An evaluation and modification of Simon's basket design in oncology

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1. Introduction

- Recent development of molecular biology and genomics allow to classify patients with a common organ-specific cancer into the several subpopulations depending on their molecular profiles including biomarker or genomic feature.
- To accommodate this growing trend, basket trial which evaluates the efficacy of the targeted therapy to the corresponding molecular characterization across the cancer types has been operated.
- For screening a targeted therapy that should be forwarded to confirmatory trial, non-randomized basket trials are generally used in the context of phase II trials.
- Simon (2017) provided a basic framework of new basket design that evaluate the posterior probability of the drug activity in the context of Bayesian model averaging, but little is known about the operating characteristic of this design. The posterior probability of the drug activity is calculated based on the assumption that response rates of all subpopulations are equal (or not equal) using the interim data of all the subpopulations during the trial.
- However, the response rates are sometimes different among the subpopulations; for example, vemurafenib is active in several histologies with V600E BRAF mutation, but not in colorectal cancer (Hyman et al., 2015).

2. Purpose

- To accommodate the inconsistency of the drug activity among subpopulations, we propose the modified Simon's method, and examine the operating characteristics of it by simulation studies.
- The Bayesian hierarchical model (BHM) design is one of the successful approach for evaluating the drug activity across several subpopulations. In recent times, BHM with exchangeability–nonexchangeability (EXNEX) has developed. We therefore compare the operating characteristics between Simon's methods and the BHM methods.

3. Simon's basket design

- Let n_k denote the number of patients for stratum k (= 1, …, K) and r_k denote the number of response for stratum k. Let p_k denote the response rate for stratum k. We assume that: if $p_k \geq p_{high}$, then the drug is active in stratum k; and if $p_k \leq p_{low}$, then the drug is not active in stratum k.
- In the Simon's design (Simon, 2017), given the data ($\mathbf{r} = (r_1, r_{2,\ldots}, r_K)$, $\mathbf{n} = (n_1, n_{2,\ldots}, n_K)$) at that time, the posterior probability of the drug activity $\Pr[p_k = p_{high} | \mathbf{r}, \mathbf{n}]$ that are used to assess whether the drug is active at stratum k during and at the end of the trial, is defined as the weighted probability under the two hypotheses H_0 and H_1:

$$\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n}] = \Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_0]\Pr[H_0|\mathbf{r},\mathbf{n}] + \Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_1]\Pr[H_1|\mathbf{r},\mathbf{n}], \quad (1)$$

where H_0 indicates that the response rates in all the stratum are equal, H_0: $p_1 = p_2 = \cdots = p_K$ and H_1 indicates that the response rates are independent random variables from a common two point prior distribution (i.e., $\Pr[p_k = p_{high} \mid H_1](= \gamma)$ and $\Pr[p_k = p_{low} \mid H_1](= 1-\gamma)$).

- To obtain the $\Pr[H_0|\mathbf{r},\mathbf{n}]$, Simon (2017) derived the posterior probability for H_0 as follows based on the Bayesian theorem:

$$\Pr[H_0|\mathbf{r},\mathbf{n}] = \left\{1 + \frac{(1-\lambda)\prod_{k=1}^{K}\{\gamma \cdot b(r_k; p_{high}, n_k) + (1-\gamma)\cdot b(r_k; p_{low}, n_k)\}}{\lambda\{\gamma\prod_{k=1}^{K} b(r_k; p_{high}, n_k) + (1-\gamma)\prod_{k=1}^{K} b(r_k; p_{low}, n_k)\}}\right\}^{-1}, \quad (2)$$

where $b(r; p, n)$ denotes binomial distribution with parameter p, λ is the prior probability of H_0, and 1-λ is the prior probability of H_1.

- $Pr[\mathbf{r}|\mathbf{n}, H_0]$ is defined as the probability mixed joint probabilities $\prod_{k=1}^{K} b(r_k; p_{high}, n_k)$ and $\prod_{k=1}^{K} b(r_k; p_{low}, n_k)$ with mixture probability γ; and $Pr[\mathbf{r}|\mathbf{n}, H_1]$ is defined as the joint probability with mixture probabilities for each stratum $\gamma \cdot b(r_k; p_{high}, n_k) + (1-\gamma) \cdot b(r_k; p_{low}, n_k)$.
- On the basis of this context, the $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_0]$ and $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_1]$ in Equation (1) can be also derived as follows:

$$\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_0] = \left\{1 + \frac{(1-\gamma)\cdot\prod_{k=1}^{K}\{b(r_k; p_{low}, n_k)\}}{\gamma\cdot\prod_{k=1}^{K} b(r_k; p_{high}, n_k)}\right\}^{-1}, \quad (3)$$

$$\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n},H_1] = \frac{\gamma\cdot b(r_k; p_{high}, n_k)}{\gamma\cdot b(r_k; p_{high}, n_k) + (1-\gamma)\cdot b(r_k; p_{low}, n_k)}. \quad (4)$$

