

A flexible joint model for time-to-event and a sequence of longitudinal biomarker data, a full dynamic hierarchical approach.

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Motivation

Cirrhosis

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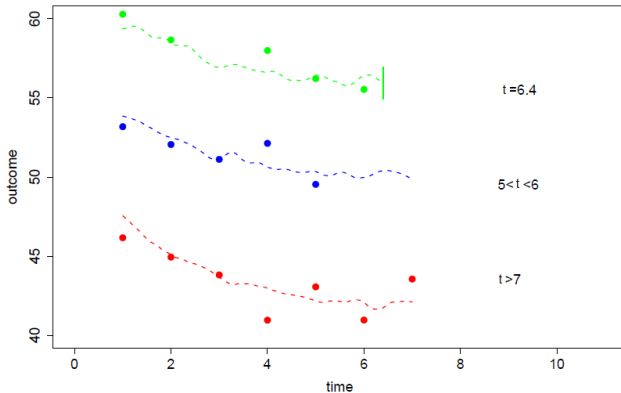
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Prothrombin index is an indirect marker of severe liver condition.

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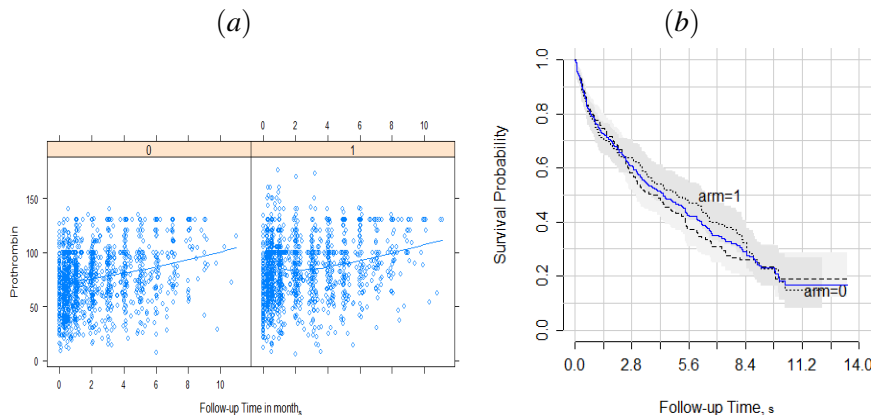
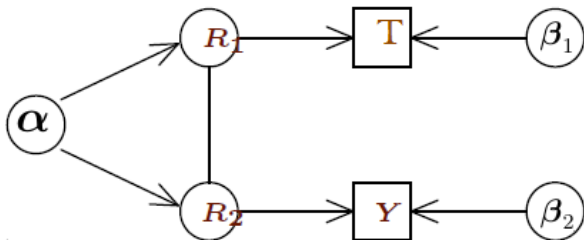
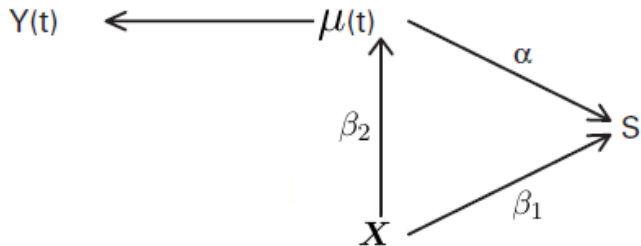


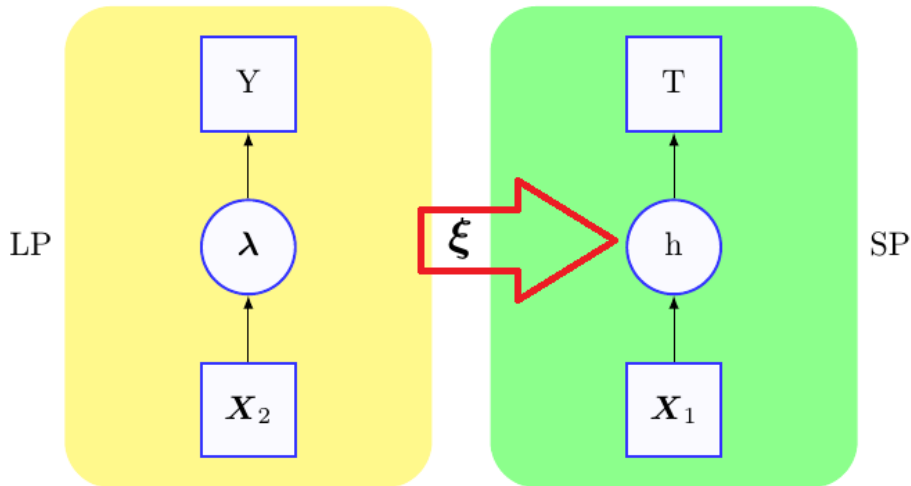
Figure: (a) Prothrombin index for the following times, the lines represents the median trajectory. (b) Empirical survival probability (Kaplan-Meier) for Prednisone ($arm = 1$) versus Placebo

Henderson, Diggle and Dobson (2000)





Our Propost



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- d_i represent an indicator of right censoring for the i^{th} ;
- y_{ij} , on individuals i followed up in J determined interviews denoted $s_{ij}, j = 1, \dots, J$;
- X covariates.

