spBayesSurv: Fitting Bayesian Spatial Survival Models Using R

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Abstract

Spatial survival analysis has received a great deal of attention over the last 20 years due to the important role that geographical information can play in predicting survival. This paper provides an introduction to a set of programs for implementing some Bayesian spatial survival models in R using the package **spBayesSurv, version 1.1.1**. The function `survregbayes` includes three most commonly-used semiparametric models: proportional hazards, proportional odds, and accelerated failure time. All manner of censored survival times are simultaneously accommodated including uncensored, interval censored, current-status, left and right censored, and mixtures of these. Left-truncated data are also accommodated leading to models for time-dependent covariates. Both georeferenced and areally observed spatial locations are handled via frailties. Model fit is assessed with conditional Cox-Snell residual plots, and model choice is carried out via LPML and DIC. The accelerated failure time frailty model with a covariate-dependent baseline is included in the function `frailtyGAFT`. In addition, the package also provides two marginal survival models: proportional hazards and linear dependent Dirichlet process mixture, where the spatial dependence is modeled via spatial copulas. Note that the package can also handle non-spatial data using non-spatial versions of aforementioned models.

Keywords: Bayesian nonparametric, survival analysis, spatial dependence, semiparametric models, parametric models.

1. Introduction

Spatial location plays a key role in survival prediction, serving as a proxy for unmeasured regional characteristics such as socioeconomic status, access to health care, pollution, etc. Literature on the spatial analysis of survival data has flourished over the last decade, including the study of leukemia survival (Henderson, Shimakura, and Gorst 2002), childhood mortality (Kneib 2006), asthma (Li and Lin 2006), breast cancer (Banerjee and Dey 2005; Zhou, Hanson, Jara, and Zhang 2015a), political event processes (Darmofal 2009), prostate cancer (Wang, Zhang, and Lawson 2012; Zhou, Hanson, and Zhang 2017), pine trees (Li, Hong, Thapa, and Burkhart 2015a), threatened frogs (Zhou, Hanson, and Knapp 2015b), health and pharmaceutical firms (Arbia, Espa, Giuliani, and Micciolo 2016), emergency service response times (Taylor 2017), and many others.

Here we introduce the **spBayesSurv** package for fitting various survival models to spatially-referenced survival data. Note that all models included in this package can also be fit without spatial information, including nonparametric models as well as semiparametric proportional

hazards (PH), proportional odds (PO), and accelerated failure time (AFT) models. The model parameters and statistical inference are carried out via self-tuning adaptive Markov chain Monte Carlo (MCMC) methods; no manual tuning is needed. The R syntax is essentially the same as for existing R **survival** functions. Sensible, well-tested default priors are used throughout, however, the user can easily implement informative priors if such information is available. The primary goal of this paper is to introduce **spBayesSurv** and provide extensive examples of its use. Comparisons to other models and R packages can be found in Zhou *et al.* (2015b), Zhou *et al.* (2017), and Zhou and Hanson (2017).

Section 2 discusses **spBayesSurv**'s implementation of PH, PO, and AFT frailty models for georeferenced (e.g. latitude and longitude are recorded) and areally-referenced (e.g. county of residence recorded) spatial survival data; the functions also work very well for exchangeable or no frailties. The models are centered at a parametric family through a novel transformed Bernstein polynomial prior and the centering family can be tested versus the Bernstein extension via Bayes factors. All manner of censoring is accommodated as well as left-truncated data; left-truncation also allows for the inclusion of time-dependent covariates. Both the DIC and LPML statistics are available for model selection; spike-and-slab variable selection is also implemented.

In Section 3, a generalized AFT model is implemented allowing for *continuous stratification*. That is, the baseline survival function is itself a function of covariates: baseline survival changes smoothly as a function of continuous predictors; for categorical predictors the usual stratified AFT model is obtained. Note that even for the usual stratified semiparametric AFT model with one discrete predictor (e.g. clinic) it is extremely difficult to obtain inference using frequentist approaches; see Chiou, Kang, and Yan (2015) for a recent development. The model fit in **spBayesSurv** actually extends discrete stratification to continuous covariates, allowing for very general models to be fit. The generalized AFT model includes the easy computation of Bayes factors for determining which covariates affect baseline survival and whether a parametric baseline is adequate.

Finally, Section 4 offers a spatial implementation of the completely nonparametric linear dependent Dirichlet process mixture (LDDPM) model of De Iorio, Johnson, Müller, and Rosner (2009) for georeferenced data. The LDDPM does not have one simple "linear predictor" as do the models in Sections 2 and 3, and therefore a marginal copula approach was taken to incorporate spatial dependence. A piecewise-constant baseline hazard PH model is also implemented via spatial copula for comparison purposes, i.e. a Bayesian version of the model presented in Li and Lin (2006). Section 5 concludes the paper with a discussion.

Although there are many R packages for implementing survival models, there are only a handful of that allow the inclusion of spatial information and these focus almost exclusively on variants of the PH model. BayesX (Belitz, Brezger, Klein, Kneib, Lang, and Umlauf 2015) is an immensely powerful standalone program for fitting various generalized additive mixed models, including both georeferenced and areally-referenced frailties in the PH model. The package **R2BayesX** (Umlauf, Adler, Kneib, Lang, and Zeileis 2015) interfaces BayesX with R, but does not appear to include the full functionality of BayesX, e.g. a Bayesian approach for interval-censored data is not included. For georeferenced frailties BayesX uses what have been termed "Matern splines," first introduced in an applied context by Kammann and Wand (2003). Several authors have used this approach including Kneib (2006), Hennerfeind, Brezger, and Fahrmeir (2006), and Kneib and Fahrmeir (2007). This approximation was termed a "predictive process" and given a more formal treatment by Banerjee, Gelfand,

Finley, and Sang (2008) and Finley, Sang, Banerjee, and Gelfand (2009). In our experience, the predictive process tends to give biased regression effects and prediction when the rank (i.e. the number of knots) was chosen too low; the problem worsened with no replication and/or when spatial correlation was high. In **spBayesSurv** the full-scale approximation (FSA) of Sang and Huang (2012) is used to fix the predictive process via tapering; see Section 2.1.4.

The package **spatsurv** (Taylor and Rowlingson 2017) includes an implementation of PH allowing for georeferenced Gaussian process frailties. The frailty process is approximated on a fine grid and the covariance matrix inverted via the discrete Fourier transform on block circulent matrices; see Taylor (2015) for details. Taylor's approach vastly improves computation time over a fully-specified Gaussian process. Both **R2BayesX** and **spatsurv** focus on the PH model with right-censored data. The **spBayesSurv** includes several other spatial frailty models for general interval-censored and/or left-truncated data, and two marginal copula models for right-censored data, which have been shown to provide dramatically improved fit over frailty models (Zhou *et al.* 2015b; Li, Hanson, and Zhang 2015b).

To set notation, suppose subjects are observed at m distinct spatial locations $\mathbf{s}_1, \ldots, \mathbf{s}_m$. Let t_{ij} be a random event time associated with the jth subject in $\mathbf{s}_i$ and $\mathbf{x}_{ij}$ be a related p-dimensional vector of covariates, $i = 1, \ldots, m, j = 1, \ldots, n_i$. Then $n = \sum_{i=1}^{m} n_i$ is the total number of subjects under consideration. Assume the survival time t_{ij} lies in the interval (a_{ij}, b_{ij}), $0 \leq a_{ij} \leq b_{ij} \leq \infty$. Here left censored data are of the form $(0, b_{ij})$, right censored (a_{ij}, ∞), interval censored (a_{ij}, b_{ij}) and uncensored values simply have $a_{ij} = b_{ij}$, i.e., we define $(x, x) = \{x\}$. Therefore, the observed data will be $\mathcal{D} = \{(a_{ij}, b_{ij}, \mathbf{x}_{ij}, \mathbf{s}_i); i = 1, \ldots, m, j = 1, \ldots, n_i\}$. For areally-observed outcomes, e.g. county-level, there is typically replication (i.e. $n_i > 1$); for georeferenced data, there may or may not be replication. Note although the models are discussed for spatial survival data, non-spatial data are also accommodated. All code below is run in R version 3.3.3 under the platform x86_64-apple-darwin13.4.0 (64-bit).

2. Semiparametric Frailty Models

2.1. Models

The function `survregbayes` supports three commonly-used semiparametric frailty models: AFT, PH, and PO. The AFT model has survival and density functions

$$S_{\mathbf{x}_{ij}}(t) = S_0(e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i}t), \;\; f_{\mathbf{x}_{ij}}(t) = e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i} f_0(e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i}t), \tag{1}$$

while the PH model has survival and density

$$S_{\mathbf{x}_{ij}}(t) = S_0(t)^{e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i}}, \;\; f_{\mathbf{x}_{ij}}(t) = e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i} S_0(t)^{e^{\mathbf{x}_{ij}'\boldsymbol{\beta}+v_i}-1} f_0(t), \tag{2}$$

and the PO model has survival and density

$$S_{\mathbf{x}_{ij}}(t) = \frac{e^{-\mathbf{x}_{ij}'\boldsymbol{\beta}-v_i} S_0(t)}{1+(e^{-\mathbf{x}_{ij}'\boldsymbol{\beta}-v_i}-1)S_0(t)}, \;\; f_{\mathbf{x}_{ij}}(t) = \frac{e^{-\mathbf{x}_{ij}'\boldsymbol{\beta}-v_i} f_0(t)}{[1+(e^{-\mathbf{x}_{ij}'\boldsymbol{\beta}-v_i}-1)S_0(t)]^2}, \tag{3}$$

where $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$ is a vector of regression coefficients, v_i is an unobserved frailty associated with $\mathbf{s}_i$, and $S_0(t)$ is the baseline survival with density $f_0(t)$ corresponding to $\mathbf{x}_{ij} = \mathbf{0}$

and $v_i = 0$. Let $\Gamma(a, b)$ denote a gamma distribution with mean a/b. The `survregbayes` function implements the following prior distributions:

$$\begin{aligned}
\boldsymbol{\beta} &\sim N_p(\boldsymbol{\beta}_0, \mathbf{S}_0), \\
S_0(\cdot)|\alpha, \boldsymbol{\theta} &\sim \text{TBP}_L(\alpha, S_{\boldsymbol{\theta}}(\cdot)),\ \alpha \sim \Gamma(a_0, b_0),\ \boldsymbol{\theta} \sim N_2(\boldsymbol{\theta}_0, \mathbf{V}_0), \\
(v_1, \ldots, v_m)'|\tau &\sim \text{ICAR}(\tau^2),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau),\ \text{or} \\
(v_1, \ldots, v_m)'|\tau, \phi &\sim \text{GRF}(\tau^2, \phi),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau),\ \phi \sim \Gamma(a_\phi, b_\phi),\ \text{or} \\
(v_1, \ldots, v_m)'|\tau &\sim \text{IID}(\tau^2),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau)
\end{aligned} \tag{4}$$

where TBP_L, ICAR, GRF and IID refer to the transformed Bernstein polynomial (TBP) (Chen, Hanson, and Zhang 2014; Zhou and Hanson 2017) prior, intrinsic conditionally autoregressive (ICAR) (Besag 1974) prior, Gaussian random field (GRF) prior, and independent Gaussian (IID) prior distributions, respectively. We briefly introduce these priors but leave details to Zhou and Hanson (2017).

TBP prior

In semiparametric survival analysis, a wide variety of Bayesian nonparametric priors can be used to model $S_0(\cdot)$; see Müller, Quintana, Jara, and Hanson (2015) and Zhou and Hanson (2015) for reviews. The TBP prior is attractive in that it is centered at a given parametric family and it selects only smooth densities. For a fixed positive integer L, the prior $\text{TBP}_L(\alpha, S_{\boldsymbol{\theta}}(\cdot))$ is defined as

$$S_0(t) = \sum_{j=1}^{L} w_j I(S_{\boldsymbol{\theta}}(t)|j, L-j+1),\ \mathbf{w}_L \sim \text{Dirichlet}(\alpha, \ldots, \alpha), \tag{5}$$

where $\mathbf{w}_L = (w_1, \ldots, w_L)'$ is a vector of positive weights, $I(\cdot|a, b)$ denotes a beta cumulative distribution function (cdf) with parameters (a, b), and $\{S_{\boldsymbol{\theta}}(\cdot) : \boldsymbol{\theta} \in \boldsymbol{\Theta}\}$ is a parametric family of survival functions with support on positive reals $\mathbb{R}^+$. The log-logistic $S_{\boldsymbol{\theta}}(t) = \{1+(e^{\theta_1}t)^{\exp(\theta_2)}\}^{-1}$, the log-normal $S_{\boldsymbol{\theta}}(t) = 1-\Phi\{(\log t+\theta_1)\exp(\theta_2)\}$, and the Weibull $S_{\boldsymbol{\theta}}(t) = 1-\exp\left\{-(e^{\theta_1}t)^{\exp(\theta_2)}\right\}$ families are implemented in `survregbayes`, where $\boldsymbol{\theta} = (\theta_1, \theta_2)'$. In our experience, the three centering distributions yield almost identical posterior inferences but in small samples one might be preferred. The random distribution $S_0(\cdot)$ is centered at $S_{\boldsymbol{\theta}}(\cdot)$, i.e. $E[S_0(t)|\alpha, \boldsymbol{\theta}] = S_{\boldsymbol{\theta}}(t)$. The parameter α controls how close the weights $\mathbf{w}_j$ are to $1/L$, i.e. how close the shape of the baseline survival $S_0(\cdot)$ is relative to the prior guess $S_{\boldsymbol{\theta}}(\cdot)$. Large values of α indicate a strong belief that $S_0(\cdot)$ is close to $S_{\boldsymbol{\theta}}(\cdot)$; as $\alpha \to \infty$, $S_0(\cdot) \to S_{\boldsymbol{\theta}}(\cdot)$ with probability 1. Smaller values of α allow more pronounced deviations of $S_0(\cdot)$ from $S_{\boldsymbol{\theta}}(\cdot)$. This adaptability makes the TBP prior attractive in its flexibility, but also anchors the random $S_0(\cdot)$ firmly about $S_{\boldsymbol{\theta}}(\cdot)$: $w_j = 1/L$ for $j = 1, \ldots, L$ implies $S_0(t) = S_{\boldsymbol{\theta}}(t)$ for $t \geq 0$. Moreover, unlike the mixture of Polya trees (Lavine 1992) or mixture of Dirichlet process (Antoniak 1974) priors, the TBP prior selects smooth densities, leading to efficient posterior sampling.

