Analysis of Censored Data
IMS Lecture Notes – Monograph Series (1995) Volume 27

Competing Risks In Bioassay : A Nonparametric Bayesian Approach*

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Abstract

We extend the well known bioassay formulation to allow two competing risks at each dose level / stress level. The non-parametric Bayesian analysis is based on two cumulative incidence functions. After suggesting a suitable prior distribution we derive the exact posterior means for any finite number of stress levels in case of competing risks bioassay. Incidentally, exact posterior means in the usual bioassay problem can also be given on the same lines without much difficulty. Sampling based approaches to approximate marginal posterior distributions and their interesting features are also illustrated. A useful modification in the prior distribution which treats the case of ordered cumulative incidence functions is presented. Illustrative examples are provided.

1 Introduction

Suppose $0 = s_0 < s_1 < ... < s_k < s_{k+1} = \infty$ are the k dose or stress levels in a bioassay problem. The potency p_i which is the probability of the desired response (death/ failure etc.) of the stimulus when the i-th dose level s_i is administered to the subject is given by $F(s_i)$, the value of the potency curve F at s_i. Here F is assumed to be an appropriate distribution function with $F(0) = 0$ and $F(\infty) = 1$. In many situations, the subject shows one of several possible responses or none at all. This situation may be observed when the stimulus or stress leads to death due to a particular risk out of several possible competing risks. In the usual analysis concerning accelerated testing the emphasis is on discovering a relationship between the stress levels and the probability of failure. If there are competing failure modes then there would be interest in estimating and comparing the probabilities of failure at

*AMS 1991 subject classification: Primary 62G99, Secondary 62F15.
Key Words and Phrases: Dirichlet Distribution; Gibbs Sampling; Incidence Function; Potency Curve; Sampling / Importance Resampling.

each stress level of the various modes of failure. The methodology proposed in this paper would be useful in this situation.

We have a concrete example from automobile industry which is not directly from accelerated testing. Three models of cars are manufactured by a company and sold. They are subject to a warranty for 18 months. When a fault is discovered within this period, the cars come back to the dealers who notify the manufacturer. We regard the time periods 3 months, 6 months, ..., 18 months as the stress levels $s_i, i = 1, 2, ..., 6$. Then $p_i = F(s_i)$ is the probability that the fault is, in a particular component, discovered up to time s_i. This particular component has two possible modes of failure, $p_{1i} = F_1^*(s_i)$ and $p_{2i} = F_2^*(s_i)$ with $p_i = p_{1i} + p_{2i}$, being the probabilities of failure due to these modes of failure respectively up to time s_i. See Shaked and Singpurwalla (1990) for such modelling when the failure is due to only one risk. It is clear that F_1^* and F_2^* are two sub-distribution functions with $F_1^* + F_2^*$ yielding a distribution function, F, which is the potency curve corresponding to total failure. The restrictions on the parameters p_{ji}, $i = 1, ..., k$ and $j = 1, 2$ then give the parametric space,

$$\begin{aligned} S^{(2k+1)} &= \{0 \leq p_{j1} \leq ... \leq p_{jk} \leq p_{jk+1} \leq 1; j = 1, 2; \\ &\quad p_{1k+1} + p_{2k+1} = 1\} \end{aligned} \tag{1}$$

Here $p_{jk+1} = F_j^*(\infty)$ and $F_1^*(\infty) + F_2^*(\infty) = F(\infty) = 1$. It means that at dose level ∞, a subject certainly fails due to either of the two risks.

At first glance this model may seem to be similar to the polychotomous response model described by Gelfand and Kuo (1991). But there are major differences. Their model is applicable when there are two responses say A and B such that $A \subset B$, that is the occurrence of A implies the occurrence of B, whereas we consider two mutually exclusive responses. Their model applies to the situations where A may represent acute manifestation of some disease and B the mild manifestation of the same disease. Thus the subject proceeds from the state B to the state A, hence they have certain different conditions on the probabilities of the responses to the stimulus.

To formalize the problem let us suppose that n_i subjects are given the i-th dose level s_i. Let $(X_{1i}, X_{2i}, n_i - X_{1i} - X_{2i})$ be the vector of observations at the i-th level, representing the response of the first type, the second type and no response respectively, having multinomial distribution with parameters $(n_i, p_{1i}, p_{2i}, 1 - p_{1i} - p_{2i})$. Thus the joint probability distribution of all the k vectors $(i = 1, 2, ..., k)$ will be the product multinomial distribution. As in bioassay, we assign a single Dirichlet prior distribution to the successive differences of p_{1i}'s and p_{2i}'s subject to the prior constraints (1). The Gelfand and Kuo (1991) prior, on the other hand, is based on the product of two Dirichlet distributions. Our prior distribution and the corresponding posterior distributions are naturally suitable to the sub- distribution functions describing the two potency curves. After describing the posterior distribution, we derive exact posterior means of p_{ji}'s. For convenience of reading, the derivation of the exact posterior means is in an appendix. As an additional bonus we are able to provide the exact posterior means in the bioassay formulation as the linear combination of means of beta distributions. Antoniak (1974) has expressed the posterior density as a mixture of the Dirichlet distributions for the two stress levels leading to posterior means as linear combinations of means of Dirichlet distributions. Though his result can easily be theoretically extended to any number of stress levels, Gelfend and Kuo (1991) have commented that the means become extremely complicated even for as small a number of levels as 4 or 5, giving reference of the unpublished Ph.D. thesis of M. N. Wesley. Our treatment is amenable to any number of levels and explicit computations are not too difficult. Other features of the distribution, viz. the mode, the quantiles, etc. are elusive. We emulate Shaked and Singpurwalla (1990), Gelfend and Kuo (1991) and Ramgopal, Laud and Smith (1993) and suggest the use of the Markov chain Monte Carlo technique (Gibbs sampling) to estimate these feature of the posterior distribution. We consider the example introduced above which was encountered by us during industrial interaction which is modelled through the competing risks bioassay formulation of this paper.

In the end we also consider the problem where the prior information includes the constraints that $p_{1i} \leq p_{2i}, i = 1, 2, ..., k$, that is to say, at each of the k dose levels the response of type I is more likely to occur than the response of type II . It should be remarked that we still do not contemplate the nested type of response ($A \subset B$) as considered by Gelfend and Kuo (1991). To the best of our knowledge, competing risks in bioassay are introduced formally for the first time here.

