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Bayesian Inference for Cox Proportional Hazard Models with Partial Likelihoods, Semi-Parametric Covariate Effects and Correlated Observations

Ziang Zhang, Alex Stringer Patrick Brown and James Stafford

Abstract. We introduce a novel approximate Bayesian inference methodology for the Cox Proportional Hazards model with partial likelihood that allows the inclusion of semi-parametric covariate effects and correlated survival times. We use quasi-newton optimization to improve computation in the presence of a dense log likelihood Hessian matrix, in contrast with existing methods for Bayesian inference in similar models which require this to be sparse and hence cannot be used with partial likelihood. A simulation study shows that our proposed method provides accurate inference in a variety of settings. We demonstrate the practical utility of our method through the analysis of Leukaemia survival times, with a semi-parametric covariate effect, and Kidney infection times, which are paired. An R package implementing our method will be released publicly.

Keywords: Cox Proportional Hazard Model, Partial Likelihood, Approximate Bayesian inference, Semi-parametric Smoothing.

1 Introduction

For problems involving time-to-event data, the combination of Cox proportional hazard (Cox PH) models and inference via partial likelihood has been the dominant methodology following its development by Cox (Cox, 1972). The Cox PH model assumes that any two subjects' event hazards are proportional as a function of time, with the ratio depending on unknown covariate effects which are inferred from the observed data. Event times may be correlated within the sample, for example when the response is time to kidney failure for the left and right kidneys from the same subject. Inference that is conducted via partial likelihood does not require assumptions to be made about the form of the baseline hazard. Further, the use of Bayesian inference with the Cox PH model is desirable as this yields model-based estimation and uncertainty quantification for all parameters of interest. However, existing methods for approximate Bayesian inference based on Integrated Nested Laplace Approximations (INLA) (Rue et al., 2009) cannot be applied to the Cox PH model with partial likelihood because the Hessian matrix of the log partial-likelihood is fully dense while INLA requires this matrix to be diagonal. Application of the INLA methodology to the Cox PH model without partial likelihood has been considered (Martino et al., 2011), but this requires restrictive smoothness assumptions to be made about the baseline hazard.

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Recently, Stringer et al. (2020) developed an approximate Bayesian inference methodology for case-crossover models, which applies the approximation strategy of INLA to a log-partial likelihood with a non-diagonal Hessian matrix. Their methodology includes semi-parametric covariate effects and yields full posterior uncertainty for the corresponding smoothness parameters, an improvement over existing frequentist methods. Though related, the partial likelihood they consider is simpler than that of the Cox PH model, and the Hessian matrix of their log-partial likelihood is block-diagonal and sparse. In contrast, the Hessian matrix of log-partial likelihood of Cox PH model is fully dense, so the method of Stringer et al. (2020) does not apply to this model.

In this paper we extend the approximate Bayesian inference methodologies of Stringer et al. (2020) and Martino et al. (2011) to the Cox proportional hazard model with partial likelihood. Our methodology accommodates semi-parametric smoothing effects and correlation between observed survival times, which we demonstrate through a simulation study and the analysis of two datasets.

The remainder of this paper is organized as follows. In §2 we describe the semi-parametric Cox PH model and the existing approach to approximate Bayesian inference. In §3, we describe our proposed methodology and how the quasi-Newton method is used to mitigate the computational problems brought by the dense Hessian matrix. In §4 we illustrate our methodology in a simulation study and through the analysis of Leukaemia survival data analysed by Martino et al. (2011) and the Kidney catheter data analysed by McGilchrist and Aisbett (1991). We conclude in §5 with a discussion.

2 Model

2.1 A latent Gaussian Cox PH Model

Suppose we observe n groups indexed by i, each with n_i observations indexed by j. For example, we may observe n subjects with n_i measurements per subject. Denote the random variable representing the j^{th} survival time in the i^{th} group by T_{ij}, and denote its realization by t_{ij}. Let c_{ij} denote the censoring time for observation T_{ij} such that T_{ij} is not directly observable when $c_{ij} < T_{ij}$. The observed survival time is $y_{ij} = \min\{t_{ij}, c_{ij}\}$. Define $d_{ij} = 1$ if $y_{ij} = t_{ij}$ (a survival time) and $d_{ij} = 0$ if $t_{ij} > y_{ij}$ (a censoring time). The observations for each i, j are hence denoted by pairs $y = \{(y_{ij}, d_{ij}) : i = 1, \ldots, n; j = 1, \ldots, n_i\}$. The total number of rows in the data set will be denoted by $N = \sum_{i=1}^{n} n_i$.

Define $h_{ij}(t)$ to be the hazard function for the random variable T_{ij}. The Cox PH model assumes $h_{ij}(t) = h_0(t)\exp(\eta_{ij})$ where $h_0(t)$ is an unknown baseline hazard function that does not depend on the covariates. An additive predictor η_{ij} links the covariates

for the ijth observation to the survival time T_{ij}:

$$\begin{aligned} \eta_{ij} &= x_{ij}^T\beta + \sum_{q=1}^{r}\gamma_q(u_{qij}) + \xi_i \\ \xi_i|\sigma_\xi &\overset{iid}{\sim} \mathcal{N}(0,\sigma_\xi) \\ \gamma_q(\cdot)|\sigma_q &\overset{ind}{\sim} \mathcal{GP}\left(0,\mathcal{C}_{\sigma_q}\right), q = 1,\ldots,r \end{aligned} \tag{1}$$

Let $\eta = \{\eta_{ij} : i = 1,\ldots,n; j = 1,\ldots,n_i\}$ be the vector of all the additive linear predictors. Here x_{ij} is a p-dimensional vector of covariates that are modelled as having linear associations with the log-hazard, and $\beta = (\beta_1,\ldots,\beta_p)$ are regression coefficients. The $u_q = \{u_{qij} : i = 1,\ldots,n; j = 1,\ldots,n_i\}, q = 1,\ldots,r$ are covariate vectors whose association with the log-hazard is modelled semi-parametrically through unknown smooth functions $\gamma_1,\ldots,\gamma_r$. The vector of group intercepts $\xi = \{\xi_i : i = 1,\ldots,n\}$, referred to as "frailty" coefficients in the context of survival analysis (Vaupel et al., 1979), are included to model correlation between survival times coming from the same group i. There is no global intercept β_0 as this would be absorbed by $h_0(t)$.

