Ranking and Selection with Covariates for Personalized Decision Making

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Abstract

We consider a problem of ranking and selection via simulation in the context of personalized decision making, where the best alternative is not universal but varies as a function of some observable covariates. The goal of ranking and selection with covariates (R&S-C) is to use simulation samples to obtain a selection policy that can specify the best alternative with certain statistical guarantee for subsequent individuals upon observing their covariates. A linear model is proposed to capture the relationship between the mean performance of an alternative and the covariates. Under the indifference-zone formulation, we develop two-stage procedures for both homoscedastic and heteroscedastic simulation errors, respectively, and prove their statistical validity, which is defined in terms of average probability of correct selection. We also generalize the well-known slippage configuration, and prove that the generalized slippage configuration is the least favorable configuration for our procedures. Extensive numerical experiments are conducted to investigate the performance of the proposed procedures, the experimental design issue, and the robustness to the linearity assumption. Finally, we demonstrate the usefulness of R&S-C via a case study of selecting the best treatment regimen in the prevention of esophageal cancer. We find that by leveraging disease-related personal information, R&S-C can substantially improve patients’ expected quality-adjusted life years by providing patient-specific treatment regimen.

Key words: ranking and selection; covariates; probability of correct selection; least favorable configuration; experimental design

1 Introduction

Ranking and selection (R&S) is one of the most studied problems in the area of stochastic simulation. It aims to select the one with the best mean performance from a set of alternatives through running simulation experiments (see Kim and Nelson (2006) and Chen et al. (2015) for reviews). In the
conventional R&S setting, the mean performance of an alternative is considered as a constant. In context of personalized decision making, however, such setting may be too rigid. For instance, medical studies show that the effectiveness of a cancer chemotherapy treatment depends on the biometric characteristics of a patient such as tumor biomarker and gene expression (Yap et al. 2009, Kim et al. 2011). Therefore, for two patients with different characteristics, the best treatment regimen may be different. Similar examples can also be found in marketing, where research shows that the effect of an online advertisement depends on customer purchasing preference (Arora et al. 2008), and in training self-driving cars, where the best driving decision depends on the real-time ambient information collected by all the sensors (Katrakazas et al. 2015). In all the above examples, it appears more reasonable to consider the mean performance of an alternative as a function of the covariates, which include all of the additional contextual information, such as the biometric characteristics in the cancer treatment example, the purchasing preference in the marketing example, and the ambient information in the self-driving car example.

One approach to solve the problem is to run conventional R&S procedures once the covariates are observed. However, this approach may not be practical in many situations, and the reasons are two-fold. The first reason is feasibility, i.e., the decision maker may not have the access or the time to run the complicated simulation model. For instance, in the cancer treatment example, the doctor may not have the access to the simulation model that needs to run on super computer systems; in the marketing example, the online retailer has to display the advertisement once the customer is logged in and, therefore, has no time to run the simulation experiments; and in the self-driving car example, the time is more precious and the decisions have to be made in real time. The second reason is efficiency. Personalized decisions typically need to be made repeatedly for different people upon observing their covariates. Then, using conventional R&S for every person is often not as efficient as developing a selection policy, which maps the covariates to the identify of the best alternative, and using it repeatedly for different people.

In this paper we consider a new R&S setting where the mean performances of all alternatives are functions of the covariates and, therefore, the identity of the best alternative is also a function of the covariates. One may run simulation experiments to learn the mean performance functions of all alternatives and to use these learned functions to select the best alternative upon observing the covariates. We call this problem ranking and selection with covariates (R&S-C). Notice that, under this setting, the time-consuming component is the learning of the mean performance functions of all alternatives, and it requires a significant amount of simulation effort. However, this can be done off-line. Once the mean performance functions are learned, only these learned functions (which form the selection policy) need to be deployed. Then, the selection of the best upon observing the covariates is basically computing the function values of all alternatives at the values of the covariates and it can be done on-line in real time, with negligible computation. Notice that such “off-line learning on-line application” approach allows the learned functions to be deployed to many users (e.g., many doctors and many self-driving cars) and used repeatedly with no additional cost.
1.1 Main Contributions

To tackle the R&S-C problem, we first provide a quite general frequentist’s formulation. We generalize important frequentist R&S concepts, such as the indifference zone and the probability of correct selection (PCS), to the R&S-C setting, and define the corresponding finite-sample statistical guarantee. We also show that the R&S-C formulation in general gives a better outcome than the R&S formulation if one chooses to average the effects of the covariates.

Second, we consider a specific situation of the R&S-C problem, where the mean performances of all alternatives are linear functions of the covariates with unknown coefficients that may be estimated through linear regression, and show that the famous Stein’s lemma (Stein 1945), which is a major cornerstone of conventional frequentist’s R&S, may be extended to linear regression contexts. Despite its simplicity, linear models have distinct advantages in terms of their interpretability and robustness to model misspecification, and often show good performance in prediction [James et al. 2013]. Moreover, they can be generalized easily to accommodate nonlinearity by applying covariate transformation via basis functions [Hastie et al. 2009].

Third, we propose two-stage procedures to solve R&S-C problems with linear performance functions. These procedures may be viewed as the extensions of the famous Rinott’s procedure [Rinott 1978] in conventional frequentist’s R&S, and they can handle both homoscedastic and heteroscedastic errors, respectively, in the linear models. Based on the extended Stein’s lemma that we develop, we prove that these procedures deliver the desired finite-sample statistical guarantee. We also conduct numerical studies to assess the performances of the procedures and discuss their robustness to the linearity assumption and to the experimental design.

Lastly, we consider the personalized prevention regimen for esophageal cancer, where the effectiveness of the prevention regimens are evaluated using a Markov simulation model developed and calibrated by domain experts in cancer research. We compare the R&S-C formulation with the conventional R&S formulation, and show that the R&S-C formulation can significantly improve the expected quality adjusted life years of the patients who are diagnosed with Barrett’s esophagus, a mild precursor to esophageal cancer.

1.2 Related Literature

R&S has been studied extensively in the statistics and stochastic simulation literature. In general, there are two streams of procedures: frequentist’s and Bayesian. Frequentist’s procedures typically aim to deliver the PCS under the indifference-zone formulation. There are two-stage procedures [Rinott 1978], sequential procedures [Kim and Nelson 2001; Hong 2006], and procedures designed to handle very large number of alternatives in parallel computing environments [Luo et al. 2015; Ni et al. 2017]. These procedures are typically conservative and require more samples than necessary for average cases. Bayesian procedures, on the other hand, often aim to allocate a finite computational budget to different alternatives either to maximize the posterior PCS or to minimize the expected opportunity cost. There are a variety of approaches to developing Bayesian procedures, including value of information [Chick and Inoue 2001], knowledge gradient [Frazier et al. 2008], optimal
computing budget allocation (Chen et al. 1997), and economics of selection procedures (Chick and Gans 2009, Chick and Frazier 2012). Bayesian procedures often require fewer samples than frequentist’s ones to achieve the same level of PCS. However, they do not provide a (frequentist) statistical guarantee in general. Frazier (2014) develops a Bayes-inspired procedure that includes many of the Bayesian features while still guaranteeing a frequentist PCS.

The R&S-C problems have been tackled in the Bayesian framework. Hu and Ludkovski (2017) propose to model the performance functions of alternatives as Gaussian random fields, and use the expected improvement criteria to develop Bayesian procedures. Pearce and Branke (2017) follow the same framework of Hu and Ludkovski (2017), but focus on how to efficiently estimate the expected improvement over a continuous domain. In contrast to their approaches, we take a frequentist perspective in this paper, for the first time, to model and solve the R&S-C problems.

Our research is also related to the literature on multi-arm bandit (MAB) with covariates. MAB is an important class of sequential decision making problems in the fields of operations research, statistics and machine learning. It was first proposed by Robbins (1952) and has been studied extensively since then; see, for instance, Bubeck and Cesa-Bianchi (2012) for a comprehensive review of MAB. In recent years, MAB with covariates (also known as contextual MAB) has drawn considerable attention as a tool for personalized decision making. The mean performances in these problems are often modeled as linear functions of the covariates (Auer 2002, Rusmevichientong and Tsitsiklis 2010). In particular, Goldenshluger and Zeevi (2013) consider a linear model whose coefficients are arm-dependent, which motivates our formulation of R&S-C. Nonparametric models have also been considered in the literature of MAB with covariates (Perchet and Rigollet 2013, Slivkins 2014), and this may be a direction of future study for R&S-C.

Linear models have also been considered in R&S problems. For example, Negoescu et al. (2011) adopt a linear model when solving a R&S problem in the context of drug discovery, where the mean performance of an alternative is a linear combination of attribute contributions. However, the intention of introducing the linear model in Negoescu et al. (2011) is quite different from ours. Specifically, the linear model in their work forms a linear projection from the space of alternatives to the space of attributes, which dramatically reduce the computational complexity. Their final goal is still to select the best alternative as a static decision, rather than the kind of decision policy that we seek. Therefore, their R&S problem is still in the conventional sense, which is different from the R&S-C problems considered in this paper.

The remaining of the paper is organized as follows. In §2 we present the formulation of R&S-C problem, and in §3 we introduce the linear models and establish the extended Stein’s lemma. We then develop a two-stage selection procedure for homoscedastic simulation errors in §4 and present another one to take care of heteroscedasticity in §5. In §6 we discuss the least favorable configuration of the means for R&S-C problems. Extensive numerical experiments are conducted in §7 to investigate the performance of the proposed procedures in various settings. We also address the issues on experimental design and robustness of linearity assumptions in §8. Section 9 demonstrates the practical value of R&S-C in the context of personalized treatment for esophageal
cancer prevention. Finally, we conclude in §10 and include some technical results and proofs in the appendix.

2 Problem Formulation

Suppose there are \(k\) alternatives whose mean performances, denoted as \(\mu_1(X), \ldots, \mu_k(X)\), are functions of \(X = (X_1, \ldots, X_d)^T\), which is the vector of the observable random covariates with support \(\Theta \subset \mathbb{R}^d\). Our goal is to develop a policy that selects the alternative with the largest mean performance upon observing the values of the covariates, i.e., identifying \(i^*(x) := \arg \max_{1 \leq i \leq k} \{\mu_i(X) | X = x\}\) for any \(x \in \Theta\). In the cancer treatment example considered in §1, for instance, the alternatives are the different treatments, the covariates are the biometric characteristics of a patient, the mean performances are the expected quality adjusted life years of the patient under different treatments, and the goal is to identify a policy that selects the best treatment for the patient once the biometric characteristics of the patient are observed.

In this paper we suppose that there are simulation models that allow us to estimate \(\mu_i(X), i = 1, \ldots, k\), once the values of \(X\) are given. The critical issue is how to design off-line simulation experiments to learn \(\mu_1(x), \ldots, \mu_k(x)\) accurately so that they may be used to select the best alternative on-line in real time upon observing the values of \(X\) with a predetermined level of precision (e.g., PCS in a frequentist sense). We call this problem ranking and selection with covariates (R&S-C) to emphasize that the decision is conditional on the covariates.

Remark 1. Throughout this paper, we assume that the value of \(X\) is observable before making the selection decision. This assumption is reasonable in many practical situations, including the three examples introduced in §1. Specifically, in the cancer treatment example, patients’ characteristics such as tumor biomarkers and gene expressions can be identified through medical tests; in the marketing example, customer preference information can be inferred from purchasing history; and in the self-driving car example, the ambient information is collected directly by the sensors.

2.1 Value of Covariates

In conventional R&S problems, the goal may be viewed as selecting the unconditional best, i.e., to identify \(i^* := \arg \max_{1 \leq i \leq k} \mu_i\), where \(\mu_i := E[\mu_i(X)], i = 1, \ldots, k\), and the expectation is taken with respect to the distribution of \(X\). In the cancer treatment example, for instance, the conventional R&S selects the best treatment for the entire population instead of the best for an individual patient. Notice that, by Jensen’s Inequality,

\[
E[\mu_{i^*}(X)] = E \left[ \max_{1 \leq i \leq k} \mu_i(X) \right] \geq \max_{1 \leq i \leq k} E[\mu_i(X)] = E[\mu_{i^*}(X)].
\]

Therefore, the R&S-C formulation typically outperforms the R&S formulation if the covariates are observable before the selection decision is made. In the cancer treatment example, for instance,
Equation (1) implies that the personalized-best treatment typically outperforms the population-best treatment. This point will also be demonstrated in the cancer prevention example considered in §9.

Remark 2. The distribution of $X$ is assumed to be known in this paper. This is a common assumption even in conventional R&S, where the distribution of $X$ needs to be known to evaluate $E[\mu_i(X)]$ for all $i = 1, \ldots, k$. The distribution of $X$ is typically estimated through the input modeling process (Law and Kelton 2000).

2.2 Indifference Zone

Indifference zone (IZ) plays a very important role in conventional frequentist’s R&S (Bechhofer 1954). It defines the smallest difference $\delta$ that the decision maker considers worth detecting. Therefore, alternatives whose mean performances are within $\delta$ to the best are in the IZ and considered “indifferent” from the best. In frequentist’s setting, R&S procedures need to deliver the PCS under any configurations of means. Without the IZ, the means of the best and other alternatives may be arbitrarily close and, therefore, one needs infinitely many samples to identify the true best. With the IZ, the goal is often softened to select one of the alternatives in the IZ and, therefore, only a finite number of samples are necessary.

In the setting of R&S-C, the configurations of the means depend on the values of the covariates. They may be arbitrarily close if the mean surfaces $\mu_1(x), \ldots, \mu_k(x)$ intersect at some values of $x \in \Theta$ (see, for instance, Figure 1). Therefore, we also need IZ. Given an IZ parameter, we define the event of correct selection (CS) given $X = x$ as

$$\text{CS}(x) := \{\mu_{i^*}(x) - \hat{\mu}_{i^*}(x) < \delta\},$$

where $\hat{i^*}(x)$ denotes the selected best, and a CS event implies that the selected best is in the IZ. Notice that our definition of a CS event is also known as a good selection (GS) event in some of the R&S literature (see, for instance, Ni et al. (2017)), where a CS event may be defined more restrictively as $\{i^*(x) = \hat{i^*}(x)\}$ given that there are no alternatives in the IZ other than the best. However, this more restrictive definition of CS often does not make sense in the context of R&S-C. For instance, when the support of the covariates cover the intersection points of the mean surfaces (see point $x^*$ in Figure 1), no matter how small the IZ parameter $\delta$ is, for certain values of the covariates that are in the neighborhood of the intersection points, there are always alternative in the IZ other than the best, which makes the more restrictive definition of CS inapplicable.

Remark 3. Recently, Fan et al. (2016) show that IZ may be unnecessary in conventional frequentist’s R&S if sequential procedures are used. However, in order for their procedures to stop in finite time, the means of all alternatives have to be different. In R&S-C context, however, the mean values of some alternatives are the same at the intersection points (see Figure 1). Therefore, it is not clear how the procedures of Fan et al. (2016) may be applied in the R&S-C context.
2.3 Probability of Correct Selection

We are now ready to define the PCS, which is the statistical guarantee that frequentist’s R&S procedures typically deliver. Let $\hat{i}^*(x)$ denote the selection policy produced by a R&S-C procedure. Notice that the presence of the covariates complicates the definition of PCS, because one has to answer whether the PCS is defined for an individual or the population. To address the issue, we first define the conditional PCS, given $X = x$, as

$$
\text{PCS}(x) := \mathbb{P}\left\{\mu_{i^*(x)}(X) - \mu_{\hat{i}^*(x)}(X) < \delta \mid X = x\right\},
$$

(2)

where the probability is taken with respect to the distribution of simulated samples that are used to estimate the mean functions $\mu_1(x), \ldots, \mu_k(x)$ and to derive the selection policy $\hat{i}^*(x)$ for all $x \in \Theta$.