2 Formulation and Inference for the Competing Risks Bioassay Model

The likelihood of response probabilities in the framework described in the first section is given by

$$\ell(\underline{p}; \underline{x}, \underline{n}) = \prod_{i=1}^{k} \frac{n_i!}{x_{1i}! x_{2i}! (n_i - x_{1i} - x_{2i})!} p_{1i}^{x_{1i}} p_{2i}^{x_{2i}} (1 - p_{1i} - p_{2i})^{n_i - x_{1i} - x_{2i}} \quad (2)$$

Define $Z_{ji} = p_{ji} - p_{ji-1}, i = 1, 2, ..., k+1$ and $j = 1, 2$. Note that $\sum_{j=1}^{2} \sum_{i=1}^{k+1} Z_{ji} = 1$. We assign the Dirichlet distribution with parameters $(\alpha_{11}, ..., \alpha_{1k+1}, \alpha_{21}, ..., \alpha_{2k+1})$, denoted as $\mathcal{D}(\underline{\alpha})$, to $(Z_{11}, ..., Z_{2k})$. Transforming back to p_{ji}'s, this gives the following prior density for $\underline{p}$,

$$\pi(\underline{p}) = \frac{\Gamma\alpha}{\prod_{i=1}^{k+1}\Gamma\alpha_{1i}\,\Gamma\alpha_{2i}}\prod_{i=1}^{k+1}(p_{1i}-p_{1i-1})^{\alpha_{1i}-1}(p_{2i}-p_{2i-1})^{\alpha_{2i}-1},\ \ \underline{p}\epsilon S^{(2k+1)}, \tag{3}$$

where $\alpha_{ji} > 0, i = 1,2,...,k, j = 1,2, \alpha_1 = \sum_{i=1}^{k+1}\alpha_{1i}, \alpha_2 = \sum_{i=1}^{k+1}\alpha_{2i}$ and $\alpha = \alpha_1 + \alpha_2$.

It can be easily seen that $\pi(\underline{p})$ is not a conjugate prior with respect to (2). Another way to obtain (2) is through specifying the conditional distributions of the generalized beta type.

$$\begin{aligned} p_{1k+1} &\sim beta(\alpha_1,\alpha_2;0,1), \\ (p_{1i} \mid p_{1k+1},...,p_{1i+1}) &\sim beta(\sum_{\ell=1}^{i}\alpha_{1\ell},\alpha_{1i+1};0,p_{1i+1}), \end{aligned} \tag{4}$$

and

$$(p_{2i} \mid p_{2k+1},...,p_{2i+1},p_{11},...,p_{1k+1}) \sim beta(\sum_{\ell=1}^{i}\alpha_{2\ell},\alpha_{2i+1};0,p_{2i+1})$$

where $U \sim beta(a,b;c,d)$ denotes that $U = c + (d-c)V$ where V is the $beta(a,b)$ variate. Before giving more formal treatment we note the following important points.

(1) For each i, the vector (p_{1i}, p_{2i}) has Dirichlet distribution with parameters $(\alpha_{1i}, \alpha_{2i}, \alpha - \alpha_{1i} - \alpha_{2i})$. Marginally for each multinomial trial also we have the Dirichlet prior.

(2) Note that, $\sum_{i=1}^{k+1} Z_{1i} = p_{1k+1}$ and $\sum_{i=1}^{k+1} Z_{2i} = p_{2k+1} = 1 - p_{1k+1}$, leading to the beta (α_1, α_2) distribution for p_{1k+1}.

(3) The conditional distribution of $(Z_{j1},...,Z_{jk+1})$ given p_{jk+1} is $\mathcal{D}\,(\alpha_{j1},\alpha_{j2},...,\alpha_{jk+1};\alpha_{3-j})$ where $0 \le Z_{ji} \le p_{jk+1}$ and $\sum_{i=1}^{k+1} Z_{ji} = p_{jk+1}, j = 1,2$.

The role of α_{ji}'s in the prior specification in (3) is clear from the conditional distributions described in (4).

The posterior density of $\underline{p}$ is then proportional to the product of (2) and (3).

$$\begin{aligned} \pi(\underline{p} \mid \underline{x},\underline{n}) \;\propto\; & c(\underline{x},\underline{n},\underline{\alpha})\prod_{i=1}^{k} p_{1i}^{x_{1i}}p_{2i}^{x_{2i}}(1-p_{1i}-p_{2i})^{x_{3i}} \\ & \prod_{i=1}^{k+1}(p_{1i}-p_{1i-1})^{\alpha_{1i}-1}(p_{2i}-p_{2i-1})^{\alpha_{2i}-1},\ \ \underline{p}\epsilon S^{(2k+1)} \end{aligned} \tag{5}$$

where

$$c(\underline{x}, \underline{n}, \underline{\alpha}) = \prod_{i=1}^{k} \frac{n_i!}{x_{1i}!x_{2i}!x_{3i}!} \cdot \frac{\Gamma\alpha}{\prod_{i=1}^{k+1} \Gamma\alpha_{1i}\Gamma\alpha_{2i}}$$

and $x_{3i} = n_i - x_{1i} - x_{2i}$. The immediate problem is that of estimation of p_{ji}'s. The posterior means, $E[p_{ji} \mid \underline{x}, \underline{n}]$ are Bayes estimates with respect to the squared error loss function and are thus reasonable estimators. Next, we obtain these posterior means. First we sketch the proof of the following theorem.

