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Piecewise Exponential Frailty Model on Survival Data using Bayesian Approach

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Abstract

Survival analysis is a data analysis on the survival or duration of life of an individual or a unit in certain circumstances. A significant development in the study of survival analysis is to model a dependency form in survival data by considering Frailty models. This paper examines Bayesian estimation of piecewise exponential Frailty models for multivariate survival data. The method that is used in this paper as follows; first, we construct likelihood function of the model and determine the prior distribution information thus the posterior distribution can be obtained, and the second, Gibbs sampling algorithm is used to generate random samples from the posterior distribution. The methodology is applied to the recurrence of infection time data at the point of catheter insertion for kidney patients using portable equipment sourced from McGilchrist and Aisbett research. In implementing to the kidney infectious times, our result shows that covariates that influence the individual survival time are sex and the frailty.

Keywords: *Bayesian Estimation, Frailty Model, Gibbs Sampling, Piecewise Exponential, Survival Analysis,*

1. Introduction

Statistical field has rapidly grown with findings the methods that can be used to analyze many problems. One of them is survival analysis which is the study of unit or individuals survival in a particular situation. Survival analy is often used in fields of engineering, science and biomedicine. Survival analysis covers some of statistical techniques that are useful for analyzing some variety of random variables. The random variables in survival analysis are survival times or failure times.

The important developm t in study of survival analysis is modeling dependence in survival data consider the frailty models. Frequently in the analysis of survival data, survival times within the same group are correlated due to unobserved covariates. One way these covariates can be included in the model is as frailties. The idea of frailty provides a simple way to show the unobserved random effect, relationships, and heterogeneity into the model for survival data. Frailty model in its simplest form is nobserved proportionality factors that modify hazard function. Frailty model is commonly known as shared-f ilty model. This model is an extension of the Cox proportional hazard model (Wienke, 2011).

Gamma distribution is the most commonly used to frailty model (Ibrahim et al., 2001). Bayesian method is an attractive method for this model because this method is using the full likelihood in the proces of analysis. The purpose of this study are to estimate the parameters of piecewise exponential frailty model and apply the piecewise exponential frailty model on the survival data.

2. Literature Review

2.1. Basic Concepts of Survival Analysis

Survival analysis is a statistical procedure used to analyze the data which the variables studied is time until the occurrence of an event or end point (Kleinbaum and Klein, 2005). If the final event of study is a failure, then the result of the data is said survival time.

According to Lee (2003), there are three factors that are needed in determining the survival

time, namely:

1. The initial time of an event (time origin/ starting point)
2. The final time of an event (end point)
3. Measurement scale in part of the time must be clear

The differences between survival analysis with another statistical analysis is the existence of censorship. According to Collet (1994) data is said to be censored if the observation of survival time only partially, not until the failure event. The cause of the data censored include :

1. Object moved, died or refused to participate (loss to follow-up)
2. The treatment is stopped for any reason (drop out)
3. The period of study ended while the observed object has no reached the failed event (termination).

There are several types of censors as follows :

1. Interval censor, occurs when the events of concern are known to have occurred between time a and b
2. Right censor, if the observed data Y_i is the data after censor time. Y_i is in interval $[C_i, \infty)$
3. Left censor, if the observed data Y_i is the data before censor time. Y_i is in the interval $(-\infty, C_i]$ (Lawless, 1982).
4. Type I censor (time censor), when the test was stopped at a certain time.
5. Type II censor (failure censor), when the test was stopped after a certain number of failure is obtained.
6. Type III censor (random censor), because the incoming time is different, so the time censored are also different. (Lee and Wang, 2003).

The type of censor used in this study is the right censor because the observed data is the data after time censor.