Notice that PCS($x$) may be viewed as the PCS for an individual whose covariates take the value $x$. However, the covariates are random variables and, therefore, PCS($X$) is also a random variable. To use it as the statistical guarantee for R&S-C procedures, one way is to consider some summary statistics of PCS($X$). To that end, we define the average PCS, denoted by $\text{PCS}_E$, as

$$
\text{PCS}_E := \mathbb{E}\left[\text{PCS}(X)\right].
$$

(3)

Notice that

$$
\text{PCS}_E = \mathbb{E}\left[\mathbb{P}\left\{\mu_{i^*(X)}(X) - \mu_{\hat{i}^*(X)}(X) < \delta \mid X\right\}\right] = \mathbb{P}\left\{\mu_{i^*(X)}(X) - \mu_{\hat{i}^*(X)}(X) < \delta \right\}.
$$

Therefore, $\text{PCS}_E$ is the unconditional PCS and it is for the entire population. If we set $\text{PCS}_E \geq 1 - \alpha$, we are $(1 - \alpha)$ confident that a random individual from the population will select his or her personalized best decision or a decision that is within the IZ. We want to point out that other summary statistics of PCS($X$) may also be used as decision criterion, for instance, one may define it to be the certain quantile of the random variable PCS($X$) or even $\min_{x \in \Theta} \text{PCS}(x)$ to be more risk averse. However,
we leave it as a topic for future research.

3 Linear Models and the Extended Stein’s Lemma

Notice that the general formulation of R&S-C problems, presented in §2, allows the mean performance functions $\mu_1(x), \ldots, \mu_k(x)$ to take any forms. To solve the problems, however, one needs to decide how to estimate these functions. There are two approaches, parametric approach and nonparametric approach. Both have pros and cons, and both are widely used in function estimations. In this paper we take a parametric approach and assume that $\mu_1(x), \ldots, \mu_k(x)$ are linear functions of the covariates $x$ with unknown coefficients that need to be estimated through simulation experiments. Let $Y_i(x)$ denote the random performance of alternative $i$ at the covariates $x$ for all $i = 1, \ldots, k$ and $x \in \Theta$. We make the following assumption on the forms of $\mu_1(x), \ldots, \mu_k(x)$ and distributions of $Y_1(x), \ldots, Y_k(x)$.

**Assumption 1.** For all $i = 1, \ldots, k$, conditionally on $X = x$,

\[
\begin{align*}
\mu_i(x) &= x^\top \beta_i, \\
Y_i(x) &= \mu_i(x) + \epsilon_i,
\end{align*}
\]

where $\beta_i = (\beta_{i1}, \ldots, \beta_{id})^\top \in \mathbb{R}^d$ is a vector of unknown coefficients and $\epsilon_i$ follows a normal distribution with mean 0 and variance $\sigma_i^2$.

Notice that Assumption 1 basically requires all $Y_i(x)$’s to follow the standard linear regression assumption (James et al. 2013) so that the unknown coefficient vectors $\beta_i$’s may be estimated using standard ordinary least squares (OLS) method. Moreover, the covariates may be redefined to include the intercept term (by setting $X_1 \equiv 1$) or transformed to handle nonlinearity (by using nonlinear basis functions of the covariates).

Furthermore, Assumption 1 is a natural extension of the normality assumption commonly used in the R&S literature. For instance, both Rinott (1978) and Kim and Nelson (2001) assume that $Y_i = \mu_i + \epsilon_i$ for all $i = 1, \ldots, k$. We basically extend the mean $\mu_i$ to a linear function $\mu_i(x) = x^\top \beta_i$ to add the effect of the covariates. Moreover, we will see later in this section, the OLS estimators of the unknown parameters $\beta_i$’s under Assumption 1 resemble the sample-mean estimators of the unknown means under the normality assumption. This resemblance gives us great convenience to develop statistically valid R&S-C procedures.

3.1 Fixed Design

Based on Assumption 1, a critical issue in solving a R&S-C problem is to obtain estimates of $\beta_1, \ldots, \beta_k$ that are accurate enough. Therefore, we need to decide where to run simulation experiments (i.e., the design points) and how many observations to run (i.e., the sample sizes). Here we want to emphasize again that estimations of $\beta_i$’s are conducted offline based on simulation
experiments at the chosen design points, instead of real experiments at randomly observed values of the covariates. Hence, we are free in choosing the design points as well as the sample sizes.

In this paper we choose to use a fixed set of design points to estimate $\beta_i$ for all $i = 1, \ldots, k$. In particular, we select a set of $m$ design points, denoted as $x_1, \ldots, x_m \in \Theta$, with $m \geq d$, and conduct simulation experiments only at these design points for all alternatives. Notice that the use of fixed design points eliminates the randomness in choosing design points. It simplifies the analysis and makes statistically valid R&S-C procedures significantly easier to develop. When adopting a fixed design, the placement of the design points is a very important issue. We will discuss it in §8. As for now, we simply consider the situation where $m$ design points are chosen and they satisfy that $X^\top X$ is a nonsingular matrix, where $X = (x_1, \ldots, x_m)^\top \in \mathbb{R}^{m \times d}$. Notice that the nonsingularity of $X^\top X$ is a standard condition in linear regression (James et al. 2013). It ensures that all $\beta_i$’s may be estimated properly.

### 3.2 Extended Stein’s Lemma

Conventional R&S procedures often have a first stage to estimate the means and variances of all alternatives, and use them to determine the remaining sample sizes (or sampling policy). For instance, the two-stage procedures of Dudewicz and Dalal (1975) and Rinott (1978) and the sequential procedures of Kim and Nelson (2001) and Hong (2006) use the sample variances, and the OCBA procedure of Chen et al. (1997) use both the sample means and variances. However, this may create a statistical issue because the overall sample size of an alternative now depends on its first-stage samples. Then, what is the distribution of the overall sample mean?

The Stein’s lemma (Stein 1945) critically answers this question. The lemma shows that, if $Y_1, Y_2, \ldots$, are independent and identically distributed (i.i.d.) normal random variables and $N$ depends on the first-stage samples only through the sample variance, then the overall sample mean $(Y_1 + \cdots + Y_N)/N$, conditionally on the first-stage sample variance, still has a normal distribution. Consequently, this lemma became a cornerstone of conventional frequentist’s R&S procedures in proving finite-sample statistical guarantees with unknown variances; see Dudewicz and Dalal (1975) and Rinott (1978) for early use of this lemma in designing two-stage R&S procedures, and Theorem 2 of Kim and Nelson (2006) for a rephrased version of the lemma.

In R&S-C we also face the problem of unknown variances, i.e., $\sigma_1^2, \ldots, \sigma_k^2$ are unknown in the linear models. Moreover, we have to deal with the OLS estimators $\hat{\beta}_i$’s instead of only the sample means as in conventional R&S. Suppose that we have $m \geq d$ design points with the design matrix $X$ and each sample includes an observation from every design point. Then, we have the following extended Stein’s lemma. We defer its proof to Appendix A where a more general version is stated and proved, but remark here that the assumption of the linear models is crucial.

**Lemma 1** (Extended Stein’s Lemma). Let $Y = X\beta + \epsilon$, where $\beta \in \mathbb{R}^d$, $X \in \mathbb{R}^{m \times d}$, and $\epsilon \sim \mathcal{N}(0, \sigma^2 \mathcal{I})$ with $0$ denoting the zero vector in $\mathbb{R}^m$ and $\mathcal{I}$ the identity matrix in $\mathbb{R}^{m \times m}$. Assume that $X^\top X$ is nonsingular. Let $T$ be a random variable independent of $\sum_{\ell=1}^n Y_\ell$ and of $\{Y_\ell : \ell \geq n + 1\}$,
where $Y_1, Y_2, \ldots$, are independent samples of $Y$. Suppose that $N \geq n$ is an integer-valued function of $T$ and no other random variables. Let $\hat{\beta} = N^{-1}(X^T X)^{-1} X^T \sum_{\ell=1}^N Y_\ell$. Then, for any $x \in \mathbb{R}^d$,

(i) $x^T \hat{\beta}|T \sim N\left(x^T \hat{\beta}, \frac{\sigma^2}{N} x^T (X^T X)^{-1} x\right)$;

(ii) $\sqrt{N} \left( x^T \hat{\beta} - x^T \beta \right) / \sigma \sqrt{x^T (X^T X)^{-1} x}$ is independent of $T$ and has the standard normal distribution.

Remark 4. If we set $m = d = 1$ and $X = 1$, $Y$ becomes a scalar and it follows $N(\beta_1, \sigma^2)$. Then, Lemma 1 becomes the Stein’s lemma (Stein 1945). In this sense, Lemma 1 is an extension of the Stein’s lemma to the linear regression context.

Remark 5. In Lemma 1 if we let $T$ denote the OLS estimator of the variance $\sigma^2$ computed using only the first stage samples $Y_1, \ldots, Y_n$, by Rencher and Schaalje (2008 Theorem 7.6b), $(nm - d)T/\sigma^2$ follows a chi-squared distribution with $(nm - d)$ degrees of freedom and it is independent of $\sum_{\ell=1}^n Y_\ell$ and of $\{Y_\ell : \ell \geq n + 1\}$. Therefore, similar to conventional frequentist’s R&S, we may let the sample sizes of all alternatives depend on their first-stage OLS variance estimators and still keep the desired statistical properties.

4 Two-Stage Procedure

For conventional frequentist’s R&S procedures, there are two-stage and sequential procedures. Even though both types of procedures are designed based on the least favorable configuration of means, sequential procedures, such as those of Kim and Nelson (2001) and Hong (2006), take advantage of the information on means and allow the procedures to terminate earlier if the differences between the best and the rest alternatives are significantly larger than the IZ parameter. On the other hand, two-stage procedures, such as those of Dudewicz and Dalal (1975) and Rinott (1978), do not take the mean information into consideration and are thus often more conservative.

In R&S-C problems, however, the configurations of the means depend on the realizations of the covariates. For some realizations of the covariates, the differences may be larger than the IZ parameter; while for other realizations, the differences may be much smaller, even close to zero (see, for instance, Figure 1). The procedures that we intend to design need to deliver a selection policy $\hat{i}(x)$ for all $x \in \Theta$ before the covariates are realized, and the policy may be used repeatedly for many realizations of the covariates. Therefore, it is not clear whether sequential procedures may still be advantageous in the R&S-C context. In this paper we focus on designing two-stage procedures that deliver the desired finite-sample statistical guarantee.

4.1 The Procedure

We develop a two-stage procedure, called Procedure TS, for R&S-C problems under Assumption 1. In the first stage, the procedure takes a small number of samples from all design points to estimate the total sample size required to deliver the desired statistical guarantee; and in the second stage, it
takes the additional samples and produces a selection policy based on all samples. The structure of the procedure resembles many of the conventional two-stage R&S procedures, including those of Dudewicz and Dalal (1975) and Rinott (1978).

**Procedure TS**

**Setup:** Specify the target PCS $E_{1 - \alpha}$, the IZ parameter $\delta > 0$, the first-stage sample size $n_0 \geq 2$, the number of design points $m \geq d$, and the design matrix $X$ with a nonsingular $X^\top X$. Let $h$ satisfy the following equation

$$E \left\{ \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h}{\sqrt{(n_0m - d)(t^2 + s)}} X^\top (X^\top X)^{-1} X \right) \eta(s)ds \right]^{k-1} \eta(t)dt \right\} = 1 - \alpha, \quad (4)$$

where $\Phi(\cdot)$ is the cumulative distribution function (CDF) of the standard normal distribution, $\eta(\cdot)$ is the probability density function (PDF) of the chi-squared distribution with $(n_0m - d)$ degrees of freedom, and the expectation is taken with respect to the distribution of $X$.

**First-stage Sampling:** Take $n_0$ independent samples from each alternative $i$ at each design point $x_j$ through simulation, and denote them by $Y_{i\ell} = (Y_{i\ell}(x_1), \ldots, Y_{i\ell}(x_m))^\top$, $i = 1, \ldots, k$, $\ell = 1, \ldots, n_0$. For each $i = 1, \ldots, k$, let

$$\hat{\beta}_{i0} = \frac{1}{n_0} (X^\top X)^{-1} \sum_{\ell=1}^{n_0} Y_{i\ell},$$

$$S_{i}^2 = \frac{1}{n_0m - d} \sum_{\ell=1}^{n_0} (Y_{i\ell} - X\hat{\beta}_{i0})^\top (Y_{i\ell} - X\hat{\beta}_{i0}).$$

**Second-stage Sampling:** Compute the total sample size $N_i = \max \{ \lceil h^2 S_i^2 / \delta^2 \rceil, n_0 \}$ for each $i$, where $\lceil a \rceil$ denotes the smallest integer no less than $a$. Take $N_i - n_0$ additional independent samples from alternative $i$ at all design points through simulation, $Y_{i,n_0+1}, \ldots, Y_{iN_i}$, $i = 1, \ldots, k$. For each alternative $i$, let

$$\hat{\beta}_i = \frac{1}{N_i} (X^\top X)^{-1} \sum_{\ell=1}^{N_i} Y_{i\ell}.$$

**Selection:** Return $\hat{i}^*(x) = \arg \max_{1 \leq i \leq k} \{ x^\top \hat{\beta}_i \}$ as the selection policy.

**Remark 6.** The constant $h$, defined in (4), is computed numerically. In our implementation, the integrations and expectations are computed by the MATLAB built-in numerical integration function `integral`, and $h$ is solved by the MATLAB built-in root finding function `fzero`. However, the numerical integration may suffer from the curse of dimensionality if the dimension of $X$ is large. In such situations one may use the Monte Carlo method to approximate the expectation or directly apply stochastic approximation algorithm (Robbins and Monro 1951) to find the root $h$. 

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4.2 Statistical Validity

In this subsection we establish the statistical validity of Procedure TS, i.e., we prove that, when Procedure TS is used to solve R&S-C problems and Assumption 1 is satisfied, the PCS is at least 1 − α.

Besides the extended Stein’s lemma (i.e., Lemma 1) that we establish in [8] we also need the following lemma, often known as the Slepian’s Inequality (Slepian 1962).

**Lemma 2 (Slepian’s Inequality).** Suppose that (Z₁, . . . , Zₖ)ᵀ has a multivariate normal distribution. If Cov(Zᵢ, Zⱼ) ≥ 0 for all 1 ≤ i, j ≤ k, then, for any constants cᵢ, i = 1, . . . , k,

\[ P \left( \bigcap_{i=1}^{k} \{ Z_i \geq c_i \} \right) \geq \prod_{i=1}^{k} P(Z_i \geq c_i). \]

Now we are ready to state and prove the finite-sample statistical validity of Procedure TS.

**Theorem 1.** Suppose that Procedure TS is used to solve a R&S-C problem and Assumption 1 is satisfied. Then, PCS ≥ 1 − α.

