PERFORMANCE OF PIECEWISE GAMMA BASELINE HAZARD FUNCTION IN BAYESIAN SURVIVAL ANALYSIS

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To my beloved father, mother, fiancé, brother and sisters

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ABSTRACT

Bayesian analysis can compute estimator for a wide range of models, such as hierarchical models and missing data problems. It provides a theoretical framework for combining prior information with the data to produce posterior distribution. In the context of survival analysis, Cox proportional hazards model (PHM) is popular for its unique feature in measuring the effects of covariates on survival data without making any assumptions concerning the nature and shape of the underlying baseline hazard function. In this study, different models are used as prior distribution of baseline hazard function in conducting Bayesian analysis of censored survival data. The purpose of this study is to investigate the effect of hyperparameters of gamma process prior on parameter estimation in relation to hyper distribution used in piecewise gamma model. The study intends to assess the performance of piecewise gamma model in estimating parameters for non-informative and censored survival data. The Bayesian estimator of the parameter is computed by using Markov chain Monte Carlo (MCMC) method. Gibbs sampler is applied to simulate samples from Markov chains to estimate the quantities of interest without integrating the posterior distribution analytically. OpenBUGS statistical software is employed in this study to implement Bayesian analysis of survival data. The results obtained show that by increasing values fixed for hyperparameters of gamma process prior, it will decrease the parameter estimates. In addition, piecewise gamma model is found to be adequate in estimating parameters of Cox proportional hazards model for leukemia and hepatitis data as the Monte Carlo error is less than 5% of standard deviation of parameter. Hence, piecewise gamma model can be an alternative model for baseline hazard function.

ABSTRAK

Analisis Bayesian dapat menganggar parameter untuk pelbagai model, seperti model hierarki dan masalah hilang data. Analisis Bayesian menyediakan rangka kerja teori yang menggabungkan informasi *prior* dengan data untuk menghasilkan taburan *posterior*. Dalam konteks analisis kemandirian, Model *Cox proportional hazards* (PHM) terkenal dengan ciri unik yang dapat mengukur kesan kovariat terhadap data mandirian tanpa membuat sebarang andaian mengenai sifat dan bentuk untuk fungsi bahaya asas. Dalam kajian ini, model yang berbeza digunakan sebagai taburan *prior* untuk fungsi bahaya asas dalam analisis Bayesian untuk penyensoran data mandirian. Tujuan kajian ini adalah untuk mengkaji kesan hiperparameters dalam *gamma process prior* terhadap penganggaran parameter berhubung dengan taburan hiper yang digunakan dalam model *piecewise gamma*. Kajian ini bertujuan untuk menilai prestasi model *piecewise gamma* dalam penganggaran parameter untuk data mandirian yang tidak berinformasi dan *censored*. Parameter Bayesian dianggar dengan menggunakan kaedah *Markov Chain Monte Carlo* (MCMC). *Gibbs sampler* digunakan untuk mensimulasikan sampel dari rantai Markov untuk mendapat penganggaran tanpa mengintegrasikan taburan *posterior* secara analitikal. OpenBUGS perisian statistik digunakan dalam kajian ini untuk melaksanakan analisis Bayesian terhadap data hepatitis. Hasil kajian menunjukkan bahawa dengan meningkatkan nilai yang ditetapkan untuk hiperparameter dalam model *gamma process prior*, nilai parameter akan berkurangan. Selain itu, model *piecewise gamma* didapati sesuai dalam penganggaran parameter untuk Model *Cox proportional hazards* bagi data leukemia dan hepatitis dimana ralat Monte Carlo adalah kurang 5% daripada sisihan piawai untuk parameter. Oleh itu, model *piecewise gamma* boleh dijadikan sebagai satu model alternatif untuk fungsi bahaya asas.

