Longitudinal + Reliability = Joint Modeling

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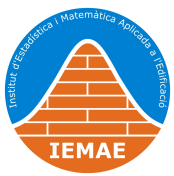
Mainly from Rizopoulos, D (2012)
Joint Models for Longitudinal and Time-to-Event Data
with Applications in R
Chapman & Hall/CRC Biostatistics Series



Outline

Goals

- In follow-up studies, we are interested in studying the association structure between several longitudinal responses and the time until an event of interest (*e.g.* biomarkers with strong prognostic capabilities for even time outcomes)
- Dynamic nature (*i.e.* between patients and within patients across time)

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- In follow-up studies, we are interested in studying the association structure between several longitudinal responses and the time until an event of interest (*e.g.* biomarkers with strong prognostic capabilities for even time outcomes)
- Dynamic nature (*i.e.* between patients and within patients across time)
- Former works by Self and Pawitan (1992) and DeGrutola and Tu (1994) in AIDS research
- Seminal papers by Faucett and Thomas (1996) and Wulfshon and Tsiatis (1997) introducing the "standard joint model"
- JM R package to for joint modelling by Rizopoulos (2012, 2010)

A Motivating Dataset

- A cohort of 467 HIV-infected patients during antiretroviral treatment who had failed or were intolerant to zidovudine therapy.
- Main goal: To compare the efficacy of two alternative drugs, didanosine (ddI) and zalcitabine (ddC), in the time-to-death.
- Longitudinal information: CD4 cell counts at 0 (randomization), 2, 6, 12 and 18 months
- More details in Abrams *et al.* (1994)

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Other Applications/Examples

- In sociology or educational testing
- In civil engineering or building construction

Inferential Objectives in Longitudinal Studies

Explicit versus implicit outcomes

- Explicit: Those variables explicitly specified in the study protocol
- Implicit: Those outcomes that are not of direct interest in the study but they condition the analysis (*e.g.* missing data or visit times issues)

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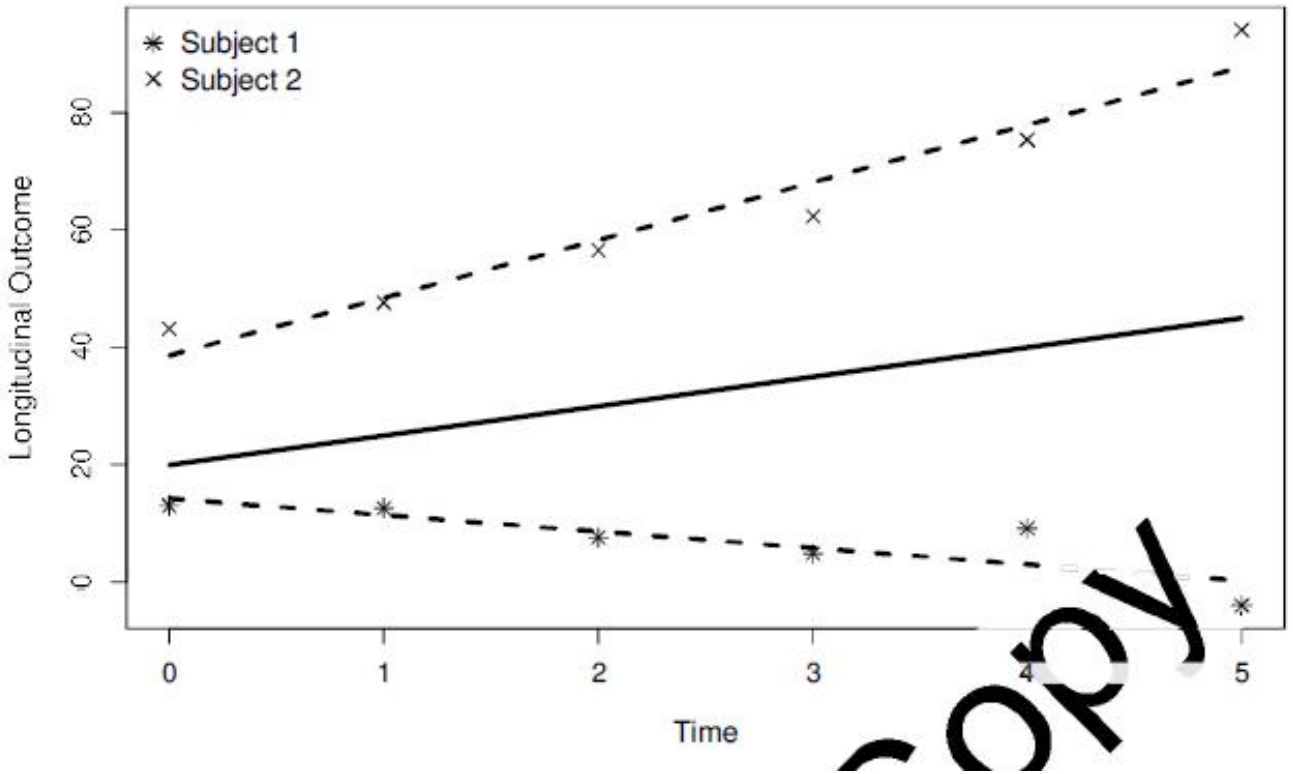
Research questions in longitudinal studies (Rizopoulos and Lesaffre, 2012)