2.2 Modelling Semi-parametric covariate effect

The semi-parametric covariate effect γ_q are modelled as independent zero-mean Gaussian processes defined by their covariance functions C_{σ_q} which in turn parametrized by $\sigma_q > 0$. A typical choice of covariance function is the Random Walk of order 2 (RW2, Lindgren and Rue (2008)), which has a connection to cubic smoothing splines.

Let $U_q = \{U_{ql}; l = 1,....,m_q\}$ be the ordered vector of distinct values of covariate $u_q, q = 1,\ldots,r$; often these values are set by the user by discretizing the covariate u_q into m_q pre-specifed bins. To infer the infinite-dimensional parameters $\gamma_q, q = 1,\ldots,r$, we approximate each γ_q by a piecewise constant function with jumps at the U_{ql}, which we denote as $\gamma_q(U_{ql}) = \Gamma_{ql}$. We define the vectors of function values $\Gamma_q = \left\{\Gamma_{q1},\ldots,\Gamma_{qm_q}\right\}$ having distributions $\Gamma_q|\sigma_q \sim \mathcal{N}\left[0,\Sigma_q(\sigma_q)\right]$ for each $q = 1,\ldots,m_q$. These distributions are parametrized through their precision matrices $\Sigma_q^{-1}(\sigma_q)$ corresponding to the specific Gaussian processes chosen, which depend on parameters σ_q. We define $\Gamma = (\Gamma_1,\ldots,\Gamma_r)$ and write $\Gamma|\sigma_1,\ldots,\sigma_q \sim \mathcal{N}\left(0,\Sigma_\Gamma^{-1}\right)$ with $\Sigma_\Gamma^{-1} = \text{diag}\left[\Sigma_1^{-1}(\sigma_1),\ldots,\Sigma_r^{-1}(\sigma_r)\right]$. These precision matrices are available in closed form and no large matrices need to be inverted to compute them in the present application (Lindgren and Rue, 2008).

These models usually contain an intercept β_0 and a *sum-to-zero* constraint $\sum_{l=1}^{m_q}\Gamma_{ql} = 0$, for identifiability of parameters. However, β_0 is not identifiable when using the partial likelihood for inference, and hence the sum-to-zero constraint is difficult to interpret in this setting. We fit the following modified RW2 model for each $q = 1,\ldots,r$:

$$\begin{aligned} \Gamma_{q,l+1} - 2\Gamma_{q,l} + \Gamma_{q,l-1} &\overset{iid}{\sim} \text{N}\left(0,\sigma_q^2\right), \\ \Gamma_{q,a} &= 0, \end{aligned} \tag{2}$$

where $a \in \{1,\ldots,m_q\}$ is some chosen reference value. This parametrization is identifiable under the partial likelihood and gives a clear interpretation of $\Gamma_{q,l}$ as the change

in log-risk for an individual with covariate value $u_{q,l}$ compared to an individual with covariate value $u_{q,a}$.

Finally, define the variance parameter vector $\theta = (\theta_0, \ldots, \theta_r)$ where $\theta_q = -2\log\sigma_q, q = 1, \ldots, r$, and $\theta_0 = -2\log\sigma_\xi$. The variance parameters are given prior distribution $\theta \sim \pi(\theta)$.

2.3 Approximate Bayesian Inference

Inference is carried out via a partial likelihood function. Define the *risk set* $R_{ij} = \{k, l : y_{kl} \geq y_{ij}\}$. Assuming $y_{ij} \neq y_{kl}$ when $(i, j) \neq (k, l)$, the partial likelihood can be written as follows:

$$\begin{aligned}\pi(y|\eta) &= \prod_{i=1}^{n}\prod_{j=1}^{n_i}\left\{\frac{\exp[\eta_{ij}]}{\sum_{l,k\in R_{ij}}\exp[\eta_{lk}]}\right\}^{d_{ij}} \\ &= \prod_{i=1}^{n}\prod_{j=1}^{n_i}\left\{\frac{1}{1+\sum_{l,k\in R_{ij},(l,k)\neq(i,j)}\exp[\Delta_{lk,ij}]}\right\}^{d_{ij}}\end{aligned} \tag{3}$$

where $\Delta_{lk,ij} = \eta_{lk} - \eta_{ij}$. In practice there may be tired survival times present in the data, and these are handled according to the method of Breslow (1974). Note that $h_0(t)$ does not appear in the partial likelihood, and hence inference may be carried out in the absence of assumptions about $h_0(t)$.

The partial likelihood (3) can be written in the following form:

$$\pi(y|\eta) = \prod_{i=1}^{n}\prod_{j=1}^{n_i}\pi(y_{ij}|\eta), \tag{4}$$

while in order for a model to be compatible with INLA, its likelihood must have the form:

$$\pi(y|\eta) = \prod_{i=1}^{n}\prod_{j=1}^{n_i}\pi(y_{ji}|\eta_{ij}), \tag{5}$$

Martino et al. (2011) are able to write the likelihood for their Cox PH model in the form (5) using the full, not partial likelihood (3). Because of this, they require assumptions to be made about the baseline hazard.

