Testing the E ectiveness of Treatment for Cancers for which the Endpoint is Survival Using Bayesian Subgroup Analysis

by

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Abstract

We propose a basket trial design that tests the e ectiveness of a new treatment for several types of cancers where the endpoint is the survival time. During the trial conduct, Bayesian subgroup analysis is conducted to classify the cancer types into di erent clusters according to both the survival time and the longitudinal biomarker measurements of the patient. Finally, we make Bayesian inferences to decide whether to stop recruiting patients for each cluster early and make conclusions about whether the treatment is e ective for each cluster according to the estimated median survival time. The simulation study shows that our proposed method performs better than the independent approach and the Bayesian Hierarchical Modeling (BHM) method in most of the scenarios.

Keywords: Bayesian subgroup analysis; Longitudinal biomarkers; Phase I/II trials; Clinical trials for cancer

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is a need to incorporate biomarker measurements when classifying the cancer types into subgroups with di erent e cacy. There are some clinical trial designs which incorporate biomarkers as classi- ers which can help to classify cancer types into di erent subgroups. Takeda et al. (2022 [TLR22]) proposed a Bayesian subgroup design where the cancer types are classi ed into subgroups according to both the cancer type itself and a second classi er (biomarker). Liu et al. (2023 [LTR23]) also proposed a two-stage design where only patients whose biomarkers measured in the rst stage are positive are enrolled in the second stage. These studies highlight the importance of biomarkers as a potential classi er for cancer types because higher values in some biomarkers can be associated with better clinical outcomes. Yin et al. (2021 [Yin+21]) proposed a method that combines nding the biomarker cuto and testing the e ectiveness of the treatment using Bayesian hierarchical modelling. However, these three designs only allow measuring the biomarker one time instead of allowing longitudinal biomarker measurements, and their endpoints are binary instead of continuous.

Longitudinal biomarkers are biomarkers that are collected multiple times over time during the clinical study, which can be used to track the progression and predict the outcome of the disease. Some clinical trials utilize longitudinal biomarker measurements to help predict the outcome of the disease. van Delft et al. (2022 [van+22]) conducted research in which serum tumor marker measurements, which are longitudinal biomarkers, are used to predict the immunotherapy non-response in patients with non-small cell lung cancer. However, this study did not consider classifying more than one cancer type into subgroups. Some clinical studies demonstrate longitudinal biomarkers are associated with a certain clinical outcome. Wu et al. (2017[Wu+17]) found that there is a longitudinal association between fasting blood glucose, which is a type of biomarker, and arterial sti ness risk in non-diabetic individuals. Paulo et al. (2020[Pau+20]) found that a longitudinal increase of HbA1c was independently associated with higher rates of cardiovascular events in patients with type 2 diabetes and multivessel CAD , where HbA1c is a biomarker.

In some clinical trials, researchers are more interested in the progression-free survival time (PFS) instead of the binary indicator of whether the treatment is e ective. Consequently, there is a need to develop a clinical trial method that evaluates the e ectiveness of a treatment for cancers for which the endpoint is progression-free survival time (PFS) instead of a binary endpoint.

We propose the basket trial design to test the e ectiveness of a speci c new treatment for several types of cancers for which the endpoint is the survival time. Unlike traditional studies which treat each type of cancer separately, we use Bayesian subgroup analysis to rst classify the cancer types into di erent clusters according to both the survival time and the biomarker measurements of the patients, and then estimate the parameters to nd out whether the treatment is e ective for each cluster of cancer types. We conclude that the treatment is e ective for a cluster of cancer types if the estimated median survival time for this cluster is greater than the threshold that we desire.

In summary, our proposed clinical trial design has many advantages. First, we incorporate the longitudinal biomarker measurements along with the survival outcomes to help classify the cancer

Chapter 2

Methods

2.1 Model

In this study, we consider I types of cancer. For each type of cancer, we recruit n_i patients. We measure the biomarker for each patient L-times, where the measurement times are denoted by t_1, $\cdots$, t_L. The biomarker measurement of the j-th patient in the i-th cancer type measured at time t_l is denoted by Z_{ijl}. We assume that we will measure the biomarker at the same time points for all patients. After we complete the biomarker measurements, we measure the survival time for each patient, denoted by t_{ij}. Let ω_{ij} be the censoring indicator for the j-th patient in the i-th cancer type, where $\omega_{ij} = 1$ if the patient is not censored, and $\omega_{ij} = 0$ if the patient is censored. We assume that the I types of cancer can be grouped into K clusters according to the biomarker measurements and the survival time. In this article, we consider the case where $K = 2$, which means that there is one effective cluster and one ineffective cluster. However, the method can be generalized for the cases where $K > 2$. The objective of the study is to determine whether the treatment is effective for each cluster of patients, which is reflected by the median survival time for each cluster of patients. The hypothesis test is

$$H_0 : \rho_i < q_0 \text{ versus } H_a : \rho_i > q_1,$$

where ρ_i is the median survival time for cluster i, q_0 is the median survival time cutoff under which the treatment is deemed ineffective, and q_1 is the median survival time cutoff over which the treatment is deemed effective.

Let π_{ik} denote the probability that cancer type i belongs to cluster k. Let C_i be an indicator of which cluster the cancer type belongs to. For example, $C_1 = 2$ means that the first cancer type belongs to the second cluster. We assume that C_i has the multinomial distribution:

$$C_i \sim \text{Multinomial}(\pi_{i1}, \ldots, \pi_{iK}).$$

Recall that Z_{ijl} is the biomarker measurement of the j-th patient in the i-th cancer type measured at time t_l. We assume the biomarker measures are structured as follows,

$$Z_{ijl}|(C_i = k) = \mu_k(t_l) + v_i + w_{ij} + \varepsilon_{ijl},$$

which reflects the grouping structure of the model. Specifically, every cluster has a mean trajectory of the biomarker, which is denoted by $\mu_k(t_l)$. Every group within the cluster can have a mean trajectory that varies from the mean trajectory of the cluster, and the difference is denoted by

$$\sigma^2 \quad \text{IG}(10^{-3}, 10^{-3}).$$

$$\theta_2 \quad \text{Uniform}(-1, 1).$$

$$\lambda \quad \text{Gamma}(0.1, 0.1).$$

$$r \quad \text{Gamma}(0.1, 0.1).$$

In the distributions above, IG(α, β) denotes the inverse Gamma distribution with shape parameter α and scale parameter β.

2.3 Trial Design

This trial has M planned interim analyses. Let D_m be the observed data at the m-th interim analysis. Recall that ρ_i is the median survival time for cluster i.