ICAR and IID priors

For areal data, the ICAR prior smooths neighboring geographic-unit frailties $\mathbf{v} = (v_1, \ldots, v_m)'$. Let e_{ij} be 1 if regions i and j share a common boundary and 0 otherwise; set $e_{ii} = 0$. Then the $m \times m$ matrix $\mathbf{E} = [e_{ij}]$ is called the adjacency matrix for the m regions. The prior

ICAR(τ^2) on $\mathbf{v}$ is defined through the set of the conditional distributions

$$v_i|\{v_j\}_{j\neq i} \sim N\left(\sum_{j=1}^{m} e_{ij}v_j/e_{i+},\ \tau^2/e_{i+}\right),\ i=1,\ldots,m, \tag{6}$$

where $e_{i+}=\sum_{j=1}^{m} e_{ij}$ is the number of neighbors of area $\mathbf{s}_i$. The induced prior on $\mathbf{v}$ under ICAR is improper; the constraint $\sum_{j=1}^{m} v_j = 0$ is used for identifiability (Banerjee, Carlin, and Gelfand 2014).

For non-spatial data, we consider the independent Gaussian prior IID(τ^2), defined as

$$v_1, v_2, \ldots, v_m \overset{iid}{\sim} N(0,\tau^2). \tag{7}$$

GRF priors

For georeferenced data, it is commonly assumed that $v_i = v(\mathbf{s}_i)$ arises from a Gaussian random field (GRF) $\{v(\mathbf{s}), \mathbf{s}\in\mathcal{S}\}$ such that $\mathbf{v}=(v_1,\ldots,v_m)$ follows a multivariate Gaussian distribution as $\mathbf{v}\sim N_m(\mathbf{0},\tau^2\mathbf{R})$, where τ^2 measures the amount of spatial variation across locations and the (i,j) element of $\mathbf{R}$ is modeled as $\mathbf{R}[i,j]=\rho(\mathbf{s}_i,\mathbf{s}_j)$. Here $\rho(\cdot,\cdot)$ is a correlation function controlling the spatial dependence of $v(\mathbf{s})$. In `survregbayes` the powered exponential correlation function $\rho(\mathbf{s},\mathbf{s}')=\rho(\mathbf{s},\mathbf{s}';\phi)=\exp\{-(\phi\|\mathbf{s}-\mathbf{s}'\|)^\nu\}$ is used, where $\phi>0$ is a range parameter controlling the spatial decay over distance, $\nu\in(0,2]$ is a pre-specified shape parameter, and $\|\mathbf{s}-\mathbf{s}'\|$ refers to the distance (e.g., Euclidean, great-circle) between $\mathbf{s}$ and $\mathbf{s}'$. Therefore, the prior GRF(τ^2,ϕ) is defined as

$$v_i|\{v_j\}_{j\neq i} \sim N\left(-\sum_{\{j:j\neq i\}} p_{ij}v_j/p_{ii},\ \tau^2/p_{ii}\right),\ i=1,\ldots,m, \tag{8}$$

where p_{ij} is the (i,j) element of $\mathbf{R}^{-1}$.

Full-scale approximation

As m increases evaluating $\mathbf{R}^{-1}$ from $\mathbf{R}$ becomes computationally impractical. To overcome this computational issue, we consider the FSA (Sang and Huang 2012) due to its capability of capturing both large- and small-scale spatial dependence. Consider a fixed set of "knots" $\mathcal{S}^*=\{\mathbf{s}_1^*,\ldots,\mathbf{s}_K^*\}$ chosen from the study region. These knots are chosen using the function `cover.design` within the R package **fields**, which computes space-filling coverage designs using the swapping algorithm (Johnson, Moore, and Ylvisaker 1990). Let $\rho(\mathbf{s},\mathbf{s}')$ be the correlation between locations $\mathbf{s}$ and $\mathbf{s}'$. The FSA approach approximates the correlation function $\rho(\mathbf{s},\mathbf{s}')$ with

$$\rho^\dagger(\mathbf{s},\mathbf{s}')=\rho_l(\mathbf{s},\mathbf{s}')+\rho_s(\mathbf{s},\mathbf{s}'). \tag{9}$$

The $\rho_l(\mathbf{s},\mathbf{s}')$ in (9) is the reduced-rank part capturing the long-scale spatial dependence, defined as $\rho_l(\mathbf{s},\mathbf{s}')=\rho'(\mathbf{s},\mathcal{S}^*)\rho_{KK}^{-1}(\mathcal{S}^*,\mathcal{S}^*)\rho(\mathbf{s}',\mathcal{S}^*)$, where $\rho(\mathbf{s},\mathcal{S}^*)=[\rho(\mathbf{s},\mathbf{s}_i^*)]_{i=1}^K$ is a $K\times 1$ vector, and $\rho_{KK}(\mathcal{S}^*,\mathcal{S}^*)=[\rho(\mathbf{s}_i^*,\mathbf{s}_j^*)]_{i,j=1}^K$ is a $K\times K$ correlation matrix at knots $\mathcal{S}^*$. However, $\rho_l(\mathbf{s},\mathbf{s}')$ cannot well capture the short-scale dependence due to the fact that it discards entirely the residual part $\rho(\mathbf{s},\mathbf{s}')-\rho_l(\mathbf{s},\mathbf{s}')$. The idea of FSA is to add a small-scale part $\rho_s(\mathbf{s},\mathbf{s}')$ as

a sparse approximate of the residual part, defined by $\rho_s(\mathbf{s},\mathbf{s}') = \{\rho(\mathbf{s},\mathbf{s}') - \rho_l(\mathbf{s},\mathbf{s}')\}\,\Delta(\mathbf{s},\mathbf{s}')$, where $\Delta(\mathbf{s},\mathbf{s}')$ is a modulating function, which is specified so that $\rho_s(\mathbf{s},\mathbf{s}')$ can well capture the local residual spatial dependence while still permitting efficient computation. Motivated by Konomi, Sang, and Mallick (2014), we first partition the total input space into B disjoint blocks, and then specify $\Delta(\mathbf{s},\mathbf{s}')$ in a way such that the residuals are independent across input blocks, but the original residual dependence structure within each block is retained. Specifically, the function $\Delta(\mathbf{s},\mathbf{s}')$ is taken to be 1 if $\mathbf{s}$ and $\mathbf{s}'$ belong to the same block and 0 otherwise. The approximated correlation function $\rho^\dagger(\mathbf{s},\mathbf{s}')$ in (9) provides an exact recovery of the true correlation within each block, and the approximation errors are $\rho(\mathbf{s},\mathbf{s}') - \rho_l(\mathbf{s},\mathbf{s}')$ for locations $\mathbf{s}$ and $\mathbf{s}'$ in different blocks. Those errors are expected to be small for most entries because most of these location pairs are farther apart. To determine the blocks, we first use the R function `cover.design` to choose $B \leq m$ locations among the m locations forming B blocks, then assign each $\mathbf{s}_i$ to the block that is closest to $\mathbf{s}_i$. Here B does not need to be equal to K. When $B = 1$, no approximation is applied to the correlation ρ. When $B = m$, it reduces to the approach of Finley *et al.* (2009), so the local residual spatial dependence may not be well captured.

Applying the above FSA approach to approximate the correlation function $\rho(\mathbf{s},\mathbf{s}')$, we can approximate the correlation matrix $\mathbf{R}$ with

$$\boldsymbol{\rho}^\dagger_{mm} = \boldsymbol{\rho}_l + \boldsymbol{\rho}_s = \boldsymbol{\rho}_{mK}\boldsymbol{\rho}^{-1}_{KK}\boldsymbol{\rho}'_{mK} + \left(\boldsymbol{\rho}_{mm} - \boldsymbol{\rho}_{mK}\boldsymbol{\rho}^{-1}_{KK}\boldsymbol{\rho}'_{mK}\right) \circ \boldsymbol{\Delta}, \tag{10}$$

where $\boldsymbol{\rho}_{mK} = [\rho(\mathbf{s}_i,\mathbf{s}^*_j)]_{i=1:m,j=1:K}$, $\boldsymbol{\rho}_{KK} = [\rho(\mathbf{s}^*_i,\mathbf{s}^*_j)]^K_{i,j=1}$, and $\boldsymbol{\Delta} = [\Delta(\mathbf{s}_i,\mathbf{s}_j)]^m_{i,j=1}$. Here, the notation "$\circ$" represents the element-wise matrix multiplication. To avoid numerical instability, we add a small nugget effect $\epsilon = 10^{-10}$ when defining $\mathbf{R}$, that is, $\mathbf{R} = (1-\epsilon)\boldsymbol{\rho}_{mm} + \epsilon\mathbf{I}_m$. It follows from equation (10) that $\mathbf{R}$ can be approximated by

$$\mathbf{R}^\dagger = (1-\epsilon)\boldsymbol{\rho}^\dagger_{mm} + \epsilon\mathbf{I}_m = (1-\epsilon)\boldsymbol{\rho}_{mK}\boldsymbol{\rho}^{-1}_{KK}\boldsymbol{\rho}'_{mK} + \mathbf{R}_s,$$

where $\mathbf{R}_s = (1-\epsilon)\left(\boldsymbol{\rho}_{mm} - \boldsymbol{\rho}_{mK}\boldsymbol{\rho}^{-1}_{KK}\boldsymbol{\rho}'_{mK}\right) \circ \boldsymbol{\Delta} + \epsilon\mathbf{I}_m$. Applying the Sherman-Woodbury-Morrison formula for inverse matrices, we can approximate $\mathbf{R}^{-1}$ by

$$\left(\mathbf{R}^\dagger\right)^{-1} = \mathbf{R}^{-1}_s - (1-\epsilon)\mathbf{R}^{-1}_s\boldsymbol{\rho}_{mK}\left[\boldsymbol{\rho}_{KK} + (1-\epsilon)\boldsymbol{\rho}'_{mK}\mathbf{R}^{-1}_s\boldsymbol{\rho}_{mK}\right]^{-1}\boldsymbol{\rho}'_{mK}\mathbf{R}^{-1}_s. \tag{11}$$

In addition, the determinant of $\mathbf{R}$ can be approximated by

$$\det\left(\mathbf{R}^\dagger\right) = \det\left\{\boldsymbol{\rho}_{KK} + (1-\epsilon)\boldsymbol{\rho}'_{mK}\mathbf{R}^{-1}_s\boldsymbol{\rho}_{mK}\right\}\det(\boldsymbol{\rho}_{KK})^{-1}\det(\mathbf{R}_s). \tag{12}$$

Since the $m \times m$ matrix $\mathbf{R}_s$ is a block matrix, the right-hand sides of equations (11) and (12) involve only inverses and determinants of $K \times K$ low-rank matrices and $m \times m$ block diagonal matrices. Thus the computational complexity can be greatly reduced relative to the expensive computational cost of using original correlation function for large value of m.

