CHAPTER-5

A BAYSIAN ESTIMATION APPROACH TO PROPORTIONAL HAZARD MODELS FOR COVARIATES AND INSTITUTIONAL EFFECTS

50 INTRODUCTION

Institutional variation is an important factor to examine in a randomized clinical trials. In randomized clinical trials for comparing treatments for disease such as cancer, it is sometimes necessary to include patients from different institutions to compare the sample size in a reasonable period of time. One of the reasons to examine institutional variations is that the objective of clinical trial is to try to draw conclusion about the overall effect of therapy in the population. Since the institutions are not selected at random and only a small random subset of the patients are entered on trials with substitutional institutional variation it would not be clear exactly what effect would be seen in the general population. Another reason to examine institutional variation is that it might be possible to learn more about how the therapy should be given or to whom it should be given. There are several
papers which deals with affect of institutions in clinical trials. S'ane and Weisfield (1990) use the same type of hierarchical Bayesian structure to model data from multi center binary response trials. Boos and Brownie (1992) proposed rank based methods for analysing data from multi center trials with continuous or order categorical outcomes with a linear model structure.

Burgl and Greenhouse (1992) developed hierarchical Bayesian survival model for examining institutional differences. Grey (1994) considered a Bayesian analysis of institutional effects in a multi center cancer clinical trial. The structure of their model is quite different from the proportional hazard model used here.

51 BAYSIAN MODEL

A proportional hazard model is assumed for institutional effects and covariates. Let $x_{ik}$ be covariate $k$ for subject $i$ from institution $1$.

Let us assume that there are $N$ institutions with $r_i$ cases/patients from institution $i$ and $(p-1)$ covariates with $p-1$ as treatment variables.

Let $0 < t_0 < t_1 < \cdots < t_m$ be the boundaries of time intervals and set $I_i(t) = I(t_{i-1} < t \leq t_i)$. 

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The full hazard model for subject \( i \) can be written as

\[
\log h(t | \xi_i, \alpha, \beta, \theta) = \sum_{l=1}^{m} \alpha_l I_l(t) + \sum_{k=1}^{p} \gamma_k \beta_k + \Theta \gamma_{lp} \tag{5.2}
\]

where

\[
\alpha = \begin{pmatrix} \alpha_1 \\ \alpha_2 \\ \vdots \\ \alpha_m \end{pmatrix}, \quad \beta = \begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{pmatrix}, \quad \theta = \begin{pmatrix} \theta_{0l} \\ \theta_{1l} \end{pmatrix}
\]

are unknown parameters.

\[
\gamma = \begin{pmatrix} \gamma_{11} \\ \gamma_{12} \\ \cdots \\ \gamma_{1p} \end{pmatrix}
\]

\( \theta_{0l} \) are the institutional deviations from an overall underlying log hazards \( \sum_{l=1}^{m} \alpha_l I_l(t) \).

\( \gamma_{1i} \) is the deviation in the \( i \)th institution from overall effect \( \beta_i \).

Let us consider four covariates \( x_1, x_2, x_3 \) and \( x_4 \).

where \( x_1 \) : performance status

\( x_2 \) : months from diagnosis

\( x_3 \) : age in years

\( x_4 \) : prior therapy
\[
\log h(t; \alpha_l, \beta_l, \theta_l) = \sum_{i=1}^{m} \alpha_l^i t_i^{\alpha_l} + \theta_l^{+} t_i^{\beta_l} + \theta_l^{-} t_i^{\beta_l}, \ldots \ldots (5.3)
\]

Let us assume the following prior for the model given above \( \beta_l \) follows double exponential distribution or Laplace distribution with probability density function

\[
g(\beta_l) = \frac{1}{2} e^{-|\beta_l|}; \quad -\omega < \beta < \omega
\]

Let \( \theta_l \) is independent and identically multivariate normally distributed with mean zero and variance unity.

\[
\theta_l \sim N(0, I)
\]

\[
g(\theta_l) = \frac{1}{\sqrt{2\pi}} e^{-\theta_l^2/2}
\]

\[
\alpha_l - \alpha_{l-1} | v \sim N(0, v^{-1}) \quad l = 1, 2, \ldots, m
\]

and

\[
v \sim \Gamma (\mu, \lambda)
\]

i.e.,

\[
g(v) = \frac{\mu^\mu}{\Gamma(\mu)} e^{-\lambda v} v^{\mu-1}; \quad v \geq 0
\]

The prior for \( \alpha \) restricts the magnitude of the jump between adjacent intervals in a piece-wise constant model.