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LIST OF ABBREVIATIONS

BGR	-	Brooks-Gelman-Rubin
BUGS	-	Bayesian inference Using Gibbs Sampling
DIC	-	Deviance Information Criterion
DSR	-	Diabetic Retinopathy Study
MCMC	-	Markov Chain Monte Carlo
MRC	-	Medical Research Council
PHM	-	Proportional Hazards Model

LIST OF SYMBOLS

β - parameter (beta)

CHAPTER 1

INTRODUCTION

1.1 Introduction

Survival analysis is a set of methods used to analyze survival data. Survival data refers to the length of time until the occurrence of a specified event. The survival data is also called as survival time. The time to event can be measured in days, weeks or even years. In medical research, the event of interest is usually referred to as death, disease incurrence or relapse from remission. The event of interest is typically called as failure. Generally, in survival analysis, only one event is of designated interest. Statistical problems which consider more than one event of interest are usually analyzed under competing risk or recurrent events problem.

Survival analysis focuses on the duration of time from a subject enters a study until the occurrence of the event. The survival time is a response variable which is non-negative. The goal of survival analysis is to model the distribution of the survival time, compare the survival probability for two or more groups of data and to study the relationship between the survival time and the independent covariates.

A special feature of the survival data that makes it distinct from other data is the censorship of the data. The observation is called censored when the information of the survival time is incomplete. There are three types of censored data, which are right-censored data, left-censored data and interval censored data. The data is said to be right-censored when only lower bound of the survival time of the censored data is known. Right-censoring occurs when the event of interest has not occurred before the study is terminated. Right-censoring can arise from withdrawal of the subject from the study because of competing risk or the subject is lost to follow up before the termination of the study. Maddala (1983) and Kalbfleisch and Prentice (1980) discussed several types of censoring situations. Censored survival data cannot be omitted during the data analysis as it represents the missing data. Ordinary linear regression cannot deal with the non-negativity and censoring of the survival data effectively. However, survival analysis can handle this kind of data by taking the censoring into account and incorporate information from both censored and uncensored observations to estimate the parameters.

In survival analysis, survival and hazard functions are used to describe the distribution of the survival data. The survival function gives the probability of not experiencing the failure or event up to time *t*. The hazard function, on the other hand, measures the potential of getting the failure or event per unit of time conditioned that the individual has survived up to time *t*. There are a number of models which are appropriate to describe the relationship between the survival time and the covariates. The models include parametric, non-parametric and semiparametric.

The common parametric models used in fitting the survival data are exponential, Weibull, lognormal and Gompertz distributions. By using parametric model, the survival data is assumed to follow the specified probability distributions. A non-parametric model is widely used to graph the survival probabilities when Kaplan Meier method (Kaplan and Meier, 1958) was introduced. Log-rank test is used to compare the Kaplan Meier curves for each group of data. A well-known semiparametric model used for survival analysis is Cox proportional hazards regression model (Cox, 1972).

Survival analysis is mostly applied to biological data. For example, survival model was used by Lee and Mallick (2004) for DNA microarray data. However, survival analysis has been extended to other fields nowadays. Survival analysis is widely applied in engineering field, which is used to analyze data such as lifetime of engines and reliability of the function of a system. In addition, survival analysis is also broadly used for sociological data such as duration of recidivism and economic data such as unemployment data. Fox (2002) applied survival model for the analysis of survival data that measures the time for a prisoner to be arrested after being released from prison. Beamonte and Bermúdez (2003) and Ganjali and Baghfalaki (2012) carried out survival analysis for unemployment duration data. In this study, right-censored medical data which is hepatitis data is analyzed by using semiparametric Cox proportional hazards model.

1.2 Background of Study

Chronic active hepatitis is referred to as inflammation of liver for at least six months (Anthony et al., 1978) which is caused by specific hepatitis viruses, autoimmune mechanism, alcohol and drugs. Autoimmune hepatitis is an organ-specific autoimmune disease characterized by a break of humoral and cellular immunotolerance that mainly affects the liver (Manns and Taubert, 2014). This disease is commonly observed in women from all age groups and races. It is also called as lupoid hepatitis. The early death that is caused by this disease is due to hepatocellular failure (Mackay and Wood, 1962). Those who survive at the beginning stage of the disease might suffer macronodular cirrhosis and die from its complications (Read et al., 1963).

