model that relates
  - ▷ the CD4 cell count, with
  - ▷ the time to dropout

Joint Models for Longitudinal and Time-to-Event Data

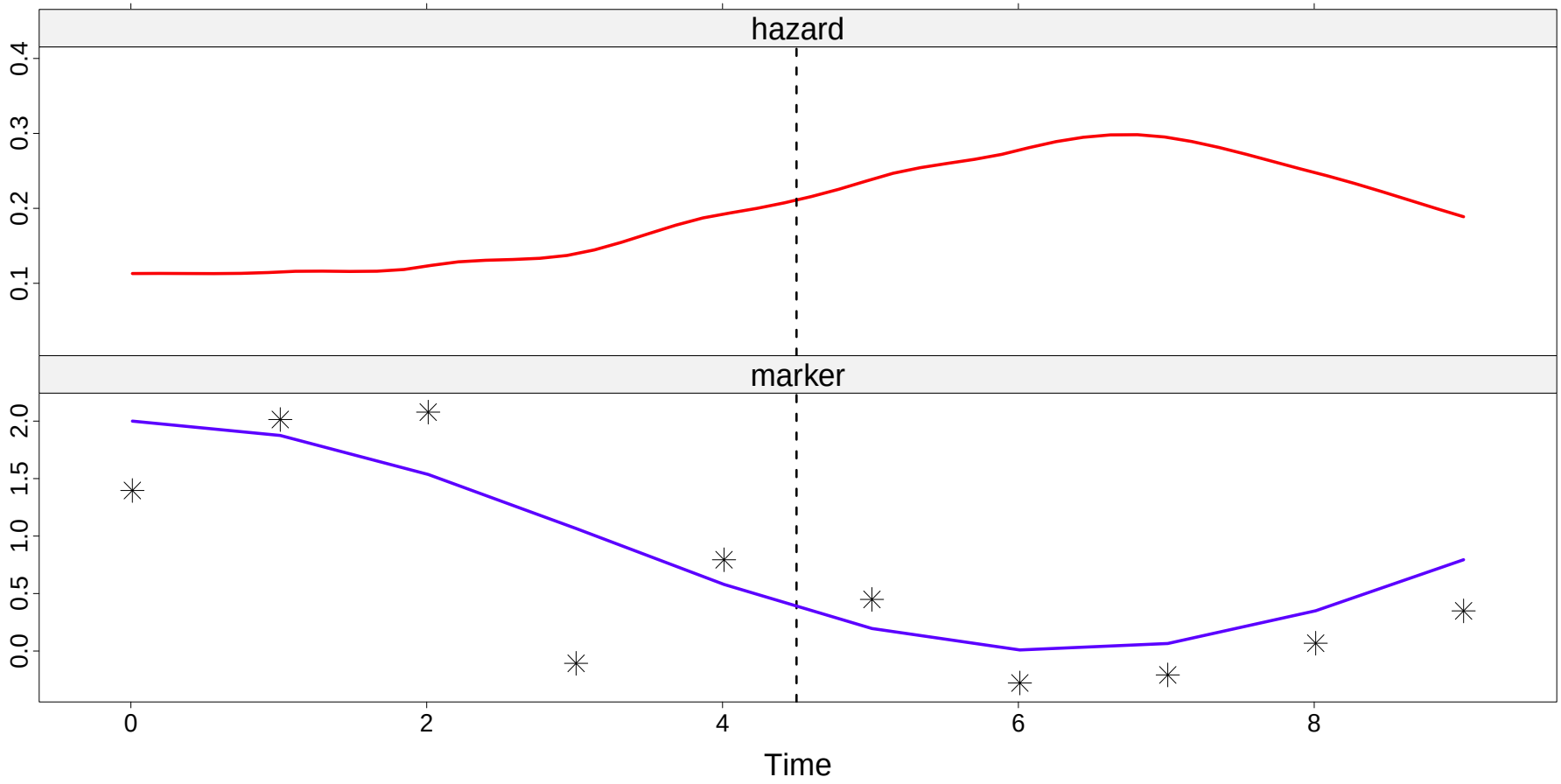
- Intuitive idea behind these models
  1. use an appropriate model to describe the evolution of the marker in time for each patient
  2. the estimated evolutions are then used in a Cox model