- Effect of covariates on a single outcome
- Association between outcomes
- Complex hypothesis testing
- Prediction
- Statistical analysis with implicit outcomes

Linear Mixed-Effects Models

Let y_{ij} denote the response of subjects $i, i = 1, \ldots, n$ at time $t_{ij}, j = 1, \ldots, n_i$



Linear Mixed-Effects Models (cont')

First linear approach:

$$y_{ij} = \beta_{i0} + \beta_{i1} t_{ij} + \epsilon_{ij}$$

with $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$

Second linear approach:

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

where

- $\beta = (\beta_0, \beta_1)'$ fixed effects
- $b_i = (b_{i0}, b_{i1})'$ random effects with $b_i \sim \mathcal{N}_2(0, D)$
- $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$

LME formulation

$$\begin{cases} y_i & = & X_i\beta + Z_i b_i + \epsilon_i \\ b_i & \sim & \mathcal{N}(0, D) \\ \epsilon_i & \sim & \mathcal{N}(0, \sigma^2 I_{n_i}) \end{cases}$$

where

- X_i and Z_i known design matrices for the fixed and random effects
- I_{n_i} denotes the n_i-dimensional identity matrix
- b_i are supposed to be independent on ϵ_i

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Main advantages

- It allows to describe how the mean response changes in the population
- It allows to estimate individual response profiles over time
- It can accommodate any degree of imbalanced data
- The random effects part accounts for the correlation structure between the repeated measurements for each subject in a relative parsimonious way
- Errors can be modeled like $\epsilon_i \sim \mathcal{N}(0, \Sigma_i)$, if it is necessary (Verbeke and Molenberghs, 2000; Pinheiro and Bates, 2000)

LME estimation

The conditional (hierarchical) formulation implies the marginal model for y_i

$$y_i = X_i\beta + \epsilon_i^* \text{ with } \epsilon_i^* \sim \mathcal{N}(0, V_i = Z_i D Z_i' + \sigma^2 I_{n_i})$$

- If V_i is known β can be estimated by generalized least squares.
- If V_i is not known, β is estimated by REML (Harville, 1974)
- Standard errors for the fixed-effects via robust estimation by sandwich estimator

EM algorithm (Dempster *et al.*,1977) and Newton-Raphson algorithms (Lange, 2004) are needed.
Implementations can be found in Laird and Ware (1982) and Lindstrom and Bates (1988).

