Mixture of Finite Mixtures Model for Basket Trial

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Abstract

With the recent paradigm shift from cytotoxic drugs to new generation of target therapy and immuno-oncology therapy during oncology drug developments, patients with various cancer (sub)types may be eligible to participate in a basket trial if they have the same molecular target. Bayesian hierarchical modeling (BHM) are widely used in basket trial data analysis, where they adaptively borrow information among different cohorts (subtypes) rather than fully pool the data together or doing stratified analysis based on each cohort. Those approaches, however, may have the risk of over shrinkage estimation because of the invalidated exchangeable assumption. We propose a two-step procedure to find the balance between pooled and stratified analysis. In the first step, we treat it as a clustering problem by grouping cohorts into clusters that share the similar treatment effect. In the second step, we use shrinkage estimator from BHM to estimate treatment effects for cohorts within each cluster under exchangeable assumption. For clustering part, we adapt the mixture of finite mixtures (MFM) approach to have consistent estimate of the number of clusters. We investigate the performance of our proposed method in simulation studies and apply this method to Vemurafenib basket trial data analysis.

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1 Introduction

With the recent paradigm shift from cytotoxic drugs to new generation of target therapy and immunoncology therapy during oncology drug developments, clinical trials in oncology no longer solely target for a specific cancer type based on the anatomic location of the primary tumor (e.g., breast, lung or GI). Patients with various cancer (sub)types may be eligible to participate in a clinical trial if they have the same molecular target. The term basket trial is used to represent those studies where a single targeted or immunoncology therapy is investigated in the context of multiple diseases or disease subtypes (Woodcock and LaVange, 2017).

For oncology drug development, we usually start patients studies in Phase I. The phase I study is typically comprised of two parts, Phase Ia and Phase Ib. The objective in Phase Ia is to find Maximum Tolerated Dose (MTD) or Optimal Biological Dose (OBD) based mainly on safety data with the supplements of initial efficacy information, and we usually call this part dose escalation. After the optimal dose is determined, we enroll more patients to that dose level to mainly evaluate efficacy while still monitoring safety of the drug, where we name as expansion part of the study (Phase Ib). During Phase Ib, basket trial design are widely used to evaluate the efficacy of the new treatment in multiple cohorts.

Assume single-arm settings for all cohorts in phase Ib without control arm, a binary endpoint of response (yes/no) is usually used. There are different criterion for various tumor types. For example, RECIST criteria (Eisenhauer et al., 2009) is used for solid tumor and RANO criteria (Lin et al., 2015) is used for brain tumor. Even with slight different definitions among different criterion, response is typically defined as a tumor shrinkage more than a certain threshold (e.g. 30% in RECIST criteria). The reasonable positive correlation with time-to-event endpoints such as Progression Free Survival (PFS) and Overall Survival (OS) along with much earlier readout, makes the binary endpoint of response widely acceptable efficacy endpoint in early phase oncology studies. Eventually the treatment effect will be reflected in response rate, which is defined as the number of patients with responses divided by the total number of patients. Thus without further discussion on the validity of the endpoint, a binary endpoint is assumed in this paper.
When dealing with multiple cohorts in one study, there are two directions as we conduct data analysis: pooled analysis or stratified analysis. If the assumption is the treatment effect is homogeneous among all cohorts, a pooled analysis may be conducted where we get a response rate by combining the data from all cohorts. If the assumption is that different cohorts have totally heterogeneous treatment effect, separate response rate will be estimated in each cohort. In practice, however, both of these two assumptions might not be true. It’s very hard to justify a drug has homogeneous effect on different tumor types, but it’s also difficult to claim that totally different treatment effects are expected among those cohorts taking the same drug. In addition, fully pooled analysis might dilute the positive signal if the drug works only in some of the cohorts and fully stratified analysis might be either lack of power or costly inefficient.

