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RESEARCH ARTICLE

Two-stage Adaptive Biomarker-Targeted Clinical Trial Design: Non-Parametric Bayesian and MLE Approaches

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Abstract

Biomarker targeted two-stage adaptive design is used increasingly in early-stage clinical trials in a variety of therapeutic areas including oncology, where the sample size of the trial is re-estimated based on the first stage data. In such trials often the sample size is moderate, and so incorporating prior information and using robust methods are desirable. In this article, to improve upon existing methods using parametric normal models, we propose a nonparametric Bayesian approach for designing such adaptive trials in a phase IIb/IIIa setting comparing a treatment vs. a control. Extensive simulation studies are conducted to evaluate the performance of the proposed method and compare it with the existing normal parametric model. Our results indicate that with good prior information, more reasonable and robust inference than with existing parametric methods can be obtained.

Keywords

Adaptive design, Biomarker targeted design, Maximum likelihood estimate, Non-parametric Bayes model, Sample size, Two-stage clinical trial

Introduction

Biomarker targeted design is an important step towards precision medicine, which can improve efficiency of randomized clinical trial [1,2]. Zhou, et al. [3] and Lee, et al. [4] proposed Bayesian approach and Wang, et al. [5] applied this design in therapeutic trials, Freidlin, et al. [6] discussed issues with this design, Tang and Zhou [7] proposed a general framework. The two or three stage designs are commonly used in recent phase IIb-IIa trials comparing treatment vs. control. Such sequential monitoring has become an integral part of clinical trial. It allows for early stopping of the trial for extreme results observed in interim stage(s) [8-11].

More recently, Gao, Roy, and Tan [12,13] proposed a two-stage adaptive design for biomarker targeted population where only biomarker positive subjects enter the trial study. However, the test is imperfect subject to false positive and false negative errors. Thus a mixture normal model is used for the biomarker positive subjects. The final sample size re-estimation is based on the positive predict value (PPV), the proportion of true positives among test positives, estimated from the first stage data, deviates slight from a more common adaptive designs [14-16]. Proschan [17] and Xiong, Tan and Boyett [18] discussed sample size re-estimation in clinical trials. Since for early-stage clinical trial, often the sample size is relatively small, and so incorporating valuable prior information, if available, and using a robust method would be desirable. For the first goal a Bayesian model is preferable, while for robustness the nonparametric method is more suitable. Thus, we propose a nonparametric Bayesian method to achieve both goals.

The rest of this article is organized as follows. Section 2 introduces the problem, then develops the proposed nonparametric Bayesian method, and compares with the frequentist parametric method, the two-stage sequential test, and sample size re-estimation. In Section 3, extensive simulation studies are conducted to evaluate the performance of the proposed method, compared it with the existing normal parametric model. We leave the technical details in the Appendix.

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Background and the Proposed Method

Background and review of the existing methods

We first introduce the setting by briefly reviewing the related targeted design in Gao, Roy, and Tan [13]. Consider a two-stage clinical trial with continuous or response endpoint comparing two groups, control and treatment, to assess the effect of a new treatment. The observed data at stage k is $D_{n_k} = \{x_{Ci}, x_{Tj} : i = 1,\ldots,n_{Ck}, j = 1,\ldots,n_{Tk}\}$ from independent biomarker test positive individuals (k = 1, 2), x_{Ci} is response from the i-th individual in the control group, and x_{Tj} is that from the control group. By convention, the sample size n_{C2} and n_{T2} include n_{C1} and n_{T1}; $n_1 = n_{C1} + n_{T1}$ is the planned sample size for stage I; and $n_2 = n_{C2} + n_{T2}$ is the total sample size at end of the trial, which is subject to updating based on parameters estimates from stage I data. Let μ_C be the mean response of the control group, μ_T be that for the treatment group, and $\vartheta = \mu_T - \mu_C$ be the treatment difference in the overall study population. The objective of the trial is to test whether there is treatment difference between the two arms, i.e. to test $H_0 : \vartheta = 0$ versus $H_A : \vartheta \neq 0$, with pre-specified significance level α and power β, and determine the total sample size n_2.

Since only biomarker test positive patients enter the trial, and a proportion ω of them are truly positive. Hence the trial population consists of true biomarker enrichment group (E) and the non-enrichment (NE) group. Let μ_{0C} and μ_{1C} be the mean response for NE and E group in control arm respectively; μ_{0T} and μ_{1T} be those for NE and E portion in the treatment arm respectively, and μ_C and μ_T be those of the control and treatment groups. Then

$$\mu_C = (1-\omega)\mu_{0C} + \omega\mu_{1C} \text{ and } \mu_T = (1-\omega)\mu_{0T} + \omega\mu_{1T}.$$

In Gao, Roy and Tan [13], the following normal mixture model are used

$$X_{Ci} \sim (1-B_i)N(\mu_C,\sigma^2) + B_i N(\mu_C,\sigma^2) \sim N(\mu_C,\sigma^2),\ (i = 1,\ldots,n_C),$$

$$X_{Ti} \sim (1-B_i)N(\mu_C,\sigma^2) + B_i N(\mu_T,\sigma^2),\ (i = 1,\ldots,n_T),$$

where $B_i \sim$ *Bernoulli* (ω).

