# LIMIT THEOREMS ON DEVIATION PROBABILITIES WITH APPLICATIONS IN TWO-ARMED CLINICAL TRIALS

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Institute of Statistics and Decision Sciences in the Graduate School of Duke University

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# ABSTRACT

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# Abstract

I consider design problems of two-armed clinical trials conducted in two stages. The goal of the design is to maximize the expected treatment mean over all patients by properly choosing the number of patients in the first stage. Using a Bayesian approach, the treatment means of each arm are considered random. When the responses from both arms are Bernoulli and one arm has known success rate, Berry and Pearson (1985) conjectured that the optimal first-stage sample size should be in the order of $\sqrt{N}$, provided that the prior on the unknown success rate is beta-distributed, where $N$ is the total number of patients in the trial or in consideration. Cheng (1992) proved this claim for the case in which the known success rate is a rational number. In this dissertation, I give a first-order approximation of the optimal sample size in the first stage under a more general condition. I also obtain the asymptotically optimal sample sizes in the first stage when both arms are unknown. The coefficients of the approximations are explicitly given.

These asymptotic results are derived using the limit theorems on deviation probabilities established in this dissertation. The concept of deviation probabilities is an extension of the classical large deviations to the Bayesian context. For many applications in Bayesian analysis, an expression which estimates a limiting behavior can be decomposed into two parts: the limit of the expression and a deviation probability. Limit theorems on deviation probabilities provide

a way of estimating these expressions analytically. Finding optimal assignment procedures in two-armed clinical trials is an application of these limit theorems. Some other applications of the limit theorems are also provided.

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# Contents

# List of Symbols

| | |
|---|---|
| $\lceil x \rceil$ | the smallest integer greater than or equal to $x$ |
| $a \vee b$ | maximum of real numbers $a$ and $b$ |
| $\psi(\cdot)$ | the cumulant function of an exponential family |
| $\mathcal{K}$ | convex hull of sample space of an exponential family |
| $\mathcal{N}$ | natural parameter space |
| $\rho_x$ | mapping from space $\mathcal{N}$ to $\mathcal{K}$ |
| $\theta_x$ | inverse mapping of $\rho_x$ |
| $\mathrm{supp}(f)$ | support of function $f$ |
| $\mathrm{conhull}(A)$ | convex hull of a set $A$ |
| $D(\cdot\|\|\cdot)$ | Kullback-Leibler information measure between two distributions in terms of canonical parameters |
| $D_1(\cdot\|\|\cdot)$ | Kullback-Leibler information measure in terms of treatment means |
| $W(n_1, n_2; \pi)$ | worth function of a two-armed clinical trial using strategy $(n_1, n_2)$ and prior $\pi = \pi(\rho_1, \rho_2)$ |
| $W(n_1, n_2)$ | $W(n_1, n_2; \pi)$, with prior suppressed when there can be no confusion |
| $W(n; \pi)$ | worth function of a two-armed clinical trial with one arm known and with prior $\pi(\rho)$ |
| $W(n)$ | $W(n; \pi)$ with prior suppressed |
| $W_{avg}$ | average worth function |

# Chapter 1

# Introduction

Consider a clinical trial involving two treatments. The objective is to treat as many patients as effectively as possible. Take this to mean in an average sense and to include all patients in some set, possibly including patients outside the trial whose treatment will be based on the results from the trial. For example, if the endpoint is dichotomous (tumor does or does not respond, say) then the objective is to maximize the total expected number of successes over all patients considered.

I consider a clinical trial in stages, with results from previous stages being available for use in assigning treatment to patients in the current stage. However, information accrues only at the end of a stage and so patient responses are not available for use in assigning treatment to patients in the same stage. Therefore, information from the last stage of the trial has no use in treatment assignment and so the treatment currently regarded as better is used for all patients in the last stage. (Both treatments could be used in the last stage under an optimal assignment only if they are regarded as equivalent.) If patients outside of the clinical trial are considered then these patients are part of the last stage. Suppose $k$ is the number of stages and $N$ is the total number of patients in the $k$ stages. Both $k$ and $N$ are taken to be fixed and known. The decision problem is to choose the lengths of the various stages. A principal focus in this dissertation is $k = 2$. The decision problem is then to find the length of the first stage. A length that gives the maximal total expected effectiveness is optimal.

If one arm is known and the responses are dichotomous, Berry & Pearson (1985) conjectured that the optimal first-stage sample size is the order of $\sqrt{N}$ when the prior distribution on the unknown success rate is beta. Cheng (1992) verified this claim under the condition that the success rate for the known arm is a rational number. However, the problem remains open when the sample distribution is not Bernoulli or the prior is not beta-distributed.

Colton (1963) and Canner (1970) considered both arms unknown and assumed that the lengths of stages on each arm are equal. In the work of Cornfield, et al, (1969), unbalanced designs are studied, however, they assumed that the lengths of stages are linear in $N$ and then calculated the best linear coefficients.

In this dissertation I develop some new results in deviation probability and use them to obtain a closed-form first order approximation to optimal sample sizes. The results confirm Berry & Pearson's conjecture that the first-stage sample size is of order $\sqrt{N}$. Furthermore, the coefficients of this approximation are given explicitly. Applying the same method, I derive asymptotically optimal sample sizes for two-armed clinical trials with both arms unknown. This result shows that balanced designs may not be optimal.

An important aspect of this dissertation is extending some classical limit theorems on large deviation probabilities to the Bayesian context. In early work on classical large deviations, the limiting behavior of large deviation probabilities is studied with respect to a single distribution, $f(x|\theta)$. In Bayesian applications, $\theta$ is random. When averaged over $\theta$, the whole family of distributions, $\{f(x|\theta), \theta \in \Theta\}$, needs to be considered. In Chapter 3, limit theorems are established to cover this case.

For many applications in Bayesian analysis, an expression which estimates a limiting behavior can be decomposed into two parts: the limit of the expression and a deviation probability. Limit theorems on deviation probabilities provide a way of estimating these expressions analytically. Finding optimal assignment procedures in two-armed clinical trials is an application of these limit theorems.

The organization of this thesis is as follows. In Chapter 2, two-armed bandit problems with dichotomous responses are discussed, and some numerical examples are given. Chapter 3 establishes limit theorems on deviation probabilities to be used in generalizing the results of Chapter 2 to a wider class of distributions. In Chapter 4, using limit theorems of Chapter 3, asymptotically optimal sample sizes are obtained with coefficients explicitly given. In Chapter 5, I deal with two-armed bandit problems with both arms unknown. An asymptotic approximation to optimal sample sizes is developed and a numerical comparison among different procedures is provided.

# Chapter 2

# Two-armed clinical trials with dichotomous responses and beta priors

In this chapter, I will address two-armed bandit problems with dichotomous responses using clinical trial terminology. An asymptotic approximation of the optimal sample size will be presented in Section 2.5 when the prior is beta-distributed, which extends Cheng's (1992) result. Numerical examples are given in Section 2.6.

## 2.1 Statement of the problem

Suppose that there are two treatments (or arms) available in a clinical trial, treatment 1 and treatment 2. There are $N$ patients to be treated. For each patient, one of the two treatments is assigned and a response observed. Outcomes are dichotomous: success or failure. The goal is to find optimal lengths for each arm so that the expected number of successes over all $N$ patients is maximized.

I consider only two-stage designs in this dissertation. For one-stage design problems, the solution is clear: the apparently superior treatment (the one with the larger success rate based on prior information) should be used for all patients. Refer to DeGroot (1970) and Berry & Fristedt (1985) for $k > 2$ cases.

## 2.2 Assumptions

The numbers of patients allocated to treatment 1 and treatment 2 in the first stage are denoted by $n_1$ and $n_2$. The responses from two treatments are $X_{11}, ..., X_{1n_1}$ and $X_{21}, ..., X_{2n_2}$ respectively. Let $\rho_1$ and $\rho_2$ be the success rates for each treatment, so

$$X_{ij} \sim p(x|\rho_i) = \rho_i^x(1-\rho_i)^{1-x}, \qquad x = 0, 1,$$

for $j = 1, ..., n_i$ and $i = 1, 2$.

**Assumptions of independence:**

Given $(\rho_1, \rho_2)$, we assume that the responses from each arm are independent and identically distributed. Unconditionally, of course, the responses may not be independent, though they are exchangeable. We also assume that the responses from different arms are independent.

Define $S_{n_1}$ and $S_{n_2}$ to be the sums of total successes on each arm in the first stage:

$$S_{n_i} = \sum_{j=1}^{n_i} X_{ij}, \qquad i = 1, 2.$$

By the assumptions of independence, $(S_{n_1}, S_{n_2})$ are sufficient for $(\rho_1, \rho_2)$, and $S_{n_1}$ and $S_{n_2}$ are independent and have binomial distributions:

$$P(S_{n_i} = k|\rho_i) = \binom{n_i}{k}\rho_i^k(1-\rho_i)^{n_i-k}, \qquad k = 0, ..., n_i; \quad i = 1, 2.$$

The success rates, $\rho_1$ and $\rho_2$, are unknown parameters. Taking a Bayesian approach, $(\rho_1, \rho_2)$ is random. Information concerning the treatments at the beginning of the trial is in the form of a joint prior distribution, $\pi(\rho_1, \rho_2)$. This information is updated by Bayes' theorem using data from the first stage. Let $p(\rho_1, \rho_2 | S_{n_1}, S_{n_2})$ be the posterior of $(\rho_1, \rho_2)$ after observing $S_{n_1}$ and $S_{n_2}$, then

$$p(\rho_1, \rho_2 | S_{n_1}, S_{n_2}, \pi) \propto p(S_{n_1}, S_{n_2} | \rho_1, \rho_2) \pi(\rho_1, \rho_2).$$

In the second stage the treatment regarded as superior from the first stage and from prior information is used exclusively. The success rate in the second stage can be written as

$$g(n_1, n_2 | S_{n_1}, S_{n_2}, \pi) = E(\rho_1 | S_{n_1}, S_{n_2}, \pi) \vee E(\rho_2 | S_{n_1}, S_{n_2}, \pi),$$

where $E(\rho_i | S_{n_1}, S_{n_2}, \pi)$ are the posterior means, given by

$$E(\rho_i | S_{n_1}, S_{n_2}, \pi) = \frac{\int \rho_i p(S_{n_1}, S_{n_2} | \rho_1, \rho_2) \pi(\rho_1, \rho_2) d\rho_1 d\rho_2}{\int p(S_{n_1}, S_{n_2} | \rho_1, \rho_2) \pi(\rho_1, \rho_2) d\rho_1 d\rho_2}, \quad i = 1, 2.$$

The maximal expected success rate in the second stage but based on first stage information is

$$g(n_1, n_2) = E\{E(\rho_1 | S_{n_1}, S_{n_2}) \vee E(\rho_2 | S_{n_1}, S_{n_2})\}. \tag{2.1}$$

$\pi$ is suppressed for economy of notation where there can be no confusion.

Given prior information a strategy is completely determined by $n_1$ and $n_2$. We denote a *strategy* by $\tau = (n_1, n_2)$. The worth under strategy $\tau$ is defined to be the total expected number of successes among the $N$ patients:

$$W(n_1, n_2; \pi) \quad = \quad n_1 E(\rho_1) + n_2 E(\rho_2) + (N - n_1 - n_2) g(n_1, n_2), \tag{2.2}$$

and an *average worth* is defined as

$$W_{avg}(n_1, n_2; \pi) = W(n_1, n_2; \pi)/N.$$

The design problem is to find $(n_1, n_2)$ to maximize $W(n_1, n_2; \pi)$. The optimal pair is denoted as $(n_1^*, n_2^*)$. The optimization problem depends on the prior distribution of $(\rho_1, \rho_2)$. The prior $\pi$ plays a central role in a bandit problem, which is sometimes called a $\pi$-bandit.

To find the optimal sample sizes $n_1^*$ and $n_2^*$ for large $N$ requires the limiting behavior of $g(n_1, n_2)$. For example, knowing the analytical properties of $g(n_1, n_2)$ may allow for finding $(n_1^*, n_2^*)$ by letting $\frac{\partial}{\partial n_i} W(n_1, n_2) = 0$, $i = 1, 2$.

**Trivial bandits**

We say a bandit is trivial if $P(\rho_1 \geq \rho_2 | \pi) = 0$ or 1. The decision in this case is clear since the better arm is known with probability 1 and no amount or type of data can change this. The better treatment should be used exclusively. The bandit problems considered here are assumed to be non-trivial.

## 2.3 Some properties of two-armed bandits

In this section I show some properties of two-armed bandit problems. Results in this section apply for general response types and are not restricted to the dichotomous case.

I first present a monotonicity property. The next theorem says that in a two-stage trial, the more observations taken in the first stage, the more benefit can be achieved in the second one. Thus, the first stage may be regarded as an information-gathering stage.

**Theorem 2.1** *Where $g(n_1, n_2)$ is defined at (2.1), $g(n_1, n_2)$ is increasing as either $n_1$ or $n_2$ increases.*

**Proof:** We prove only monotonicity in $n_2$ for $n_1$ fixed. Let $Y_{n_1,n_2} = E(\rho_1 - \rho_2|S_{n_1}, S_{n_2})$ then $Y_{n_1,n_2}$ forms a martingale with index $n_2$ (Doob's martingale process). See, for example, Karlin and Taylor (1975, p246). Since $|\cdot|$ is a convex function, $\{|E(\rho_1 - \rho_2|S_{n_1}, S_{n_2})|, n_2 > 0\}$ is a submartingale; therefore, $E\{|E(\rho_1 - \rho_2|S_{n_1}, S_{n_2})|\}$ is increasing, and so is $E\{|E(\rho_1 - \rho_2|S_{n_1}, S_{n_2})|\} + E(\rho_1) + E(\rho_2) = 2E\{E(\rho_1|S_{n_1}, S_{n_2}) \vee E(\rho_2|S_{n_1}, S_{n_2})\}$. □

Let $T$ denote the set $\{(\rho_1, \rho_2) : \rho_1 = \rho_2\}$. The following theorem states that the probability on set $T$ does not affect the determination of optimal strategies. Thus the set $T$ and the prior probability of $T$ can be ignored or assumed to be 0 as necessary. This property is useful when the underlying distribution is not continuous with respect to Lebesgue measure.

**Theorem 2.2** *Where $T = \{(\rho_1, \rho_2) : \rho_1 = \rho_2\}$, define $\pi_0(\rho_1, \rho_2) = \frac{\pi(\rho_1,\rho_2)}{1-\pi(T)}$ if $\rho_1 \neq \rho_2$; and $= 0$, otherwise. Let $I_T(\cdot)$ denote the indicator function of $T$, i.e., $I_T(x) = 1$ if $x \in T$; 0, otherwise. Then*

$$W(n_1, n_2; \pi) = (1 - \pi(T))W(n_1, n_2; \pi_0) + NE(\rho_1 I_T|\pi). \tag{2.3}$$

**Proof:** Let $a_1 = E(\rho_1|\pi)$, $a_2 = E(\rho_2|\pi)$, $a_1^0 = E(\rho_1|\pi_0)$ and $a_2^0 = E(\rho_2|\pi_0)$, then

$$a_i = E(\rho_i I_T|\pi) + E(\rho_i - \rho_i I_T|\pi) = E(\rho_1 I_T|\pi) + (1 - \pi(T))a_i^0,$$

and

$$g(n_1, n_2; \pi) \quad = \quad E\{E(\rho_1|S, \pi) \vee E(\rho_2|S, \pi)\}$$

$$
\begin{aligned}
&= \frac{1}{2}E\{|E(\rho_1|S,\pi) - E(\rho_2|S,\pi)| + E(\rho_1|S,\pi) + E(\rho_2|S,\pi)\} \\
&= \frac{1}{2}E\{|E(\rho_1 - \rho_2|S,\pi)|\} + \frac{1}{2}(a_1 + a_2) \\
&= (1-\pi(T))\left(\frac{1}{2}E\{|E(\rho_1 - \rho_2|S,\pi_0)|\}\right) + \frac{1}{2}(a_1 + a_2) \\
&= (1-\pi(T))g(n_1, n_2; \pi_0) + \frac{1}{2}(a_1 + a_2) - \frac{1-\pi(T)}{2}(a_1^0 + a_2^0) \\
&= (1-\pi(T))g(n_1, n_2; \pi_0) + E(\rho_1 I_T|\pi).
\end{aligned}
$$

(2.3) is immediate by the definition of worth function. □

If one arm is known in a two-armed bandit, then the nature of optimal strategies is special. Let arm 1 be known, say, with success rate $\rho_1 = \lambda$. The following theorem asserts that the optimal strategy should be sought among those of form $(0, n)$, where $n$ is the sample size in the unknown arm.

