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Survival Data Analysis using Additive and Multiplicative Gamma Polygonal Hazards Function

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Abstract Proportional hazards model (PHM) is commonly used in survival analysis for estimating the effects of different covariates influencing the survival data. The hazard function in proportional hazards model (PHM) is commonly defined as a product of the baseline hazard function and a non-negative function of covariates. However, the hazard function may also be presented as the sum of the baseline hazard function and a non-negative function of covariates. We propose the new additive and multiplicative Gamma Polygonal in the hazards function using OpenBugs Statistical Packages. Both models are an alternative to the existing additive and multiplicative models but the new additive Gamma polygonal intensity model is quite complex compared to the new multiplicative Gamma polygonal intensity model. The application for right-censored data from Bayesian perspective will be discussed and the Markov Chain Monte Carlo (MCMC) method will be used to compute the Bayesian estimator using Leukemia data and DSR data. The results obtained show that the propose model is as good as the existing models in analyzing paired survival data.

Keywords Additive model, Multiplicative model, Baseline hazards function, MCMC

2010 Mathematics Subject Classification 46N60, 92B99

1 Introduction

Statistical analysis in survival times, also known as survival analysis has been widely used recently in biomedical sciences and also in other areas of knowledge such as economics and social sciences. These statistical techniques is used in predicting the survival times and investigating the effects of risk factors. Survival distributions is typically characterized by their hazard functions which is the conditional density function at time t given survival up to time t. Many modeling techniques focus on the evaluation of a covariate effect.

General classes of semi-parametric hazards regression model for survival data are flexible and might yield more accurate prediction of an individual's survival process by including Cox proportional hazards model, the accelerated failure time model and the accelerated hazards model [1].

Simple procedures and techniques which was developed with high efficiencies for making inference about the regression parameters under the additive risk model with an unspecified baseline hazard function resembled the method of partially likelihood-based for the proportional hazards model [2]. A new method was proposed to estimate the differential or relative probability of failure from one cause under two sets of covariate values over time using the semiparametric additive model for the prediction and comparison of cause-specific cumulative incidence functions for given values of the covariate [3].

Semiparametric Bayesian analyses of proportional hazards model has become computationally feasible recently due to modern technology and advancement in computing techniques such as the Gibbs sampler and other MCMC methods. Gibbs Sampling is one of the new numerical algorithms and the best known Markov Chain Monte Carlo (MCMC) sampling which allow the obtaining of samples from posterior of interest. Arjas and Gasbarra proposed a common unknown hazard rate in which the hazard rate is modelled non-parametrically by considering a simple right censored data and the sample paths of the hazard rate were generated from the posterior distribution using Gibbs Sampler [4].

An overview of Bayesian semiparametric methods for the multiplicative risk model has been provided by Sinha and Dey [5]. One of the advantages is that both the baseline hazard and the regression coefficients are joined together and can be used accurately to compute the target posterior quantities using MCMC simulation techniques. A class of semiparametric informative prior distributions for the Cox model specified a non-parametric prior for the baseline hazard rate and a parametric prior for the regression coefficients via the development of Markov chain Monte Carlo (MCMC) techniques for sampling from the posterior distribution of the parameters [6]. The potential of Bayes methods for the analysis of survival data have been investigated using semiparametric models based on either the hazard or the intensity function. The nonparametric part of every model is assumed to be a realization of a stochastic process. The parametric part, which may include a regression parameter is assumed to have a prior distribution with possibly unknown hyperparameters.

An additive hazard model for the regression analysis of censored data is an alternative to Cox's proportional hazards model since it allows both the parameter and the covariate vectors to vary with time. The additive and multiplicative risk models in survival analysis provide frameworks that associate between risk factors, disease occurrence or death and the survival time. The survival time, *T* is subject to right censoring since at the end of the study, certain individuals might be survived. Even though the statistical analysis of additive risk models is harder than that of proportional hazards model, it describes the association between survival time and covariates in different aspect. The risks are assumed to be independent so that the additive model will appear to be in a natural way in competing the risk situations.