**Proof.** Notice that \( P(X) := X^\top(X^\top X)^{-1}X \) and temporarily write \( i^* = i^*(X) \) to suppress the dependence on \( X \). Let \( \Omega(x) := \{ i : X^\top \beta_{i^*} - X^\top \beta_i \geq \delta \} \) be the set of alternatives outside the IZ given \( X = x \). For each \( i \in \Omega(X) \), \( X^\top \beta_{i^*} \) is independent of \( X^\top \beta_i \) given \( X \). It then follows from (5) that

\[ X^\top \beta_{i^*} - X^\top \beta_i \left( X, S_i^2, S_{i^*}^2 \right) \sim N \left( X^\top \beta_{i^*} - X^\top \beta_i, (\sigma_i^2/N_i + \sigma_{i^*}^2/N_{i^*})V(X) \right). \]

Hence, letting \( Z \) denote a standard normal random variable, for each \( i \in \Omega(X) \), we have

\[
P \left( X^\top \beta_{i^*} - X^\top \beta_i > 0 \bigg| X, S_i^2, S_{i^*}^2 \right) = P \left( Z > \frac{- (X^\top \beta_{i^*} - X^\top \beta_i)}{\sqrt{\sigma_i^2/N_i + \sigma_{i^*}^2/N_{i^*}}V(X)} \bigg| X, S_i^2, S_{i^*}^2 \right) \\
\geq P \left( Z > \frac{-\delta}{\sqrt{\sigma_i^2 \delta^2/(h^2 S_i^2) + \sigma_{i^*}^2 \delta^2/(h^2 S_{i^*}^2)}}V(X) \bigg| X, S_{i^*}^2, S_i^2 \right) \\
= \Phi \left( \frac{h}{\sqrt{(n_0m - d - 1)(\xi_i^{-1} + \xi_{i^*}^{-1})V(X)}} \right),
\]

(7)
Therefore, applying (8) and Lemma 2, we have

\[ \text{PCS}(X) \geq \mathbb{P} \left( \bigcap_{i \in \Omega(X)} \left\{ X^\top \hat{\beta}_i^* - X^\top \hat{\beta}_i > 0 \right\} \bigg| X \right) \]

\[ = \mathbb{E} \left[ \mathbb{P} \left( \bigcap_{i \in \Omega(X)} \left\{ X^\top \hat{\beta}_i^* - X^\top \hat{\beta}_i > 0 \right\} \bigg| X, S^2_i, \{ S^2_i : i \in \Omega(X) \} \right) \bigg| X \right] \]

where the equality is due to the tower law of conditional expectation. Notice that conditionally on \( \{ X, S^2_i, \{ S^2_i : i \in \Omega(X) \} \} \), \( \{ X^\top \hat{\beta}_i^* - X^\top \hat{\beta}_i : i \in \Omega(X) \} \) is multivariate normal by (6). Moreover, for \( i, i' \in \Omega(X) \) and \( i \neq i' \), due to the conditional independence between \( X^\top \hat{\beta}_i \) and \( X^\top \hat{\beta}_{i'} \),

\[ \text{Cov} \left( X^\top \hat{\beta}_i^* - X^\top \hat{\beta}_i, X^\top \hat{\beta}_{i'} - X^\top \hat{\beta}_{i'} \bigg| X, S^2_i, \{ S^2_i : i \in \Omega(X) \} \right) = \text{Var} \left( X^\top \hat{\beta}_i^* \bigg| X, S^2_i \right) > 0. \]

Therefore, applying (8) and Lemma 2 we have

\[ \text{PCS}(X) \geq \mathbb{E} \left[ \prod_{i \in \Omega(X)} \mathbb{P} \left( X^\top \hat{\beta}_i^* - X^\top \hat{\beta}_i > 0 \bigg| X, S^2_i, S^2_i \right) \bigg| X \right] \]

\[ \geq \mathbb{E} \left[ \prod_{i \in \Omega(X)} \Phi \left( \frac{h}{\sqrt{(n_0 m - d - 1)(\xi_i^{-1} + \xi_i^{-1})V(X)}} \right) \bigg| X \right] \]

\[ = \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h}{\sqrt{(n_0 m - d - 1)(t^{-1} + s^{-1})V(X)}} \right) \eta(s)ds \right]^{\Omega(X)} \eta(t)dt, \]

where the second inequality follows from [7]. Since \( 0 \leq \Phi(\cdot) \leq 1 \) and \( \eta(\cdot) \) is a pdf, the integral inside the square brackets in (9) is no greater than 1. Moreover, since \( |\Omega(X)| \leq k - 1 \), hence,

\[ \text{PCS}(X) \geq \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h}{\sqrt{(n_0 m - d - 1)(t^{-1} + s^{-1})V(X)}} \right) \eta(s)ds \right]^{k-1} \eta(t)dt. \]

Then, it follows immediately from the definition of \( h \) in (4) that \( \text{PCS}_E = \mathbb{E}[\text{PCS}(X)] \geq 1 - \alpha. \)

## 5 Handling Heteroscedastic Errors

In Assumption 1 we assume that the variance of simulated samples of an alternative does not change with respect to the values of the covariates. This implies that the linear models all have homoscedastic simulation errors. However, this assumption may not always hold. In many practical situations, such as queueing and financial applications, simulation errors are often heteroscedastic.
In this section we present a two-stage R&S-C procedure to take care of the heteroscedasticity in the linear models.

We first extend Assumption 1 to the following to allow heteroscedastic errors.

**Assumption 2.** For all \( i = 1, \ldots, k \), conditionally on \( X = x \),

\[
\mu_i(x) = x^\top \beta_i, \\
Y_i(x) = \mu_i(x) + \epsilon_i(x),
\]

where \( \beta_i = (\beta_{i1}, \ldots, \beta_{id})^\top \in \mathbb{R}^d \) is a vector of unknown coefficients and \( \epsilon_i(x) \) follows a normal distribution with mean 0 and variance \( \sigma_i^2(x) \).

When linear models have heteroscedastic errors, OLS estimators of \( \beta_i \)'s are still consistent estimators. However, subtle controls are needed to deliver the required PCS. Because our experiments are controlled simulation experiments, we may run multiple simulation runs at each design point to calculate the sample variance at the design point. We then use these sample variances to determine the (different) total sample sizes at different design points. We call this new two-stage procedure Procedure TS\(^+\). One distinct feature of Procedure TS\(^+\) is that it allows different design points to have different total sample sizes to handle heteroscedastic errors; while Procedure TS always assign the same total sample size to all design points. The following is the procedure. For simplicity, we use \( \chi^2_\nu \) to denote the chi-squared distribution with \( \nu \) degrees of freedom.

**Procedure TS\(^+\) Setup:** Specify the target PCS \( 1 - \alpha \), the IZ parameter \( \delta > 0 \), the first-stage sample size \( n_0 \geq 2 \), the number of design points \( m \geq d \), and the design matrix \( X \) with a nonsingular \( X^\top X \). Let \( h_{\text{Het}} \) satisfy the following equation

\[
\mathbb{E} \left\{ \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1)(t^{-1} + s^{-1})X^\top(\lambda^\top X)\lambda X}} \right) \gamma_{(1)}(s) ds \right]^{k-1} \gamma_{(1)}(t) dt \right\} = 1 - \alpha,
\]

where \( \gamma_{(1)}(\cdot) \) is the pdf of the smallest order statistic of \( m \) i.i.d. \( \chi^2_{n_0-1} \) random variables, i.e.,

\[
\gamma_{(1)}(t) = m \gamma(t)(1 - \Gamma(t))^{m-1},
\]

with \( \gamma(\cdot) \) and \( \Gamma(\cdot) \) denoting the pdf and cdf of the \( \chi^2_{n_0-1} \) distribution, respectively, and the expectation is taken with respect to the distribution of \( X \).

**First-stage Sampling:** Take \( n_0 \) independent samples of each alternative \( i \) from each design point \( x_1 \) through simulation, and denote them by \( Y_{i\ell}(x_1), \ldots, Y_{i\ell}(x_m), i = 1, \ldots, k, \ell = 1, \ldots, n_0 \). For each \( i \) and \( j \), let

\[
Y_{ij} = \frac{1}{n_0} \sum_{\ell=1}^{n_0} Y_{i\ell}(x_j) \quad \text{and} \quad S^2_{ij} = \frac{1}{n_0 - 1} \sum_{\ell=1}^{n_0} (Y_{i\ell}(x_j) - Y_{ij})^2.
\]
Second-stage Sampling: Compute the total sample size \( N_{ij} = \max \left\{ \left\lceil \frac{h_{Het}^2 S_{ij}^2}{\delta^2} \right\rceil, n_0 \right\} \) for each \( i \) and \( j \). Take \( N_{ij} - n_0 \) additional independent samples from alternative \( i \) at design point \( x_j \) through simulation, \( Y_{i,n_0+1}(x_j), \ldots, Y_{i N_{ij}}(x_j), \quad j = 1, \ldots, m, \quad i = 1, \ldots, k \). For each alternative \( i \), let
\[
\hat{\beta}_i = (X^\top X)^{-1} X^\top \hat{Y}_i,
\]
where \( \hat{\beta}_i = (\hat{Y}_{i1}, \ldots, \hat{Y}_{im})^\top \) and
\[
\hat{Y}_{ij} = \frac{1}{N_{ij}} \sum_{\ell=1}^{N_{ij}} Y_{i\ell}(x_j).
\]

Selection: Return \( i^*(x) = \arg \max_{1 \leq i \leq k} \left\{ x^\top \hat{\beta}_i \right\} \) as the selection policy.

Remark 7. A noticeable difference of Procedure TS\(^+\) from Procedure TS is the involvement of the smallest order statistic, which is introduced to make the computation of \( h_{Het} \) feasible. Without it, the equation for computing the constant \( h_{Het} \) would involve \((2^m)-\)dimensional numerical integration, which becomes prohibitively difficult to solve for \( m \geq 3 \). See Remark \([11]\) in Appendix \([B]\) for more details.

The following theorem states that Procedure TS\(^+\) is statistically valid under Assumption \([2]\). Its proof is similar to that of Theorem \([1]\) but technically more involved. So we include it to Appendix \([B]\), but remark here that the proof relies critically on a more generalized extension of the Stein’s lemma \((\text{Stein} 1945)\), which is stated and proved as Lemma \([3]\) in Appendix \([A]\).

**Theorem 2.** Suppose that Procedure TS\(^+\) is used to solve a R\&S-C problem and Assumption \([2]\) is satisfied. Then, \( \text{PCS}_E \geq 1 - \alpha \).

Clearly, the assumption of homoscedasticity yields more analytical and computational tractability than the assumption of heteroscedasticity. However, if Procedure TS is used in the presence of heteroscedastic errors, it may fail to deliver the desired PCS\(_E\) guarantee. An intuitive explanation is that using a single variance estimate for all the design points may underestimate the variance at some design points, leading to insufficient sampling effort at those design points. On the other hand, Procedure TS\(^+\) may behave in an overly conservative manner in the presence of homoscedastic error. This is because Procedure TS\(^+\) requires estimation of the variances at all design points, which amounts to estimating the common variance repeatedly in the homoscedasticity setting, resulting in excessive sampling effort. Furthermore, the use of the order statistic in Procedure TS\(^+\) further loosens the lower bound of the PCS\(_E\) and results in more excessive sample sizes. These behaviors are revealed clearly through the numerical experiments in \([7]\).

The above discussion provides us a rule of thumb for choosing the procedures in practice. Procedure TS may be preferred if either the problem has approximately homoscedastic errors, or the decision maker can tolerate some underachievement relative to the desired PCS\(_E\). On the other hand, Procedure TS\(^+\) may be a better choice if the errors are notably heteroscedastic or if the decision maker is stringent on delivering the PCS\(_E\) guarantee.
### 6 Least Favorable Configuration

For conventional R&S problems, the so-called least favorable configuration (LFC) is an important concept, because it defines the most difficult mean configuration of alternatives for the selection procedures (Bechhofer 1954). Indeed, many selection procedures are designed by analyzing the LFC. If a selection procedure can meet the target PCS for the LFC, it can certainly meet the same target for all configurations. It is well known that under the IZ formulation, the LFC for R&S problems is the slippage configuration (SC) for many procedures (Gupta and Miescke 1982). The SC is a configuration where there exists a unique best alternative and all other alternatives have equal means which differ from the best by exactly the IZ parameter.

To better understand our proposed procedures for R&S-C, it is important to investigate their LFCs. We first generalize the SC to the R&S-C setting and define the generalized slippage configuration (GSC) as follows:

\[ \mu_1(x) - \mu_i(x) = \delta, \quad \text{for all } x \in \Theta \text{ and all } i = 2, \ldots, k. \]  

Under the linearity assumption (e.g., Assumption 1 or 2), the GSC becomes

\[ x^\top \beta_1 - x^\top \beta_i = \delta, \quad \text{for all } x \in \Theta \text{ and all } i = 2, \ldots, k. \]  

Hence, under the GSC, the best alternative is the same for all \( x \in \Theta \), and all other alternatives have equal mean performances. It is worth mentioning that, the GSC of linear mean surfaces implies the existence of an intercept term (i.e., \( X_1 \equiv 1 \)). Geometrically, the GSC means that the hyperplanes formed by the mean performances of the inferior alternatives are identical and parallel to the hyperplane of the best alternative, and the vertical distance between the two hyperplanes (i.e, the difference between the intercepts) is exactly \( \delta \); see Figure 2 for an illustration for \( d = 3 \).

It turns out that the GSC defined in (12) is the LFC for both Procedures TS and TS\(^+\) under the IZ formulation. We summarize this result in the following theorem. A slightly more general result is provided and proved in Appendix C.

**Theorem 3.** The GSC is the LFC for Procedures TS and TS\(^+\).

**Remark 8.** Theorem 3 not only deepens our understanding of our procedures, but also helps us design numerical experiments to serve as a stress test for the proposed procedures.

### 7 Numerical Experiments

In this section, we investigate numerically the statistical validity of the two proposed procedures. We create a number of problem instances to test the procedures. For each problem instance, we need to specify the number of alternatives \( k \), the dimension of the covariates \( d \), the design matrix \( X \), the mean configuration parameters \( \beta_i \)'s, the variance configuration \( \sigma^2_i(\cdot) \)'s, and the distribution of \( X \). Instead of specifying the above aspects in a combinatorial fashion, which would result in
an excessively large number of problem instances, we first create a benchmark problem and then investigate the effect of a factor by varying it while keeping others unchanged.

The benchmark problem is formulated as follows. Let \( d = 4 \) and \( k = 5 \). Suppose that \( X = (1, X_2, \ldots, X_d)^\top \), and \( X_2, \ldots, X_d \) are i.i.d. Uniform\([0, 1]\) random variables. Here the first covariate is always 1, which is used to include the intercept terms for linear models. We set each except the first entry of a \( d \)-dimensional design point to be 0 or 0.5, so there are \( m = 2^{d-1} \) design points in total. We set the configuration of the means to be the GSC, i.e., \( \beta_{1} - \delta = \beta_{i1} = 0, \beta_{1w} = \beta_{iw} = 1 \), for \( i = 2, \ldots, k \) and \( w = 2, \ldots, d \), and set the simulation errors to be homoscedastic, particularly \( \sigma_i(x) \equiv \sigma_i = 10 \) for \( i = 1, \ldots, k \).

We then create 9 test problems below by varying one factor of the benchmark problem at a time, while keeping other factors the same.

(1) \( k = 2 \).
(2) \( k = 8 \).
(3) Randomly generated components of \( \beta_i \) from Uniform\([0, 5]\), \( i = 1, \ldots, 5 \).
(4) Increasing variances (IV) configuration: \( \sigma_1 = 5, \sigma_2 = 7.5, \sigma_3 = 10, \sigma_4 = 12.5, \sigma_5 = 15 \).
(5) Decreasing variances (DV) configuration: \( \sigma_1 = 15, \sigma_2 = 12.5, \sigma_3 = 10, \sigma_4 = 7.5, \sigma_5 = 5 \).
(6) Heteroscedastic simulation errors: \( \sigma_i(x) = 10x^\top \beta_i, i = 1, \ldots, 5 \).
(7) \( d = 2 \).
(8) \( d = 6 \).
(9) \( X_i \sim \mathcal{N}(0.5, 1) \) truncated on \([0, 1]\), and \( \text{Cov}(X_i, X_j) = 0.5 \), for \( i, j = 2, 3, 4 \) and \( i \neq j \).

Compared to the benchmark problem, Problems (1) and (2) change the number of alternatives, Problem (3) changes the configuration of the means so it is no longer the GSC, Problems (4) and (5) change the configuration of the variances while retaining homoscedasticity, Problem (6)
considers heteroscedasticity, and Problems (7) and (8) change the dimensionality of the covariates, and Problem (9) changes the distribution of the covariates.

In all the problem instances, we set $\alpha = 0.05$, $\delta = 1$, and $n_0 = 50$. We conduct $R = 10^4$ macro-replications for each problem-procedure combination. In each macro-replication $r = 1, \ldots, R$, we apply Procedure TS and TS+, respectively, to a problem to obtain a selection policy $\hat{i}^r_i(x)$, and then apply it to select the best alternative for each $x_t$, a realization of $X$ that is randomly generated from its distribution, for $t = 1, \ldots, T$ with $T = 10^5$. We calculate the achieved $\text{PCS}_E$ as

$$\text{PCS}_E := \frac{1}{R} \sum_{r=1}^{R} \frac{1}{T} \sum_{t=1}^{T} \mathbb{I}\{\mu^*_i(x_t) - \mu^*_{i^r_i(x_t)}(x_t) < \delta\},$$

where $\mathbb{I}\{\cdot\}$ denotes the indicator function. We also report the average total sample size used by each procedure for producing the selection policy.

