A Bayesian Analysis of Univariate Proportional Hazard, Accelerated Failure Time and Proportional Odds Model under Frailty Approach

Kuki Kalpita Mahanta¹ & Jiten Hazarika²

¹Research Scholar, Department of Statistics, Dibrugarh University, Dibrugarh (Assam), India ²Professor, Department of Statistics, Dibrugarh University, Dibrugarh (Assam), India

Abstract: The frailty approach is a statistical modeling concept which aims to account for heterogeneity, caused by unmeasured covariates. In statistical terms, a frailty model is a random effect model for time to event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function. With recent advances in computing technology, Bayesian approaches to frailty models are now computationally feasible and several researchers have been developing Bayesian methodologies to analyse survival data with different frailty models. In this paper an attempt has been made to derive three survival models Proportional Hazard (PH), Accelerated Failure Time (AFT) and Proportional Odds (PO) model under frailty approach by using a parametric Weibull baseline hazard function in case of univariate survival data in context of Bayesian mechanism. The methodologies are applied to a real life survival data set and the analysis is performed using Markov Chain Monte Carlo simulation methods and model comparisons are also done using the deviance information criteria (DIC) and the log pseudo marginal likelihood (LPML) and check the fit of the models by using Cox-Snell residual plot.

Index Terms- Proportional Hazards(PH), Accelerated Failure Time(AFT), Proportional Odds(PO), Frailty model, Markov Chain Monte Carlo simulation methods, DIC, LPML, Cox-Snell residual plot.

1. Introduction:

Frailty models, a specific area in survival analysis provides a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data. Frailty is an unobserved random proportionality factor that modifies the hazard function of an individual, or of related individuals. In many survival data analysis it is impossible to measure all relevant covariates related to the disease of interest, sometimes because of economical reasons, sometimes the importance of some covariates is still unknown. The frailty approach is a statistical modeling concept which aims to account for heterogeneity, caused by unmeasured covariates. In statistical terms, a frailty model is a random effect model for time to event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function. With recent advances in computing technology, Bayesian approaches to frailty models are now computationally feasible and several researchers have been developing Bayesian methodologies to analyse survival data with different frailty models. The most popular type of frailty model is the proportional hazard frailty model. For example Aslanidou et al [1998], Sahu et al. [1997], Sahu and Day[2004] and Chen and Lio [2008], Ruktiari et al. [2014] use this model for multivariate case. Banerjee et al. [2003] ,Li and Lin[2006], and Zhou et al.[2015] are the examples of application of this model in case of spatially correlated data. Again Pan [2001] and Zhang and Lawson [2012] are the examples of application of Accelerated failure time frailty model. Banerjee and Day

[2005] also derived a multivariate Proportional Odds model under frailty approach in case of spatially correlated data. Zhou[2017] give an idea for derivation of different kinds of frailty models in case of spatial frailty models only.

So far our knowledge goes still there are some frailty models in survival analysis which are remained undiagnosed under Bayesian mechanism. In this paper an attempt has been made to derive such type of three survival models Proportional Hazard (PH), Accelerated Failure Time (AFT) and Proportional Odds (PO) model under univariate frailty approach together by using a parametric Weibull baseline hazard function in context of Bayesian mechanism. The methodologies are applied to a real life survival data set and the analysis is performed using Markov Chain Monte Carlo simulation methods and model comparisons are also done using the deviance information criteria (DIC) and the log pseudo marginal likelihood (LPML) and check the fit of the models by using Cox-Snell residual plot.

2. Frailty Models Under Consideration:

In case of Proportional Hazard (PH) Frailty Model the hazard rate of an individual, survival function and the density is given by,

| $h(t) = h_0(t)e^{\beta' X + Z_i}$ | (2.1) |
|--|-------|
| $S(t) = S_0(t)^{e^{\beta' X + Z_i}}$ | (2.2) |
| $f(t) = e^{\beta' X + Z_i} S_0(t)^{e^{\beta' X + Z_i} - 1} f_0(t)$ | (2.3) |

In case of Accelerated Failure Time (AFT) Frailty Model the hazard rate of an individual, survival function and the density is given by,

$$h(t) = h_0(e^{\beta' X + Z_i}t)e^{\beta' X + Z_i}$$
(2.4)

$$S(t) = S_0(e^{\beta' X + Z_i}t)$$
(2.5)

$$f(t) = e^{\beta' X + Z_i}f_0(e^{\beta' X + Z_i}t)$$
(2.6)