2.1.1. Survival Function

According to Lawless (1982) survival function is the probability of individual can survived until time y. Survival function S(y) can be written as :

$$S(y) = P(Y \geq y) = \int_y^{\infty} f(x)dx \tag{2.1}$$

and have a cumulative distribution function :

$$F(y) = P(Y \leq y) = \int_0^{y} f(x)dx \tag{2.2}$$

2.1.2. Hazard Function

According to Lawless (1982) hazard function is the probability of individual that fail in the time interval y until $y + \Delta y$, if known individuals are still able survive until the time y which is expressed as follows :

$$h(y) = \lim_{\Delta y \to 0} \frac{P(y \leq Y < y + \Delta y | Y \geq y)}{\Delta y} \tag{2.3}$$

if $f(y)$ is the probability density function of the time y, so the equation (2.2) can be decomposed into :

$$\begin{aligned} h(y) &= \lim_{\Delta y \to 0} \left[\frac{P(y \leq Y < y + \Delta y | Y \geq y)}{\Delta y} \right] \\ &= \lim_{\Delta y \to 0} \left[\frac{F(y + \Delta y) - F(y)}{\Delta y} \cdot \frac{1}{S(y)} \right] \\ &= \frac{F'(y)}{S(y)} = \frac{f(y)}{S(y)} \end{aligned} \tag{2.4}$$

2.2. Frailty Model

Frailty model is the model that entering the survival time of individual into the sub group (cluster subject). This model is an extension of the Cox proportional hazard model (Wienke, 2011).

2.2.1. Proportional Hazard Model

Frailty model is commonly known as shared-frailty model. Hazard function in the shared-frailty model is given by :

$$h(y_{ij}|\boldsymbol{z}_{ij}, w_i) = \lambda_0(y_{ij})\exp(\boldsymbol{\beta}'\boldsymbol{z}_{ij})w_i \quad (2.5)$$

where :

- y_{ij} : survival time for subjects i in groups j, $i = 1,2,\dots,n$, and $j = 1,2,\dots,m_i$. m_i represent the number of subjects in the groups j , so total $N = \sum_{i=1}^{n} m_i$ subjects.
- w_i : the unobserved *frailty* parameters for groups j
- $\boldsymbol{z}_{ij}$: fixed covariate vector or p x 1 covariate vector for subjects i in groups j, and time bound
- $\boldsymbol{\beta}$: p x 1 vector from unobserved regression coefficient
- $\lambda_0(.)$: general baseline hazard function to each subject.

2.2.2. Frailty using gamma distribution

Gamma distribution is most commonly distribution used to frailty model. Frailty used to introduce the random effects, associations, and unobserved heterogeneity for survival data. Frailty model is an extension of Cox proportional hazard model (Ibrahim et al., 2001).

In this study given frailty that use gamma distribution, as follows :

$$w_i \sim Gamma(\eta, \eta), i = 1, \dots, n$$

where η^{-1} is unknown variance of w_i,so the smaller values on η implies greater heterogeneity between groups.

2.2.3. Piecewise exponential model

Piecewise exponential model is a useful and simple model to construct frailty model (Ibrahim et al., 2001). Piecewise exponential models and prior processes on the components provide a very flexible framework for modeling univariate survival data. Modeling the baseline hazard using prior processes is very common, see Sinha and Dey (1997) for a review. Often in real life problems, not the actual baseline hazard, but the smoothness of it, is available as prior information (see e.g., Leonard, 1978 and Gamerman, 1991). We divide time into g specified interval $I_k = (y_{k-1}, y_k]$ for $k = 1,2,\dots,g$ where $0 = y_0 < y_1 < \cdots < y_g < \infty$, y_g being the last survival or censored time and assume the baseline hazard to be constant within intervals. The model was first introduced by Breslow (1974) who used distinct failure times as end points of intervals. Kalbfleisch and Prentice (1973) suggested that the selection of the grid $\{y_1, y_2, \dots, y_g\}$ should be made independent of the data. We will discuss the choice of g later in this section.