LME implementation in R

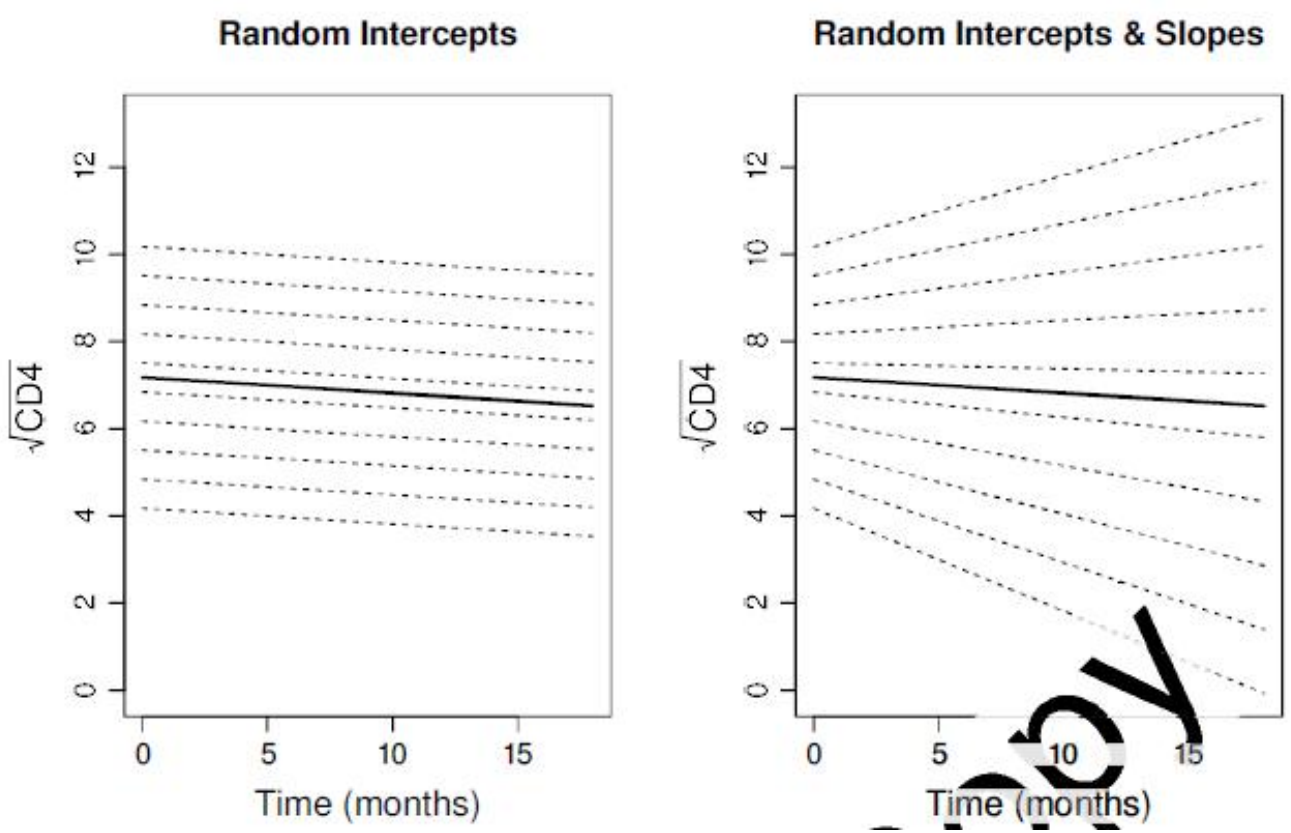
Two main packages has been implemented

- `nlme` package (Pinheiro *et al.*, 2012; Pinheiro and Bates, 2000) for continuous data and complex error structures.

- `lme4` package (Bates *et al.*, 2011) for continuous and categorical responses and correlation in the repeated measurements only using random effects.

JM package by Dimitris Rizopoulos has been implemented considering the `lme` class of objects coming from the `lme()` function in the `nlme` package.

Illustration in R



Notation and definitions

- Let T_i^* be a true survival time of interest with density function f
- Survival function: $S(t) = P(T^* > t) = \int_t^\infty f(s)ds$
- Hazard function: $h(t) = \lim_{dt \to 0} \dfrac{P(t \leq T^* < t + dt | T^* \geq t)}{dt}$

  Consequently, $S(t) = \exp\left\{ - \int_0^t h(s)ds \right\}$.

Under the presence of right censoring....

- Let C_i be the censoring time
- $\delta_i = I(T_i^* \leq C_i)$ the event indicator
- T_i the observed survival time, i.e. $T_i = \min\{T_i^*, C_i\}$

Estimation

- Non-parametric approach: K-M estimator (Kaplan and Meier, 1958; Greenwood, 1926)
- Semi-parametric approach: Proportional Hazards model (Cox, 1972), by maximizing the partial loglikelihood function

Under the Relative risk regression models

$$h_i(t|w_i) = h_0(t)\exp(\gamma' w_i)$$

where

- $w_i' = (w_{i1}, \ldots, w_{ip})$ is a vector of covariates
- $\gamma' = (\gamma_1, \ldots, \gamma_p)$ is the corresponding regression coefficients

and the ratio of hazards for two subjects i and k is

$$\frac{h_i(t|w_i)}{h_k(t|w_k)} = \exp\{\gamma'(w_i - w_k)\}$$

Time dependent covariates

Exogenous versus Endogenous covariates

- Exogenous or external: when the covariate vector $y(.)$ is associated with the rate of failure over time, but its future path up to time $t > s$ is not affected by the occurrence of failure at time s. It is a predictable process (Kalbfleisch and Prentice, 2002) (*e.g.* time of the day, season of the year, predeterminated administrative therapy, environmental factors,...)
- Endogenous or internal: otherwise. (*e.g.* often measurements taken on the subjects under study, like biomarkers and clinical parameters)
  - typically measured with error
  - their complete path up to time t is not fully observed