In case of Proportional Odds (PO) Frailty Model the hazard rate of an individual, survival function and the density is given by,

$$h(t) = h_0 \frac{1}{1 + \{e^{-(\beta' X + Z_i)} - 1\}S_0(t)}$$
(2.7)

$$S(t) = \frac{e^{-(\beta' X + Z_i)} S_0(t)}{1 + \{e^{-(\beta' X + Z_i)} - 1\} S_0(t)}$$
(2.8)

$$f(t) = \frac{e^{-(\beta' X + Z_i)} f_0(t)}{\left[1 + \left\{e^{-(\beta' X + Z_i)} - 1\right\} S_0(t)\right]^2}$$
(2.9)

Where X is the vector of observed covariates and $\beta = (\beta_1, \beta_2, ..., \beta_p)^{\prime}$ is a vector of regression parameters to be estimated, Z_i is an unobserved frailty for the *i*th individual, $S_0(t)$, $f_0(t)$ and $h_0(t)$ are the baseline survival function, baseline density and baseline hazard function assumed to be unique for all individuals in the study population respectively.

3. Hazard Function Modeling:

In this paper for all the three frailty models a Weibull distribution with parameter μ and γ is considered for modeling the baseline hazard function. The second parameter γ allows great flexibility to the model and different shapes of the hazard function. The respective baseline hazard function, survival function and the density in case of Weibull distribution is given by,

$$h(t) = \mu \gamma t^{\gamma - 1} \tag{3.1}$$

$$S(t) = e^{-\mu t^{\gamma}} \tag{3.2}$$

$$f(t) = \mu \gamma t^{\gamma - 1} e^{-\mu t^{\gamma}}, \, \mu > 0, \, \gamma > 0 \quad (3.3)$$

4. Model Specification: 4.1 Likelihood Specification:

Let us consider right censored survival data (t_i, δ_i) , i=1,2,...,n and assume that the censoring is non informative. Let δ_i be the indicator variable taking value 1 if the *i*th individual fails (or happening of the event) and value 0 otherwise. Hence t_i is a failure if $\delta_i=1$ and it is a censoring time if $\delta_i=0$. Hence the triplet (t_i, δ_i, x_i) , i=1,2,...,n is observed for all n individuals. Given the unobserved frailty z_i , t_i 's are independent. Hence the complete data likelihoods for Proportional Hazard (PH), Accelerated Failure Time (AFT) and Proportional Odds (PO) model under frailty approach are given by,

$$L_{PHFM} = \prod_{i=1}^{n} \left[\mu \gamma t_{i}^{\gamma-1} e^{\beta' X + Z_{i}} \right]^{\delta_{i}} e^{-\mu t^{\gamma}} e^{\beta' X + Z_{i}}$$
(4.1.1)
$$L_{AFTFM} = \prod_{i=1}^{n} \left[\mu \gamma (e^{\beta' X + Z_{i}} t_{i})^{\gamma-1} e^{\beta' X + Z_{i}} \right]^{\delta_{i}} e^{-\mu (e^{\beta' X + Z_{i}} t_{i})^{\gamma}}$$
(4.1.2)
$$L_{POFM} = \prod_{i=1}^{n} \left[\mu \gamma t_{i}^{\gamma-1} \frac{1}{1 + \{e^{-(\beta' X + Z_{i})} - 1\}e^{-\mu t_{i}^{\gamma}}} \right]^{\delta_{i}} \frac{e^{-(\beta' X + Z_{i})} e^{-\mu t_{i}^{\gamma}}}{1 + \{e^{-(\beta' X + Z_{i})} - 1\}e^{-\mu t_{i}^{\gamma}}}$$
(4.1.3)

4.2 Frailty Distribution:

In case of frailty models the most important thing to assign a appropriate probability distribution to the frailty variable. Several researchers used different distributions for this purpose. But the most common distribution among them is the Gamma distribution. Gamma is the most commonly used finite mean distribution to model the frailty term in frequentist as well as in Bayesian Analysis. Vaupel et al. [1979], Yashin and Iachine(1995), Oakes[1989], Winke [2003] are such kind of applications of gamma frailty models in case of frequentist analysis. Aslanidou et al. [1998], Sahu et al. [1997] use gamma prior for modeling the frailty variable in case of Bayesian analysis. Banerjee et al. [2003], Banerjee and Day [2005],Li and Lin[2006], Zhou et al.[2015],Zhang and Lawson[2012] are some application of nonparametric prior for the frailty variable in case of spatial frailty models. Sahu and Dey [2004] use a skewed distribution (log-skew-t) for modeling the