Let $\bar{x}_C^{(1)}$ and $\bar{x}_T^{(1)}$ be the sample means of the control and treatment group at end of stage I, $\hat{\mu}_C = \bar{x}_C^{(1)} / \omega, \hat{\mu}_T^{(1)} = \bar{x}_T^{(1)} / \omega,$

$$\hat{\sigma}_C^2 = \frac{1}{n_{C1}-1}\sum (x_{Ci}{}^{(1)} - \bar{x}_C^{(1)})^2,\quad \hat{\sigma}_T^2 = \hat{\sigma}_C^2 + \omega(1-\omega)(\hat{\mu}_T^{(1)} - \hat{\mu}_C^{(1)})^2.$$

Then the total sample size n_2 needed for the whole trial is estimated as

$$\hat{n}_2 = \frac{(Z_{\alpha/2} + Z_\beta)^2 \sigma_{T-C}^2}{\mu_{T-C}^2},$$

$$\text{where } \mu_{T-C} = (1-\omega)(\hat{\mu}_{0T} - \hat{\mu}_{0C}) + \omega(\hat{\mu}_{1T} - \hat{\mu}_{1C}) = \omega(\hat{\mu}_T - \hat{\mu}_C),\ \text{and } \sigma_{T-C}^2 =$$
$$[\sigma^2 + \omega(1-\omega)(\hat{\mu}_{1T} - \hat{\mu}_{0T})^2] + [\sigma^2 + \omega(1-\omega)(\hat{\mu}_{1C} - \hat{\mu}_{0C})^2] = 2\sigma^2 + \omega(1-\omega)(\hat{\mu}_T - \hat{\mu}_C)^2.$$

Maximum likelihood estimation (MLE) for mixture model is more conveniently obtained by the EM algorithm, given in the Appendix.

The proposed method

For early-stage clinical trial often the sample size is relatively small, and in some cases there is prior knowledge about the data distribution. A subjectively specified parametric model however may not be able to describe the distribution, so a nonparametric prior is preferred. Thus we adopt a nonparametric Bayesian model for this problem.

Let F_C and F_T be the distribution function of the control and treatment arm respectively. Often there are prior information for them. Let $\pi(F_C)$ and $\pi(F_T)$ be their priors, we assume $\pi(F_C) \sim \mathscr{D}(P_C(\cdot))$, and $\pi(F_T) \sim \mathscr{D}(P_T(\cdot))$, where $\mathscr{D}(P_C(\cdot))$ is the Dirichlet process with parameter $P_C(\cdot)$; similarly for $\mathscr{D}(P_T(\cdot))$. The distribution P_C is the prior knowledge about F_C, and similarly for P_T.

We adopt the following assumptions assumed in Gao, Roy and Tan [13].

A1) $\mu_{0C} = \mu_{1C} = \mu_{0T} := \mu_C$;

A2) $Var(X_{0C}) = Var(X_{1C}) = Var(X_{0T}) = Var(X_{1T}) := \sigma^2$.

The reason for A1) is that a predictive biomarker is associated with response or lack of response to a particular therapy. Ideally, a predictive biomarker positive patient receiving therapy is expected to show a substantially higher response than negatively-biomarker patients receiving the therapy as well as those in the control group regardless of the marker status. Therefore, A1) with the treatment potentially making μ_{1T} different from $_{0C}$, μ_{1C} and μ_{0T}. Thus, the treatment effect, if any, is assumed to be a result of differential response to the treatment in the positively-biomarker group. A2) is a reasonable assumption to reduce model complexity.

For notational brevity, we will just write n_C for $n_{C,1}$ and n_T for $n_{T,1}$ etc. At end of stage I, using the non-parametric Bayesian formula for mean [19], in our case we have for μ_C and μ_T

$$\breve{x}_C^{(1)} = \frac{1}{n_C}\mu_{PC} + \frac{n_C}{n_C+1}\bar{x}_C^{(1)},$$

$$\breve{x}_T^{(1)} = \frac{1}{n_T}(\omega_0\mu_{PT} + (1-\omega_0)\mu_{PC}) + \frac{n_T}{n_T+1}\bar{x}_T^{(1)},$$

where μ_{PC} and μ_{PT} are the prior means of P_C and P_T. We have the estimates for means of the two distributions

$$\breve{\mu}_C = \breve{x}_C^{(1)},\quad \breve{\mu}_T = \frac{\breve{x}_T - (1-\omega_0)\breve{x}_C}{\omega_0}.$$

Also, using the non-parametric Bayesian formula for variance [19], we have $\breve{\sigma}_C^2$ of $Var(X_C)$ and $\breve{\sigma}_T^2$ of $Var(X_T)$ in our case as

$$\breve{\sigma}_C^2 = \frac{\mu_{2,P_C} + \sum_{i=1}^{n_C} x_{Ci}^2}{n_C+2} - \frac{(\mu_{P_C} + \sum_{i=1}^{n_C} x_{Ci})^2}{(n_C+1)(n_C+2)},$$

$$\breve{\sigma}_T^2 = \frac{\mu_{2,P_T} + n_T(\breve{\sigma}_C^2 + \omega_0\breve{\mu}_T + (1-\omega_0)\breve{\mu}_C) - \frac{(\mu_{P_T} + n_T(\omega_0\mu_{P_T} + (1-\omega_0)\mu_{P_C}))^2}{(n_T+1)(n_T+2)}}{n_T+2},$$

where $\mu_{2,P_C} = \int x^2 dP_C(x)$ is the prior second moment, similarly for μ_{2,P_T}.

To update the estimation of PPV ω, let $S^{(1)} = n_1\bar{x}_C^{(1)} + n_1\bar{x}_T^{(1)}$ be the total responses at end of stage I. Since $E[S^{(1)}] = \omega n_T\mu_T + [n_C + n_T(1-\omega)]\mu_C$, we substitute means and total responses to estimate ω as

$$\breve{\omega} = \frac{S^{(1)} - n_1\breve{\mu}_C}{n_T(\breve{\mu}_T - \breve{\mu}_C)}.$$

The two-stage sequential test

For given significance level α and power β, the decision boundaries are determined to satisfy type I error no greater than α and with power at least β. Consider test statistics T_j at stage j (j = 1, …, k), the flexible class of boundaries proposed by Wang and Tsiatis [20] are, for some (c, γ) to be determined,

$$b \quad cj^{(\ 0.5)}$$

Under H_0, (T_1, …, T_k) is multivariate normal distributed with zero mean vector. The sequential test will reject the null hypothesis at stage j if $|T_j| \geq b_j$. Then we have equation

$$P_{H_0}\{\bigcap_{j=1}^{k} |T_j| < cj^{\gamma-0.5}\} = 1-\alpha$$

Here we adopt O'Brien-Fleming boundaries having shape parameter γ = 0. In our case, k = 2, α = 0.05, c = 2.7967. The corresponding threshold of p-value at stage I is approximately 0.0054.