Extended Cox Model: Implementation

The Cox model can be extended to handle exogenous time-dependent covariates (Andersen and Gill, 1982)

$$h_i(t|\mathcal{Y}_i(t), w_i) = h_0(t)R_i(t)\exp(\gamma' w_i + \alpha y_i(t))$$

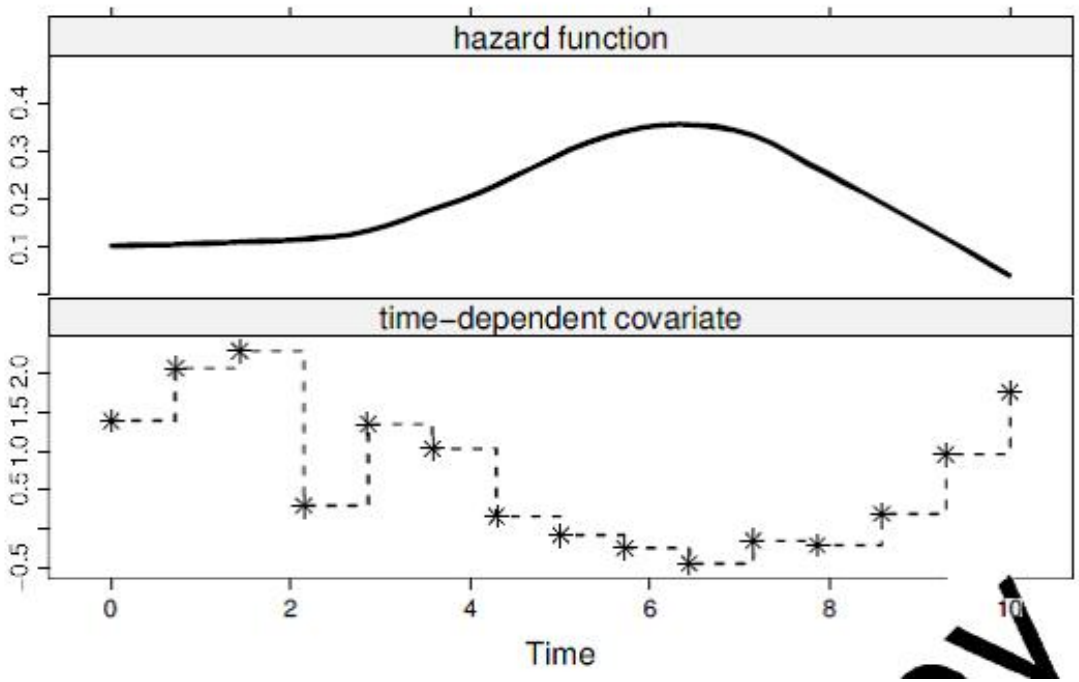
where

- $\mathcal{Y}_i(t)$ is the covariate history of y_i up to time t
- $R_i(t)$ is a left continuous at risk process ($R_i(t) = 1$ iff subject i is at risk a time t)

and parameters γ and α are again estimated by partial loglikelihood maximization.

Implementation: `survival` package (Therneau and Lumley, 2012)
`Surv()` and `coxph()` functions.

Extended Cox Model: Illustration in R



The survival submodel: Notation and definitions

- Aim: To measure the association between the longitudinal marker level and the risk for an event
- Let $m_i(t)$ be the true and unobserved value of the longitudinal outcome at time t (Remark: $m_i(t) \neq y_i(t)$)
- Let $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$ be the longitudinal process up to time t
- The relative risk model is formulated in the form

$$h_i(t|\mathcal{M}_i(t), w_i) = h_0(t) \exp(\gamma' w_i + \alpha m_i(t))$$

Remark: To let $h_0(t)$ without specifying may lead to an underestimation of the starndard errors of the parameteres (Hsieh *et al.*, 2006))

Solution: Explicitly define $h_0(t)$.

The survival submodel (cont')

Options for specifying the baseline risk

- To use known parametric distributions
- To use parametric but flexible specifications of baseline hazard
  - Step functions and linear splines (Whittemore and Killer, 1986)
  - B-splines (Rosenberg, 1995)
  - Restricted cubic splines (Herndon and Harrell, 1996)

Under the piecewise-constant model we formulate

$$h_0(t) = \sum_{q=1}^{Q} \xi_q I(v_{q-1} < t \leq v_q)$$

where

- $0 = v_0 < v_1 < \ldots < v_Q$ denotes a partition of the time scale, with v_Q larger than the larger observed time
- ξ_q constant hazard in the interval $(v_{q-1}, v_q]$