In order to mitigate the above mentioned problems, several methods were proposed to find a balance between pooled analysis and stratified analysis, where they adaptively borrow information among different cohorts rather than fully pool the data together. Many of those methods are based on Bayesian hierarchical modeling (BHM). Thall et al. (2003) and Berry et al. (2013) proposed exchangeable assumptions among the parameters (logit transformation of response rate) for different cohorts, which led to shrinkage estimators for each cohort. Those exchangeable assumptions, however, can easily lead to over shrinkage to a common mean, thus introduce bias to the estimators. Neuenschwander et al. (2016) and Chu and Yuan (2018) further allow each cohort-specific parameter to be exchangeable with other similar strata parameters or nonexchangeable with any of them in order to mitigate the risk of over shrinkage. These methods sometimes may suffer from too many pre-specified parameters.

In this article, we propose a two-step procedure to find the balance between pooled and stratified analysis in basket trial design. In the first step, we treat it as a clustering problem by grouping cohorts into clusters that share the similar treatment effect. In the second step, we use shrinkage estimator proposed by Berry et al. (2013) to estimate treatment effects for cohorts within each cluster under exchangeable assumption. For clustering, we adapt the mixture of finite mixtures (MFM) approach (Miller and Harrison, 2018; Geng et al., 2019; Geng and Slate, 2020), which admits a clustering scheme similar to the famous Chinese restaurant process (CRP) but alleviates the drawback of CRP by automatic model-based pruning of the tiny extraneous clusters leading to consistent estimate of the number of clusters. The contribution of this paper is threefold. First, a full Bayesian framework is developed and the clustering results yield useful probabilistic interpretation. In addition, we establish consistency results for the estimation of clusters for the binary data.
Thirdly, high probability of selecting the correct number of clusters and the better estimation performance than benchmark methods when heterogeneity exits between cohorts are empirically demonstrated.

The rest of the paper is organized as follows. We start with a brief review of the existing popular models for basket trial design and MFM model, as well as propose our two-step procedures in Section 2. The Bayesian methods for simultaneous inference on the number of clusters and cluster-specific estimates are discussed in Section 3 and the MCMC algorithm is provided in Section 3.1. Simulation studies and comparisons with existing methods are provided in Section 4 and illustrations of our method by two case studies are presented in section 5. Finally, we have some discussions in Section 6.

2 Methodology

2.1 Existing models for basket design

Suppose there are $N$ cohorts in the proposed basket design. In cohort $i$, there are $n_i$ patients enrolled with response rate $p_i$. If the number of responses in cohort $i$ is denoted as $r_i$, we have:

$$r_i \mid n_i, p_i \overset{\text{ind}}{\sim} \text{Binomial}(n_i, p_i), \quad i = 1, \ldots, N$$

In a single arm setting in early phase oncology trials, the goal is to get an estimation of $p_i$ for each cohort $i$ and compare that estimate to the benchmark response rate threshold. If the estimated response rate is greater than the pre-specified threshold in a cohort, the sponsor will consider continuing the development of the tested drug for that indication.

A popular Bayesian hierarchical modeling used to get estimations of $p_i$'s is proposed by Berry et al. (2013), where they use shrinkage estimators for each cohort under exchangeable assumptions and we call
this approach Berry’s BHM in the rest of the paper. Then model and prior can be briefly expressed as:

\[ \theta_i = \log\left( \frac{p_i}{1 - p_i} \right) - \log\left( \frac{p_{Ti}}{1 - p_{Ti}} \right) \]  
\[ \theta_i \sim N(\mu, \sigma^2), \quad i = 1, \ldots, N, \]
\[ \mu \sim N(0, 2^2), \quad \sigma^2 \sim HN(0, 1), \]
\[ r_i | n_i, p_i \overset{\text{ind}}{\sim} \text{Binomial}(n_i, p_i), \quad i = 1, \ldots, N \]

Where \( p_{Ti} \) is usually set as the benchmark response rate or control rate for cohort \( i \). \( \theta_i \) can be understood as the logit transformed treatment effect relative to the control rate. The values of the hyperparameters in aforementioned model for \( \mu \) and \( \sigma^2 \) are popular used and they are generally not too sensitive to different choices.