2.2. MCMC

The likelihood function for $(\mathbf{w}_L, \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{v})$ is given by

$$\mathcal{L}(\mathbf{w}_L, \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{v}) = \prod_{i=1}^{m}\prod_{j=1}^{n_i}\left[S_{\mathbf{x}_{ij}}(a_{ij}) - S_{\mathbf{x}_{ij}}(b_{ij})\right]^{I\{a_{ij}<b_{ij}\}} f_{\mathbf{x}_{ij}}(a_{ij})^{I\{a_{ij}=b_{ij}\}}. \tag{13}$$

MCMC is carried out through an empirical Bayes approach coupled with adaptive Metropolis samplers (Haario, Saksman, and Tamminen 2001). Recall that $w_j = 1/L$ implies the underlying parametric model with $S_0(t) = S_{\boldsymbol{\theta}}(t)$. Thus, the parametric model provides good starting values for the TBP survival model. Let $\hat{\boldsymbol{\theta}}$ and $\hat{\boldsymbol{\beta}}$ denote the parametric estimates of $\boldsymbol{\theta}$ and $\boldsymbol{\beta}$, e.g. maximum likelihood estimates, and let $\hat{\mathbf{V}}$ and $\hat{\mathbf{S}}$ denote their estimated covariance matrices, respectively. Set $\mathbf{z}_{L-1} = (z_1, \ldots, z_{L-1})'$ with $z_j = \log(w_j) - \log(w_L)$. The $\boldsymbol{\beta}$, $\boldsymbol{\theta}$, $\mathbf{z}_{L-1}$, α and ϕ are all updated using adaptive Metropolis samplers, where the initial proposal variance is $\hat{\mathbf{S}}$ for $\boldsymbol{\beta}$, $\hat{\mathbf{V}}$ for $\boldsymbol{\theta}$, $0.16\mathbf{I}_{L-1}$ for $\mathbf{z}_{L-1}$ and 0.16 for α and ϕ. Each frailty term v_i is updated via Metropolis-Hastings, with proposal variance as the conditional prior variance of $v_i|\{v_j\}_{j\neq i}$; τ^{-2} is updated via a Gibbs step from its full conditional. A complete description and derivation of the updating steps are available in Zhou and Hanson (2017).

The function `survregbayes` sets the following hyperparameters as defaults: $\boldsymbol{\beta}_0 = \mathbf{0}$, $\mathbf{S}_0 = 10^{10}\mathbf{I}_p$, $\boldsymbol{\theta}_0 = \hat{\boldsymbol{\theta}}$, $\mathbf{V}_0 = 10\hat{\mathbf{V}}$, $a_0 = b_0 = 1$, and $a_\tau = b_\tau = .001$. Note here we assume a somewhat informative prior on $\boldsymbol{\theta}$ to obviate confounding between $\boldsymbol{\theta}$ and $\mathbf{w}_L$. For the GRF prior, we set $a_\phi = 2$ and $b_\phi = (a_\phi - 1)/\phi_0$ so that the prior of ϕ has mode at ϕ_0 and the prior mean of $1/\phi$ is $1/\phi_0$ with infinite variance. Here ϕ_0 satisfies $\rho(\mathbf{s}', \mathbf{s}''; \phi_0) = 0.001$, where $\|\mathbf{s}' - \mathbf{s}''\| = \max_{ij} \|\mathbf{s}_i - \mathbf{s}_j\|$. Note that Kneib and Fahrmeir (2007) simply fix ϕ at ϕ_0, while we allow ϕ to be random around ϕ_0.

2.3. Model Diagnostics and Comparison

For model diagnostics, we consider a general residual of Cox and Snell (1968), defined as $r(t_{ij}) = -\log S_{\mathbf{x}_{ij}}(t_{ij})$. Given $S_{\mathbf{x}_{ij}}(\cdot)$, $r(t_{ij})$ has a standard exponential distribution. If the model is "correct," and under the arbitrary censoring, the pairs $\{r(a_{ij}), r(b_{ij})\}$ are approximately a random arbitrarily censored sample from an Exp(1) distribution, and the estimated (Turnbull 1974) integrated hazard plot should be approximately straight with slope 1. Uncertainty in the plot is assessed through several cumulative hazards based on a random sample from $[\boldsymbol{\beta}, \boldsymbol{\theta}, \mathbf{w}_L, \mathbf{v}|\mathcal{D}]$. This is in contrast to typical Cox-Snell plots which only use point estimates.

For model comparison, we consider two popular model choice criteria: the deviance information criterion (DIC) (Spiegelhalter, Best, Carlin, and Van Der Linde 2002) and the log pseudo marginal likelihood (LPML) (Geisser and Eddy 1979), where where DIC (smaller is better) places emphasis on the relative quality of model fitting and LPML (larger is better) focuses on the predictive performance. Both criteria are readily computed from the MCMC output; see Zhou and Hanson (2017) for more details.

2.4. Leukemia Survival Data

A dataset on the survival of acute myeloid leukemia in $n = 1,043$ patients (Henderson *et al.* 2002) is considered, named as `LeukSurv` in the package. It is of interest to investigate possible spatial variation in survival after accounting for known subject-specific prognostic factors, which include `age`, `sex`, white blood cell count (`wbc`) at diagnosis, and the Townsend score (`tpi`) for which higher values indicates less affluent areas. Both exact residential locations of all patients and their administrative districts (the boundary file is named as `nwengland.bnd` in the package) are available, so we can fit both geostatistical and areal models.

PO model with ICAR frailties

We first need to sort the dataset by `district`, then obtain the adjacency matrix **E**.

```
> library(coda)
> library(survival)
> library(spBayesSurv)
> library(fields)
> library(BayesX)
> library(R2BayesX)
> data(LeukSurv);
> attach(LeukSurv);
> d = LeukSurv[order(district),]; n = nrow(d); detach(LeukSurv);
> head(d);
    time cens    xcoord    ycoord age sex   wbc  tpi district
24     1    1 0.4123484 0.4233738  44   1 281.0 4.87        1
62     3    1 0.3925028 0.4531422  72   1   0.0 7.10        1
68     4    1 0.4167585 0.4520397  68   0   0.0 5.12        1
128    9    1 0.4244763 0.4123484  61   1   0.0 2.90        1
129    9    1 0.4145535 0.4520397  26   1   0.0 6.72        1
163   15    1 0.4013230 0.4785006  67   1  27.9 1.50        1
> nwengland=read.bnd(system.file("otherdata/nwengland.bnd",
+                                package="spBayesSurv"));
> adj.mat=bnd2gra(nwengland)
> E = diag(diag(adj.mat)) - as.matrix(adj.mat);
```

The following code is used to fit the PO model with ICAR frailties using the TBP prior with $L = 15$ and default settings for other priors. A burn-in period of 5,000 iterates was considered and the Markov chain was subsampled every 5 iterates to get a final chain size of 2,000. The argument `ndisplay=1000` will display the number of saved scans after every 1,000 saved iterates. If the argument `InitParamMCMC=TRUE` (not used here as it is the default setting), then an initial chain with `nburn=5000`, `nsave=5000`, `nkip=0` and `ndisplay=1000` will be run; otherwise, the initial values are obtained from fitting parametric non-frailty models via `survreg`. The total running time is 166 seconds.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> prior=list(maxL=15);
> ptm<-proc.time()
> res1 = survregbayes(formula=Surv(time,cens)~age+sex+wbc+tpi
+                     +frailtyprior("car",district),data=d,survmodel="PO",
+                     dist="loglogistic",mcmc=mcmc,prior=prior,Proximity=E);
Starting initial MCMC based on parametric model:
scan = 1000
scan = 2000
scan = 3000
scan = 4000
scan = 5000
```

```
Starting the MCMC for the semiparametric model:
scan = 1000
scan = 2000
> systime1=proc.time()-ptm; systime1;
   user  system elapsed
165.919   0.296 166.354
```

The term `frailtyprior("car",district)` indicates that the ICAR prior in (6) is used. One can also incorporate the IID prior in (7) via `frailtyprior("iid",district)`. The non-frailty model can be fit by removing the `frailtyprior` term. The argument `survmodel` is used to indicate which model will be fit; choices include `"PH"`, `"PO"`, and `"AFT"`. The argument `dist` is used to specify the distribution family of $S_{\boldsymbol{\theta}}(\cdot)$ defined in Section 2.1, and the choices include `"loglogistic"`, `"lognormal"`, and `"weibull"`. The argument `prior` is used to specify user-defined hyperparameters, e.g., for $p = 3$, $L = 15$, $\boldsymbol{\beta}_0 = \mathbf{0}$, $\mathbf{S}_0 = 10\mathbf{I}_p$, $\boldsymbol{\theta}_0 = \mathbf{0}$, $\mathbf{V}_0 = 10\mathbf{I}_2$, $a_0 = b_0 = 1$, and $a_\tau = b_\tau = 1$, the prior can be specified as below.

```
> prior=list(maxL=15,beta0=rep(0,3),S0=diag(10,3),theta0=rep(0,2),
+            V0=diag(10,2),a0=1,b0=1,taua0=1,taub0=1)
```

If `prior=NULL`, then the default hyperparameters given in Section 2.2 would be used. Note by default `survregbayes` standardizes each covariate by subtracting the sample mean and dividing the sample standard deviation. Therefore, the user-specified hyperparameters should be based on the model with scaled covariates unless the argument `scale.designX=FALSE` is added.

The output from applying the `summary` function to the returned object `res1` is given below.

```
> sfit1=summary(res1); sfit1
Proportional Odds model:
Call:
survregbayes(formula = Surv(time, cens) ~ age + sex + wbc + tpi +
    frailtyprior("car", district), data = d, survmodel = "PO",
    dist = "loglogistic", mcmc = mcmc, prior = prior, Proximity = E)

Posterior inference of regression coefficients
(Adaptive M-H acceptance rate: 0.2731):
      Mean        Median      Std. Dev.   95%CI-Low   95%CI-Upp
age   0.0519835   0.0518955   0.0034329   0.0455544   0.0589767
sex   0.1238558   0.1241657   0.1061961  -0.0854203   0.3274537
wbc   0.0059439   0.0059223   0.0008163   0.0043996   0.0074789
tpi   0.0598826   0.0597254   0.0159244   0.0286519   0.0904957

Posterior inference of precision parameter
(Adaptive M-H acceptance rate: 0.2723):
       Mean    Median  Std. Dev.  95%CI-Low  95%CI-Upp
alpha  1.2910  1.1227  0.7158     0.4364     3.1922

Posterior inference of conditional CAR frailty variance
```

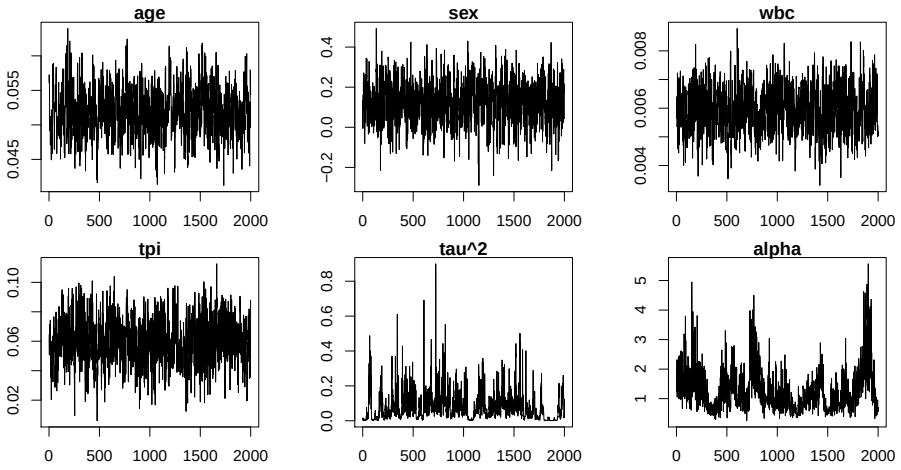


Figure 1: Leukemia survival data. Trace plots for $\boldsymbol{\beta}$, τ^2 and α under the PO model with ICAR frailties.

```
          Mean      Median    Std. Dev.   95%CI-Low   95%CI-Upp
variance  0.080346  0.056350  0.082950    0.001709    0.299395

Log pseudo marginal likelihood: LPML=-5925.194
Deviance Information Criterion: DIC=11849.82
Number of subjects: n=1043
```

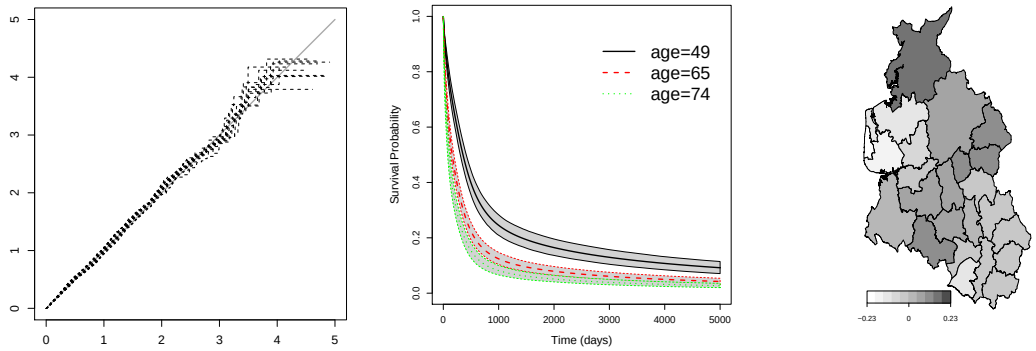
We can see that `age`, `wbc` and `tpi` are significant risk factors for leukemia survival. For example, lower `age` decreases the odds of a patient dying by any time; holding other predictors constant, a 10-year decrease in age cuts the odds of dying by $\exp(-10 \times 0.05) \approx 60\%$. The posterior mean for τ^2 is 0.08, and is 1.29 for precision parameter α. The LPML and DIC are -5925 and 11850, respectively.

The following code is used to produce trace plots (Figure 1) for $\boldsymbol{\beta}$, τ^2 and α. Note that the mixing for τ^2 is not very satisfactory. This is not surprising, since we are using very vague gamma prior $\Gamma(0.001, 0.001)$ and the total number of districts is only 24.