The longitudinal submodel

By using the linear mixed effects paradigm $y_i(t)$ is modeled like

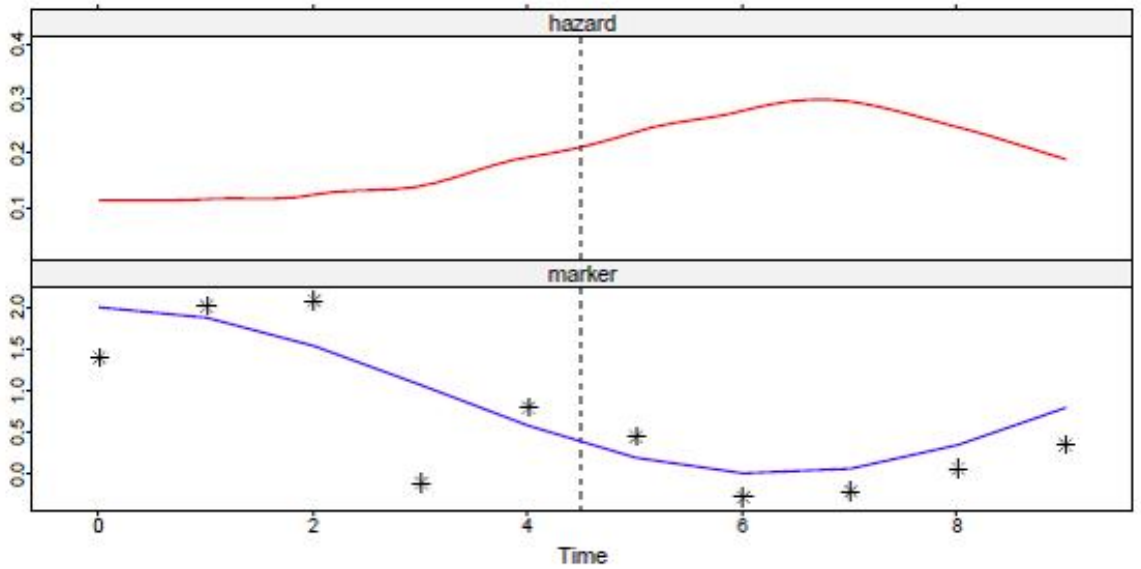
$$\begin{cases} y_i(t) &= m_i(t) + \epsilon_i(t) \\ m_i(t) &= X_i'(t)\beta + Z_i'b_i \\ b_i &\sim \mathcal{N}(0, D) \\ \epsilon_i(t) &\sim \mathcal{N}(0, \sigma^2) \end{cases}$$

where

- $x_i(t)$ and $z_i(t)$ are time-dependent design vectors and $\epsilon_i(t)$ is also time-dependent
- errors terms are mutually independent and independent of the random effects.

The longitudinal submodel

Intuitive representation of joint models



Implementation of Joint Models in R

- `JM` package by Dimitris Rizopoulos (2010, 2012) follows the random effects strategy.
  Currently only works with linear mixed-effects submodels with iid error terms and no serial correlation structure.

- The main function is `jointModel()` that needs and `lme` class of mixed-effects model under an unstructured variance-covariance matrix for the random effects and a `coxph` model for the survival submodel. `method` argument in `jointModel()` allows `piecewise-PH-GH`, `spline-PH-GH`, `Cox-PH-GH`, `weibull-PH,GH` and `weibull-AFT-GH` specifications for the baseline hazard function.

Further reading

- Semiparametric maximul likelihood estimation (Wulfshon and Tsiatis, 1997; Henderson *et al.*, 2000; Hsieh *et al.*, 2006)
- Asymptotic properties under unspecified baseline hazard (Zeng and Cai, 2005)
- Bayesian estimation of joint models using MCMC (Hanson *et al.*, 2011; Chi and Ibrahim, 2006, Xu and Zeger, 2001)
- Conditional score approach for the random effects as a nuisance parameter (Tsiatis and Davidian, 2001)

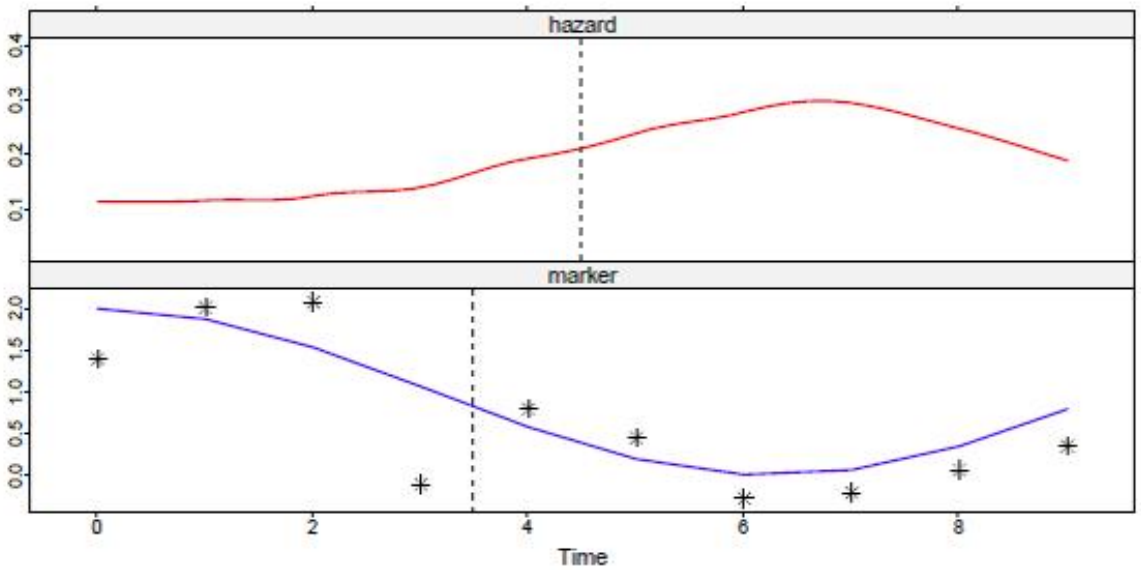
Parameterizations (1/3)