Sample size re-estimation

If the null hypothesis is not rejected at stage I, the sample size for the next stage need be determined by considering the required global power. Recall that n_1 and n_2 are the sample sizes at the end of stage I and II respectively. For simplicity we assume $n_T = n_C = n_1/2$. Then under H_0,

$$T_j = \sqrt{n_j}\frac{\bar{x}_T^{(j)} - \bar{x}_C^{(j)}}{2\sigma} \sim N(0,1), \quad (j = 1,2).$$

Under H_1,

$$(T_1, T_2)^T \sim N(\mu, \Omega),$$

$$\mu = \begin{bmatrix} \frac{\sqrt{n_1}\omega(\mu_T - \mu_C)}{2\sigma} \\ \frac{\sqrt{n_2}\omega(\mu_T - \mu_C)}{2\sigma} \end{bmatrix},$$

$$\Omega = \left(1 + \frac{\omega(1-\omega)(\mu_T - \mu_C)^2}{2\sigma^2}\right)\begin{bmatrix} 1 & \sqrt{\frac{n_1}{n_2}} \\ \sqrt{\frac{n_1}{n_2}} & 1 \end{bmatrix},$$

with family-wise power function

$$\beta = P_{H_1}(|T_1| \geq b_1) + P_{H_1}\left(|T_2| \geq \frac{b_2}{\sqrt{2}} \middle| |T_1| < b_1\right)$$

$$= P_{H_1}(|T_1| \geq b_1) + \frac{P_{H_1}(|T_1| < b_1) - P_{H_1}(|T_2| < \frac{b_2}{\sqrt{2}}, |T_1| < b_1)}{P_{H_1}(|T_1| < b_1)}.$$

Denote $p_1 = P_{H_1}(|T_1| \geq b_1)$ and

$p(n_2) = P_{H_1}(|T_2| < b_2/\sqrt{2}, |T_1| < b_1)$, which is determined by n_2 given other parameters. Then n_2 is determined by the least integer satisfies

$$p_1 + 1 - \frac{p(n_2)}{1-p_1} \geq 1-\beta, \quad \text{or} \quad (p_1+\beta)(1-p_1) \geq p(n_2).$$

Simulation Study

Extensive simulation studies are conducted to compare three methods, the method of Gao, Roy and Tan [13], the proposed nonparametric Bayesian method, and the parametric maximum likelihood (MLE) based method. We considered both truncated normal and skewed normal (with skewness parameter α). The reason for the first is that the treatment effects should be negative values; the latter represent departure from the normality assumption. For the sequential test, we assume $n_1 = n_2/2$, i.e., the sample sizes are the same for the two stages. If the re-estimated sample size is less than n_2, we will keep the original design. Moreover, the estimation of $\breve{\sigma}_T^2$ can be obtained using the formula below

$$\breve{\sigma}_T^2 = \breve{\sigma}_C^2 + \omega_0(1-\omega_0)(\breve{\mu}_T - \breve{\mu}_C)^2$$

which is the formula we actually used in the simulation study.

The results are displayed in Table 1, Table 2, Table 3, Table 4 and Table 5, with different parameter settings and sample sizes, with estimated treatment effects μ_T, μ_C, their difference ϑ, test result, and estimated sample size $\hat{n}_2$, (if the null hypothesis is not rejected in stage I), the probability of reject H_0 (so not continue the trial to stage II). In all the tables, results from the method of Gao, Roy and Tan [13] is named `empirical'; the proposed method, named `NP Bayes', and the MLE with EM-algorithm, named `MLE(EM), are compared. The sample size estimate n_2 depends on the estimated PPV is not stable. So we display the mean, median and trimmed mean (with trim proportion 10% on both sides) from all three methods, with 500 repetitions. Also, the corresponding disease prevalence (*prev*), sensitivity (*sen*), specificity (*spec*), the true ω_0, and the effect size (EF, |mean| /*s.d*) used in the simulation are given at the top of each Table.

To reflect the effects on estimated sample size of the skewness of the skewed normal and of EF, Figure 1, Figure 2, Figure 3 and Figure 4 are shown for the mean and trimed mean estimation methods below. We see that the empirical Bayesian estimate seems more rea-

Table 1: Estimation results from three methods (data from truncated-normal).

Setups	Parameters	True	Empirical	NP Bayes	MLE (EM)
n_1 = 50	μ_T	3.71	3.7381	3.7110	3.7881
$\alpha_T() \sim N(3.52, 0.89)$	μ_C	3.23	3.2266	3.2176	3.2208
$\alpha_C() \sim N(3.02, 0.89)$		0.48	0.5125	0.5119	0.5673
	σ_C^2	0.35	0.3502	0.3463	0.3209
	σ_T^2	0.3754	0.3889	0.3781	0.3761
	ω_1	0.8738	0.85	0.8915	0.8272
	Reject H_0	-	0.4371	0.4371	0.4910
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(100,237,115)	(100,181,109)	(100,201,111)
n_1 = 70	μ_T	5.21	5.2313	5.2381	5.3072
$\alpha_T() \sim N(5.47, 0.87)$	μ_C	4.51	4.5168	4.5118	4.5115
$\alpha_C() \sim N(4.34, 0.87)$		0.70	0.7145	0.7262	0.7958
	σ_C^2	0.74	0.7447	0.7087	0.6917
	σ_T^2	0.7940	0.8173	0.7829	0.8024
	ω_1	0.8378	0.85	0.8494	0.8103
	Reject H_0	-	0.5489	0.5928	0.6128
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(140,202,145)	(140,183,144)	(140,194,144)
n_1 = 90	μ_T	9.82	9.8387	9.8360	9.9123
$\alpha_T() \sim N(9.93, 1.05)$	μ_C	9.04	9.0501	9.0497	9.0445
$\alpha_C() \sim N(9.03, 1.05)$		0.78	0.7885	0.7879	0.8678
	σ_C^2	0.93	0.9263	0.8886	0.8704
	σ_T^2	0.9971	1.0138	0.9748	0.9986
	ω_1	0.8738	0.85	0.8519	0.8265
	Reject H_0	-	0.6627	0.6786	0.7186
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(180,258,184)	(180,285,184)	(180,257,185)