2.3. Parameter estimation

2.3.1. Bayesian Approach

In estimation theory, there are two approaches, namely the statistical classical approach and statistical Bayesian approach. Statistical classical is fully used inference process on data samples taken from the population sample also takes into account an initial distribution called priors. Statistical inference with statistical approach *Bayesian* is different from the classical statistical approach. Classical statistical approach sees the parameter θ as fixed-value parameters. While the statistical *Bayesian* approach sees the parameter θ as a random variable having distribution, called the prior distribution. Of the prior distribution can then be determined in order to obtain the posterior distribution of estimator *the* Bayesian is the mean or the mode of the posterior distribution (Hidayah, 2010).

2.3.1.1. Likelihood Function

joint density function $f(x_1, \dots, x_n; \theta)$ of random variables $X_1, X_2, \dots, X_n$ called the likelihood function. Suppose there are n observations $x_1, x_2, \dots, x_n$ each of which has a density functionopportunities $f(x_i, \theta)$, the likelihood function ofa function θ is

$$f(x_1, x_2 \cdots x_n; \theta) = f(x_1, \theta) \dots f(x_n, \theta) = \prod_{i=1}^{n} f(x_i, \theta) \quad (2.6)$$

2.3.1.2. Prior

main problem in this Bayesian approach is to choose a prior distribution $\pi(\theta)$which indicates uncertainty aboutparameter θ. the unknown Box and Tiao (1973) divides into two groups based on their prior likelihoodnya function:

1. With regard to the shape of the distribution of the identification data pattern
   a. Prior conjugate, referring to the benchmark analysis of the model, especially in the formation likelihoodnya function so that the determination of conjugate priors are always thinking about the determination of the prior distribution pattern that has form conjugates with density function likelihoodnya builder opportunities.
   b. Prior non-conjugate, prior administration of the model does not consider the pattern forming likelihoodnya function.
2. In connection with the determination of each parameter on the prior distribution pattern.
   a. Prior informative, referring to the administration of the parameters of the prior distribution which has chosen either conjugate prior distribution or not.
   b. Prior non-informative, if the selection priornya distribution is not based on existing information.

2.3.1.3. Posterior

In estimation of Bayesian also known as the posterior distribution. The posterior distribution is the conditional density function of θ if the observed values *of X* are known which can be written as follows:

$$f(\theta; x_i) = \frac{f(\theta, x_i)}{f(x_i)} \tag{2.7}$$

If θ is continuous, prior and posterior distribution of θ is expressed by the density function. Conditional density function of the random variable if the known value of the random variable is the joint density function of two random variables were divided by the marginal density function of the random variable. However, joint density function $f(\theta, x_i)$ and the marginal density function $f(x_i)$ in general is not known, only the prior distribution and likelihood function that is normally expressed (Rahmawati, 2011).

According to Soejoeti and Soebanar (1988), the function together with the required density can be written in the form of the prior distribution and likelihood function is specified as follows:

$$f(\theta, x_i) = f(\theta) f(x_i; \theta) \tag{2.8}$$

2.3.2. Gibbs Sampling

Gibbs sampling is a technique to generate random variables of the marginal distributions are not directly without having to calculate the density.

Suppose $\beta = \theta$ is the vector of coefficients to be expected, the set of full conditional distribution for θ indenote with Θ and defined as $\pi(\Theta) = (\theta_i|\theta_{-i})$ for $i = 1,\ldots,$k,wherenotation θ_{-i} indicates the parametric form of Θ without coefficients θ_i.method Gibbs sampling is given as follows:

1. Select the initial value $\theta^0 = \left[\theta_1^{[0]}, \theta_2^{[0]}, \ldots, \theta_k^{[0]}\right]$
2. In order *j* starts with *j*= 1, complete one lap (single cycle)by taking the value of the distribution of k is given as follows:
   $\theta_2^{[j]} \sim \pi(\theta_2|\theta_1^{[j]}, \theta_3^{[j-1]}, \ldots, \theta_{k-1}^{[j-1]}, \theta_k^{[j-1]})$
   $\theta_3^{[j]} \sim \pi(\theta_3|\theta_1^{[j]}, \theta_2^{[j]}, \ldots, \theta_{k-1}^{[j-1]}, \theta_k^{[j-1]})$
   .
   .