**Theorem 2.3** (Berry and Pearson, 1985) *For a non-trivial bandit with arm 1 known, the optimal strategy has form $\tau = (0, n)$. That is, use the unknown arm exclusively in the first stage.*

**Proof:** Let $\tau = (n_1, n_2)$. We shall show that if $n_1 \neq 0$, then $\tau$ is not optimal. Construct strategy $\tau' = (0, n_2)$. Strategy $\tau'$ can be interpreted as reassigning those $n_1$ patients from arm 1 of stage 1 to the apparently superior arm in stage 2. Notice that

$$
\begin{aligned}
W(\tau') &= n_2 E(\rho_2) + (N - n_2)E(\lambda \vee E(\rho_2|S_2)), \\
W(\tau) &= n_1\lambda + n_2 E(\rho_2) + (N - n_1 - n_2)E(\lambda \vee E(\rho_2|S_2)).
\end{aligned}
$$

Hence, $W(\tau') - W(\tau) = n_1(E(\lambda \vee E(\rho_2|S_2)) - \lambda) > 0$. The inequality holds strictly by the assumption that the bandit is non-trivial. □

## 2.4 Homogeneous polynomials and asymptotic properties

Before we derive the optimal sample size, we introduce some notations and asymptotic properties to be used in asymptotic operations. These results will also be used extensively in the remaining chapters.

Let $a(x)$ and $b(x)$ be functions of $x = (x_1, ..., x_m)'$ on $R^m$, and $||x|| = \left(\sum_1^m x_i^2\right)^{1/2}$ be its norm. "$x \to x_0$" means $||x - x_0|| \to 0$. The notations $o(\cdot)$, $O(\cdot)$, and "$\sim$" are used in the following sense as the argument $x$ tends to a limit $x_0$.

(i) $a = o(b)$, $x \to x_0$, if and only if $\lim_{x \to x_0} \frac{a(x)}{b(x)} = 0$;

(ii) $a = O(b)$, $x \to x_0$, if and only if there exist constants $c_0$, $c_1 > 0$ such that $c_0 \leq \left|\frac{a(x)}{b(x)}\right| \leq c_1$ as $x \to x_0$;

(iv) $a \sim b$, $x \to x_0$, if and only if $\lim_{x \to x_0} \frac{a(x)}{b(x)} = 1$.

Thus, for $x \in R$, $x^3 = o(x^2)$, $x = O(2x + x^3)$, and $x \sim \sin x$, as $x \to 0$.

For a vector $c \in R^m$, $c > 0$ means that each of the components of $c$ is positive. For vectors $c$, $c_1 \in R^m$, we say $c > c_1$ if $c - c_1 > 0$. A function $g$ is increasing if $g(c) > g(c_1)$ whenever $c > c_1$.

Let $u = (u_1, u_2, ..., u_m)' \in R^m$. For $\alpha > 0$, a *homogeneous polynomial* of order $\alpha$, $h_\alpha(u)$, is defined as

$$h_\alpha(u) = \sum_{\substack{\alpha_1 + \cdots + \alpha_m = \alpha \\ \alpha_1, \cdots, \alpha_m \geq 0}} c_{\alpha_1, ..., \alpha_m} u_1^{\alpha_1} \cdots u_m^{\alpha_m}. \quad (2.4)$$

An important property associated with homogeneous polynomials is

$$h_\alpha(tu) = t^\alpha h_\alpha(u).$$

A more general definition on *homogeneous functions* can be given through the above equation. For example, $\sqrt{x^2+y^2}$ is a homogeneous function of order 1, but not a homogeneous polynomial. However, in this content, we only consider homogeneous polynomials.

Suppose $h_r(u)$ and $h_\alpha(u)$ are two homogeneous polynomials and for $t \geq 1$ define

$$I(t) = \int_0^\infty h_r(u) e^{-t h_\alpha(u)} du. \tag{2.5}$$

If $I(1) = \int_0^\infty h_r(u) e^{-h_\alpha(u)} du$ exists, then, for any $c > 0$, as $t \to +\infty$,

$$\begin{aligned} \int_0^c h_r(u) e^{-t h_\alpha(u)} du &= t^{-\frac{r+m}{\alpha}} \int_0^{\sqrt[\alpha]{t}c} h_r(u) e^{-h_\alpha(u)} du \\ &\sim t^{-\frac{r+m}{\alpha}} \cdot I(1). \end{aligned}$$

We shall prove that under certain conditions, adding higher order infinitesimals to $h_r(u)$ and $h_\alpha(u)$ will not change the asymptotic behavior of $I(t)$.

**Lemma 2.4** *Suppose that $f(u)$, $g(u) \geq 0$ for $u \geq 0$, and $g(u)$ is increasing and continuous in $[0, +\infty)$ and has a unique minimum at 0. If the integral $\int_0^\infty f(u) e^{-g(u)} du$ exists, then for any $c > 0$, as $t \to +\infty$,*

$$\int_0^\infty f(u) e^{-t g(u)} du \sim \int_0^c f(u) e^{-t g(u)} du.$$

**Proof:** Let $m = \min_{[c,\infty)} g(u)$, then $m > g(0)$. There exists a $c_1 \in (0, c)$ and a number $\epsilon > 0$ such that $g(u) < m - \epsilon$ for $u \in (0, c_1)$. Then

$$\int_0^\infty f(u) e^{-t g(u)} du = \int_0^{c_1} + \int_{c_1}^c + \int_c^\infty = I_1 + I_2 + I_3. \tag{2.6}$$

For $t > 1$,

$$\begin{aligned} I_1(t) &= \int_0^{c_1} f(u)e^{-(t-1)g(u)-g(u)}du \geq e^{-(t-1)(m-\epsilon)} \int_0^{c_1} f(u)e^{-g(u)}du, \\ I_3(t) &= \int_c^{\infty} f(u)e^{-(t-1)g(u)-g(u)}du \leq e^{-(t-1)m} \int_c^{\infty} f(u)e^{-g(u)}du. \end{aligned}$$

Since $\int_0^{c_1} f(u)e^{-g(u)}du > 0$, $I_3(t)$ can be omitted in (2.6). □

**Lemma 2.5** *Let $g_r(u) = h_r(u)(1+o(1))$ and $g_\alpha(u) = h_\alpha(u)(1+o(1))$. Assume that $h_r$, $h_\alpha$, $g_r$, $g_\alpha \geq 0$ and $g_\alpha(u)$ is increasing and continuous in $[0, +\infty)$ and has unique minimum at 0. If integrals $\int_0^\infty h_r(u)e^{-h_\alpha(u)}du$ and $\int_0^\infty g_r(u)e^{-g_\alpha(u)}du$ exist, then for $c > 0$, as $t \to +\infty$,*

$$\int_0^c g_r(u)e^{-tg_\alpha(u)}du \sim \int_0^c h_r(u)e^{-th_\alpha(u)}du \sim t^{-\frac{r+m}{\alpha}} \cdot I(1),$$

*where $I(\cdot)$ is defined in (2.5).*

**Proof:** For $\epsilon > 0$, we can find $\delta > 0$ such that $\left|1 - (1 \pm \delta)(1 \mp \delta)^{-\frac{r+m}{\alpha}}\right| < \epsilon$. For this $\delta$, there exists $c' > 0$ such that $|h_\alpha(u) - g_\alpha(u)| < \delta h_\alpha(u)$ and $|h_r(u) - g_r(u)| < \delta h_r(u)$ for $u < c'$, or equivalently

$$\begin{aligned} (1-\delta)h_r(u) < g_r(u) < (1+\delta)h_r(u), \\ (1-\delta)h_\alpha(u) < g_\alpha(u) < (1+\delta)h_\alpha(u). \end{aligned} \tag{2.7}$$

Let $I_1'(t) = \int_0^{c'} h_r(u)e^{-th_\alpha(u)}du$, and $I_2'(t) = \int_0^{c'} g_r(u)e^{-tg_\alpha(u)}du$, then

$$\frac{|I_2'(t) - I_1'(t)|}{I_1'(t)} \leq \frac{\int_0^{c'}(1+\delta)h_r(u)e^{-t(1-\delta)h_\alpha(u)}du - \int_0^{c'}(1-\delta)h_r(u)e^{-t(1+\delta)h_\alpha(u)}du}{\int_0^{c'} h_r(u)e^{-th_\alpha(u)}du}$$

$$\to (1+\delta)(1-\delta)^{-\frac{r+m}{\alpha}} - (1-\delta)(1+\delta)^{-\frac{r+m}{\alpha}} < 2\epsilon.$$

Therefore, for sufficiently large $t$,

$$\frac{|I_2'(t) - I_1'(t)|}{I_1'(t)} \le 2\epsilon \quad \text{and} \quad \frac{I_2'(t)}{I_1'(t)} = 1 + \frac{I_2'(t) - I_1'(t)}{I_1'(t)} \le 1 + 2\epsilon.$$

Let $I_1(t) = \int_0^c h_r(u)e^{-th_\alpha(u)}du$ and $I_2(t) = \int_0^c g_r(u)e^{-tg_\alpha(u)}du$. By Lemma 2.4, $I_i' \sim I_i$. That is, for sufficiently large $t$, $\left|\frac{I_i - I_i'}{I_i'}\right| < \epsilon$ and $\frac{I_i'(t)}{I_i(t)} \le 1 + \epsilon$ hold for $i = 1, 2$. It follows that

$$\left|\frac{I_1 - I_2}{I_1}\right| = \frac{I_1'}{I_1}\left(\frac{I_1 - I_1'}{I_1'} - \frac{I_2 - I_2'}{I_2'} \cdot \frac{I_2'}{I_1'} + \frac{I_1' - I_2'}{I_1'}\right)$$

$$\le (1+\epsilon)(\epsilon + \epsilon(1+2\epsilon) + 2\epsilon) = \epsilon(1+\epsilon)(4+2\epsilon).$$

The result follows since $\epsilon$ is arbitrary. □

**Lemma 2.6** *In addition to the conditions of Theorem 2.5, let $\epsilon_1(t), \epsilon_2(t) \in R^m$ and $\sqrt[\alpha]{t}\epsilon_i(t) \to 0$, then*

$$\int_0^c g_r(u + \epsilon_1(t))e^{-tg_\alpha(u+\epsilon_2(t))}du \sim \int_0^c h_r(u)e^{-th_\alpha(u)}du \sim t^{-\frac{r+m}{\alpha}} \cdot I(1),$$

*where $I(\cdot)$ is defined in (2.5).*

**Proof:** We first look at the polynomial case. By the continuity of polynomial functions, we have

$$\begin{aligned}\int_0^c h_r(u + \epsilon_1(t))e^{-th_\alpha(u+\epsilon_2(t))}du &= t^{-\frac{r+m}{\alpha}} \int_0^{\sqrt[\alpha]{t}c} h_r(u + \sqrt[\alpha]{t}\epsilon_1(t))e^{-h_\alpha(u+\sqrt[\alpha]{t}\epsilon_2(t))}du \\ &\sim t^{-\frac{r+m}{\alpha}} I(1).\end{aligned}$$

It can be checked that Theorem 2.4 still holds upon replacing $u$ with $u + \epsilon_t$. The inequalities in (2.7) also hold with the replacement. Thus, by the same procedure as in the proof of Theorem 2.5, the result follows. □

**Lemma 2.7** *Let* $u = (u^{(1)}, u^{(2)})$. *Assume that the conditions of Lemma 2.5 hold and, further, that the integration range for* $u^{(1)}$ *is* $(0, \epsilon(t))$ *and* $\sqrt[\alpha]{t}\epsilon(t) \to 0$, *as* $t \to +\infty$. *Then we have*

$$I_{\epsilon(t)} = \int_0^{\epsilon(t)} \left( \int_0^c g_r(u) e^{-tg_\alpha(u)} du^{(2)} \right) du^{(1)} = o(I(t)).$$

**Proof:** Given $\delta > 0$ there exists $c' < c$ such that (2.7) holds. Let $m = \min_{[0,\infty)\times[c',c]} g(u^{(1)}, u^{(2)})$ then $\int_0^{\epsilon(t)} \int_{c'}^c$ can be omitted since for $t > 1$

$$\int_0^{\epsilon(t)} \int_{c'}^c g_r(u) e^{-tg_\alpha(u)} du^{(2)} du^{(1)} \le e^{-(t-1)m} \int_0^\infty g_r(u) e^{-g_\alpha(u)} du = o(I(t)).$$

Let $I_{1\pm\delta}(t) = \int_0^\epsilon \int_0^{c'} h_r(u) e^{-t(1\pm\delta)h_\alpha(u)} du$. Since $\int_0^{\epsilon(t)} \int_0^{c'} g_r(u) e^{-tg_\alpha(u)} du^{(2)} du^{(1)}$ is bracketed by $(1 \mp \delta) I_{1\pm\delta}(t)$, it suffices to show $I_{1\pm\delta}(t) = o(I(t))$. Let

$$\varphi(u^{(1)}) = \int_0^{\sqrt[\alpha]{t}c'} h_r(u) e^{-(1\pm\delta)h_\alpha(u)} du^{(2)}.$$

By the integrability of $I_{1\pm\delta}(1)$ and Fubini's theorem, $\varphi(u^{(1)})$ is integrable, thus $\int_0^{\sqrt[\alpha]{t}\epsilon(t)} \varphi(u^{(1)}) du^{(1)} \to 0$ as $\sqrt[\alpha]{t}\epsilon(t) \to 0$. Therefore,

$$\frac{I_{1\pm\delta}(t)}{I(t)} = I^{-1}(1) \int_0^{\sqrt[\alpha]{t}\epsilon(t)} \left( \int_0^{\sqrt[\alpha]{t}c'} h_r(u) e^{-(1\pm\delta)h_\alpha(u)} du^{(2)} \right) du^{(1)} \to 0. \Box$$

**Example 1:** Consider $m = 1$. Let $f_\alpha(u) = au^\alpha$, then for $c > 0$,

$$\int_0^c u^r e^{-th_\alpha(u)} du \sim t^{-\frac{r+1}{\alpha}} \int_0^\infty y^r e^{-ay^\alpha} dy.$$

In particular, if $a = 1$ and $\alpha = 1$ then $I \sim t^{-(r+1)}\Gamma(r+1)$. And, if $a = \frac{1}{2}$ and $\alpha = 2$ then $I \sim t^{-\frac{r+1}{2}} J(r+1)$, where

$$J(u) = \int_0^\infty z^u e^{-\frac{1}{2}z^2} dz. \tag{2.8}$$

If $u$ is an integer,

$$J(2k) = (2k-1)\cdot(2k-3)\cdots 3\cdot 1\cdot \frac{\sqrt{2\pi}}{2} = (2k-1)!!\cdot\frac{\sqrt{2\pi}}{2}$$
$$J(2k+1) = (2k)\cdot(2k-2)\cdots 4\cdot 2 = (2k)!!. \quad \square$$

**Example 2:** Let $R_r(t) = \int_t^\infty (u-t)^r e^{-\frac{u^2}{2}}du$. This expression is often used in normal approximations and asymptotic expansions. Note that $u^r e^{-\frac{1}{2}u^2} \sim u^r$ as $u \to 0$ and, using Lemma 2.5, we have

$$R_r(t) = \int_0^\infty u^r e^{-\frac{1}{2}(u+t)^2}du \sim e^{-\frac{t^2}{2}}\int_0^\infty u^r e^{-ut}du = r!t^{-(r+1)}e^{-\frac{t^2}{2}}. \tag{2.9}$$