prev = 0.55, *sen* = *spec* = 0.85, ω_0 = 0.85, *EF* = 0.81

sonable, the empirical methods tend to over-estimate the sample size, and the MLE tends to under estimate it, and that the trimed mean method is much more stable. For comparison, we altered settings for parameters and kept EF the same for each graph.

From the Tables, the empirical and non-parametric Bayesian estimates are close to each other when the sample size is relatively large, which is consistent with

Table 2: Comparison between different response rate (Truncated-normal).

Setups	Parameters	True	Empirical	NP Bayes	MLE (EM)
n_1 = 70	μ_T	2.85	2.8630	2.8675	2.9550
$\alpha_T() \sim N(2.92, 0.97)$	μ_C	2.45	2.4592	2.4601	2.4503
$\alpha_C() \sim N(2.49, 0.97)$		0.40	0.4038	0.4045	0.5047
EF = 0.485	σ_C^2	0.68	0.6747	0.6464	0.6332
	σ_T^2	0.6927	0.6974	0.6670	0.6933
	ω_1	0.9132	0.88	0.8354	0.8714
	Reject H_0	-	0.1856	0.1936	0.2335
	$\hat{n}_2(Med / Mean / Trim)$	-	(142,496,241)	(140,463,232)	(140,460,219)
n_1 = 70	μ_T	2.85	2.8631	2.8677	2.9295
$\alpha_T() \sim N(2.92, 0.793)$	μ_C	2.45	2.4546	2.4556	2.4503
$\alpha_C() \sim N(2.49, 0.793)$	θ	0.40	0.4086	0.4092	0.4124
EF = 0.603	σ_C^2	0.44	0.4421	0.4279	0.4124
	σ_T^2	0.4527	0.4633	0.4497	0.4581
	ω_1	0.9132	0.88	0.8777	0.8245
	Reject H_0	-	0.3154	0.3134	0.3613
	$\hat{n}_2(Med / Mean / Trim)$	-	(142,340,187)	(140,335,180)	(140,335,175)
n_1 = 70	μ_T	2.85	2.8636	2.8681	2.9225
$\alpha_T() \sim N(2.92, 0.468)$	μ_C	2.45	2.4537	2.4547	2.4511
$\alpha_C() \sim N(2.49, 0.468)$	θ	0.40	0.4098	0.4104	0.4714
EF = 0.699	σ_C^2	0.33	0.3320	0.3179	0.3083
	σ_T^2	0.3427	0.3525	0.3390	0.3483
	ω_1	0.9132	0.88	0.8691	0.8229
	Reject H_0	-	0.4371	0.4531	0.5050
	$\hat{n}_2(Med / Mean / Trim)$	-	(140,252,157)	(140,273,157)	(140,300,156)

prev = 0.65, *sen* = *spec* = 0.85, ω_0 = 0.88

Table 3: Comparison in different scales (Skewed-normal).

Setups	Parameters	True	Empirical	NP Bayes	MLE (EM)
n_1 = 50	μ_T	3.71	3.7335	3.7068	3.7802
$\alpha_T() \sim N(3.52, 0.89)$	μ_C	3.23	3.2273	3.2192	3.2242
$\alpha_C() \sim N(3.02, 0.89)$		0.48	0.5062	0.5059	0.5560
α = 1	σ_C^2	0.35	0.3476	0.3440	0.3214
	σ_T^2	0.3754	0.3853	0.3751	0.3746
	ω_1	0.8738	0.85	0.8918	0.8357
	Reject H_0	-	0.4391	0.4691	0.4750
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(100,252,116)	(100,202,110)	(100,232,113)
n_1 = 50	μ_T	3.71	3.7344	3.7076	3.7714
$\alpha_T() \sim N(3.52, 0.89)$	μ_C	3.23	3.2271	3.2190	3.2305
$\alpha_C() \sim N(3.02, 0.89)$	θ	0.48	0.5073	0.5070	0.5409
α = 4	σ_C^2	0.35	0.3489	0.3452	0.3282
	σ_T^2	0.3754	0.3868	0.3763	0.3775
	ω_1	0.8738	0.85	0.8969	0.8701
	Reject H_0	-	0.4511	0.4810	0.4451
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(100,253,123)	(100,235,116)	(100,251,116)
n_1 = 50	μ_T	3.71	3.7347	3.7079	3.7528
$\alpha_T() \sim N(3.52, 0.89)$	μ_C	3.23	3.2269	3.2188	3.2313
$\alpha_C() \sim N(3.02, 0.89)$	θ	0.48	0.5078	0.5075	0.5214
α = 10	σ_C^2	0.35	0.3494	0.3456	0.3322
	σ_T^2	0.3754	0.3873	0.3768	0.3757
	ω_1	0.8738	0.85	0.8986	0.8933
	Reject H_0	-	0.4511	0.4850	0.4291
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(100,294,126)	(100,199,117)	(100,242,116)