.

$\theta_{k-1}^{[j]} \sim \pi(\theta_{k-1} | \theta_1^{[j]}, \theta_2^{[j]}, \theta_3^{[j]}, \ldots, \theta_k^{[j-1]})$

$\theta_k^{[j]} \sim \pi\left(\theta_k \middle| \theta_1^{[j]}, \theta_2^{[j]}, \theta_3^{[j]}, \ldots, \theta_{k-1}^{[j]}\right)$

3. Add the value of j and over until reaching convergent.

After reaching convergent then estimated parameters $\beta = \theta$ is used to calculate the posterior by first calculating the priors and likelihood (Gill, 2002).

3. Methods

3.1. Data Sources

The data used for this study is the recurrence times to infection, at the point of insertion of the catheter, for kidney patients using portable dialysis equipment sourced from research and Aisbett McGilchrist (1991) (Ibrahim, *et*al.,2001).

3.2. Methods of Analysis

Data analysis methods used in this study is Bayesian method where by data modeling observed and measured with Bayesian methods is done first by:

1. Determine the function of the baseline hazard, where the baseline hazard exponential distribution.
2. Determine frailty models the distribution Gamma
3. Build frailty models.
4. Constructing a function likelihood based on frailty models.
5. Determine priors to determine the posterior distribution. In this study selected Gamma prior distribution.
6. Estimating parameters using gibbs sampling algorithm.
7. Application to the data.

4. Results and Discussion

4.1. Construct Likelihood Function

Proportional hazard piecewise exponential model can be formed into:

$$h\,(y_{ij}) = \lambda_k \theta_{ij} w_i \tag{4.1}$$

where $\theta_{ij} = \exp(\boldsymbol{\beta}' \boldsymbol{z}_{ij})$.

The likelihood function for equation (4.1) is as follows:

$$L(y_{ij}) = \prod_{i=1}^{n} \prod_{j=1}^{m} h(y_{ij})^{\delta_{ij}} S_H(y_{ij}), \tag{4.2}$$

where $S_H(y_{ij})$ is the survival function of hazard the cumulative $(H(y_{ij}))$.

According to equation (4.2) then the likelihood function of piecewise exponential with frailty w_i given by:

$$L(\boldsymbol{\beta}, \boldsymbol{\lambda} | \boldsymbol{W}, \boldsymbol{Y}, \boldsymbol{Z}) = \prod_{i=1}^{n} \prod_{j=1}^{m_i} \left[\{ \prod_{k=1}^{g_{ij}} \exp(-\lambda_k \Delta_k \theta_{ij} w_i) \} \left(\lambda_{g_{ij}+1} \theta_{ij} w_i \right)^{\delta_{ij}} \exp\left\{ -\lambda_{g_{ij}+1} (y_{ij} - \right.\right.$$
$$\left.\left. y_{g(ij)}) \theta_{ij} w_i \right.\right. \tag{4.3}$$

where $\Delta_k = y_k - y_{k-1}$, y_k is interval time, δ_{ij} is an indicator variable, which is 1 if the subject i in group j fail and the other way will be 0 if the subject i in group j censored, and g_{ij} resemble $y_{ij} \in \left(y_{g_{ij}}, y_{g_{ij}+1}\right] = l_{g_{ij}+1}$, $\boldsymbol{W}$ is the w_i vector are not observed, and $\boldsymbol{Y}, \boldsymbol{Z}$ is the observation data $\left(y_{ij}, \delta_{ij}, \boldsymbol{z}_{ij}\right)$

Likelihood of (β, λ) based on observational data $(\boldsymbol{Y}, \boldsymbol{Z})$ can be obtained by integrating w_i the gamma distribution.