Theorem : The marginal posterior density of p_{1i} is a linear combination of beta densities and is given by,

$$\pi(p_{1i} \mid \underline{x}, \underline{n}) = \sum_{\underline{r}} \frac{w_1(\underline{x}, \underline{r}, \underline{\alpha})}{w_1(\underline{x}, ., \underline{\alpha})} g(p_{1i} \mid \nu_1(\underline{x}, \underline{r}, \underline{\alpha}), \nu_2(\underline{x}, \underline{r}, \underline{\alpha}); 0, 1) \tag{6}$$

where,

$$d(\underline{x}, \underline{r}, \underline{\alpha}) = (-1)^{\sum_1^k r_{2\ell}} \prod_{\ell=1}^{k} \binom{x_{2\ell}}{r_{2\ell}} \prod_{\ell=1}^{k} \beta(\sum_{m=1}^{\ell}(x_{2m} + \alpha_{2m} + r_{2m}), \alpha_{2\ell+1}),$$

$$w(\underline{x}, \underline{r}, \underline{\alpha}) = d(\underline{x}, \underline{r}, \underline{\alpha}) \prod_{\ell=1}^{i-1} \binom{x_{3\ell} - r_{2\ell}}{r_{1\ell}} \beta(\sum_{m=1}^{\ell}(x_{1m} + \alpha_{1m} + r_{1m}), \alpha_{1\ell+1})$$

$$(-1)^{\sum_{\ell \neq i} r_{1\ell}} \prod_{\ell=i+1}^{k} \beta(\alpha_{1\ell}, \sum_{m=\ell}^{k}(x_{3m} - r_{2m} + r_{1m}) + \beta_k + \sum_{m=\ell+1}^{k+1} \alpha_{1m}) \binom{x_{1\ell}}{r_{1\ell}},$$

$$w_1(\underline{x}, \underline{r}, \underline{\alpha}) = \beta(\nu_1(\underline{x}, \underline{r}, \underline{\alpha}); \nu_2(\underline{x}, \underline{r}, \underline{\alpha}))w(\underline{x}, \underline{r}, \underline{\alpha}),$$

$$w_1(\underline{x}, ., \underline{\alpha}) = \sum_{\underline{r}} w_1(\underline{x}, \underline{r}, \underline{\alpha}),$$

$$\nu_1(\underline{x}, \underline{r}, \underline{\alpha}) = x_{1i} + \sum_{1}^{i-1}(x_{1\ell} + \alpha_{1\ell} + r_{1\ell}) + \alpha_{1i}$$

and

$$\nu_2(\underline{x}, \underline{r}, \underline{\alpha}) = x_{3i} - r_{2i} + \sum_{\ell=i+1}^{k} (x_{3\ell} - r_{2\ell} + r_{1\ell} + \alpha_{1\ell}) + \beta_k + \alpha_{1k+1}.$$

The posterior mean of p_{1i} is,

$$E(p_{1i} \mid \underline{x}, \underline{n}) = \sum_{\underline{r}} \frac{w_1(\underline{x}, \underline{r}, \underline{\alpha})}{w_1(\underline{x}, ., \underline{\alpha})} \cdot \frac{\nu_1(\underline{x}, \underline{r}, \underline{\alpha})}{\nu_1(\underline{x}, \underline{r}, \underline{\alpha}) + \nu_2(\underline{x}, \underline{r}, \underline{\alpha})}. \tag{7}$$

Proof . See appendix.

Remarks

1. Note that there are no observations at the stress level infinity. $\pi(\underline{p})$ can be written as,

$$\pi(p_{11},...,p_{1k},p_{21},p_{22},...,p_{2k}).\pi(p_{1k+1} \mid p_{11},...,p_{2k}).$$

The conditional density of p_{1k+1} given remaining p_{1i}'s is

$$g(p_{1k+1} \mid \alpha_{1k+1},\alpha_{2k+1};p_{1k},1-p_{2k}).$$

This gives

$$\begin{aligned} E[p_{1k+1} \mid \underline{x}] &= E[p_{1k} + (1-p_{2k}-p_{1k})\frac{\alpha_{1k+1}}{\alpha_{1k+1}+\alpha_{2k+1}} \mid \underline{x}] \\ &= \frac{\alpha_{1k+1}}{\alpha_{1k+1}+\alpha_{2k+1}} + \frac{\alpha_{2k+1}}{\alpha_{1k+1}+\alpha_{2k+1}}E(p_{1k} \mid \underline{x}) \\ &- \frac{\alpha_{1k+1}}{\alpha_{1k+1}+\alpha_{2k+1}}E(p_{2k} \mid \underline{x}) \end{aligned} \tag{8}$$

2. Incidentally, similar calculations based on the posterior density of $\underline{p} = (p_1,...,p_k)$ with Dirichlet prior in the usual bioassay problem leads to the exact expression for the posterior means, $E(p_i \mid \underline{x}), i = 1,2,...,k$ which can be evaluated easily using a computer.

The joint density of $\underline{p}$ and $\underline{x}$ is the product of the likelihood function and the prior density and is given by,

$$h(\underline{p},\underline{x}) = \prod_{i=1}^{k}\binom{n_i}{x_i}p_i^{x_i}(1-p_i)^{n_i-x_i}\frac{\Gamma\alpha}{\prod_{i=1}^{k+1}\Gamma\alpha_i}\prod_{i=1}^{k+1}(p_i-p_{i-1})^{\alpha_i-1},$$

$$p_0 = 0 \le p_1 \le p_2 \le ... \le p_k \le 1 = p_{k+1}$$

where $\alpha = \sum_{i=1}^{k+1}\alpha_i$.

Then integrating out $p_j's, j \neq i$, gives

$$\begin{aligned} h(p_i,\underline{x}) &= c(\underline{n},\underline{x},\underline{\alpha})\sum_{\underline{r}} d_1(\underline{x},\underline{r},\underline{\alpha})p_i^{\sum_1^{i-1}(x_j+\alpha_j+r_j)+\alpha_i+x_i-1} \\ & (1-p_i)^{\eta_2(\underline{x},\underline{r},\underline{\alpha})-1}, 0 < p_i < 1, i = 1,2,...,k \end{aligned}$$

where,

$$\sum_{\underline{r}} \text{ denotes the multiple sums } \sum_{r_1=0}^{n_1-x_1}\sum_{r_2=0}^{n_2-x_2}\cdots\sum_{r_{i-1}=0}^{n_{i-1}-x_{i-1}}\sum_{r_{i+1}=0}^{x_{i+1}}\cdots\sum_{r_k=0}^{x_k},$$

$$d_1(\underline{x},\underline{r},\underline{\alpha}) = (-1)^{\Sigma r_j}\prod_{j=1}^{i-1}\binom{n_j-x_j}{r_j}\beta(\sum_{\ell=1}^{j}(x_\ell+\alpha_\ell+r_\ell),\alpha_{j+1})$$

$$\prod_{j=i+1}^{k} \begin{pmatrix} x_j \\ r_j \end{pmatrix} \beta(\alpha_j, \sum_{\ell=j}^{k}(n_\ell - x_\ell + r_\ell) + \sum_{\ell=j+1}^{k+1} \alpha_\ell),$$

$$c(\underline{n}, \underline{x}, \underline{\alpha}) = \prod_{i=1}^{k} \begin{pmatrix} n_i \\ x_i \end{pmatrix} \frac{\Gamma\alpha}{\prod_1^{k+1} \Gamma\alpha_i},$$

$$\eta_2(\underline{x}, \underline{r}, \underline{\alpha}) = n_i - x_i + \sum_{j=i+1}^{k} (n_j - x_j + r_j + \alpha_j) + \alpha_{k+1}.$$