The performance of this model, however, is highly dependent on the validity of the exchangeable assumptions as well as the choices of control rate, which sometimes is hard to justify in real studies. If the exchangeable assumptions are not valid for \( \theta \)'s, there is high risk of over shrinkage on the estimations of cohort-specific response rate.

Neuenschwander et al. (2016) proposed a method that further allow each cohort-specific parameter to be exchangeable with other similar strata parameters or nonexchangeable with any of them, which is a data-drive approach to mitigate the risk of over shrinkage and we call this approach EXNEX in the rest of the paper. The model and prior can be briefly expressed as:

\[ \theta_i = \log\left( \frac{p_i}{1 - p_i} \right) \]  

EX: with probability \( \pi_i \);
\[ \theta_i \sim N(\mu, \sigma^2), \quad i = 1, \ldots, N, \]
\[ \mu \sim N(a, b^2), \quad \sigma^2 \sim HN(c, d), \]

NEX: with probability \( 1 - \pi_i \);
\[ \theta_i \sim N(\mu_i, \sigma^2_i), \quad i = 1, \ldots, N, \]
\[ r_i | n_i, p_i \overset{\text{ind}}{\sim} \text{Binomial}(n_i, p_i), \quad i = 1, \ldots, N \]

Where \( \pi_i \) is the weight of exchangeable component for cohort \( i \), which is usually set the same for all cohorts by default; the hyperparameters \( a, b, c, d \) for the exchangeable part is usually from the method for setting
weakly informative priors given in the on-line Appendix of Neuenschwander et al. (2016) unless there are specific prior information; the hyperparameters $\mu_i$ and $\sigma_i^2$ for each cohort are usually set so that $\mu_i$ equals to the log-odds of a plausible guess (or benchmark response rate) for cohort $i$ and $\sigma_i^2$ makes approximately one observation.

This model sometimes may suffer from too many pre-specified parameters or parameters that need to be tuned.

2.2 Mixture of Finite Mixtures model for binary data

To mitigate the possible issues mentioned above, we first cluster the cohorts into groups based on the observed response rates and then get shrinkage estimators within each group by assuming the exchangeable assumption.

Bayesian models offer a natural solution to simultaneously estimate the number of clusters and cluster assignments. The Chinese restaurant process (CRP; Neal, 2000) offers choices to allow for uncertainty in the number of clusters by assigning a prior distribution on the cluster assignments parameters $(z_1, z_2, \ldots, z_N)$, where $z_i$ denotes the cluster assignment for cohort $i$. In the CRP, $z_i, i = 2, \ldots, N$ have the following conditional distribution (i.e., a Pólya urn scheme, Blackwell et al., 1973)

$$P(z_i \mid z_1, \ldots, z_{i-1}) \propto \begin{cases} |c|, & \text{at an existing cluster labeled } c \\ \alpha, & \text{at a new cluster.} \end{cases} \tag{4}$$

Here $|c|$ refers to the size of cluster labeled $c$, and $\alpha$ is the concentration parameter of the underlying Dirichlet process. The prior distribution on the cluster assignments induces a prior distribution on the sizes of the clusters in the partition. Let $\mathcal{C}_N$ denotes a partition of the set $\{1, 2, 3, \ldots, N\}$ and $t = |\mathcal{C}_N|$ denote the number of blocks in the partition $\mathcal{C}_N$.

Under (4), one can obtain the probability of block-sizes $b = (b_1, b_2, \ldots, b_t)$ of a partition $\mathcal{C}_N$ as

$$p_{DP}(b) \propto \prod_{j=1}^{t} b_j^{-1}. \tag{5}$$

It is clear from (5) that CRP tends to assign large probabilities to highly imbalanced cluster sizes in
which, necessarily, some clusters will be quite small. This results in producing extraneous clusters in the posterior that leads inconsistent estimation on the number of clusters even when the sample size goes to infinity.