4.2. Determination Prior Distribution

In this case, to correlate λ_k in adjacent intervals, a discrete-time martingale process is used similar to univariate survival model (Arjas and Gasbarra, 1994). Arjas and Gasbara assumes that:

1. The jump times $T_1, T_2, \ldots$ form a time- homogeneous Poisson process with parameter μ
2. The initial rate λ_0 has Gamma distribution $\gamma(\cdot; \alpha_0, \beta_0)$ (with α_0 as the shape parameter and β_0 as scale parameter)
3. Given $\lambda_0, \ldots, \lambda_{i-1}$, and independently of the jump times T_k, λ_i has distribution $\gamma(\cdot; \alpha_i, \beta_i)$, where α_i is the shape parameter and $\beta_i = \frac{\alpha_i}{\lambda_{i-1}}$.

If $(\lambda_1, \ldots, \lambda_{k-1})$, then

$$\lambda_k | \lambda_1, \ldots, \lambda_{k-1} \sim Gamma\left(\alpha_k, \frac{\alpha_k}{\lambda_{k-1}}\right), k = 1, \ldots, g$$

where $\lambda_0 = 1$ and $\lambda_{k-1} = E(\lambda_k | \lambda_1, \lambda_2, \ldots, \lambda_{k-1})$.

The parameter α_k controls the amount of smoothness available, i.e., small α_k indicates less information in the smoothing of λ_k. If $\alpha_k = 0$,then λ_k and λ_{k-1} independent. When $\alpha_k \to \infty$, then the baseline hazard is in the same interval I_k and I_{k-1} i.e., $\lambda_k = \lambda_{k-1}$.

4.3. The posterior

Posterior distribution is conditional density function θ if the observed values of X are known. The form of Posterior $(\boldsymbol{\beta}, \boldsymbol{\lambda})$ is given as follows:

$$p(\boldsymbol{\beta}, \boldsymbol{\lambda}) \propto L(\boldsymbol{\beta}, \boldsymbol{\lambda} | \boldsymbol{D}) p(\boldsymbol{\lambda}) p(\boldsymbol{\beta}),$$

where $\boldsymbol{D} = (\boldsymbol{Y}, \boldsymbol{Z})$.

The final form of the likelihood in equation (4.3) after integration are too complicated to work with. Thus, it is not easy to evaluate the marginal posterior distribution analytically. To circumvent this problem, we use Gibbs sampling (Gelfand and Smith, 1990; and Gilks *et*al.,1996).

4.4. Application of *Piecewise* Exponential *Frailty* Models on Kidney Infection Data

The data used for this study is data recurrence of infection at the time of catheter insertion point for kidney patients originating from research McGilchrist and Aisbett (1991), the number of patients as many as 38 people, in which the research was conducted as twice and the variables are patient, time, status, age, sex (0=male, 1=female),

Processing of data in this study using statistical software WinBUGS 14. For piecewise exponential frailty model first built intervals $g = 5$, $g = 10$ and $g = 20$, After that, update from 1000 to 100000. The model has demonstrated convergent iteration 100000 moment with a good plot in the form $g = 5$. It can be seen from the trace plots β and $\sigma^2_{Frailty}$ (Figure 1, 2 and 3) that already did not show any trend.