n_1 = 50 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$ α = 25	μ_T	3.71	3.7348	3.7080	3.7526
	μ_C	3.23	3.2268	3.2187	3.2314
	θ	0.48	0.5080	0.5077	0.5212
	σ_C^2	0.35	0.3495	0.3457	0.3326
	σ_T^2	0.3754	0.3875	0.3770	0.3754
	ω_1	0.8738	0.85	0.8988	0.8969
	Reject H_0	-	0.4511	0.4790	0.4271
	$\hat{n}_2(Med / Mean / Trim)$	-	(100,301,125)	(100,200,116)	(100,246,116)
n_1 = 50 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$ α = -1	μ_T	3.71	3.7331	3.7064	3.7880
	μ_C	3.23	3.2274	3.2193	3.2207
	θ	0.48	0.5057	0.5054	0.5674
	σ_T^2	0.35	0.3468	0.3433	0.3182
	σ_T^2	0.3754	0.3845	0.3744	0.3731
	ω_1	0.8738	0.85	0.8911	0.8193
	Reject H_0	-	0.4251	0.4711	0.4910
	$n_2(Med / Mean / Trim)$	-	(100,221,114)	(100,177,109)	(100,221,111)
n_1 = 50 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$ α = -4	μ_T	3.71	3.7320	3.7053	3.7908
	μ_C	3.23	3.2277	3.2196	3.2104
	θ	0.48	0.5043	0.5041	0.5804
	σ_C^2	0.35	0.3453	0.3420	0.3133
	σ_T^2	0.3754	0.3829	0.3730	0.3662
	ω_1	0.8738	0.85	0.8901	0.8124
	Reject H_0	-	0.4052	0.4551	0.5549
	$n_2(Med / Mean / Trim)$	-	(100,203,111)	(100,212,109)	(100,217,108)

n_1 = 50 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$ α = -10	μ_T	3.71	3.7317	3.7050	3.7991
	μ_C	3.23	3.2277	3.2196	3.2067
	θ	0.48	0.5040	0.5038	0.5924
	σ_C^2	0.35	0.3449	0.3416	0.3101
	σ_T^2	0.3754	0.3825	0.3726	0.3654
	ω_1	0.8738	0.85	0.8903	0.8040
	Reject H_0	-	0.4132	0.4611	0.6008
	$n_2(Med / Mean / Trim)$	-	(100,195,111)	(100,180,108)	(100,211,109)
N = 50 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$ α = -25	μ_T	3.71	3.7316	3.7049	3.8008
	μ_C	3.23	3.2277	3.2195	3.2056
	θ	0.48	0.5039	0.5037	0.5952
	σ_C^2	0.35	0.3448	0.3415	0.3092
	σ_T^2	0.3754	0.3824	0.3725	0.3651
	ω_1	0.8738	0.85	0.8905	0.8017
	Reject H_0	-	0.4132	0.4691	0.6048
	$n_2(Med / Mean / Trim)$	-	(100,194,110)	(100,182,108)	(100,200,109)

prev = 0.55, *sen* = *spec* = 0.85, ω_0 = 0.85, *EF* = 0.81

Table 5: Comparison in different sample sizes (Skewed-normal).

Setups	Parameters	True	Empirical	NP Bayes	MLE (EM)
n_1 = 30 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$	μ_T	3.71	3.7252	3.6858	3.7603
	μ_C	3.23	3.2153	3.2025	3.2070
	θ	0.48	0.5099	0.5098	0.5533
	σ_C^2	0.35	0.3481	0.3421	0.3071
	σ_T^2	0.3754	0.3897	0.3729	0.3564
	ω_1	0.8738	0.85	0.9003	0.8468
	Reject H_0	-	0.2655	0.2834	0.3273
	$\hat{n}_2(Med / Mean / Trim)$	-	(60,281,95)	(60,174,79)	(60,301,84)

n_1 = 70 $\alpha_T() \sim N(5.47, 0.87)$ $\alpha_C() \sim N(4.34, 0.87)$	μ_T	5.21	5.2311	5.2378	5.3036
	μ_C	4.51	4.5205	4.5154	4.5126
	θ	0.70	0.7106	0.7224	0.7910
	σ_C^2	0.74	0.7455	0.7094	0.6890
	σ_T^2	0.7940	0.8177	0.7832	0.7942
	ω_1	0.8738	0.85	0.8525	0.8130
	Reject H_0	-	0.5409	0.5868	0.6148
	$\hat{n}_2(Med / Mean / Trim)$	-	(140,219,145)	(140,194,144)	(140,210,143)
n_1 = 90 $\alpha_T() \sim N(9.93, 1.01)$ $\alpha_C() \sim N(9.93, 1.01)$	μ_T	9.82	9.8425	9.8459	9.9307
	μ_C	9.04	9.0478	9.0474	9.0390
	θ	0.78	0.7947	0.7970	0.8917
	σ_C^2	0.93	0.9247	0.8871	0.8618
	σ_T^2	0.9971	1.0132	0.9763	0.9994
	ω_1	0.8738	0.85	0.8482	0.8092
	Reject H_0	-	0.6866	0.7086	0.7565
	$\hat{n}_2(Med / Mean / Trim)$	-	(180,221,183)	(180,211,182)	(180,214,184)