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frailty variable. Following the concept of using normal prior to frailty variable by Ruktiari et al.[2014] and Zhou[2017] in this paper a independent normal frailty prior is used, which can be defined as, $Z_i \sim N(0, \tau^2)$, for i=1,2,...,n. Then the density of the frailty variable Z is given by,

$$f(Z) = \frac{1}{\tau \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{Z}{\tau}\right)^2}; -\infty < Z < \infty, \ \tau > 0.....(4.2.1)$$

4.3 Prior Specification:

Considering wide acceptability of gamma distribution as a conjugate prior in Bayesian statistics and it is the conjugate prior for the precision (i.e, inverse of the variance) of a normal distribution. So here a gamma prior is considered for τ i.e, $\tau^{-2} \sim Gamma(a_{\tau}, b_{\tau})$. Following Sahu et al. [1997], Sahu and Dey [2004], Zhou et al.[2017] a normal prior for the regression parameters are considered here which is given by $\beta \sim N(0, m)$. For the hyper parameters of the baseline hazard function a gamma prior is assumed here due to its simplicity and flexibility [Sahu et al., 1997]. Here it is assumed that $\mu \sim \text{Gamma}(\rho, \rho)$ and $\gamma \sim \text{Gamma}(a, b)$.

4.4 Posterior Calculation:

The joint posterior distribution for all the parameters of the three models are given by,

$$P_{PHFM} = \prod_{i=1}^{n} \left[\mu \gamma t_{i}^{\gamma-1} e^{\beta' X + Z_{i}} \right]^{\delta_{i}} e^{-\mu t^{\gamma}} e^{\beta' X + Z_{i}} \pi(z) \pi(\mu) \pi(\gamma) \pi(\beta) \pi(\tau^{2})$$
(4.3.1)

$$P_{AFTFM} = \prod_{i=1}^{n} \left[\mu \gamma (e^{\beta' X + Z_{i}} t_{i})^{\gamma-1} e^{\beta' X + Z_{i}} \right]^{\delta_{i}} e^{-\mu (e^{\beta' X + Z_{i}} t_{i})^{\gamma}} \pi(z) \pi(\mu) \pi(\gamma) \pi(\beta) \pi(\tau^{2})$$
(4.3.2)

$$P_{POFM} = \prod_{i=1}^{n} \left[\mu \gamma t_{i}^{\gamma-1} \frac{1}{1 + \{e^{-(\beta' X + Z_{i})} - 1\} e^{-\mu t_{i}^{\gamma}}} \right]^{\delta_{i}} \frac{e^{-(\beta' X + Z_{i})} e^{-\mu t_{i}^{\gamma}}}{1 + \{e^{-(\beta' X + Z_{i})} - 1\} e^{-\mu t_{i}^{\gamma}}} \pi(z) \pi(\mu) \pi(\gamma) \pi(\beta) \pi(\tau^{2})$$
(4.3.3)

 π (.) be the respective prior distributions.

To get the data likelihood of the various parameters we have to integrate out the z_i 's with the independent Normal prior density given in section 4.2. The final forms of the data likelihoods after integration are too complicated to work with. Thus, it is not easy to evaluate the marginal posterior distributions analytically. To overcome this difficulty we have to use Metropolis-Hastings algorithm (Hastings [1970]) and Gibbs sampling (Geman and Geman [1984]) to generate samples from the appropriate marginal posterior distributions. Metropolis-Hastings algorithm and Gibbs sampling or a Gibbs sampler is a Markov chain Monte Carlo (MCMC) algorithm for obtaining a sequence of observations which are approximated from a specified multivariate probability distribution, when direct sampling is difficult.

5. An Example Using a Real Life Data Set:

In this paper we consider a real life survival data set of 38 kidney patients on dialysis used by McGilchrist and Aisbett [1991]. Originally the data set is recorded for time to first and second time of infection from the time of insertion of the catheter for 38 kidney patients using portable dialysis equipment. Age and sex of the patients along with the presence or absence of three disease type GN, AN, PKD are considered as the covariates of the model. Since we want to fit three univariate frailty models, so we take only the first time of infection of the catheter for 38 kidney patients along with the covariates from this data set.

Using this data set we have done the Bayesian Analysis of the three frailty models mentioned in section 2 with the hazard function modeling and prior specification given in section 3, 4.2 and 4.3 with the help of the R Software. In case of $e^{\beta' X + Z_i}$, $\beta = (\beta_{Age}, \beta_{Sex}, \beta_{GN}, \beta_{AN}, \beta_{PKD})'$ and we consider Sex_{*i*} =1, if the *i*th patient is a female and 0 otherwise. For the disease types GN, AN and PKD, GN_{*i*}/AN_{*i*},/PKD_{*i*}=1, if the *i*th patient have the disease and 0 otherwise.