Alternatively, direct calculation gives that

$$R_r(t) = r!t^{-(r+1)}e^{-\frac{t^2}{2}}\left\{\sum_{i=0}^{n}(-1)^i\frac{(2i-1)!!}{t^{2i}}\binom{2i+r}{r} + o\left(\frac{1}{t^{2n}}\right)\right\}, \tag{2.10}$$

where $(2i-1)!! = (2i-1)(2i-3)\cdots 3\cdot 1$. In particular, when $r=0$,

$$R_0(t) = e^{-\frac{t^2}{2}}\left(\frac{1}{t} - \frac{1}{t^3} + \frac{3}{t^5} + \cdots + (-1)^n\frac{(2n-1)!!}{t^{2n+1}} + o\left(\frac{1}{t^{2n+1}}\right)\right). \tag{2.11}$$

Again, we have that $R_r(t) \sim r!t^{-(r+1)}e^{-\frac{t^2}{2}}$, as $t \to \infty$, which is in agreement with (2.9). To derive (2.11), define

$$f_n(t) = e^{-\frac{t^2}{2}}\sum_{i=0}^{n}(-1)^i\frac{(2i-1)!!}{t^{2i+1}}.$$

Let $D_n = R_0(t) - f_n(t)$, then $D_n'(t) = e^{-\frac{t^2}{2}}(-1)^{n+2}\frac{(2n+1)!!}{t^{2n+2}}$. $D_n'(t) < 0$ if $n$ is odd; $> 0$ if $n$ is even. Since $D_n(+\infty) = R_0(+\infty) = 0$, so $D_n(t) > 0$ if $n$ is odd; $< 0$ if $n$ is even. Therefore, $R_0(t)$ is bracketed by $f_n(t)$ and $f_{n+1}(t)$ for any integer $n$, and

$$|D_n(t)| \le |f_{n+1}(t) - f_n(t)| = e^{-\frac{t^2}{2}} \cdot \frac{(2n+1)!!}{t^{2n+3}} = o\left(\frac{1}{t^{2n+1}}\right) e^{-\frac{t^2}{2}}.$$

This proves (2.11). Note that $R_1(t) = e^{-\frac{t^2}{2}} - tR_0(t)$ and $R_r(t) = (r-1)R_{r-2}(t) - tR_{r-1}(t)$ for $r \ge 2$. By induction and further calculation on $R_r(t)$, (2.10) holds for any $r \ge 0$. □

## 2.5 Approximation to optimal sample size

Reconsider the two-armed bandit problem with dichotomous responses. In this section, we assume that the first arm has known success rate, say $\lambda$, and the second arm has unknown success rate $\rho$ having a beta prior with parameters $a$ and $b$,

$$\pi(\rho) = \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\rho^{a-1}(1-\rho)^{b-1}. \tag{2.12}$$

By Theorem 2.3, we restrict to strategies of the form $(0, n)$. The corresponding worth function can be written as

$$W(n) = nE(\rho) + (N-n)E\{E(\rho|S_n) \vee \lambda\}, \tag{2.13}$$

where $S_n$ is the sum of responses from the unknown arm in the first stage, a statistic that is sufficient for $\rho$.

When the prior $\pi$ is uniform on $(0, 1)$, Berry & Pearson (1985) found that the optimal length of the first stage is

$$n^* = (\lambda^{-1} - 1)^{1/2}\sqrt{N+1} - 2, \tag{2.14}$$

and conjectured that the order of square root of $N$ applies for any beta distribution, the parameters of the beta determining the magnitude of $n$. Cheng

(1992) proved that if $\lambda$ is a rational number, then the optimal first stage length is of order $\sqrt{N}$. In the following, I will give an asymptotic approximation to the optimal $n^*$ for any $\lambda \in (0,1)$, which confirms Berry and Pearson's conjecture, and, furthermore, the coefficient is given explicitly.

Let $g(n) = E\{E(\rho|S_n) \vee \lambda\} = E\{\frac{a+S_n}{a+b+n} \vee \lambda\}$. First, we prove

$$g(n) \sim E\{\rho \vee \lambda\} - \frac{\pi(\lambda)\lambda(1-\lambda)}{2n}. \qquad (2.15)$$

**Lemma 2.8** *Define $s_0 = \lambda(a+b+n) - a$, then*

$$g(n) = E\{\rho \vee \lambda|\pi\} - I_1 - I_2,$$

*where*

$$I_1 = \int_0^\lambda \sum_{s \geq s_0} \binom{n}{s} \rho^s (1-\rho)^{n-s} (\lambda - \rho)\pi(\rho) d\rho,$$

$$I_2 = \int_\lambda^1 \sum_{s < s_0} \binom{n}{s} \rho^s (1-\rho)^{n-s} (\rho - \lambda)\pi(\rho) d\rho.$$

**Proof:** Let $p(s)$ denote the marginal distribution of $S_n$, $\int_0^1 p(s|\rho)\pi(\rho)d\rho$, then

$$\begin{aligned} g(n) &= \sum_{s<s_0} p(s)\lambda + \sum_{s \geq s_0}^{n} p(s) E(\rho|S_n = s) = \lambda + \int_0^1 \sum_{s \geq s_0} p(s|\rho)(\rho - \lambda)\pi(\rho) d\rho \\ &= \lambda + \int_0^\lambda \sum_{s \geq s_0} p(s|\rho)(\rho-\lambda)\pi(\rho)d\rho + \int_\lambda^1 \left(1 - \sum_{s<s_0} p(s|\rho)\right)(\rho - \lambda)\pi(\rho)d\rho \\ &= \lambda + \int_\lambda^1 (\rho - \lambda)\pi(\rho)d\rho - I_1 - I_2 = E\{\rho \vee \lambda|\pi\} - I_1 - I_2. \quad \square \end{aligned}$$

A Kullback-Leibler distance between two Bernoulli distributions is defined as $D_1(z||\rho) = z \log \frac{z}{\rho} + (1-z) \log \frac{1-z}{1-\rho}$, where $z$, $p \in (0,1)$ are two success rates.

A Taylor expansion at $\rho$ gives that

$$D_1(z||\rho) = \frac{(z-\rho)^2}{2\rho(1-\rho)} + \frac{1}{6}\frac{d^3}{dz^3}D_1(\xi||\rho)(z-\rho)^3, \tag{2.16}$$

where $\xi$ lies between $z$ and $\rho$.

The following lemma gives an approximation to large deviation probabilities for a binomial distribution, which is a special case of a result of Bahadur & Rao (1960).

**Lemma 2.9** *Let $p+q=1$ and $p<z$. Let $\lceil x \rceil$ denote the smallest integer greater than or equal to $x$. Then*

$$\sum_{\frac{s}{n}\geq z} \binom{n}{s} p^s q^{n-s} = e^{-nD_1(z||p)} \frac{qz(\frac{p(1-z)}{qz})^{(nz-\lceil nz \rceil)}}{\sqrt{2\pi n}\sqrt{z(1-z)}(z-p)}(1+O(n^{-1/2})). \tag{2.17}$$

*When $z=\frac{\lceil nz \rceil}{n}$ the numerator of (2.17) becomes $qz$; otherwise it takes values between $qz$ and $p(1-z)$.*

**Lemma 2.10** *Where $s_0$ is defined in Lemma 2.8, for $\lambda \in (0,1)$, as $n \to \infty$,*

$$\int_0^\lambda \sum_{\frac{s}{n}\geq \frac{s_0}{s}} \binom{n}{s} \rho^s (1-\rho)^{n-s}(\lambda-\rho)\pi(\rho)d\rho \sim \frac{\pi(\lambda)\lambda(1-\lambda)}{4n}. \tag{2.18}$$

**Proof:** For any $0<\delta<\min(\lambda, 1-\lambda)$, when $n$ is sufficiently large it holds that $\frac{s_0}{n} > \lambda - \frac{\delta}{2}$, and by Lemma 2.9,

$$\begin{aligned} \int_0^{\lambda-\delta} \sum_{\frac{s}{n}\geq\frac{s_0}{n}} &\leq \int_0^{\lambda-\delta} \sum_{\frac{s}{n}\geq \lambda-\frac{\delta}{2}} \binom{n}{s}\rho^s(1-\rho)^{n-s}|\lambda-\rho|\pi(\rho)d\rho \\ &\leq \int_0^{\lambda-\delta} e^{-nD_1(\lambda-\frac{\delta}{2}||\rho)}d\rho \leq O\left(e^{-nD_1(\lambda-\frac{\delta}{2}||\lambda-\delta)}\right), \end{aligned}$$

which converges to 0 exponentially.

Similarly, $\int_0^\lambda \sum_{\frac{s}{n}\geq\lambda+\delta}$ also has an exponential rate converging to 0. Thus it suffices to show $I \triangleq \int_{\lambda-\delta}^{\lambda} \sum_{\frac{s}{n}\geq\frac{s_0}{n}}^{\lambda+\delta} \sim \frac{\pi(\lambda)\lambda(1-\lambda)}{4n}$. Because $\frac{s_0}{n} \leq \frac{s}{n} \leq \lambda+\delta$, it can be seen that as $n \to \infty$ both $s$ and $(n-s)$ tend to infinity. Applying Stirling's formula to $\binom{n}{s}$ gives

$$I \;\sim\; \int_{\lambda-\delta}^{\lambda} \frac{\sqrt{n}}{\sqrt{2\pi}} \left( \frac{1}{n} \sum_{\frac{s}{n}\geq\frac{s_0}{n}}^{\lambda+\delta} \frac{e^{-nD_1(\frac{s}{n}||\rho)}}{\sqrt{\frac{s}{n}(1-\frac{s}{n})}} \right) (\lambda-\rho)\pi(\rho)d\rho.$$

By the upcoming Lemma 2.11 and Lemma 2.5, we have

$$\begin{aligned} I &\sim \int_{\lambda-\delta}^{\lambda} \frac{\sqrt{n}}{\sqrt{2\pi}} \int_{\lambda}^{\lambda+\delta} \frac{e^{-nD_1(x||\rho)}}{\sqrt{x(1-x)}}(\lambda-\rho)\pi(\rho)dxd\rho \\ &\sim \frac{\sqrt{n}\pi(\lambda)}{\sqrt{2\pi}\sigma} \int_{\lambda-\delta}^{\lambda} \int_{\lambda}^{\lambda+\delta} e^{-\frac{1}{2\sigma^2}n(x-\rho)^2}(\lambda-\rho)dxd\rho \\ &= \frac{\pi(\lambda)\sigma^2}{n\sqrt{2\pi}} \int_0^{\sqrt{n}\delta} \int_0^{\sqrt{n}\delta} e^{-\frac{1}{2}(y+z)^2} zdydz, \qquad (2.19) \end{aligned}$$

where $\sigma^2 = \lambda(1-\lambda)$. In the last equality we used transformation $y = \sigma^{-1}\sqrt{n}(x-\lambda), z = \sigma^{-1}\sqrt{n}(\lambda-\rho)$. Notice that

$$\begin{aligned} &\int_0^{\sqrt{n}\delta} \int_0^{\sqrt{n}\delta} e^{-\frac{1}{2}(y+z)^2} zdydz \sim \int_0^{\infty} \int_0^{\infty} e^{-\frac{1}{2}(y+z)^2} zdydz \\ &= \frac{1}{2} \int_0^{\infty} \int_0^{\infty} e^{-\frac{1}{2}(y+z)^2}(y+z)dydz = \frac{1}{2} \int_0^{\infty} \left[-e^{-\frac{1}{2}(y+z)^2}\right]_{y=0}^{\infty} dz \\ &= \frac{1}{2} \int_0^{\infty} e^{-\frac{1}{2}z^2} dz = \frac{\sqrt{2\pi}}{4}. \end{aligned}$$

The result follows by substituting this into (2.19). $\square$

**Lemma 2.11** *For any $c > 0$, as $n \to \infty$, the following hold:*

$$\frac{1}{n}\int_{\lambda-\delta}^{\lambda} \sum_{\lambda-\frac{c}{n}\le\frac{s}{n}\le\lambda-\frac{c}{n}} \frac{e^{-nD_1(\frac{s}{n}||\rho)}}{\sqrt{\frac{s}{n}(1-\frac{s}{n})}}(\lambda-\rho)\pi(\rho)d\rho \le O(n^{-2}), \tag{2.20}$$

$$\frac{1}{n}\int_{\lambda-\delta}^{\lambda} \sum_{\frac{s}{n}\ge\lambda}^{\lambda+\delta} \frac{e^{-nD_1(\frac{s}{n}||\rho)}}{\sqrt{\frac{s}{n}(1-\frac{s}{n})}}(\lambda-\rho)\pi(\rho)d\rho \sim \int_{\lambda-\delta}^{\delta}\int_{\lambda}^{\lambda+\delta} \frac{e^{-nD_1(x||\rho)}}{\sqrt{x(1-x)}}(\lambda-\rho)\pi(\rho)dxd\rho. \tag{2.21}$$

**Proof:** First, we show that for any $c > 0$, if $|\frac{s}{n}-\lambda| \le \frac{c}{n}$ then

$$\frac{1}{n}\int_{\lambda-\delta}^{\lambda} \frac{e^{-nD_1(\frac{s}{n}||\rho)}}{\sqrt{\frac{s}{n}(1-\frac{s}{n})}}(\lambda-\rho)\pi(\rho)d\rho \le O(n^{-2}). \tag{2.22}$$

In this proof we use $L, L_1, L_2, \cdots$ as unspecified positive constants. From (2.16), when $|\frac{s}{n}-\rho|$ is sufficiently small, the following holds

$$D_1(\tfrac{s}{n}||\rho) \ge L_1(\tfrac{s}{n}-\rho)^2 - L_2(\tfrac{s}{n}-\rho)^3 = L_1y^2 - L_2y^3 + O(n^{-1}),$$

where $y = \lambda-\rho$. Note that $\pi(\rho)\left(\frac{s}{n}(1-\frac{s}{n})\right)^{-1/2} \le L$ for some number $L > 0$, and hence the left-hand side of (2.22) is smaller than

$$\frac{L}{n}\int_{\lambda-\delta}^{\lambda} e^{-nD_1(\frac{s}{n}||\rho)}(\lambda-\rho)d\rho \le \frac{L}{n}\int_0^{\delta} e^{-n(L_1y^2-L_2y^3)+O(1)}ydy = O(n^{-2}).$$

The last equality holds due to Lemma 2.5. There are only finitely many terms in the sum in (2.20) in the range $[\lambda-\frac{c}{n}, \lambda+\frac{c}{n}]$, and so (2.20) holds.