Hence

$$E(p_i \mid \underline{x}) = \sum_{\underline{r}} \frac{w_2(\underline{x}, \underline{r}, \underline{\alpha})}{w_2(\underline{x}, ., \underline{\alpha})} \frac{\eta_1(\underline{x}, \underline{r}, \underline{\alpha})}{\eta_1(\underline{x}, \underline{r}, \underline{\alpha}) + \eta_2(\underline{x}, \underline{r}, \underline{\alpha})} \tag{9}$$

where,

$$w_2(\underline{x}, \underline{r}, \underline{\alpha}) = \beta(\eta_1(\underline{x}, \underline{r}, \underline{\alpha}), \eta_2(\underline{x}, \underline{r}, \underline{\alpha}))d_1(\underline{x}, \underline{r}, \underline{\alpha}),$$

$$w_2(\underline{x}, ., \underline{\alpha}) = \sum_{\underline{r}} w_2(\underline{x}, \underline{r}, \underline{\alpha}),$$

and

$$\eta_1(\underline{x}, \underline{r}, \underline{\alpha}) = \sum_{1}^{i-1}(x_j - \alpha_j + r_j) + \alpha_i + x_i.$$

Note that there is no restriction on k, the number of stress levels. One needs to evaluate $(k-1)$ summations to get the exact values for $E(p_i \mid \underline{x})$, unlike $k(k-1)$ as required by Antoniak (1974).

For any $s^* \epsilon [s_i, s_{i+1}]$, the estimate of $F(s^*)$ may be taken as,

$$E[F(s^*) \mid \underline{x}] = (\frac{\alpha_{i+1} - \alpha^*}{\alpha_{i+1}})E(p_i \mid \underline{x}) + \frac{\alpha^*}{\alpha_{i+1}} E(p_{i+1} \mid \underline{x})$$

which can also be evaluated using (9), where α^* is an additional parameter in the revised prior defined to include the parameter $F(s^*)$.

3. The posterior mode plays important role in Bayesian inference. Here, posterior mode, if it exists, is a $(2k+1)$ dimensional point $\hat{p} = (\hat{p}_{11}, ..., \hat{p}_{1k+1}, \hat{p}_{21}, ..., \hat{p}_{2k})$ which maximizes (5). Due to the constraints in the support, it is a difficult task to actually evaluate it even in case of the bioassay problem. We adopt the sampling based approach to approximate posterior marginal modes. (See Gelfand and Kuo (1991)).

3 Study of Posterior Density through Gibbs Sampler

First, we describe the Gibbs sampling approach for simulation from (5), the joint posterior density of $\underset{\sim}{p}$. For this, we need to specify the conditional densities for p_{ji} given $\underset{\sim}{x}, \underset{\sim}{n}$ and remaining $p_{j\ell}$'s up to the constant of proportionality, (Ramgopal et al. (1993)) which are

$$\pi(p_{ji} \mid \underset{\sim}{x}, p_{j\ell}, \ell \neq i, j = 1,2) \propto p_{ji}^{x_{ji}}(1 - p_{1i} - p_{2i})^{x_{3i}} I_{(p_{ji-1}, p_{ji+1})}(p_{ji}) \prod_{\ell=i-1}^{i} g(p_{j\ell} \mid \sum_{m=1}^{\ell} \alpha_{jm}, \alpha_{j\ell+1}; 0, p_{j\ell+1}), \tag{10}$$

$i = 1,2,...,k, j = 1,2.$

The conditional density of p_{1k+1} given $\underset{\sim}{x}$ and remaining p_{ji}'s is

$$g(p_{1k+1} \mid \alpha_{1k+1}, \alpha_{2k+1}; p_{1k}, 1 - p_{2k}) \tag{11}$$

as described in Remark 1. Given an arbitrary starting value, a long sequence of iterations of successive random variable generations from (10) and (11) results in realizations $(p_{11}, ..., p_{1k+1}, p_{21}, ..., p_{2k})$ which are close to being drawn from (5). Replication of this process then provides a sample from the joint posterior, which can be used as a basis for drawing inferences. What remains is the generation of $p_{ji}, i = 1,2,...,k+1, j = 1,2$ from (10) and (11). We adopt the Sampling/Importance Resampling (SIR) technique (Smith and Gelfand (1992)), which is a convenient method for the densities of the type (10) and (11). We describe SIR briefly below.

Step - 1. Generate $p_{ji}^1, p_{ji}^2, ..., p_{ji}^N$ respectively from the $beta(x_{ji}+1, n_i - x_{1i} - x_{2i} + 1)$ distribution truncated to (p_{ji-1}, p_{ji+1}) for suitable N. (Devroye (1986)).

Step - 2. Evaluate

$$q_m = \frac{\prod_{\ell=i-1}^{i} g(p_{j\ell}^m \mid \sum_{r=1}^{\ell} \alpha_{jr}, \alpha_{j\ell+1}; 0, p_{j\ell+1})}{\sum_{m=1}^{N}(\prod_{\ell=i-1}^{i} g(p_{j\ell}^m \mid \sum_{r=1}^{\ell} \alpha_{jr}, \alpha_{j\ell+1}; 0, p_{j\ell+1}))}, m = 1,2,...,N$$

Step - 3. Sample one of p_{ji}^m's, $m = 1,2,...,N$ using $\{q_1, ..., q_N\}$ distribution.

Finally, the sampled p_{ji}'s can be treated as from the conditional distribution (10) and (11) for large enough N.

4 Ordered Incidence Function

We now consider the prior specification for $\underset{\sim}{p}$, when it is known a priori that the first cumulative incidence function lies below the other, that is, $F_1^*(s) \leq F_2^*(s)$ for all s with strict inequality for some s.