Table 1: Results When the Target $\text{PCS}_E$ is $\geq 95\%$.

| Problem   | Procedure TS | Procedure TS+ |
|-----------|--------------|---------------|
|           | $h$          | $\text{Sample Size}$ | $\text{PCS}_E$ | $h_{\text{Het}}$ | $\text{Sample Size}$ | $\text{PCS}_E$ |
| (0) Benchmark | 3.423        | 46,865        | 0.9610         | 4.034         | 65,138        | 0.9801         |
| (1) $k = 2$    | 3.263        | 8,947         | 0.9540         | 2.781         | 13,280        | 0.9702         |
| (2) $k = 8$    | 3.822        | 93,452        | 0.9652         | 4.510         | 130,200       | 0.9842         |
| (3) Non-GSC    | 3.423        | 46,865        | 0.9987         | 4.034         | 65,138        | 0.9994         |
| (4) IV         | 3.423        | 52,698        | 0.9618         | 4.034         | 73,265        | 0.9807         |
| (5) DV         | 3.423        | 52,720        | 0.9614         | 4.034         | 73,246        | 0.9806         |
| (6) Het        | 3.423        | 58,626        | 0.9232         | 4.034         | 81,555        | 0.9846         |
| (7) $d = 2$    | 4.612        | 28,228        | 0.9593         | 4.924         | 24,266        | 0.9662         |
| (8) $d = 6$    | 2.141        | 73,428        | 0.9656         | 2.710         | 117,630       | 0.9895         |
| (9) Normal Dist| 3.447        | 47,529        | 0.9626         | 4.063         | 66,061        | 0.9821         |

Note. In the presence of heteroscedasticity, the boxed number suggests that Procedure TS fails to deliver the target $\text{PCS}_E$, whereas the bold number suggests that Procedure TS+ succeeds to do so.

The numerical results are shown in Table 1, from which we have the following observations. First, as expected, both procedures can deliver the target $\text{PCS}_E$ in their respective domains. Procedure TS can deliver the designed $\text{PCS}_E$ if the simulation errors are homoscedastic, while Procedure TS+ can deliver the designed $\text{PCS}_E$ even when the simulation errors are heteroscedastic. Moreover, the achieved $\text{PCS}_E$ is higher than the target in general; see, e.g., the column “$\text{PCS}_E$” under “Procedure TS” of Table 1 except the entry for Problem (6). This is especially the case if the configuration of the means is not the GSC, i.e., Problem (3). Overshooting the target $\text{PCS}_E$ suggests that the total sample size is larger than necessary for meeting the target $\text{PCS}_E$. Such conservativeness is a well known issue for R&S procedures under the IZ formulation; see Fan et al. (2016) for an exposition on the issue.

Second, if Procedure TS is applied to the instance of heteroscedasticity, (i.e., Problem (6)), the target $\text{PCS}_E$ cannot be met. By contrast, if Procedure TS+ is applied to the instances of homoscedasticity, (i.e., all problem instances except (6)), it becomes overly conservative. This is
reflected by the achieved PCS_E being substantially higher than the target and the sample size being substantially larger than that of Procedure TS.

Third, as the number of alternative k increases, which corresponds to Problems (1), (0), and (2), the sample size allocated to each alternative on average (measured by the ratio of the total sample size to k) increases as well. This is caused by the increase in the constant h as k increases. Notice that the sample size required for alternative i in Procedure TS is \( N_i = \max\{\lceil h^2 S_i^2 / \delta^2 \rceil, n_0 \} \). Thus, a larger h means a larger \( N_i \). A similar argument holds for Procedure TS+ as well. This suggests that as k increases, each alternative must be estimated more accurately in order to differentiate them.

Last, the numerical results of Problems (4) and (5) are almost identical. In particular, the value of h is identical for both problems, because the equations that determine h (Equation (4)) and \( h_{\text{Het}} \) (Equation (10)) do not depend on the configuration of the variances. Then, as the sum of the variances is the same for both problems, the total sample size that is approximately proportional to \( h^2 \) times the sum of the variances is almost the same for both problems.

8 Experimental Design and Robustness to Linearity Assumptions

We have assumed so far that the designs points are given with the design matrix \( \mathcal{X} \) satisfying that \( \mathcal{X}^\top \mathcal{X} \) is nonsingular. In this section we discuss how to select the design points. We show that the extreme design, i.e., locating the design points at the corners of the design region \( \Theta \), is typically a good strategy under the linearity assumptions (i.e., Assumption 1 or 2). In practice, however, linearity assumptions are often satisfied only approximately. Then, the selection of design points is critically related to the robustness of the linearity assumptions. We show through numerical experiments that the extreme design may perform poorly when the linearity assumptions are violated mildly, but distributing the design points evenly in the design region \( \Theta \) appears to be quite robust to the linearity assumptions.

8.1 Optimal Design Under Linearity Assumptions

Experimental design is a classical problem in statistics. In classical design for linear regression, the objective is often to choose a design that optimizes a certain criterion given a fixed total sample size. Popularly used criteria include D-optimal design that minimizes the determinant of the covariance matrix of the OLS estimator of \( \beta \), G-optimal design that minimizes the maximal variance of the fitted response over the design region, and many others; see Silvey (1980, Chapter 2) for more details on the subject. Some of the optimal designs are equivalent under certain conditions. For instance, Kiefer and Wolfowitz (1960) prove that the D-optimal design and G-optimal design are equivalent in the continuous case (also called the approximate case) where the integer constraint on the sample size at each design point is relaxed; see Silvey (1980, Chapter 3) for a more careful and complete discussion on the general equivalence theory.

However, the optimal design in R&S-C context is different from the classical ones. In our
procedures, an optimal design is the design that minimizes the total sample size required by the procedures to deliver the predetermined PCS. Using Procedure TS as an example, the total sample size is \( \sum_{i=1}^{k} N_i m \), where \( N_i \) is approximately \( h^2 S_i^2 / \delta^2 \). Recall that the design matrix \( \mathbf{X} = (\mathbf{x}_1, \ldots, \mathbf{x}_m)^T \). Therefore, we may formulate the optimal design problem as the following optimization problem:

\[
\min_{m, \mathbf{x}_1, \ldots, \mathbf{x}_m} h^2 m \\
\text{s.t. } \mathbb{E} \left\{ \int_0^\infty \int_0^\infty \Phi \left( \frac{h}{\sqrt{(n_0 m - d)(t-1+s^{-1})}} \right) \eta(s) ds \right\} = 1 - \alpha,
\]

\[
\text{rank } (\mathbf{X}^T \mathbf{X}) = d, \\
m \geq d, \text{ integer}, \\
\mathbf{x}_j \in \Theta, \ j = 1, \ldots, m,
\]

where the first constraint is exactly (4), and the second constraint ensures the nonsingularity of \( \mathbf{X}^T \mathbf{X} \). The problem is in general a nonconvex integer programming problem, and it is difficult to solve. Moreover, even without concerning the integer constraint, the optimal design is a function of the distribution of \( \mathbf{X} \) and is often difficult to characterize. In this subsection, we derive an optimal design, which is invariant to the distribution of \( \mathbf{X} \), for a simplified case where \( m \) is fixed and an additional constraint is imposed.

![Figure 3: Geometrical Illustration of the Symmetric Design for \( d = 3 \) and \( b = 2 \).](image)

Note. Coordinate \( x_1 \) is omitted since it is always 1.

Specifically, we assume that

\[
\Theta = \{1\} \times [l_2, u_2] \times \cdots \times [l_d, u_d], \ d \geq 2 \text{ and } l_w < u_w \text{ for all } w = 2, \ldots, d. \tag{14}
\]

Here the first covariate is always 1, which is used to take care of the intercept terms in the linear models, and all other \( d - 1 \) covariates are in an interval \( [l_w, u_w] \) for \( w = 2, \ldots, d \). Suppose that we
want to allocate \( m = b(2^{d-1}) \) design points in \( \Theta \), where \( b \geq 1 \) is a fixed integer. We denote these design points by \( a_i^j \in \Theta \), \( i = 1, \ldots, 2^{d-1} \) and \( j = 1, \ldots, b \). Moreover, for any \( j \), we let \( a_1^j, \ldots, a_{2^{d-1}}^j \) be symmetric with respect to the Cartesian coordinate system located at the center of \( \Theta \). See Figure 3 for an illustration with \( d = 3 \) and \( b = 2 \). Let \( S^j := \{a_1^j, \ldots, a_{2^{d-1}}^j\} \) for \( j = 1, \ldots, b \). Then \( \{S^1, \ldots, S^b\} \) denotes a set of \( b(2^{d-1}) \) design points (where duplicates are allowed) and we call it a symmetric design. Notice that the symmetric design ensures that rank \( (X^\top X) \) = \( d \). The reason that we only consider symmetric designs is, without considering the distribution of the covariates \( X \), symmetric designs are natural choices due to the symmetric nature of the design region \( \Theta \).

Let \( S^0 \) denote the set of corner points of \( \Theta \). It is easy to see that \( S^0 \) has \( 2^{d-1} \) elements. A simple design is to use all the points in \( S^0 \) for \( b \) times, i.e., \( S^1 = \cdots = S^b = S^0 \), and we call it the extreme design. Notice that the extreme design aims to spread out all the design points so that the OLS estimators of \( \beta \)'s can have small variances.

The extreme design is also a symmetric design. In the following theorem, we show that the extreme design is the best symmetric design regardless of the distribution of \( X \). The proof is included in Appendix D.

**Theorem 4.** Suppose that Assumption 1 holds, Procedure TS is used to solve a R&S-C problem, and \( m = b(2^{d-1}) \) design points are allocated in \( \Theta \) as assumed in (14). Then, among all symmetric designs, the extreme design \( S^1 = \cdots = S^b = S^0 \) minimizes the expected total sample size.

There is an interesting link between the optimal design in R&S-C with that in classical linear regression setting. That is, the extreme design is also both the D-optimal and G-optimal design in linear regression when the total sample size is \( b(2^{d-1}) \), among all feasible designs (without the symmetry constraint). This result is formally stated in Theorem 5 and its proof is included in Appendix E, where the formal definitions of D-optimality and G-optimality are also given. We want to emphasize that Theorem 5 further justifies the consideration of the extreme designs for R&S-C problems.

**Theorem 5.** Consider the linear regression problem \( Y(x) = x^\top \beta + \epsilon \), where \( \beta, x \in \mathbb{R}^d \) and \( \epsilon \) is random error with mean 0 and variance \( \sigma^2 \). Let \( d \geq 2 \) and \( x_1 \equiv 1 \) so that the intercept term is included. Suppose that \( m = b(2^{d-1}) \) design points are allocated in \( \Theta \) as assumed in (14). Then, among all feasible designs, the extreme design \( S^1 = \cdots = S^b = S^0 \) is both D-optimal and G-optimal.

**Remark 9.** The total sample size of Procedure TS + depends on the variances of the design points, which are not known a priori. Therefore, we can only prove that, among all symmetric designs, the extreme design minimizes the constant \( h_{Het} \) defined in Equation (10).

### 8.2 Robustness to Linearity Assumptions

In practice, linearity assumptions (i.e., Assumptions 1 and 2) are often only satisfied approximately. James et al. (2013) argue that linear models are often robust to nonlinear behaviors and lead to good predictions. However, the extreme design is in general not robust to nonlinearity, because it
allocates no design points in the interior of the design region and leave the fitted models depending completely on the corner points. To improve the robustness of the experimental design, one can allocate design points evenly in the design region. A frequently-used even design is the so-called minimax design, which, roughly speaking, ensures that all points in the design region are not too far from the design points (Johnson et al. 1990). It is shown by Johnson et al. (1990) that the minimax design is asymptotically equivalent to the Bayesian G-optimal design for general Gaussian processes, which mimics the classical G-optimal design but is defined in a Bayesian framework. In the rest of this subsection, we conduct numerical studies to compare the extreme design and the minimax design, and to understand their behaviors under different scenarios.

We consider the case where $\Theta = \{1\} \times [0, 1]^{d-1}$, and generate the true surfaces randomly from a $(d-1)$-dimensional second-order stationary Gaussian random field with mean 0 and isotropic covariance $\text{Cov}(z, z') = \exp\{-\lambda \|z - z'\|^2\}$ for $z, z' \in \mathbb{R}^{d-1}$, where $\|\cdot\|$ represents the Euclidean norm. Notice that parameter $\lambda$ controls the scale of the random field and larger $\lambda$ often leads to higher level of violation of the linearity assumption. To keep the linearity assumptions approximately true, we discretize the surfaces with a step size $0.01$ for each coordinate, calculate the $R^2$ of the discretized observations, and only keep the surfaces whose $R^2$ is above 0.8. We first obtain 50 such approximately linear random surfaces. Then we randomly create 100 R&S-C problems, each with 5 surfaces that are randomly drawn from those 50 surfaces. We consider only the homoscedastic errors, and add normal noises with $\sigma^2_1 = \cdots = \sigma^2_5 = 1$. We consider $\lambda = 0.5$ and $\lambda = 3$ to capture small and large violations of the linearity assumption. We also consider $d = 2$ and $d = 3$. Figure 4 shows the typical shapes of these randomly generated surfaces. For each R&S-C problem, we let $X_2, \ldots, X_d$ be i.i.d. Uniform[0,1] random variables, and set $\alpha = 0.05$, $\delta = 0.2$, $n_0 = 50$, $R = 10^3$ and $T = 10^4$. We compare the extreme design and minimax design with $2(2^{d-1})$ points, i.e., 4 design points when $d = 2$ and 8 design points when $d = 3$. The design matrices are listed in Table 2. We report the means and standard deviations (SD) of the average total sample size and the achieved PCS$_E$ (i.e., $\hat{\text{PCS}}_E$) over 100 problems in Table 3. We also calculate the average regret (also called the opportunity cost in Bayesian R&S literature), which is defined as $\frac{1}{R} \sum_{r=1}^{R} \frac{1}{T} \sum_{t=1}^{T} \{\mu^*(x_t)(x_t) - \mu^*_E(x_t)(x_t)\}$. The means and SD of the average regrets are also reported in Table 3.

From Table 3 we see that the extreme designs lead to significantly smaller total sample sizes than the minimax designs if the linearity assumption is more or less satisfied (e.g., $\lambda = 0.5$); but their achieved PCS$_E$ and regrets are significantly poorer than those of the minimax designs if the linearity assumption is more violated (e.g., $\lambda = 3$). Based on these observations, we have the following conclusions on experimental design and robustness on linearity assumptions.

- The proposed procedures perform well when the surfaces are approximately linear, though the statistical guarantee may not always hold.

- When the true surfaces are exactly linear or only slightly nonlinear, the extreme design is preferred because it requires fewer samples to deliver the required PCS$_E$.
• When the true surfaces are relatively nonlinear, even designs, such as the minimax design, are preferred because they are more robust to nonlinearity.

![Randomly Generated Surfaces with $R^2 \geq 0.8$.](image)

**Figure 4:** Randomly Generated Surfaces with $R^2 \geq 0.8$.

**Table 2:** Extreme Designs and Minimax Designs for $d = 2, 3$.

| $d = 2$ | $d = 3$ |
|---------|---------|
| **Extreme Design** | **Minimax Design** |
| $1 0$ | $1 1/8$ |
| $1 1$ | $1 3/8$ |
| $1 0$ | $1 5/8$ |
| $1 1$ | $1 7/8$ |
| $1 0 0$ | $1 0.1557 0.2086$ |
| $1 0 1$ | $1 0.1557 0.7914$ |
| $1 1 0$ | $1 0.8443 0.2086$ |
| $1 1 1$ | $1 0.8443 0.7914$ |
| $1 0 0$ | $1 0.2468 0.5000$ |
| $1 0 1$ | $1 0.7532 0.5000$ |
| $1 1 0$ | $1 0.5000 0.1794$ |
| $1 1 1$ | $1 0.5000 0.8206$ |

* See Melissen and Schuur (1996).