- Interaction effects

$$h_i(t) = h_0(t) \exp(\gamma' w_{i1} + \alpha' \{w_{i2} \times m_i(t)\})$$

- Lagged effects

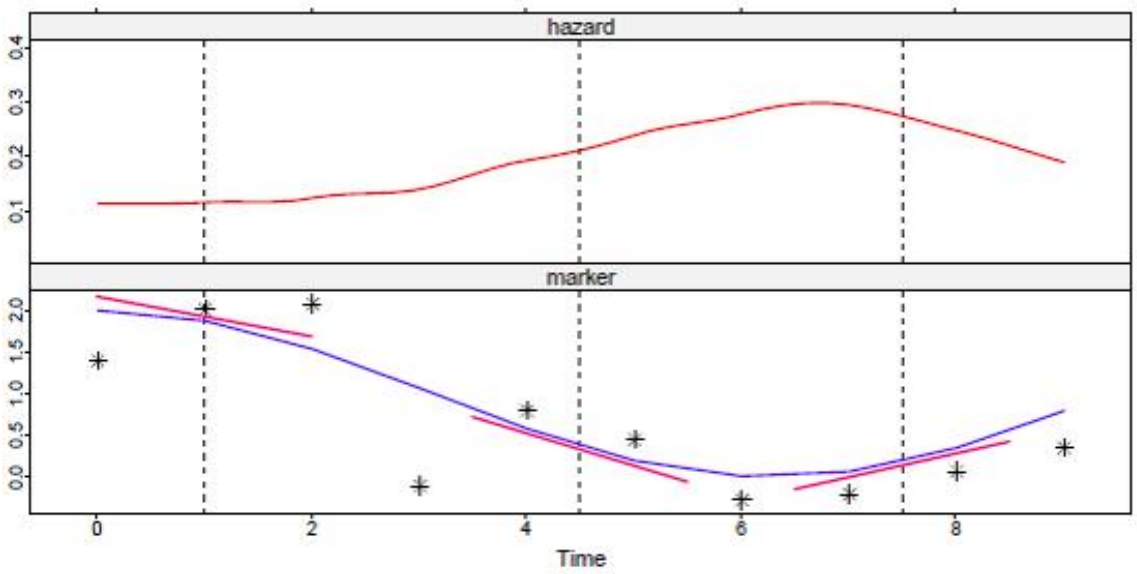
$$h_i(t) = h_0(t) \exp(\gamma' w_i + \alpha m_i \{\max(t - c, 0)\})$$



Parameterizations (2/3)

- Time-Dependent slopes parameterization

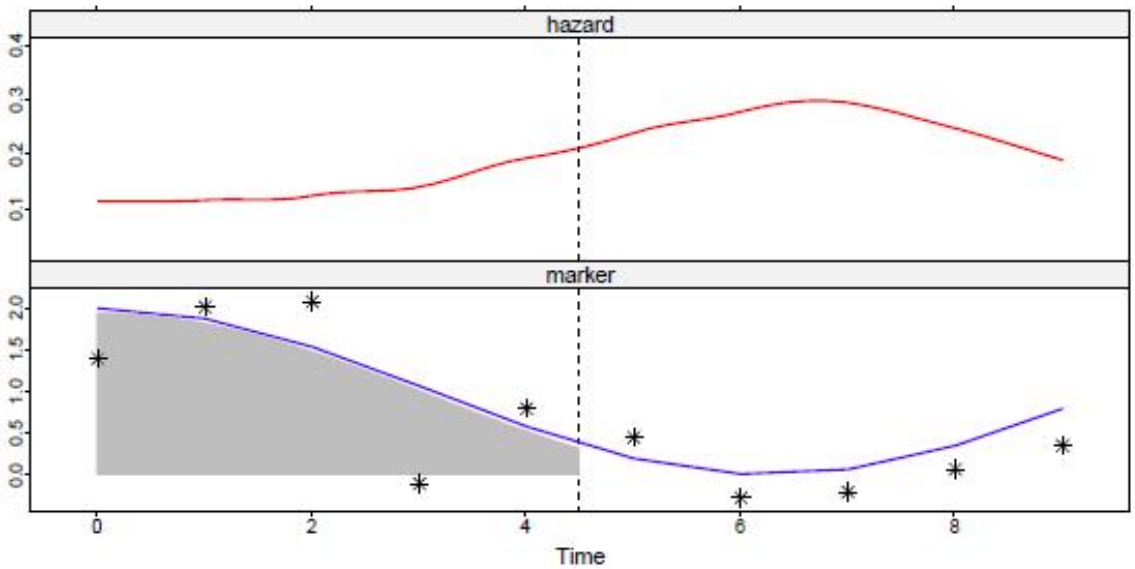
$$h_i(t) = h_0(t) \exp(\gamma' w_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t))$$