Further define $\Delta_{lk,ij} = \eta_{lk} - \eta_{ij}$ in terms of the additive predictors (1). Note that $\Delta_{lk,ij} = \Delta_{11,ij} - \Delta_{11,lk}$ for every (i, j, l, k). To simplify notation, define $\Delta_{ij} = \Delta_{11,ij}$, and note that $\Delta_{11} = 0$. The entire partial likelihood (3) depends on η only through $\Delta = \{\Delta_{ij} : i = 1, \ldots, n; j = 1, \ldots, n_i\}$. For the remainder of the paper we reflect this in our notation, writing $\pi(y|\Delta) \equiv \pi(y|\eta)$ and defining the log-likelihood $\ell(\Delta; y) = \log\pi(y|\Delta)$.

Define $W = (\Delta, \Gamma, \beta, \xi)$ which we refer to as the *latent parameters* and let $\dim(W) = m$. The RW2 prior for γ is improper, and the precision matrix Σ_Γ is singular. Approximate Bayesian inference of the type we consider requires the precision matrix of W to be nonsingular (Rue et al., 2009; Martino et al., 2011; Stringer et al., 2020). We

follow Rue et al. (2009) and Stringer et al. (2020) and introduce a small noise term $\epsilon_{ij} \overset{iid}{\sim} \mathrm{N}(0, \tau^{-1})$ (for some large, fixed τ) into the model to make the required matrices nonsingular. However, in contrast to Stringer et al. (2020), we redefine:

$$\Delta_{ij} = \eta_{11} - \eta_{ij} + \epsilon_{ij}, \tag{6}$$

adding the noise onto the *differenced* additive predictor. It will be shown in §3 that this improves computation by improving the sparsity of large matrices involved in the required calculations. The addition of these ϵ_{ij} gives the joint distribution of $(\Delta, \Gamma, \beta, \xi)$ a non-singular precision matrix, and enables the use of improper prior in the model specification. We set $\tau = \exp(7)$ which is well within the broad range of $\exp(2), \ldots, \exp(14)$ which Stringer et al. (2020) found to yield very similar inferences and running times.

Our model specifies $W|\theta \sim \mathrm{N}\left[0, Q_\theta^{-1}\right]$. An expression for Q_θ is given in §3 and a derivation is given in Appendix A. Our main inferential interest is to obtain the marginal posterior distributions of the latent parameters:

$$\pi(W_s|y) = \int \pi(W_s|y,\theta)\pi(\theta|y)d\theta, s = 1, \ldots, m \tag{7}$$

These are used for point estimates and uncertainty quantification of the latent parameters, which often include the effects of primary interest. We are also interested in the joint posterior distributions of the variance parameters:

$$\pi(\theta|y) = \frac{\int \pi(W, y, \theta)dW}{\int\int \pi(W, y, \theta)dW\, d\theta} \tag{8}$$

These are used for point estimates and uncertainty quantification of the variance parameter θ, and appear as integration weights in (7). Of secondary inference is the joint posterior distribution of the latent parameters:

$$\pi(W|y) = \int \pi(W|y,\theta)\pi(\theta|y)d\theta \tag{9}$$

This appears primarily as an intermediate step in the calculation of the marginal posteriors (7).

All of the quantities of interest (7) – (9) depend on intractable high-dimensional integrals. Stringer et al. (2020) utilize Gaussian and Laplace approximations combined with numerical quadrature to approximate each of these integrals accurately and efficiently. Their approximations take the form:

$$\begin{aligned} \tilde{\pi}(W_s|y) &= \sum_{k=1}^{K} \tilde{\pi}_G(W_s|y,\theta^k)\tilde{\pi}_{LA}(\theta^k|y)\delta_k, s = 1, \ldots, m \\ \tilde{\pi}(W|y) &= \sum_{k=1}^{K} \tilde{\pi}_G(W|y,\theta^k)\tilde{\pi}_{LA}(\theta^k|y)\delta_k \end{aligned} \tag{10}$$

where $\left\{\theta^k, \delta_k\right\}_{k=1}^K$ is a set of nodes and weights corresponding to an appropriate numerical quadrature rule. The $\tilde{\pi}_G(W_s|y,\theta^k)$ is a Gaussian approximation for $\pi(W_s|y,\theta^k)$ and the $\tilde{\pi}_{LA}(\theta^k|y)$ is a Laplace approximation for $\pi(\theta^k|y)$, which we describe at below.

The approximations (10) are computed as follows. For any fixed θ, define

$$\begin{aligned}\widehat{W}_\theta = \left(\widehat{\Delta}_\theta, \widehat{\Gamma}_\theta, \widehat{\beta}, \widehat{\xi}_\theta\right) &= \text{argmax}_W \log \pi(W|\theta, y) \\ H_\theta(W) &= -\frac{\partial^2}{\partial W \partial W^T} \log \pi(W|\theta, y) \\ v^2_{\theta,s} &= \left[H_\theta\left(\widehat{W}_\theta\right)^{-1}\right]_{ss}, s = 1, \ldots, m\end{aligned} \tag{11}$$

For the conditional posterior

$$\pi(W|\theta, y) \propto \exp\left\{-\frac{1}{2}W^T Q_\theta W + \ell\left(\Delta; Y\right)\right\}, \tag{12}$$

a second-order Taylor expansion of $\log \pi(W|\theta, y)$ about $W = \widehat{W}_\theta$ yields a Gaussian approximation:

$$\pi(W|\theta, y) \approx \tilde{\pi}_G(W|y, \theta) \propto \exp\left\{-\frac{1}{2}\left(W - \widehat{W}_\theta\right)^T H_\theta\left(\widehat{W}_\theta\right)\left(W - \widehat{W}_\theta\right)\right\} \tag{13}$$