3.1 Joint Modeling Framework (cont'd)

- Some notation
  - ▷ y_i: Longitudinal responses
  - ▷ T_i: Dropout time for patient i
  - ▷ δ_i: Dropout indicator, i.e., equals 1 for MNAR events

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

3.1 Joint Modeling Framework (cont'd)



3.1 Joint Modeling Framework (cont'd)

- We define a standard joint model

  ▷ Survival Part: Relative risk model

$$h_i(t) = h_0(t) \exp\{\gamma^\top w_i + \alpha m_i(t)\},$$

  where
  * $m_i(t)$ = underlying CD4 cell count at time t
  * α quantifies how strongly associated CD4 cell count with the risk of dropping out
  * w_i baseline covariates

3.1 Joint Modeling Framework (cont'd)

▷ Longitudinal Part: Reconstruct $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$ using $y_i(t)$ and a mixed effects model (we focus on continuous markers)

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

where

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

3.1 Joint Modeling Framework (cont'd)

- 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

3.2 Link with Missing Data Mechanisms

- To show this connection more clearly
  - ▷ T_i^*: true time-to-event
  - ▷ y_i^o: longitudinal measurements before T_i^*
  - ▷ y_i^m: longitudinal measurements after T_i^*

- **Important to realize** that the model we postulate for the longitudinal responses is for the complete vector $\{y_i^o, y_i^m\}$
  - ▷ implicit assumptions about missingness

3.2 Link with Missing Data Mechanisms (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

3.3 Link with Missing Data Mechanisms (cont'd)

- What about censoring?
  - ▷ censoring also corresponds to a discontinuation of the data collection process for the longitudinal outcome

- Likelihood-based inferences for joint models provide valid inferences when censoring is 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)
  - ▷ censoring depends on random effects (MNAR)

3.3 Link with Missing Data Mechanisms (cont'd)

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

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

the association between the longitudinal and missingness processes is explained by the *shared* random effects b_i

3.3 Link with Missing Data Mechanisms (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

3.4 MNAR Analysis of the AIDS data

- Example: In the AIDS dataset
  - ▷ 58 (5%) completers
  - ▷ 184 (39%) died before completing the study
  - ▷ 225 (48%) dropped out before completing the study

- A comparison between
  - ▷ linear mixed-effects model $\Rightarrow$ all dropout MAR
  - ▷ joint model $\Rightarrow$ death is set MNAR, and dropout MAR

  is warranted

3.4 MNAR Analysis of the AIDS data (cont'd)

- We fitted the following joint model

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

  where

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

- The MAR analysis entails only the linear mixed model

3.4 MNAR Analysis of the AIDS data (cont'd)

	LMM (MAR)	JM (MNAR)
	value (s.e.)	value (s.e)
Intercept	7.19 (0.22)	7.20 (0.22)
Time	−0.16 (0.02)	−0.23 (0.04)
Treat:Time	0.03 (0.03)	0.01 (0.06)

- ▷ We observe some sensitivity for the time effect
- ▷ The interaction with treatment remains non significant under both analyses