For convenience, denote $\sigma(x) = \sqrt{x(1-x)}$, $g_\rho(x) = e^{-D_1(x||\rho)}$. Then $g_\rho(x)$ is decreasing in $x$ for $x \ge \rho$. The continuous function $\sigma^{-1}(x)$ is bounded on $[\lambda, \lambda+\delta]$, and so is its derivative. Hence, there exist $L_3$ and $L_4$ such that $\sigma^{-1}(x) \le L_3$ and $|\frac{d}{\partial x}\sigma^{-1}(x)| \le L_4$. Let $m_s$ and $M_s$ be the minimum and maximum of $\sigma^{-1}(x)$ on $[\frac{s}{n}, \frac{s+1}{n}]$, then $|m_s - \sigma^{-1}(\frac{s}{n})|$ and $|M_s - \sigma^{-1}(\frac{s}{n})| < n^{-1}L_4$. Also,

$$\begin{aligned}
\sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} m_s g_\rho^n(\tfrac{s+1}{n}) &= \sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} (\sigma(\tfrac{s+1}{n}) + m_s - \sigma(\tfrac{s+1}{n}))g_\rho^n(\tfrac{s+1}{n}) \\
&\geq \sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} \sigma(\tfrac{s}{n})g_\rho^n(\tfrac{s}{n}) - \sigma(\tfrac{[n\lambda]}{n})g_\rho^n(\tfrac{[n\lambda]}{n}) - g_\rho^n(\tfrac{[n\lambda]}{n})\delta L_4 \\
\sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} M_s g_\rho^n(\tfrac{s}{n}) &= \sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} (\sigma(\tfrac{s}{n}) + M_s - \sigma(\tfrac{s}{n}))g_\rho^n(\tfrac{s}{n}) \\
&\leq \sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} \sigma(\tfrac{s}{n})g_\rho^n(\tfrac{s}{n}) + g_\rho^n(\tfrac{[n\lambda]}{n})\delta L_4.
\end{aligned}$$

From (2.22), $\frac{1}{n}\int_{\lambda-\delta}^{\lambda} g_\rho^n(\frac{[n\lambda]}{n})(\lambda-\rho)\pi(\rho)d\rho \leq O(n^{-2})$. Using the fact that $\frac{1}{n}\sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} m_s g_\rho^n(\frac{s+1}{n}) \leq \int_\lambda^{\lambda+\delta} \sigma^{-1}(x)g_\rho^n(x)dx \leq \frac{1}{n}\sum_{\frac{s}{n}\geq\lambda}^{\lambda+\delta} M_s g_\rho^n(\frac{s}{n})$, (2.21) follows. □

Similarly, it follows that

$$\int_\lambda^1 \sum_{\frac{s}{n}<\frac{s_0}{s}} \binom{n}{s}\rho^s(1-\rho)^{n-s}(\lambda-\rho)\pi(\rho)d\rho \sim \frac{\pi(\lambda)\lambda(1-\lambda)}{4n}.$$

Together with (2.18), we have proved (2.15). Define

$$\hat{W}_N(n) = nE(\rho) + (N-n)\left(E(\rho\vee\lambda) - \frac{\pi(\lambda)\lambda(1-\lambda)}{2n}\right). \tag{2.23}$$

The mode of $\hat{W}_N(n)$, denoted as $\hat{n}$, is called an *asymptotically optimal* sample size. Differentiating (2.23) gives $\hat{n}(N) = \left(\sqrt{\frac{\pi(\lambda)\lambda(1-\lambda)}{E(\rho\vee\lambda)-E(\rho)}}\right)^{1/2}\sqrt{N}$. The following lemma gives the relation between $\hat{n}$ and the optimal length $n^*$.

**Lemma 2.12** *Let $n^*$ be the optimal sample size of the first stage, then*

$$\lim_{N\to+\infty} n^*(N) = +\infty, \text{ and } \lim_{N\to+\infty} n^*(N)/N = 0.$$

*Let $\hat{n}$ be the asymptotically optimal sample size, then*

$$\lim_{N\to+\infty} n^*(N)/\hat{n}(N) = 1. \tag{2.24}$$

**Proof:** We first show $\lim_{N\to+\infty} n^*(N) = +\infty$. Otherwise, there exists a subsequence $\{N_j\}$ such that $n^*(N_j) \to n_0 < \infty$ and $W(n^*(N_j))/N_j \to g(n_0)$. On the other hand, since $\hat{n} = O(\sqrt{N})$ and $g(\hat{n}(N_j)) \to E(\rho \vee \lambda)$ by (2.15), $W(\hat{n}(N_j))/N_j \to E(\rho \vee \lambda)$. Since $g(n)$ is increasing, $g(n_0) < E(\rho \vee \lambda)$ which contradicts the optimality of $n^*(N_j)$.

Denote $h = \pi(\lambda)\lambda(1-\lambda)$ and $C = E(\rho \vee \lambda) - E(\rho)$ then $\hat{n}(N) = \sqrt{(h/C)N}$. Let $c_1 = \underline{\lim}_{N\to\infty} n^*(N)/\hat{n}(N) \le \overline{\lim}_{N\to\infty} n^*(N)/\hat{n}(N) = c_2$. If $c_1 < 1$, there exists a subsequence $\{N_j\}$ such that $n^*(N_j) < (1-\delta)\hat{n}(N_j)$ for some $\delta \in (0,1)$. Select $\epsilon > 0$ such that $\epsilon \le \min\{\delta, \delta^2/(2-\delta)\}$. By (2.15), for sufficient large $n$, it holds that $\frac{h}{n}(1-\epsilon) \le E(\rho \vee \lambda) - g(n) \le \frac{h}{n}(1+\epsilon)$. Thus, as $N_j \to \infty$,

$$\begin{aligned}
W(n^*(N_j)) - W(\hat{n}(N_j)) &\le -n^*C - \frac{h}{n^*}(1-\epsilon)N_j + \hat{n}C + \frac{h}{\hat{n}}(1+\epsilon)N_j + 2\epsilon h \\
&\le -(1-\delta)\hat{n}C - \frac{(1-\epsilon)hN_j}{(1-\delta)\hat{n}} + (2+\epsilon)\sqrt{hCN_j} + 2\epsilon h \\
&= \left(2 + \epsilon - (1-\delta) - \frac{1-\epsilon}{1-\delta}\right)\sqrt{hCN_j} + 2\epsilon h \\
&= \frac{\epsilon(2-\delta) - \delta^2}{1-\delta}\sqrt{hCN_j} + 2\epsilon h < 0.
\end{aligned}$$

The second inequality holds due to the facts that the function $-n^*C - \frac{h}{n^*}(1-\epsilon)N_j$ is increasing for $n^* \le (\sqrt{1-\epsilon})\hat{n}(N_j)$ and that $n^*(N_j) < (1-\delta)\hat{n}(N_j) <$

$(\sqrt{1-\epsilon})\hat{n}(N_j)$. Therefore, $c_1 \geq 1$. Similarly, it follows that $c_2 \leq 1$. Thus $c_1 = c_2 = 1$ and $n^*(N) \sim \hat{n}(N)$ as $N \to \infty$. $\square$

**Theorem 2.13** *Let $n^*$ be the optimal first stage sample size, then as $N \to \infty$,*

$$n^* \sim \left(\frac{\pi(\lambda)\lambda(1-\lambda)}{2C}N\right)^{1/2},$$

*where $C = E(\rho \vee \lambda|\pi) - E(\rho|\pi)$.*

If $\pi(\rho)$ is uniformly distributed, then $E(\rho \vee \lambda) - E(\rho) = \frac{1}{2}\lambda^2$ and $n \sim (\lambda^{-1}-1)^{1/2}\sqrt{N}$. The coefficient is the same as the one in (2.14).

## 2.6 Numerical examples

Let $C = E(\rho \vee \lambda|\pi) - E(\rho|\pi)$, then it can be expressed by incomplete beta function as $C = \lambda\int_0^\lambda \pi(\rho)d\rho - \int_0^\lambda \rho\pi(\rho)d\rho = \lambda B(\lambda; a, b) - \frac{a}{a+b}B(\lambda; a+1, b)$, where

$$B(x; a, b) = \int_0^x \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\rho^{a-1}(1-\rho)^{b-1}d\rho$$

is the incomplete beta function. The average worth can be approximated by

$$\hat{W}_{avg}(n) = \frac{\hat{W}(n)}{N} = \frac{a}{a+b} + C\left(1 - \frac{n}{N}\right)^2,$$

which achieves its maximum $\frac{a}{a+b} + \left(\sqrt{C} - \sqrt{\frac{\pi(\lambda)\lambda(1-\lambda)}{2N}}\right)^2$ at $\hat{n}$.

The following is an $S$ program to calculate asymptotically optimal length $\hat{n}$ and average worth.

```
# Given lambda(=l), alpha(=a) and beta(=b), this program
# returns the asymptotically optimal n and the average worth.
```

```
function(N, l, a, b)
{
        C <- l*pbeta(l,a,b)-a/(a+b)*pbeta(l,a+1,b)
        g <- dbeta(l,a,b)*l*(1-l)/2
        n <- sqrt(N*g/C)
        w <- a/(a+b)+C*(1-n/N)**2
        cat("n=",n,", w=",w,"\n")
}
```

In the following, I compare different procedures. $W^*_{avg}$ denotes the optimal worth and $\hat{W}_{avg}$ the asymptotic worth. Table 2.1 shows that the difference between them is small, even for moderate values of $N$. This difference is smaller when $\lambda$ is closer to the expectation of $\rho$. Figure 2.6 gives the plots of $W^*_{avg}$ and $\hat{W}_{avg}$ as functions of $n$. For $N = 200$, the two functions are quite close, and for $N = 1000$, two worth functions are nearly indistinguishable.

A procedure that might be considered is to assign half of the $N$ patients to stage 1 and half of them to each arm, with the second half of the $N$ patients to the better performer from stage 1. The worth of this procedure is shown in Table 2.1 as $\tilde{W}$. The calculation for worth $\tilde{W}$ is given by

$$\begin{aligned} \tilde{W}(N, \lambda, a, b) &= \frac{N}{4}\lambda + \frac{N}{4} \cdot \frac{a}{a+b} + \frac{N}{2} E\{\lambda \vee E(\rho|S_n)\} \\ &= \frac{N}{4}\lambda + \frac{3}{4} W(\tfrac{3}{4}N, \lambda, a, b; \tau_1 = \tfrac{1}{4}N), \end{aligned} \tag{2.25}$$

where $S_n$ is the total number of successes from the first stage on the unknown arm. The percentage decreased in $\tilde{W}_{avg}$ from $W^*_{avg}$ ranges from 7% to 13%.

The factor $\sqrt{\frac{\pi(\lambda)\lambda(1-\lambda)}{2C}}$ makes a difference. For example in the last case in

| $\lambda, (a,b)$ | $N$ | $n^*$ | $\hat{n}$ | $W^*_{avg}$ | $\hat{W}_{avg}$ | $\tilde{W}_{avg}$ | $W^*_{avg} - \hat{W}_{avg}$ | $W^*_{avg} - \tilde{W}_{avg}$ |
|---|---|---|---|---|---|---|---|---|
| | 40 | 8 | 11 | .6909 | .6899 | .6410 | .0010 | .0499 |
| 0.5 | 100 | 14 | 17 | .6962 | .6958 | .6435 | .0004 | .0527 |
| | 200 | 22 | 24 | .6993 | .6993 | .6447 | .0000 | .0546 |
| (2,1) | 500 | 36 | 39 | .7024 | .7023 | .6453 | .0001 | .0571 |
| | 1,000 | 52 | 55 | .7040 | .7040 | .6456 | .0000 | .0584 |
| | 40 | 2 | 4 | .4875 | .4782 | .4419 | .0093 | .0456 |
| 0.5 | 100 | 3 | 6 | .4960 | .4906 | .4437 | .0054 | .0523 |
| | 200 | 3 | 8 | .4998 | .4973 | .4444 | .0025 | .0554 |
| (1,3) | 500 | 9 | 13 | .5041 | .5035 | .4450 | .0006 | .0591 |
| | 1,000 | 15 | 19 | .5069 | .5067 | .4451 | .0002 | .0618 |
| | 40 | 7 | 10 | .5275 | .5273 | .4681 | .0002 | .0594 |
| 0.3 | 100 | 13 | 15 | .5331 | .5328 | .4705 | .0003 | .0626 |
| | 200 | 20 | 22 | .5362 | .5361 | .4715 | .0001 | .0647 |
| (1,1) | 500 | 33 | 34 | .5392 | .5392 | .4721 | .0000 | .0671 |
| | 1,000 | 46 | 48 | .5408 | .5408 | .4723 | .0000 | .0685 |
| | 40 | 3 | 2 | .7110 | .7054 | .6469 | .0056 | .0641 |
| 0.75 | 100 | 4 | 3 | .7310 | .7294 | .6476 | .0016 | .0834 |
| | 200 | 5 | 5 | .7396 | .7396 | .6480 | .0000 | .0916 |
| (1,2) | 500 | 6 | 7 | .7460 | .7455 | .6483 | .0004 | .0977 |
| | 1,000 | 6 | 11 | .7485 | .7477 | .6484 | .0008 | .1001 |

Table 2.1: Comparison of worths for three different approaches. In the table, $n^*$ is optimal sample size, and $\hat{n}$ is asymptotically optimal sample size. $W^*$ is optimal worth, and $\hat{W}$ is worth calculated at $\hat{n}$. The worth $\tilde{W}$ is calculated according to (2.25).

Table 2.1, where $\lambda = 0.75$ and $(a,b) = (1,2)$, using $n = \sqrt{N} = \sqrt{1000} \approx 32$ gives an average worth of 0.7405, which has 0.008 difference from $W^*/N = 0.7485$, compared with 0.001 when using $\hat{n} = 11$.

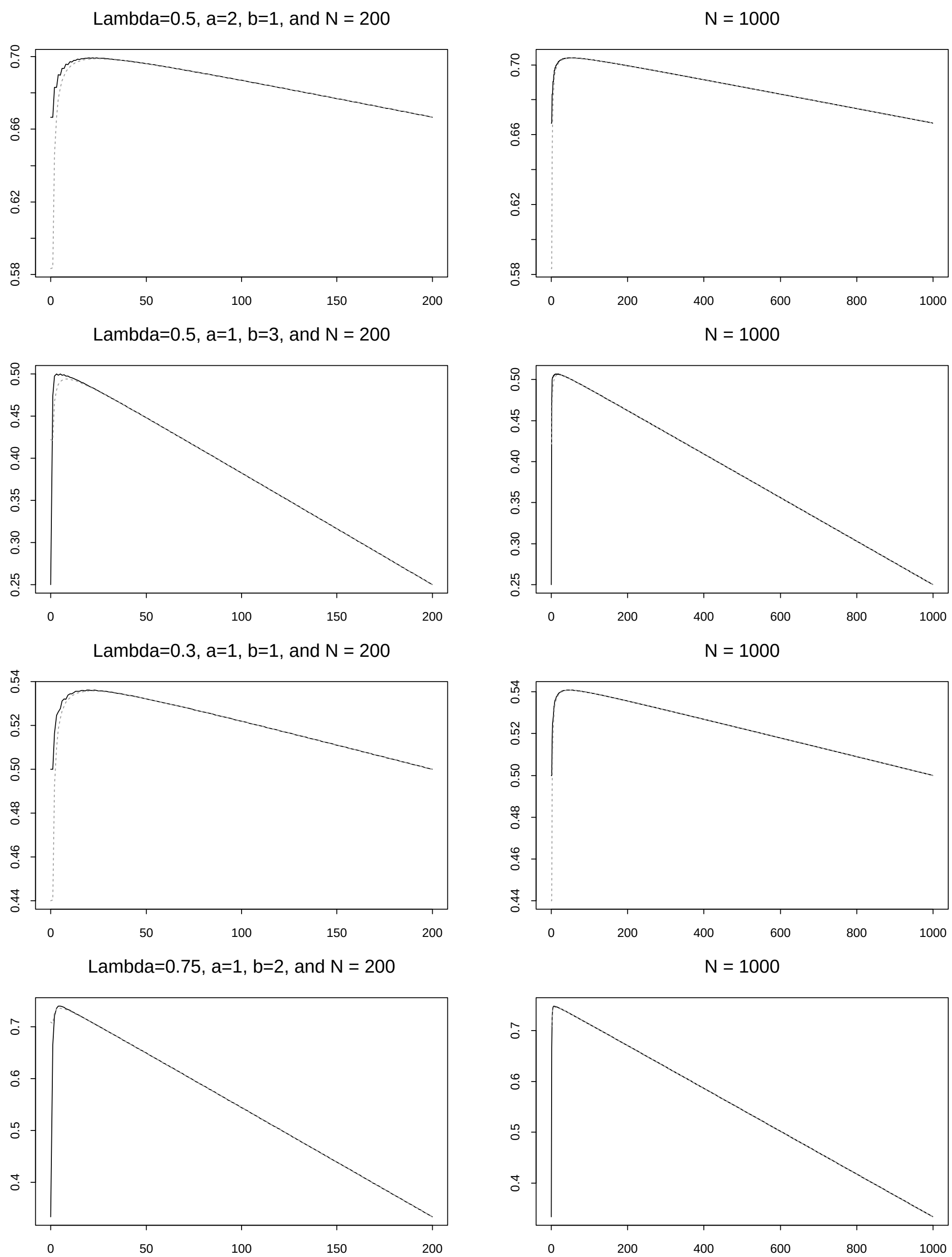


Figure 2.1: Asymptotically optimal and exactly optimal worth functions: (1) $\lambda = 0.5, Beta(2,1)$; (2) $\lambda = 0.5, Beta(1,3)$; (3) $\lambda = 0.3, Beta(1,1)$; (4) $\lambda = 0.75, Beta(1,2)$ for $N = 200$, and $N = 1000$. Solid lines stand for $W(n)/N$, and dotted lines for asymptotic worth $\hat{W}(n)/N$. When $N = 1000$, the two are nearly indistinguishable.