Miller and Harrison (2018) proposed a modification to the CRP, which is called a mixture of finite mixtures (MFM) model, to mitigate this issue:

\[ k \sim p(\cdot), \]
\[ \pi = (\pi_1, \ldots, \pi_k) \mid k \sim \text{Dir}(\gamma, \ldots, \gamma), \]
\[ z_i \mid k, \pi \sim \sum_{s=1}^{k} \pi_s \delta_s, \quad i = 1, \ldots, N, \]

where \( p(\cdot) \) is a proper probability mass function on \( \{1, 2, \ldots\} \), and \( \delta_s \) is a point-mass at \( s \). The joint distribution of \( (z_1, \ldots, z_n) \) under (6) admits a Pólya urn scheme akin to the CRP:

\[
P(z_i \mid z_1, \ldots, z_{i-1}) \propto \begin{cases} |c| + \gamma, & \text{at an existing cluster labeled } c \\ \frac{V_i(t+1)}{V_i(t)} \gamma, & \text{at a new cluster}, \end{cases}
\]

where the coefficients \( V_i(t) \) are given by,

\[ V_i(t) = \sum_{k=1}^{+\infty} \frac{k(t)}{(\gamma k)^{i}} p(k) \]

where \( k(t) = k(k-1)\ldots(k-t+1) \), and \( (\gamma k)^{(i)} = \gamma k(\gamma k + 1)\ldots(\gamma k + i - 1) \). (By convention, \( x^{(0)} = 1 \) and \( x^{(0)} = 1 \)). While this restaurant process bears close resemblance to the CRP, the introduction of new clusters is slowed down by a factor \( V_i(|C_{i-1}| + 1)/V_i(|C_{i-1}|) \), thereby pruning the tiny extraneous clusters.

An alternative way to understand the natural pruning of extraneous clusters is through the probability distribution induced on the cluster sizes. Again, let \( C_N \) denotes a partition with block-sizes \( b = (b_1, b_2, \ldots, b_t) \) and \( t = |C_N| \) under MFM. In contrast to (5), the probability of the cluster sizes \( (b_1, \ldots, b_t) \) under the MFM is

\[
p_{MFM}(b) \propto \prod_{j=1}^{t} b_j^{\gamma - 1}. \]

7
From (5) and (8), the comparison easily reveals that MFM assigns comparatively smaller probabilities to highly imbalanced cluster sizes.

We adapt MFM to our model setting in order to group different cohorts into clusters, then the model and prior can be expressed hierarchically as:

\[ k \sim q(\cdot), \text{where } q(\cdot) \text{ is a p.m.f on } \{1,2,\ldots\} \]
\[ P_s \sim \text{Beta}(\alpha,\beta), \quad s = 1,\ldots,k, \]
\[ \text{Pr}(z_i = s \mid \pi, k) = \pi_s, \quad s = 1,\ldots,k, i = 1,\ldots,N, \]
\[ \pi \mid k \sim \text{Dirichlet}(\gamma,\ldots,\gamma), \]
\[ r_i \mid n_i, z, P, k \sim \text{Binomial}(n_i, p_i), \quad p_i = P_{z_i}, i = 1,\ldots,N, \quad (9) \]

We assume \( q(\cdot) \) is a Poisson(1) distribution truncated to be positive through the rest of the paper, which has been proved by Miller and Harrison (2018) and Geng et al. (2019) to guarantee consistency for the mixing distribution and the number of clusters. Here, we define \( G = \sum_{s=1}^{k} \pi_s \delta_{P_s} \), where \( \delta \) is the point mass measure, and \( P_s \) is the collection of parameters for the binomial distribution in cluster \( s \) for \( s = 1,\ldots,k \) and \( P \) is Beta probability measure.

Let \( k_0, G_0, P_0 \) be the true number of clusters, the true mixing measure, and the corresponding probability measure, respectively. Then the following proposition establishes the posterior consistency and contraction rate for \( k \) and \( G \).

**Proposition 1.** Let \( \Pi_N(\cdot \mid r_1,\ldots,r_N) \) be the posterior distribution obtained from (9) given a random sample \( r_1,\ldots,r_N \). Assume that all the parameters are restricted to a compact space \( \Theta^* \). Then we have

\[ \Pi_N(k = k_0 \mid r_1,\ldots,r_N) \to 1, \quad \Pi_N(W(G, G_0) \lesssim (\log N/N)^{-1/2} \mid r_1,\ldots,r_N) \to 1, \]

almost surely under \( P_0 \) as \( N \to \infty \).