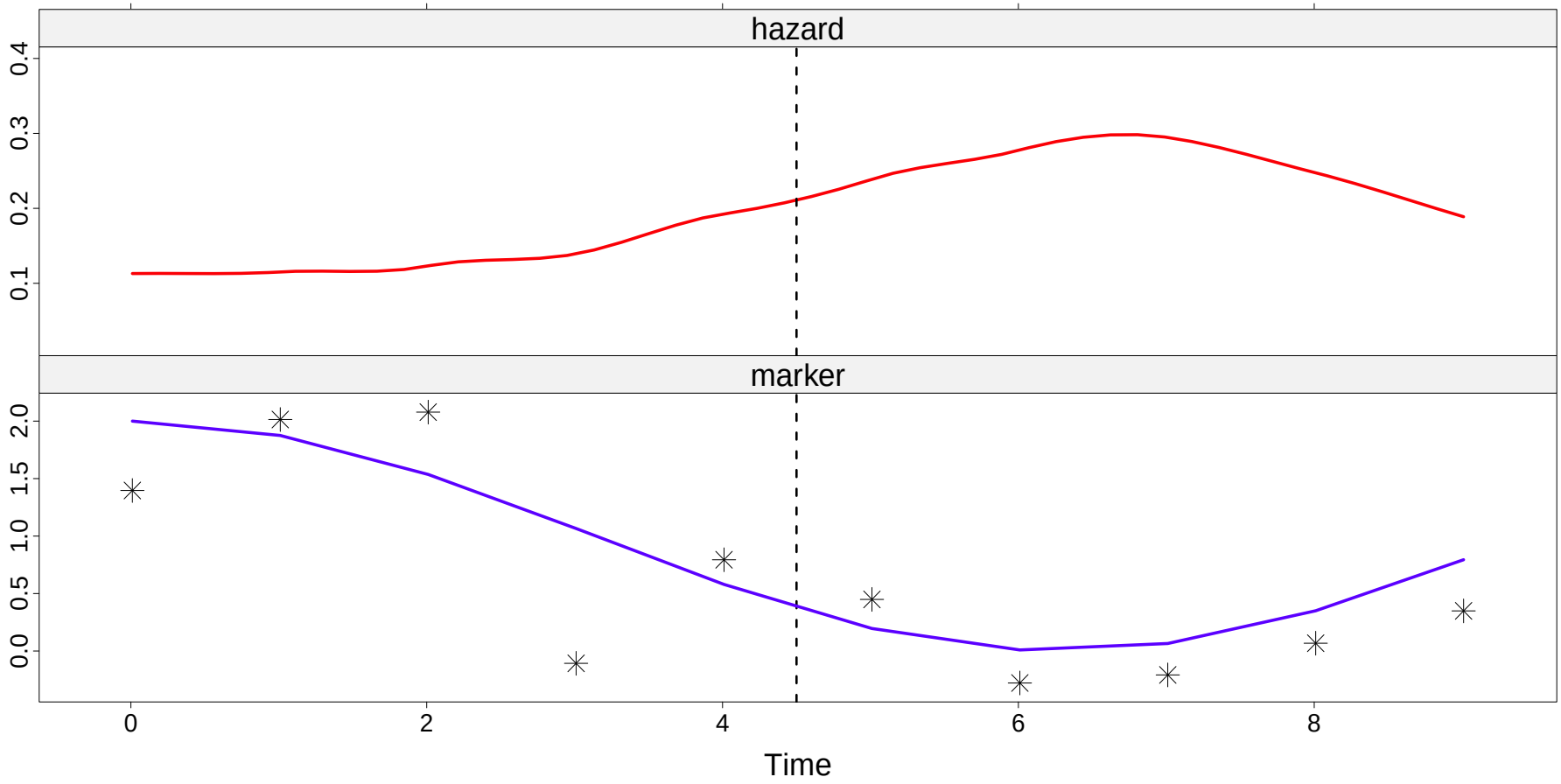
4.1 Association Structures

- The standard assumption is

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

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

4.1 Association structures (cont'd)



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

Is this the only option? What is the impact on longitudinal inferences?