- In each interim analysis, we calculate the posterior probability of the drug activity $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n}]$ from Equation (1). If $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n}] > \delta$ which is the prespecified threshold, then we determine that the drug is active in stratum k and terminate the patient enrollment for the stratum k; and similarly if $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n}] < 1-\delta$, then we determine that the drug is not active in that stratum and terminate the patient enrollment for the stratum k; otherwise, we continue to enroll patients to the stratum k.
- The recruitment of patients continues until the sample size reach to N_{max} or the accrual to all the strata close.

4. Modified method

- We proposed the homogeneous probabilities of the response rates between subpopulations and the calculating method of the posterior probability of the drug activity based on the homogeneous probabilities. Specifically, we evaluate the homogeneous probabilities of the response rates between subpopulations, then divide the subpopulations into the homogeneous subsets based on the homogeneous probabilities. We calculate the posterior probabilities of the drug activity based on the homogeneous subsets.
- We calculate the homogeneous probability of the response rates between the stratum l and m ($l \neq m$) using Equation (2) as follows:

$$\Pr[p_l = p_m|r_l, r_m, n_l, n_m] = \left\{1 + \frac{(1-\lambda)\prod_{k=l,m}\{\gamma\cdot b(r_k;p_{high},n_k)+(1-\gamma)\cdot b(r_k;p_{low},n_k)\}}{\lambda\{\gamma\prod_{k=l,m} b(r_k;p_{high},n_k)+(1-\gamma)\prod_{k=l,m} b(r_k;p_{low},n_k)\}}\right\}^{-1}. \quad (5)$$

- We extract the strata that satisfy $\Pr[p_l = p_m|r_l, r_m, n_l, n_m] > \varepsilon$, then the extracted strata is defines as a homogeneous set.
- Let $r_{HS,i,j}$ denotes the number of response at stratum *i* in a homogeneous set *j*; and $n_{HS,i,j}$ denotes the number of patients at stratum *i* in a homogeneous set *j*. The number of response in a homogeneous subset *j* is $\mathbf{r}_{HS,j} = \sum_{i=1}^{I} \mathbf{r}_{HS,i,j}$; the number of patients in a homogeneous subset *j* as $\mathbf{n}_{HS,j} = \sum_{i=1}^{I} \mathbf{n}_{HS,i,j}$.
- We calculate the posterior probability of the drug activity of stratum *k* based on the homogeneous subset which includes stratum *k* (i.e., $\Pr[p_k = p_{high}|\mathbf{r}_{HS,j}, \mathbf{n}_{HS,j}]: r_k \in \mathbf{r}_{HS,j}, n_k \in \mathbf{n}_{HS,j}$).
- The other procedures are same as those of the Simon's method.

5. Simulation studies

Simulation Settings

- The procedure of each simulation experiment is based on that of the Simon R (2017).
- Let N_{max} denote maximum sample size of the trial, and denote *t* is the number of interim analyses. Nt (*t*=1, …, T) denotes the sample size for each interim analysis. Let $N_{add,t}$ denote the number of patients which are added from t-1th interim analysis to tth interim analysis.
- We assumed that p_{high} and p_{low} are 0.25 and 0.05, respectively. The prior probability of $\Pr[p_k = p_{high} \mid H_1]$, γ, was set to 0.33, 0.50, or 0.80; the prior probability of H_0, λ, was set to 0.33, 0.50, or 0.80; and the number of strata K was set to 2, 5, or 10. From practical views and examples of basket trial, we also assumed that maximum sample size of the trial is 50 or 100, and the number interim analysis is one. The two thresholds of δ and ε were set to 0.8 and 0.3. Thus, we conducted the simulation experiments under the 54 scenarios based on different γ, λ, K, and N_{max}.
- Refer to Thall et al. (2003), we set the values of hyperparameters for BHM as follows: $\tilde{\mu} = -1.734$ (i.e., $p = 0.15$), $\widetilde{\sigma^2} = 10$, $\alpha = 2, \beta = 20$.
- For the EXNEX model, we assumed two EX models and NEX model. According to Neuenschwander et al. (2015), we set the values of hyperparameters of EXNEX model as follows: $\widetilde{\mu_1} = -2.944$ (i.e., $p = 0.05$), $\widetilde{\sigma_1^2} = 20.052$, $\widetilde{\mu_2} = -1.098$ (i.e., $p = 0.25$), $\widetilde{\sigma_2^2} = 4.333$, $s = 1, m_\omega = -1.734$ (i.e., $p = 0.15$), $v_\omega = 7.843, \rho_1 = 0.25, \rho_2 = 0.25$, and $\rho_3 = 0.50$.
- Let *u* be the number of the strata that the drug is truly active among K strata. We considered K + 1 combinations of u and K - u, that is, (0, K), (1, K - u), … , (K, 0), and operated the following steps for each of the combination.