Direct integration of this Gaussian approximation yields a Gaussian approximation for the corresponding marginal density:

$$\tilde{\pi}_G(W_s|y,\theta) = \int \tilde{\pi}_G(W|y,\theta) dW_{-s} \propto \exp\left\{-\frac{1}{2v^2_{\theta,s}}\left(W_s - \widehat{W}_{\theta s}\right)^2\right\}, s = 1, \ldots, m \tag{14}$$

For the joint posterior of the variance parameters, the method of Tierney and Kadane (1986) yields a Laplace approximation:

$$\pi(\theta|y) \approx \tilde{\pi}_{LA}(\theta|y) \propto \pi(\theta)\left\{\frac{|Q_\theta|}{\left|H_\theta\left(\widehat{W}_\theta\right)\right|}\right\}^{1/2} \exp\left\{-\frac{1}{2}\widehat{W}_\theta^T Q_\theta \widehat{W}_\theta + \ell\left(\widehat{\Delta}_\theta; y\right)\right\} \tag{15}$$

With these approximations available, inference for W makes use of the approximation (10).

3 Methods

3.1 Quantities required for fitting

For fixed design matrices A, B and X, it is convenient to write η and Δ as:

$$\begin{aligned}\eta &= A\Gamma + B\xi + X\beta \\ \Delta &= D\eta + \epsilon\end{aligned} \tag{16}$$

where $\epsilon \sim \mathrm{N}\left(0, \tau^{-1} I_N\right)$ and D is an $(N-1) \times N$-dimensional matrix of rank $N-1$. The partial likelihood (3) depends on η only through Δ, which explains why a global intercept β_0 is not estimable when using partial likelihood.

The precision matrix is given by

$$Q_\theta = \tau \begin{pmatrix} I & -DA & -DB & -DX \\ -A^T D^T & \frac{1}{\tau}\Sigma_\Gamma^{-1} + A^T D^T DA & A^T D^T DB & A^T D^T DX \\ -B^T D^T & B^T D^T DA & \frac{1}{\tau}\Sigma_\xi^{-1} + B^T D^T DB & B^T D^T DX \\ -X^T D^T & X^T D^T DA & X^T D^T DB & \frac{1}{\tau}\Sigma_\beta^{-1} + X^T D^T DX \end{pmatrix} \tag{17}$$

Expressions for D and the derivation of this precision matrix are given in Appendix A. Contrasting (17) with the precision matrix given by Stringer et al. (2020), we observe that ours is more sparse, owing to the addition of the noise term to Δ where they instead add it to η.

The Hessian matrix $H_\theta(W)$ has the form $H_\theta(W) = Q_\theta + C(W)$ where

$$C(W) = -\frac{\partial^2}{\partial W \partial W^T}\ell(\Delta) = -\begin{pmatrix} \frac{\partial^2 \ell(\Delta;y)}{\partial \Delta \partial \Delta^T} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

where the upper left block $\frac{\partial^2 \ell(\Delta;y)}{\partial \Delta \partial \Delta^T}$ is a dense matrix.

Because the partial likelihood in the Cox PH model takes the form (4), $C(W)$ has a dense structure. In contrast, Rue et al. (2009) assume that the likelihood takes the form (5) which enforces the constraint that $C(W)$ is diagonal and hence their method cannot fit the Cox PH model with partial likelihood. Stringer et al. (2020) relax this assumption to allow $C(W)$ to have a block-diagonal structure, introducing increased computational burden when fitting the approximations. This burden becomes too limiting when $C(W)$ is dense, and an alternate method of fitting the approximations is required.

3.2 Optimization method

The objective function (11) is convex and high-dimensional, and hence *trust region methods* (Braun, 2014) are well-suited to this problem. However, evaluating the Hessian at each iteration is computationally expensive. To compute the conditional mode $\hat{W}(\theta)$, we use Symmetric Rank-1 (SR1) quasi-Newton updates within trust region optimization. The SR1 updates replace this matrix with a low-rank approximation at each iteration and hence do not require evaluation or storage of it during optimization. While this can increase the number of iterations, the computation loads brought by the dense Hessian matrix are greatly reduced and we are able to perform the optimization (11) when $H_\theta(W)$ is dense.

The quantities $\widehat{W}_\theta$ and $H_\theta(\widehat{W}_\theta)$ are used to compute the approximations (10) and the associated marginal moments and quantiles, and hence the dense $H_\theta(\widehat{W}_\theta)$ does need to be stored in memory. However, the use of SR1 means this storage only occurs *after*

each optimization. The total number of Hessian matrices that needs to be evaluated and stored equals to the number of quadrature points being used for the approximations (10).

4 Examples

In this section we present a simulation study and two data analysis examples. Code is available in the online supplementary materials.

4.1 Simulation study

To illustrate the accuracy of our proposed approach, we simulate six different datasets, under three baseline hazard functions, and two true covariate effect functions. The three baseline hazard functions are respectively a hazard function constant at 0.03, an regular hazard function that is periodic and continuous, and a complicated hazard function that has three different types of oscillating behaviours and two discontinuities. The two true covariate effect functions are a simple function $\gamma(u) = \log((u+1)^2) - 1$ for $u \in (0, 6)$, and a complicated function $\gamma(u) = 1.5\sin(0.8u)$ for $u \in (-5, 5)$.