The hazard function for the survival time *T* under the additive risk model takes the form

$$h(t|\mathbf{x}) = h_0(t) + \omega_0'\mathbf{x}(t) \tag{1}$$

while the hazard function for the survival time *T* under the multiplicative risk model takes the form

$$h(t|\mathbf{x}) = h_0(t)\exp\left(\beta_0'\mathbf{x}(t)\right) \tag{2}$$

where ω_0 and β_0 are *p*-vectors of regression parameters.

Survival analysis has found widespread applications in medicine. It is well known that any clinical trial is an experiment carried out to gain knowledge about the relative benefits of two or more treatments. In this paper, we consider leukemia data in additive Gamma Polygonal where the effect of 6-MP (6-Mercaptopurine) therapy for the duration of remissions induced by adrenal corticosteroids [7]. Patients in remission were assigned randomly to maintenance therapy with either 6-MP or placebo. A sequential experimental design was used in analysing remission times while the study was in progress. This resulted in the study being stopped after analysis of the remission times of 21 pairs of leukemia patients (42 patients).

In the multiplicative Gamma Polygonal model, both data Leukemia and Diabetic Retinopathy Study (DRS) [8] was used. The Diabetic Retinopathy Study was conducted by the National Eye Institute to test the laser treatment (laser photocoagulation) in delaying blindness among patients and examine how age at onset of diabetes can affect the eyes to become blind. One eye of each patient was selected at random to receive photocoagulation technique based on two different types of laser treatment (xenon and argon), and the other eye was observed with no treatment, which served as untreated controls. The event of interest for each eye was the time from initiation of treatment to the time when visual acuity dropped below 5/200 in two consecutive visits, called 'blindness'. Censoring was caused by the death, drop out or end of the study. The only data available are from the 197 patients defined as high-risk by DRS criteria. A subset of the data set of 197 high-risk diabetes patients was used to assess the effectiveness of the laser treatment in delaying severe vision loss, which is actually provided on Professor Therneau's web page (see; http://mayoresearch.mayo.edu/mayo/research/biostat/therneau-book.cfm).

Specialized software packages called BUGS [9,10] are created for implementing MCMC-based analyses of full probability models. These packages will treat all unknowns as random variables.

2 Gamma Polygonal Hazards Model

2.1 Additive Gamma Polygonal Hazards Model

Let T be the survival time of an individual with a vector covariates $\mathbf{x}$. Suppose T is a random variable and follows an additive Gamma-polygonal model if its hazard function takes the following form

$$h\left(t\middle|\mathbf{x}\right) = h_0(t) + h_1\left(t\middle|\mathbf{x}\right), \quad \text{for } t > 0 \tag{3}$$

where $h_0(t)$ and $h_1\left(t\middle|\mathbf{x}\right)$ are the nonparametric and the parametric parts of the above model, respectively. $h_0(t)$ is the nonparametric part and supposed to be a nonnegative polygonal function. The polygonal will take the values $\tau_{0,}\tau_1,\ldots,\tau_k$ with the vertices that will be located at times $a_{0,}a_1,\ldots,a_k$ and it will becomes constant after time a_k

$$h_0(t) = \begin{cases} \tau_{j-1} + \dfrac{(\tau_j - \tau_{j-1})(t - a_{j-1})}{(a_j - a_{j-1})} & \text{if} \quad a_{j-1} \le t \le a_j,\ j = 1,...,k \\ \tau_k & \text{if} \quad t > a_k \end{cases} \tag{4}$$

The hazard function, $h_1(t|\mathbf{x})$ is a Gamma distribution hazard function with mean, α/γ and variance, α/γ^2.

$$h_1(t|\mathbf{x}) = \frac{t^{\alpha-1}\exp(-\gamma t)}{\int_t^\infty y^{\alpha-1}\exp(-\gamma y)dy}, \quad \text{for } t > 0. \tag{5}$$

Both parameters α and γ are specific for each individual in the population and related to the covariates **x** through a probabilistic model. A hierarchical structure were considered in the model with the second level of hierarchy given as follows

$$\begin{aligned} \alpha\,|\,\gamma,\mathbf{x} &\sim N\left(\log\frac{\alpha}{\gamma}\,|\,\omega'\mathbf{x},\sigma_\alpha^2\right) \\ \gamma &\sim N(\log\gamma\,|\,\mu_\gamma,\sigma_\gamma^2). \end{aligned} \tag{6}$$