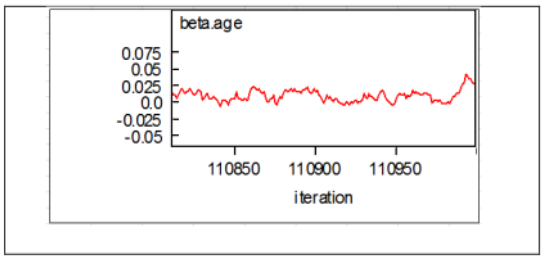

Figure 1. Trace plot β_{age}

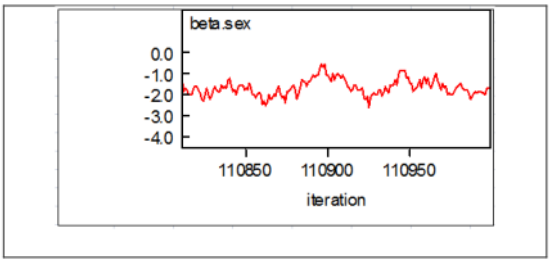

Figure 2.Trace plot β_{sex}

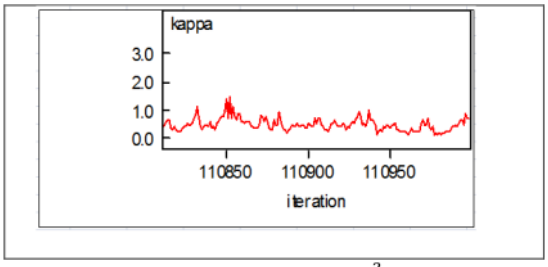

Figure 3. Trace plots $\sigma^2_{Frailty}$

In addition to seeing the results of the trace plots, can also be viewed history plot (Figure 4.5, and 6) and the density plots (Figure 7, 8 and 9). If a model has a convergent then the results of history plots would seem meetings and able to respond to all the parameters and subtle forms of density plots.