9 A Case Study: Personalized Treatment for Cancer Prevention

Esophageal cancer (see Figure 5) is the seventh-leading cause of cancer death among males (making up 4%) in the United States, according to Cancer Facts & Figures 2016 by American Cancer Society.
Table 3: Means and SD (in brackets) over 100 Problems.

| Case   | $R^2$ | Sample Size | PCS_E | Regret | Sample Size | PCS_E | Regret |
|--------|-------|-------------|-------|--------|-------------|-------|--------|
| $d = 2, \lambda = 0.5$ | 0.964 (0.002) | 1,730 (2) | 0.9931 (0.0118) | 0.009 (0.010) | 2,869 (5) | 0.9975 (0.0045) | 0.005 (0.005) |
| $d = 2, \lambda = 3$  | 0.921 (0.003) | 1,730 (2) | 0.8555 (0.1399) | 0.100 (0.108) | 2,941 (50) | 0.9801 (0.0292) | 0.013 (0.016) |
| $d = 3, \lambda = 0.5$ | 0.917 (0.003) | 2,282 (70) | 0.9528 (0.0586) | 0.024 (0.027) | 4,659 (16) | 0.9876 (0.0118) | 0.008 (0.007) |
| $d = 3, \lambda = 3$  | 0.863 (0.002) | 2,425 (121) | 0.7358 (0.1306) | 0.204 (0.139) | 4,904 (96) | 0.9133 (0.0502) | 0.047 (0.030) |

Esophageal adenocarcinoma (EAC) is a main sub-type of esophageal cancer, and its incidence has increased by 500% over the past 40 years ([Hur et al. 2013] [Choi et al. 2014]). Thus, the management of Barrett’s esophagus (BE), a precursor to EAC, is an active topic in cancer research. A common strategy for BE management is endoscopic surveillance, which attempts to prevent EAC through dysplasia treatment or to identify EAC before it becomes invasive. Recently, chemoprevention has received substantial attention as a method to lower the progression of BE to EAC, and aspirin and statin are two particular drugs that are demonstrated to be effective ([Kastelein et al. 2011]). For each BE patient, the progression rate to cancer depends on a variety of factors including age, weight, lifestyle habits such as smoking and alcohol use, the grade of dysplasia, etc. In addition, each patient may have a different response to drugs depending on his or her drug resistance and tolerance. Hence, it is conceivable that the best treatment regimen for BE is patient-specific.

![Diagram of Esophageal Cancer](image-source)

**Figure 5:** Diagram of Esophageal Cancer.

*Note.* Image source: Cancer Research UK / Wikimedia Commons, licensed under CC BY-SA 4.0.

We formulate the problem of selecting the best treatment regimen for each BE patient as a R&S-C problem. There are three alternatives: endoscopic surveillance only ($i = 1$), aspirin chemoprevention with endoscopic surveillance ($i = 2$), and statin chemoprevention with endoscopic surveillance ($i = 3$). For simplicity, we consider only the starting age of a treatment regimen, risk (i.e., the annual progression rate of BE to EAC) and drug effects (i.e., the progression reduction effect of a drug) as patient characteristics that determine the effectiveness of a treatment regimen.
More specifically, the vector of covariates is $X = (1, X_1, X_2, X_3, X_4)^\top$, where $X_1$ is the starting age, $X_2$ is the risk, $X_3$ and $X_4$ are the drug effects of aspirin and statin, respectively. We use the expected quality-adjusted life years (QALYs) as the performance measure to compare different alternatives.

To solve this R&S-C problem, we need a model to simulate the QALYs of the treatment regimens for different patients. Fortunately, a discrete-time Markov chain model developed by Hur et al. (2004) and Choi et al. (2014) may be used. The model simulates the transitions among different health states of a BE patient until death, and the transition diagram of the model is shown in Figure 6. The transition probability matrices are well calibrated so that the simulation outputs match the published results. We adopt this model to simulate individual patients with specific characteristics which are defined by the covariates $X$ and assumed to be observable. This Markov chain model is, of course, a highly simplified model compared to those having more detailed biological mechanisms (see for example, the MSCE-EAC model of Curtius et al. (2015)). However, as an illustrative purpose, we adopt this simple model due to its accessibility and relatively short running time, because we need to run the model in a brute force way to obtain the mean performance surfaces of all alternative, i.e., $\mu_i(x)$ for $i = 1, 2, 3$, and use them as the true values to evaluate the performance of the proposed procedures.

In this case study, we assume that the distributions of the covariates are known because there are often ample historical data to calibrate these distributions in practice. Furthermore, we specify these distributions as follows: We assume $X_1 \in [55, 80]$, as it is documented by Naef and Savary (1972) that there is a BE incidence peak for individuals with ages within this range. We assume $X_2 \in [0, 0.1]$ following the specification in Hur et al. (2004), and set $X_3 \in [0, 1]$ and $X_4 \in [0, 1]$ by definition. Moreover, assume $E[X_3] = 0.53$ and $E[X_4] = 0.54$ following the study by Kastelein et al. (2011). Nevertheless, due to lack of detailed data, we do not know the distribution of covariates.
exactly among the entire population of BE patients. Instead, we suppose that $X_1, \ldots, X_4$ are independent and their distributions are specified in Table 4. The design points are specified as follows. We take $X_1$ from \{61, 74\}, $X_2$ from \{0.1/4, 0.3/4\}, $X_3$ from \{1/4, 3/4\}, and $X_4$ from \{1/4, 3/4\}, then combine them in a full factorial way. Therefore, it is a relatively even design with 16 design points.

**Table 4: Distributions of the Covariates.**

| Covariate | Distribution | Support | Mean |
|-----------|--------------|---------|------|
| $X_1$     | Discrete (Figure 7) | \{55, \ldots, 80\} | 64.78 |
| $X_2$     | Uniform (0, 0.1) | [0, 0.1] | 0.05 |
| $X_3$     | Triangular (0, 0.59, 1) | [0, 1] | 0.53 |
| $X_4$     | Triangular (0, 0.62, 1) | [0, 1] | 0.54 |

**Figure 7:** Probability Mass Function of $X_1$ (Truncated).

*Note.* Data source: U.S. 2016 population data, U.S. Census Bureau.

Before carrying out the R&S-C procedures, we conduct several trial runs of the simulation model, and we find that the linearity assumptions hold approximately and the simulation errors are clearly heteroscedastic. Therefore, Procedure TS$^+$ is used. Notice that, to calculate the achieved PCS$E$ (i.e., $\hat{\text{PCS}}_E$) of our procedure, we need the true response surfaces $\mu_i(x)$, for all $x \in \Theta$ and $i = 1, 2, 3$, to identify the true best selection policy $i^*(x)$. To that end, we use extensive simulation to approximate the true response surfaces. We discretize $X_2$ with a step size 0.01 and discretize $X_3$ and $X_4$ with a step size 0.1. At each discretization point, we run the simulation model for $10^6$ replications so that the estimation error is negligible (e.g., the half-width of the 95% confidence interval is less than 0.02 QALYs). The response at any other $x$ is approximated via a linear interpolation. To compute $\hat{\text{PCS}}_E$, we conduct $R = 300$ macro-replications. For each macro-replication $r$, we apply Procedure TS$^+$ to obtain the selection policy $\hat{i}_r^*(x)$, and then apply it to select the best treatment regimen for $T = 10^5$ simulated BE patients whose characteristics are randomly generated from the distribution of $X$. Other parameters of Procedure TS$^+$ are specified as follows: $\alpha = 0.05$, $\delta = 1/6$ (i.e., 2 months) and $n_0 = 100$. Our case study shows that the $\hat{\text{PCS}}_E = 99.5\%$, which is substantially
higher than the target level $1 - \alpha = 95\%$. This is because the configuration of the means of this problem is much more favorable than the GSC, and thus the selection procedure behaves in an overly conservative manner in this situation. (Recall that Problem (3) in §7 has a similar behavior.)

To demonstrate the usefulness of R&S-C as a decision-making framework, we compare the personalized approach with a more traditional approach, which selects the treatment regimen that is the best for the entire population, i.e., $i^* = \arg \max_{1 \leq i \leq 3} E[\mu_i(X)]$. The latter corresponds to a conventional R&S approach. In this problem, we find $i^* = 3$, which indicates that alternative 3 is better than the others based on the population average. Notice that choosing the population best, i.e., always selecting alternative 3, can also be regarded as a selection policy. Based on our numerical study, we find that this policy correspond a PCSE of 75.8%, i.e., alternative 3 is indeed the best or within the IZ for 75.8% of the population. In contrast, the personalized approach that we reported earlier has a PCSE of 99.5%. The 23.7% difference in PCSE demonstrates clearly the advantage of the personalized approach.

In addition to PCSE, we consider QALYs regret as another criterion to compare the two approaches. More specifically, we consider the expected QALYs regret, which is the expected difference between the QALYs under the true optimal treatment regimen and the selected one by each approach. Conditionally on $X = x$, the expected regret is $\mu_{i^*(x)}(x) - \mu_3(x)$ for the traditional approach and $\mu_{i^+(x)}(x) - \mu_{\hat{i}^+(x)}(x)$ for the personalized approach, where $\hat{i}^+(x)$ comes from one macro-replication of Procedure TS$^+$. The results are plotted in Figure 8, where the left panel shows the distribution of regret for the entire BE population (i.e., $X \in \Theta$), and the right panel shows the distribution of regret for a specific group of patients (i.e., $X_3 = 0.9$ and $X_4 = 0.2$).

![Figure 8: Bar Charts of $E[\text{QALYs}|X]$ Regret under the Selected Treatment Regimen. Note. Left: Entire population, $X \in \Theta$. Right: Specific population, $X = (1, X_1, X_2, 0.9, 0.2)^T$.](image)

From these results, we see that, using the personalized approach (i.e., the R&S-C approach), the BE patients have much lower expected QALYs regret than using the traditional approach (i.e., the conventional R&S approach). Among the entire BE population (left panel of Figure 8), when the personalized approach is used, over 99% of the patients have either no regret or a regret that is less than or equal to 2 months (i.e., the IZ parameter). However, when the traditional approach is used,
close to a quarter (i.e., 24%) of the patients have a regret that is more than 2 months and 2% of them have a regret that is above 12 months.

If we look at the specific group of patients, e.g., the group as considered in the right panel of Figure 8, we see that the reduction of the regret using the personalized approach is even more substantial, which demonstrates the key point of personalized medicine, that is, a universal treatment, even it seems fairly good for the entire population, may perform quite poorly for certain groups of patients, where we can do much better with the help of personalized medicine.

10 Conclusions

Ranking and selection is a long-standing research problem in simulation literature. The emerging popularity of personalized decision making leads us to consider this classical problem in a new environment where the performance of an alternative depends on some observable random covariates. A critical feature in the new setting is that the goal is not to seek a single alternative having a superior performance, but a selection policy as a function of the covariates. Albeit computed offline via simulation model, the selection policy can be applied online to specify the best alternative for the subsequent individuals after observing their covariates. Therefore, R&S-C reflects a shift in perspective regarding the role of simulation: a tool for system control instead of system design. In particular, we demonstrate the practical value of R&S-C via a case study of personalized medicine for selecting the best treatment regimen in prevention of esophageal cancer.

This paper uses a linear model to capture the relationship between the response of an alternative and the covariates, and develops two-stage selection procedures accordingly under the IZ formulation. However, the presence of covariates complicates the concept of PCS, since the best alternative varies as a function of the covariates. We define statistical validity of a procedure in terms of average PCS, while other forms of unconditional PCS are also possible. This paper is a first step towards understanding R&S-C problems under a frequentist perspective. There are many potential directions for future work such as nonparametric models and sequential selection procedures.

A Proof of Lemma 1

The following Lemma 3 is a more general version of Lemma 1 in §3. Therefore we only provide the proof of Lemma 3 and remark that Lemma 1 is a special case. Also note that Lemma 3 is used directly in the proof of Theorem 2.

**Lemma 3.** For each $j = 1, \ldots, m$, let $Y_j = x_j^\top \beta + \epsilon_j$, where $\beta, x_j \in \mathbb{R}^d$ and $\epsilon_j \sim \mathcal{N}(0, \sigma_j^2)$. Suppose that $\epsilon_1, \ldots, \epsilon_m$ are independent. Let $Y_1, Y_2, \ldots$ be independent samples of $Y_j$. Let $T$ be a set of random variables independent of $\sum_{\ell=1}^n Y_\ell$ and of $\{Y_\ell : \ell \geq n + 1\}$, for all $j = 1, \ldots, m$. Suppose $N_j \geq n$ is an integer-valued function of $T$ and no other random variables. Let $\hat{Y}_j = N_j^{-1} \sum_{\ell=1}^{N_j} Y_\ell$, $\hat{Y} = (\hat{Y}_1, \ldots, \hat{Y}_m)^\top$, $X = (x_1, \ldots, x_m)^\top$, $\hat{\beta} = (X^\top X)^{-1} X^\top \hat{Y}$, and $\Sigma = \text{Diag}(\sigma_1^2/N_1, \ldots, \sigma_m^2/N_m)$. Then, for any $x \in \mathbb{R}^d$,
Remark 10. It is easy to see that Lemma 1 in [3] is a special case of Lemma 3 with $\sigma_1 = \cdots = \sigma_m = \sigma$ and $N_1 = \cdots = N_m = N$.

B Proof of Theorem 2

The proof of Theorem 2 critically relies on Lemma 3 in Appendix A.

Proof of Theorem 2 Under Assumption 2 for $i = 1, \ldots, k; j = 1, \ldots, m$, $Y_{ij}$ is independent of $S_{ij}^2$; moreover, let $\sigma_{ij} = \sigma_i(x_j)$, then $\xi_{ij} := (n_0 - 1)S_{ij}^2/\sigma_{ij}^2 \sim \chi^2_{n_0 - 1}$; see, e.g., Examples 5.6a and 5 in Rencher and Schaalje (2008). Let $S_i := \{S_{i1}, \ldots, S_{im}\}$, for $i = 1, \ldots, k$. Then, $S_i$ is independent of $\sum_{\ell=1}^{n_0} Y_{\ell id}(x_j)$ and of $\{Y_{\ell id}(x_j) : \ell \geq n_0 + 1\}$. Since $N_{i1}, \ldots, N_{im}$ are integer-valued functions only of $S_i$, by Lemma 3 for $i = 1, \ldots, k$,

$$X^\top \hat{\beta}_i \mid (X, S_i) \sim \mathcal{N}(X^\top \beta_i, X^\top (\Sigma_i X')^{-1} X).$$

Proof. For part (i), by the definition of $\hat{\beta}$, it suffices to show that $\hat{Y} \mid T \sim \mathcal{N}(X\beta, \Sigma)$. We first notice that $Y(x_j) \sim \mathcal{N}(x_j^\top \beta, \sigma_j^2)$. Since $T$ is independent of $\sum_{\ell=1}^n Y_{\ell}(x_j)$,

$$\sum_{\ell=1}^n Y_{\ell}(x_j) \mid T \sim \mathcal{N}(nx_j^\top \beta, n\sigma_j^2).$$

On the other hand, since $T$ is independent of $\{Y_{\ell}(x_j) : \ell \geq n + 1\}$ and $N_j$ is a function only of $T$,

$$\sum_{\ell=n+1}^{N_j} Y_{\ell}(x_j) \mid T \sim \mathcal{N}((N_j - n)x_j^\top \beta, (N_j - n)\sigma_j^2).$$

Since $\sum_{\ell=1}^n Y_{\ell}(x_j)$ and $\sum_{\ell=n+1}^{N_j} Y_{\ell}(x_j)$ are independent,

$$\hat{Y}_j \mid T = \frac{1}{N_j} \left( \sum_{\ell=1}^n Y_{\ell}(x_j) + \sum_{\ell=n+1}^{N_j} Y_{\ell}(x_j) \right) \mid T \sim \mathcal{N}\left(x_j^\top \beta, \sigma_j^2/N_j\right).$$

Notice that $\hat{Y}_1, \ldots, \hat{Y}_m$ are independent conditionally on $T$, so $\hat{Y} \mid T \sim \mathcal{N}(X\beta, \Sigma)$.

For part (ii), let

$$V = \frac{x^\top \hat{\beta} - x^\top \beta}{\sqrt{x^\top (X'X)^{-1} X' \Sigma X (X'X)^{-1} x}},$$

then $V \mid T \sim \mathcal{N}(0, 1)$ by part (i). Notice that $P(V < v | T) = \Phi(v)$ is not a function of $T$ for any $v$, so $V$ is independent of $T$. \qed
where $\Sigma_i = \text{Diag}(\sigma^2_{i1}/N_{i1}, \ldots, \sigma^2_{im}/N_{im})$.

