Joint Analysis of Longitudinal and Survival AIDS Data with a Spatial Fraction of Long-term Survivors: A Bayesian Approach

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CENTRO DE INVESTIGAÇÃO INTERDISCIPLINAR EGAS MONIZ

Overview

The objective is to model longitudinal and survival data jointly taking into account the dependence between the two responses in a real HIV/AIDS dataset. We employ here a Bayesian hierarchical approach to jointly model spatial-clustered survival data with a fraction of long-term survivors along with longitudinal measurements of CD4$^+$T lymphocyte counts for a random sample of 500 HIV/AIDS individuals collected in all the 27 states of Brazil during the period 2002–2006.

In order to accommodate a more flexible choice for the longitudinal model we propose to use a specification via penalized B-Splines [2]. To deal with the possible fact that only a subpopulation undergoes the event we propose a spatial cure model, which helps in explaining the behavior of chronic or potentially terminal diseases in different regions. Classical survival models (e.g. Cox model) are not-well suited to take into account long-term survivors.

Results show that using a cure fraction allows us to improve the results comparatively to a survival analysis without it. The inclusion of spatial frailties eases in mapping the heterogeneity in the risk among the Brazilian states and helps in the explanation of the hazard.

Dataset

- **Data origin**: Brazilian database on HIV;
- **Period (years)**: 2002–2006;
- **Sample size**: $n = 500$ individuals
- **Response variables**: $y = \sqrt{\text{CD4}^+\text{T}}$ lymphocyte counts and survival time (years since the patient's entry in the study until death)
- **Explanatory variables**: age (<50=0, ≥50=1); gender (Female=0, Male=1); PrevOI (previous opportunistic infection at study entry=1, no previous infection=0); region of residence (one of the 27 Brazilian States)
- 34 deaths. 88% of the patients were between 15 and 49 years old; 60% were males. The CD4 counts initial median was 245 cells/mm^3 (men - 226 cells/mm^3; women - 263 cells/mm^3).

References

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Model

Consider the CD4 repeated measurements, $\mathbf{y}_{ik} = (y_{ik1}, \ldots, y_{in_{ik}})$, and the observed (possibly right censored) time-to-death, T_{ik}, for the ith individual living in the kth region, $k = 1, \ldots, K$, $i = 1, \ldots, n_k$. **Longitudinal data** is described by a **nonlinear mixed effects model**,

$$y_{ikj}|\boldsymbol{b}_{ik}, \sigma_e^2 \sim \mathcal{N}(y^*_{ik}(t_{ikj}), \sigma_e^2), \quad j = 1, \ldots, n_{ik}, \tag{1}$$

$$y^*_{ik}(t_{ikj}) = (\beta_{10} + b_{ik0}) + \mathbf{z}_{ik}^\top \boldsymbol{\beta}_1 + m_p(t_{ikj}; \boldsymbol{\beta_2}) + m_{ik}(t_{ikj}; \boldsymbol{b}_{ik}), \tag{2}$$

where $m_p(.)$ and $m_{ik}(.)$ are the overall and individual nonlinear effects, respectively, considered here as **Penalized cubic B-Splines**. β_{10} and b_{ik0} are the common and subject-specific intercept, respectively. $\boldsymbol{\beta}_1 = (\beta_{11}, \ldots, \beta_{1r})^\top$, whose elements are assumed to be mutually independent, represents the fixed effects of the subject-specific vector of covariates, $\mathbf{z}_{ik}$; $\boldsymbol{\beta}_2 = (\beta_{21}, \ldots, \beta_{2Q})^\top$ and $\boldsymbol{b}_{ik} = (b_{ik1}, \ldots, b_{ikQ})^\top$ are, respectively, population and individual-specific **regression parameters for each basis function, penalized through a second order random-walk**.
Assuming the time-to-death for the non-cured group is Weibull distributed, $\mathcal{W}(\rho, e^{\eta(t)})$, the **spatial cure model** [1] is described as,

$$S_p(t) = (1 - \theta_k) + \theta_k S(t) = (1 - \theta_k) + \theta_k \exp\left\{-t^\rho e^{\eta(t)}\right\}, \tag{3}$$

being S_p and S the survival functions for the entire population and for the non-cured group, respectively. $(1 - \theta_k)$ is a region-specific cure fraction. The baseline covariates and the longitudinal information will be introduced through the scale parameter, $e^{\eta(t)}$, allowing it to **vary across individuals and regions**:

$$\eta_{ik}(t) = \mathbf{x}_{ik}^\top \boldsymbol{\beta}_3 + \gamma\, y^*_{ik}(t) + W_k, \tag{4}$$

where γ is a parameter quantifying the effect of the CD4 values to the survival; $\mathbf{x}_{ik}$ is a vector of baseline covariates (can coincide with $\mathbf{z}_{ik}$), $\boldsymbol{\beta}_3$ is the respective vector of coefficients and W_k is a region-specific frailty, $W_k|\sigma^2_W \sim ICAR(\sigma^2_W)$.