These prior constraints on $\underline{p}$ give the parametric space,

$$\begin{aligned} S_1^{(2k+1)} &= \{\underline{p} \mid 0 < p_{j1} \leq p_{j2} \leq \ldots \leq p_{jk} \leq p_{jk+1} < 1, j = 1,2, \\ &\quad p_{1i} \leq p_{2i}, \;\; i = 1,2,\ldots,k+1, \;\; p_{1k+1} + p_{2k+1} = 1\}. \end{aligned}$$

Modifying the conditional densities given by (4) we obtain the prior appropriate for $\underline{p} \in S_1^{(2k+1)}$.

$$p_{1k+1} \sim beta(\alpha_1, \alpha_2; 0, 1),$$

$$(p_{1i} \mid p_{1k+1}, \ldots, p_{1i+1}) \sim beta(\sum_{\ell=1}^{i} \alpha_{1\ell}, \alpha_{1i+1}; 0, p_{1i+1}), \tag{12}$$

and

$$(p_{2i} \mid p_{2k+1}, \ldots, p_{2i+1}, p_{11}, \ldots, p_{1k+1}) \sim beta(\sum_{\ell=1}^{i} \alpha_{2\ell}, \alpha_{2i+1}, p_{1i}, p_{2i+1}),$$

$i = 1, 2, \ldots, k$.

Then the joint prior density of $\underline{p}$ is obtained by multiplying all the above densities.

$$\begin{aligned} \pi(\underline{p}) &= \prod_{i=1}^{k} g(p_{1i} \mid \sum_{1}^{i} \alpha_{1\ell}, \alpha_{1i+1}; 0, p_{1i+1}) g(p_{2i} \mid \sum_{1}^{i} \alpha_{2\ell}, \alpha_{2i+1}; p_{1i}, p_{2i+1}) \\ &\quad g(p_{1k+1} \mid \alpha_1, \alpha_2; 0, 1), \quad \underline{p} \epsilon S_1^{(2k+1)} \end{aligned} \tag{13}$$

The posterior density of $\underline{p}$ given $\underline{x}$ is then proportional to the product of (2) and (13). Here it is not as straight forward to obtain posterior means, as in Section 2. Hence we adopt the sampling based approach to study interesting features of the marginal posterior densities described in Section 3. Noting the changes in conditional densities (10) and (11) we see that the posterior density for $\underline{p} \epsilon S_1^{(2k+1)}$ is,

$$\begin{aligned} \pi(\underline{p} \mid \underline{x}) &\propto \prod_{i=1}^{k} \binom{n_i}{x_i} p_{1i}^{x_{1i}} p_{2i}^{x_{2i}} (1 - p_{1i} - p_{2i})^{x_{3i}} \\ & g(p_{1i} \mid \sum_{1}^{i} \alpha_{1\ell}, \alpha_{1i+1}; 0, p_{1i+1}) g(p_{2i} \mid \sum_{1}^{i} \alpha_{2\ell}, \alpha_{2i+1}; p_{1i}, p_{2i+1}) \\ & g(p_{1k+1} \mid \alpha_1, \alpha_2; 0, 1). \end{aligned} \tag{14}$$

Examination of (14) reveals that,

$$\pi(p_{1i} \mid \underline{x}, p_{j\ell}, \ell \neq i, j = 1, 2,) \propto p_{1i}^{x_{1i}}(1 - p_{1i} - p_{2i})^{n_i - x_{1i} - x_{2i}} I_{(p_{1i-1}, m_{1i})}(p_{1i}) \prod_{\ell=i-1}^{i} g(p_{1\ell} \mid \sum_{r=1}^{\ell} \alpha_{1r}, \alpha_{1r+1}; 0, p_{1\ell+1}) g(p_{2i} \mid \sum_{1}^{i} \alpha_{2\ell}, \alpha_{2i+1}; p_{1i}, p_{2i+1}), \tag{15}$$

$$\pi(p_{2i} \mid \underline{x}, p_{j\ell}, \ell \neq i, j = 1, 2) \propto p_{2i}^{x_{2i}}(1 - p_{1i} - p_{2i})^{n_i - x_{1i} - x_{2i}} I_{(m_{2i}, p_{2i+1})}(p_{2i}) \prod_{\ell=i-1}^{i} g(p_{2\ell} \mid \sum_{r=1}^{\ell} \alpha_{2r}, \alpha_{2\ell+1}; p_{1\ell}, p_{2\ell+1}) \tag{16}$$

$$\pi(p_{1k+1} \mid \underline{x}, p_{j\ell}, \ell \neq k+1, j = 1, 2) \propto g(p_{1k} \mid \sum_{1}^{k} \alpha_{1\ell}, \alpha_{1k+1}; 0, p_{1k+1}) g(p_{2k} \mid \sum_{1}^{k} \alpha_{2\ell}, \alpha_{2k+1}; p_{1k}, p_{2k+1}) g(p_{1k+1} \mid \alpha_1, \alpha_2; 0, 1) I_{(p_{1k}, M_{k+1})}(p_{1k+1}) \tag{17}$$

where $m_{1i} = min(p_{1i+1}, p_{2i})$, $m_{2i} = max(p_{1i}, p_{2i-1})$ and $M_{k+1} = min(1/2, 1-p_{2k})$.

5 An Example

Here we discuss the example mentioned in Section 1. It is from the automobile reliability to which the above model is appropriate. Several cars were put on test. Each car was observed for the predetermined time period of 3 months, 6 months, ..., or 18 months with respect to two modes of failure. Hence 3, 6, ..., 18 are identified as the stress levels s_i, i=1, 2, ..., 6. The number of responses to each mode of failure is recorded if a car fails within its specified time. It is expected that $F_j^*(s_i)$, i = 1, 2, ..., 7, j=1, 2, with $s_0 = 0$ and $s_7 = \infty$ will be two incidence functions adding up to a cumulative distribution function. Table 1 gives the numbers of cars put on test and the observed numbers of failures due to each of the two causes at each s_i, 1, 2, ..., 6.

The sampling techniques described in Section 3 and Section 4 are applied to these car failure data. The proportions of different kinds of failures in the past data were used as the best guesses for p_{ji}'s and hence the prior parameters. The prior parameters are (0.073, 0.119, 0.115, 0.115, 0.090, 0.066, 0.022, 1.167, 0.011, 0.007, 0.004, 0.004, 0.004, 0.002, 0.518). Gibbs sampling was carried out with 50 iterations for the SRS and 1500 replications.