The logarithm of the mean, $\log(\alpha/\gamma)$ is modeled as a Normal distribution with mean $\omega'\mathbf{x}$ as a linear combination of the covariates and variance σ_ω^2, while the logarithm of parameter γ is also modeled as a Normal distribution with mean μ_γ^2 and variance σ_γ^2, ω, σ_ω^2, μ_γ and σ_γ^2 are the hyperparameters and an unknown constant common to all individuals in the population. In other words, the mean and the shape of the Gamma distribution in the expression (5) are independent and log-Normally distributed. The log-Normal distribution is used in those hyperparameters since it is easier to work with it and spread enough for this level of the hierarchy.

2.2 Multiplicative Gamma Polygonal Hazards Model

Let T be a random variable for the survival time of an individual with vector covariates **x**. Suppose T is a random variable and follows a multiplicative Gamma-polygonal model if its hazard function has the following form

$$h(t \mid \mathbf{x}) = h_0(t) \exp(\beta' \mathbf{x}), \quad \text{for } t > 0$$

where $h_0(t)$ is an unknown baseline hazard function which supposed to be the nonparametric and a nonnegative polygonal function as in expression (4). Ayman and Anis [11] proposed this approach by changing the baseline hazard function to a polygonal function using OpenBUGS Statistical Packages.

3 Inference Procedure

In survival data, the counting process analysis is usually based on the modeling of the intensity function. The counting process, $N_i(t)$ can be observed for subjects i = 1, 2, … , n, that count the number of failures which have occurred up to time t. The counting process increments $dN_i(t)$ in the time interval [t,t+dt) are assumed to be independent Poisson random variables with means, $I_i(t)dt$, where

$$dN_i(t) \sim \text{Poisson}(I_i(t)dt) \tag{7}$$

The new failure rate is then seen to be interval and defined as

$$I_i(t)dt = Y_i(t)\lambda(t \mid \mathbf{x}_i) = Y_i(t)d\Lambda(t \mid \mathbf{x}_i) \tag{8}$$

where $Y_i(t)$ is an observed process and take the value 1 or 0 according to whether or not subject i is observed at time t. Using ideas from Beamonte and Bermúdez [12], the proposed additive intensity model is given by

$$I_i(t)dt = Y_i(t)(d\Lambda_0(t) + d\Lambda_1(t \mid \mathbf{x}_i)dt) \tag{9}$$

where the nonparametric part, $d\Lambda_0(t)$ is a nonnegative polygonal function and can be written as expression (3) while the parametric part, $d\Lambda_1(t)$ is a Gamma distribution and dt is the different between two times in the time interval, [t, $t + dt$).

The multiplicative intensity model which was adopted by Cox's model is given by

$$I_i(t)dt = Y_i(t) \exp(\beta \mathbf{x}_i) d\Lambda_0(t) \tag{10}$$

where $d\Lambda_0(t)$ is the increment or jump in the integrated baseline hazard function occurring during the time interval [t, $t + dt$).

Therefore, the proposed of a new baseline hazard function for the multiplicative intensity model which has the combination of both parametric and nonparametric distributions has the form

$$I_i(t)dt = Y_i(t) \exp(\beta \mathbf{x}_i) [d\Lambda_1(t) + d\Lambda_2(t)] \tag{11}$$

where $d\Lambda_1(t)$ is the non-parametric part which takes the form of polygonal function [11] while $d\Lambda_2(t)$ is the parametric part which takes the form of Gamma distribution, modified by Ismail et al [13].