4.2 Time-dependent Slopes

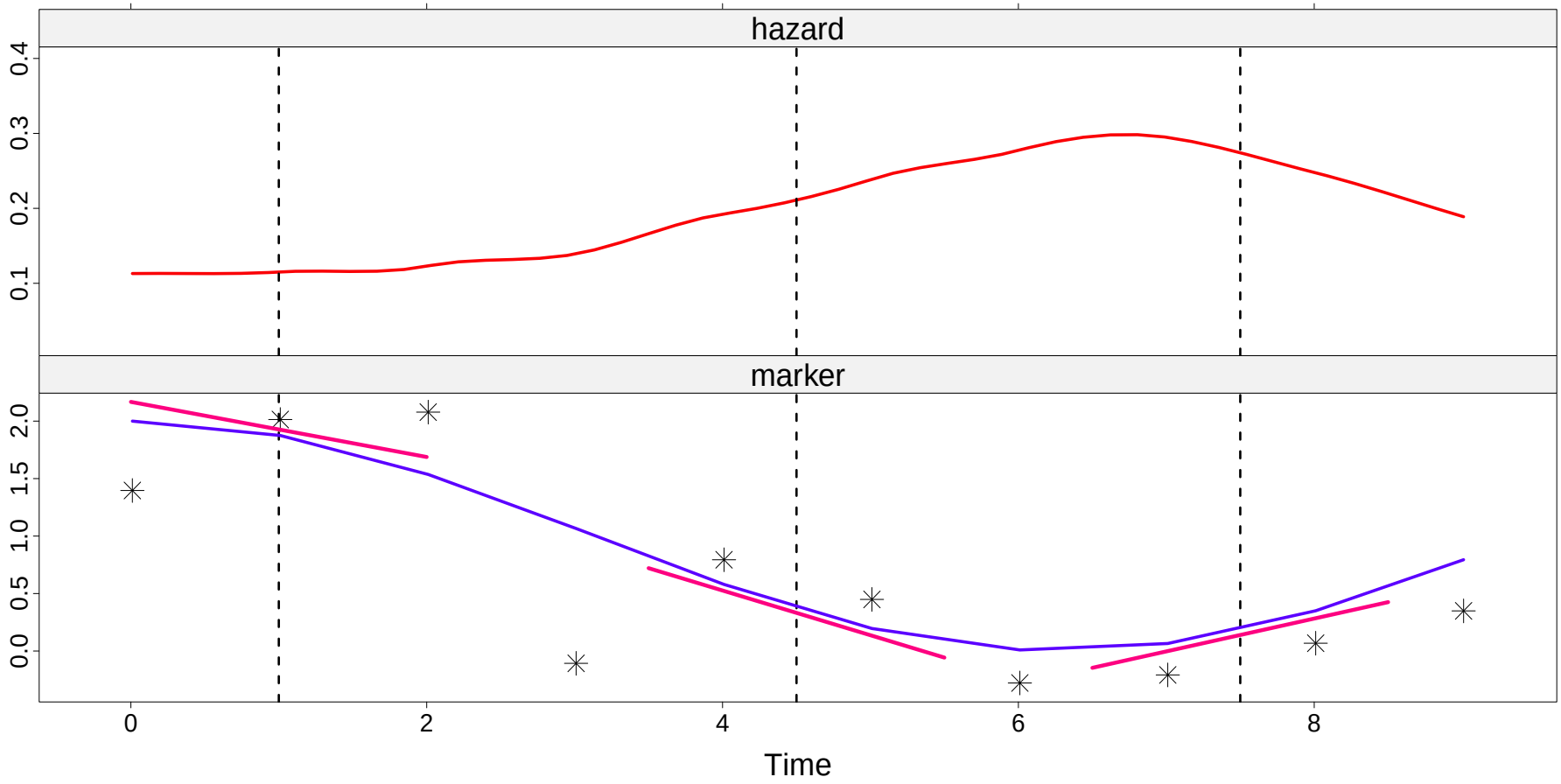
- The hazard for an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