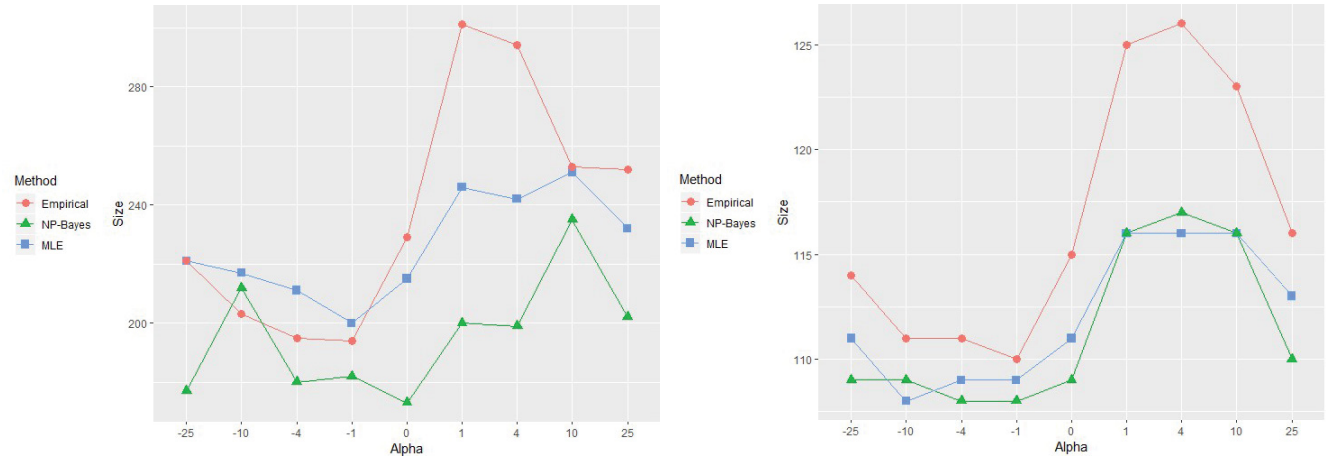
prev = 0.55, *sen* = *spec* = 0.85, ω_0 = 0.85, *EF* = 0.81, α = -1

Table 4: Comparison in different sample sizes (Skewed-normal).

Setups	Parameters	True	Empirical	NP Bayes	MLE (EM)
n_1 = 30 $\alpha_T() \sim N(3.52, 0.89)$ $\alpha_C() \sim N(3.02, 0.89)$	μ_T	3.71	3.7246	3.6861	3.7579
	μ_C	3.23	3.2150	3.2022	3.2102
	θ	0.48	0.5097	0.5096	0.5477
	σ_C^2	0.35	0.3454	0.3400	0.3080
	σ_T^2	0.3754	0.3869	0.3708	0.3588
	ω_1	0.8738	0.85	0.9006	0.8530
	Reject H_0	-	0.2754	0.2954	0.3253
	$\hat{n}_2(Med / Mean / Trim)$	-	(62,322,97)	(60,188,80)	(60,269,86)

n_1 = 70 $\alpha_T() \sim N(5.47, 0.87)$ $\alpha_C() \sim N(4.34, 0.87)$	μ_T	5.21	5.2311	5.2377	5.2956
	μ_C	4.51	4.5209	4.5157	4.5186
	θ	0.70	0.7102	0.7221	0.7769
	σ_C^2	0.74	0.7487	0.7123	0.6901
	σ_T^2	0.7940	0.8209	0.7860	0.7984
	ω_1	0.8738	0.85	0.8540	0.8226
	Reject H_0	-	0.5289	0.5868	0.5689
	$\hat{n}_2(Med\ /\ Mean\ /\ Trim)$	-	(140,227,146)	(140,200,144)	(140,213,143)
n_1 = 90 $\alpha_T() \sim N(9.93, 1.01)$ $\alpha_C() \sim N(9.03, 1.01)$	μ_T	9.82	9.8422	9.8456	9.9131
	μ_C	9.04	9.0477	9.0473	9.0446
	θ	0.78	0.7946	0.7969	0.8686
	σ_C^2	0.93	0.9270	0.8892	0.8701
	σ_T^2	0.9971	1.0155	0.9784	0.9995
	ω_1	0.8738	0.85	0.8482	0.8296
	Reject H_0	-	0.6647	0.6886	0.7246
	$\hat{n}\ (Med\ /\ Mean\ /\ Trim)$	-	(180,220,183)	(180,212,183)	(180,218,184)

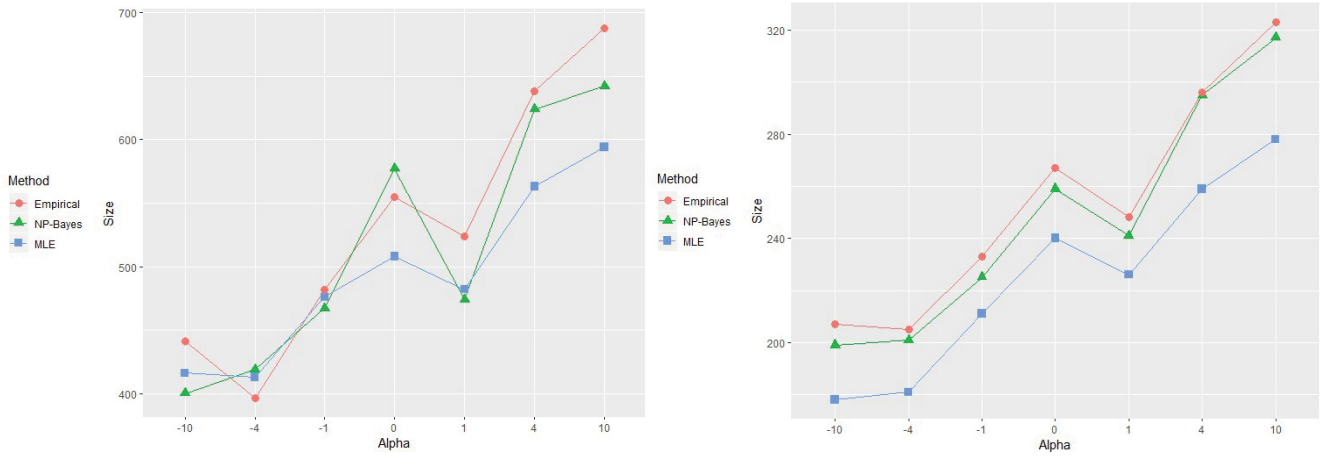
prev = 0.55, *sen* = *spec* = 0.85, ω_0 = 0.85, *EF* = 0.81, α = 1