In order to prove the Proposition 1, we need to verify the conditions (P.1)-(P.4) in Guha et al. (2019) hold. Condition (P.1) is satisfied since we restrict our parameters of interest to a compact space \( \Theta^* \) and beta distribution is first-order identifiable. Condition (P.2) also holds since we assign a non-zero continuous distribution on the parameters within a bounded support. Beta base distribution is sufficient for Condition
Condition (P.4) holds since we choose a truncated Poisson distribution on $q(\cdot)$. The proof can be finished by using the results in Yin et al. (2020).

### 2.3 Proposed two-step procedure

We now propose a two-step procedure to find the balance between pooled and stratified analysis in basket trial design. In the first step, we treat it as a clustering problem by grouping cohorts into clusters that share the similar treatment effect using the model proposed in (9). In the second step, we further address heterogeneity for cohorts within each cluster by fitting the Bayesian Hierarchical model by Berry et al. (2013) in each cluster. For cluster $s$, the model and prior can be expressed as:

$$
\theta_j = \log\left(\frac{p_j}{1-p_j}\right) - \log\left(\frac{p_T}{1-p_T}\right)
$$

(10)

$$
\theta_j \sim N(\mu, \sigma^2), \quad j = 1, \ldots, n_s,
$$

$$
\mu \sim N(0, 2^2), \quad \sigma^2 \sim HN(0, 1),
$$

$$
r_j \mid n_j, p_j \overset{\text{ind}}{\sim} \text{Binomial}(n_j, p_j), \quad j = 1, \ldots, n_s,
$$

where $n_s$ denotes the number of cohorts in cluster $s$.

### 3 Bayesian Inference

#### 3.1 MCMC Algorithm

For the step one of our proposed methods, we design an efficient Gibbs sampler algorithm without reversible jumps algorithm which is easier to get the posterior samples for clustering labels. The Gibbs sampler for step one is presented in Algorithm 1.

For step two, we don’t derive MCMC algorithm ourselves since the full conditional distributions are not in closed form. The gMAP function in Rbest package in R is used to handle Berry’s BHM.
Algorithm 1 Collapsed sampler for MFM-BD

1: procedure C-MFM-BD
2: Initialize $z = (z_1, \ldots, z_N)$ and $P = (P_s)$.
3: for each iter = 1 to M do
4: Update $P = (P_s)$ conditional on $z$ in a closed form as

$$P_s \mid r, n, z \sim \text{Beta}(\alpha + r_s, \beta + N_s - r_s)$$

Where $r_s = \sum_{z_i = s} r_i$ and $N_s = \sum_{z_i = s} n_i$, $r = 1, \ldots, k$. Here $k$ is the number of clusters formed by current $z$.
5: Update $z = (z_1, \ldots, z_N)$ conditional on $P = (P_s)$, for each $i$ in $(1, \ldots, N)$, we can get a closed form expression for $P(z_i = c \mid z_{-i}, r, n, P)$:

$$\propto \begin{cases} |c| + \gamma \text{dbinom}(r_i, n_i, P_{z_i}) & \text{at an existing table } c \\ \frac{V_n(|c_{-i}| + 1)}{V_n(|\tilde{c}_{-i}|)} m(S_i) & \text{if } c \text{ is a new table} \end{cases}$$

where $c_{-i}$ denotes the partition obtained by removing $z_i$ and

$$m(S_i) = \binom{n_i}{r_i} \frac{B(r_i + \alpha, n_i - r_i + \beta)}{B(\alpha, \beta)}$$

Where $B(.,.)$ is beta function.
6: end for
7: end procedure
Another important task for our proposed method is the inference of MCMC results.