3.1 Prior Distribution

The prior for the vector τ can be specified as an autocorrelated first order process and takes the form as

$$\tau_i = \tau_{i-1} \exp(\epsilon_i) \quad i = 1, 2, \ldots, k$$

where $\epsilon_1, \epsilon_2, \ldots, \epsilon_k$ are independent and Normally distributed with mean zero and variance σ_ϵ^2 , a parameter that has a conjugate analysis.

$$\tau_0 \sim Ga(\tau_0 \mid a_\tau, b_\tau)$$

$$\sigma_\epsilon^2 \sim N(\log(1/\sigma_\epsilon^2) | a_\epsilon , b_\epsilon).$$

A prior distribution for the hyperparameters $\omega, \sigma_\omega^2, \mu_\gamma, \sigma_\gamma^2$ and σ_α^2 has to be specified in order to do the Bayesian analysis for Gamma polygonal additive hazard model. We need to assume an independence priori between $\tau, (\omega, \sigma_\omega^2), (\mu_\gamma, \sigma_\gamma^2)$ and σ_α^2 . In this paper, we use hyperparameters $\sigma_{\omega_j}^2$ for each one of parameter ω_j for $j = 1, 2, \ldots, p$ and the expressions are as follows

$$\sigma_\alpha^2 \sim Ga(1/\sigma_\alpha^2 \mid a_\alpha, b_\alpha)$$

$$\mu_\gamma \mid \sigma_\gamma^2 \sim N(\mu_\gamma \mid m_\gamma, \sigma_\gamma^2 v_\gamma^2)$$

$$\sigma_\gamma^2 \sim Ga(1/\sigma_\gamma^2 \mid a_\gamma, b_\gamma)$$

$$\omega_j \mid \sigma_{\omega_j}^2 \sim N(\omega_j \mid m_{\omega_j}, \sigma_{\omega_j}^2 v_{\omega_j}^2)$$

$$\sigma_{\omega_j}^2 \sim Ga(1/\sigma_{\omega_j}^2 \mid a_{\omega j}, b_{\omega j})$$

These $\sigma_{\omega_j}^2$ is introduced in the proposed additive gamma polygonal model and will use the usual Inverse Gamma conjugate priors for the hyperparameters. Since we proposed a new multiplicative intensity model in this paper, we also introduced β to have a Log-Normal distribution with mean 1 and variance σ_β^2 instead of having Normal distribution. A new hyperparameter, σ_β^2 will also be introduced in the model and will use the usual Inverse Gamma conjugate priors. The expressions are

$$\beta \mid \sigma_\beta^2 \sim N(\log \beta \mid \mu_\beta, \sigma_\beta^2)$$

$$\sigma_\beta^2 \sim Ga(1/\sigma_\beta^2 \mid m_\beta, s_\beta).$$

3.2 Posterior Distribution

The posterior distribution will become complicated although the simple prior has been chosen and this problem is common to almost every model in populations. The posterior complete conditional for the hyperparameters $(\mu_\gamma, \sigma_\gamma^2)$ is proportional to

$$\left[\prod_{i=1}^{n} N(\log\gamma_i \mid \mu_\gamma, \sigma_\gamma^2)\right] N(\mu_\gamma \mid m_\gamma, \sigma_\gamma^2 v_\gamma^2) Ga(1/\sigma_\gamma^2 \mid a_\gamma, b_\gamma).$$

In a similar way, the posterior complete conditional distribution for $(\omega, \sigma_\omega^2)$ is proportional to

$$\left[\prod_{i=1}^{n} N\left(\log\frac{\alpha}{\gamma} \mid \omega'\mathbf{x}, \sigma_\alpha^2\right)\right][N(\omega \mid m_\omega, \sigma_\omega^2 v_\omega^2) Ga(1/\sigma_\omega^2 \mid a_\omega, b_\omega)] Ga(1/\sigma_\alpha^2 \mid a_\alpha, b_\alpha).$$

Finally, the complete posterior conditional for τ is proportional to

$$\left[\prod_{i=1}^{n} S_0(t_i \mid \tau)[h(t_i \mid \tau, \alpha_i, \gamma_i)]^{\delta_i}\right]\left[\prod_{i=1}^{n} N(\log\tau_i \mid \log\tau_{i-1}, \sigma_\varepsilon^2)\right] Ga(1/\tau_0 \mid a_\tau, b_\tau\Big].$$