(a) Mean (b) Trimmed Mean

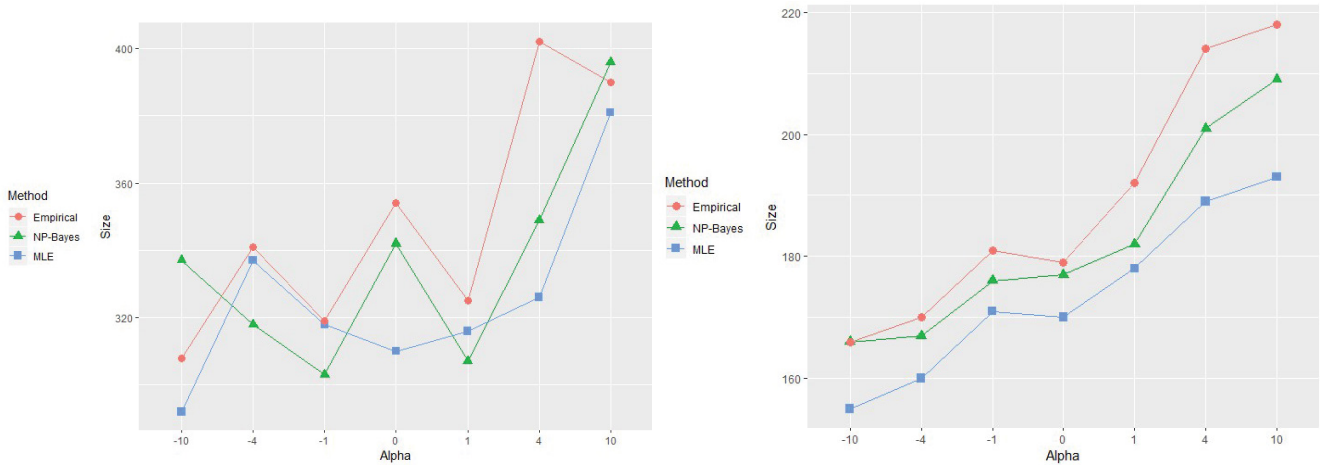
Figure 1: Means for different alpha settings (Table 3), EF = 0.81.

the Bayes-frequentist estimation theory. However, the non-parametric Bayesian estimators were more robust than empirical ones, especially in cases where the sample size is relatively small. The variance of the empirical estimators was hugely inflated, which would require large increase of patients in stage-II. Moreover, as expected the non-parametric Bayesian estimators were not very sensitive to the selection of the prior, likely due to the fact that essential information was captured by the prior already. MLE method by EM algorithm can give smallest increase in sample size, especially when the sample were precisely from normal distribution, with zero-skewness. However, the estimators were significantly biased, which may be caused by the exceedingly high power of the stage-I test than the specified level. Therefore, non-parametric Bayesian estimators per-



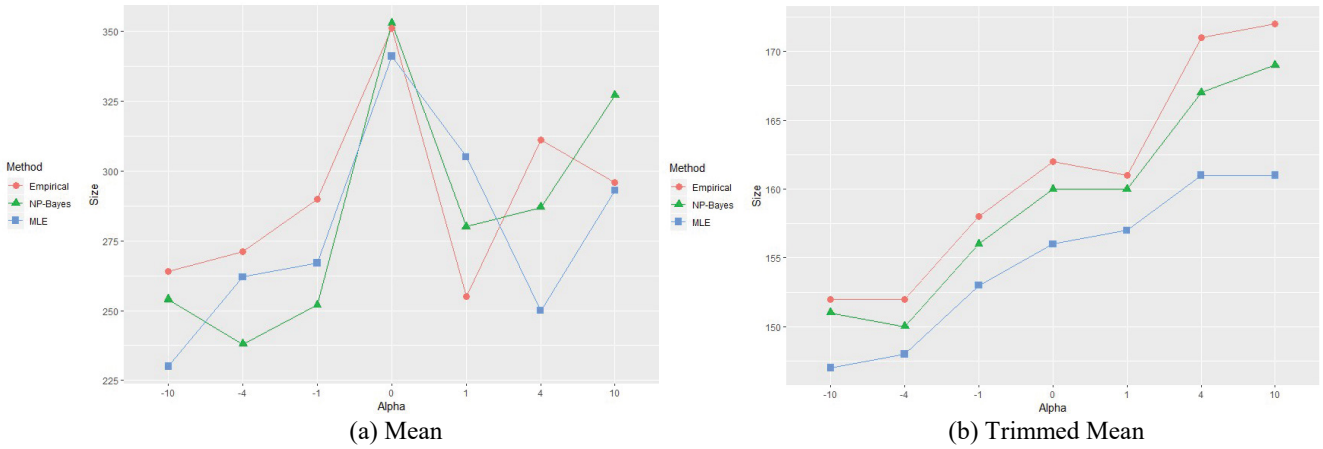
(a) Mean (b) Trimmed Mean

Figure 2: Means for different alpha settings, EF = 0.485.



(a) Mean (b) Trimmed Mean

Figure 3: Means for different alpha settings, EF = 0.603.



(a) Mean (b) Trimmed Mean

Figure 4: Means for different alpha settings, EF = 0.699.

formed the best in the proposed adaptive design since they are more robust and require weak assumption on prior. They utilize the prior information but are not too dependent on prior selection. In smaller scales, it could reduce the unexpected variance, which may lead to large sample size increase in the next stage. In addition, they asymptotically converged to empirical estimators, indicating unbiasedness with large sample sizes.