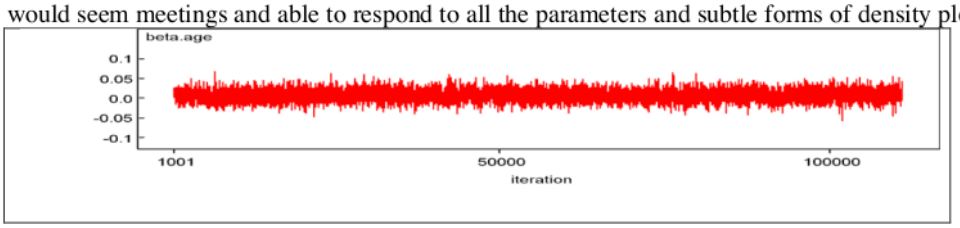

Figure 4. history plot β_{age}

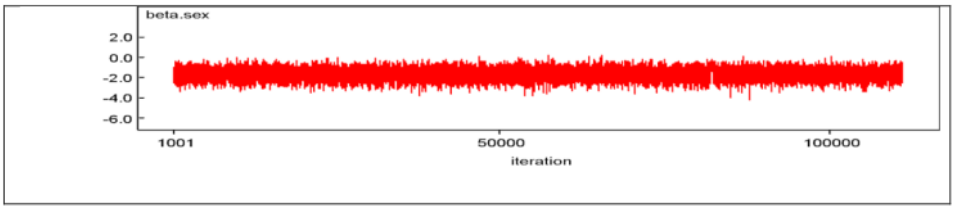

Figure 5. history plot $\beta_{of\ sex}$

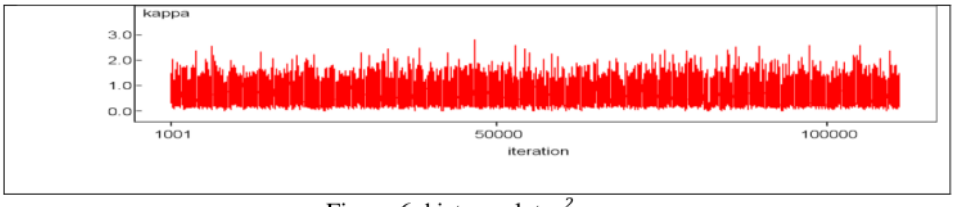

Figure 6. history plot $\sigma^2_{Frailty}$

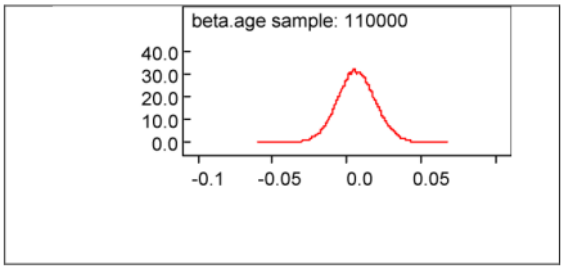

Figure 7. Graphdensity β_{age}

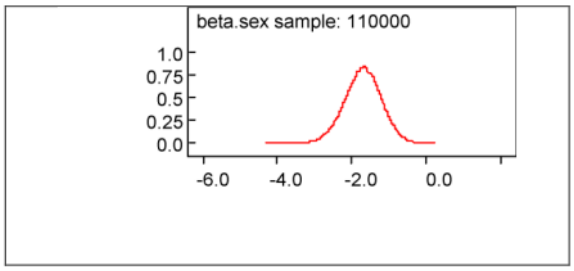

Figure 8. Graph density β_{sex}

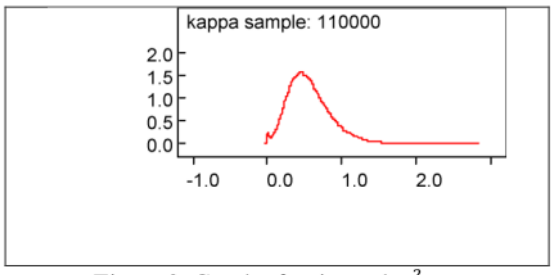

Figure 9. Graph of estimated $\sigma^2_{Frailty}$

From the iterating results we obtain the estimated parameter values as follows:

Table 1. estimated parameters results

Parameter	Rata-rata	Standar Deviasi	95% Credible Interval
beta.age	0.00653	0.01293	(-0.0185, 0.03228)
beta.sex	-1.702	0.4882	(-2.695, -0.7719)
Kappa ($\sigma^2_{frailty}$)	0.5656	0.2899	(0.1157, 1.245)

Based on Table 1, shown covariates that influence the survival time of patients are sex and Frailty because results the estimated parameters of the two covariates does not contain the value zero, where β_{sex} is negative on the interval (-2695,-0.7719). Also the value of σ^2 at 0.5656 this shows the population variance in frailty is more than zero so that there is heterogeneity in the data. To see the effect of covariates sex between men and women then given a survival time graph of patients

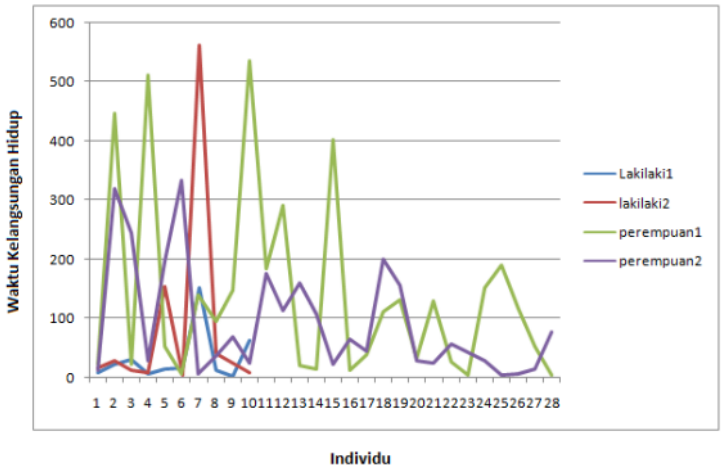

Figure 10 . Graph the relationship between survival and sex of the patient

Figure 10 shows that the women have a lower probability then men to recurrence with numbering heterogeneity of patients.

5. Conclusion

1. Parameter estimation of piecewise exponential frailty model with Bayesian approach :
   a. Construct the likelihood function of the piecewise exponential frailty model
   b. Determine the prior of the parameter which be estimate
   c. Determine posterior, i.e., proportional likelihood times prior

   Because of the last likelihood form is very complicated to analytically integrated so to get the results of the parameter estimation is used Gibbs Sampling algorithm.
2. Based on data processing, we get the covariates that influences the survival time of individual are sex and frailty where women have a lower probability then men to recurrence with numbering heterogeneity of patients.

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