1. Table 2(a) and 2(b) give the non-parametric Bayes estimates of probabilities of failure due to mode 1 and 2 respectively at each stress level along with their standard errors (S.E.) and 95 % equal tailed credible intervals (C.I.). These were obtained using the empirical distribution of the p_{ji} from the 1500 replications. It is apparent from the tables that the probabilities of failures due to mode 2 is extremely small. It was observed that in 18 months, almost 25 % of the cars failed due to mode 1 while only 0.66 % failed due to mode 2. Note that the probability of failure due to mode 2 is less than that due to mode 1 for each s_i, which is in agreement with the past experience.

2. The sample data is analyzed to illustrate the technique designed in Section 4 assuming a priori that $F_2^*(s) \leq F_1^*(s)$ for all $s > 0$. The results are listed in Table 3(a) and Table 3(b). The additional restriction of ordered incidence functions has resulted in a slight increase in the probabilities of the failures. In 18 months, 30 % of the cars are estimated to fail due to mode 1 while 0.71 % due to mode 2.

Table 1 : Automobile reliability data

s_i (months)	3	6	9	12	15	18
n_i	188	222	199	262	99	383
x_{1i}	8	28	22	67	51	60
x_{2i}	1	5	2	3	2	5

Table 2 : Analysis of automobile reliability data

(unordered incidence functions)

(a) Posterior means, S.E., 95 % C.I. for p_{1i}

s_i	Mean	S.E.	C.I.
3	0.00007	0.00009	(0.00003,0.00017)
6	0.00114	0.00051	(0.00067,0.00229)
9	0.00743	0.00248	(0.00457,0.01272)
12	0.05104	0.01364	(0.03179,0.08054)
15	0.16700	0.03346	(0.10886,0.23985)
18	0.25998	0.04601	(0.16988,0.34421)
∞	0.71603	0.20674	(0.30542,0.98348)

(b) Posterior means, S.E., 95 % C.I. for p_{2j}

S_i	Mean	S.E.	C.I.
3	$0.2\text{x}10^{-9}$	$0.8\text{x}10^{-9}$	$(0.15861\text{x}10^{-10}, 0.1\text{x}10^{-8})$
6	$0.116\text{x}10^{-7}$	$0.1225\text{x}10^{-7}$	$(0.11\text{x}10^{-8}, 0.416\text{x}10^{-7})$
9	$0.315\text{x}10^{-6}$	$0.3688\text{x}10^{-6}$	$(0.27\text{x}10^{-7}, 0.1132\text{x}10^{-5})$
12	$0.14025\text{x}10^{-4}$	$0.14387\text{x}10^{-4}$	$(0.13674\text{x}10^{-5}, 0.46652\text{x}10^{-4})$
15	$0.53657\text{x}10^{-3}$	$0.59124\text{x}10^{-3}$	$(0.53693\text{x}10^{-4}, 0.16049\text{x}10^{-2})$
18	$0.66208\text{x}10^{-2}$	$0.49326\text{x}10^{-2}$	$(0.66252\text{x}10^{-3}, 0.17076\text{x}10^{-1})$
∞	0.28397	0.20675	$(0.16148\text{x}10^{-1}, 0.69455)$

Table 3 : Analysis of automobile reliability data

(ordered incidence functions)

(a) Posterior means, S.E., 95 % C.I. for p_{1j}

s_i	Mean	S.E.	C.I.
3	0.00011	0.00013	(0.00005,0.00047)
6	0.00191	0.00205	(0.00093,0.00699)
9	0.01103	0.00771	(0.00646,0.03088)
12	0.06314	0.01881	(0.04475,0.11019)
15	0.19476	0.032966	(0.14666,0.28163)
18	0.29942	0.04304	(0.23009,0.39175)
∞	0.81187	0.13546	(0.52624,0.99106)

(b) Posterior means, S.E., 95 % C.I. for p_{2j}

s_i	Mean	S.E.	C.I.
3	$0.47\text{x}10^{-8}$	$0.474\text{x}10^{-6}$	$(0.28451\text{x}10^{-10}, 0.229\text{x}10^{-7})$
6	$0.35\text{x}10^{-6}$	$0.32545\text{x}10^{-5}$	$(0.24\text{x}10^{-8}, 0.20722\text{x}10^{-5})$
9	$0.352\text{x}10^{-5}$	$0.14626\text{x}10^{-4}$	$(0.551\text{x}10^{-7}, 0.27493\text{x}10^{-4})$
12	$0.68309\text{x}10^{-4}$	$0.28752\text{x}10^{-3}$	$(0.20202\text{x}10^{-5}, 0.41341\text{x}10^{-3})$
15	$0.12827\text{x}10^{-2}$	$0.32262\text{x}10^{-2}$	$0.66742\text{x}10^{-3}, 0.71809\text{x}10^{-2})$
18	$0.71435\text{x}10^{-2}$	$0.14838\text{x}10^{-1}$	$(0.58643\text{x}10^{-3}, 0.27659\text{x}10^{-1})$
∞	0.18813	0.13546	$(0.88838\text{x}10^{-2}, 0.47309)$

Appendix

A Proof of Theorem.

First, we obtain $h(p_{ji};\underline{x},\underline{n})$, the joint density of p_{ji} and $\underline{x}$ and then integrating out p_{ji} gives $m(\underline{x})$, the marginal density of $\underline{x}$. Then the posterior density of p_{ji} is,

$$\pi(p_{ji} \mid \underline{x},\underline{n}) = \frac{h(p_{ji};\underline{x},\underline{n})}{m(\underline{x})}; \quad 0 < p_{ji} < 1, i = 1,2,...,k, j = 1,2. \tag{18}$$

The joint density of $\underline{p}$ and $\underline{x}$ for $\underline{p}\epsilon S^{(2k+1)}$ is the product of (2) and (3),

$$h(\underline{p},\underline{x}) = c(\underline{x},\underline{n},\underline{\alpha}) \prod_{i=1}^{k} p_{1i}^{x_{1i}} p_{2i}^{x_{2i}} (1-p_{1i}-p_{2i})^{x_{3i}} (p_{1i}-p_{1i-1})^{\alpha_{1i}-1}$$

$$(p_{2i}-p_{2i-1})^{\alpha_{2i}-1}(p_{1k+1}-p_{1k})^{\alpha_{1k+1}-1}(p_{2k+1}-p_{2k})^{\alpha_{2k+1}-1}, \tag{19}$$

where

$$c(\underline{x},\underline{n},\underline{\alpha}) = \prod_{i=1}^{k} \frac{n_i!}{x_{1i}!x_{2i}!x_{3i}!} \cdot \frac{\Gamma\alpha}{\prod_{i=1}^{k+1}\Gamma\alpha_{1i}\Gamma\alpha_{2i}}$$

and $x_{3i} = n_i - x_{1i} - x_{2i}$.