If $P\{\rho_i > (q_0 + q_1)/2 | D_m\} < Q_f$, then stop recruiting patients for cancer types that belong to the i-th cluster and conclude that the treatment is ineffective for these types of cancers. Otherwise, continue to recruit patients for these cancer types. Here, Q_f is a probability cutoff; in this study, we set Q_f to be a small value, e.g., 0.05.

At the end of the study, declrddTd 9t -340(theTd 936(b)-27(elongr]TJ/F49 74(median)-33152 7.9701 Tf 8.624 -1.7

Chapter 3

Illustration

We illustrate how to implement our proposed design using a hypothetical clinical trial. Suppose we would like to evaluate whether a new drug is effective for each of the 12 types of cancers which share the same molecular aberration. Suppose the maximum number of patients in each cancer type is 50, and we have one planned interim analysis. In the first stage, we only recruit 30 patients for each cancer type. We first measure the biomarkers for each patient 20 times. After that, we record the observed survival time and censoring status of each patient.

After we collect the data, we fit the model and sample from the posterior distributions of the parameters. Recall that the interim stopping rule is that if $P\{\rho_i > (q_0 + q_1)/2 | D_m\} < Q_f = 0.05$, then we stop recruiting patients for cancer types which belong to the i-th cluster, and conclude that the treatment is ineffective for these types of cancers. The posterior distribution of ρ_1 and ρ_2 are shown below.

The posterior probabilities are $P(C_1 = 1) = P(C_2 = 1) = P(C_3 = 1) = P(C_4 = 1) = P(C_5 = 1) = P(C_6 = 1) = 1$, and $P(C_7 = 1) = P(C_8 = 1) = P(C_9 = 1) = P(C_{10} = 1) = P(C_{11} = 1) = P(C_{12} = 1) = 0$, which means that cancer type 1, 2, 3, 4, 5, 6 belong to the first cluster, and cancer type 7, 8, 9, 10, 11, 12 belong to the second cluster. Since $P\{\rho_1 > (q_0 + q_1)/2 | D_m\} = 0 < Q_f$, we declare that the treatment is ineffective for all the cancer types that are classified into the first cluster. Since $P\{\rho_2 > (q_0 + q_1)/2 | D_m\} = 0.984 > Q_f$, we continue to recruit 20 more patients for each of the cancer types that are classified into the second cluster, and record the observed survival time and censoring status of each patient in these cancer types. In the second stage, we only use the data of the cancer types that are classified into the second cluster in the previous stage. After that, we fit the model again and estimate the posterior distribution of the parameters again. Recall that at the end of the study, we declare that the treatment is effective if $P\{\rho_i > (q_0 + q_1)/2 | D_m\} > Q$ for the i-th cluster of patients. The posterior distribution of ρ_1 is shown below.

The posterior probabilities show that $P(C_7 = 1) = P(C_8 = 1) = P(C_9 = 1) = P(C_{10} = 1) = P(C_{11} = 1) = P(C_{12} = 1) = 1$, which means that cancer type 7, 8, 9, 10, 11, 12 are classified into

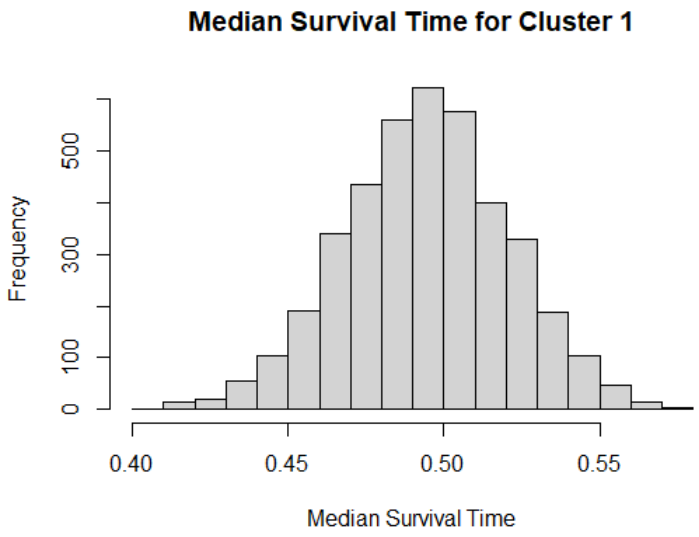

Figure 3.1: The posterior distribution of the median survival time for cluster 1 at the interim analysis.

the rst cluster in this stage. Since $P\{\rho_1 > (q_0 + q_1)/2 | D_m\} = 0.999$, we declare that the treatment is e ective for all these six cancer types.

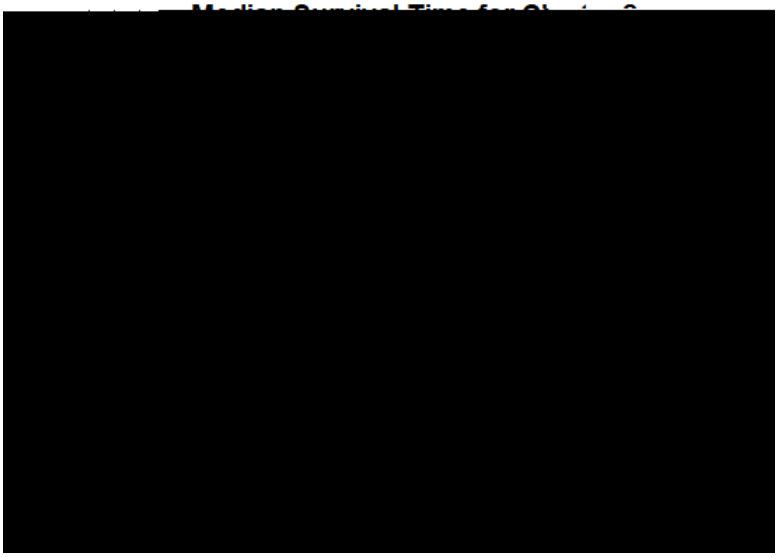

Figure 3.2: The posterior distribution of the median survival time for cluster 2 at the interim analysis.