# Chapter 3

# Limit theorems for deviation probabilities

It is a natural step to generalize the results in previous chapter to a wider class of distributions of responses and of priors. The crucial part in deriving the asymptotic sample size in Chapter 2 is Lemma 2.10, that is, the approximation to the expression

$$\int_A \int_B f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho, \tag{3.1}$$

for a pair of disjoint sets $A$ and $B$, where $f(\bar{x}_n|\rho)$ is the distribution function of sample mean $\bar{X}_n = (X_1 + \cdots + X_n)/n$ with distribution mean $\rho$ as parameter. We call it a *deviation probability*. In this chapter, I aim to evaluate this probability when the response distribution is from an exponential family.

The deviation probability expressed in (3.1) is an extension of classical large deviations to a Bayesian setting. The classical large deviation probabilities can be viewed as taking a one-point distribution as a prior in (3.1).

I first introduce exponential families in Section 3.1. In Section 3.2, I give the definition of large deviation rate functions and its properties. In Section 3.3, a technique called exponential centering is introduced, which reduces a large deviation probability to an application of the central limit theorem. Finally, I present some new limit theorems for deviation probabilities. These results play an important role in deriving optimal sample sizes in two-armed clinical trials and in other problems as well.

## 3.1 Exponential families

The following definitions and properties of an exponential family are well known; I list them here for completeness. See, for example, Brown (1986) for further details and references. The proofs for all propositions listed below can be found there.

Let $\mu$ be a $\sigma$-finite measure on the Borel subsets of $R^k$, and $\theta \cdot x$ the inner product of $\theta \in R^k$ and $x \in R^k$. Define $\mathcal{N}$, a subset of $R^k$, as

$$\mathcal{N} = \mathcal{N}_\mu = \{\theta : \int e^{\theta \cdot x} \mu(dx) < \infty\}.$$

A *cumulant generating function* $\psi(\theta)$, where $\theta \in \mathcal{N}$, is defined as

$$\psi(\theta) = \log\left(\int e^{\theta \cdot x} \mu(dx)\right). \tag{3.2}$$

Given $\Theta \subset \mathcal{N}$, let

$$f(x|\theta) = e^{\theta \cdot x - \psi(\theta)}, \qquad \theta \in \Theta, \tag{3.3}$$

then $\{f(x|\theta) : \theta \in \Theta\}$ is called a $k$-dimensional *standard exponential family* (of probability densities) with parameter space $\Theta$. The associated family of distribution functions $\{F(x|\theta)\}$ is also referred to as the standard exponential family (of probability distributions), where

$$F(x|\theta) = \int_{(-\infty, x)} f(x|\theta) \mu(dx).$$

$\mathcal{N}$ is called the *natural parameter space*. The family is called *full* if $\Theta = \mathcal{N}$. It is called *regular* if $\mathcal{N}$ is open. And $\theta$ is called a *canonical parameter* and $x$ is called a *canonical observation*.

**Proposition 3.1** (Convexity property) *Let $\mathcal{N}$ be the natural parameter space of an exponential family and $\psi$ the cumulant generating function. Then $\mathcal{N}$ is a convex set and $\psi$ is convex on $\mathcal{N}$.*

Let $\nabla$ and $\nabla^2$ denote gradient and Hessian, respectively. That is,

$$\begin{aligned}\nabla &= \left(\frac{\partial}{\partial\theta_i}\right)_{k\times 1} = \left(\frac{\partial}{\partial\theta_1}, \ldots, \frac{\partial}{\partial\theta_k}\right)' \\ \nabla^2 &= \left(\frac{\partial^2}{\partial\theta_i\partial\theta_j}\right)_{k\times k}.\end{aligned}$$

The following proposition ascertains the differentiability of a cumulant generating function $\psi$ on the interior region of $\mathcal{N}$.

**Proposition 3.2** *Let $\mathcal{N}^\circ$ denote the interior of $\mathcal{N}$. For $\theta_0 \in \mathcal{N}^\circ$, all derivatives of $\psi(\theta)$ exist at $\theta_0$, and in particular,*

$$\nabla\psi(\theta) = E_\theta(X) \quad \textit{and} \quad \nabla^2\psi(\theta) = \mathrm{Cov}_\theta(X).$$

Let supp$(\mu)$ denote the *support* of $\mu$, a minimal closed set $S \subset R^k$ for which $\mu(S^c) = 0$, where $S^c$ denotes the complement of $S$. Let $H = \mathrm{conhull}(\mathrm{supp}(\mu))$ be the convex hull of the support. The *convex hull* of a set $S \subset R^k$ is the set

$$\{\textstyle\sum \alpha_i x_i\colon\ x_i \in S, \sum \alpha_i = 1, \alpha_i > 0\}.$$

Define $\mathcal{K} = \bar{H}$, the closure of $H$, then $\mathcal{K}$ is called the convex support of $\mu$. A $k$-dimensional standard family is called *minimal* if $\dim \mathcal{N} = \dim \mathcal{K} = k$. Clearly, any exponential family with only one parameter is minimal.

Any $k$-dimensional exponential family can be reduced by sufficiency, reparameterization, and proper choice of $\mu$ to an $m$-dimensional minimal standard exponential family, for some $m \leq k$. (See Brown, 1986, Theorem 1.9.)

**Proposition 3.3** *If an exponential family is minimal, then $\psi$ is strictly convex on $\mathcal{N}$. Consequently, $\nabla\psi$ is strictly increasing.*

For $\theta \in \mathcal{N}$, define a mapping, or a reparameterization $\rho(\theta) = E(X|\theta)$, then $\rho$ is one-to-one. The following proposition asserts that if the exponential family is also steep then this mapping is onto. A standard exponential family is called *steep* if

$$(\theta_1 - \theta_0) \cdot \nabla\psi(\theta_0 + r(\theta_1 - \theta_0)) \to \infty$$

for $r \to 1^-$ whenever $\theta_1 \in \mathcal{N} - \mathcal{N}^\circ$ and $\theta_0 \in \mathcal{N}^\circ$.

**Proposition 3.4** *For a minimal steep standard exponential family, $\rho(\theta) = E(X|\theta)$ defines a homomorphism of $\mathcal{N}^\circ$ and $\mathcal{K}^\circ$.*

$$\mathcal{N}^\circ \quad \underset{\theta}{\overset{\rho}{\rightleftarrows}} \quad \mathcal{K}^\circ.$$

Let $\theta$ denote the inverse mapping of $\rho$. In this dissertation, either $\theta$ or $\rho$ may be used as a parameter in the presentation of theorems and proofs. Given a point $x \in \mathcal{K}$, $\theta_x$ stands for a point in $\mathcal{N}$ such that $\rho(\theta_x) = x$; and for point $y \in \mathcal{N}$, $\rho_y = E(X|\theta = y) \in \mathcal{K}$.

**Definition:** A prior distribution of $\theta$ on $\Theta$ is called a conjugate prior if it has form

$$\pi(\theta) \propto e^{\theta\gamma - \kappa\psi(\theta)}, \tag{3.4}$$

where $\gamma$ and $\kappa > 0$ are constants.

## 3.2 Large deviation rate functions

Let $X_1, X_2, \ldots$ be iid random variables, and $\bar{X}_n = (X_1 + \cdots + X_n)/n$. To evaluate the deviation probability defined in (3.1), we first need to evaluate the inner integral,

$$P(\bar{X}_n \in B|\rho) = \int_B f(\bar{x}_n|\rho)d\bar{x}_n, \tag{3.5}$$

where $\rho = E(X_1|\rho) \notin B$. Expression (3.5) is called a large deviation probability. It tends to 0 exponentially as $n \to \infty$. The convergence rate depends on the distance between $\rho$ and $B$, which is characterized as a large deviation rate function. Formally, *the large deviation rate function* is defined as

$$r(\Lambda, \rho) \equiv \lim_{n\to\infty} n^{-1} \log P(\bar{X}_n \in \Lambda|\rho), \tag{3.6}$$

for $\Lambda \subset \mathcal{K}$ and $\rho \in \mathcal{K}$. For two points $\nu, \rho \in \mathcal{K}$, the large deviation rate function is defined by

$$r(\nu, \rho) = \inf_{\Lambda}\{r(\Lambda, \rho) : \nu \in \Lambda, \Lambda \text{ is open convex}\}. \tag{3.7}$$

The large deviation rate function can be calculated using moment generating functions. If $X_1$ is a real valued random variable, $B = (b, +\infty)$ and $\rho = E(X_1) < b$, it follows that $r(B, \rho) = r(b, \rho) = \inf_{t\geq 0}\{-bt + E(e^{tX_1})\}$ – see Chernoff (1952). In general, if $X_1$ is from an exponential family, then the following equation holds,

$$r(\nu, \rho) = \inf_{t}\{-t \cdot \nu + \log E(e^{t \cdot X_1})\}. \tag{3.8}$$

If $\Lambda$ is an open convex set, then

$$r(\Lambda, \rho) = \sup_{\nu}\{r(\nu, \rho) : \nu \in \Lambda\}. \tag{3.9}$$

These results are due to Bahadur and Zabell (1979), who also gave large deviation properties in much more general spaces than $R^k$.

For exponential families, the large deviation rate functions can be explicitly given via the Kullback-Leibler information measure. Given densities $f(x|\theta_0)$ and $f(x|\theta)$, the Kullback-Leibler information measure in terms of canonical parameters is defined as

$$D(\theta_0||\theta) = \int_{R^k} \log \frac{f(x|\theta_0)}{f(x|\theta)} f(x|\theta_0)\mu(dx).$$

For later convenience, we also define Kullback-Leibler distance in terms of distribution means as

$$D_1(\rho_0||\rho) = D_1(\nabla\psi(\theta_0)||\nabla\psi(\theta)) = D(\theta_0||\theta).$$

Let $\psi$ be the cumulant generating function of an exponential family, then the K-L information measure can be written as

$$D(\theta_0||\theta) = (\theta_0 - \theta) \cdot \nabla\psi(\theta_0) - \psi(\theta_0) + \psi(\theta). \tag{3.10}$$

Notice that $\log E_\theta(e^{t \cdot X_1}) = \psi(t+\theta) - \psi(\theta)$. Differentiating the inner part of braces on the right-hand side of (3.8) with respect to $t$, we obtain $\nu - \nabla\psi(t+\theta) = 0$. By the monotonicity of $\nabla\psi(\cdot)$, we have $\theta_v = t + \theta$. The maximum is attained at $\tau = \theta_\nu - \theta$, and

$$\begin{aligned} r(\nu, \rho) &= -\tau \cdot \nu + \psi(\tau + \theta) - \psi(\theta) \\ &= -(\theta_\nu - \theta) \cdot \nabla\psi(\theta_\nu) + \psi(\theta_\nu) - \psi(\theta) \\ &= -D(\theta_\nu||\theta) = -D_1(\nu||\rho). \end{aligned} \tag{3.11}$$

That is, for exponential families, the large deviation rate functions are equal to the negative of Kullback-Leibler information measure.

We now give some properties of $D(\cdot||\cdot)$ that will be used in later chapters. Expanding $\psi(\theta)$ in (3.10) gives that, as $\theta \to \theta_0$,

$$\begin{aligned} D(\theta_0||\theta) &= \frac{1}{2}(\theta-\theta_0)'\nabla^2\psi(\theta_0)(\theta-\theta_0) + o(||\theta-\theta_0||^3) \\ &\sim \frac{1}{2}(\theta-\theta_0)'\nabla^2\psi(\theta_0)(\theta-\theta_0), \qquad (3.12) \\ D_1(\rho_0||\rho) &\sim \frac{1}{2}(\rho-\rho_0)(\nabla^2\psi(\theta_0))^{-1}(\rho-\rho_0). \qquad (3.13) \end{aligned}$$

Differentiating both sides of (3.10) with respect to $\theta$ and $\theta_0$, we have the following convexity theorem.

**Theorem 3.5** (Convexity of $D(\cdot||\cdot)$) *Assume $\theta_0$, $\theta \in \mathcal{N}^\circ$. $D(\theta_0||\theta)$, as a function of $\theta$, is convex, and attains its minimum of 0 at $\theta_0$. $D(\theta_0||\theta)$, as a function of $\theta_0$, is decreasing on $(-\infty, \theta)$ and increasing on $(\theta, \infty)$; also it is convex in a neighborhood of $\theta$ and attains its minimum of 0 at $\theta$.*

*Those properties also hold for $D_1(\cdot||\cdot)$ with corresponding parameterization.*

**Theorem 3.6** *Suppose $X = x$ is observed from a minimal steep exponential family, and define $\theta_x = (\nabla\psi)^{-1}(x)$, then*

$$f(x|\theta) \propto e^{-D(\theta_x||\theta)}.$$

**Proof:** Note that $\theta_x = \rho^{-1}(x)$ is equivalent to $\rho(\theta_x) = x$, thus we obtain

$$\begin{aligned} f(x|\theta) &= \exp\{\theta \cdot x - \psi(\theta)\} \\ &= \exp\{\theta \cdot x - \psi(\theta) - \theta_x \cdot x + \psi(\theta_x)\} f(x|\theta_x) \\ &= \exp\{-D(\theta_x||\theta)\} f(x|\theta_x) \\ &\propto \exp\{-D(\theta_x||\theta)\}. \qquad \square \end{aligned}$$

By the convexity of $D(\cdot||\cdot)$, $\theta_x$ is the maximum likelihood estimator of $\theta$.

## 3.3 Exponential centering

The central limit theorem cannot be directly applied in evaluating the large deviation probability expressed in (3.5). This can be seen from the following example.

**Example 3:** $X_1, X_2, \cdots$ are iid from a Bernoulli distribution with success rate $a$. Consider the probability $P(\bar{X}_n > b)$ where $b > a$. Applying the CLT to this probability gives

$$P_a(\bar{X}_n > b) = P_a\left(\frac{\sqrt{n}(\bar{X}_n - a)}{\sqrt{a(1-a)}} > \frac{\sqrt{n}(b-a)}{\sqrt{a(1-a)}}\right) \sim 1 - \Phi\left(\frac{\sqrt{n}(b-a)}{\sqrt{a(1-a)}}\right)$$
$$\sim \frac{\sqrt{a(1-a)}}{\sqrt{2\pi n}(b-a)} e^{-n\frac{(b-a)^2}{a(1-a)}}.$$

The last equality holds due to (2.11). However, by Lemma 2.8, we have the following

$$P_a(\bar{X}_n > b) = \sum_{k \geq nb}^{n} \binom{n}{k} a^k (1-a)^{n-s} \sim \frac{(1-a)b}{\sqrt{2\pi n}\sqrt{b(1-b)}(b-a)} e^{-nD_1(b||a)},$$

where $D_1(b||a) = b \log \frac{b}{a} + (1-b)\log\frac{1-b}{1-a}$ is the Kullback-Leibler information measure. Since $D_1(b||a) \neq \frac{(b-a)^2}{a(1-a)}$, the two results are different by an exponential factor. □

The reason for not being able to apply the central limit theorem is that $E(X_1|\rho = a) < b$. The following technique of exponential centering remedies this situation. See Bahadur and Rao (1960).

For a convex set $B$ and $\rho \notin B$, there exists a $\nu \in \bar{B}$ such that $D_1(B,\rho) = D_1(\nu,\rho)$ for some $\nu \in \bar{B}$. Let $Y = X - \nu$ and $M_Y(t) = E(e^{Y\cdot t})$ be its moment generating function, then (3.8) becomes

$$e^{D_1(\nu||\rho)} = e^{D_1(\nu||\rho)} = \inf_t M_Y(t) = M_Y(\tau),$$

where $\tau = \theta_\nu - \theta$, and $\theta = \theta_\rho$ is natural parameter. Let $F$ denote the distribution function of $Y$. Define $G$ through the following equation,

$$G(dx) = e^{-r(\nu,\rho)} e^{\tau\cdot x} F(dx). \tag{3.14}$$

Since $\int G(dx) = e^{-D_1(\nu||\rho)} \int e^{\tau\cdot x} F(dx) = e^{-D_1(\nu||\rho)} M_Y(\tau) = 1$, $G$ is a distribution function. We refer to $G$ as a distribution obtained from $X$ by *exponential centering at* $\nu$.