Application

Several scenarios for the Penalized splines were tried. Namely the internal knots were fixed every: 1 month, 2 months, 3 months, 4 months, 6 months and 12 months providing, respectively, 59, 29, 19, 14, 9 and 4 internal knots. The best fit was always achieved with 19 internal knots, corresponding roughly to a knot every 3 months during the 5 years, resulting in $Q = 23$ cubic basis functions.

$$y^*_{ikj} = (\beta_{10} + b_{ik0}) + \beta_{11}\text{sex}_{ik} + \beta_{12}\text{age}_{ik} + \beta_{13}\text{PrevOI}_{ik} + \sum_{q=1}^{Q=23} \beta_{2q} B_q(t_{ikj}) + \sum_{q=1}^{Q=23} b_{ikq} B_q(t_{ikj}) \tag{5}$$

$$\eta_{ik}(t) = \beta_{31} + \beta_{32}\text{sex}_{ik} + \beta_{33}\text{age}_{ik} + \beta_{34}\text{PrevOI}_{ik} + \gamma\, y^*_{ik}(t) + W_k \tag{6}$$

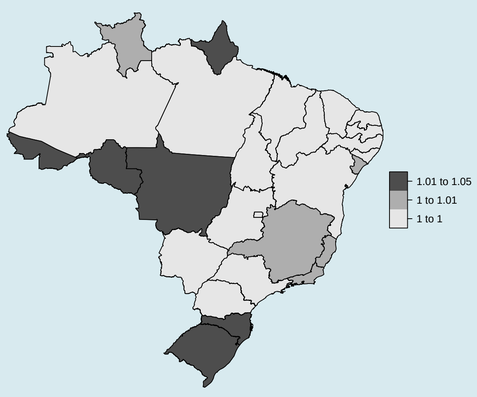
Results

$\pi(\theta)$	W_k	Measure
Common Cure	0	14867
		-7473
$\theta_k = \theta, \forall k$	W_k	**14540**(SM)
$\theta \sim \mathcal{U}(0,1)$		**-7453**(SM)
Regional Cure	0	14578
		-7482
$\theta_k \neq \theta_l, \forall k \neq l$	W_k	14596
$\theta_k \sim \mathcal{U}(0,1)$		-7487
	0	14575
No Cure		-7461
$1 - \theta_k = 0, \forall k$	W_k	14577
		-7496

Model choice: Watanabe-Akaike Information Criterion (WAIC); Logarithm of the Pseudo Marginal Likelihood (LPML).

	Mean	95% CI
(β_{10})	14.65	$(8.37, 18.78)$
(β_{11}) sex	-0.15	$(-2.66, 2.08)$
(β_{12}) age	-1.30	$(-4.25, 1.30)$
(β_{13}) PrevOI	-1.84	$(-3.67, -0.01)$
σ_e^2	4.99	$(4.54, 5.26)$
(β_{31})	-3.14	$(-4.42, -1.87)$
(β_{32}) sex	0.47	$(-0.35, 1.36)$
(β_{33}) age	0.58	$(-0.45, 1.61)$
(β_{34}) PrevOI	0.67	$(-0.15, 1.49)$
γ	-0.17	$(-0.25, -0.11)$
σ^2_W	0.015	$(0.0002, 0.13)$
ρ	2.34	$(1.67, 3.11)$
$1 - \theta$	0.17	$(0.01, 0.47)$

Parameters: posterior mean and its 95% Credibility Interval (CI).



Spatial frailties - Brazil's map presenting the posterior median of the region-specific relative risks, $\exp\{W_k\}$.

The model choice measures, WAIC and LPML, agree in the the selected model (SM) ⇒ Considering a common cure fraction for all patients and a spatial frailty outperforms the traditional joint model approach for the HIV/AIDS data, which does not considers a fraction of long-term survivors. The estimated cure fraction, $(1 - \theta)$, indicates that nearly 17% of the HIV/AIDS patients in this study may be considered long-term survivors.