Step1: Let $N_{add,t,k}$ be the number of patients in stratum k added between the t-1th and tth interim analyses and $N_{add,t,k}$ are randomly generated from polynomial distribution which generating probabilities for each stratum are equal.

Step2: Let $r_{add,t,k}$ denote the number of response patients for the stratum k from t-1th interim analysis to tth interim analysis. If the drgu is truly active in the stratum k, then $r_{add,t,k}$ is randomly generated from binomial distribution whose parameters are p_{high} and $N_{add,t,k}$; if the drug is truly inactive in the stratum k, then $r_{add,t,k}$ is randomly generated from binomial distribution whose parameters are p_{low} and $N_{add,t,k}$.

Step3: We calculated the posterior probabilities of the drug activity of $\Pr[p_k = p_{high}|\mathbf{r},\mathbf{n}]$ from the generated data in each interim analysis and final analysis.

Step 4: Step 1—3 are repeated until the sample size of the trial reach to N_{max} or all strata close.

- The above simulation was performed 1000 times for each K + 1 combinations of u and K – *u*.
- For each simulation, we calculated the number of stratum for true positive (TP), false positive (FP), false negative (FN), and true negative (TN), as defined in Table 1; and the number of sample size at termination of an simulation (NST) and the number of indeterminable strata at termination of an simulation (NIS).
- For each combinations, the average numbers of TP (TP_u) , FP (FP_u), NST (NST_u) and NIS (NIS_u) in 1000 simulations were reported.
- We also examined the average of TP_u, FP_u, NST_u, NIS_u respectively as follows: $\overline{TP} = \sum_{u=1}^{K} TP_u/K$; $\overline{FP} = \sum_{u=0}^{K-1} FP_u/K$; $\overline{NST} = \sum_{u=0}^{K} NST_u/K + 1$; $\overline{NIS} = \sum_{u=0}^{K} NIS_u/K + 1$.

Table 1. Result of the drug activity for each stratum

True probability of p_k	Result of the drug activity for each stratum	
	$\Pr[p_k = p_{high}\|\mathbf{r},\mathbf{n}] > \delta$	$\Pr[p_k = p_{high}\|\mathbf{r},\mathbf{n}] < 1-\delta$
p_{high}	TP	FN
p_{low}	FP	TN

Simulation Results

- Simon R (2017) recommended parameter values $\gamma = 0.50$ and λ= 0.33, therefore we have shown $\overline{TP}$, $\overline{FP}$, $\overline{NST}$ *and* $\overline{NIS}$ for each K when $\gamma = 0.50$, λ= 0.33, and N_{max} = 50 in Figure 1, respectively. We also have shown TPu, FP_u, NST_u, NIS_u for each *u* when λ= 0.33, $\gamma = 0.50$, K=10, and N_{max} = 50 in Figure 2, respectively.