Autoimmune hepatitis was one of the first liver diseases for which effective treatment had been developed. The benefit of the treatment is proven by randomized controlled trials. Corticosteroid therapy is shown to increase the survival time of the

autoimmune hepatitis patients during the early-active phase of chronic hepatitis (Cook et al., 1971; Wright et al., 1977). Although corticosteroid therapy can reduce the mortality of the patients at the early stage of the disease, the dose of steroids should be restricted and be withdrawn when the liver function tests return to normal. This study is conducted to evaluate the effect of prednisolone (steroid) treatment on the survival time of hepatitis patients who are randomly distributed into treatment and control groups. The survival probability of treatment and control groups are then compared to examine the effect of prednisolone therapy.

To estimate hazard rate and survival probability for survival data, numerous studies has been carried out to fit the survival data. There are numerous models which are available in literature. The famous model used to define hazard function is Cox proportional hazards model proposed by Cox (1972). Cox proportional hazards model is a multiplicative hazard function, which is a product of unspecified baseline hazard function with an exponential function of explanatory variables. Cox proportional hazards model is popular and widely used for its unique characteristic in estimating the unknown regression coefficients. The estimation of the parameters for Cox model can be done by using partial likelihood function, which eliminates the baseline hazard function and accounts for censored survival times.

Cox proportional hazards model can be used to fit the survival data by using both frequentist and Bayesian methods. Since frequentist method does not work well for small sample size and censored survival data, Cox proportional hazards model is usually analyzed by using Bayesian approach. In conducting Bayesian analysis, posterior distribution of the parameters is obtained by incorporating the likelihood of the observed data and the prior distribution of the parameters. The posterior distribution is the probability distribution of the unknown parameters conditioned on the observed data. The likelihood function is the joint distribution of the observed samples while prior distribution of the parameters expresses the belief of a researcher before any data is collected. An adequate and flexible prior distribution of the baseline hazard function which does not heavily influence the computation of posterior distribution is often the concern of the researchers. Kalbfleisch (1978)

proposed gamma process prior with fixed values of *r* (a guess at the failure rate per unit time) and *c* (degree of confidence at the guess) as the baseline hazard function in estimating the parameters for leukemia data.

Later, numerous studies had been carried out to propose prior of the baseline hazard function for Cox proportional hazards model in recent years. Ayman and Anis (2011) proposed polygonal function as the prior of the baseline hazard function. They applied the model in the analysis of leukemia data and proved that the polygonal baseline hazard function is a better model compared to gamma process prior based on Deviance Information Criterion (DIC) values. Ismail et al. (2012) modified the original gamma process prior of Kalbfleisch by assuming *r* and *c* to have uniform and gamma distributions respectively. Once again, the modified gamma baseline hazard function appears to be more appropriate than original gamma process prior as the DIC value of original gamma process prior is higher than modified gamma baseline hazard. Although several studies have shown that new proposed baseline hazard functions are better models than original gamma process prior, there is no research done in examining the limitation of gamma process prior that causes the DIC value of the original gamma process prior to be higher than the other new baseline hazard functions.

Ismail et al. (2013) analyzed leukemia data and Diabetic Retinopathy Study (DSR) eye data by using additive and multiplicative gamma polygonal as the prior of the baseline hazard functions. The additive and multiplicative gamma polygonal hazard functions have been proven to be suitable and appropriate in analyzing paired survival data. However, gamma process prior is not applicable for the analysis of DSR eye data. A new multiplicative piecewise gamma baseline hazard function was proposed by Ismail et al. (2014). The parameter estimation for leukemia data by using multiplicative piecewise gamma baseline function shows similar results as the results by using other baseline hazard functions. Since most of the literature was made based on leukemia data, hepatitis data is used in this study to analyze the performance of piecewise gamma baseline hazard function in estimating the parameters for Cox model.