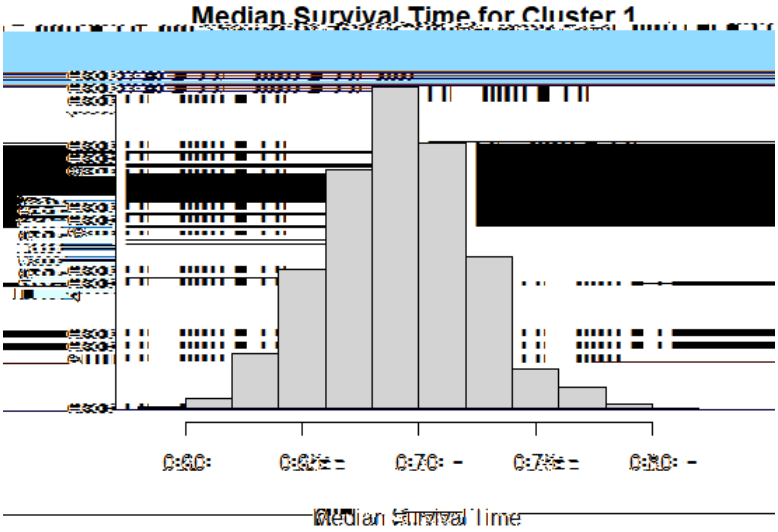

Figure 3.3: The posterior distribution of the median survival time for cluster 1 at the end of the trial.

Chapter 4

Simulation Study

We conduct a simulation study to evaluate the performance of the proposed design. We assume that the cancer types can be grouped into two clusters. The first cluster is the group where the treatment is ineffective, and the second cluster is the group where the treatment is effective. Let q

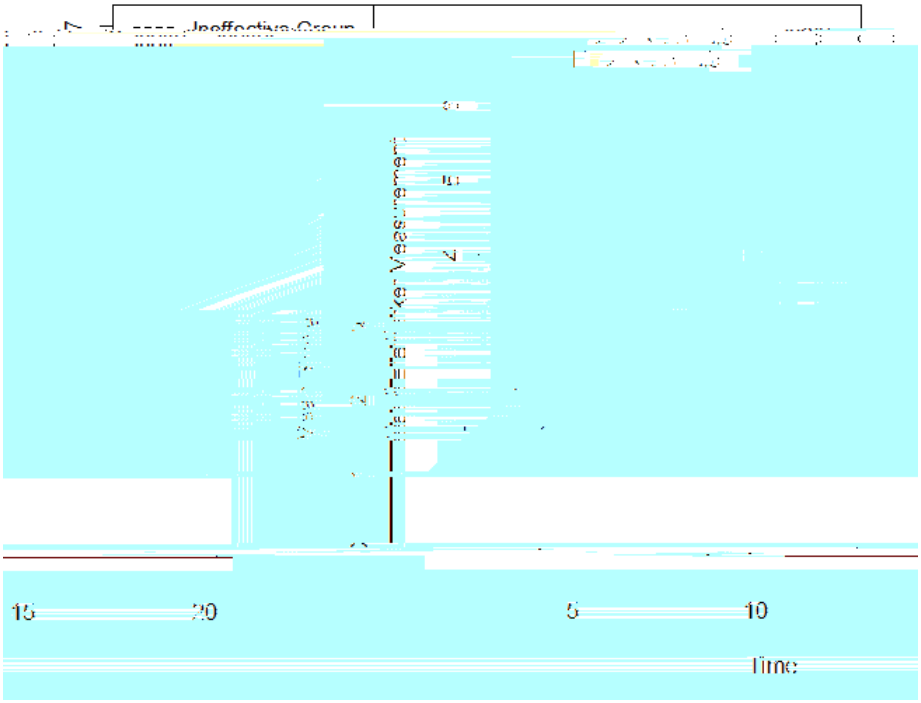

Figure 4.1: Mean biomarker measurement. The solid and dashed line represents the mean biomarker measurement for the e ective group and the ine ective group, respectively.

is stopped for this cancer type after the interim analysis because the treatment is considered to be ine ective. If the trial is stopped early for a cancer type, then no new patients will be recruited for this cancer type. Reject means that the null hypothesis is rejected for this cancer type, and we conclude that the treatment is e ective for this cancer type. No-Reject means that the trial is not early stopped and the null hypothesis is not rejected after interim 2. Sample Size means the average number of patients that are recruited in each cancer type, which are averaged over the cluster. In scenario A1, there are 12 e ective cancer types and no ine ective cancer types. The early stopping rate for the e ective group using our proposed model (0.0%) is lower than that using the independent approach (0.7%) or the BHM method (1.6%), which means that fewer patients who are actually in the e ective group are wrongly stopped being recruited using our proposed model. The rejection rate for the e ective group after interim 2 using our proposed model (99.6%) is higher than that using the independent approach (70.5%) or the BHM (73.6%) method, which means that

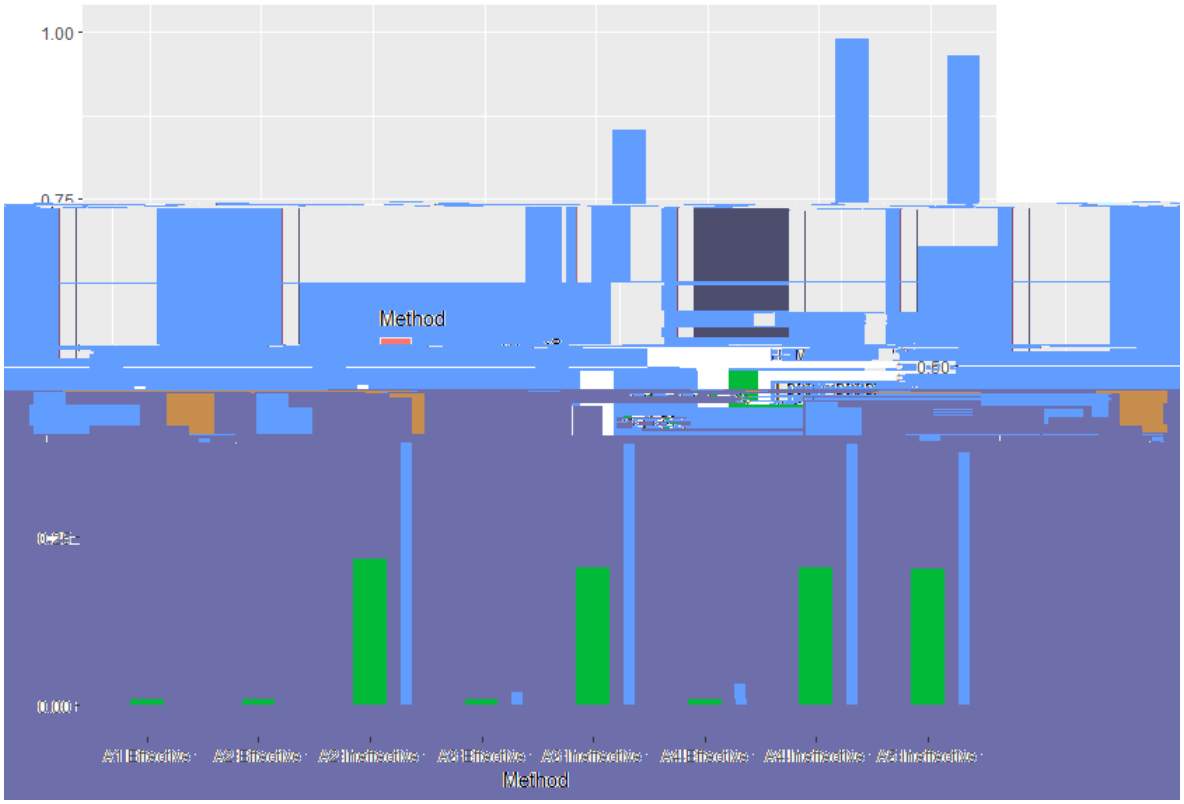

Figure 4.2: Early stopping rate in the main simulation study. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios A1 to A5 vary regarding the number of e ective/ine ective treatments.