For notational simplicity, let $\mathbf{a} := (a_1, \ldots, a_m)^\top := \mathcal{X}(\mathcal{X}^\top \mathcal{X})^{-1} \mathbf{X}$ and write $i^* = i^*(\mathbf{X})$ to suppress the dependence on $\mathbf{X}$. Then,

$$\mathbf{X}^\top \hat{\mathbf{\beta}}_i \mid (\mathbf{X}, S_i) \sim N \left( \mathbf{X}^\top \hat{\mathbf{\beta}}_i, \sum_{j=1}^m a^2_j \sigma^2_{ij}/N_{ij} \right). \tag{15}$$

Let $\Omega(\mathbf{x}) := \{i : \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i \geq \delta | \mathbf{X} = \mathbf{x}\}$ be the set of alternatives outside the IZ given $\mathbf{X} = \mathbf{x}$. For each $i \in \Omega(\mathbf{X})$, $\mathbf{X}^\top \hat{\mathbf{\beta}}_i$ is independent of $\mathbf{X}^\top \hat{\mathbf{\beta}}_i$ given $\mathbf{X}$. It then follows from (15) that

$$\mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i \mid (\mathbf{X}, S_{i^*}, S_i) \sim N \left( \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i, \sum_{j=1}^m a^2_j (\sigma^2_{i^*j}/N_{i^*j} + \sigma^2_{ij}/N_{ij}) \right). \tag{16}$$

Hence, letting $Z$ denote a standard normal random variable, for each $i \in \Omega(\mathbf{X})$, we have

$$\mathbb{P} \left( \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i > 0 \mid \mathbf{X}, S_{i^*}, S_i \right) = \mathbb{P} \left( Z > \frac{-\mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i}{\sqrt{\sum_{j=1}^m a^2_j (\sigma^2_{i^*j}/N_{i^*j} + \sigma^2_{ij}/N_{ij})}} \right) \mid \mathbf{X}, S_{i^*}, S_i \right)$$

$$\geq \mathbb{P} \left( Z > \frac{-\delta}{\sqrt{\delta^2 h_{\text{het}}^2 \sum_{j=1}^m a^2_j (\sigma^2_{i^*j}/N_{i^*j} + \sigma^2_{ij}/N_{ij})}} \right) \mid \mathbf{X}, S_{i^*}, S_i \right)$$

$$= \Phi \left( \frac{h_{\text{het}}}{\sqrt{(n_0 - 1) \sum_{j=1}^m a^2_j (1/\xi_{i^*j} + 1/\xi_{ij})}} \right), \tag{17}$$

where the inequality follows the definition of $\Omega(\mathbf{X})$ and $N_{ij}$, and the last equality from that of $\xi_{ij}$.

Then, conditionally on $\mathbf{X}$, by the definition (2), the CS event must occur if alternative $i^*$ eliminates all alternatives in $\Omega(\mathbf{X})$. Thus,

$$\text{PCS}(\mathbf{X}) \geq \mathbb{P} \left( \bigcap_{i \in \Omega(\mathbf{X})} \left\{ \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i > 0 \right\} \right) \mid \mathbf{X} \right)$$

$$= \mathbb{E} \left[ \mathbb{P} \left( \bigcap_{i \in \Omega(\mathbf{X})} \left\{ \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i > 0 \right\} \mid \mathbf{X}, S_{i^*}, \{S_i : i \in \Omega(\mathbf{X})\} \right) \right] \mid \mathbf{X} \right), \tag{18}$$

where the equality is due to the tower law of conditional expectation. Notice that conditionally on $\{\mathbf{X}, S_{i^*}, \{S_i : i \in \Omega(\mathbf{X})\}\}$, $\{\mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i : i \in \Omega(\mathbf{X})\}$ is multivariate normal by (16). Moreover, for $i, i' \in \Omega(\mathbf{X})$ and $i \neq i'$, due to the conditional independence between $\mathbf{X}^\top \hat{\mathbf{\beta}}_i$ and $\mathbf{X}^\top \hat{\mathbf{\beta}}_{i'}$,

$$\text{Cov} \left( \mathbf{X}^\top \hat{\mathbf{\beta}}_i - \mathbf{X}^\top \hat{\mathbf{\beta}}_i, \mathbf{X}^\top \hat{\mathbf{\beta}}_{i'} - \mathbf{X}^\top \hat{\mathbf{\beta}}_{i'} \mid \mathbf{X}, S_{i^*}, \{S_i : i \in \Omega(\mathbf{X})\} \right) = \text{Var} \left( \mathbf{X}^\top \hat{\mathbf{\beta}}_i \mid \mathbf{X}, S_{i^*} \right) > 0.$$
Therefore, applying (18) and Lemma 2,

\[
\text{PCS}(X) \geq \mathbb{E} \left[ \prod_{i \in \Omega(X)} \mathbb{P} \left( X^\top \tilde{\beta}_i - X^\top \hat{\beta}_i > 0 \bigg| X, S_i^*, S_i \right) \right],
\]

where the second inequality follows from (17).

Notice that \( h_{\text{Het}} \), \( \xi_{ij}, i = 1, \ldots, k, j = 1, \ldots, m \), are i.i.d. \( \chi^2_{n_0-1} \) random variables. Let \( \xi^{(1)}_i = \min \{ \xi_{i1}, \ldots, \xi_{im} \} \) be their smallest order statistic. Then for each \( i \in \Omega(X) \),

\[
\sum_{j=1}^{m} a_j^2 \left( 1/\xi_{ij} + 1/\xi_{ij}^{(1)} \right) = \left( 1/\xi_{ij} + 1/\xi_{ij}^{(1)} \right) a^\top a.
\]

It then follows from (19) and (20) that

\[
\text{PCS}(X) \geq \mathbb{E} \left[ \prod_{i \in \Omega(X)} \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1) \sum_{j=1}^{m} a_j^2 \left( 1/\xi_{ij} + 1/\xi_{ij}^{(1)} \right)}} \right) \right] \left[ \frac{\gamma^{(1)}(s)}{\gamma^{(1)}(t)} \right]^{\frac{|\Omega(X)|}{k-1}} \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1) (t^{-1} + s^{-1}) a^\top a}} \right) \gamma^{(1)}(s) ds \right]^{k-1} \gamma^{(1)}(t) dt,
\]

Since \( 0 \leq \Phi(\cdot) \leq 1 \) and \( \gamma^{(1)}(\cdot) \) is a pdf, the integral inside the square brackets in (21) is no greater than 1. Moreover, since \( |\Omega(X)| \leq k - 1 \), hence,

\[
\text{PCS}(X) \geq \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1) (t^{-1} + s^{-1}) a^\top a}} \right) \gamma^{(1)}(s) ds \right] \gamma^{(1)}(t) dt
\]

\[
= \int_0^\infty \left[ \int_0^\infty \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1) (t^{-1} + s^{-1}) a^\top a}} \right) \gamma^{(1)}(s) ds \right]^{k-1} \gamma^{(1)}(t) dt,
\]

where the equality holds because

\[
a^\top a = (X(X^\top X)^{-1}X)^\top X(X^\top X)^{-1}X = X^\top (X^\top X)^{-1}X.
\]

Then, it follows immediately from the definition of \( h_{\text{Het}} \) in (10) that \( \text{PCS}_E = \mathbb{E}[\text{PCS}(X)] \geq 1 - \alpha. \)

Remark 11. We have introduced the smallest order statistics in (20) for computational feasibility. Without it, Procedure TS+ would still be valid provided that we can compute the constant \( h_{\text{Het}} \).
from the following equation,

\[ \mathbb{E} \left\{ \int_{\mathbb{R}_+^m} \left[ \int_{\mathbb{R}_+^m} g(X, h_{\text{Het}}) \prod_{j=1}^{m} \gamma(s_j) ds_1 \cdots ds_m \right]^{k-1} \prod_{j=1}^{m} \gamma(t_j) dt_1 \cdots dt_m \right\} = 1 - \alpha, \]

where

\[ g(X, h_{\text{Het}}) = \Phi \left( \frac{h_{\text{Het}}}{\sqrt{(n_0 - 1) \sum_{j=1}^{m} a_j^2 (t_j^{-1} + s_j^{-1})}} \right). \]

However, it is prohibitively challenging to solve the above two equations numerically for \( m \geq 3 \). By introducing the smallest order statistic, we can instead solve (10) for \( h_{\text{Het}} \), which is much easier computationally.

C Proof of Theorem 3

Theorem 3 can be viewed as a corollary of the following Theorem 6. Therefore we only provide the proof of Theorem 6 and remark that Theorem 3 holds immediately.

**Theorem 6.** Let \( N_{ij} \) denote the number of samples of alternative \( i \) taken at design point \( x_j \), and \( \hat{Y}_{ij} \) denote their means, for \( i = 1, \ldots, k \), \( j = 1, \ldots, m \). Let \( \hat{Y}_i = (\hat{Y}_{i1}, \ldots, \hat{Y}_{im})^\top \) and \( \hat{\beta}_i = (X^\top X)^{-1} X^\top \hat{Y}_i \) for \( i = 1, \ldots, k \). Under Assumption 1 or 2, the GSC defined in (12) is the LFC for a selection procedure of the R&S-C problem with the IZ formulation and a fixed design, if all the following properties hold:

1. The selected alternative is \( \hat{i}^*(x) = \arg \max_{1 \leq i \leq k} \{ x^\top \hat{\beta}_i \} \).
2. Conditionally on \( \{N_{ij} : 1 \leq i \leq k, 1 \leq j \leq m\} \), \( \hat{Y}_{ij} \sim N(\hat{x}_j^\top \beta_i, \sigma_i^2(\hat{x}_j)/N_{ij}) \) for all \( i = 1, \ldots, k \), \( j = 1, \ldots, m \), and \( \hat{Y}_{ij} \) is independent of \( \hat{Y}_{ij'} \) if \( (i, j) \neq (i', j') \).
3. \( N_{ij} \) is independent of the configuration of the means, for all \( i = 1, \ldots, k \), \( j = 1, \ldots, m \).

Proof. Suppose that \( \beta = (\beta_i : 1 \leq i \leq k) \) follows the GSC. Then, \( i^*(x) \equiv 1 \) and by Property (i), conditionally on \( X = x \),

\[ \text{PCS}(x; \beta) = \mathbb{P} \left( x^\top \hat{\beta}_1 - x^\top \hat{\beta}_i > 0, \forall i = 2, \ldots, k \right) \]

\[ = \mathbb{E} \left[ \mathbb{P} \left( x^\top \hat{\beta}_1 - x^\top \hat{\beta}_i > 0, \forall i = 2, \ldots, k \mid N_{ij}, 1 \leq i \leq k, 1 \leq j \leq m \right) \right], \tag{22} \]

where the expectation is taken with respect to the \( N_{ij} \)’s and we write \( \text{PCS}(x; \beta) \) to stress its dependence on \( \beta \) since we will consider a different configuration of the means later.
By Property (ii), conditionally on $X = x$ and $\{N_{ij} : 1 \leq i \leq k, 1 \leq j \leq m\}$, $x^\top \hat{\beta}_i$ is independent of $x^\top \hat{\beta}_{i'}$ for $i \neq i'$; moreover,
\[
x^\top \hat{\beta}_i | \{N_{i,j} : 1 \leq i \leq k, 1 \leq j \leq m\} \sim \mathcal{N}(x^\top \beta_i, \tilde{\sigma}^2(x, \Sigma_i)),
\]
where $\tilde{\sigma}^2(x, \Sigma_i) := x^\top (X^\top X)^{-1} X^\top \Sigma_i X (X^\top X)^{-1} x$ and $\Sigma_i := \text{Diag}(\sigma_i^2(x_1)/N_{i1}, \ldots, \sigma_i^2(x_m)/N_{im})$. In particular, $\tilde{\sigma}^2(x, \Sigma_i)$ does not depend on $\beta$ by Property (iii). Hence, if we let $\phi(\cdot; \mu, \sigma^2)$ denote the pdf of $\mathcal{N}(\mu, \sigma^2)$, it follows from (22) that
\[
\text{PCS}(x; \beta) = E \left[ \int_{-\infty}^{+\infty} \prod_{i=2}^{k} \Phi \left( \frac{t - x^\top \beta_i}{\tilde{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \beta_1, \tilde{\sigma}^2(x, \Sigma_1)) dt \right].
\tag{23}
\]

We now consider a different configuration of the means, $\beta^\dagger = (\beta_i^\dagger : 1 \leq i \leq k)$. We will show below that $\text{PCS}(x; \beta^\dagger) \geq \text{PCS}(x; \beta)$ for all $x \in \Theta$. For each $i = 1, \ldots, k$, we define sets $\Theta_i^{(1)}$ and $\Theta_i^{(2)}$ as follows,
\[
\begin{align*}
\Theta_i^{(1)} &= \{ x \in \Theta : x^\top \beta_i^\dagger - x^\top \beta_1^\dagger \geq \delta \text{ for all } j \neq i \}, \\
\Theta_i^{(2)} &= \{ x \in \Theta : x^\top \beta_i^\dagger - x^\top \beta_1^\dagger \geq 0 \text{ for all } j \neq i, \text{ and } x^\top \beta_i^\dagger - x^\top \beta_j^\dagger < \delta \text{ for some } j \neq i \}.
\end{align*}
\]
Clearly, $\{\Theta_i^{(1)}, \Theta_i^{(2)} : i = 1, \ldots, k\}$ are mutually exclusive and $\Theta = \bigcup_{i=1}^{k} (\Theta_i^{(1)} \cup \Theta_i^{(2)})$. We next conduct our analysis for each $\Theta_i^{(1)}$ and $\Theta_i^{(2)}$, respectively.

- **Case 1:** $\Theta_1^{(1)} \neq \emptyset$. For any $x \in \Theta_1^{(1)}$, $x^\top \beta_i^\dagger - x^\top \beta_1^\dagger \geq \delta$ for each $i = 2, \ldots, k$. By the same analysis that leads to (23), we can show that for any $x \in \Theta_1^{(1)},$
\[
\begin{align*}
\text{PCS}(x; \beta^\dagger) &= E \left[ \int_{-\infty}^{+\infty} \prod_{i=2}^{k} \Phi \left( \frac{t - x^\top \beta_i^\dagger}{\tilde{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \beta_1^\dagger, \tilde{\sigma}^2(x, \Sigma_1)) dt \right] \\
&= E \left[ \int_{-\infty}^{+\infty} \prod_{i=2}^{k} \Phi \left( \frac{t + (x^\top \beta_i^\dagger - x^\top \beta_1^\dagger - x^\top \beta_1^\dagger)}{\tilde{\sigma}(x, \Sigma_i)} \right) \phi(t + (x^\top \beta_i^\dagger - x^\top \beta_1^\dagger); x^\top \beta_1^\dagger, \tilde{\sigma}^2(x, \Sigma_1)) dt \right] \\
&= E \left[ \int_{-\infty}^{+\infty} \prod_{i=2}^{k} \Phi \left( \frac{t - (x^\top \beta_i^\dagger - x^\top \beta_1^\dagger + x^\top \beta_1^\dagger)}{\tilde{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \beta_1^\dagger, \tilde{\sigma}^2(x, \Sigma_1)) dt \right].
\end{align*}
\]
Due to (12) and the fact that $x^\top \beta_i^\dagger - x^\top \beta_1^\dagger \geq \delta$ for each $i = 2, \ldots, k$, $(x^\top \beta_i^\dagger - x^\top \beta_1^\dagger + x^\top \beta_1^\dagger) \leq x^\top \beta_i^\dagger$, for $i = 2, \ldots, k$. Since $\Phi(\cdot)$ is an increasing function, it is straightforward to see that $\text{PCS}(x; \beta^\dagger) \geq \text{PCS}(x; \beta)$ for any $x \in \Theta_1^{(1)}$.