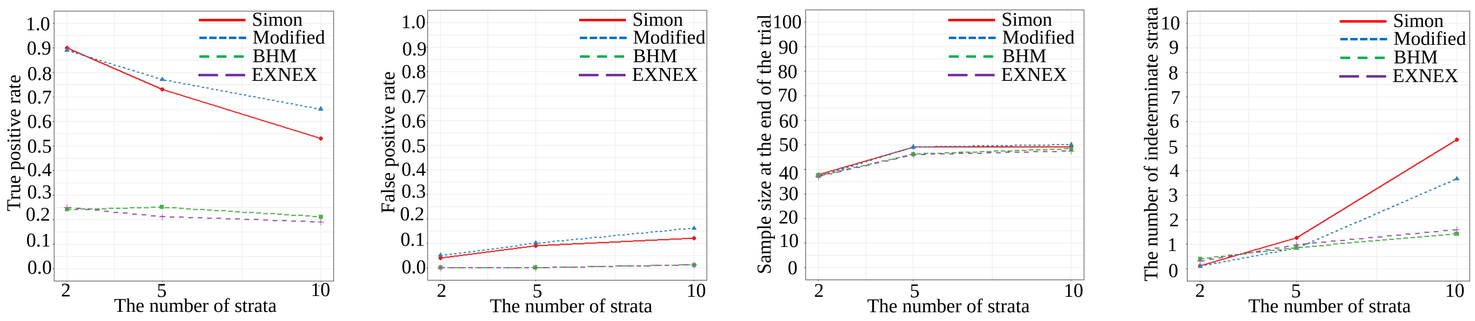

Figure 1. Result of the $\overline{TP}$, $\overline{FP}$, $\overline{NST}$, $\overline{NIS}$ ($\gamma = 0.5, \lambda = 0.33$, and N_{max}=50)

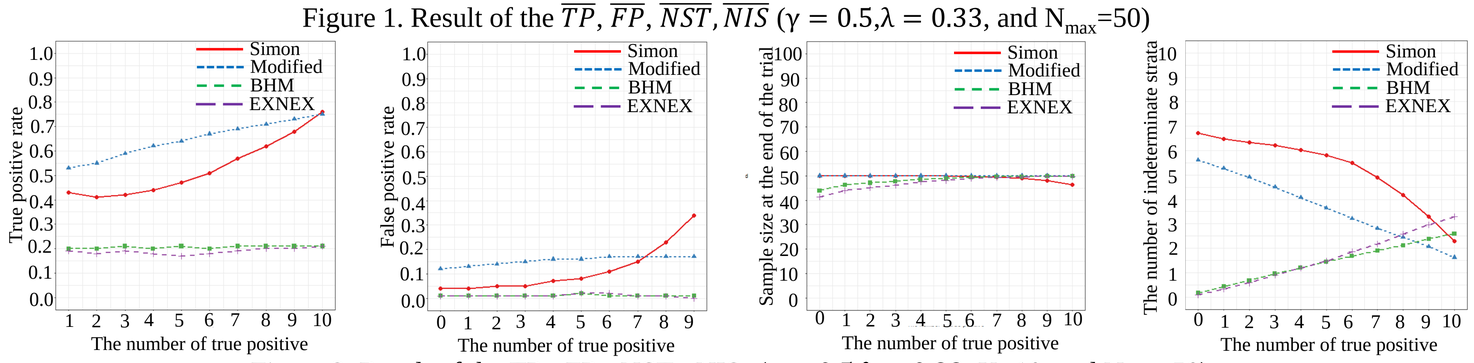

Figure 2. Result of the TP_u, FP_u, NST_u, NIS_u ($\gamma = 0.5, \lambda = 0.33$, K=10, and N_{max}=50)

- We have evaluated the results of $\overline{TP}$, $\overline{FP}$, $\overline{NST}$, $\overline{NIS}$ under other conditions (The results are not shown). The results when N_{max} =100 were similar to that when N_{max} =50. $\overline{TP}$ and $\overline{FP}$ for Simon's and the modified methods increased with increase in γ. While $\overline{FP}$ of the modified method was similar to that of Simon's method when γ=0.33 and 0.50, $\overline{FP}$ of the modified method was much lower than that of Simon's method when γ=0.8. $\overline{NST}$ *and* $\overline{NIS}$ for Simon's and the modified methods did not depend to values of γ. $\overline{TP}$ for Simon's and the modified methods did not depend to values of λ. $\overline{FP}$ of the modified method was much less than that of Simon's method if λ= 0.8. $\overline{NST}$ for Simon's and the modified methods did not depend to values of λ, whereas $\overline{NIS}$ for Simon's and the modified methods decreased with increase in λ.

6. Discussion

- Our modified outperformed the Simon's method with respect to true positive determinations, and the number of indeterminable strata when the number of strata is large. The number of strata in real example such as BRAF V600E study (Hyman, 2015) is sometimes more than 10 subpopulations; therefore, our modified is relatively suitable to the practical settings of the non-randomized basket trials.
- BHM and EXNEX model did not work well in detecting the drug activity in the simulation studies of Simon's basket design.
- The homogeneous probability indicates the quantitative relationships between the strata. This information may be useful for determining which strata should be forwarded to confirmatory trial.

7. References

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