We obtain the marginal posterior density of p_{1i} given $\underline{x}$ by integrating p_{2i}'s, i = 1,2,..., k in (A.2),

$$I_1 = \int_0^{1-p_{1k+1}} \int_0^{p_{2k}} \cdots \int_0^{p_{22}} \prod_{i=1}^{k} p_{2i}^{x_{2i}} (1-p_{1i}-p_{2i})^{x_{3i}} (p_{2i}-p_{2i-1})^{\alpha_{2i}-1} dp_{2i}$$

Consider $\int_0^{p_{22}} p_{21}^{x_{21}}(1-p_{11}-p_{21})^{x_{31}} p_{21}^{\alpha_{21}-1}(p_{22}-p_{21})^{\alpha_{22}-1}dp_{21}$.
Expanding $(1-p_{11}-p_{21})^{x_{31}}$ using Binomial expansion, we obtain

$$\sum_{r_{21}=0}^{x_{31}} (-1)^{r_{21}} \binom{x_{31}}{r_{21}} \int_0^{p_{22}} p_{21}^{x_{21}}(1-p_{11})^{x_{31}-r_{21}} p_{21}^{\alpha_{21}-1} p_{21}^{r_{21}} (p_{22}-p_{21})^{\alpha_{22}-1} dp_{21}$$

$$= \sum_{r_{21}=0}^{x_{31}} (-1)^{r_{21}} \binom{x_{31}}{r_{21}} (1-p_{11})^{x_{31}-r_{21}} p_{22}^{x_{21}+r_{21}+\alpha_{22}+\alpha_{21}-1}$$

$$\beta(x_{21}+r_{21}+\alpha_{21},\alpha_{22}),$$

where $\beta(r,s) = \frac{\Gamma r \Gamma s}{\Gamma(r+s)}$. Continuing, we get,

$$I_1 = \sum_{r_{21}=0}^{x_{31}} \sum_{r_{22}=0}^{x_{32}} \cdots \sum_{r_{2k}=0}^{x_{3k}} (-1)^{\sum_{\ell=1}^{k} r_{2\ell}} \prod_{\ell=1}^{k} \binom{x_{3\ell}}{r_{2\ell}} \beta(\sum_{m=1}^{\ell}(x_{2m}+r_{2m}+\alpha_{2m}),\alpha_{2\ell+1})$$

$$(1-p_{1\ell})^{x_{3\ell}-r_{2\ell}}(1-p_{1k+1})^{\Sigma_1^k(x_{2\ell}+\alpha_{2\ell}+r_{2\ell})+\alpha_{2k+1}-1}.$$

Write $\beta_k = \sum_{\ell=1}^{k}(x_{2\ell}+\alpha_{2\ell}+r_{2\ell})+\alpha_{2k+1}$.

The joint density of $\underline{p}_1 = (p_{11},...,p_{1k+1})$ and $\underline{x}$ is then given by

$$h(\underline{p}_1,\underline{x},\underline{n}) = c(\underline{n},\underline{x},\underline{\alpha})\sum\sum...\sum d(\underline{x},\underline{r},\underline{\alpha})\prod_{\ell=1}^{k} p_{1\ell}^{x_1{}^{\ell}}(1-p_{1\ell})^{x_{3\ell}-r_{2\ell}}$$

$$(p_{1\ell}-p_{1\ell-1})^{\alpha_{1\ell}-1}(1-p_{1k+1})^{\beta_k-1}(p_{1k+1}-p_{1k})^{\alpha_{1k+1}-1};$$

$$0\le p_{11}\le p_{12}\le ... \le p_{1i}\le p_{1i+1}\le ...\le p_{1k+1}\le 1,$$

where,

$$d(\underline{x},\underline{r},\underline{\alpha}) = (-1)^{\sum_1^k r_{2\ell}}\prod_{\ell=1}^{k}\binom{x_{2\ell}}{r_{2\ell}}\prod_{\ell=1}^{k}\beta(\sum_{m=1}^{\ell}(x_{2m}+\alpha_{2m}+r_{2m}),\alpha_{2\ell+1}),$$

$$h(p_{1i},\underline{x},\underline{n}) = \int_0^{p_{1i}}...\int_0^{p_{12}}\int_{p_{1i}}^{1}...\int_{p_{1k}}^{1} h(\underline{p}_1,\underline{x},\underline{n})\prod_{l\neq i} dp_{1\ell}.$$

Consider,

$$I_2 = \int\prod_{\ell=i+1}^{k} p_{1\ell}^{x_{1\ell}}(1-p_{1\ell})^{x_{3\ell}-r_{2\ell}}(p_{1\ell}-p_{1\ell-1})^{\alpha_{1\ell}-1}dp_{1\ell}$$
$$(1-p_{1k+1})^{\beta_k-1}(p_{1k+1}-p_{1k})^{\alpha_{1k+1}-1}dp_{1k+1},$$

where $\int$ indicates multiple integration over the range $\int_{p_{1i}}^{1}\int_{p_{1i}+1}^{1}\cdots\int_{p_{1k}}^{1}$