In all the six simulation settings, we generated $N = 500$ data points from the corresponding model $h(t) = h_0(t)\exp(\gamma(u))$, and randomly censored 10% of the data points for each setting. The covariate u is generated uniformly from its corresponding domain, and discretized into 50 disjoint, evenly-spaced bins. For the single variance parameter θ that controls the smoothness of the inferred γ, we use an Exponential(λ) prior with λ chosen such that $\mathbb{P}(\theta > 2.5) = 0.5$ for the setting when true γ is complicated, and $\mathbb{P}(\theta > 1) = 0.5$ for the setting when true γ is smooth. This is a penalized complexity prior of Simpson et al. (2017).

We fit a RW2 model using our proposed approach to infer the true smoothing function γ, with inferred γ constrained to be zero at the median of the observed covariate values of each dataset. The resulting plots are shown in Figure 1, where the covariate effect functions are exponentiated to represent the relative risk function, and the variance parameter θ is transformed back to standard deviation σ.

According to Figure 1, it can be seen that our proposed method gives relative accurate point estimation for the true risk functions regardless of the true baseline hazard function, even with a sample size that is comparatively small. In all of these six simulation examples, our 95 percent credible interval contains the true risk function throughout the domain, with an reasonable interval width at most of the regions in the domain.

4.2 Leukaemia Data

We implemented our proposed procedure to fit a semi-parametric Cox PH model to the Leukaemia data set analysed by Martino et al. (2011). The dataset contains information from 1043 independent adult leukaemia patients, with 16% of observations right-censored. We are interested in quantifying the relationship between survival rate of leukaemia patients with the age of the patient, the count of white blood cells at

diagnosis (wbc), the Townsend deprivation index (tpi) corresponding to the patient's location, and sex of the patient.

The effects of age, sex and white blood cell count were modelled linearly. Martino et al. (2011) also included a spatial effect in the model, which we ignore for computational reason. The deprivation index was discretized into 50 equally spaced bins and modelled as a semi-parametric effect. Prior distributions $\beta \overset{iid}{\sim} \mathcal{N}(0, 0.001^{-1})$, were used for the regression coefficients. The semi-parametric effects $\Gamma = \{\Gamma_1, \cdots, \Gamma_{50}\}$ were modelled using the RW2 model of §2.2 with the reference constraint $\gamma(0) = 0$. The single variance parameter σ_1 was given an Exponential prior with a prior median of 2.

Figure 3 shows the posterior result of the exponentiated covariate effect of tpi and the corresponding standard deviation σ. Our inferred covariate effect of tpi is similar to the result reported by Martino et al. (2011), where the risk of death initially grows with the value of tpi with diminishing rate and eventually begins to decrease after tpi reaches around 5. However, the approach utilized by Martino et al. (2011) relies on the use of full likelihood function with baseline hazard function modelled semi-parametrically. Our approach implements the approximate Bayesian inference using the partial likelihood, hence has no assumption on the form of the baseline hazard function.

4.3 Kidney Catheter Data

Therneau et al. (2003) analysed a Kidney Catheter dataset using their proposed penalized partial likelihood method. The Kidney Catheter dataset contains 76 times to infection at the point of insertion of a catheter, for $n = 38$ patients. Each patient $i = 1, \ldots, n$ forms a group, and the survival times are the time to infection of each patient's $n_i = 2$ kidneys. An observation for the survival time of a kidney is censored if the catheter is removed for reasons other than an infection.

The method of Therneau et al. (2003) allows the inclusion of subject-level random effect (frailty) in the model to account for the within subject correlations. They suggested two different ways to get the estimated covariance matrix of their estimators using either the "pseudo standard error" $\mathscr{H}^{-1}$ or $\mathscr{H}^{-1}\mathscr{I}\mathscr{H}^{-1}$ which is recommended by Gray (1992), where $\mathscr{H}$ denotes the Hessian matrix of the penalized partial likelihood and $\mathscr{I}$ denotes the Hessian matrix of the regular partial likelihood without penalization. They mentioned in the paper that the first method tends to be more conservative standard errors, but they do not have definitive result to support the use of any specific one when these two methods give different estimates of the covariance matrix (Therneau et al., 2003). Moreover the penalized partial likelihood method that they proposed is a frequentist method, where the variance of random effects is treated as a fixed value estimated through either MLE or REML. As they have mentioned in the paper, ignoring the uncertainty with estimating the variance parameter in this way can severely underestimate the standard errors (Therneau et al., 2003).

As a comparison, we also use our procedure to fit a Cox PH model to these grouped data, providing full posterior uncertainty over the between-subject standard deviation. We associate survival times with covariates sex, age, and indicator of one of four types

of pre-existing disease each patient may have. Subject-specific intercepts $\xi_i \overset{iid}{\sim} \mathrm{N}(0, \sigma_\xi^2)$ are included to account for correlation between kidneys from the same subject. We use an Exponential prior distribution for σ_ξ with median 2.

Table 1 shows the results of our procedure compared to that obtained using the penalized partial likelihood method of Therneau et al. (2003). In the table, SD1 is the version of standard error obtained using pseudo standard approach, and SD2 is the version of standard error obtain using the second approach recommended by (Gray, 1992). Our posterior means for the linear covariate effects are comparable to the frequentist estimates, whereas our posterior standard deviations of linear effects seem to be in the middle of the two versions of estimated standard errors from the penalized likelihood method. We also compared the 95 percent interval estimates for frailties of the first five subjects in figure 4, and it can be seen again that our intervals are shorter than the intervals obtained from penalized partial likelihood method using the "pseudo standard error", but longer than the intervals obtained when using the standard error obtained from the second method. Therefore, it shows that our approach addresses the ambiguity of which version of estimated standard errors to be used for the penalized likelihood method. Furthermore, as shown in Figure 5, our method provides full posterior uncertainty for σ_ξ while the penalized partial likelihood approach does not. The red vertical line in the plot represents the estimated variance parameter in the penalized partial likelihood approach.