We first discuss the inference on cluster assignment parameter $z$. The posterior mean or median of $z$ is not suitable. Dahl’s method (Dahl, 2006) provides a remedy for posterior inference of the clustering configurations $z$. It chooses the iteration in the posterior sample that optimizes a least squares criterion as the estimate for $z$. We firstly define an $n \times n$ membership matrix

$$B = (B(i, j)) = \left(1(z_i = z_j)\right), \quad i, j \in \{1, 2, \ldots, n\},$$

(11)

where $1(\cdot)$ is the identical function. The $(i, j)$-th element of membership matrix is 1 if the $i$-th and $j$-th observations belong to the same component (or have the same baseline intensity); it is 0 otherwise. For the MCMC samples, we calculate the $B^{(i)}$ for $i$-th iterations. And then calculate the element-wise mean of the membership matrices $\bar{B} = \frac{1}{L} \sum_{l=1}^{L} B^{(l)}$, where the summation is element-wise. Finally, we identify the most close posterior draw as the one that is closest to $\bar{B}$ with respect to the element-wise Euclidean distance $\sum_{i=1}^{n} \sum_{j=1}^{n} (B^{(l)}(i, j) - \bar{B}(i, j))^2$ among the retained $l = 1, \ldots, L$ posterior draws. The posterior estimates of cluster memberships $z_1, \ldots, z_n$ can be summarized based on the draw identified by Dahl’s method.

Within each cluster, the cohort specific parameter $\theta_j$’s will be summarized by posterior mean and the Bayesian estimate for response rate $p_j$ will be directly from solving the equation in (10).

4 Simulation

In this section, we investigate the performance of our proposed method from a variety of measures.

4.1 Simulation Settings and Evaluation Metrics

In the simulation study, we have five different scenarios with two different sample sizes (20 or 30) in each cohort. The response rates for each scenarios are shown in Table 1.

In all the simulation scenarios considered below, we employed Algorithm 1 with $\gamma = 1$ and $\alpha = \beta = 1$ to fit the MFM-BD model. We arbitrarily initialized our algorithm with 5 clusters and randomly allocated the cluster assignments. We experimented with various other choices and did not find any evidence of sensitivity
Scenario Response Rate Design

| Scenario     | Response Rate Design                           |
|--------------|-----------------------------------------------|
| Scenario 1   | $P_1 = P_2 = \ldots = P_{10} = 0.4$          |
| Scenario 2   | $P_1 = \ldots = P_5 = 0.2$, $P_6 = \ldots = P_{10} = 0.6$ |
| Scenario 3   | $P_1 = \ldots = P_5 = 0.2$, $P_6 = \ldots = P_{10} = 0.5$ |
| Scenario 4   | $P_1 = P_2 = P_5 = 0.1$, $P_4 = P_5 = P_6 = 0.4$, $P_7 = \ldots = P_{10} = 0.7$ |
| Scenario 5   | $P_1 = P_2 = \ldots = P_{10} = 0.2$          |

Table 1: Simulation designs for different scenarios

to the initialization. Results from our method is based on 5000 MCMC iterations leaving out a burn-in of 2000 in step one and 8000 MCMC iterations leaving out a burn-in of 2000 in step two.

For Berry’s BHM and EXNEX approach, the choice of hyper-parameters are from the default settings as stated in section 2.1. Results from those two approaches are based on 10000 MCMC iterations leaving out a burn-in of 2000.

For our proposed method, the estimated number of clusters $\hat{K}$ for each replicate is summarized from the MCMC iteration picked by Dahl’s method which is introduced in Section 3.2. The performance of the posterior estimates of parameters for all methods were evaluated by the average absolute bias (AAB) and the mean square error (AMSE) in the following ways, take $\theta_i$ as an example:

$$
\text{AAB} = \frac{1}{10} \sum_{i=1}^{10} \left| \frac{1}{500} \sum_{r=1}^{500} (\theta_{i}^{r} - \theta_{i}^{0}) \right| ,
$$

$$
\text{MMSE} = \frac{1}{10} \sum_{i=1}^{10} \sqrt{ \frac{1}{500} \sum_{r=1}^{500} (\theta_{i}^{r} - \theta_{i}^{0})^2 },
$$

where $\theta_{i}^{r}$ is the posterior mean of rth replicate for ith cohort and $\theta_{i}^{0}$ is the true value of ith cohort.