We write $p_{1\ell}^{x_{1\ell}} = (1-(1-p_{1\ell}))^{x_{1\ell}}$ and use Binomial expansion to get,

$$I_2 = \sum_{\underline{r}_1}\prod_{\ell=i+1}^{k}\binom{x_{1\ell}}{r_{1\ell}}\beta(\alpha_{1\ell},\sum_{m=\ell}^{k}(x_{3m}-r_{2m}+r_{1m})+\beta_k+\sum_{m=\ell+1}^{k+1}\alpha_{1m})$$

$$(-1)^{\sum_{\ell=i+1}^{k} r_{1\ell}}\beta(\alpha_{1k+1},\beta_k+\alpha_{1k+1})(1-p_{1i})^{\sum_{\ell=i+1}^{k}(x_{3\ell}-r_{2\ell}+r_{1\ell}+\alpha_{1\ell})+\beta_k+\alpha_{1k+1}-1},$$

where

$$\sum_{\underline{r}_1}\text{denotes the multiple sum}\sum_{r_{1k}=0}^{x_{1k}}\sum_{r_{1k-1}=0}^{x_{1k-1}}\cdots\sum_{r_{1i+1}=0}^{x_{1i+1}}$$

Note that I_2 does not involve $(p_{11},...,p_{1i-1})$. Consider,

$$I_3 = \int_0^{p_{1i}}...\int_0^{p_{12}}\prod_{\ell=1}^{i-1} p_{1\ell}^{x_{1\ell}}(1-p_{1\ell})^{x_{3\ell}-r_{2\ell}}(p_{1\ell}-p_{1\ell-1})^{\alpha_{1\ell}-1}dp_{1\ell}.$$

Here, expanding $(1-p_{1\ell})^{x_{3\ell}-r_{2\ell}}$ and then integrating, we get

$$I_3 = \sum_{r_{11}=0}^{x_{31}-r_{21}} \sum \cdots \sum_{r_{1i-1}=0}^{x_{3i-1}-r_{2i-1}} \prod_{\ell=1}^{i-1} \binom{x_{3\ell}-r_{2\ell}}{r_{1\ell}} (-1)^{\sum_1^{i-1} r_{1\ell}}$$

$$p_{1i}^{\sum_1^{i-1}(x_{1\ell}+\alpha_{1\ell}+r_{1\ell})+\alpha_{1i}-1} \prod_{\ell=1}^{i-1} \beta(\sum_{m=1}^{\ell}(x_{1m}+\alpha_{1m}+r_{1m}), \alpha_{1\ell+1}).$$

Combining these results yields,

$$h(p_{1i};\underline{x},\underline{n}) = c(\underline{n},\underline{x},\underline{\alpha}) \sum_{\underline{r}} w(\underline{x},\underline{r},\underline{\alpha}) p_{1i}^{x_{1i}+\sum_1^{i-1}(x_{1\ell}+\alpha_{1\ell}+r_{1\ell})+\alpha_{1i}-1}$$

$$(1-p_{1i})^{x_{3i}-r_{2i}+\sum_{\ell=i+1}^{k}(x_{3\ell}-r_{2\ell}+r_{1\ell}+\alpha_{1\ell})+\beta_k+\alpha_{1k+1}-1};\ 0 \le p_{1i} \le 1$$

where

$$\sum_{\underline{r}} = \sum_{r_{21}} \cdots \sum_{r_{2k}} \sum_{r_{11}} \sum_{r_{12}} \cdots \sum_{r_{1i-1}} \sum_{r_{1i+1}} \cdots \sum_{r_{1k}},$$

$$w(\underline{x},\underline{r},\underline{\alpha}) = d(\underline{x},\underline{r},\underline{\alpha}) \prod_{\ell=1}^{i-1} \binom{x_{3\ell}-r_{2\ell}}{r_{1\ell}} \beta(\sum_{m=1}^{\ell}(x_{1m}+\alpha_{1m}+r_{1m}), \alpha_{1\ell+1})$$

$$(-1)^{\sum_{\ell \ne i} r_{1\ell}} \prod_{\ell=i+1}^{k} \beta(\alpha_{1\ell}, \sum_{m=\ell}^{k}(x_{3m}-r_{2m}+r_{1m})+\beta_k+\sum_{m=\ell+1}^{k+1}\alpha_{1m}) \binom{x_{1\ell}}{r_{1\ell}}.$$

Lastly integrating p_{1i} gives $m(x)$.

Hence, (A.1) implies that,

$$\pi(p_{1i} \mid \underline{x},\underline{n}) = \sum_{\underline{r}} \frac{w_1(\underline{x},\underline{r},\underline{\alpha})}{w_1(\underline{x},.,\underline{\alpha})} g(p_{1i} \mid \nu_1(\underline{x},\underline{r},\underline{\alpha}), \nu_2(\underline{x},\underline{r},\underline{\alpha}); 0, 1) \tag{20}$$

where,

$$w_1(\underline{x},\underline{r},\underline{\alpha}) = \beta(\nu_1(\underline{x},\underline{r},\underline{\alpha}); \nu_2(\underline{x},\underline{r},\underline{\alpha})).w(\underline{x},\underline{r},\underline{\alpha}),$$

$$w_1(\underline{x},.,\underline{\alpha}) = \sum_{\underline{r}} w_1(\underline{x},\underline{r},\underline{\alpha}),$$

$$\nu_1(\underline{x},\underline{r},\underline{\alpha}) = x_{1i} + \sum_1^{i-1}(x_{1\ell}+\alpha_{1\ell}+r_{1\ell}) + \alpha_{1i}$$

and

$$\nu_2(\underline{x},\underline{r},\underline{\alpha}) = x_{3i} - r_{2i} + \sum_{\ell=i+1}^{k}(x_{3\ell}-r_{2\ell}+r_{1\ell}+\alpha_{1\ell}) + \beta_k + \alpha_{1k+1}.$$

The posterior mean of p_{1i} is,

$$E(p_{1i} \mid \underline{x}, \underline{n}) = \sum_{\underline{r}} \frac{w_1(\underline{x}, \underline{r}, \underline{\alpha})}{w_1(\underline{x}, \cdot, \underline{\alpha})} \cdot \frac{\nu_1(\underline{x}, \underline{r}, \underline{\alpha})}{\nu_1(\underline{x}, \underline{r}, \underline{\alpha}) + \nu_2(\underline{x}, \underline{r}, \underline{\alpha})}. \tag{21}$$

Interchanging the first subscript 1 and 2 gives similar expression for the conditional density of p_{2i} and hence for $E(p_{2i} \mid \underline{x}, \underline{n})$.

Acknowledgments

The first author thanks the Council of Scientific and Industrial Research, India for supporting this work. The second author wishes to acknowledge with thanks financial support from the National Board for Higher Mathematics of Department of Atomic Energy through grant of a research award.

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