```
> par(mfrow=c(3,2));
> par(cex=1,mar=c(2.5,4.1,1,1))
> traceplot(mcmc(res1$beta[1,]), xlab="", main="age")
> traceplot(mcmc(res1$beta[2,]), xlab="", main="sex")
> traceplot(mcmc(res1$beta[3,]), xlab="", main="wbc")
> traceplot(mcmc(res1$beta[4,]), xlab="", main="tpi")
> traceplot(mcmc(res1$tau2), xlab="", main="tau^2")
> traceplot(mcmc(res1$alpha), xlab="", main="alpha")
```

The code below is used to generate the Cox-Snell plots with 10 posterior residuals (Figure 2, panel a).

```
> set.seed(1)
> nrand = 10;
```



(a) (b) (c)

Figure 2: Leukemia survival data. PO model with ICAR frailties. (a) Cox-Snell plot. (b) Survival curves with 95% credible interval bands for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages. (c) Map for the posterior mean frailties; larger frailties mean higher mortality rate overall.

```
> Resid = cox.snell.survregbayes(res1, ncurves=nrand);
> r.max = ceiling(quantile(res1$Surv.cox.snell[,1], .99))+1
> xlim=c(0, r.max); ylim=c(0, r.max); width=8; height=8;
> xx = seq(0, r.max, 0.01);
> fit = survfit(Resid$resid1~1);
> par(cex=1.5,mar=c(2.1,2.1,1,1),cex.lab=1.4,cex.axis=1.1)
> plot(fit, fun="cumhaz", conf.int=F, mark.time=FALSE, xlim=xlim,
+      ylim=ylim, lwd=2, lty=2)
> lines(xx, xx, lty=1, lwd=3, col="darkgrey")
> for(i in 2:nrand){
+   fit = survfit(Resid[[i+1]]~1);
+   lines(fit, fun="cumhaz", conf.int=F, mark.time=FALSE, xlim=xlim,
+         ylim=ylim, lwd=2, lty=2)
+ }
```

The code below is used to generate survival curves for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages (Figure 2, panel b).

```
> tgrid = seq(0.1,5000,length.out=300);
> xpred = rbind(c(49, 0, 38.59, 0.3398),
+               c(65, 0, 38.59, 0.3398),
+               c(74, 0, 38.59, 0.3398));
> estimates=plot(res1, xpred=xpred, tgrid=tgrid);
> par(mfrow=c(1,1));
> par(cex=1.2,mar=c(4.1,4.1,1,1),cex.lab=1.3,cex.axis=1.1)
> plot(estimates$tgrid, estimates$Shat[,1], "l", lwd=3, ylim = c(0, 1),
+      xlab = "Time (days)", ylab="Survival Probability")
> polygon(x=c(rev(tgrid),tgrid),
+         y=c(rev(estimates$Shatlow[,1]),estimates$Shatup[,1]),
+         border=c("black"),col="lightgray");
```

```
> lines(estimates$tgrid, estimates$Shat[,1], lty=1, lwd=3)
> polygon(x=c(rev(tgrid),tgrid),
+         y=c(rev(estimates$Shatlow[,2]),estimates$Shatup[,2]),
+         border=c("red"),lty=2, col="lightgray");
> lines(estimates$tgrid, estimates$Shat[,2], lty=2, lwd=3, col="red")
> polygon(x=c(rev(tgrid),tgrid),
+         y=c(rev(estimates$Shatlow[,3]),estimates$Shatup[,3]),
+         border=c("green"),lty=2, col="lightgray");
> lines(estimates$tgrid, estimates$Shat[,3], lty=3, lwd=3, col="green")
> legend(2600,0.95, legend=c("age=49","age=65","age=74"),
+        lty=c(1,2,3),lwd=c(3,3,3),col=c("black","red","green"),bty="n",cex=2)
```

The code below is used to generate the map of posterior means of frailties for each district (Figure 2, panel c).

```
> frail0=(rowMeans(res1$v)); #$
> frail = frail0[as.integer(names(nwengland))];
> values = cbind(as.integer(names(nwengland)), frail)
> op <- par(no.readonly = TRUE)
> par(mar=c(3,0,0,0))
> plotmap(nwengland, x=values, col=(gray.colors(10,0.3,1))[10:1],
+         pos = "bottomleft",width = 0.5, height = 0.04)
```

PO model with GRF frailties

Note that all coordinates are distinct, so we have $m = 1043$ and $n_i = 1$ in terms of our notations. To use `frailtyprior` to specify the prior, we need to create an `ID` variables consisting of 1043 distinct values. The powered exponential correlation function with $\nu = 1$ is used. To specify the number of knots and blocks for the FSA of $\mathbf{R}$, we consider $K = 100$ and $B = 1043$. The code below is used to fit a PO model with GRF frailties under above settings. The running time is 10177 seconds.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> prior=list(maxL=15, nu=1, nknots=100, nblock=1043);
> d$ID=1:nrow(d); #$
> locations=cbind(d$xcoord,d$ycoord);
> ptm<-proc.time()
> res2 = survregbayes(formula=Surv(time,cens)~age+sex+wbc+tpi
+                     +frailtyprior("grf",ID),data=d,survmodel="PO",
+                     dist="loglogistic",mcmc=mcmc,prior=prior,
+                     Coordinates=locations);
> sfit2=summary(res2); sfit2

Posterior inference of regression coefficients
(Adaptive M-H acceptance rate: 0.2726):
      Mean        Median      Std. Dev.   95%CI-Low   95%CI-Upp
```

```
age   0.0526668   0.0527180   0.0034351   0.0460261   0.0596917
sex   0.1310119   0.1318825   0.1069728  -0.0748948   0.3457847
wbc   0.0060590   0.0060293   0.0008156   0.0044876   0.0077388
tpi   0.0606026   0.0609221   0.0158076   0.0300292   0.0918792

Posterior inference of precision parameter
(Adaptive M-H acceptance rate: 0.1867):
       Mean    Median  Std. Dev.  95%CI-Low  95%CI-Upp
alpha  0.8931  0.7675  0.5354     0.2479     2.3162

Posterior inference of frailty variance
          Mean    Median  Std. Dev.  95%CI-Low  95%CI-Upp
variance  0.06179  0.05290  0.03261    0.02376    0.14086

Posterior inference of correlation function range phi
        Mean    Median  Std. Dev.  95%CI-Low  95%CI-Upp
range  19.138  17.245   7.305      8.701     35.094

Log pseudo marginal likelihood: LPML=-5923.402
Deviance Information Criterion: DIC=11845.78
Number of subjects: n=1043
> systime2=proc.time()-ptm; systime2;
     user    system   elapsed
10079.006    97.039 10176.650
```

The trace plots for $\boldsymbol{\beta}$, τ^2 and ϕ (Figure 3), Cox-Snell residuals and survival curves (Figure 4) can be obtained using the same code used for the PO model with ICAR frailties. The code below is used to generate the map of posterior means of frailties for each location (Figure 4).

```
> frail= round((rowMeans(res2$v)),3); nclust=5; #$
> frail.cluster = cut(frail, breaks = nclust);
> frail.names = names(table(frail.cluster))
> rbPal <- colorRampPalette(c('blue','red'))
> frail.colors=rbPal(nclust)[as.numeric(frail.cluster)]
> par(mar=c(3,0,0,0))
> plot(nwengland)
> points(cbind(d$xcoord,d$ycoord), col=frail.colors)
> legend("topright",title="frailty values",legend=frail.names,
+        col=rbPal(nclust),pch=20,cex=1.7)
```

2.5. Variable Selection

Let $\mathbf{x} = (x_1, \ldots, x_p)'$ denote the p-vector of covariates in general. The most direct approach is to multiply β_ℓ by a latent Bernoulli variable γ_ℓ for $\ell = 1, \ldots, p$, where $\gamma_\ell = 1$ indicates the presence of covariate x_ℓ in the model, and then assume an appropriate prior on $(\boldsymbol{\beta}, \boldsymbol{\gamma})$, where $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_p)'$. Following Kuo and Mallick (1998) and Hanson, Branscum, and Johnson

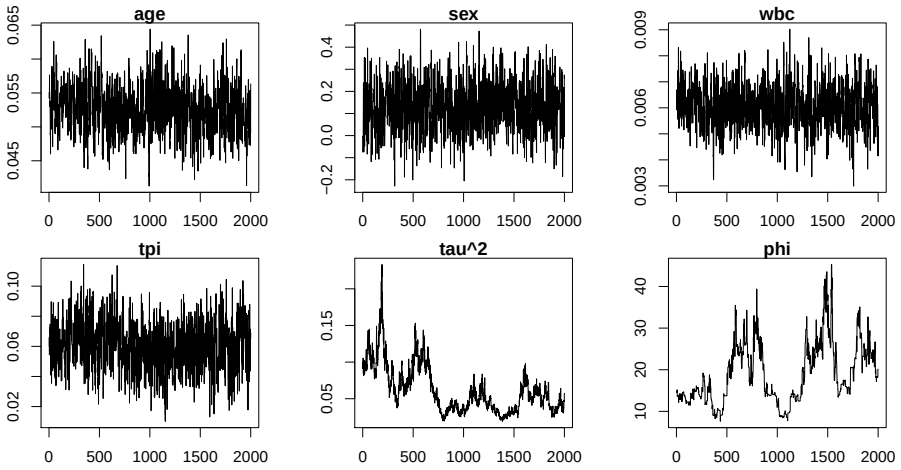
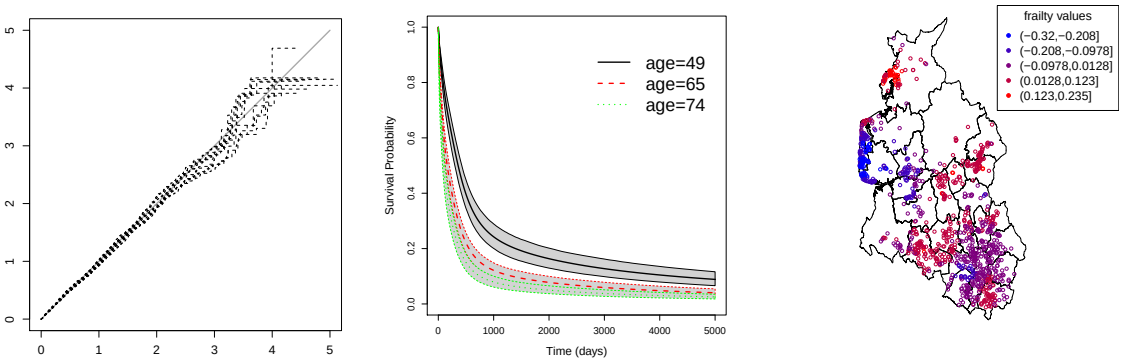


Figure 3: Leukemia survival data. Trace plots for $\boldsymbol{\beta}$, τ^2 and α under the PO model with GRF frailties.



(a) (b) (c)

Figure 4: Leukemia survival data. PO model with GRF frailties. (a) Cox-Snell plot. (b) Survival curves with 95% credible interval bands for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages. (c) Map for the posterior mean frailties; larger frailties mean higher mortality rate overall.

(2014), we consider below independent priors

$$\gamma_1, \ldots, \gamma_p \overset{iid}{\sim} \text{Bern}(0.5) \text{ and } \boldsymbol{\beta} \sim N_p(\mathbf{0}, gn(\mathbf{X}'\mathbf{X})^{-1}), \tag{14}$$

where $\mathbf{X}$ is the usual design matrix, but with mean-centered covariates, i.e. $\mathbf{1}_n'\mathbf{X} = \mathbf{0}_p'$, and g is chosen by picking a number M such that a random $e^{\mathbf{x}'\boldsymbol{\beta}}$ is less than M with probability q, i.e. approximately $g = \left[\log M/\Phi^{-1}(q)\right]^2/p$. The function `survregbayes` sets $M = 10$ and $q = 0.9$ as the defaults. The MCMC procedure is described in Zhou and Hanson (2017).