the BHM method and the independent approach. The early stopping rate for the e ective group using our proposed model (1.7%) is only slightly higher than that using the independent approach (0.7%) and is lower than that using the BHM method (1.9%). The rejection rate for the e ective group after interim 2 using our proposed model (92.5%) is higher than that using the independent approach (63.3%) or the BHM (69.7%) method, which indicates that our proposed method yields much higher power than the other two methods. Again, the reason why our proposed model per-

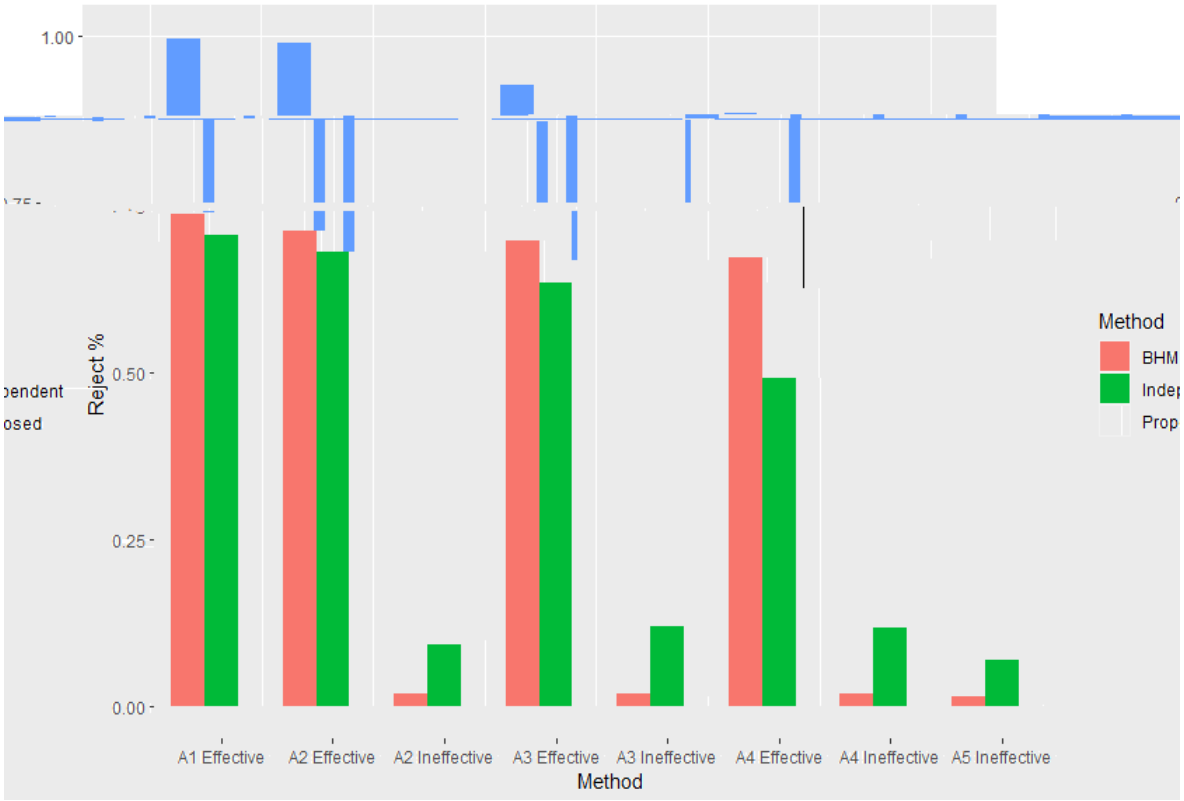

Figure 4.3: Rejection rate, which is the proportion of trials where the null hypothesis is rejected, in the main simulation study. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios A1 to A5 vary regarding the number of e ective/ine ective treatments.

rate for the e ective group, higher rejection rate for the e ective group, and lower rejection rate for the ine ective group.