### 4.2 Simulation Results

First, we present the cluster estimates of our proposed methods in Table 2. From the results shown in Table 2, we see that our proposed methods successfully recover the number of clusters within a reasonable range for all five different scenarios under two different sample size. In addition, the large sample size will cause better estimates of the number of clusters by comparing results between $n = 20$ and $N = 30$.

Furthermore, we compare our proposed methods with Berry’s BHM and EXNEX under the criteria we proposed in Section 4.1. The simulation results are presented in Table 3 and Table 4. All simulations results
Table 2: Clustering Performance for Simulation Studies

| Scenario | n  | \( \hat{K} \) | S.D. of \( \hat{K} \) |
|----------|----|---------------|---------------------|
| Scenario 1 | n = 20 | 1.046 | 0.210 |
|           | n = 30 | 1.036 | 0.186 |
| Scenario 2 | n = 20 | 2.168 | 0.417 |
|           | n = 30 | 2.131 | 0.346 |
| Scenario 3 | n = 20 | 1.945 | 0.516 |
|           | n = 30 | 2.105 | 0.376 |
| Scenario 4 | n = 20 | 2.661 | 0.612 |
|           | n = 30 | 2.929 | 0.559 |
| Scenario 5 | n = 20 | 1.026 | 0.159 |
|           | n = 30 | 1.020 | 0.140 |

are based on 500 replicates. From the results shown in Table 3 and Table 4, we see that our proposed methods have better estimation performance based on AAB when heterogeneity exits among different cohorts and the AMSE is comparable with benchmark methods.

Table 3: Simulation Results (\( n = 20 \))

| Scenario | Berry’s BHM | EXNEX | MFM-BD |
|----------|-------------|-------|--------|
| Scenario 1 | AAB       | 0.0015 | 0.0026 | 0.0025 |
|           | AMSE       | 0.0024 | 0.0056 | 0.0026 |
| Scenario 2 | AAB       | 0.0430 | 0.0274 | 0.0131 |
|           | AMSE       | 0.0091 | 0.0095 | 0.0069 |
| Scenario 3 | AAB       | 0.0485 | 0.0304 | 0.0266 |
|           | AMSE       | 0.0087 | 0.0093 | 0.0096 |
| Scenario 4 | AAB       | 0.0305 | 0.0256 | 0.0261 |
|           | AMSE       | 0.0086 | 0.0086 | 0.0102 |
| Scenario 5 | AAB       | 0.0023 | 0.0064 | 0.0119 |
|           | AMSE       | 0.0016 | 0.0037 | 0.0016 |

In order to have a closer look of estimation performance, we have the boxplots of posterior estimates of different cohorts in Figure 1. From the results shown in Figure 1, we see that in each cohort our proposed method performs better than other two methods when there exist heterogeneities among different cohorts.
Table 4: Simulation Results \((n = 30)\)

| Scenario | Method | Berry’s BHM | EXNEX | MFM-BD |
|----------|--------|-------------|-------|--------|
| Scenario 1 | AAB    | 0.0012      | 0.0019 | 0.0015 |
|           | AMSE   | 0.0016      | 0.0036 | 0.0017 |
| Scenario 2 | AAB    | 0.0303      | 0.0180 | 0.0056 |
|           | AMSE   | 0.0063      | 0.0064 | 0.0035 |
| Scenario 3 | AAB    | 0.0349      | 0.0223 | 0.0107 |
|           | AMSE   | 0.0061      | 0.0065 | 0.0053 |
| Scenario 4 | AAB    | 0.0207      | 0.0179 | 0.0136 |
|           | AMSE   | 0.0059      | 0.0060 | 0.0061 |
| Scenario 5 | AAB    | 0.0015      | 0.0039 | 0.0068 |
|           | AMSE   | 0.0011      | 0.0024 | 0.0010 |