To perform variable selection for the leukemia survival data, we simply need to add the argument `selection=TRUE` to the function `survregbayes`. A part of the output from `summary` is also shown. The model with `age`, `wbc` and `tpi` has the highest proportion (89.8%), and thus can be served as the final model.

```
> set.seed(1)
> res3 = survregbayes(formula=Surv(time,cens)~age+sex+wbc+tpi
+                     +frailtyprior("car",district),data=d,survmodel="PO",
+                     dist="loglogistic",mcmc=mcmc,prior=prior,Proximity=E,
+                     selection=TRUE);
> systime3=proc.time()-ptm; systime3;
   user  system elapsed
308.490   0.585 309.524
> sfit3=summary(res3); sfit3
Variable selection:
       age,wbc,tpi  age,sex,wbc,tpi  age,wbc
prop.  0.8975       0.1010           0.0015

Log pseudo marginal likelihood: LPML=-5924.529
Deviance Information Criterion: DIC=11847.91
Number of subjects: n=1043
```

2.6. Parametric vs. Semiparametric

Many authors have found parametric models to fit as well or better than competing semiparametric models (Cox and Oakes 1984, p. 123; Nardi and Schemper 2003). The proposed semiparametric models have their baseline survival functions centered at a parametric family $S_{\boldsymbol{\theta}}(t)$. Note that $\mathbf{z}_{J-1} = \mathbf{0}$ implies $S_0(t) = S_{\boldsymbol{\theta}}(t)$. Therefore, testing $H_0 : \mathbf{z}_{J-1} = \mathbf{0}$ versus $H_1 : \mathbf{z}_{J-1} \neq \mathbf{0}$ leads to the comparison of the semiparametric model with the underlying parametric model. Let BF_{10} be the Bayes factor between H_1 and H_0. Zhou *et al.* (2017) proposed to estimate BF_{10} by a large-sample approximation to the generalized Savage-Dickey density ratio (Verdinelli and Wasserman 1995). Adapting their approach BF_{10} is estimated

$$\widehat{BF}_{10} = \frac{p(\mathbf{0}|\hat{\alpha})}{N_{J-1}(\mathbf{0}; \hat{\mathbf{m}}, \hat{\boldsymbol{\Sigma}})}, \tag{15}$$

where $p(\mathbf{0}|\alpha) = \Gamma(\alpha J)/[J^{\alpha}\Gamma(\alpha)]^J$ is the prior density of $\mathbf{z}_{J-1}$ evaluated at $\mathbf{z}_{J-1} = \mathbf{0}$, $\hat{\alpha}$ is the posterior mean of α, $N_p(\cdot; \mathbf{m}, \boldsymbol{\Sigma})$ denotes a p-variable normal density with mean $\mathbf{m}$ and covariance $\boldsymbol{\Sigma}$, and $\hat{\mathbf{m}}$ and $\hat{\boldsymbol{\Sigma}}$ are posterior mean and covariance of $\mathbf{z}_{J-1}$.

The Bayes factor BF_{10} under the semiparametric PO model with ICAR frailties can be obtained using the code below (here the object `res1` is obtained in Section 2.4).

```
> BF.survregbayes(res1)
[1] 82.12799
```

The $BF_{10} = 82 > 1$ indicates that the semiparametric model outperforms the loglogistic parametric model.

The function `survregbayes` also supports the efficient fitting of parametric frailty models with loglogistic, lognormal or Weibull baseline functions. In parametric models, the prior for $\boldsymbol{\theta}$ can be set to be relatively vague. Setting a_0 at any negative value will force the α to be fixed at the value specified in the argument `state`. For example, setting `prior=list(a0=-1)` and `state=list(alpha=1)` will fix $\alpha = 1$ throughout the MCMC; setting `prior=list(a0=-1)` and `state=list(alpha=Inf)` will fit a parametric model. The following code fits a parametric loglogistic PO model with ICAR frailties to the leukemia survival data. The LPML is -5950, much worse than the value under the semiparametric PO model.

```
> set.seed(1)
> prior=list(maxL=15, a0=-1,thete0=rep(0,2),V0=diag(1e10,2));
> state=list(alpha=Inf);
> ptm<-proc.time()
> res11 = survregbayes(formula=Surv(time,cens)~age+sex+wbc+tpi
+                      +frailtyprior("car",district),data=d,survmodel="PO",
+                      dist="loglogistic",mcmc=mcmc,prior=prior,state=state,
+                      Proximity=E,InitParamMCMC=FALSE);
scan = 1000
scan = 2000
> sfit11=summary(res11); sfit11
Proportional Odds model:
Call:
survregbayes(formula = Surv(time, cens) ~ age + sex + wbc + tpi +
frailtyprior("car", district), data = d, survmodel = "PO",
dist = "loglogistic", mcmc = mcmc, prior = prior, state = state,
Proximity = E, InitParamMCMC = FALSE)

Posterior inference of regression coefficients
(Adaptive M-H acceptance rate: 0.2844):
      Mean        Median      Std. Dev.    95%CI-Low    95%CI-Upp
age   0.0504253   0.0504362   0.0033318    0.0439945    0.0568477
sex   0.1187297   0.1134544   0.1109109   -0.0912841    0.3374972
wbc   0.0062192   0.0062147   0.0007395    0.0048068    0.0076600
tpi   0.0602207   0.0603376   0.0156038    0.0299010    0.0915584

Posterior inference of baseline parameters
Note: the baseline estimates are based on scaled covariates
(Adaptive M-H acceptance rate: 0.2723):
         Mean      Median    Std. Dev.  95%CI-Low  95%CI-Upp
```

```
theta1  -5.12778  -5.12791   0.06432   -5.25384   -5.00723
theta2  -0.10741  -0.10619   0.02759   -0.16125   -0.05445

Posterior inference of conditional CAR frailty variance
          Mean     Median   Std. Dev.  95%CI-Low  95%CI-Upp
variance  0.078627  0.055078  0.082164   0.002005   0.305202

Log pseudo marginal likelihood: LPML=-5949.919
Deviance Information Criterion: DIC=11899.46
Number of subjects: n=1043
> systime11=proc.time()-ptm; systime11;
  user  system elapsed
25.037   0.115  25.239
```

2.7. Left-Truncation and Time-Dependent Covariates

The survival time t_{ij} is left-truncated at $u_{ij} \geq 0$ if u_{ij} is the time when the ijth subject is first observed. Left-truncation often occurs when age is used as the time scale. Given the observed left-truncated data $\{(u_{ij}, a_{ij}, b_{ij}, \mathbf{x}_{ij}, \mathbf{s}_i)\}$, where $a_{ij} \geq u_{ij}$, the likelihood function (13) becomes

$$L(\mathbf{w}_J, \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{v}) = \prod_{i=1}^{m} \prod_{j=1}^{n_i} \left[S_{\mathbf{x}_{ij}}(a_{ij}) - S_{\mathbf{x}_{ij}}(b_{ij})\right]^{I\{a_{ij}<b_{ij}\}} f_{\mathbf{x}_{ij}}(a_{ij})^{I\{a_{ij}=b_{ij}\}} / S_{\mathbf{x}_{ij}}(u_{ij}).$$

Note that the left censored data under left-truncation are of the form (u_{ij}, b_{ij}). Allowing for left-truncation allows the semiparametric AFT, PH and PO models to be easily extended to handle time-dependent covariates. Following Kneib (2006) and Hanson, Johnson, and Laud (2009), assume the covariate vector $\mathbf{x}_{ij}(t)$ is a step function that changes at o_{ij} ordered times $t_{ij,1} < \ldots < t_{ij,o_{ij}} \leq a_{ij}$, i.e.,

$$\mathbf{x}_{ij}(t) = \sum_{k=1}^{o_{ij}} \mathbf{x}_{ij,k} I(t_{ij,k} \leq t < t_{ij,k+1}),$$

where $t_{ij,1} = u_{ij}$ and $t_{ij,o_{ij}+1} = \infty$. Assuming one of PH, PO, or AFT holds conditionally on each interval, the survival function for the ijth individual at time a_{ij} is

$$\begin{aligned} P(t_{ij} > a_{ij}) &= P(t_{ij} > a_{ij} | t_{ij} > t_{ij,o_{ij}}) \prod_{k=1}^{o_{ij}-1} P(t_{ij} > t_{ij,k+1} | t_{ij} > t_{ij,k}) \\ &= \frac{S_{\mathbf{x}_{ij,o_{ij}}}(a_{ij})}{S_{\mathbf{x}_{ij,o_{ij}}}(t_{ij,o_{ij}})} \prod_{k=1}^{o_{ij}-1} \frac{S_{\mathbf{x}_{ij,k}}(t_{ij,k+1})}{S_{\mathbf{x}_{ij,k}}(t_{ij,k})}. \end{aligned}$$

Thus one can replace the observation $(u_{ij}, a_{ij}, b_{ij}, \mathbf{x}_{ij}(t), \mathbf{s}_i)$ by a set of new o_{ij} observations $(t_{ij,1}, t_{ij,2}, \infty, \mathbf{x}_{ij,1}, \mathbf{s}_i)$, $(t_{ij,2}, t_{ij,3}, \infty, \mathbf{x}_{ij,2}, \mathbf{s}_i)$, …, $(t_{ij,o_{ij}}, a_{ij}, b_{ij}, \mathbf{x}_{ij,o_{ij}}, \mathbf{s}_i)$. This way we get a

new left-truncated data set of size $\sum_{i=1}^{m}\sum_{j=1}^{n_i} o_{ij}$. Then the likelihood function becomes

$$L(\mathbf{w}_J,\boldsymbol{\theta},\boldsymbol{\beta},\mathbf{v}) = \prod_{i=1}^{m}\prod_{j=1}^{n_i}\left\{ \left[S_{\mathbf{x}_{ij,o_{ij}}}(a_{ij}) - S_{\mathbf{x}_{ij,o_{ij}}}(b_{ij})\right]^{I\{a_{ij}<b_{ij}\}} f_{\mathbf{x}_{ij,o_{ij}}}(a_{ij})^{I\{a_{ij}=b_{ij}\}}/S_{\mathbf{x}_{ij,o_{ij}}}(t_{ij,o_{ij}}) \times \prod_{k=1}^{o_{ij}-1}\frac{S_{\mathbf{x}_{ij,k}}(t_{ij,k+1})}{S_{\mathbf{x}_{ij,k}}(t_{ij,k})}\right\}.$$

Note that the derivations above still hold for time-dependent covariates without left-truncation (i.e. $u_{ij} = 0$ for all i and j).

PBC data

We use the primary biliary cirrhosis (PBC) dataset (available in the package `survival` as `pbc`) as an example to show how to incorporate time-dependent covariates in the function `survregbayes`. Although this is not a spatial dataset, spatial frailties can be added similarly as in Section 2.4. The following code is copied from Therneau, Crowson, and Atkinson (2017) to create the data frame with time-dependent covariates.

```
> temp <- subset(pbc, id <= 312, select=c(id:sex, stage)) # baseline data
> pbc2 <- tmerge(temp, temp, id=id, endpt = event(time, status))
> pbc2 <- tmerge(pbc2, pbcseq, id=id, ascites = tdc(day, ascites),
+                bili = tdc(day, bili), albumin = tdc(day, albumin),
+                protime = tdc(day, protime), alk.phos = tdc(day, alk.phos))
> pbc2 = pbc2[,c("id","tstart","tstop","endpt","bili","protime")];
> head(pbc2);
  id tstart tstop endpt bili protime
1  1      0   192     0 14.5    12.2
2  1    192   400     2 21.3    11.2
3  2      0   182     0  1.1    10.6
4  2    182   365     0  0.8    11.0
5  2    365   768     0  1.0    11.6
6  2    768  1790     0  1.9    10.6
> coxph(Surv(tstart,tstop,endpt==2)~log(bili)+log(protime), data=pbc2)
Call:
coxph(formula = Surv(tstart, tstop, endpt == 2) ~ log(bili) +
log(protime), data = pbc2)

coef exp(coef) se(coef)     z      p
log(bili)     1.241     3.460    0.097 12.80 <2e-16
log(protime)  3.983    53.699    0.436  9.14 <2e-16

Likelihood ratio test=332  on 2 df, p=0
n= 1807, number of events= 125
```

We can fit the Bayesian PH model with TBP baseline as follows. The output for regression coefficients is partial.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> ptm<-proc.time()
> fit1 = survregbayes(Surv(tstart,tstop,endpt==2)~log(bili)+log(protime),
+                     data=pbc2, survmodel="PH", dist="loglogistic",
+                     mcmc=mcmc, subject.num=id);
> fit1
Proportional hazards model:
Call:
survregbayes(formula = Surv(tstart, tstop, endpt == 2) ~ log(bili) +
        log(protime), data = pbc2, survmodel = "PH", dist = "loglogistic",
        mcmc = mcmc, subject.num = id)

Posterior means for regression coefficients:
   log(bili)  log(protime)
       1.299         4.185

LPML: -1018.496
DIC: 2032.754
n=1807
> systime1=proc.time()-ptm; systime1;
   user  system elapsed
227.626   0.434 228.243
```

Equivalently, one can also run the following code to obtain the same analysis. The argument `truncation_time` is used to specify the start time point for each time interval, i.e. `tstart`. The end time point `tstop` together with `endpt` are formulated as interval censored data using `type="interval2"` of `Surv`. This format is more general than the former one, as one can easily incorporate interval censored data.