- **Case 2:** $\Theta_1^{(2)} \neq \emptyset$. Fix an arbitrary $x \in \Theta_1^{(2)}$, let $\Omega(x) := \{ i = 2, \ldots, k : x^\top \beta_i^\dagger - x^\top \beta_1^\dagger \geq \delta \}$. Then, $\Omega(x) \subset \{ 2, \ldots, k \}$ by the definition of $\Theta_1^{(2)}$. If $\Omega(x) = \emptyset$, then each alternative $i$, $i = 2, \ldots, k$, is in the IZ, and thus $\text{PCS}(x, \beta^\dagger) = 1$. Otherwise, $(x^\top \beta_1^\dagger - x^\top \beta_i^\dagger + x^\top \beta_1^\dagger) \leq x^\top \beta_i^\dagger$
for each \( i \in \Omega(x) \). Hence,

\[
\text{PCS}(x; \beta^\dagger) \geq \mathbb{E} \left( x^\top \tilde{\beta}^\dagger_i - x^\top \tilde{\beta}_i > 0, \forall i \in \Omega(x) \right)
\]

\[
= \mathbb{E} \left[ \int_{-\infty}^{+\infty} \prod_{i \in \Omega(x)} \Phi \left( \frac{t - x^\top \beta^\dagger_i}{\hat{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \tilde{\beta}_1, \hat{\sigma}^2(x, \Sigma_1)) \, dt \right]
\]

\[
= \mathbb{E} \left[ \int_{-\infty}^{+\infty} \prod_{i \in \Omega(x)} \Phi \left( \frac{t - x^\top \beta_1 - x^\top \tilde{\beta}_1 + x^\top \beta^\dagger_i}{\hat{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \beta_1, \hat{\sigma}^2(x, \Sigma_1)) \, dt \right]
\]

\[
\geq \mathbb{E} \left[ \int_{-\infty}^{+\infty} \prod_{i \in \Omega(x)} \Phi \left( \frac{t - x^\top \beta_i}{\hat{\sigma}(x, \Sigma_i)} \right) \phi(t; x^\top \beta_1, \hat{\sigma}^2(x, \Sigma_1)) \, dt \right]
\]

\[
\geq \text{PCS}(x; \beta),
\]

where the last inequality holds because \( 0 \leq \Phi(\cdot) \leq 1 \) and \(|\Omega(x)| < k - 1\).

**Other Cases.** For each \( i = 2, \ldots, k \), if \( \Theta_i^{(1)} \neq \emptyset \), then we can simply swap the indexes of alternative 1 and alternative \( i \), and follow the same analysis as in Case 1. Likewise, for each \( i = 2, \ldots, k \), if \( \Theta_i^{(2)} \neq \emptyset \), we can follow the analysis in Case 2.

Therefore, we conclude that \( \text{PCS}(x; \beta^\dagger) \geq \text{PCS}(x; \beta) \) for any \( x \in \Theta \). So \( \mathbb{E} \left[ \text{PCS}(X; \beta^\dagger) \right] \geq \mathbb{E} \left[ \text{PCS}(X; \beta) \right] \). Moreover, the foregoing analysis also shows that, the equality may hold only if random vector \( X \) is degenerate to a constant vector. Thus, the GSC is the LFC. \( \square \)

Remark 12. Obviously, both Procedure TS and TS+ possess those properties specified in Theorem 4 so Theorem 3 in 4 holds immediately as a corollary of Theorem 6.

### D Proof of Theorem 4

**Proof of Theorem 4.** It suffices to show that the extreme design yields the minimal value of the solution \( h \) to (4) among all symmetric designs. We first notice that by (1), the design matrix \( X \) takes effect on the total sample size of Procedure TS only through the form \( X^\top X \). In the sequel, two design matrices \( X \) and \( \tilde{X} \) are said to be equivalent if \( X^\top X = \tilde{X}^\top \tilde{X} \). For instance, swapping any two rows of \( X \) leads to an equivalent design matrix since it does not change \( X^\top X \).

Let \( X_* \) denote the design matrix corresponding to the extreme design \( S^1 = \cdots = S^h = S^0 \), and \( X_i \) denote a nonequivalent design matrix corresponding to a symmetric design. The key of the proof is to show that

\[
x^\top (X_i^\top X_*)^{-1} x \leq x^\top (X_i^\top X_i)^{-1} x, \quad x \in \Theta,
\]

where the equality holds if and only if \( x = \left( 1, \frac{l_1 + u_1}{2}, \ldots, \frac{l_k + u_k}{2} \right)^\top \), which is the center of \( \Theta \).

To see this, let \( h_* \) and \( h_i \) denote the solution \( h \) of (4) for \( X_* \) and \( X_i \), respectively. Notice that the double integral on the left-hand side of (4) is strictly increasing in \( h \) whereas strictly decreasing
in $x^\top (X^\top X)^{-1} x$. Hence, if (24) holds, then $h_s \leq h_\dagger$, where the equality holds if and only if the random vector $X \equiv (1, l_2 + u_2, \ldots, l_d + u_d)^\top$.

Now we prove (24). For ease of presentation, we first consider a design matrix that corresponds to a general symmetric design. Since the first element of the covariates is always 1, the $b(2^{d-1}) \times d$ design matrix $\mathcal{X}$ is

$$
\mathcal{X} = \begin{pmatrix}
(a_1^1)^\top \\
\vdots \\
(a_{2^{d-1}}^1)^\top \\
\vdots \\
(a_b^1)^\top \\
\vdots \\
(a_{2^{d-1}}^b)^\top \\
\end{pmatrix} = \begin{pmatrix}
1 & a_{1,2}^1 & \cdots & a_{1,d}^1 \\
\vdots & \vdots & \ddots & \vdots \\
1 & a_{2^{d-1},2}^1 & \cdots & a_{2^{d-1},d}^1 \\
\vdots & \vdots & \ddots & \vdots \\
1 & a_{1,2}^b & \cdots & a_{1,d}^b \\
\vdots & \vdots & \ddots & \vdots \\
1 & a_{2^{d-1},2}^b & \cdots & a_{2^{d-1},d}^b \\
\end{pmatrix} \triangleq \begin{pmatrix} 1 & v_2 & \cdots & v_d \end{pmatrix},
$$

where $1$ denotes the $b(2^{d-1}) \times 1$ vector of ones. We further set $Z := (v_2, \ldots, v_d)$. Then $\mathcal{X} = (1, Z)$, and

$$
\mathcal{X}^\top \mathcal{X} = \begin{pmatrix}
1^\top & 1^\top Z \\
Z^\top 1 & Z^\top Z \\
\end{pmatrix}.
$$

Notice that $m = b(2^{d-1}) = 1^\top 1$. Then, for any $x = (1, z^\top)$, where $z \in \mathbb{R}^{d-1}$, standard matrix calculation (Horn and Johnson 2013, §0.8.5) yields that

$$
x^\top (\mathcal{X}^\top \mathcal{X})^{-1} x = (z - Z^\top 1 m^{-1})^\top A(Z)^{-1} (z - Z^\top 1 m^{-1}) + m^{-1},
$$

where $A(Z) := Z^\top Z - Z^\top 1 m^{-1} Z$ is the Schur complement of the block $1^\top 1$ of $\mathcal{X}^\top \mathcal{X}$ in (25) and it is nonsingular because $\mathcal{X}^\top \mathcal{X}$ is nonsingular. The symmetry of design points implies that $v_w^\top 1 m^{-1} = \frac{l_w + u_w}{2}$, for $w = 2, \ldots, d$. So, by letting $s := (\frac{l_2 + u_2}{2}, \ldots, \frac{l_d + u_d}{2})^\top$, we have $Z^\top 1 m^{-1} = s$ and

$$
x^\top (\mathcal{X}^\top \mathcal{X})^{-1} x = (z - s)^\top A(Z)^{-1} (z - s) + m^{-1}.
$$

Hence, if $x = \left(1, \frac{l_2 + u_2}{2}, \ldots, \frac{l_d + u_d}{2}\right)^\top$, then $z = s$ and thus $x^\top (\mathcal{X}^\top \mathcal{X})^{-1} x = m^{-1}$. Since both $\mathcal{X}_s$ and $\mathcal{X}_\dagger$ are symmetric designs, $x^\top (\mathcal{X}_s^\top \mathcal{X}_s)^{-1} x = x^\top (\mathcal{X}_\dagger^\top \mathcal{X}_\dagger)^{-1} x$ if $x = \left(1, \frac{l_2 + u_2}{2}, \ldots, \frac{l_d + u_d}{2}\right)^\top$.

It remains to prove the strict inequality in (24) for $z \neq s$. Let $\mathcal{X}_s = (1, Z_s)$ and $\mathcal{X}_\dagger = (1, Z_\dagger)$. Due to (26), it suffices to show that $A(Z_\dagger)^{-1} - A(Z_s)^{-1}$ is positive definite. This is equivalent to showing that $A(Z_s) - A(Z_\dagger)$ is positive definite (Horn and Johnson 2013, Corollary 7.7.4), i.e., for any nonzero $z \in \mathbb{R}^{d-1}$,

$$
z^\top A(Z_s) z > z^\top A(Z_\dagger) z.
$$

Let $I$ denote the $b(2^{d-1}) \times b(2^{d-1})$ identity matrix. Then,

$$
A(Z) = Z^\top (I - 1 m^{-1} 1^\top) Z = Z^\top (I - 1 m^{-1} 1^\top) (I - 1 m^{-1} 1^\top) Z = (Z - 1 s^\top) (Z - 1 s^\top),
$$

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since \( Z^\top m^{-1} = s \). Denote \( z := (z_2, \ldots, z_d)^\top \) and \( s := (s_2, \ldots, s_d)^\top \). Then

\[
z^\top A(Z) z = \sum_{w=2}^{d} \sum_{q=2}^{d} z_w z_q (v_w - 1 s_w)^\top (v_q - 1 s_q).
\]

Thanks to the symmetry of the design points, it is easy to verify that

\[
(v_w - 1 s_w)^\top (v_q - 1 s_q) = \begin{cases} 
0, & \text{if } w \neq q, \\
2^{d-1} \sum_{j=1}^{b} (\rho^j_w)^2, & \text{if } w = q,
\end{cases}
\]

where \( \rho^j_w := |a^j_{1,w} - s_w| = \cdots = |a^j_{2d-1,w} - s_w| \) is the common distance of \( a^j_1, \ldots, a^j_{2d-1} \) to the center of \( \Theta \) along coordinate \( x_w \), for \( w = 2, \ldots, d \) and \( j = 1, \ldots, b \). Hence,

\[
z^\top A(Z) z = 2^{d-1} \sum_{w=2}^{d} \sum_{j=1}^{b} (\rho^j_w)^2.
\]

Since \( \rho^j_w \in (0, \frac{u_w - l_w}{2}] \), obviously, \( \{ \rho^j_w = \frac{u_w - l_w}{2} | w = 2, \ldots, d, j = 1, \ldots, b \} \) maximizes \( z^\top A(Z) z \). Because \( z \) is nonzero, i.e., at least one \( z_w \) is not zero, the solution is unique in terms of \( \rho^j_w \). Notice that this solution exactly means that \( S^1 = \cdots = S^b = S^0 \), i.e., the extreme design. Hence, (27) is proved and the proof of (24) is completed. \( \square \)

E Proof of Theorem 5

Before the proof, we first introduce formally the D-optimality and the G-optimality of experimental designs in the linear regression setting. Consider the linear regression model

\[
Y(x) = x^\top \beta + \epsilon,
\]

where \( \beta, x \in \mathbb{R}^d \) and \( \epsilon \) is random error with mean 0 and variance \( \sigma^2 \). Assuming the design region is \( \Theta \), we choose \( m \) design points with \( x_i \in \Theta, i = 1, \ldots, m \). Let \( Y = (Y(x_1), \ldots, Y(x_m))^\top \), \( \mathcal{X} = (x_1, \ldots, x_m)^\top \), and \( \mathcal{Y} = \{ \mathcal{X} : \text{rank}(\mathcal{X}^\top \mathcal{X}) = d, x_i \in \Theta, i = 1, \ldots, m \} \). It is known that if \( \mathcal{X} \in \mathcal{Y} \), the OLS estimator of \( \beta \) is \( \hat{\beta} = (\mathcal{X}^\top \mathcal{X})^{-1} \mathcal{X}^\top Y \). Moreover, \( \text{Var}(\hat{\beta}) = \sigma^2 (\mathcal{X}^\top \mathcal{X})^{-1} \) and \( \text{Var}(x^\top \hat{\beta}) = \sigma^2 x^\top (\mathcal{X}^\top \mathcal{X})^{-1} x \). The D-optimality and the G-optimality are related to the two variances, respectively.

A design \( \mathcal{X}_* \) is said to be D-optimal if

\[
\mathcal{X}_* = \arg \max_{\mathcal{X} \in \mathcal{T}} \det(\mathcal{X}^\top \mathcal{X}).
\]

The D-optimal design aims to minimize the volume of confidence ellipsoid for \( \beta \) given a fixed confidence level under the assumption that the errors are normally distributed.
A design $\mathcal{X}_* \in \mathcal{Y}$ is said to be $G$-optimal if

$$\mathcal{X}_* = \arg \min_{\mathcal{X} \in \mathcal{Y}} \left\{ \max_{\mathcal{X} \in \mathcal{Y}} \mathcal{X}^\top \mathcal{X}^{-1} \right\}.$$

The $G$-optimal design aims to minimize the maximum variance of the fitted response over the design region.

Theorem 5 is an application of the general equivalence theory; see, e.g., Silvey (1980, Chapter 3) for a careful discussion on this subject. Some concepts need to be introduced before the proof.

The first concept is the continuous design, also called approximate design. Suppose that we relax the constraint that the number of samples at each design point must be an integer, that is, we can allocate any portion of a given total sample size $m$ to any point in $\Theta$. Formally speaking, the allocation can be described by a probability distribution $\psi$ on $\Theta$, which can be either continuous or discrete. Let $\mathbf{X}$ be a random vector with distribution $\psi$, and define $M(\psi) := \mathbb{E}_\psi(\mathbf{X} \mathbf{X}^\top)$. For example, if $\mathcal{X}$ is an exact design which contains distinct points $\mathbf{x}_1, \ldots, \mathbf{x}_n$ having $m_1, \ldots, m_n$ samples, respectively, where $m_1 + \cdots + m_n = m$, then the distribution $\psi$ for sample allocation is defined by $\mathbb{P}(\mathbf{X} = \mathbf{x}_i) = m_i/m$, $i = 1, \ldots, n$, and thus $M(\psi) = m^{-1}\mathcal{X}^\top \mathcal{X}$. However, a continuous design may not be an exact design due to the integrality constraint.

By allowing continuous designs, the D-optimal design is extended to be a distribution

$$\psi_* = \arg \max_{\psi \in \Psi} \det (M(\psi)),$$

where $\Psi$ denotes the set of all $\psi$ such that $M(\psi)$ is nonsingular. Notice that $\Psi$ is also the set of all $\psi$ such that $M(\psi)$ is positive definite. Likewise, the G-optimal design can be extended as follows

$$\psi_* = \arg \min_{\psi \in \Psi} \left\{ \max_{\mathcal{X} \in \mathcal{Y}} \mathcal{X}^\top M(\psi)^{-1} \mathcal{X} \right\}.$$

More generally, consider a function $f$ of positive definite matrices. A continuous design $\psi_*$ is said to be $f$-optimal if

$$\psi_* = \arg \max_{\psi \in \Psi} f (M(\psi)).$$

For instance, the D-optimal design and the G-optimal design can be obtained by setting $f(M) = \log \det (M)$ and $f(M) = -\max_{\mathcal{X} \in \mathcal{Y}} \mathcal{X}^\top M^{-1} \mathcal{X}$, respectively. It is easy to verify that both functions are concave in $\mathcal{M}$. The use of concavity will become clear in Lemma 4 below.

At last, we introduce two kinds of derivatives. The Gâteaux derivative of $f$ at $\mathcal{M}_1$ in the direction of $\mathcal{M}_2$ is defined as

$$G_f(\mathcal{M}_1, \mathcal{M}_2) := \lim_{\varepsilon \to 0^+} \frac{1}{\varepsilon} [f(\mathcal{M}_1 + \varepsilon \mathcal{M}_2) - f(\mathcal{M}_1)].$$

We say $f$ is differentiable at $\mathcal{M}_1$ if $G_f(\mathcal{M}_1, \mathcal{M}_2)$ is well defined. The Fréchet derivative of $f$ at $\mathcal{M}_1$
in the direction of $\mathcal{M}_2$ is defined as

$$F_f(\mathcal{M}_1, \mathcal{M}_2) := \lim_{\varepsilon \to 0^+} \frac{1}{\varepsilon} [f \{ (1 - \varepsilon)\mathcal{M}_1 + \varepsilon \mathcal{M}_2 \} - f(\mathcal{M}_1)] = G_f(\mathcal{M}_1, \mathcal{M}_2 - \mathcal{M}_1).$$

We state Theorem 3.7 of Silvey (1980) as Lemma 4 below and will apply it to prove Theorem 5.