4 Results and Discussion

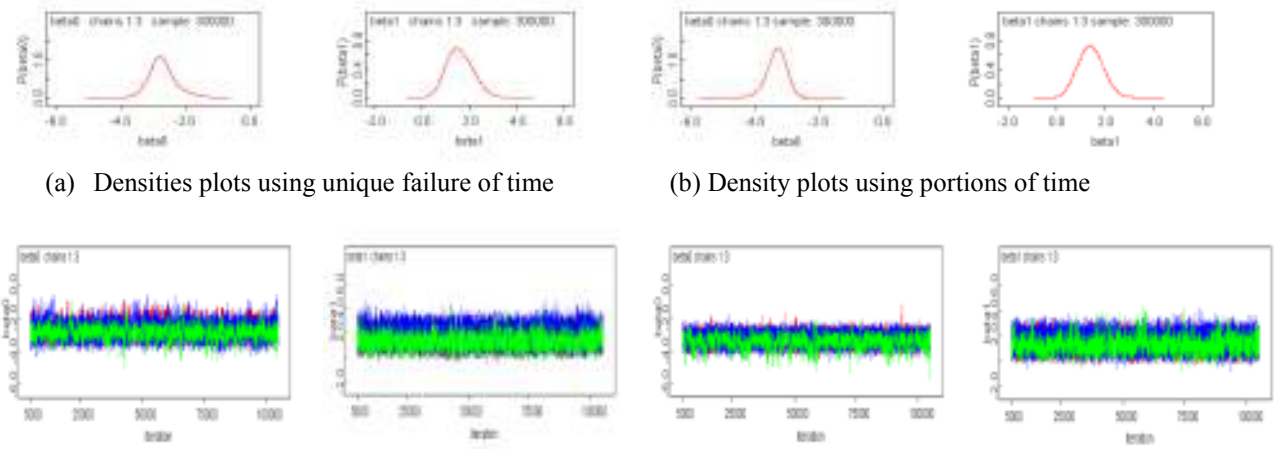
The aim of this paper is to introduced additive gamma polygonal hazards model with Bayesian approach using BUGS software program. We did not use prior information about the hyperparameters in this paper but using a member of the family introduced in Section 3.1 and 3.2 with reasonable variances, as prior distribution. The following priors were set for the additive model: $m_\gamma = 0$, $v_\gamma^2 = 1$, $a_\alpha = 1$, $b_\alpha = 1$, $a_\gamma = 1$, $b_\gamma = 1$, $m_{\omega j} = 0$, $v_{\omega_j}^2 = 1$, $a_{\omega_j} = 1$, $b_{\omega_j} = 1$, $a_\tau = 0.01$, $b_\tau = 0.01$ and $a_\epsilon = 1, b_\epsilon = 1000$, and we set the following priors for the multiplicative model: $m_\beta = 1$, $s_\beta = 1$.

Table 1 Summaries of parameter estimation for additive gamma polygonal

		Mean β	Std Dev	MC Error	2.5% CI	Median	97.5% CI	Log Likelihood
Unique failure time	β_0	-2.709	0.4477	0.009705	-3.5040	-2.750	-1.666	-100.6
	β_1	1.590	0.5767	0.009942	0.5482	1.554	2.802	
Portions of time	β_0	-3.324	0.3383	0.006554	-4.0750	-3.304	-2.719	-111.9
	β_1	1.404	0.5488	0.008476	0.3757	1.389	2.531	

Table 1 shows the summaries of parameter estimation for additive Gamma polygonal hazards model including the log-likelihood for two different types of time intervals. The time intervals are the unique failure time which is observed from a non-censoring observations of survival time and the portions of time which is chosen as disjoint intervals to be vertices at time points in the time interval. Both types of time intervals gave different results for the parameter estimation because the difference of time between two time points in the unique failure time interval is not equal compared to the portions of time that have the equality of differences between two time points. We can say that the

additive Gamma polygonal hazards model is better using the unique failure time than that of portions of time by comparing the log-likelihood.



(a) Densities plots using unique failure of time (b) Density plots using portions of time

(c) History plots using portions of time (d) History plots using portions of time

Figure 1 OpenBUGS plots associated to the coefficient of the covariates.