5 Discussion

The methodology we proposed in this paper provides a flexible way to carry out Bayesian inference for Cox proportional hazard models with partial likelihood, that accommodates the inference for semi-parametric covariate effects and correlated survival times. The use of partial likelihood does not require any assumption on the baseline hazard function, which is an advantage over existing approaches for Bayesian inference in this model. We have demonstrated the accuracy of our new approach through some simulation studies, even when the sample size is small, and we have implemented our proposed method to analyse two classical datasets in survival analysis. Our proposed method is an appealing option to adopt for the analysis of time-to-event data.

One limitation of our proposed methodology is the manner in which it scales with the sample size N. Since the Hessian matrix in our methodology is fully dense, its number of non-zero entries increases as $O(N^2)$. The scalability of our procedure is limited by the need to store this matrix in memory. We avoid the computation of this Hessian matrix during the optimization step by using a quasi-Newton method, however the true Hessian matrix is still required to be evaluated and stored at the maximum to compute the posterior approximations that we use. The computational requirements will increase with the dimension of θ as well, a limitation that our method shares with Rue et al. (2009) and Stringer et al. (2020).

The framework of this proposed methodology can be extended to fit more complex models, by modifying the covariance structure of the covariate with semi-parametric effect. Temporally- and spatially-correlated survival data may be analysed through a simi-

lar procedure. Because we accommodate the dense Hessian matrix of the log-likelihood, our approach could be extended to approximate Bayesian inference for other models with a dense Hessian matrix. We leave such extensions to future work.

Data Availability Statement

The simulated data of example 3.1 are available in the code available with this paper at the Statistics in Medicine website on Wiley Online Library. Data for example 3.2 were obtained from R package "INLA" (Rue et al., 2009) and are freely available. Data for example 3.3 were obtained from R package "survival" (Therneau, 2015) and are freely available.

Appendix A: Derivation of Precision Matrix

In this section we give a brief derivation of the precision matrix Q_θ from Equation (17). The derivation is similar to that of Stringer et al. (2020) (Web Appendix C), with a different differencing matrix. The differencing matrix D is:

$$D = \begin{pmatrix} 1 & -1 & 0 & & 0 \\ 1 & 0 & -1 & & 0 \\ & & & \ddots & \\ 1 & & & 0 & -1 \end{pmatrix} \tag{18}$$

As described in §3 ,our model specifies:

$$\Gamma|\theta \sim \text{Normal}\left(0, \Sigma_\Gamma\right);\ \xi|\theta \sim \text{Normal}\left(0, \Sigma_\xi\right);\ \beta \sim \text{Normal}\left(0, \Sigma_\beta\right);\ \epsilon \sim \text{Normal}\left(0, \tau^{-1}I\right)$$

all independent of each other unless otherwise specified. The vector of additive linear predictors can be written as $\eta = A\Gamma + B\xi + X\beta + \epsilon$ and $\Delta = D\eta$ where D is defined through Equation (18). This gives a joint Gaussian distribution for $W|\theta$ as:

$$W|\theta = \begin{pmatrix} \Delta \\ \Gamma \\ \xi \\ \beta \end{pmatrix} = \begin{pmatrix} DA & DB & DX & I \\ I & 0 & 0 & 0 \\ 0 & I & 0 & 0 \\ 0 & 0 & I & 0 \end{pmatrix} \begin{pmatrix} \Gamma \\ \xi \\ \beta \\ \epsilon \end{pmatrix} \sim \text{Normal}\left(0, \Sigma\right)$$

where

$$\Sigma = \begin{pmatrix} DA\Sigma_\Gamma A^T D^T + DB\Sigma_\xi B^T D^T + DX\Sigma_\beta X^T D^T + \tau^{-1}I & DA\Sigma_\Gamma & DB\Sigma_\xi & DX\Sigma_\beta \\ \Sigma_\Gamma D^T A^T & \Sigma_\Gamma & 0 & 0 \\ \Sigma_\xi D^T B^T & 0 & \Sigma_\xi & 0 \\ \Sigma_\beta D^T X^T & 0 & 0 & \Sigma_\beta \end{pmatrix}$$

The precision matrix $Q(\theta) = \Sigma^{-1}$ is obtained through direct inversion.