Parameterizations (3/3)

- Cummulative effects parameterization

$$h_i(t) = h_0(t) \exp\{\gamma' w_i + \alpha \int_0^t m_i(s) ds\}$$



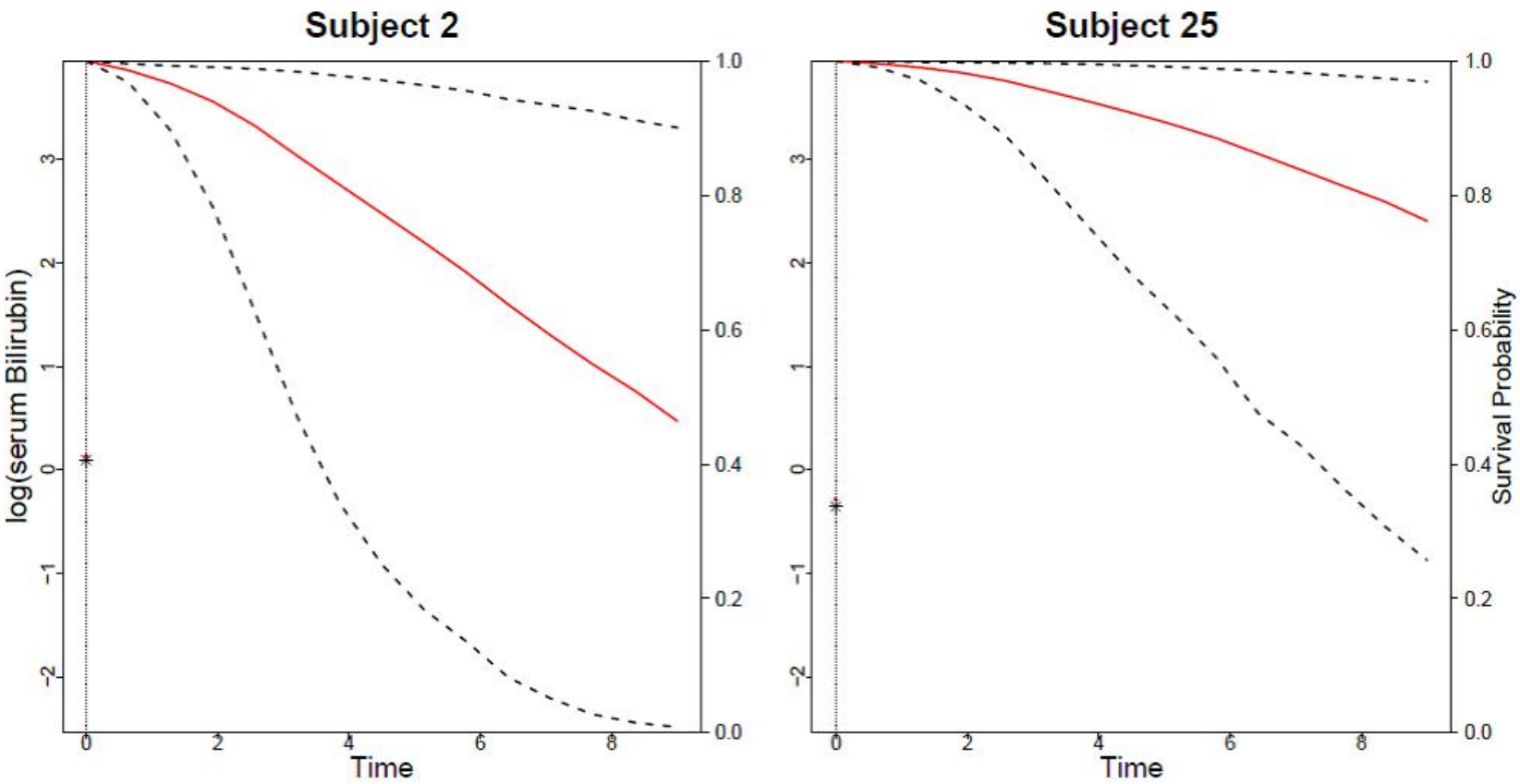
- Random effects parameterization

$$h_i(t) = h_0(t) \exp(\gamma' w_i + \alpha' b_i)$$

More on the Standard Joint Model

- To handle Exogenous time-dependent covariates