Survival process

$$\begin{aligned} T_i \mid \boldsymbol{\xi}_i &\sim PE[\mathbf{h}_k(\cdot \mid \boldsymbol{\xi}_i), \boldsymbol{\tau}], \mathbf{h}_k = (h_{1k}, \dots, h_{Nk}); \\ h_{ik}(t \mid \boldsymbol{\xi}_i) &= h_{0k}(t) \exp\{\mathbf{X}'_{1i}\boldsymbol{\beta}_1 + \boldsymbol{\xi}'_i\boldsymbol{\alpha}\}. \end{aligned} \tag{1}$$

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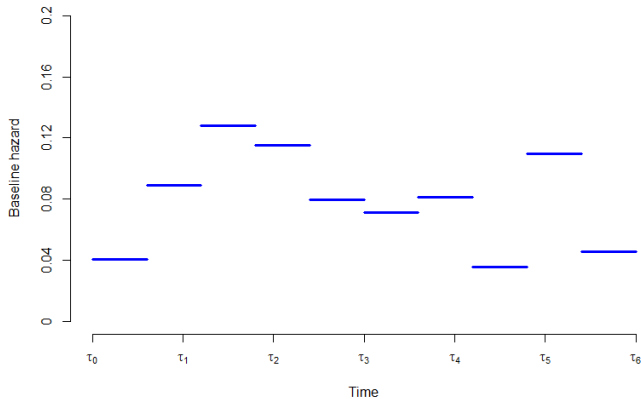


Figure: Piecewise baseline

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- 2) Dependence of the $\log h_{0k}$ over time based on Gamerman (1991)

Longitudinal sub-model

$$\begin{aligned}y_{ij} &\sim Ef[\eta_{ij}, \phi], \quad i, \dots, N; \\g(E[y_{ij}|\eta_{ij}, \phi]) &= \lambda_{ij}, \quad j, \dots, J; \\\lambda_{ij} &= \mathbf{F}'_i \boldsymbol{\theta}_j + v_i, v_i \sim \mathcal{N}(0, V); \\\boldsymbol{\theta}_j &= \mathbf{G}(\delta_j) \boldsymbol{\theta}_{j-1} + \mathbf{w}_j, \mathbf{w}_j \sim \mathcal{N}(0, \mathbf{W}); \\\boldsymbol{\theta}_0 | \mathcal{D}_0 &\sim \mathcal{N}(\mathbf{m}_0, \mathbf{C}_0).\end{aligned}\tag{2}$$

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- K : natural choice based on number of longitudinal measurements
- Dynamic model provides natural framework for data forecast \rightarrow prediction of survival probabilities.

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Posterior

$$\pi(\Theta \mid x) \propto L_{\mathcal{D}}(\Theta)\pi(\Theta),$$

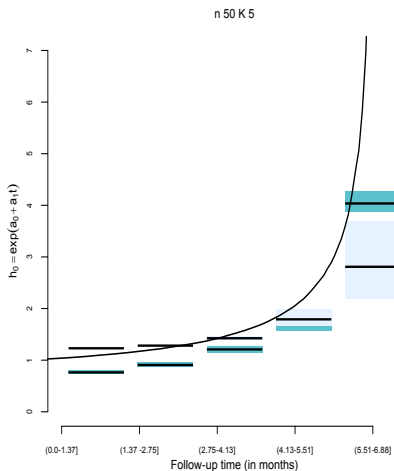
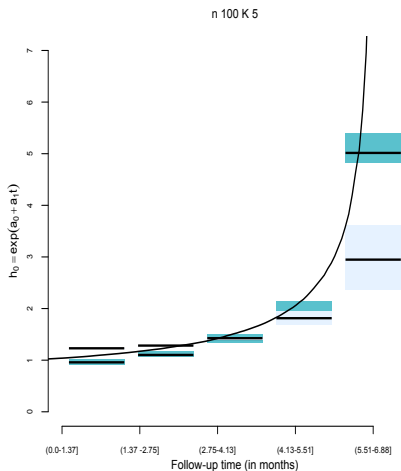
Simulation study: $n= 50,100$; $K= 3,5,7$

Hierarchical dynamic joint using ξ_{ij} as a bridge function.