Concluding Remarks

We have proposed a nonparametric Bayesian method for the two-stage adaptive biomarker-targeted clin-

ical trial design. Compared with the existing parametric model, it has the advantage of incorporating prior information into the design, and being robust to model assumption. Extensive simulation studies are conducted to evaluate the performance of the proposed method, and compare with the commonly used methods for this problem. In our simulation studies, we considered the non-skewed and skewed, to reflect correct and incorrect model specifications. It was found that the skewness will influence the estimation accuracy in this design. The estimate is most accurate with left-skewed distributions, least accurate with right-skewed distributions, and modest with truncated normal distributions. Cases gave moderate results, and would be the hardest to estimate. Moreover, the more left-skewed, the more accurate for the estimations.

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Appendix

EM Formula Derivation.

Denote ϕ_1 for the pdf of $N(\mu_T, \sigma^2)$, ϕ_2 for that of $N(\mu_C, \sigma^2)$. Under the normal model assumption, the likelihood is the following mixture

$$f_X(\boldsymbol{X} \mid \boldsymbol{D}_{n_1}) = \prod_{i=1}^{n_T}\left[\omega\phi_1(X_{T_i}) + (1-\omega)\phi_2(X_{T_i})\right] \times \prod_{j=1}^{n_C}\phi_2(X_{T_j})$$

It is known that that parameter estimation in mixture model is not easy, and often the EM algorithm is used for such computation. For this, let z_i be the treatment latent indicator of the *i*-th observation, i.e., z_i = 1 as belonging to the treatment group (with pdf ϕ_1) and z_i = 0 for the control group (with pdf ϕ_2), and denote $\boldsymbol{Z}$ = (z_1, z_2, …, z_{nT}).

Then based on the `complete' data (***X, Z***), the likelihood is

$$f_X(\boldsymbol{X} \mid \boldsymbol{D}_{n_1}, \boldsymbol{Z}) = \prod_{i=1}^{n_T}\left[(\omega\phi_1(X_{T_i}))^{z_i}((1-\omega)\phi_2(X_{T_i}))^{1-z_i}\right] \times \prod_{j=1}^{n_C}\phi_2(X_{T_j})$$

and the corresponding log-likelihood is

$$\ell(\beta \mid \boldsymbol{D}_{n_1}, \boldsymbol{Z}) = \sum_{i=1}^{n_T}\left\{z_i[\log(\omega) + \log\phi_1(X_{T_i})] + (1-z_i)[\log(1-\omega) + \log\phi_2(X_{T_i})]\right\} + \sum_{j=1}^{n_C}\log\phi_2(X_{C_j}).$$

Given the *k*-th iteration value $\beta^{(k)} = (\mu_C^{(k)}, \mu_T^{(k)}, \sigma^{2^{(k)}}, \omega^{(k)})$, in the E-step we compute

$$z_i^{(k)} = E(z_i \mid \beta^{(k-1)}, \boldsymbol{Z}^{(k-1)}) = P(z_i = 1 \mid \beta^{(k-1)}, \boldsymbol{Z}^{(k-1)})$$

$$= \frac{\omega^{(k-1)}\phi_1(x_{T_i} \mid \mu_T^{(k-1)}, \sigma^{2(k-1)})}{\omega^{(k-1)}\phi_1(x_{T_i} \mid \mu_T^{(k-1)}, \sigma^{2(k-1)}) + (1-\omega^{(k-1)})\phi_2(x_{T_i} \mid \mu_C^{(k-1)}, \sigma^{2^{(k-1)}})}$$

In the M-step, we set

$$\begin{cases} \partial\ell(\beta \mid D_{n_1}, Z^{(k)})/\partial\omega = 0, & \partial\ell(\beta \mid D_{n_1}, Z^{(k)})/\partial\mu_T = 0, \\ \partial\ell(\beta \mid D_{n_1}, Z^{(k)})/\partial\mu_C = 0, & \partial\ell(\beta \mid D_{n_1}, Z^{(k)})/\partial\sigma^2 = 0 \end{cases}$$

to get the following equations (Unrelated terms omitted):

$$\begin{cases} \frac{1}{\omega^{(k)}}\sum^{n_T} z_i^{(k)} - \frac{1}{1-\omega^{(k)}}\sum^{n_T}(1-z_i^{(k)}) = 0, \quad \sum^{n_T} z_i^{(k)}(x_{T_i} - \mu_T^{(k)}) = 0, \\ \sum^{n_T}(1-z_i^{(k)})(x_{T_i} - \mu_C^{(k)}) + \sum^{n_C}(x_{C_i} - \mu_C^{(k)}) = 0, \\ \sum^{n_T}\left\{(1-z_i^{(k)})[-\frac{1}{2\sigma^{2(k)}} + \frac{(x_{T_i}-\mu_T^{(k)})^2}{2\sigma^{4(k)}}] + z_i^{(k)}[-\frac{1}{2\sigma^{2(k)}} + \frac{(x_{T_i}-\mu_C^{(k)})^2}{2\sigma^{4(k)}}]\right\} + \sum^{n_C}[-\frac{1}{2\sigma^{2(k)}} + \frac{(x_{C_i}-\mu_C^{(k)})^2}{2\sigma^{4(k)}}] = 0. \end{cases}$$

Then we have

$$\begin{cases} \omega^{(k)} = \frac{1}{n_T}\sum^{n_T} z_i^{(k)}, \quad \mu_T^{(k)} = \frac{\sum^{n_T} z_i^{(k)} x_{T_i}}{\sum^{n_T} z_i^{(k)}}, \\ \mu_C^{(k)} = \frac{\sum^{n_C} x_{C_i} + \sum^{n_T}(1-z_i^{(k)})x_{T_i}}{n_C + \sum^{n_T}(1-z_i^{(k)})}, \\ \sigma^{2^{(k)}} = \frac{\sum^{n_T}\left[(1-z_i^{(k)})(x_{T_i}-\mu_C^{(k)})^2 + z_i^{(k)}(x_{T_i}-\mu_T^{(k)})^2\right] + \sum^{n_C}(x_{C_i}-\mu_C^{(k)})^2}{n_T + n_C}. \end{cases}$$

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