Let \( \delta_{l} = \)

\[
\begin{cases} 
1 & \text{if subject } (i, j) \text{ is observed to fail in time interval } l \\
0 & \text{otherwise}
\end{cases}
\]

Let \( T_{l} \) if the failure or censoring time - \( t_{l-1} \). The likelihood function corresponding to this model is given by
\[ L(\alpha, \beta, \theta) = \prod_{i=1}^{N} L_i(\alpha, \beta, \theta) \]

\[ = \prod_{i=1}^{N} \prod_{j=1}^{n_i} h(t|\gamma_{ij}, \alpha, \beta, \theta) \exp \left( -\int_{0}^{t_{ij}} h(t|\gamma_{ij}, \alpha, \beta, \theta) \, dt \right) \]

\[ = \prod_{i=1}^{N} \prod_{j=1}^{n_i} \left[ \sum_{m=1}^{M} \delta_{ijl} \eta_{ijl} e^{-t_{ijl} e^{\eta_{ijl}}} \right] \]

\[ = \prod_{i=1}^{N} \exp \left[ \delta_{ijl} \eta_{ijl} - T_{ijl} \eta_{ijl} \right] \]

\[ \text{where } \eta_{ijl} = \alpha + \beta + \gamma_{ijl} \beta + \gamma_{ij2} \beta + \gamma_{ij3} \beta + (\beta + \gamma_{ij4} \beta \cdots (5.4) \]

The joint posterior is then proportional to

\[ \left[ \prod_{i=1}^{N} L_i(\alpha, \beta, \theta) \right] g(\alpha|\gamma) g(\beta) \]

\[ \text{where } g(\cdot) \text{ function are is the prior densities. This is not} \]

\[ \text{easy to compute directly but it is possible to generate} \]

\[ \text{samples from the joint posterior using Gibbs sampling. In} \]

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Gibbs sampling observations are generated from the joint posterior distribution by sampling from full conditional distributions. See Gelfand and Smith (1990), Gelfand et al (1990), Zejer and Harim (1991) and Clayton (1991).

The parameters that are require to specify the prior densities are \( \lambda \) and \( \mu \) in the prior for \( v \). Proper priors are used but the parameters are chosen to keep the priors fairly weak. For institutional effects this justified since there is little prior information on the magnitude of these parameters for the prior \( v \). It is noted that \( 1/v \) is the variance of jumps in the log-underlying hazards at the boundaries of the time intervals. The question of the magnitude of survival difference can also be addressed using predictive distributions. The survival curve for the predictive distribution for a new case from institution 1 is given by the integral of

\[
\ell(t) = e^{-\int_0^t h(x|x_{ij},\alpha_j,\beta_1,\theta) du}
\]

over the posterior distribution where \( h(.) \) is given by (5.1) with Gibbs sampling, the integral over the posterior is calculated by averaging over the generated parameter value.

Data analysis has not been done because of non-availability of data.
CONCLUSION

This chapter deals with a Bayesian estimation procedure for study the amount of institutional variation in a multicentre clinical trial using proportional hazard models. A hierarchical structure is used with prior for covariates coefficients as double exponential distribution and prior for institutional deviations $\theta_i$ as standard multivariate normal density with mean vector zero and variance-covariance matrix $I$. The prior for $\alpha$ restricts the magnitude of the jump between adjacent intervals $\alpha_i - \alpha_{i-1}$ is iid normal variate with variance $1/\nu$. Further the prior for $\nu$ is a Gamma distribution with parameter $\mu$ and $\lambda$. The posterior distribution calculated using Gibbs sampling. The methods can not be applied to data from Lung Cancer trial because non-availability of data. This study can be proceeded further by applying it to Lung Cancer trial data. We can predict that there appears substantial variation in the treatment effect across institutions. Although the reason for this have not been identified. It would be possible to investigate this further through a detailed examination of the data from the institutions with extreme effects.