```
> pbc2$tleft=pbc2$tstop; pbc2$tright=pbc2$tstop;
> pbc2$tright[which(pbc2$endpt!=2)]=NA;
> fit11 = survregbayes(Surv(tleft,tright,type="interval2")~log(bili)
+                      +log(protime), data=pbc2, survmodel="PH",
+                      dist="loglogistic", mcmc=mcmc,
+                      truncation_time=tstart, subject.num=id);
```

3. GAFT Frailty Models

3.1. The Model

The generalized accelerated failure time (GAFT) frailty model (Zhou *et al.* 2017) generalizes the AFT model (1) to allow the baseline survival function $S_0(t)$ to depend on certain covariates, say a q-dimensional vector $\mathbf{z}_{ij}$ which is usually a subset of $\mathbf{x}_{ij}$. Specifically, the GAFT frailty model is given by

$$S_{\mathbf{x}_{ij}}(t) = S_{0,\mathbf{z}_{ij}}\left(e^{-\mathbf{x}_{ij}'\boldsymbol{\beta}-v_i}t\right), \tag{16}$$

or equivalently,

$$y_{ij} = \log(t_{ij}) = \tilde{\mathbf{x}}_{ij}'\tilde{\boldsymbol{\beta}} + v_i + \epsilon_{ij}, \tag{17}$$

where $\tilde{\mathbf{x}}_{ij} = (1, \mathbf{x}_{ij}')'$ includes an intercept, $\tilde{\boldsymbol{\beta}} = (\beta_0, \boldsymbol{\beta}')'$ is a vector of corresponding coefficients, ϵ_{ij} is a heteroscedastic error term independent of v_i, and $P(e^{\beta_0+\epsilon_{ij}} > t|\mathbf{z}_{ij}) = S_{0,\mathbf{z}_{ij}}(t)$. Note the regression coefficients $\boldsymbol{\beta}$ here are defined differently with those in model (1). Here we assume

$$\epsilon_{ij}|G_{\mathbf{z}_{ij}} \overset{ind.}{\sim} G_{\mathbf{z}_{ij}},$$

where $G_{\mathbf{z}}$ is a probability measure defined on $\mathbb{R}$ for every $\mathbf{z} \in \mathcal{X}$; this defines a model for the entire collection of probability measures $\mathcal{G}_{\mathcal{X}} = \{G_{\mathbf{z}} : \mathbf{z} \in \mathcal{X}\}$ so that each element is allowed to smoothly change with the covariates $\mathbf{z}$. The `frailtyGAFT` function considers the following prior distributions:

$$\begin{aligned}
\tilde{\boldsymbol{\beta}} &\sim N_{p+1}(\mathbf{m}_0, \mathbf{S}_0) \\
G_{\mathbf{z}}|\alpha, \sigma^2 &\sim \text{LDTFP}_L(\alpha, \sigma^2),\ \alpha \sim \Gamma(a_0, b_0),\ \sigma^{-2} \sim \Gamma(a_\sigma, b_\sigma), \\
(v_1, \ldots, v_m)'|\tau &\sim \text{ICAR}(\tau^2),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau),\ \text{or} \\
(v_1, \ldots, v_m)'|\tau, \phi &\sim \text{GRF}(\tau^2, \phi),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau),\ \phi \sim \Gamma(a_\phi, b_\phi),\ \text{or} \\
(v_1, \ldots, v_m)'|\tau &\sim \text{IID}(\tau^2),\ \tau^{-2} \sim \Gamma(a_\tau, b_\tau)
\end{aligned} \tag{18}$$

where LDTFP_L refers to the linear dependent tailfree process prior (LDTFP) prior as described in (Zhou *et al.* 2017).

The LDTFP prior considered in Zhou *et al.* (2017) is centered at a normal distribution Φ_σ with mean 0 and variance σ^2, that is, $E(G_{\mathbf{z}}) = \Phi_\sigma$ for every $\mathbf{z} \in \mathcal{X}$. Define the function $k_\sigma(x) = \lceil 2^L \Phi_\sigma(x) \rceil$, where $\lceil x \rceil$ is the ceiling function, the smallest integer greater than or equal to x. Further define probability $p_{\mathbf{z}}(k)$ for $k = 1, \ldots, 2^L$ as

$$p_{\mathbf{z}}(k) = \prod_{l=1}^{L} Y_{l,\lceil k2^{l-L} \rceil}(\mathbf{z}),$$

where $Y_{j+1,2k-1}(\mathbf{z}) = \left(1 + \exp\{-\tilde{\mathbf{z}}'\boldsymbol{\gamma}_{j,k}\}\right)^{-1}$ and $Y_{j+1,2k}(\mathbf{z}) = 1 - Y_{j+1,2k-1}(\mathbf{z})$ for $j = 0, \ldots, L-1$, $k = 1, \ldots, 2^j$, where $\tilde{\mathbf{z}} = (1, \mathbf{z}')'$ includes an intercept, and $\boldsymbol{\gamma}_{j,k} = (\gamma_{j,k,0}, \ldots, \gamma_{j,k,q})'$ is a vector of coefficients. Note there are $2^L - 1$ regression coefficient vectors $\boldsymbol{\gamma} = \{\boldsymbol{\gamma}_{j,k}\}$, e.g. for $L = 3$, $\boldsymbol{\gamma} = \{\boldsymbol{\gamma}_{0,1}, \boldsymbol{\gamma}_{1,1}, \boldsymbol{\gamma}_{1,2}, \boldsymbol{\gamma}_{2,1}, \boldsymbol{\gamma}_{2,2}, \boldsymbol{\gamma}_{2,3}, \boldsymbol{\gamma}_{2,4}\}$. For a fixed integer $L > 0$, the random density associated with $\text{LDTFP}_L(\alpha, \sigma^2)$ is defined as

$$f_{\mathbf{z}}(e) = 2^L \phi_\sigma(e) p_{\mathbf{z}}\{k_\sigma(e)\},\ \boldsymbol{\gamma}_{j,k} \overset{ind.}{\sim} N_{q+1}\left(\mathbf{0}, \frac{2n}{\alpha(j+1)^2}(\mathbf{Z}'\mathbf{Z})^{-1}\right) \tag{19}$$

with cdf

$$G_{\mathbf{z}}(e) = p_{\mathbf{z}}\{k_\sigma(e)\}\left\{2^L \Phi_\sigma(e) - k_\sigma(e)\right\} + \sum_{k=1}^{k_\sigma(e)} p_{\mathbf{z}}(k), \tag{20}$$

where $\mathbf{Z}$ is the $n \times (q+1)$ design matrix with mean-centered covariates $\tilde{\mathbf{z}}_{ij}$s. Furthermore, the LDTFP is specified by setting $\boldsymbol{\gamma}_{0,1} \equiv \mathbf{0}$, such that for every $\mathbf{z} \in \mathcal{X}$, $G_{\mathbf{z}}$ is almost surely a median-zero probability measure. This is important to avoid identifiability issues. As shown by Jara and Hanson (2011), the LDTFP has appealing theoretical properties such as

continuity as a function of the covariates, large support on the space of conditional density functions, straightforward posterior computation relying on algorithms for fitting generalized linear models, and the process closely matches conventional Polya tree priors (see, e.g., Hanson 2006) at each value of the covariate, which justify its choice here.

3.2. MCMC

Let $\Omega = (\mathbf{y}_c, \tilde{\boldsymbol{\beta}}, \mathbf{v}, \tau^2, \sigma^2, \boldsymbol{\gamma}, \alpha)$ denote collectively the model parameters to be updated, where $\mathbf{y}_c = \{y_{ij} : a_{ij} < b_{ij}\}$ are censored log-survival times. The $y_{ij} \in \mathbf{y}_c$, each component of $\tilde{\boldsymbol{\beta}}$, v_i and σ are all sampled using the single-variable slice sampling method (Neal 2003). For the LDTFP regression parameters $\gamma_{j,k}$, we utilize Metropolis-Hastings steps with Gaussian proposals based on iterative weighted least squares (Gamerman 1997), recognizing that the $\gamma_{j,k}$ full conditionals are proportional to logistic regression likelihoods. The hyperparameters τ^2 and α are sampled according to their conjugate full conditional distributions. A complete description of updating steps is available in Zhou *et al.* (2017).

The function `frailtyGAFT` sets the following hyperparameters as defaults: $\mathbf{m}_0 = \mathbf{0}$, $\mathbf{S}_0 = 10^5\mathbf{I}_{p+1}$, $a_0 = b_0 = 1$, $a_\tau = b_\tau = .001$, and $a_\sigma = 2 + \hat{\sigma}_0^4/(100\hat{v}_0)$, $b_\sigma = \hat{\sigma}_0^2(a_\sigma - 1)$, where $\hat{\sigma}_0^2$ and $\hat{v}_0$ are the estimates of σ^2 and its asymptotic variance from fitting the parametric lognormal AFT model, respectively. Note here we assume a somewhat informative prior on σ^2 so that its mean is $\hat{\sigma}_0^2$ and variance is $100\hat{v}_0$. For the GRF prior, we again set $a_\phi = 2$ and $b_\phi = (a_\phi - 1)/\phi_0$ so that the prior of ϕ has mode at ϕ_0 and the prior mean of $1/\phi$ is $1/\phi_0$ with infinite variance. Here ϕ_0 satisfies $\rho(\mathbf{s}', \mathbf{s}''; \phi_0) = 0.001$, where $\|\mathbf{s}' - \mathbf{s}''\| = \max_{ij} \|\mathbf{s}_i - \mathbf{s}_j\|$. Again, the user-defined hyperparameters can be specified via the argument `prior`, e.g., for $p = 3$, $L = 5$, $\mathbf{m}_0 = \mathbf{0}$, $\mathbf{S}_0 = 10\mathbf{I}_{p+1}$, $a_0 = b_0 = 1$, and $a_\sigma = b_\sigma = 2$, the prior can be specified as below.