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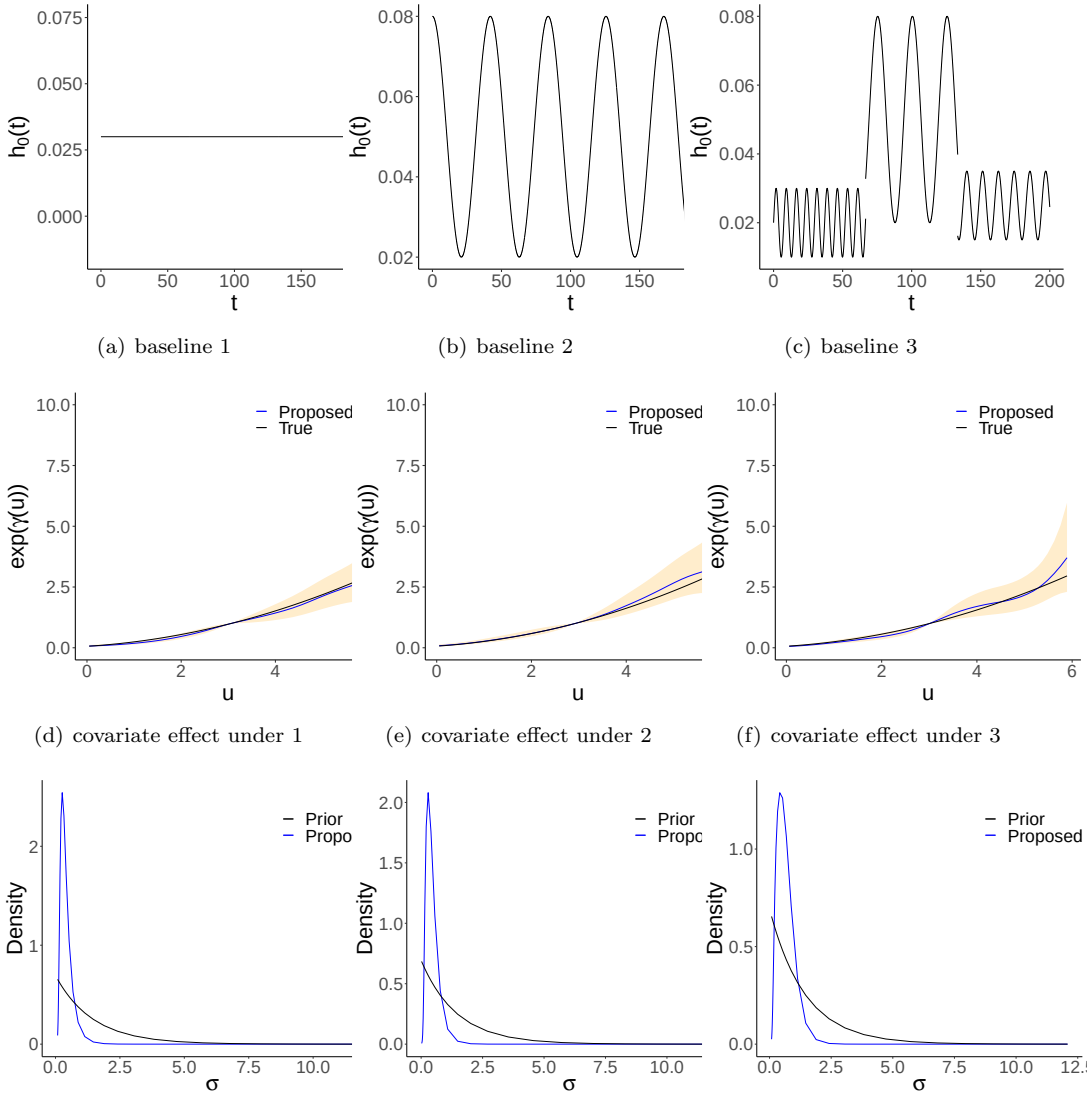
		Proposed		Freq PL		
Variables/Reference	Levels	Mean	SD	Mean	SD1	SD2
Age		0.0048	0.015	0.0052	0.015	0.011
Sex/Male	Female	-1.6	0.46	-1.7	0.46	0.36
Disease Type/Other	GN	0.17	0.53	0.18	0.54	0.40
	AN	0.39	0.53	0.39	0.54	0.41
	PKD	-1.2	0.80	-1.1	0.81	0.63

Table 1: Estimated means and standard deviations of linear effects by proposed method, frequentist penalized partial likelihood method (Freq PL) for the kidney data in section 4.3.