The generated observations of the trace plots are more convincing in terms of convergence for all generated values within a parallel zone and the densities provide a graphical representation of the posterior densities estimate for the parameter estimation, as shown in Figure 1. The convergence of Gibbs Sampler can be checked using the ideas of parallel multiple chains and the recommended use of chains are from two to five. The choice of hyperparameters and initial values in the analysis are not too sensitive to the estimation of the parameters but the use of the same starting values for each chain indicating different results and sometimes do not reach stability to indicate the convergence. To generate the Gibbs posterior samples, we choose three parallel chains with different starting values and were carried out simultaneously. 100,000 iterations are performed for each chain after 5000 iterations for burn-in to obtain convergence to the posterior distribution, and one out of each value is used to reduce the autocorrelation of the chain. The situation occurs because of the complexity of the model and to avoid the system run down. The convergence of the chains can be monitored via the Brooks-Gelman-Rubin (BGR) convergence-diagnostic, when the line converged to one for stability then the convergence is attained.

Using the same data, the analysis towards four different types of the baseline hazard function in Cox Regression is carried out. Three parallel chains with different starting values are also used and they are carried out simultaneously. 100,000 iterations are performed for each chain after 5000 iterations for burn-in to obtain convergence to the posterior distribution, and one out of every 10th values is used to reduce the autocorrelation of the chain. The convergence of the chains can be monitored via the Brooks-Gelman-Rubin (BGR) convergence-diagnostic graph.

Table 2 shows the summary of parameter estimation for Cox Regression using different types of baseline hazard functions. The parameter estimation for all types are quite similar including the log-likelihood and deviance information criterion, (DIC) as shown in Table 3.

Table 2 Summaries of parameter estimation for Cox Regression with different baseline hazard functions

	Mean β	Std Dev	MC Error	2.5% CI	Median	97.5% CI
Gamma process	1.545	0.4189	0.001847	0.7571	1.533	2.402
Modified Gamma	1.538	0.4121	0.002079	0.7611	1.525	2.385
Polygonal	1.520	0.4143	0.002920	0.7378	1.508	2.370
Gamma Polygonal	1.576	0.4026	0.003602	0.8055	1.566	2.399

Table 3 Summaries of Log-likelihood and Deviance Information Criterion

	Log-Likelihood	DIC
Gamma Process	-106.35	232.6
Modified Gamma	-102.40	209.2
Polygonal	-101.75	211.2
Gamma Polygonal	-102.15	208.3

Both Figure 2(i) and (ii) shows the posterior densities and trace plots for 300,000 iterations of each of three generated samples. The BGR convergence diagnostic graphs in Figure 2(iii) show the line converged to one for stability indicating the convergence of the algorithm. The convergence of the parameters has been achieved since auto-correlations become low only after considering a lag equal to 50 indicating good convergence of the parameter space with a reasonably small number of iterations.

The multiplicative model is tested again using DRS Eye data for all models except OGPrior since there is an error running the model on DRS Eye data. The true purpose of this analysis is to prove that the propose model is a suitable model in analysing all types of paired survival data. Therefore OGPrior model has been excluded in the analysis using DRS Eye data. The results are tabulated in Table 4 which shows the summary of parameter estimation for Cox Regression using different types of baseline hazard functions. The parameter estimation for all types are quite similar including the log-likelihood and deviance information criterion, (DIC) as shown in Table 5. Three parallel chains with different starting values are used and run simultaneously. 100,000 iterations are performed for each chain after its 50,000 iterations for burn-in to attain convergence to the posterior distribution. One out of each value is used to reduce the autocorrelation of the chain due to the large data. Both Figure 3(i) and (ii) show the posterior densities and trace plots for 300,000 iterations of each of three generated samples. The BGR convergence diagnostic graphs in Figure 3(iii) show the convergence of the chains which the line converged to one for stability.