```
> prior=list(maxL=5,m0=rep(0,4),S0=diag(10,4),siga0=1,sigb0=1,a0=1,b0=1)
```

Given a set of posterior samples $\{\boldsymbol{\Omega}^{(s)}, s = 1, \ldots, S\}$, all the inference targets can be easily estimated. For example, the baseline survival function $S_{0,\mathbf{z}}(t) = P(e^{\beta_0 + \epsilon} > t|\mathbf{z})$ given the covariate $\mathbf{z}$ is estimated by

$$S_{0,\mathbf{z}}(t) = \frac{1}{S}\sum_{s=1}^{S}\left\{1 - G_{\mathbf{z}}^{(s)}\left(\log t - \beta_0^{(s)}\right)\right\}, \tag{21}$$

where $G_{\mathbf{z}}^{(s)}(\cdot)$ is given in (20) with all unknown parameters replaced by corresponding posterior values in the sth iterate.

3.3. Bayesian Hypothesis Testing

The GAFT frailty model includes the following as important special cases: an AFT frailty model with nonparametric baseline where $G_{\mathbf{z}} = G_{\mathbf{z}'}$ for all $\mathbf{z} = \mathbf{z}'$ and parametric baseline model $G_{\mathbf{z}} = \Phi_\sigma$ for all $\mathbf{z} \in \mathcal{X}$. Hypothesis tests can be constructed based on the LDTFP coefficients $\{\boldsymbol{\gamma}_{l,k} : k = 1, \ldots, 2^l, l = 1, \ldots, L-1\}$, where $\boldsymbol{\gamma}_{l,k} = (\gamma_{l,k,0}, \ldots, \gamma_{l,k,q})'$. Let $\boldsymbol{\gamma}_{l,k,-j}$ denote the subvector of $\boldsymbol{\gamma}_{l,k}$ without element $\gamma_{l,k,j}$ for $j = 0, \ldots, q$. Set $\boldsymbol{\Upsilon}_j = (\gamma_{l,k,j}, k = 1, \ldots, 2^l, l = 1, \ldots, L-1)'$, $\boldsymbol{\Upsilon}_{-j} = (\boldsymbol{\gamma}'_{l,k,-j}, k = 1, \ldots, 2^l, l = 1, \ldots, L-1)'$ and $\boldsymbol{\Upsilon} = (\boldsymbol{\gamma}'_{l,k}, k = 1, \ldots, 2^l, l = 1, \ldots, L-1)'$. Testing the hypotheses $H_0 : \boldsymbol{\Upsilon}_{-0} = \mathbf{0}$ and $H_0 : \boldsymbol{\Upsilon} = \mathbf{0}$ leads

to global comparisons of the proposed model with the above two special cases respectively. Similarly, we may also test the null hypothesis $H_0 : \boldsymbol{\Upsilon}_j = \mathbf{0}$ for the jth covariate effect of $\mathbf{z}$ on the baseline survival, $j = 1, \ldots, q$.

Suppose we wish to test $H_0 : \boldsymbol{\Upsilon}_j = \mathbf{0}$ versus $H_1 : \boldsymbol{\Upsilon}_j \neq \mathbf{0}$, for fixed $j \in \{1, \ldots, q\}$. Following Zhou *et al.* (2017), the Bayes factor between hypotheses H_1 and H_0 can be approximated by

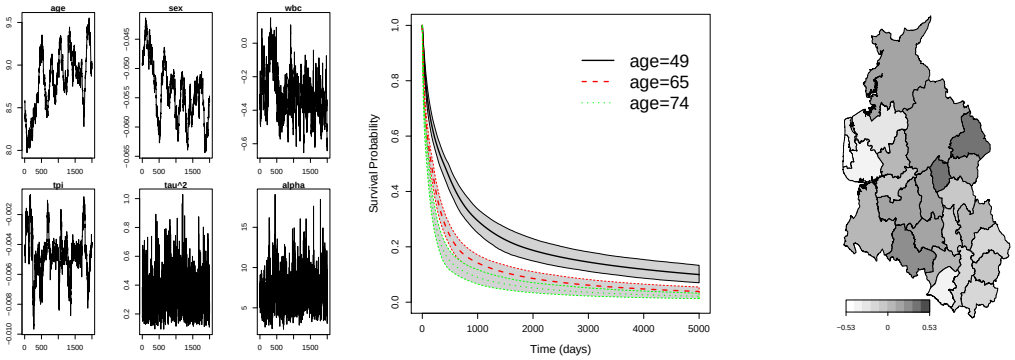
$$\hat{BF}_{10} = \frac{\prod_{l=1}^{L-1} \prod_{k=1}^{2^l} N\left(0 \middle| 0, \frac{2n}{\hat{\alpha}(l+1)^2} (\mathbf{Z}'\mathbf{Z})^{-1}_{jj}\right)}{N_{2^L-2}(\boldsymbol{\Upsilon}_j = \mathbf{0}; \hat{\mathbf{m}}_j, \hat{\mathbf{S}}_j)}, \tag{22}$$

where $N_p(\cdot; \mathbf{m}, \mathbf{S})$ denotes a p-variate normal density with mean $\mathbf{m}$ and covariance matrix $\mathbf{S}$, and $\hat{\mathbf{m}}_j$ and $\hat{\mathbf{S}}_j$ are the sample mean and covariance for $\boldsymbol{\Upsilon}_j$.

3.4. Leukemia Survival Data

The code below is used to fit the GAFT model with ICAR frailties for the leukemia survival data. As suggested by Zhou *et al.* (2017), the gamma prior $\Gamma(a_0 = 5, b_0 = 1)$ is used for α. We include all four covariates in modeling the baseline survival function.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> prior=list(maxL=4, a0=5, b0=1);
> ptm<-proc.time()
> res1 = frailtyGAFT(formula=Surv(time,cens)~age+sex+wbc+tpi
+                    +baseline(age,sex,wbc,tpi)+frailtyprior("car",district),
+                    data=d,mcmc=mcmc,prior=prior,Proximity=E);
scan = 1000
scan = 2000
> sfit1=summary(res1); sfit1
Generalized accelerated failure time frailty model:
Call:
frailtyGAFT(formula = Surv(time, cens) ~ age + sex + wbc + tpi +
    baseline(age, sex, wbc, tpi) + frailtyprior("car", district),
    data = d, mcmc = mcmc, prior = prior, Proximity = E)

Posterior inference of regression coefficients
            Mean       Median     Std. Dev.  95%HPD-Low  95%HPD-Upp
intercept   8.814068   8.854485   0.346621   8.097035    9.401137
age        -0.054063  -0.054041   0.004926  -0.063937   -0.045553
sex        -0.299306  -0.317065   0.145519  -0.531467    0.030991
wbc        -0.004581  -0.004553   0.001457  -0.007829   -0.001803
tpi        -0.060635  -0.062607   0.021067  -0.100791   -0.019597

Posterior inference of scale parameter
       Mean    Median  Std. Dev.  95%HPD-Low  95%HPD-Upp
scale  2.10578  2.09632  0.09638    1.93813     2.30722
```



(a) (b) (c)

Figure 5: Leukemia survival data. GAFT model with ICAR frailties. (a) Trace plots for $\boldsymbol{\beta}$, τ^2 and α. (b) Survival curves with 95% credible interval bands for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages. (c) Map for the negative posterior mean frailties; larger values mean higher mortality rate overall.

```
Posterior inference of precision parameter of LDTFP
        Mean    Median  Std. Dev.  95%HPD-Low  95%HPD-Upp
alpha   6.894   6.684   2.153      3.131       11.171

Posterior inference of conditional CAR frailty variance
          Mean    Median  Std. Dev.  95%HPD-Low  95%HPD-Upp
variance  0.3126  0.2860  0.1283     0.1124      0.5664

Bayes factors for LDTFP covariate effects:
intercept        age        sex        wbc        tpi    overall  normality
   0.5495     4.6231     1.2374     5.5556     0.5740     1.6032   103.1727

Log pseudo marginal likelihood: LPML=-5939.093
Number of subjects:=1043
> systime1=proc.time()-ptm; systime1;
user  system elapsed
505.052   0.606 506.547
```

The Bayes factors for testing `age` and `wbc` effects on LDTFP are 4.6 and 1.6, respectively, indicating that the baseline survival function under the AFT model depends on `age` and `wbc`, and thus GAFT should be considered. The trace plots, survival curves and frailty map (Figure 5) can be obtained using the code similarly to Section 2.4. The only difference is that we need to specify the baseline covariates for plotting survival curves by including the argument `xtfpred=xpred` into the `plot` function. We see that the mixing for covariate effects is poor due to the non-smoothness of Polya trees. In this case, we need to run a much longer chain with higher thinning.

```
> estimates=plot(res1, xpred=xpred, xtfpred=xpred, tgrid=tgrid);
```

4. Survival Models via Spatial Copulas

Currently the package only supports spatial copula models for georeferenced (without replication, i.e. $n_i = 1$), right-censored spatial data. Suppose subjects are observed at n distinct spatial locations $\mathbf{s}_1, \ldots, \mathbf{s}_n$. Let t_i be a random event time associated with the subject at $\mathbf{s}_i$ and $\mathbf{x}_i$ be a related p-dimensional vector of covariates, $i = 1, \ldots, n$. For right-censored data, we only observe t_i^o and a censoring indicator δ_i for each subject, where δ_i equals 1 if $t_i^o = t_i$ and equals 0 if t_i is censored at t_i^o. Therefore, the observed data will be $\mathcal{D} = \{(t_i^o, \delta_i, \mathbf{x}_i, \mathbf{s}_i); i = 1, \ldots, n\}$. Note although the models below are developed for spatial survival data, non-spatial data are also accommodated.

The use of copulas in the spatial context was first proposed by Bárdossy (2006), where the empirical variogram is replaced by empirical copulas to investigate the spatial dependence structure. Copulas completely describe association among random variables separately from their univariate distributions and thus capture joint dependence without the influence of the marginal distribution (Li 2010). In the context of survival models, the idea of spatial copula approach is to first assume that the survival time t_i at location $\mathbf{s}_i$ marginally follows a model $S_{\mathbf{x}_i}(t)$, then model the joint distribution of $(t_1, \ldots, t_n)'$ as

$$P(t_1 \leq a_1, \ldots, t_n \leq a_n) = C(F_{\mathbf{x}_1}(a_1), \ldots, F_{\mathbf{x}_n}(a_n)), \tag{23}$$

where $F_{\mathbf{x}_i}(t) = 1 - S_{\mathbf{x}_i}(t)$ is the cumulative distribution function and the function C is an n-copula used to capture spatial dependence.

The current package assumes a spatial version of the Gaussian copula (Li 2010), defined as

$$C(u_1, \ldots, u_n) = \Phi_n \left(\Phi^{-1}\{u_1\}, \ldots, \Phi^{-1}\{u_n\}; \mathbf{R}\right), \tag{24}$$

where $\Phi_n(\cdot, \ldots, \cdot; \mathbf{R})$ denotes the distribution function of $N_n(\mathbf{0}, \mathbf{R})$. To allow for a nugget effect, we consider $\mathbf{R}[i, j] = \theta_1 \rho(\mathbf{s}_i, \mathbf{s}_j; \theta_2) + (1 - \theta_1) I(\mathbf{s}_i = \mathbf{s}_j)$, where $\rho(\mathbf{s}_i, \mathbf{s}_j; \theta_2) = \exp\{-\theta_2 \|\mathbf{s}_i - \mathbf{s}_j\|\}$. Here $\theta_1 \in [0, 1]$, also known as a "partial sill" in Waller and Gotway (2004), is a scale parameter measuring a local maximum correlation, and θ_2 controls the spatial decay over distance. Note that all the diagonal elements of $\mathbf{R}$ are ones, so it is also a correlation matrix. Under the above spatial Gaussian copula, the likelihood function based on upon the complete data $\{(t_i, \mathbf{x}_i, \mathbf{s}_i), i = 1, \ldots, n\}$ is

$$\mathcal{L} = |\mathbf{R}|^{-1/2} \exp\left\{-\frac{1}{2}\mathbf{z}'(\mathbf{R}^{-1} - \mathbf{I}_n)\mathbf{z}\right\} \prod_{i=1}^{n} f_{\mathbf{x}_i}(t_i), \tag{25}$$

where $z_i = \Phi^{-1}\left\{F_{\mathbf{x}_i}(t_i)\right\}$ and $f_{\mathbf{x}_i}(t)$ is the density function corresponding to $S_{\mathbf{x}_i}(t)$. We next discuss two marginal spatial survival models for $S_{\mathbf{x}_i}(t)$ that are accommodated in the package. Note that for large n, the FSA introduced in Section 2.1 (with ϵ replaced by $1 - \theta_1$) can be applied.

4.1. Proportional Hazards Model via Spatial Copulas

Assume that $t_i|\mathbf{x}_i$ marginally follows the proportional hazards (PH) model with cdf

$$F_{\mathbf{x}_i}(t) = 1 - \exp\left\{-\Lambda_0(t) e^{\mathbf{x}_i'\boldsymbol{\beta}}\right\} \tag{26}$$

and density

$$f_{\mathbf{x}_i}(t) = \exp\left\{-\Lambda_0(t)e^{\mathbf{x}_i'\boldsymbol{\beta}}\right\}\lambda_0(t)e^{\mathbf{x}_i'\boldsymbol{\beta}},$$

where $\boldsymbol{\beta}$ is a $p \times 1$ vector of regression coefficients, $\lambda_0(t)$ is the baseline hazard function and $\Lambda_0(t) = \int_0^t \lambda_0(s)ds$ is the cumulative baseline hazard function. The piecewise exponential model provides a flexible framework to deal with the baseline hazard (e.g. Walker and Mallick 1997). We partition the time period $\mathbb{R}^+$ into M intervals, say $I_k = (d_{k-1}, d_k], k = 1, \ldots, M$, where $d_0 = 0$ and $d_M = \infty$. Specifically, we set d_k to be the $\frac{k}{M}$th quantile of the empirical distribution of the observed survival times for $k = 1, \ldots, M-1$. The baseline hazard is then assumed to be constant within each interval, i.e.

$$\lambda_0(t) = \sum_{k=1}^{M} h_k I\{t \in I_k\},$$

where h_ks are unknown hazard values. Consequently, the cumulative baseline hazard function can be written as

$$\Lambda_0(t) = \sum_{k=1}^{M(t)} h_k \Delta_k(t),$$

where $M(t) = \min\{k : d_k \geq t\}$ and $\Delta_k(t) = \min\{d_k, t\} - d_{k-1}$. After incorporating spatial dependence via the copula in (24), the `spCopulaCoxph` function considers the following prior distributions:

$$\begin{aligned} \boldsymbol{\beta} &\sim N_p(\boldsymbol{\beta}_0, \mathbf{S}_0), \\ h_k|h &\overset{iid}{\sim} \Gamma(r_0 h, r_0), k = 1, \ldots, M, \\ (\theta_1, \theta_2) &\sim \text{Beta}(\theta_{1a}, \theta_{1b}) \times \Gamma(\theta_{2a}, \theta_{2b}) \end{aligned} \tag{27}$$

The `spCopulaCoxph` function sets the following default hyperparameter values: $M = 10$, $r_0 = 1$, $h = \hat{h}$, $\boldsymbol{\beta}_0 = \mathbf{0}$, $\mathbf{S}_0 = 10^5\mathbf{I}_p$, $\theta_{1a} = \theta_{1b} = \theta_{2a} = \theta_{2b} = 1$, where $\hat{h}$ is the maximum likelihood estimate of the rate parameter from fitting an exponential PH model. A function `indeptCoxph` is also provided to fit the non-spatial standard PH model with above baseline and prior settings.