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

where

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

4.2 Time-dependent Slopes (cont'd)



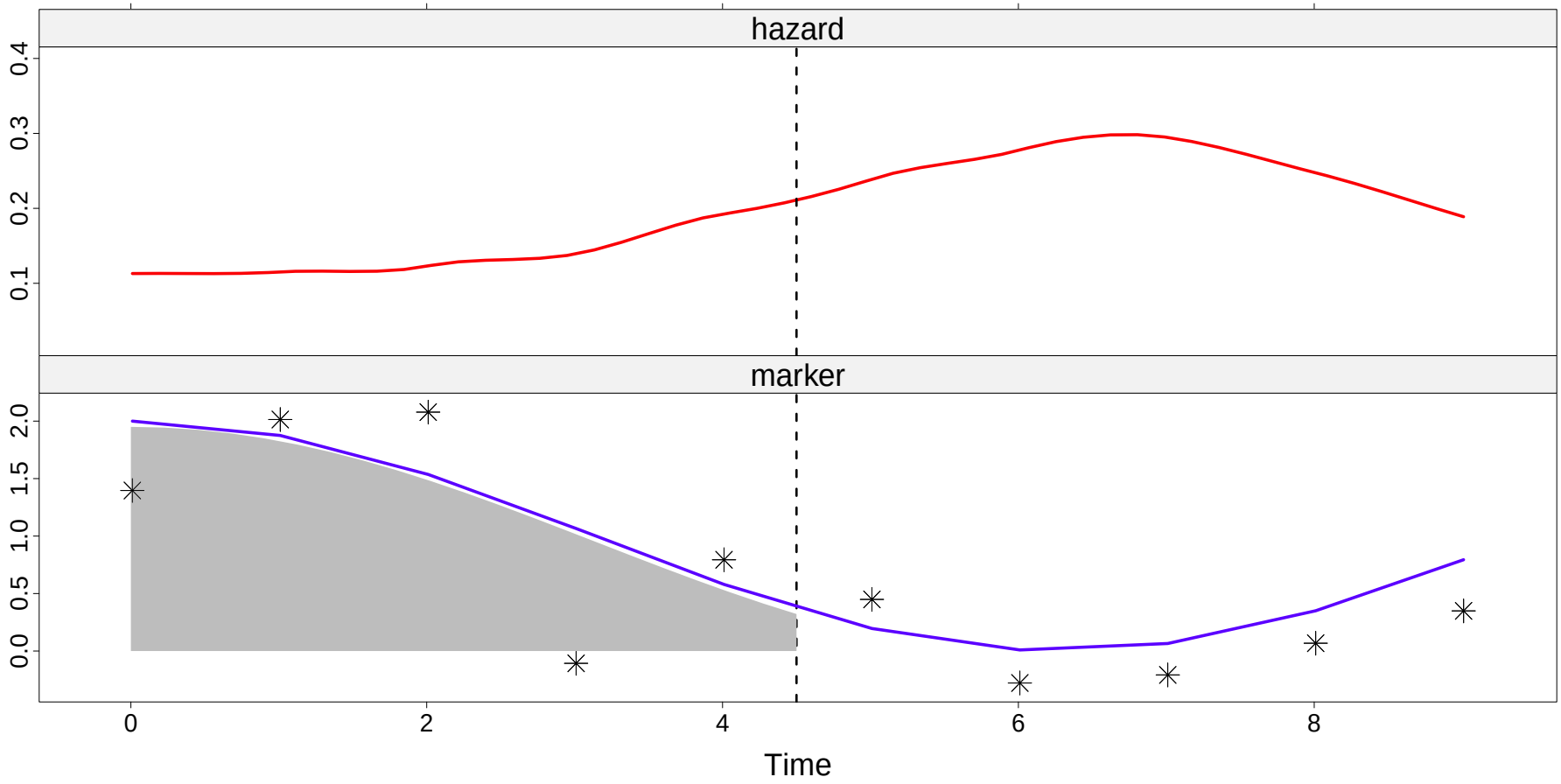
4.3 Cumulative Effects

- The hazard for an event at t is associated with area under the trajectory up to t:

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

- Area under the longitudinal trajectory taken as a summary of $\mathcal{M}_i(t)$

4.3 Cumulative Effects (cont'd)



4.4 Weighted Cumulative Effects

- 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 $\varpi(\cdot)$ appropriately chosen weight function, e.g.,

- ▷ Gaussian density
- ▷ Student's-t density
- ▷ ...

4.5 Parameterizations & Sensitivity Analysis

- 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

4.5 Parameterizations & Sens. Analysis (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

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

4.5 Parameterizations & Sens. Analysis (cont'd)

- Model III (random slope)