Let $Z$ be a random variable with distribution $G$. Since $\log M_Y(t) = \psi(t+\theta) - \psi(\theta) - t\cdot\nu$, the moment generating function of $Z$ can be written as

$$\begin{aligned} M_Z(t) &= e^{-D_1(\nu||\rho)} \int e^{(t+\tau)\cdot x} F(dx) = e^{-D(\theta_\nu||\theta)} M_Y(t+\tau) \\ &= M_Y(t+\tau)/M_Y(\tau) = e^{\psi(t+\theta_\nu) - \psi(\theta_\nu) - t\nu}, \end{aligned}$$

which is independent of parameter $\rho$. The mean and covariance of the distribution $G$ can be calculated as,

$$E(Z) = \nabla \log M_Z(t)|_{t=0} = 0,$$

$$\mathrm{Cov}(Z) = \nabla^2 \log M_Y(\tau) = \nabla^2 \psi(\theta_\nu).$$

Let $B - \nu$ denote the set $\{x - \nu, \quad x \in B\}$, then

$$\int_B f(x|\rho)dx = \int_{B-\nu} f(y|\rho)F(dy) = e^{D_1(\nu||\rho)} \int_{B-\nu} e^{-\tau\cdot z} G(dz). \tag{3.15}$$

Using this result, we have the following lemma.

**Lemma 3.7** *Let $G$ be the distribution obtained from $X$ by exponential centering at $\nu$, and $Z_1, Z_2, \cdots$ be iid random variables with distribution $G$. Denote $\bar{Z}_n = (Z_1 + \cdots + Z_n)/n$ and $H_n(x) = P(\sqrt{n}\bar{Z}_n < x)$, then*

$$P_\rho(\bar{X}_n \in B) = e^{-nD_1(\nu||\rho)} \int_{x \in \sqrt{n}(B-\nu)} e^{-\sqrt{n}\tau \cdot x} H_n(dx), \tag{3.16}$$

*where $\tau = \theta_\nu - \theta$.*

**Proof:** By (3.15), we have

$$\begin{aligned} P_\theta(\bar{X}_n \in B) &= \int \cdots \int_{\bar{x}_n \in B} f(x_1, ... x_n|\theta) dx = \int \cdots \int_{\bar{y}_n \in B-\nu} F(dy_1) \cdots F(dy_n) \\ &= e^{-nD_1(\nu||\rho)} \int \cdots \int_{\bar{z}_n \in B-\nu} e^{-\tau \cdot (z_1 + \cdots + z_n)} G(dz_1) \cdots G(dz_n) \\ &= e^{-nD_1(\nu||\rho)} \int_{x \in \sqrt{n}(B-\nu)} e^{-\sqrt{n}\tau \cdot x} H_n(dx). \qquad \square \end{aligned}$$

If $B = (b, +\infty) \subset R$ and $\rho < b$, then $D_1(B||\rho) = D_1(b||\rho)$. Using integration by parts on (3.16) gives

$$\begin{aligned} P_\rho(\bar{X} > b) &= e^{-nD_1(b||\rho)} \int_0^\infty e^{-\sqrt{n}\tau x} H_n(dx) \\ &= e^{-nD_1(b||\rho)} \sqrt{n}\tau \int_0^\infty e^{-\sqrt{n}\tau x} (H_n(x) - H_n(0)) dx, \end{aligned} \tag{3.17}$$

where $\tau = \theta_b - \theta$. This probability can be approximated by using the Berry-Esseen theorem or any other normal expansion methods.

## 3.4 Limit theorems on deviation probabilities

In this section, we use the Berry-Esseen theorem to establish a one-dimensional limit theorem on deviation probabilities, and use the results in Bhattacharya and Rao (1976) for the multi-dimensional case.

A random variable $X$ is called having a lattice type distribution if there exist $x_0, d \in R$ such that $X$ is confined to the set $\{x_0 + rd\colon r \in \mathcal{Z}\}$, where $\mathcal{Z} = \{0, \pm 1, \pm 2, \cdots\}$.

**Theorem 3.8** (Berry-Esseen) *Suppose that $X_1, X_2, \ldots$ are iid random variables with mean zero. Let $\sigma^2 \triangleq Var(X_1)$ and $\alpha_3 \triangleq E|X_1|^3$. Denote $H_n(x) = P(\sqrt{n}\bar{X}_n \leq x)$ and $\Phi(x;\sigma^2)$ the normal distribution function with mean zero and variance $\sigma^2$, then*

$$\sup_x |H_n(x) - \Phi(x;\sigma^2)| \leq \frac{C_0 \alpha_3}{\sqrt{n}\sigma^3}, \tag{3.18}$$

*where $C_0$ is a universal constant.*

*Further, if $X_1$ is not a lattice variable, then*

$$H_n(x) = \Phi(x) + n^{-1/2} f(x) + n^{-1/2} r_n(x), \tag{3.19}$$

*where $f(x) = (\text{const.})(1 - \frac{x^2}{\sigma^2})e^{-\frac{1}{2\sigma^2}x^2}$, and $r_n(x) \to 0$ uniformly in $x$ as $n \to \infty$. (Esseen 1945, p. 47).*

**Theorem 3.9** *Let the prior have the form $\pi(\rho) \sim \pi_0(a-\rho)^u$ as $\rho \to a$, and $\sigma^2 = \psi''(\theta_a)$ be the variance at $a$, then*

$$\int_{-\infty}^{a} \int_{a}^{\infty} f(\bar{x}_n|\rho)\pi(\rho) d\bar{x}_n d\rho \sim \frac{\pi_0 J(u+1)\sigma^{u+1}}{\sqrt{2\pi}(u+1)} n^{-\frac{u+1}{2}}.$$

**Remark:**

$\pi(\rho)$ does not have to be a distribution function. It can be any positive function as long as $\pi(\rho) \sim f_u(a-\rho)$ when $\rho \to a$, and the integral exists.

**Proof:** Denoting $\tau = \theta_a - \theta$, by (3.17) and the Berry-Esseen theorem, it follows that

$$\begin{aligned}
\int_{-\infty}^{a}\int_{a}^{\infty} &= \int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(a||\rho)-\sqrt{n}\tau x}\pi(\rho)\Phi(dx;\sigma^2)d\rho + e_n \\
&\overset{t=a-\rho}{=\!=\!=} \pi_0\int_{0}^{\infty}\int_{0}^{\infty} e^{-nD_1(a||a-t)-\sqrt{n}(\theta_a-\theta_{a-t})x}\phi(x;\sigma^2)t^u dxdt + e_n \\
&\overset{x\to x/\sqrt{n}}{=\!=\!=} \frac{\pi_0\sqrt{n}}{\sqrt{2\pi}\sigma}\int_{0}^{\infty}\int_{0}^{\infty} e^{-n(D_1(a||a-t)+(\theta_a-\theta_{a-t})x+\frac{1}{2\sigma^2}x^2)}t^u dxdt + e_n,
\end{aligned}$$

where

$$\begin{aligned}
e_n &\leq \frac{C_0\alpha_3}{\sqrt{n}\sigma^3}\int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(a||\rho)-\sqrt{n}\tau x}\sqrt{n}\tau\pi(\rho)dxd\rho \\
&\leq \frac{C_0\alpha_3}{\sqrt{n}\sigma^3}\int_{-\infty}^{a} e^{-nD_1(a||\rho)}\pi(\rho)d\rho \\
&\overset{t=a-\rho}{=\!=\!=} \frac{C_0'}{\sqrt{n}}\int_{0}^{\infty} e^{-nD_1(a||a-t)}t^u dt = o\left(n^{-\frac{u+1}{2}}\right).
\end{aligned}$$

Using the fact that $(\theta_a - \theta_{a-t}) \sim \sigma^{-2}t$ as $t \to 0$ and Lemma 2.5, we have

$$\begin{aligned}
\int_{-\infty}^{a}\int_{a}^{\infty} f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho &\sim \frac{\pi_0 n^{-\frac{u+1}{2}}}{\sqrt{2\pi}\sigma}\int_{0}^{\infty}\int_{0}^{\infty} e^{-\frac{1}{2\sigma^2}(x+t)^2}t^u dxdt \\
&= \frac{\pi_0 n^{-\frac{u+1}{2}}}{\sqrt{2\pi}\sigma}\int_{0}^{\infty} t^u\int_{t}^{\infty} e^{-\frac{1}{2\sigma^2}y^2}dydt \\
&= \frac{\pi_0 n^{-\frac{u+1}{2}}}{\sqrt{2\pi}\sigma}\int_{0}^{\infty}\frac{1}{u+1}t^{u+1}e^{-\frac{1}{2\sigma^2}t^2}dt.
\end{aligned}$$

Transforming $t/\sigma$ into $t$ and using the definition of $J(\cdot)$, the result follows. □

**Theorem 3.10** *Let the prior have the form* $\pi(\rho) \sim \pi_0(a-\rho)^u$ *as* $\rho \to a$, *and* $\sigma^2 = \psi''(\theta_b)$ *be the variance at* $b$. *Let* $a < b$, *then*

*(1) If $X_1$ is not a lattice variable,*

$$\int_{-\infty}^{a}\int_{b}^{\infty} f(\bar{x}|\rho)\pi(\rho)d\bar{x}d\rho \sim \frac{\pi_0\Gamma(u+1)}{\sqrt{2\pi n}\sigma(\theta_b-\theta_a)}\left(\frac{(b-a)n}{\sigma^2}\right)^{-(u+1)} e^{-nD_1(b||a)};$$

*(2) Otherwise, for any given $\epsilon > 0$,*

$$e^{-n(D_1(b||a)+\epsilon)} < \int_{-\infty}^{a}\int_{b}^{\infty} f(\bar{x}|\rho)\pi(\rho)d\bar{x}d\rho \leq e^{-nD_1(b||a)}.$$

**Proof:** (1) By (3.17) and applying (3.19), it follows that

$$\int_{-\infty}^{a}\int_{b}^{\infty} = \int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}(\theta_b-\theta)x}\pi(\rho)d\Phi(x;\sigma^2)d\rho + e_n'$$

where, by (3.19),

$$e_n' = \int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}\tau x}\sqrt{n}\tau n^{-1/2}(f(x)-f(0)+o(1))\pi(\rho)dxd\rho.$$

Denote $e(a,b) = D_1(b||a-t) + (\theta_b - \theta_{a-t})x + \frac{1}{2\sigma^2}x^2$, then

$$e(a,b) - D_1(b||a) \sim (\theta_b-\theta_a)x + \sigma^{-2}(b-a)t,$$

as $(x,t)' \to 0$. The contribution of $n^{-1/2}f(x)$ to $e_n'$ is

$$\begin{aligned} & n^{-1/2}\int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}\tau x} f'(x)\pi(\rho)dxd\rho \\ = \; & C'n^{-1/2}\int_{-\infty}^{a}\int_{0}^{\infty} e^{-n(D_1(b||a-t)+(\theta_b-\theta_{a-t})y+\frac{1}{2\sigma^2}y^2)}\left(n^{\frac{1}{2}}\frac{3y}{\sigma^2} - n^{\frac{3}{2}}\frac{y^3}{\sigma^4}\right)t^u dydt \\ = \; & e^{-nD_1(b||a)}O(n^{-(u+3)}). \end{aligned}$$

We have used transformations $t = a-\rho$, $y = x/\sqrt{n}$ and Lemma 2.5. It follows that

$$\int_{-\infty}^{a}\int_{0}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}\tau x}\sqrt{n}\tau \cdot o(n^{-1/2})\pi(\rho)dxd\rho$$

$$= o(n^{-1/2}) \int_{-\infty}^{a} e^{-nD_1(b||\rho)} \pi(\rho) d\rho = e^{-nD_1(b||a)} o(n^{-u-\frac{3}{2}}).$$

Therefore, $e_n' = e^{-nD_1(b||a)} o(n^{-u-\frac{3}{2}})$, and

$$\begin{aligned}
\int_{-\infty}^{a} \int_{b}^{\infty} &\sim \int_{-\infty}^{a} \int_{0}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}(\theta_b-\theta)x} \pi(\rho) d\Phi(x;\sigma^2) d\rho \\
&\sim e^{-nD_1(b||a)} \frac{\pi_0 \sqrt{n} n^{-(u+2)}}{\sqrt{2\pi}\sigma} \int_0^\infty e^{-(b-a)\sigma^{-2}t} t^u dt \int_0^\infty e^{-(\theta_b-\theta_a)x} dx \\
&= e^{-nD_1(b||a)} \frac{\pi_0 \Gamma(u+1) n^{-(u+1)}}{\sqrt{2\pi n}(\theta_b-\theta_a)\sigma} \left(\frac{\sigma^2}{b-a}\right)^{u+1}.
\end{aligned}$$

(2) Since $\int_0^\infty e^{-\sqrt{n}\tau x} H_n(dx) \leq 1$, by (3.17), it follows that

$$\int_{-\infty}^{a} \int_{b}^{\infty} f(\bar{x}|\rho) \pi(\rho) d\bar{x} d\rho \leq \int_{-\infty}^{a} e^{-nD_1(b||\rho)} \pi(\rho) d\rho \leq e^{-nD_1(b||a)}.$$

The last equality holds due to the convexity property of $D(\cdot||\cdot)$.

For any given $\epsilon > 0$, by the central limit theorem, $\lim_n (H_n(\epsilon) - H_n(0)) = \int_0^\epsilon \phi(x;\sigma^2) dx > 0$. Applying (3.17), we have

$$\begin{aligned}
\int_{-\infty}^{a} \int_{b}^{\infty} &\geq \int_{-\infty}^{a} \int_{\epsilon}^{\infty} e^{-nD_1(b||\rho)-\sqrt{n}\tau x} \sqrt{n}\tau (H_n(\epsilon) - H_n(0)) \pi(\rho) dx d\rho \\
&\sim c(\epsilon) \int_{a-\delta}^{a} e^{-nD_1(b||\rho)-\sqrt{n}\tau\epsilon} \pi(\rho) d\rho \geq e^{-n\epsilon/2} \int_{a-\delta}^{a} e^{-nD_1(b||\rho)} \pi(\rho) d\rho \\
&\sim e^{-n(D_1(b||a)+\epsilon/2)} \cdot O(n^{-(u+1)}) \geq e^{-n(D_1(b||a)+\epsilon)},
\end{aligned}$$

where $\delta$ is a positive number. □

**Theorem 3.11** *Let $\epsilon_n = o(n^{-1/2})$. Under the same condition of Theorem 3.9, the following holds:*

$$\int_{-\infty}^{a} \int_{a-\epsilon_n}^{a+\epsilon_n} f(\bar{x}|\rho) \pi(\rho) d\bar{x} d\rho = o(n^{-\frac{u+1}{2}}). \tag{3.20}$$

**Proof:** Partition the integral into two parts as

$$I = \int_{-\infty}^{a-\epsilon_n} \int_{a-\epsilon_n}^{a+\epsilon_n} + \int_{a-\epsilon_n}^{a} \int_{a-\epsilon_n}^{a+\epsilon_n} = I_1 + I_2.$$

Since $\pi(\rho) < (1+\delta)\pi_0(a-\rho)^u$ for some $\delta > 0$ when $(a-\rho)$ is sufficiently small, we have, for large $n$, that

$$I_2 \leq \int_{a-\epsilon_n}^{a} \pi(\rho) d\rho \leq O(\epsilon_n^{-(u+1)}) = o(n^{-\frac{u+1}{2}}).$$

For any given $\epsilon$, letting $\sigma_{a-\epsilon}^2 = \psi''(\theta_{a-\epsilon})$ and following the same procedure of the proof in Theorem 3.9, we have

$$\begin{aligned} I_1 &= \pi_0 \int_{-\infty}^{a-\epsilon} \int_0^{2\sqrt{n}\epsilon} e^{-nD(a-\epsilon||\rho)-\sqrt{n}(\theta_{a-\epsilon}-\theta)x}(a-\rho)^u dH_n(x) d\rho \\ &= \int_0^{\infty} \int_0^{2\sqrt{n}\epsilon} e^{-nD_1(a-\epsilon||a-\epsilon-t)-\sqrt{n}(\theta_{a-\epsilon}-\theta_{a-\epsilon-t})x}(t+\epsilon)^u \phi(x; \sigma_{a-\epsilon}^2) dx dt + e_n', \end{aligned}$$

where

$$\begin{aligned} e_n' &\leq \frac{C_0\alpha_3}{\sqrt{n}\sigma^3} \int_{-\infty}^{a-\epsilon} \int_0^{2\sqrt{n}\epsilon} e^{-nD(a-\epsilon||\rho)-\sqrt{n}\tau x} \sqrt{n}\tau(t+\epsilon)^u dx d\rho \\ &\leq \frac{C_0\alpha_3}{\sqrt{n}\sigma^3} \int_0^{\infty} e^{-nD(a-\epsilon||a-\epsilon-t)}(t+\epsilon)^u dt = O(n^{-\frac{u+2}{2}}). \end{aligned}$$

We have used Lemma 2.6 in the last equality. By Lemma 2.7, $I_1 = o(n^{-\frac{u+1}{2}})$ and (3.20) follows. □

If, for some integer $n_0 \geq 1$, $\bar{X}_{n_0}$ has a bounded continuous density with respect to Lebesgue measure on $R^k$, we can have a multi-dimensional version of Theorem 3.9 and 3.10 using the following lemma.