Chapter 5

Sensitivity Analysis

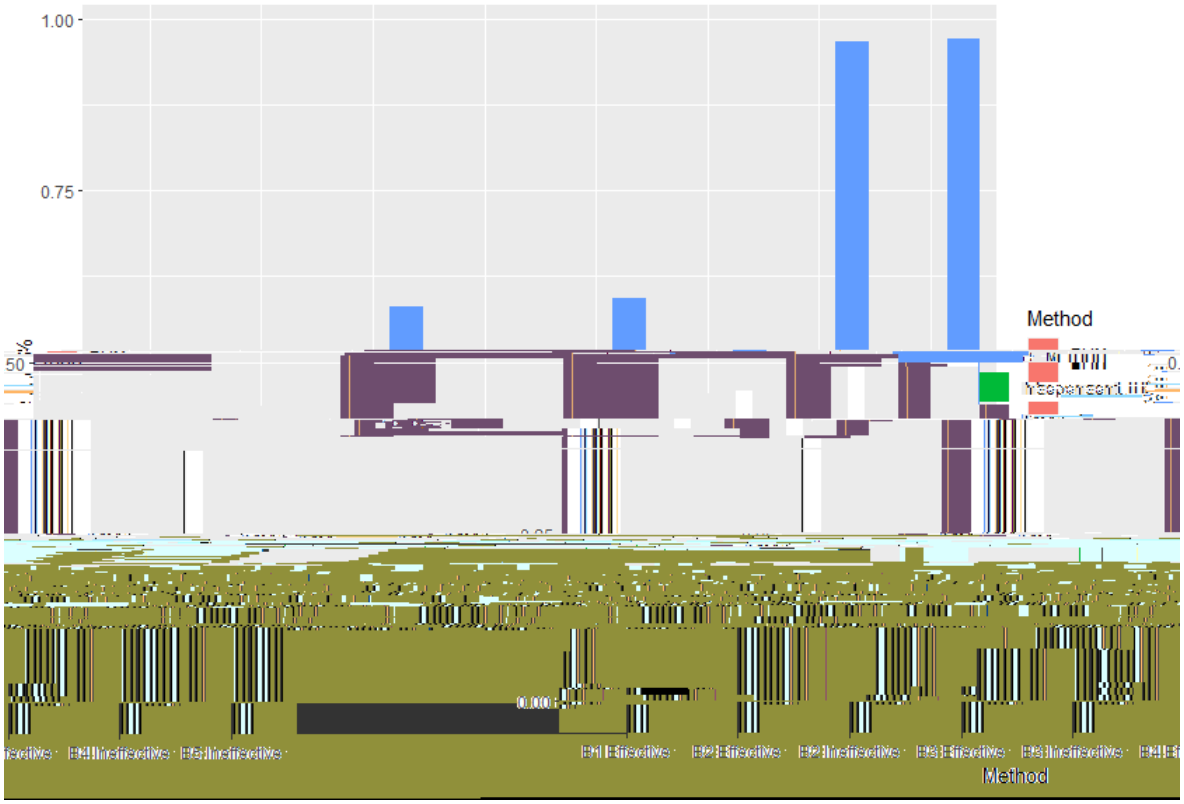

Figure 5.1: Early stopping rate when the prior distribution of one hyperparameter is changed. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios B1 to B5 vary regarding the number of e ective/ine ective treatments.

C1, C2, and C3, the number of ine ective cancer types is 5, 9, and 18, respectively, and the number of e ective cancer types is 13, 9, and 0, respectively. In these three scenarios, our proposed model performs better than the other two methods in general in terms of the early stopping rate and the rejection rate. For example, in scenario C2, the early stopping rate for the ine ective group using our proposed model (89.4%) is higher than that using the independent approach (20.1%) or the BHM method (43.4%). The rejection rate for the ine ective group after interim 2 using our proposed model (0.4%) is lower than that using the independent approach (12.2%) or the BHM method (1.9%). The rejection rate for the e ective group after interim 2 using our proposed model (93.0%) is higher than that using the independent approach (64.0%) or the BHM (69.0%) method. The only aspect in this scenario where our proposed model performs worse is that the early stopping rate for the e ective group using our proposed model (1.8%) is higher than that using the independent approach (0.5%) and is only slightly lower than that using the BHM (2.2%) method. This simulation study shows that our proposed method performs greatly even if we increase the number of cancer types.

Figure 5.2: Rejection rate, which is the proportion of trials where the null hypothesis is rejected when the prior distribution of one hyperparameter is changed. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios B1 to B5 vary regarding the number of e ective/ine ective treatments.

In the third sensitivity analysis, we increase the number of cancer types from 12 to 18 and change the prior distribution of $_2$ from Uniform(-1,1) to Uniform(-2,0), so that we can evaluate the performance of the model when there are more cancer types and the prior distribution of one hyperparameter is changed.

Table 5.3 shows the results of the simulation study of the third sensitivity analysis. In scenario D1, D2, and D3, the number of ine ective cancer types is 5, 9, and 18, respectively, and the number of e ective cancer types is 13, 9, and 0, respectively. In most cases, our proposed model outperforms the other two methods in terms of the early stopping rate and rejection rate. For example, in scenario D1, The early stopping rate for the ine ective group using our proposed model (75.4%) is higher than that using the independent approach (19.3%) or the BHM method (39.5%). The early stopping rate for the e ective group using our proposed model (0.0%) is lower than that using the independent approach (0.5%) or the BHM method (2.0%). The rejection rate for the e ective

			Early Stop %	Reject %	No-Reject %	Sample Size
C1	Proposed Model	Ine ective	82.2	4.8	13.0	33.6
		E ective	0.0	98.4	1.6	50.0
	Independent Approach	Ine ective	19.3	10.5	70.2	46.1
		E ective	0.5	68.8	30.7	49.9
	BHM	Ine ective	39.5	1.8	58.7	42.1
		E ective	2.0	70.8	27.3	49.6
C2	Proposed Model	Ine ective	89.4	0.4	10.2	32.1
		E ective	1.8	93.0	5.2	49.6
	Independent Approach	Ine ective	20.1	12.2	67.7	46.0
		E ective	0.5	64.0	35.5	49.9
	BHM	Ine ective	43.4	1.9	54.7	41.3
		E ective	2.2	69.0	28.8	49.6
C3	Proposed Model	Ine ective	97.3	0.0	2.7	30.5
		E ective	-	-	-	-
	Independent Approach	Ine ective	20.3	7.5	72.2	45.9
		E ective	-	-	-	-
	BHM	Ine ective	51.7	1.6	46.7	39.7
		E ective	-	-	-	-

Table 5.2: Simulation results of the sensitivity analysis when the number of cancer types increases. This table shows the early stopping rate, rejection rate, and sample size under three simulation scenarios.

group after interim 2 using our proposed model (96.8%) is higher than that using the independent approach (68.8%) or the BHM (70.8%) method. The only drawback to our proposed model in this scenario is that the rejection rate for the ine ective group after interim 2 using our proposed model (10.2%) is only slightly lower than that using the independent approach (10.5%) and is higher than that using the BHM (1.8%) method.

In summary, our proposed model still performs better in most of the scenarios, which means that the model is not very sensitive to the number of cancer types or the prior distribution of the hyperparameter.