Input: N, J , mean 2 for the right censoring, $\mathbf{F}, \mathbf{G}, V, \mathbf{W}, a, b, \mathbf{m}_0, \mathbf{C}_0$

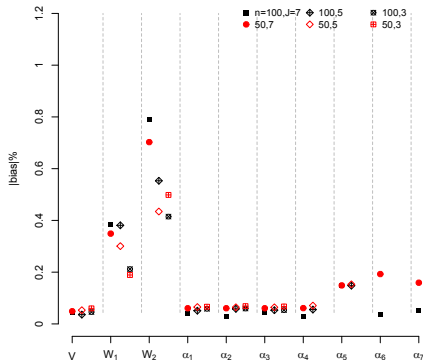
- Initial information: $(\boldsymbol{\theta}_0) \leftarrow N[\mathbf{m}_0, \mathbf{C}_0]$, $j = 1$;
- System equation: $(\boldsymbol{\theta}_j) \leftarrow \mathcal{N}(\mathbf{G}_j \boldsymbol{\theta}_{j-1}, \mathbf{W})$ to $j = 2, \dots, J$;
- Structure equation: $(\lambda_{ij}) \leftarrow \mathcal{N}(\mathbf{F}'_i \boldsymbol{\theta}_j, V)$;
- Observation equation: $y_{ij} \leftarrow Po(\exp(\lambda_{ij}))$;
- The true times t_i^* using the inverse probability method
 $(t_i^*) \leftarrow S(t) = \int_0^{t_i^*} h_0(u) \exp(\sum_{j=1}^J \beta_j \xi_{ij}) du$;
- Obtain the censored time (c_i) using exponential distribution;
- Calculate the observed time (t_i, d_i) $(t_i, d_i) \leftarrow \min(t_i^*, c_i); I(t_i^* \leq c_i)$;
- Return $\mathbf{y}, \mathbf{t}, \mathbf{d}$

Simulation results: Results based on 1000 simulated data sets. Gompertz baseline hazard $\exp\{a + bt\}$. Gamma Process vs Log Normal

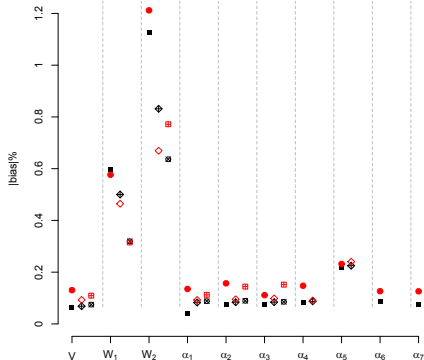


Bias (multiply by 100)

GP



log NP



Liver: Cirrhosis data set

The data are taken from Andersen(1993)(p. 19) and were analyzed in Henderson e Diggle (2002).

- longitudinal observations of prothrombin index,
- For 488 patients from a controlled trial into prednisone treatment of liver cirrhosis.
- Time-to-event information time of death (years) and associated censoring indicator

Liver:Baseline

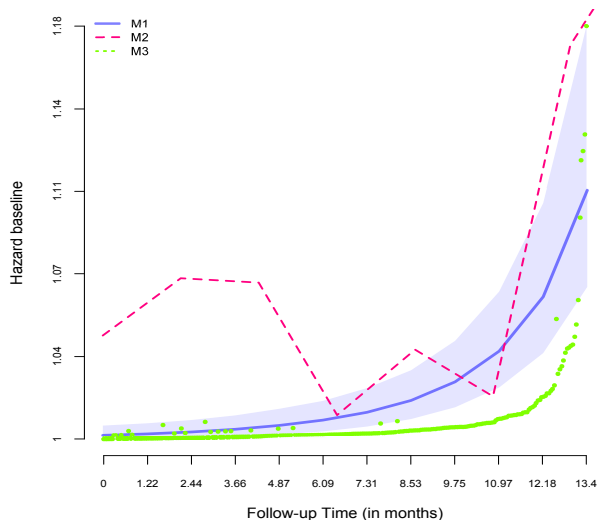


Figure: M1: proposed; M2: Rizopoulos (2016); M3: Henderson et al. (2000)

Prothrombin index level

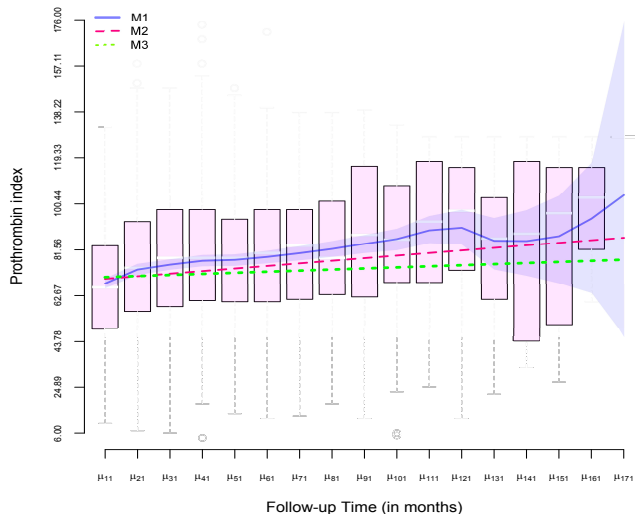


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Table: Comparison of Bayesian model selection methods for the fully dynamic joint model considering Gamma Process (GP) compared to standard joint model using the package Rizopoulos (2016). (Metrics divided by 100).

	DIC	pD	$LPML$	$\Delta LPML_{Surv}$	ΔDIC_{Surv}	ΔpD_{Surv}
Fd (GP)	346.333	330.791	-166.552	-24.304	44.674	44.614
SRE ¹	346.981	9.756	-175.249	-	-	-

¹Rizopoulos (2016)

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- Different link components between sub-models ξ_i .

References I

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