- To fit stratified relative risk models
- Allows for Multiple failure times (*e.g.* competing risks or recurrents events)
- To fit accelerated failure time models
- Diagnostics and Prediction

Prediction examples



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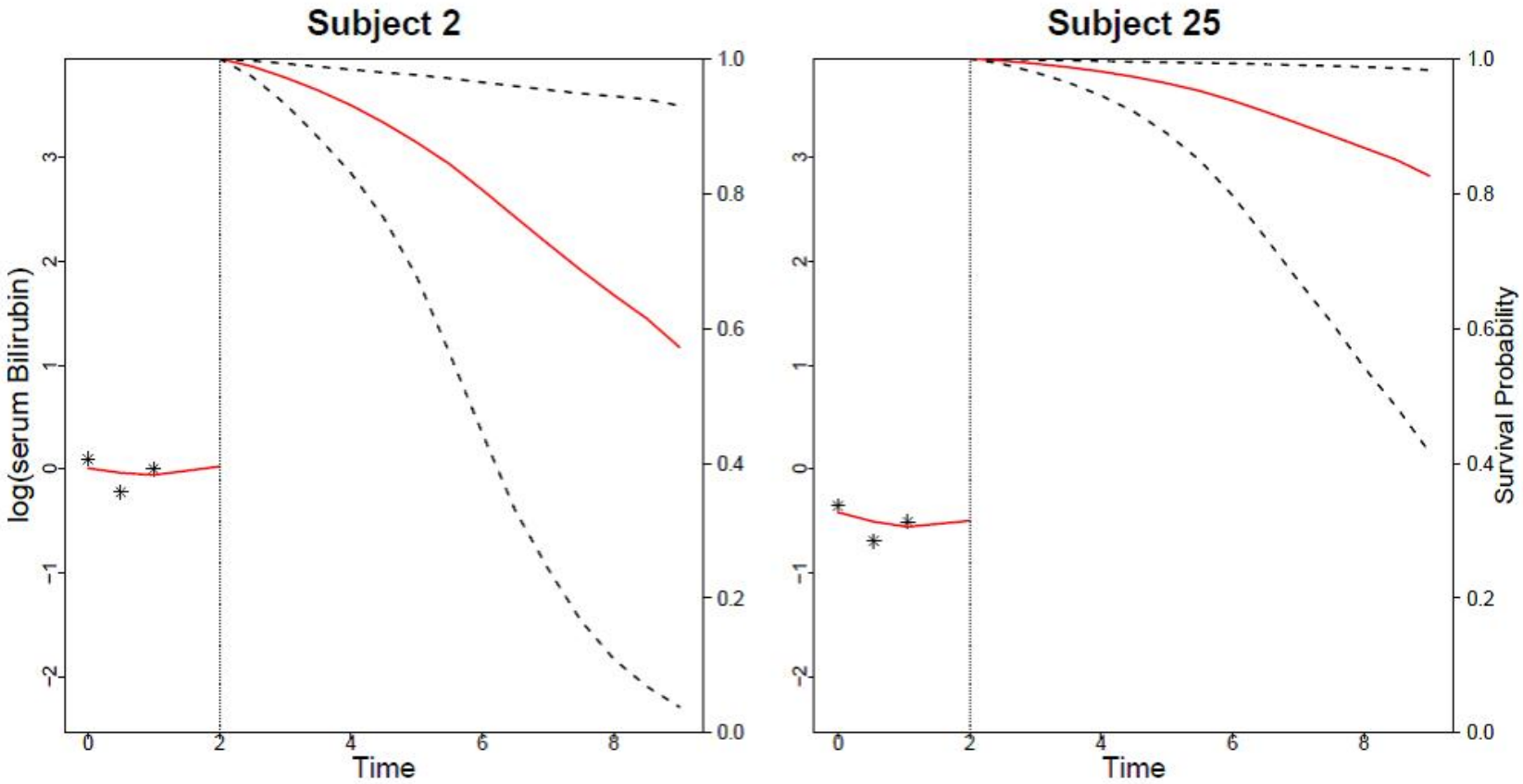

Prediction examples