The MCMC is carried out through an empirical Bayesian approach coupled with adaptive Metropoli samplers (Haario, Saksman and Tamminen [2001]). The following hyper-parameter values were used in the simulation. Here we take τ = 1 and a_{τ} = b_{τ} =1, ρ =0.001, a=0.001, b=0.001 and m=1. In case of Bayesian analysis sometimes it was difficult to sample from the resulting full conditional distribution due to computer underflow problems for different hyper-parameter initial values. Sometimes it is observed that Bayesian inference was largely insensitive to change in the values of the hyper-parameter. For example we have experimented with many combinations of values of hyper-parameters and in case of frailty variance we observe slight difference in the posterior inference of the parameters with the chance of the values. In case of the baseline hazard parameters no difference is observed with the change in the values of hyper-parameters.

5.1 Posterior Inferences:

From the above analysis we have found the posterior inferences about the parameters of the model. Here the Table 5.1.1 and Table 5.1.2 shows the posterior mean, median, standard deviation and 95% credible intervals for the regression Coefficients and the frailty variance respectively.

| Models | Regression | Mean | Median | Standard | 95% | 95% |
|---------------------|--------------|-----------|-------------------------|-----------|-----------|-----------|
| | Coefficients | | | Deviation | CI-Low | CI- Upper |
| | coefficients | | | | de la | |
| Proportional Hazard | Age | 0.009465 | 0.00 <mark>7804</mark> | 0.048606 | -0.068724 | 0.145046 |
| (PH) Frailty Model | Sex | -5.381640 | -5.54 <mark>5902</mark> | 1.679589 | -8.244297 | -2.025221 |
| | GN | 0.812252 | 0.977403 | 1.812685 | -3.993665 | 3.633916 |
| | AN | 2.245244 | 2.538451 | 1.628249 | -0.701468 | 5.181663 |
| | PKD | -2.925890 | -2.618289 | 2.782097 | -9.172584 | 2.090695 |
| Accelerated Failure | Age | 0.006096 | 0.005573 | 0.015163 | -0.019177 | 0.036585 |
| Time(AFT)Frailty | Sex | -2.258404 | -2.236451 | 0.440493 | -3.141119 | -1.375095 |
| Model | GN | 0.294523 | 0.331070 | 0.532782 | -0.805537 | 1.294589 |
| | AN | 0.777479 | 0.818338 | 0.589770 | -0.408553 | 1.786184 |
| | PKD | -1.368258 | -1.357560 | 0.823350 | -2.955395 | 0.133405 |
| Proportional | Age | 0.03133 | 0.02139 | 0.04895 | -0.03855 | 0.16473 |
| Odds(PO) Frailty | Sex | -4.79608 | -4.26527 | 2.46778 | -12.13458 | -1.56937 |
| Model | GN | 1.26692 | 1.10061 | 1.81999 | -1.81894 | 5.44217 |
| | AN | 2.32632 | 2.05825 | 1.87586 | -0.89624 | 7.41276 |
| | PKD | -2.25715 | -2.09603 | 2.34799 | -7.47483 | 1.42720 |

The analysis reveals that in case all the three fitted models β_{sex} shows the female patients have a slightly lower risk for infection. Also β_{PKD} shows that the presence of this disease has a lower impact on infection of the catheter.

| Models | Mean | Median | Standard | 95% | 95% |
|--------------------------------------|----------|----------|-----------|---------------|-----------|
| | | | Deviation | CI-Low | CI- Upper |
| Proportional Hazard (PH) Frailty | 9.910 | 9.259 | 3.792 | 4.487 | 19.384 |
| Model | | | | | |
| Accelerated Failure Time(AFT)Frailty | 0.302771 | 0.101034 | 0.414540 | 0.001129 | 1.425962 |
| Model | | | | | |
| Proportional Odds(PO) Frailty Model | 8.96182 | 3.93703 | 14.24595 | 0.01203 | 50.39084 |

Table 5.1.2: Posterior Inference of Frailty Variance

The estimates of frailty variance from different models shows that there is a strong posterior evidence of high degree of heterogeneity in the population of patients. Some patients are exposed to be very prone to infection compared to others.

Fig 5.1.1, Fig 5.1.2 and Fig 5.1.3 shows the trace plots of the parameters for different fitted models.