Figure 1: Posterior Estimates Boxplots for Different Cohorts under Scenario 3
Table 5: Response estimations Results

| Subtype     | r/n   | %   | Posterior mean (CI) | MFM-BD          | Berry’s BHM      | EXNEX          |
|-------------|-------|-----|---------------------|------------------|------------------|----------------|
| Cluster 1   |       |     |                     |                  |                  |                |
| 1. ATC      | 2/7   | 28.6| 31.8 (6.9,62.3)     | 26.7 (6.3,57.6)  | 27.5 (5.1,60.1)  |                |
| 2. ECD/LCH  | 6/14  | 42.9| 41.6 (20.3,65.7)    | 38.3 (17.7,63.2) | 40.7 (18.1,65.3) |                |
| 6. NSCLC    | 8/19  | 42.1| 41.2 (21.9,61.9)    | 38.6 (19.8,60.5) | 40.5 (20.6,62.3) |                |
| Cluster 2   |       |     |                     |                  |                  |                |
| 3. CCA      | 1/8   | 12.5| 12.6 (1.7,35.7)     | 16.2 (2.1,39.9)  | 15.4 (1.5,42.5)  |                |
| 4. CRC-V    | 1/26  | 3.8 | 6.6 (0.7,16.7)      | 7.5 (0.9,20.3)   | 5.9 (0.6,16.7)   |                |
| 5. CRC-VC   | 0/10  | 0.0 | 6.5 (0.1,20.4)      | 8.3 (0.2,26.5)   | 5.8 (0.1,23.3)   |                |

5 Real Data Analysis

In this section, we apply the proposed MFM-BD to the analysis of a famous basket trial (Hyman et al., 2015). This trial is a histology-independent “basket” study of vemurafenib in BRAF V600 mutation–positive non-melanoma cancers, where patients were enrolled in six prespecified cancer cohorts including anaplastic thyroid cancer (ATC), Erdheim-Chester disease or Langerhans’-cell histiocytosis (ECD/LCH), cholangiocarcinoma (CCA), colorectal cancer treated by vemurafenib (CRC-V), colorectal cancer treated by vemurafenib and cetuximab (CRCVC), and non small cell lung cancer (NSCLC). The primary end point was the response rate. A total of 84 evaluable patients are included in the analysis. The sample size and observed responses for each cohort are presented in Table 5.

Results from our method (MFM-BD) is based on 5000 MCMC iterations leaving out a burn-in of 2000 in step one and 8000 MCMC iterations leaving out a burn-in of 2000 in step two; initialized at a randomly generated configuration with 5 clusters. From Table 5, 6 subtypes are grouped into two clusters. The first cluster includes ATC, ECD/LCH and NSCLC and the second cluster includes CCA, CRC-V and CRC-VC.

For comparison, we also conduct analysis based on Berry’s BHM and EXNEX approach. The parameter settings for both methods are consistent from those used in simulation studies. From the results in Table 5, we can see that when comparing to the other approaches, our proposed MFM-BD give the estimations more shrinkage within each cluster and more divergence between clusters.
6 Discussion

In this article, we propose a two-step procedure to evaluate the efficacy of the new treatment (binary response endpoint) in multiple cohorts in a basket trial, which has excellent performance in both simulation and real data examples. The article provides a new way of borrowing information across different cohorts by firstly clustering into groups without pre-specifying the number of groups, and then borrow information within each group under exchangeable assumption. The clustering of those cohorts can give further directions for development of a new drug. The approach is also proved to yield consistent detection of the number of clusters.

While we recommend using Berry’s BHM in the second step of our approach, other popular approaches such as EXNEX model can also be implemented. This proposed approach is more appropriate for basket trials where the number of cohorts is relatively large (e.g. 6 cohorts or more).

Further extension of this work includes: analysing time-to-event endpoint such as Progression Free Survival (PFS) and Overall Survival (OS) (Xu et al., 2019) under the same framework; adding another layer of heterogeneity so that it can also be used in platform trials where there are multiple treatment options and multiple cancer types.
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