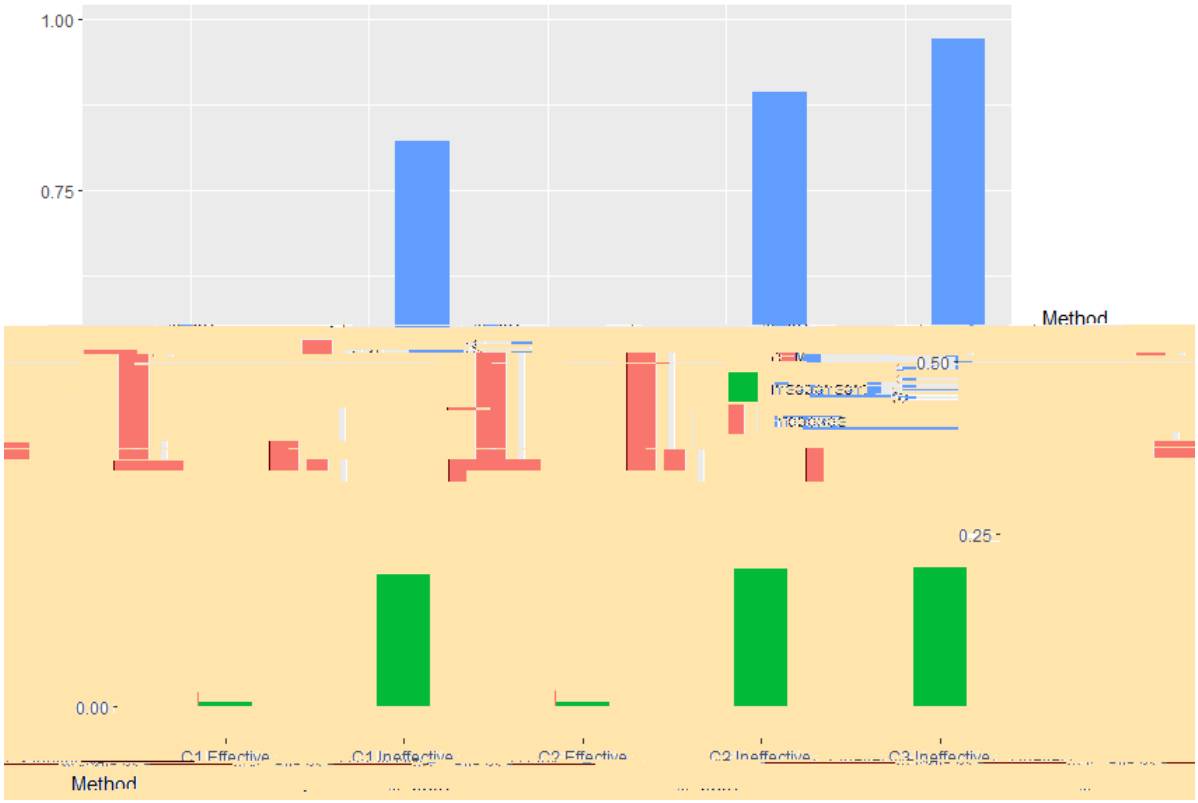

Figure 5.3: Early stopping rate when the number of cancer types increases. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios C1 to C3 vary regarding the number of e ective/ine ective treatments.

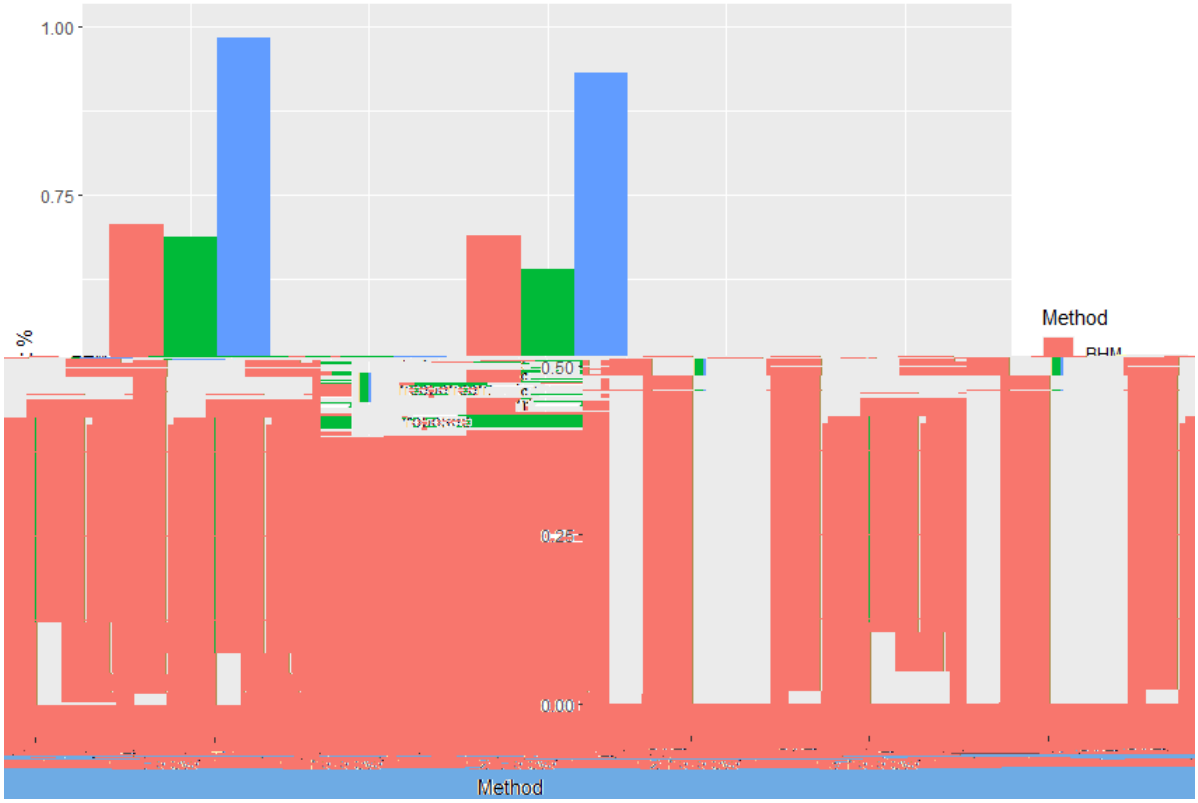

Figure 5.4: Rejection rate, which is the proportion of trials where the null hypothesis is rejected when the number of cancer types increases. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios C1 to C3 vary regarding the number of e ective/ine ective treatments.

			Early Stop %	Reject %	No-Reject %	Sample Size
D1	Proposed Model	Ine ective	75.4	10.2	14.4	34.9
		E ective	0.0	96.8	3.2	50.0
	Independent Approach	Ine ective	19.3	10.5	70.2	46.1
		E ective	0.5	68.8	30.7	49.9
	BHM	Ine ective	39.5	1.8	58.7	42.1
		E ective	2.0	70.8	27.3	49.6
D2	Proposed Model	Ine ective	73.4	1.4	25.2	35.3
		E ective	6.4	77.5	16.1	48.7
	Independent Approach	Ine ective	20.1	12.2	67.7	46.0
		E ective	0.5	64.0	35.5	49.9
	BHM	Ine ective	43.4	1.9	54.7	41.3
		E ective	2.2	69.0	28.8	49.6
D3	Proposed Model	Ine ective	97.9	0.0	2.1	30.4
		E ective	-	-	-	-
	Independent Approach	Ine ective	20.3	7.5	72.2	45.9
		E ective	-	-	-	-
	BHM	Ine ective	51.7	1.6	46.7	39.7
		E ective	-	-	-	-

Table 5.3: Simulation results of the sensitivity analysis when the number of cancer types increases, and the prior distribution of one hyperparameter is changed. This table shows the early stopping rate, rejection rate, and sample size under three simulation scenarios.