1.3 Statement of Problem

In the context of survival data analysis, Cox proportional hazards model is one of the most popular model used to measure the effects of covariates on hazard rates. In order to estimate the regression coefficients of the covariates from Bayesian perspective, the baseline hazard function of Cox model has to be specified before Bayesian analysis is conducted. A common model used as the prior distribution of the baseline hazard function is gamma process prior, which was proposed by Kalbfleisch (1978). Kalbfleisch (1978) suggested the baseline hazard function to follow gamma distribution with constant values of shape and scale parameters. He set r (a guess at the failure rate per unit time) and c (degree of confidence at the guess) as 0.1 and 0.001 respectively for the analysis of leukemia data. The question of why those particular values are chosen as the values of r and c arises. It is important to know whether other values of r and c will influence the estimation of the parameters. Hence, this study aims to investigate the effect of varying values of r and c for gamma process prior on the parameter estimation.

In 2014, Ismail et al. proposed a multiplicative piecewise gamma model as the prior of the baseline hazard function for Cox model. Ismail et al. (2014) also suggested the baseline hazard function of Cox model to be gamma distribution but the shape parameter is set to have a polygonal function instead of constant values. In their paper, piecewise gamma model is applied on leukemia data, which is non-informative and right-censored. The study intends to assess the performance of piecewise gamma model in estimating another set of data with similar characteristics as leukemia data.

1.4 Objectives of Study

Based on the above issues and needs, the objectives of this study are:

1. To investigate the effect of varying values of scale and shape parameters of gamma process prior in relation to the hyper distribution in piecewise gamma baseline hazard function.

2. To assess the performance of piecewise gamma model in estimating the parameters for censored leukemia and hepatitis data based on the percentage of Monte Carlo error with the standard deviation of the parameter.

1.5 Scope of Study

This study focuses on the survival analysis of censored medical data. Two sets of survival data are applied in this study. A total of 42 leukemia data is taken from Freireich et al. (1963) while 44 observations for hepatitis data are taken from Cook et al. (1971). Both of the survival data are right-censored and non-informative.

In this study, semiparametric multiplicative hazard function, which is Cox proportional hazards model is used to model the survival data as the effect of treatment on survival time is the subject of interest. Bayesian analysis is the main approach used in this study. Markov chain Monte Carlo (MCMC) methods are used to simulate samples from the posterior distribution of the parameter. Gibbs sampler algorithm is used to construct Markov chains which will converge to posterior distribution regardless of the initial points. The estimation of parameter is carried out

by using the simulated samples from converged Markov chains. The study emphasizes on the estimation of parameters using different types of models as the prior distribution of the baseline hazard function for Cox model. The performance of prior distributions of baseline hazard function is inspected and assessed.

1.6 Significance of Study

The statistical techniques used in survival analysis is not only restricted to the biomedical field. It has extended to other areas of knowledge such as economic and social sciences. Frequentist method is one of the common and easy ways to implement the survival analysis. However, frequentist method can only be applied to analyze simple models. Bayesian analysis is well known and widely used in survival analysis as it can deal with complicated and even hierarchical models. Hence, Bayesian approach is preferable over frequentist method in survival analysis. Cox proportional hazards model is one of the famous model used to describe the relationship between the covariates and the survival time. In implementing Bayesian analysis, a good prior for baseline hazard function which is flexible and applicable to all kinds of survival data is very much needed if prior information is not available. A good and flexible prior has a great potential in the applications of any types of censored survival data without bringing any effect on the estimation of the parameters. In other words, the applicability of a good and flexible prior for baseline hazard function is not limited to one set of data only. It can estimate the parameters accurately for any types of survival data. With a good prior distribution for baseline hazard function, the survival probability and the hazard function for survival data can be obtained easily. Thus, this study aims to obtain an appropriate and flexible model for the prior of the baseline hazard function which is applicable to any types of non-informative censored survival data in estimating the parameters.

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