**Lemma 4.** If $f$ is a concave function of positive definite matrices and is differentiable at $\mathcal{M}(\psi_*)$, then $\psi_*$ is $f$-optimal if and only if $F_f(\mathcal{M}(\psi_*), xx^\top) \leq 0$ for all $x \in \Theta$.

Now we are ready to prove Theorem 5.

**Proof.** Proof of Theorem 5. Consider the continuous design $\psi_0$ that assigns probability $1/(2^{d-1})$ at each corner point of $\Theta$. Since $m = b(2^{d-1})$, $\psi_0$ is indeed the extreme design defined in §8.1. Hence, it suffices to prove that $\psi_0$ is both D-optimal and G-optimal in the continuous case.

We first prove the D-optimality of $\psi_0$. Let $X_0$ denote the design matrix corresponding to $\psi_0$. Then, $X_0$ is a $2^{d-1} \times d$ matrix with each row corresponding one of the $2^{d-1}$ distinct corners of $\Theta$. For example, if $d = 3$,

$$X_0 = \begin{pmatrix} 1 & l_2 & l_3 \\ 1 & l_2 & u_3 \\ 1 & u_2 & l_3 \\ 1 & u_2 & u_3 \end{pmatrix}.$$ 

It is easy to see that $\mathcal{M}(\psi_0) = \frac{1}{2^{d-1}} X_0^\top X_0$. In the sequel, we verify the conditions of Lemma 4 for $f = \log \det$ to prove the D-optimality.

The concavity of $f$ is trivial; see, e.g., Theorem 7.6.6 of Horn and Johnson (2013). For the differentiability, notice that for any positive definite matrix $\mathcal{M}_1$,

$$\log \det(\mathcal{M}_1 + \varepsilon \mathcal{M}_2) - \log \det(\mathcal{M}_1) = \log \det(I + \varepsilon \mathcal{M}_1^{-1} \mathcal{M}_2) = \sum_{w=1}^{d} \log(1 + \varepsilon \lambda_w),$$

where $I$ is the $d \times d$ identity matrix and $\lambda_1, \ldots, \lambda_d$ are the eigenvalues of $\mathcal{M}_1^{-1} \mathcal{M}_2$ which are all real (Horn and Johnson 2013, Corollary 7.6.2). Hence,

$$G_f(\mathcal{M}_1, \mathcal{M}_2) = \lim_{\varepsilon \to 0^+} \frac{1}{\varepsilon} [\log \det(\mathcal{M}_1 + \varepsilon \mathcal{M}_2) - \log \det(\mathcal{M}_1)] = \sum_{w=1}^{d} \lambda_w = \text{tr}(\mathcal{M}_1^{-1} \mathcal{M}_2),$$

is well defined, so $f$ is differentiable at $\mathcal{M}_1$.

Moreover,

$$F_f(\mathcal{M}_1, \mathcal{M}_2) = G_f(\mathcal{M}_1, \mathcal{M}_2 - \mathcal{M}_1) = \text{tr}(\mathcal{M}_1^{-1} \mathcal{M}_2 - I) = \text{tr}(\mathcal{M}_1^{-1} \mathcal{M}_2) - d.$$ 

Hence, for any $x \in \Theta$,

$$F_f(\mathcal{M}(\psi_0), xx^\top) = \text{tr}(\mathcal{M}(\psi_0)^{-1} xx^\top) - d = \text{tr}(x^\top \mathcal{M}(\psi_0)^{-1} x) - d = x^\top \mathcal{M}(\psi_0)^{-1} x - d.$$
Since $\mathcal{M}(\psi_0)^{-1}$ is positive definite, $F_f(\mathcal{M}(\psi_0), xx^\top)$ is convex in $x$, thereby achieving its maximum only if $x$ is one of the corners of $\Theta$, i.e., $x \in S^0$. Therefore, to verify $F_f(\mathcal{M}(\psi_0), xx^\top) \leq d$, it suffices to show that

$$x^\top \mathcal{M}(\psi_0)^{-1} x = d, \quad x \in S^0. \quad (28)$$

We denote $\lambda_0 := (1, Z_0) \triangleq (1, v_2, \ldots, v_d)$, where $1$ is the $2^{d-1} \times 1$ vector of ones. Following the standard matrix calculations similar to those in the proof of Theorem 4, we can have that, for any $x := (1, z^\top)^\top$, where $z := (z_2, \ldots, z_d)^\top \in \mathbb{R}^{d-1},$

$$x^\top \mathcal{M}(\psi_0)^{-1} x = 2^{d-1} x^\top (\lambda_0^\top \lambda_0)^{-1} x = 2^{d-1} \left[ (z - s)^\top \{ (Z_0 - 1s^\top) (Z_0 - 1s^\top) \}^{-1} (z - s) + 1/(2^{d-1}) \right], \quad (29)$$

where $s = (s_2, \ldots, s_d)^\top := \left( \frac{l_2 + u_2}{2}, \ldots, \frac{l_d + u_d}{2} \right)^\top$. Notice that $(Z_0 - 1s^\top)^\top (Z_0 - 1s^\top)$ is a $(d - 1) \times (d - 1)$ matrix whose $(w - 1, q - 1)$-th element is $(v_w - 1s_w)^\top (v_q - 1s_q)$, for $w, q = 2, \ldots, d$, and that

$$(v_w - 1s_w)^\top (v_q - 1s_q) = \begin{cases} 0, & \text{if } w \neq q, \\ 2^{d-1} \left( \frac{u_w - l_w}{2} \right)^2, & \text{if } w = q. \end{cases}$$

Hence,

$$(Z_0 - 1s^\top)^\top (Z_0 - 1s^\top) = 2^{d-1} \text{Diag} \left\{ \left( \frac{u_2 - l_2}{2} \right)^2, \ldots, \left( \frac{u_d - l_d}{2} \right)^2 \right\},$$

and thus

$$\{(Z_0 - 1s^\top)^\top (Z_0 - 1s^\top)\}^{-1} = \frac{1}{2^{d-1}} \text{Diag} \left\{ \left( \frac{2}{u_2 - l_2} \right)^2, \ldots, \left( \frac{2}{u_d - l_d} \right)^2 \right\}.$$

Moreover, for any $x \in S^0$, $z \in \{l_2, u_2\} \times \cdots \times \{l_d, u_d\}$. Hence, $(z_w - s_w)^2 = \left( \frac{u_w - l_w}{2} \right)^2$, for $w = 2, \ldots, d$. Then,

$$(z - s)^\top \{(Z_0 - 1s^\top)^\top (Z_0 - 1s^\top)\}^{-1} (z - s) = \frac{1}{2^{d-1}} \sum_{w=2}^{d} \left( \frac{2}{u_w - l_w} \right)^2 (z_w - s_w)^2 = \frac{d - 1}{2^{d-1}}. \quad (30)$$

Then, (28) follows immediately from (29) and (30), proving the D-optimality by Lemma 4.

The G-optimality of $\psi_0$ can be proved similarly, by taking $f(\mathcal{M}(\psi)) = -\max_{x \in \Theta} x^\top (\mathcal{M}(\psi))^{-1} x$.

Or, we can conclude this immediately by applying the known equivalence between the D-optimality and the G-optimality for continuous designs established in Kiefer and Wolfowitz (1960); see also Silvey (1980) §3.11.

\[\square\]
References

Arora, N., X. Dreze, A. Ghose, J. D. Hess, et al. (2008). Putting one-to-one marketing to work: Personalization, customization, and choice. *Market. Lett.* 19(3-4), 305.

Auer, P. (2002). Using confidence bounds for exploitation-exploration trade-offs. *J. Mach. Learn. Res.* 3, 397–422.

Bechhofer, R. E. (1954). A single-sample multiple decision procedure for ranking means of normal populations with known variances. *Ann. Math. Stat.* 25(1), 16–39.

Bubeck, S. and N. Cesa-Bianchi (2012). Regret analysis of stochastic and nonstochastic multi-armed bandit problems. *Found. Trends Mach. Learn.* 5(1), 1–122.

Chen, C.-H., S. E. Chick, L. H. Lee, and N. A. Pujowidianto (2015). Ranking and selection: Efficient simulation budget allocation. In M. C. Fu (Ed.), *Handbook of Simulation Optimization*, pp. 45–80. Springer.

Chen, H.-C., C.-H. Chen, L. Dai, and E. Yücesan (1997). New development of optimal computing budget allocation for discrete event simulation. In *Proc. 1997 Winter Simul. Conf.*, pp. 334–341.

Chick, S. E. and P. I. Frazier (2012). Sequential sampling with economics of selection procedures. *Manag. Sci.* 58(3), 550–569.

Chick, S. E. and N. Gans (2009). Economic analysis of simulation selection problems. *Manag. Sci.* 55(3), 421–437.

Chick, S. E. and K. Inoue (2001). New two-stage and sequential procedures for selecting the best simulated system. *Oper. Res.* 49(5), 732–743.

Choi, S. E., K. E. Perzan, A. C. Tramontano, C. Y. Kong, and C. Hur (2014). Statins and aspirin for chemoprevention in Barrett’s esophagus: Results of a cost-effectiveness analysis. *Canc. Prev. Res.* 7(3), 341–350.

Curtius, K., W. D. Hazelton, J. Jeon, and E. G. Luebeck (2015). A multiscale model evaluates screening for neoplasia in Barrett’s esophagus. *PLoS Comput. Biol.* 11(5), e1004272.

Dudewicz, E. J. and S. R. Dalal (1975). Allocation of observations in ranking and selection with unequal variances. *Sankhyā B*, 28–78.

Fan, W., L. J. Hong, and B. L. Nelson (2016). Indifference-zone-free selection of the best. *Oper. Res.* 64(6), 1499–1514.

Frazier, P. I. (2014). A fully sequential elimination procedure for indifference-zone ranking and selection with tight bounds on probability of correct selection. *Oper. Res.* 62(4), 926–942.

Frazier, P. I., W. B. Powell, and S. Dayanik (2008). A knowledge-gradient policy for sequential information collection. *SIAM J. Control Optim.* 47(5), 2410–2439.

Goldenshluger, A. and A. Zeevi (2013). A linear response bandit problem. *Stoch. Syst.* 3(1), 230–261.

Gupta, S. S. and K.-J. Miescke (1982). On the least favorable configurations in certain two-stage selection procedures. In G. Kallianpur, P. R. Krishnaiah, and J. K. Ghosh (Eds.), *Statistics and Probability: Essays in Honor of C. R. Rao*, pp. 295–305. North Holland.

Hastie, T., R. Tibshirani, and J. Friedman (2009). *The Elements of Statistical Learning: Data Mining, Inference, and Prediction* (2nd ed.). Springer.

Hong, L. J. (2006). Fully sequential indifference-zone selection procedures with variance-dependent sampling. *Naval Res. Logist.* 53(5), 464–476.
Horn, R. A. and C. R. Johnson (2013). *Matrix Analysis* (2nd ed.). Cambridge University Press.

Hu, R. and M. Ludkovski (2017). Sequential design for ranking response surfaces. *SIAM/ASA J. Uncertain. Quantif.* 5(1), 212–239.

Hur, C., M. Miller, C. Y. Kong, E. C. Dowling, K. J. Nattinger, M. Dunn, and E. J. Feuer (2013). Trends in esophageal adenocarcinoma incidence and mortality. *Cancer* 119(6), 1149–1158.

Hur, C., N. S. Nishioka, and G. S. Gazelle (2004). Cost-effectiveness of aspirin chemoprevention for Barrett’s esophagus. *J. Natl. Canc. Inst.* 96(4), 316–325.

James, G., D. Witten, T. Hastie, and R. Tibshirani (2013). *An Introduction to Statistical Learning*, Volume 112. Springer.

Johnson, M. E., L. M. Moore, and D. Ylvisaker (1990). Minimax and maximin distance designs. *J. Statist. Plann. Inference* 26(2), 131–148.

Kastelein, F., M. C. W. Spaander, K. Biermann, et al. (2011). Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett’s esophagus. *Gastroenterology* 141(6), 2000–2008.

Katrakazas, C., M. Quddus, W.-H. Chen, and L. Deka (2015). Real-time motion planning methods for autonomous on-road driving: State-of-the-art and future research directions. *Transp. Res. C: Emerging Technol.* 60, 416–442.

Kiefer, J. and J. Wolfowitz (1960). The equivalence of two extremum problems. *Canad. J. Math.* 12, 363–366.

Kim, E. S., R. S. Herbst, I. I. Wistuba, J. J. Lee, et al. (2011). The BATTLE trial: Personalizing therapy for lung cancer. *Canc. Discov.* 1(1), 44–53.

Kim, S.-H. and B. L. Nelson (2001). A fully sequential procedure for indifference-zone selection in simulation. *ACM Trans. Model. Comput. Simul.* 11(3), 251–273.

Kim, S.-H. and B. L. Nelson (2006). Selecting the best system. In S. G. Henderson and B. L. Nelson (Eds.), *Handbooks in Operations Research and Management Science*, Volume 13, pp. 501–534. Elsevier.

Law, A. M. and W. D. Kelton (2000). *Simulation Modeling and Analysis* (3rd ed.). McGraw-Hill New York.

Luo, J., L. J. Hong, B. L. Nelson, and Y. Wu (2015). Fully sequential procedures for large-scale ranking-and-selection problems in parallel computing environments. *Oper. Res.* 63(5), 1177–1194.

Melissen, J. B. M. and P. C. Schuur (1996). Improved coverings of a square with six and eight equal circles. *Electron. J. Combin.* 3(1), R32,10 pp. (electronic).

Naef, A. and M. Savary (1972). Conservative operations for peptic esophagitis with stenosis in columnar-lined lower esophagus. *Ann. Thorac. Surg.* 13(6), 543–551.

Negoescu, D. M., P. I. Frazier, and W. B. Powell (2011). The knowledge-gradient algorithm for sequencing experiments in drug discovery. *INFORMS J. Comput.* 23(3), 346–363.

Ni, E. C., D. F. Ciocan, S. G. Henderson, and S. R. Hunter (2017). Efficient ranking and selection in parallel computing environments. *Oper. Res.* 65(3), 821–836.

Pearce, M. and J. Branke (2017). Efficient expected improvement estimation for continuous multiple ranking and selection. In *Proc. 2017 Winter Simul. Conf.*, pp. 2161–2172.

Perchet, V. and P. Rigollet (2013). The multi-armed bandit problem with covariates. *Ann. Stat.* 41(2), 693–721.

Rencher, A. C. and G. B. Schaalje (2008). *Linear Models in Statistics* (2nd ed.). John Wiley & Sons, Inc.
Rinott, Y. (1978). On two-stage selection procedures and related probability-inequalities. *Comm. Stat. Theor. Meth.* 7(8), 799–811.

Robbins, H. (1952). Some aspects of the sequential design of experiments. *Bull. Am. Math. Soc.* 58(5), 527–535.

Robbins, H. and S. Monro (1951). A stochastic approximation method. *Ann. Math. Stat.* 22(3), 400–407.

Rusmevichientong, P. and J. N. Tsitsiklis (2010). Linearly parameterized bandits. *Math. Oper. Res.* 35(2), 395–411.

Silvey, S. D. (1980). *Optimal Design: An Introduction to the Theory for Parameter Estimation.* Chapman and Hall.

Slepian, D. (1962). The one-sided barrier problem for Gaussian noise. *Bell System Tech. J.* 41(2), 463–501.

Slivkins, A. (2014). Contextual bandits with similarity information. *J. Mach. Learn. Res.* 15(1), 2533–2568.

Stein, C. (1945). A two-sample test for a linear hypothesis whose power is independent of the variance. *Ann. Math. Stat.* 16(3), 243–258.

Yap, T. A., C. P. Carden, and S. B. Kaye (2009). Beyond chemotherapy: Targeted therapies in ovarian cancer. *Nat. Rev. Canc.* 9(3), 167–181.