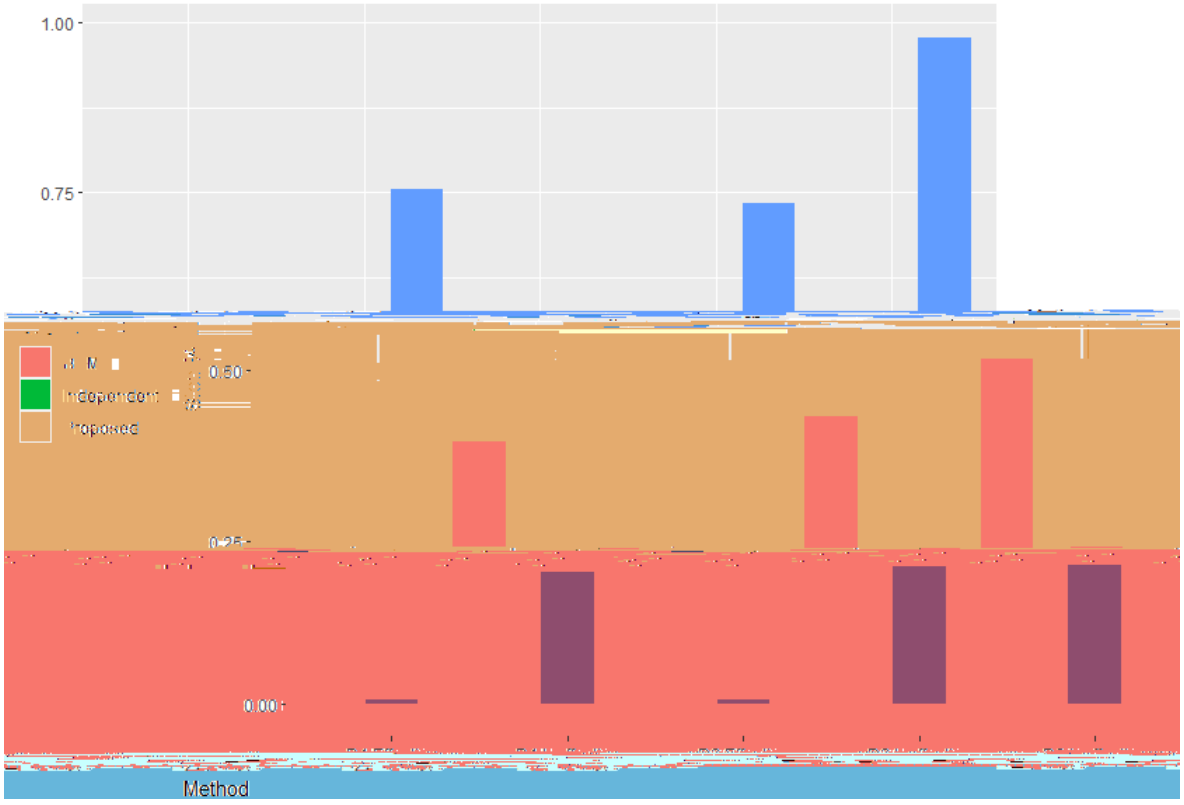

Figure 5.5: Early stopping rate when the number of cancer types increases, and the prior distribution of one hyperparameter is changed. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios D1 to D3 vary regarding the number of e ective/ine ective treatments.

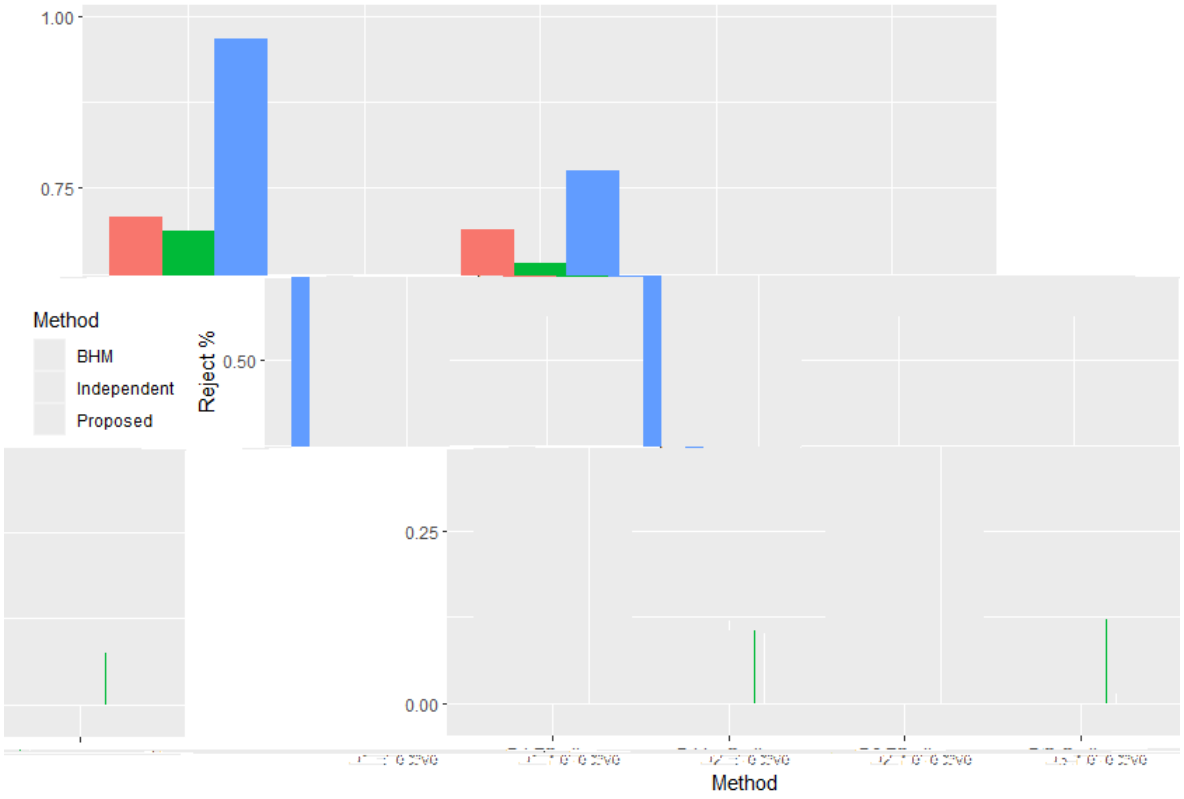

Figure 5.6: Rejection rate, which is the proportion of trials where the null hypothesis is rejected, when the number of cancer types increases, and the prior distribution of one hyperparameter is changed. The red, green, and blue bars represent the BHM method, the independent approach, and the proposed method, respectively. Scenarios D1 to D3 vary regarding the number of e ective/ine ective treatments.

Chapter 7

Gibbs Sampler for the Proposed Model

Step 1: We update C_i.