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

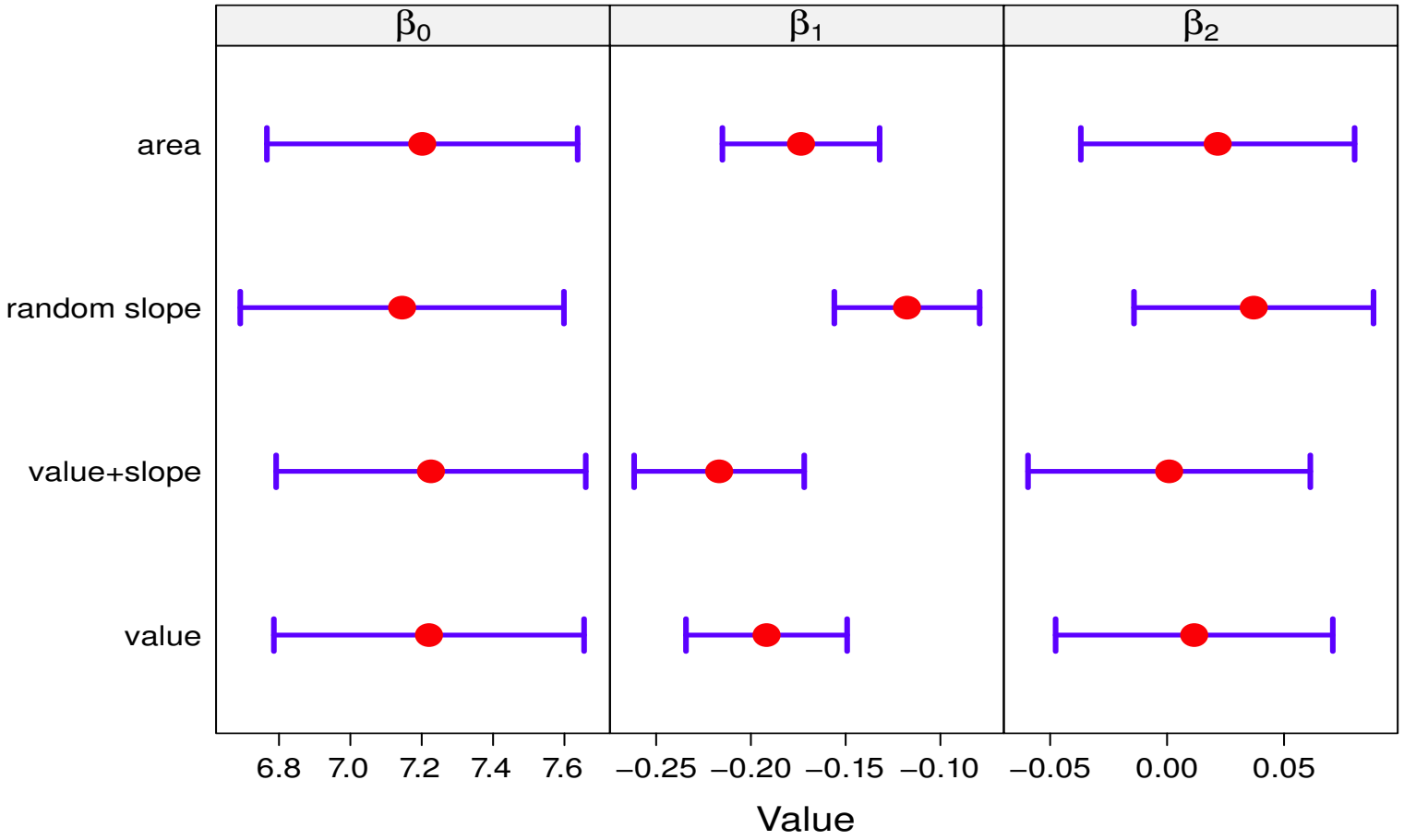
- Model IV (area)

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

where

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

4.5 Parameterizations & Sens. Analysis (cont'd)



5. Software

- Software: R package **JM** freely available via
  http://cran.r-project.org/package=JM
  - ▷ it can fit a variety of joint models + many other features

- More info available at:

> Rizopoulos, D. (2012). *Joint Models for Longitudinal and Time-to-Event Data, with Applications in R*. Boca Raton: Chapman & Hall/CRC.
>
> Web site: http://jmr.r-forge.r-project.org/

5. Software (cont'd)

- Software: R package **JMbayes** freely available via
  http://cran.r-project.org/package=JMbayes
  - ▷ it can fit a variety of multivariate joint models + many other features

- SAS macro %JM by Alberto Garcia-Hernandez & D. Rizopoulos
  http://www.jm-macro.com/

Thank you for your attention!

http://www.drizopoulos.com/