4.2. Bayesian Nonparametric Survival Model via Spatial Copulas

We assume that $y_i = \log t_i$ given $\mathbf{x}_i$ marginally follows a LDDPM model (De Iorio *et al.* 2009) with cdf,

$$F_{\mathbf{x}_i}(t) = \int \Phi\left(\frac{\log t - \mathbf{x}_i'\boldsymbol{\beta}}{\sigma}\right) dG\{\boldsymbol{\beta}, \sigma^2\}, \tag{28}$$

where $\Phi(\cdot)$ is the cdf of the standard normal, and G follows the Dirichlet Process (DP) prior. This Bayesian nonparametric model treats the conditional distribution $F_{\mathbf{x}}$ as a function-valued parameter and allows its variance, skewness, modality and other features to flexibly vary with the $\mathbf{x}$ covariates. After incorporating spatial dependence via the copula in (24), the function

`spCopulaDDP` assumes the following prior distributions:

$$\begin{aligned} G = \sum_{k=1}^{N} w_k \delta_{(\boldsymbol{\beta}_k, \sigma_k^2)},\ w_k = V_k \prod_{j=0}^{k-1}(1-V_j),\ V_0 = 0, V_N = 1 \\ V_k \overset{iid}{\sim} \text{Beta}(1, \alpha), k = 1, \ldots, N,\ \alpha \sim \Gamma(a_0, b_0) \\ \boldsymbol{\beta}_k | \boldsymbol{\mu} \overset{iid}{\sim} N_p(\boldsymbol{\mu}, \boldsymbol{\Sigma}), k = 1, \ldots, N,\ \boldsymbol{\mu} \sim N_p(\mathbf{m}_0, \mathbf{S}_0) \\ \sigma_k^{-2} | \boldsymbol{\Sigma} \overset{iid}{\sim} \Gamma(\nu_a, \nu_b), k = 1, \ldots, N,\ \boldsymbol{\Sigma}^{-1} \sim W_p\left((\kappa_0 \boldsymbol{\Sigma}_0)^{-1}, \kappa_0\right) \\ (\theta_1, \theta_2) \sim \text{Beta}(\theta_{1a}, \theta_{1b}) \times \Gamma(\theta_{2a}, \theta_{2b}). \end{aligned} \tag{29}$$

The following default hyperpriors are considered in `spCopulaDDP`: $a_0 = b_0 = 2$, $\nu_a = 3$, $\nu_b = \hat{\sigma}^2$, $\theta_{1a} = \theta_{1b} = \theta_{2a} = \theta_{2b} = 1$, $\mathbf{m}_0 = \hat{\boldsymbol{\beta}}$, $\mathbf{S}_0 = \hat{\boldsymbol{\Sigma}}$, $\boldsymbol{\Sigma}_0 = 30\hat{\boldsymbol{\Sigma}}$, and $\kappa_0 = 7$, where $\hat{\boldsymbol{\beta}}$ and $\hat{\sigma}^2$ are the maximum likelihood estimates of $\boldsymbol{\beta}$ and σ^2 from fitting the log-normal accelerated failure time model $\log(t_i) = \mathbf{x}_i'\boldsymbol{\beta} + \sigma\epsilon_i, \epsilon_i \sim N(0,1)$, and $\hat{\boldsymbol{\Sigma}}$ is the asymptotic covariance estimate for $\hat{\boldsymbol{\beta}}$. A function `indeptDDP` is also provided to fit the non-spatial LDDPM model in (28) with above prior settings.

4.3. Leukemia Survival Data

PH model with spatial copula

The following code is used to fit the piecewise exponential PH model (26) with the Gaussian spatial copula (24) using $M = 20$ and default priors. We consider $K = 100$ and $B = 1043$ for the number of knots and blocks in the FSA of **R**. The total running time is 15445 seconds.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> prior=list(M=20, nknots=100, nblock=1043);
> ptm<-proc.time()
> res1 = spCopulaCoxph(formula=Surv(time,cens)~age+sex+wbc+tpi,data=d,
+                      mcmc=mcmc,prior=prior,
+                      Coordinates=cbind(d$xcoord,d$ycoord));
> sfit1=summary(res1); sfit1
Spatial Copula Cox PH model with piecewise constant baseline hazards
Call:
spCopulaCoxph(formula = Surv(time, cens) ~ age + sex + wbc +
     tpi, data = d, mcmc = mcmc, prior = prior, Coordinates = cbind(d$xcoord,
     d$ycoord))

Posterior inference of regression coefficients
(Adaptive M-H acceptance rate: 0.2501):
      Mean        Median      Std. Dev.   95%CI-Low   95%CI-Upp
age   0.0277864   0.0278065   0.0019297   0.0240332   0.0315580
sex   0.0522938   0.0527421   0.0588919  -0.0625843   0.1662136
wbc   0.0027808   0.0027899   0.0003767   0.0020071   0.0034546
tpi   0.0257918   0.0257969   0.0081385   0.0087972   0.0411955
```

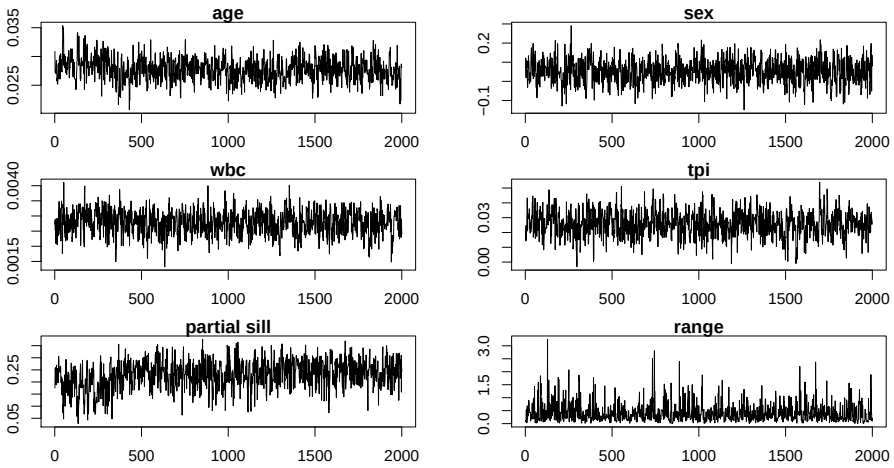


Figure 6: Leukemia survival data. Trace plots for $\boldsymbol{\beta}$, θ_1 and θ_2 under the PH model with spatial copula.

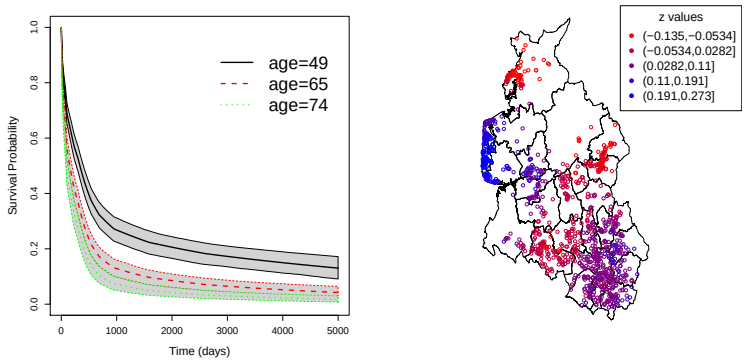
```
Posterior inference of spatial sill and range parameters
(Adaptive M-H acceptance rate: 0.2112):
       Mean     Median   Std. Dev.  95%CI-Low  95%CI-Upp
sill   0.23051  0.23352  0.05587    0.10222    0.32903
range  0.41801  0.34165  0.34272    0.03715    1.31802

Log pseudo marginal likelihood: LPML=-5929.357
Number of subjects: n=1043
> systime1=proc.time()-ptm; systime1;
     user    system   elapsed
15262.274   177.716 15444.913
```

The trace plots (Figure 6) and survival curves (Figure 7, panel a) can be obtained using the code similarly to Section 2.4, where the only difference is that we also present the trace plots for partial sill θ_1 and range θ_2.

```
> traceplot(mcmc(res1$theta[1,]), xlab="", main="partial sill")
> traceplot(mcmc(res1$theta[2,]), xlab="", main="range")
```

Note that the higher the value of $z_i = \Phi^{-1}\{F_{\mathbf{x}_i}(t_i)\}$ is, the longer the survival time t_i (i.e. lower mortality rate) would be. The posterior sample of z_is is saved in `res1$Zpred`. The following code is used to show the posterior mean of z_i values on the map (Figure 7, panel b).

```
> frail= round((rowMeans(res1$Zpred)),3); nclust=5;
> frail.cluster = cut(frail, breaks = nclust);
> frail.names = names(table(frail.cluster))
> rbPal <- colorRampPalette(c('red','blue'))
> frail.colors=rbPal(nclust)[as.numeric(frail.cluster)]
> par(mar=c(3,0,0,0))
```



(a) (b)

Figure 7: Leukemia survival data. PH model with spatial copula. (a) Survival curves with 95% credible interval bands for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages. (b) Map for the posterior mean of z_i values; smaller z values mean higher mortality rate overall.

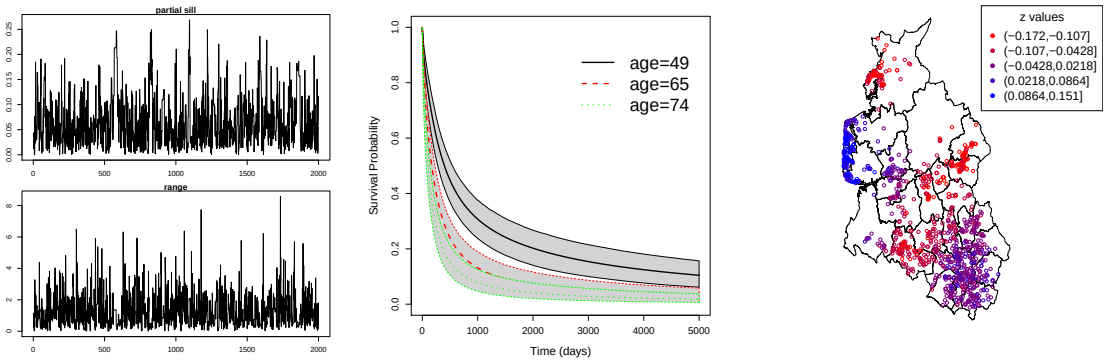
```
> plot(nwengland)
> points(cbind(d$xcoord,d$ycoord), col=frail.colors)
> legend("topright",title="z values",legend=frail.names,
+        col=rbPal(nclust),pch=20, cex=1.7)
```

LDDPM model with spatial copula

The following code is used to fit the LDDPM model (28) with the Gaussian spatial copula (24) using $N = 10$ and default priors. For the FSA, $K = 100$ and $B = 1043$ are used. The total running time is 20056 seconds. Note there is no `summary` output as before, as we are fitting a nonparametric model.

```
> set.seed(1)
> mcmc=list(nburn=5000, nsave=2000, nskip=4, ndisplay=1000);
> prior=list(N=10, nknots=100, nblock=1043);
> ptm<-proc.time()
> res1 = spCopulaDDP(formula=Surv(time,cens)~age+sex+wbc+tpi,data=d,
+                    mcmc=mcmc,prior=prior,
+                    Coordinates=cbind(d$xcoord,d$ycoord));
> systime1=proc.time()-ptm; systime1;
     user    system   elapsed
19876.947   178.595 20056.744
> sum(log(res1$cpo)); ## LPML $
[1] -5931.5
```

The trace plots, survival curves, and map of z_is (Figure 8) can be obtained using the same code used for the PH copula model, where the difference is that we only present the trace plots for partial sill θ_1 and range θ_2.



(a) (b) (c)

Figure 8: Leukemia survival data. LDDPM model with spatial copula. (a) Trace plots for partial sill θ_1 and range θ_2. (b) Survival curves with 95% credit interval bands for female patients with `wbc`=38.59 and `tpi`=0.3398 at different ages. (c) Map for the posterior mean of z_i values; smaller z values mean higher mortality rate overall.

5. Conclusions

There is a wealth of R packages for non-spatial survival data, starting with **survival** (Therneau 2015), included with all base installs of R. The **survival** package fits (discretely) stratified semiparametric PH models to right-censored data with exchangeable gamma frailties, as well as left-truncated data, time-dependent covariates, etc. Parametric log-logistic, Weibull and log-normal AFT models can also be fit by this package. From there, there are many packages for various models and types of censoring; a partial review discussing several available R packages is given by Zhou and Hanson (2015); also see Zhou and Hanson (2017). In comparison there are very few R packages for spatially correlated survival data, with the notable exceptions of **R2BayesX** and **spatsurv**, both of which focus on PH exclusively. The **spBayesSurv** package allows the routine fitting of several popular semiparametric and nonparametric models to spatial survival data.

Although examples were not provided here, **spBayesSurv** can also handle non-spatial survival data using either exchangeable Gaussian or no frailty models. Another unintroduced function is `survregbayes2` which implements the Polya tree based PH, PO, and AFT models of Hanson (2006) and Zhao, Hanson, and Carlin (2009) for areally-referenced data. As pointed out in these papers, MCMC mixing for Polya tree models can be highly problematic when the true baseline survival function is very different from the parametric family that centers the Polya tree; the TBP prior provides much improved MCMC mixing with essentially the same quality of fit as Polya trees.

Future additions to **spBayesSurv** include spatial copula (both georeferenced and areal) versions of the PH, PO, and AFT models using TBP priors, as well as continuously-stratified proportional hazards and proportional odds models. An extension of all semiparametric models to additive linear structure, which is already incorporated into **BayesX**, is also planned.

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