Fig 5.1.2: Trace plots for the Regression coefficients and Frailty variance for the Accelerated Failure Time (AFT) Frailty Model







Fig 5.1.4, Fig 5.1.5 and Fig 5.1.6 shows the Posterior Density Plots of the Parameters for Different fitted models.

Fig 5.1.4: Posterior Density plots of Regression coefficients and Frailty variance for Proportional Hazard (PH) Frailty Model



Fig 5.1.5: Posterior Density plots of Regression coefficients and Frailty variance for Accelerated Failure Time (AFT) Frailty Model



Fig 5.1.6: Posterior Density plots of Regression coefficients and Frailty variance for Proportional Odds (PO) Frailty Model

5.2 Model Diagnostics:

After the model fitting the first job of us to check the goodness of fit of the models. Because model fitting is just based on certain assumptions. Here we have to take the help of some Regression diagnostics procedures which are employed to evaluate the model assumptions and investigate whether or not there are observations with a large, undue influence on the analysis. In regression analysis residuals have a very powerful impact on diagnostic checking procedures. In case of survival analysis, where most of the time we facing with the problem of censored data we must take some special treatments to the residuals of censored observations. The idea of one such kind of residual plot was given by Cox and Snell[1968], a plot of estimated cumulative hazard function (based on Cox and Snell residual and the censored data) versus the Cox and Snell residual. Which check the overall goodness of fit in survival models. We evaluate the presumed relation of unit exponentially distributed residuals for a good model fit and evaluate under some violations of the model assumption. This is done graphically with the usual graphs of Cox-Snell residual and formally using Kolmogorov-Smirnov goodness of fit test. It is observed that residuals from a correctly fitted model follow unit exponential distribution. For the above three fitted frailty models the Cox-Snell plots are given are in Fig 5.2.1 through Fig 5.2.3 from which it can be seen that the data fits the proposed models quite good and they are competing.



Here by simple observation it is seen that the entire plot follow some same kind of pattern. And in case of the plot of AFTFM the Nelson–Aalen curve (black curve) is closer to the standard exponential curve as compared to the other two plots. But we cannot get a clear picture from this. From this we can only say that the fit of all the models are good but to get a better idea about the best fitted models we have to take the help of some model choice criteria.

5.3 Model Comparison:

In case of Bayesian survival modes two popular model choice criteria are deviance information criteria (DIC)[Spiegelhalteret al., (2002)] and log pseudo marginal likelihood (LPML) (Geisser and Eddy (1979)]. DIC is the generalization of the AIC and BIC and is particularly useful in Bayesian model selection problems where the posterior distributions of the models have been obtained by MCMC simulation. The idea behind DIC is that we have to select the model with the smaller value as the best fitted model, which give us an idea about the relative quality of model filling. But in case of LPML the complete opposite idea is taken. If a model have larger LPML value then we consider it as the better one as compare to the other having smaller LPML value. LPML focuses on the predictive performance of a model. For the above three fitted frailty models the obtained LPML and DIC are given in table 5.3.1.

| Models | Log Pseudo Marginal | Deviance Information | | | |
|--|---------------------|-----------------------------|--|--|--|
| | Likelihood: LPML | Criterion: DIC | | | |
| Proportional Hazard (PH) Frailty Model | 1146.134 | -3649.859 | | | |
| Accelerated Failure Time (AFT) Frailty | -180.0368 | 350.8143 | | | |
| Model | | | | | |
| Proportional Odds (PO) Frailty Model | -180.786 | 352.7812 | | | |
| | | | | | |

Table 5.3.1: LMPL and DIC for different models

Although Cox-Snell plots show that the AFT frailty model has a good fit among the three fitted models but from the calculated DIC and LPML a different scenario was observed. From table5.3.1 it is observed that the Proportional Hazard (PH) Frailty Model with Weibull Hazard has a largest LMPL and Smallest DIC among all the three fitted models. So in case of the above analysis we can say that Proportional Hazard (PH) Frailty Model with Weibull Hazard is the best fitted model.

6. Concluding Remarks:

In this paper, three survival models Proportional Hazard (PH), Accelerated Failure Time (AFT) and Proportional Odds (PO) model are considered under frailty approach by using a parametric Weibull baseline hazard function in case of univariate survival data in context of Bayesian mechanism. Latter the models are fitted by a real life survival data set and diagnostics checking and model comparisons are also done here by using Cox-Snell plot, LMPL and DIC. From the above study we have found that the Proportional Hazard (PH) Frailty Model with Weibull Hazard is the better model than the other two proposed models.

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