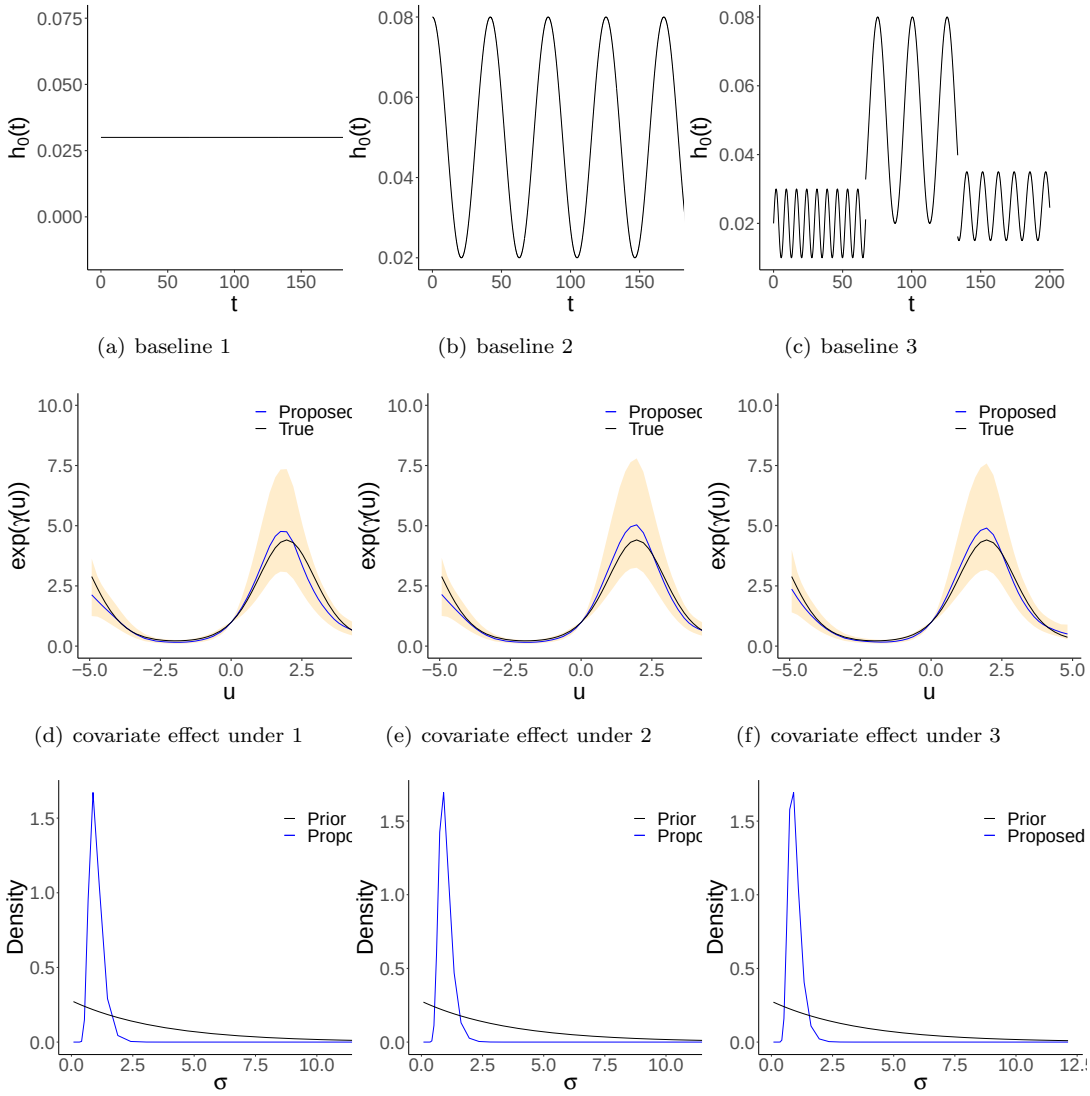


(a) baseline 1 (b) baseline 2 (c) baseline 3

(d) covariate effect under 1 (e) covariate effect under 2 (f) covariate effect under 3

(g) variance parameter under 1 (h) variance parameter under 2 (i) variance parameter under 3

Figure 1: Inferred covariate effects and variance parameters under different baseline hazard functions

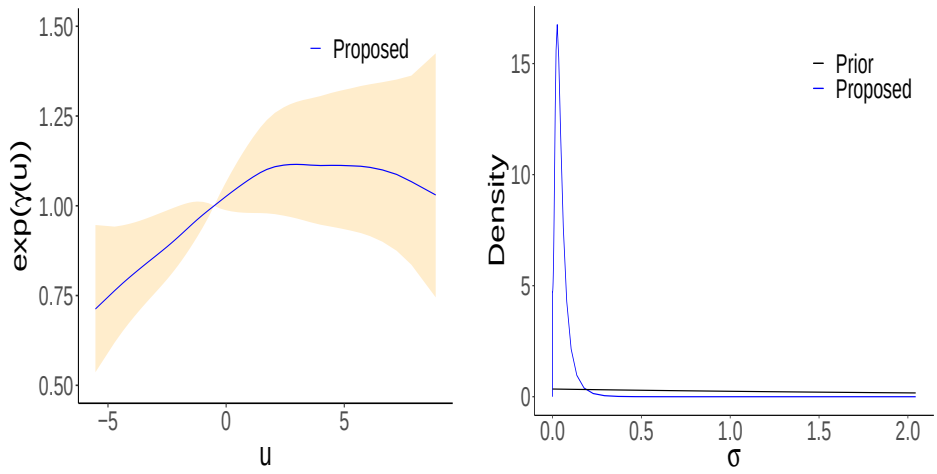


(a) baseline 1 (b) baseline 2 (c) baseline 3

(d) covariate effect under 1 (e) covariate effect under 2 (f) covariate effect under 3

(g) variance parameter under 1 (h) variance parameter under 2 (i) variance parameter under 3

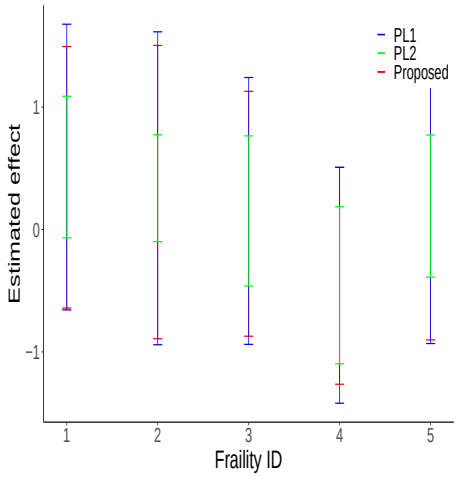
Figure 2: Inferred covariate effects and variance parameters under different baseline hazard functions



(a) Posterior effect of `tpi`

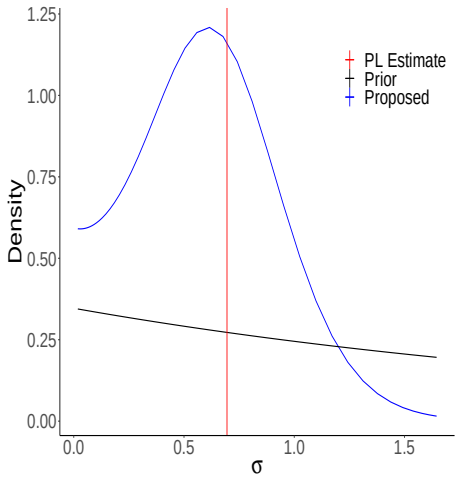
(b) Posterior distribution of σ

Figure 3: Results for the Leukaemia data in section 4.2. (a): posterior mean (blue) and 95% credible interval (shaded) using our method (b): prior (black) and approximate posterior distribution for σ using our method (blue).



(a) Interval estimates for the first five frailties

Figure 4: 95 percent interval estimates for the first five frailties, for the kidney data in section 4.3.



(a) Posterior distribution of σ

Figure 5: Posterior distribution for the between-subject standard deviation by our method (blue) and its prior (black), for the kidney data in section 4.3.