We denote $Z_{ij} = (Z_{ij1}, ..., Z_{ijL})$, and $Z_i = (Z_{i1}, ..., Z_{iJ})$. For $i = 1, ..., I$, $C_i \sim$ Multinomial$(\tau_{i1}, ..., \tau_{iK})$, where

$$\tau_{ik} = \frac{\pi_{ik} N_{Q_i}(u_{i(k)}, \sigma^2 I_{Q_i}) \prod_j [\{f_t(t_{ij})\}^{\delta_{ij}} \{S_t(t_{ij})\}^{1-\delta_{ij}}]}{\sum_{i=1}^{K} \pi_{ik} N_{Q_i}(u_{i(k)}, \sigma^2 I_i) \prod_j [\{f_t(t_{ij})\}^{\delta_{ij}} \{S_t(t_{ij})\}^{1-\delta_{ij}}]},$$

where $u_{i(k)} = X_i \alpha_{(k)} + X_{ib} b_i$, $Q_i = Ln_i$,

$$\alpha_{(k)} = (\gamma_{1(k)}, \gamma_{2(k)}, \cdots, \gamma_{S(k)})^{\top},$$

$$b_i = (v_i, w_{i1}, ..., w_{iJ})^{\top}.$$

Here, $N_{Q_i}(w, \sigma^2 I_{Q_i})$ is a Q_i-variate normal density function of Z_i, X_i is a Q_i-by-S design matrix of the i-th arm associated with $\alpha_{(k)}$, and X_{ib}

Normal distributions, and the prior distributions are $\sigma_v^2 \quad \text{IG}(10^{-3}, 10^{-3})$, $\sigma_w^2 \quad \text{IG}(10^{-3}, 10^{-3})$, and $\sigma^2 \quad \text{IG}(10^{-3}, 10^{-3})$, we are calculating the posterior distribution of the variance of the Normal distribution where the mean is known and the prior distribution of the variance follows Inverse Gamma distribution. As a result, we get the posterior distributions.

$$\sigma_v^2 | . \quad \text{IG}(10^{-3} + 0.5I, 10^{-3} + 0.5 \sum_{i=1}^{I} v_i^2),$$
$$\sigma_w^2 | . \quad \text{IG}(10^{-3} + 0.5N, 10^{-3} + 0.5 \sum_{i=1}^{I} \sum_{j=1}^{n_i} w_{ij}^2),$$
$$\sigma^2 | . \quad \text{IG}(10^{-3} + 0.5LN, 10^{-3} + 0.5 \sum_{i=1}^{I} \sum_{j=1}^{n_i} \sum_{l=1}^{L} {}^{2}_{ijl}).$$

and $X_{b(k)}$ is a Q_k-by-$(I + N)$ ith the random-e ect ve k.
The values of $y_{q(k)}$ for each o nent for each patient) $_{(k)}$
for each cluster k, where each bservation in the data and
each column corresponds to th the B-Spline basis valu
of v_i and w_{ij} for each observa each patient) are st e
cluster k, where each row co ion in the dataset f
column corresponds to one p
Since $Z_{ijl}|(C_i = k) = \mu_k(t_l) +$ e the matrix notatio
previous section to get that Z ag($\sigma^2, \cdots, \sigma^2$)). Wh
this step, we are calculating th e mean of a multivar
variable where the variance is variance matrix of
of $_k$. Since the prior distribu can derive the pos
$_k$ using exactly the same m

$_{(k)}\sigma^{-2})^{-1}$,
$- X_{b(k)}b)$.

In summary, the full condition follows,

), where
$_{(k)}\sigma^{-2})^{-1}$,

Step 6: We update θ_2 using ion of
Uniform(-1 462 Td [(Step) -542 (6.) -543 (W (up) -28 (

$$f(r\text{j}.) \; / \;\; f_{gamma}(r, 0.1, 10) \prod_{ij} [\text{f}\, f_t(t_{ij})\text{g}^{\omega_{\text{ij}}}\, \text{f}\, S_t(t_{ij})\text{g}^{1\;\;\omega_{\text{ij}}}],$$

where $f_{gamma}(x, \alpha, \beta)$ is the probability density function of a Gamma random variable where the shape is α and the rate is β.

Chapter 8

Model Specification and Gibbs Sampler for the BHM

The structure of the Bayesian Hierarchical Model is as follows. The survival function for the i-th patient in the j-th cancer type is related to the cancer type of the patient in the following way, where θ_i, λ_i, and r_i are the parameters corresponding to each cancer type.

$$S_t(t_{ij}) = \exp\{-\lambda_i t_{ij}^{r_i} \exp(\theta_i)\}.$$

We assume the parameters have the distributions, where μ_θ, σ_θ^2, α_λ, β_λ, α_r, and β_r are the hyper-parameters.

$$\begin{aligned} \theta_i &\sim N(\mu_\theta, \sigma_\theta^2), \\ \lambda_i &\sim \text{Gamma}(\alpha_\lambda, \beta_\lambda), \\ r_i &\sim \text{Gamma}(\alpha_r, \beta_r). \end{aligned}$$

We assume the hyperparameters have the prior distributions.

$$\begin{aligned} \mu_\theta &\sim N(0, 10), \\ \sigma_\theta^2 &\sim \text{Unif}(0, 10), \\ \alpha_\lambda &\sim \text{Unif}(0, 1), \\ \beta_\lambda &\sim \text{Unif}(0, 1), \\ \alpha_r &\sim \text{Unif}(0, 1), \\ \beta_r &\sim \text{Unif}(0, 1). \end{aligned}$$

The Gibbs sampler is as follows.

Step 1: We update θ_i, λ_i, and r_i using Metropolis sampling

$$f(\theta_i|.) \propto f_N(\theta_i, \mu_\theta, \sigma_\theta^2) \prod_j [\{f_t(t_{ij})\}^{\omega_{ij}} \{S_t(t_{ij})\}^{1-\omega_{ij}}] \text{Unif}(0

where $f_N(x, \mu, \sigma)$ is the probability density function of a Normal(μ, σ) random variable where the mean is μ and the standard deviation is σ, and $f_{gamma}(x, \alpha, \beta)$ is the probability density function of a Gamma random variable where the shape is α and the rate is β. Here, $f_t(t_{ij})$ is the probability density function of PFS of the i-th patient in the j-th cancer type, and $S_t(t_{ij})$ is the survival function of PFS of the i-th patient in the j-th cancer type.

Step 2: We update μ_θ, σ_θ^2, α_λ, β_λ, α_r, and β_r using Metropolis sampling

$$f(\mu_\theta|.) \propto f_N(\mu_\theta, 0, 10)f$$

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