(i) Density plots

(ii) History plots

(iii) BGR diagnostic graphs

(a) Gamma (b) Modified Gamma (c) Polygonal (d) Gamma Polygonal

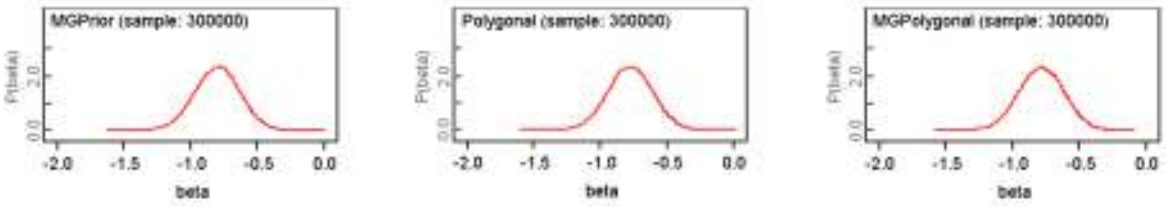
Figure 2 Estimated predictive density and history plots associated to the coefficient of the covariate using different types of baseline hazard functions.

Table 4 Summaries of parameter estimation for Cox Regression with different baseline hazard functions

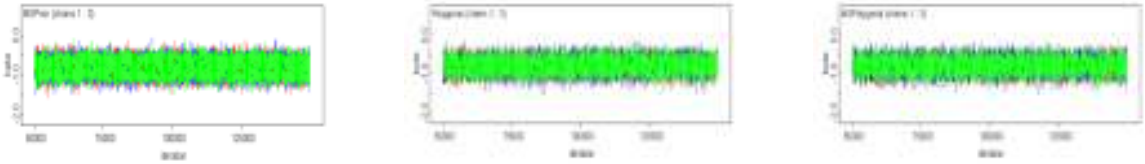
	Mean β	Std Dev	MC Error	2.5% CI	Median	97.5% CI
Modified Gamma	-0.8000	0.1690	9.466E-4	-1.136	-0.7976	-0.4729
Polygonal	-0.7768	0.1691	0.001527	-1.112	-0.7761	-0.4497
Gamma Polygonal	-0.7845	0.1702	0.001742	-1.122	-0.7833	-0.4559

Table 5 Summaries of Log-likelihood and Deviance Information Criterion

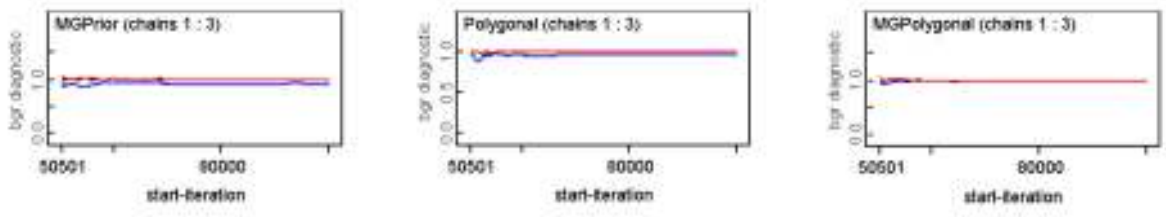
	Log-Likelihood	DIC
Modified Gamma	-808.5	1641.0
Polygonal	-785.0	1616.0
Gamma Polygonal	-787.0	1615.0



(i) Density plots



(ii) History plots



(iii) BGR diagnostic graphs

(a) Modified Gamma (b) Polygonal (c) Gamma Polygonal

Figure 3 Estimated predictive density and history plots associated to the coefficient of the covariate using different types of baseline hazard functions.

Based on the results from the analysis of DRS Eye data, a conclusion can be made that the propose model is also a suitable model to analyse paired survival data. This proves that the proposed model is also an appropriate model compared to existing models in the analysis of paired survival data. Thus, it makes the propose model as good as the existing models and can be used to analyse any types of paired survival data.

5 Conclusion

Bayesian inference has several advantages particularly in the flexibility of model-building for complex data over the frequentist approaches. The Bayesian approach enables us to make exact inference for any sample size based on the posterior distribution. OpenBUGS is a tool for analysing survival data in a Bayesian framework using Markov Chain Monte Carlo (MCMC) and provides the summary of inferences and convergence in a table and graph.

Additive and multiplicative Gamma Polygonal models using Bayesian approach were proposed to fit more flexible survival models for non-informative censored data. Bayesian models can be compared using the deviance information criterion (DIC), which are posterior distributions obtained using MCMC. DIC has been implemented as a tool in the BUGS software package. The results obtained show that the proposed model is as good as the existing models and can be used to analyse any paired survival data such as Leukemia and DRS Eye data.

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