**Lemma 3.12** (Bhattacharya & Rao, 1976, Theorem 19.2) *Let $h_n(x)$ be the density function of $n^{-1/2}(X_1 + \cdots + X_n)$, having mean 0 and covariance $\Sigma$, then*

$$h_n(x) = \frac{1}{(2\pi)^{k/2}|\Sigma|^{1/2}} e^{-\frac{1}{2}x'\Sigma^{-1}x} + o(n^{-1/2}) \tag{3.21}$$

*holds uniformly in $x$.*

Given $a, b \in R^k$, denote $S_a = \{x : \ x < a\}$, and $S^b = \{x : \ x > b\}$. For $a \leq b$, we now consider the deviation probability

$$\int_{S_a} \int_{S^b} f(\bar{x}_n|\rho)\pi(\rho) d\bar{x}_n d\rho. \tag{3.22}$$

Assume that the prior distribution $\pi(\rho)$ has the form

$$\pi(\rho) \sim f_u(a-\rho) \qquad \text{as } (a-\rho) \to 0, \tag{3.23}$$

on $S_a$, where $f_r(\cdot)$ is a homogeneous polynomial of order $r$.

**Theorem 3.13** (Multi-dimensional case) *Suppose that $f(x|\rho)$ is bounded and continuous, and from a minimal exponential family. If $a$ and $b$ are interior points of $\mathcal{N}$, and $\Sigma$ is the covariance matrix at $a$, then we have*
*(1) if $a = b$,*

$$\int_{S_a}\int_{S^b} f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho \sim \frac{|\Sigma|^{1/2} n^{-\frac{k+u}{2}}}{(2\pi)^{k/2}} \int_{S^0}\int_{S^0} f_u(\Sigma^{\frac{1}{2}}\rho) e^{-\frac{1}{2}(\rho+x)\cdot(\rho+x)} dx d\rho;$$

*(2) if $a < b$*

$$\int_{S_a}\int_{S^b} f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho \sim \frac{e^{-nD_1(b||a)} n^{-\frac{3}{2}k-u}}{(2\pi)^{k/2}|\Sigma|^{1/2}} \int_{S^0}\int_{S^0} f_u(\rho) e^{-(b-a)\Sigma^{-1}\rho-(\theta_b-\theta_a)\cdot x} dx d\rho.$$

**Proof:** Since $\rho \in S_a$, it implies that $\rho \leq a < b$. By the convexity property of $D(\cdot||\cdot)$ and by (3.7), $D_1(S_b||\rho) = D_1(b||\rho)$. By Lemma 3.7 and Lemma 3.12, it follows that

$$\begin{aligned}\int_{S_a} f(\bar{x}_n|\rho)d\bar{x}_n &\sim \frac{1}{(2\pi)^{k/2}|\Sigma|^{1/2}}\int_{S^0} e^{-nD(\theta_b||\theta)-\sqrt{n}\tau\cdot x-\frac{1}{2}x'\Sigma^{-1}x}dx \\ &= \frac{n^{k/2}}{(2\pi)^{k/2}|\Sigma|^{1/2}}\int_{S^0} e^{-n(D(\theta_b||\theta)+\tau\cdot x+\frac{1}{2}x'\Sigma^{-1}x)}dx,\end{aligned}$$

where $\tau = \theta_b - \theta$. Transform $\rho$ into $a-t$ to obtain

$$\int_{S_a}\int_{S^b} f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho \sim c_n\int_{S^0}\int_{S^0} e^{-n(D_1(b||a-t)+(\theta_b-\theta_{a-t})\cdot x+\frac{1}{2}x'\Sigma^{-1}x)}f_u(t)dxd\rho$$

where $c_n = n^{k/2}/(2\pi)^{k/2}|\Sigma|^{1/2}$. The rest of the proof is similar to those of Theorems 3.9 and 3.10. □

## 3.5 Sample size determination in hypothesis testings

In Parmigiani & Berry (1993), information measure is proposed in determining the sample sizes in experimental designs. In this section I compare the information method with the classical method for sample size determination in hypothesis testings of simple vs. simple. It is found that two methods are asymptotically equivalent under some circumstances.

Let $X_1, ..., X_n$ be iid with distribution $f(x|\theta)$ of a standard exponential family. Consider hypothesis:

$$H_0 : \theta \in \Theta_0 \leftrightarrow H_1 : \theta \in \Theta_1.$$

If $L(\theta, d(\bar{x}_n))$ denotes a loss function for $\theta \in \Theta$ and an action $d(\bar{x}_n)$, then the expected loss is

$$\begin{aligned} L(\pi, d) &= \int_{\mathcal{X}} p(\bar{x}_n) \int_{\Theta} L(\theta, d(\bar{x}_n)) p(\theta|\bar{x}_n) d\theta d\bar{x}_n \\ &= \int_{\mathcal{X}} \int_{\Theta} L(\theta, d(\bar{x}_n)) p(\bar{x}_n|\theta) \pi(\theta) d\theta d\bar{x}_n, \end{aligned}$$

where $p(\bar{x}_n)$ is the marginal distribution and $p(\theta|\bar{x}_n)$ is the posterior distribution of $\theta$ given $\bar{x}_n$.

A classical testing procedure $\tau$ is a partition of sample space $\mathcal{K}$, say $\mathcal{K} = A_0 \cup A_1$, that we accept $H_0$ if $\bar{X}_n \in A_0$ and reject it if $\bar{X}_n \in A_1$. Using 0-1 loss as given in Table 3.2, the expected loss is

$$L(\pi, \tau) = \int_{\Theta_0} \int_{A_1} p(\bar{x}_n|\theta) \pi(\theta) d\bar{x}_n d\theta + \int_{\Theta_1} \int_{A_0} p(\bar{x}_n|\theta) \pi(\theta) d\bar{x}_n d\theta.$$

The two terms resemble deviation probabilities.

| | Accept $H_0$ | Accept $H_1$ |
|---|---|---|
| $\theta \in \Theta_0$ | 0 | 1 |
| $\theta \in \Theta_1$ | 1 | 0 |

Table 3.1: Classical loss function

Consider the case that $X_1$ is a real valued random number and the hypothesis is one-sided. That is, for some $a \in R$, $\Theta_0 = \{\theta < a\}$ and $\Theta_1 = \{\theta \geq a\}$. If $A_0$ and $A_1$ are taken as $\Theta_0$ and $\Theta_1$ respectively, and assuming that the prior has the form $\pi(\theta) \sim \pi_0 |\theta - a|^u$, then applying Theorem 3.9 gives that

$$L \sim \frac{2\pi_0 J(u+1)\sigma^{u+1}}{\sqrt{2\pi}(u+1)} n^{-\frac{u+1}{2}},$$

as $n \to \infty$, where $\sigma^2$ is the variance of $X_1$ at point $a$.

Suppose that there will be a cost $c_1$ (comparable to $L$) for each observation, then the optimal sample size of maximizing $c_1 n + L(n)$ is

$$n \sim \left( \frac{\pi_0 J(u+1)\sigma^{u+1}}{\sqrt{2\pi} c_1} \right)^{\frac{2}{u+3}}.$$

**Information loss function**

Let $p(\theta|\bar{x})$ be the posterior distribution. The posterior probabilities of the two hypotheses are

$$P(\Theta_i|\bar{x}) = \frac{\int_{\Theta_i} p(\bar{x}|\theta)\pi(\theta)d\theta}{\int_{\Theta_0 \cup \Theta_1} p(\bar{x}|\theta)\pi(\theta)d\theta}, \qquad i = 0, 1.$$

The information loss is defined by the following:

$$\begin{aligned} I(n) &= \textstyle\int_{\mathcal{X}} I(\theta|\bar{x}) p(\bar{x}) d\bar{x}, \\ I(\theta|\bar{x}) &= P(\Theta_0|\bar{x}) \log \tfrac{1}{P(\Theta_0|\bar{x})} + P(\Theta_1|\bar{x}) \log \tfrac{1}{P(\Theta_1|\bar{x})}. \end{aligned} \tag{3.24}$$

If the hypothesis is simple vs simple, $I(n)$ can be approximated using limit theorems. The following example shows that $I(n)$ is asymptotically equivalent to 0-1 loss, except for a constant factor.

**Example 4:** Consider a simple vs. simple hypothesis,

$$H_0 : \theta = \theta_0 \leftrightarrow H_1 : \theta = \theta_1. \tag{3.25}$$

Let $L(n)$ be the expected loss of the test based on the likelihood ratio and $I(n)$ the loss defined in (3.24). We are going to show that if $X_1$ is not a lattice variable and the prior probabilities on $\theta_0$ and $\theta_1$ are equal, then

$$\frac{I(n)}{L(n)} \sim 1 + \log 2 + \frac{\Delta}{\tau} + \frac{\tau}{\Delta - \tau}(1 - \log 2) - \frac{\Delta}{\Delta - \tau} \int_0^1 \frac{x^{\frac{\tau}{\Delta}}}{1+x} dx, \tag{3.26}$$

where $\Delta = \theta_1 - \theta_0$, $\eta = \frac{\psi(\theta_1)-\psi(\theta_0)}{\theta_1-\theta_0}$ and $\tau = \theta_\eta - \theta_0$.

The likelihood ratio is

$$\mathcal{L} = \frac{p(\bar{x}_n|\theta_1)\pi_1}{p(\bar{x}_n|\theta_0)\pi_0} = e^{n\Delta(\bar{x}_n-\eta)}.$$

Consider testing procedures based on $\mathcal{L}$: $A_0 = \{\mathcal{L} \leq 1\} = \{\bar{X}_n \leq \eta\}$ and $A_1 = \{\mathcal{L} > 1\}$. Then $L(n) = \pi_0\alpha_n + \pi_1\beta_n$, where $\alpha_n$ and $\beta_n$ are type I and type II errors. By (3.17) and (3.19),

$$\alpha_n = \int_\eta^\infty p(\bar{x}_n|\theta_0)d\bar{x}_n = e^{-nD(\theta_\eta||\theta_0)} \int_0^\infty e^{-n\tau x}\frac{\sqrt{n}}{\sqrt{2\pi}\sigma}e^{-\frac{n}{2\sigma^2}x^2}dx + e_n,$$

and thus $L(n) \sim e^{-nD(\theta_\eta||\theta_0)}(\sqrt{2\pi n}\sigma\tau)^{-1}$.

Let $p(\bar{x}_n)$ be the marginal distribution of $\bar{X}_n$, and write the posterior entropy as $I(\theta|\bar{x}_n) = -\sum_{i\in\{0,1\}} p(\theta_i|\bar{x}_n)\log p(\theta_i|\bar{x}_n)$, then

$$\begin{aligned}
I(n) &= \int_{-\infty}^{+\infty} p(\bar{x}_n)I(\theta|\bar{x}_n)d\bar{x}_n = \int_{\{\mathcal{L}>1\}} + \int_{\{\mathcal{L}\leq 1\}} = I_1(n) + I_2(n), \\
I_1(n) &= \pi_0 \int_{\{\mathcal{L}>1\}} p(\bar{x}_n|\theta_0)\left\{\log(1+\mathcal{L}) + \mathcal{L}\log(1+\mathcal{L}^{-1})\right\}d\bar{x}_n \\
&= \pi_0 \int_\eta^\infty p(\bar{x}_n|\theta_0)\left\{\log\mathcal{L} + 1 + \sum_{k=1}^\infty \frac{(-1)^{k-1}}{k(k+1)}\mathcal{L}^{-k}\right\}d\bar{x}_n \\
&= \pi_0 e^{-nD(\theta_\eta||\theta_0)} \int_0^\infty e^{-\sqrt{n}\tau x}\left\{\sqrt{n}\Delta x + 1 + \sum_{k=1}^\infty \frac{(-1)^{k-1}}{k(k+1)}e^{-k\sqrt{n}\Delta x}\right\}dH_n(x).
\end{aligned}$$

Using (3.19), it can be seen that

$$\int_0^\infty e^{-\sqrt{n}(\tau+k\Delta)x}dH_n(x) \sim \int_0^\infty e^{-\sqrt{n}(\tau+k\Delta)x}\phi(x;\sigma^2)dx \sim \frac{1}{\sqrt{2\pi n}(\tau+k\Delta)},$$

$$\int_0^\infty e^{-\sqrt{n}\tau x}\sqrt{n}\Delta x dH_n(x) \sim \frac{\Delta}{\sqrt{2\pi n}\tau^2}.$$

Therefore, we have

$$\begin{aligned} I_1(n) &\sim \pi_0 e^{-nD(\theta_\eta||\theta_0)} \left\{ \frac{1}{\tau} + \frac{\Delta}{\tau^2} + \sum_{k=1}^{\infty} \frac{(-1)^{k-1}}{k(k+1)(k\Delta+\tau)} \right\} \cdot \frac{1}{\sqrt{2\pi n}\sigma} \\ &= \frac{\pi_0 e^{-nD}}{\sqrt{2\pi n}\sigma} \left\{ \frac{1}{\tau} + \frac{\Delta}{\tau^2} + \frac{1}{\Delta} \sum_{k=1}^{\infty} \left( (-1)^{k-1} \frac{1}{\alpha k} + \frac{(-1)^{k-1}}{(1-\alpha)(k+1)} + \right.\right. \\ &\qquad \left.\left. - \frac{(-1)^{k-1}}{\alpha(1-\alpha)(k+\alpha)} \right) \right\} \\ &= \frac{\pi_0 e^{-nD}}{\sqrt{2\pi n}\sigma} \left\{ \frac{1}{\tau} + \frac{\Delta}{\tau^2} + \frac{1}{\tau}\log 2 + \frac{1}{\Delta-\tau}(1-\log 2) - \frac{\int_0^1 \frac{x^\alpha}{1+x}dx}{\tau(1-\alpha)} \right\}, \end{aligned}$$

where $\alpha = \tau/\Delta \in (0,1)$. $I_2(n)$ can be approximated similarly. Therefore, (3.26) holds.

If $p(x|\theta)$ is normally distributed, it follows that $\psi(\theta) = \frac{1}{2}\sigma^2\theta^2$, $\eta = \frac{1}{2}\sigma^2(\theta_1 + \theta_0)$, $\tau = \frac{1}{2}(\theta_1 - \theta_0)$ and $\tau/\Delta = 1/2$. Thus,

$$\frac{I(n)}{L(n)} \sim 1 + \log 2 + 2 + (1-\log 2) - 2\int_0^1 \frac{\sqrt{x}}{1+x}dx = \pi. \quad \square$$

# Chapter 4

# Two-armed bandit problems: one arm known

In this chapter, the results of Chapter 2 will be generalized to exponential families, and, using limit theorems developed in Chapter 3, asymptotically optimal sample size for two-armed clinical trials with one arm unknown are derived.

## 4.1 Notation

Let $f(\cdot|\rho_i)$ be the probability density function of the responses from arm $i$, $i = 1, 2$. Assume $f(\cdot|\rho_i)$ is from a minimal and steep exponential family.

Let $\lambda$ be the treatment mean of the known arm, and $\rho$ for the unknown arm and $\pi(\rho)$ for its prior. By Theorem 2.3, we consider only the strategies of the form $(0, n)$. Let $(X_1, ..., X_n)$ be the responses of $n$ patients from the unknown arm in the first stage and $S_n = \sum_{k=1}^{n} X_k$, then $S_n$ is sufficient for $\rho$. Since the apparently better treatment will be used in the second stage, the treatment mean in the second stage is then $g(n, S_n) = E(\rho|S_n) \vee \lambda$. The expected treatment mean is

$$g(n) = E(g(n, S_n)) = E(E(\rho|S_n) \vee \lambda).$$

We can write the corresponding worth function as

$$\begin{aligned} W(n) &= nE(\rho) + (N-n)E\{E(\rho|S) \vee \lambda\} \\ &= nE(\rho) + (N-n)g(n). \end{aligned} \tag{4.1}$$

In the next section, we reduce $g(n)$ to a sum of deviation probabilities, then use the results developed in Chapter 3 to find the asymptotically optimal sample size.

## 4.2 Asymptotically optimal sample size

Similar to the method used in Chapter 2, we start with decomposing $g(n)$ to a sum of deviation probabilities.

**Lemma 4.1** *Define* $A \triangleq \{E(\rho|\bar{x}_n) \leq \lambda\}$ *and* $B \triangleq \{E(\rho|\bar{x}_n) > \lambda\}$*, then*

$$g(n) = E\{\rho \vee \lambda\} - I_1 - I_2,$$

*where*

$$\begin{aligned} I_1 &= \int_{\rho<\lambda} \int_B f(\bar{x}|\rho)(\lambda - \rho)\pi(\rho) d\bar{x} d\rho, \\ I_2 &= \int_{\rho>\lambda} \int_A f(\bar{x}|\rho)(\rho - \lambda)\pi(\rho) d\bar{x} d\rho. \end{aligned} \tag{4.2}$$

**Proof:** Let $f(\bar{x}_n)$ denote the marginal distribution of $\bar{X}_n$,

$$f(\bar{x}_n) = \int_\Theta f(\bar{x}_n|\rho)\pi(\rho) d\rho.$$

then

$$\begin{aligned}
g(n) &= \int_A f(\bar{x})\lambda d\bar{x} + \int_B E(\rho|\bar{x})f(\bar{x})d\bar{x} \\
&= \lambda - \int_B f(\bar{x})\lambda d\bar{x} + \int_B E(\rho|\bar{x})f(\bar{x})d\bar{x} \\
&= \lambda + \int_B \int_\Theta f(\bar{x}|\rho)(\rho-\lambda)\pi(\rho)d\rho d\bar{x} \\
&= \lambda + \left(\int_{\rho<\lambda}\int_B + \int_{\rho>\lambda}\int_B\right) f(\bar{x}|\rho)(\rho-\lambda)\pi(\rho)d\bar{x}d\rho \\
&= \lambda + \int_{\rho>\lambda}(\rho-\lambda)\pi(\rho)d\rho + \left(\int_{\rho<\lambda}\int_B - \int_{\rho>\lambda}\int_A\right) f(\bar{x}|\rho)(\rho-\lambda)\pi(\rho)d\bar{x}d\rho \\
&= E\{\rho \vee \lambda|\pi\} - I_1 - I_2. \qquad \square
\end{aligned}$$

**Lemma 4.2** *Where set $A$ is defined in Lemma 4.1, if prior $\pi(\rho) \sim \pi_0|\lambda-\rho|^u$ as $\rho \to \lambda$, the following holds*

$$A = \{E(\rho|\bar{x}_n) < \lambda\} = \{\bar{x}_n < \lambda + o(n^{-1/2})\}. \tag{4.3}$$

**Proof:** If $\pi(\rho)$ is the conjugate prior defined in (3.4), then

$$A = \{E(\rho|\bar{x}_n) < \lambda\} = \left\{\frac{n\bar{x}_n + \gamma}{n+\kappa} < \lambda\right\} = \{\bar{x}_n < \lambda + O(1/n)\},$$

and (4.3) is true. For general prior distribution, the proof proceeds in two steps: (1) $E(\rho|x)$ is an increasing function of $x$; and (2) $E(\rho|\bar{x}_n = \lambda) = \lambda + o(n^{-1/2})$.

(1) Write $\pi(\rho)d\rho = \pi_1(\theta)d\theta$, then $\pi_1 \sim \pi_{1,0}|\theta_\lambda - \theta|^u$ as $\theta \to \theta_\lambda$. Let $u(x) = \int_\Theta \psi'(\theta)e^{x\theta-\psi(\theta)}\pi_1(\theta)d\theta$ and $v(x) = \int_\Theta e^{x\theta-\psi(\theta)}\pi_1(\theta)d\theta$, then $E(\rho|x) = u(x)/v(x)$. We have used canonical parameter $\theta$. Given $\delta > 0$, we have

$$E(\rho|x+\delta) - E(\rho|x) = \frac{u(x+\delta)v(x) - u(x)v(x+\delta)}{v(x+\delta)v(x)}$$

$$= \frac{1}{2} \cdot \frac{\iint (\psi'(s)-\psi'(t))(e^{\delta s}-e^{\delta t})e^{x(s+t)-\psi(s)-\psi(t)}\pi_1(s)\pi_1(t)dsdt}{v(x+\delta)v(x)} > 0,$$

since $(\psi'(s) - \psi'(t))(e^{\delta s} - e^{\delta t}) \geq 0$ for any real numbers $s$ and $t$. This proves that $E(\rho|x)$ is increasing.

(2) To prove $E(\rho|\lambda) = \lambda + o(n^{-1/2})$. Recall Theorem 3.6 that $f(x|\rho(\theta)) \propto e^{-D(\theta_x||\theta)}$, therefore,

$$E(\rho|\lambda) - \lambda = \frac{\int_\Theta (\psi'(\theta) - \lambda)e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta}{\int_\Theta e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta}. \tag{4.4}$$

Since $D(\theta_\lambda||\theta) \sim \frac{1}{2}(\theta - \theta_\lambda)^2$ as $\theta \to \theta_\lambda$, by Lemma 2.5, the denominator has an order of $O(n^{-\frac{u+1}{2}})$.

To evaluate the numerator, we need only consider the integral on a neighborhood of $\theta_\lambda$, say $\Delta = (\theta_\lambda - \delta, \theta_\lambda + \delta)$, because the integral always has an exponential rate tending to 0 outside this region. By the differentiability of $\psi(\theta)$, there exists $M > 0$ such that $|\psi'''(\theta)| \leq M$ on $\Delta$. Let $\omega, \omega_1, \omega_2, \cdots$, be real numbers having absolute values less than or equal to 1 (it may depend on $\theta$), then we have $\psi'(\theta) - \lambda = (\theta - \theta_\lambda)\psi''(\theta_\lambda) + \frac{1}{2}(\theta - \theta_\lambda)^2\omega M$ as $\theta \to \theta_\lambda$. Using Lemma 2.5,

$$\int_\Delta \frac{1}{2}(\theta - \theta_\lambda)^2 \omega M e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta \leq \frac{1}{2}M \int_\Delta (\theta - \theta_\lambda)^2 e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta$$

$$\sim n^{-\frac{u+3}{2}}(\pi_{1,0}M/2)\int_{-\infty}^{\infty} \theta^{u+2}e^{-\frac{1}{2}\theta^2\psi''(\theta_\lambda)}d\theta = O(n^{-\frac{u+3}{2}}). \tag{4.5}$$

Now, consider the integration $\int_\Delta (\theta - \theta_\lambda)e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta$.

$$\int_\Delta (\theta - \theta_\lambda)\, e^{-nD(\theta_\lambda||\theta)}|\lambda - \theta|^u d\theta = \left(\int_{\theta_\lambda}^{\infty} - \int_{-\infty}^{\theta_\lambda}\right)(\theta - \theta_\lambda)^{u+1}e^{-nD(\theta_\lambda||\theta)}d\theta$$

$$= \int_0^\delta \theta^{u+1}\left(e^{-nD(\theta_\lambda||\theta+\theta_\lambda)} - e^{-nD(\theta_\lambda||\theta-\theta_\lambda)}\right)d\theta$$

$$= \int_0^\delta \theta^{u+1} e^{-\frac{1}{2}n\theta^2\psi''(\theta_\lambda)}\left(e^{-\frac{1}{6}n\omega_1 M\theta^3} - e^{-\frac{1}{6}n\omega_2 M\theta^3}\right)d\theta$$

$$\leq \frac{1}{3}nM\int_0^\delta \theta^{u+4} e^{-\frac{1}{2}n\theta^2\psi''(\theta_\lambda)-\frac{1}{6}n\omega_3 M\theta^3}d\theta = O(n^{-\frac{u+3}{2}}), \qquad (4.6)$$

where $\omega_3$ lies between $\omega_1$ and $\omega_2$. Given $\epsilon > 0$, we can find $\delta > 0$ such that $\left|\frac{\pi_1(\theta)-\pi_{1,0}|\lambda-\theta|^u}{|\lambda-\theta|^u}\right| < \epsilon$ on $\Delta$, and therefore

$$\left|\frac{\int_\Delta (\theta-\theta_\lambda)e^{-nD(\theta_\lambda||\theta)}(\pi_1(\theta)-\pi_{1,0}|\lambda-\theta|^u)d\theta}{n^{-\frac{u+2}{2}}}\right| \leq \epsilon. \qquad (4.7)$$

Putting (4.5), (4.6) and (4.7) together, we have proved that the numerator

$$\left|\int_\Theta (\psi'(\theta)-\lambda)e^{-nD(\theta_\lambda||\theta)}\pi_1(\theta)d\theta\right| \leq o(n^{-\frac{u+2}{2}}). \quad \square$$

Let $\sigma_\lambda^2 = \psi''(\theta_\lambda)$. By Theorem 3.9 and 3.11, it is straightforward to have that

$$\left.\begin{aligned} I_1 &= \int_{\rho<\lambda}\int_B f(\bar{x}|\rho)(\lambda-\rho)\pi(\rho)d\bar{x}d\rho \\ I_2 &= \int_{\rho>\lambda}\int_A f(\bar{x}|\rho)(\lambda-\rho)\pi(\rho)d\bar{x}d\rho \end{aligned}\right\} \sim \frac{\pi_0 J(u+2)}{\sqrt{2\pi}(u+2)}\left(\frac{\sigma_\lambda^2}{n}\right)^{\frac{u+2}{2}},$$

and the following theorem.

**Theorem 4.3** *Suppose that the probability density function $f(x|\rho)$ of the unknown arm is from a minimal steep exponential family, and that the prior has form $\pi(\rho) \sim \pi_0|\rho-\lambda|^u$ as $\rho \to \lambda$. Then as $n \to +\infty$*

$$g(n) \sim E\{\rho \vee \lambda\} - 2\cdot\frac{\pi_0 J(u+2)}{\sqrt{2\pi}(u+2)}\left(\frac{\sigma_\lambda^2}{n}\right)^{\frac{u+2}{2}},$$

*where $J(u)$ is defined in (2.8).*

Define $\hat{W}(n)$, the asymptotic worth, as

$$\hat{W}_N(n) = nE(\rho) + (N-n)\left(E(\rho \vee \lambda) - \left(\frac{\sigma_\lambda^2}{n}\right)^{\frac{u+2}{2}}\right)$$

and the asymptotically optimal sample size $\hat{n}$ as the mode of $\hat{W}_N(n)$.

**Lemma 4.4** *Let $n^*$ be the optimal sample size on the unknown arm in the first stage and $\hat{n}$ the asymptotically optimal sample size, then*

$$\lim_{N \to +\infty} n^*(N)/\hat{n}(N) = 1. \tag{4.8}$$

**Proof:** The proof is the same as for Lemma 2.12, except that now $u \neq 0$.
□

**Theorem 4.5** *Under the hypothesis of Theorem 4.3, we have*

$$n^* \sim \left(\frac{\pi_0 J(u+2)(\sigma_\lambda^2)^{\frac{u+2}{2}}}{\sqrt{2\pi}C} \cdot N\right)^{\frac{1}{\frac{u}{2}+2}},$$

*where $C = E(\rho \vee \lambda) - E(\rho)$. If $u = 0$, then*

$$n^* \sim \left(\frac{\pi(\lambda)\sigma_\lambda^2}{2C} \cdot N\right)^{\frac{1}{2}}.$$

**Example 5:** *A case where the asymptotic sample size is other than $\sqrt{N}$.* If, in a clinical trial, an investigator who believes that the new treatment is unlikely to have a same treatment mean as an existing treatment may have prior $\pi(\rho) = \pi_0|\rho - \lambda|^u$ for some $u > 0$, where $\lambda$ is the known treatment mean. According to Theorem 4.5, the asymptotic sample size will be $O(N^{\frac{2}{4+u}})$.

Consider a two-armed trial with dichotomous responses. Suppose the known success rate is $\lambda = 0.5$, and the prior on the unknown success rate $\rho$ is $\pi(\rho) = 4|\rho - 0.5|$ on $(0,1)$. We have $\pi_0 = 4$, $J(3) = 2$, $E(\rho \vee 0.5) - E(\rho) = 1/6$, and $(\sigma_{0.5}^2)^{3/2} = 1/8$, therefore, by Theorem 4.5,

$$n^* \sim \left(\frac{4 \cdot 2 \cdot 6}{\sqrt{2\pi} \cdot 8} N\right)^{\frac{2}{5}} = \left(\frac{6}{\sqrt{2\pi}} N\right)^{\frac{2}{5}}. \quad \square$$

## 4.3 The case of no prior mass near the known treatment mean

The prior considered in the preceding section has dense support around $\lambda$. Let $\mathrm{supp}(\pi)$ be the support of prior $\pi$. In this section, we consider the case in which the point $\lambda$ is not an interior point of $\mathrm{supp}(\pi)$. This is equivalent to the existence of $a < \lambda$ or $b > \lambda$ such that

$$\mathrm{P}(a < \rho < \lambda) = 0 \quad \text{or} \quad \mathrm{P}(\lambda < \rho < b) = 0. \tag{4.9}$$

By Theorem 2.2, we assume $\pi(\lambda) = 0$ and this will not affect the sample size determination.

Define constants $a$ and $b$ as

$$\begin{cases} a = \sup\{x : \mathrm{P}(x < \rho < \lambda) = 0\} \\ b = \inf\{x : \mathrm{P}(\lambda < \rho < x) = 0\} \end{cases} \tag{4.10}$$

and let $\mu \in \Theta$ be a constant satisfying the following equation

$$D_1(\mu||a) = D_1(\mu||b). \tag{4.11}$$

It is easy to verify that $\mu = \dfrac{\psi(\theta_b) - \psi(\theta_a)}{\theta_b - \theta_a}$, where $\theta$ is the inverse function of $\rho(\theta)$.

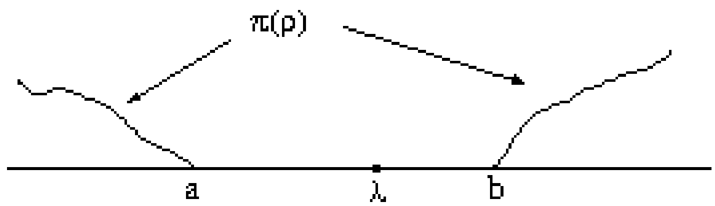


Figure 4.1: A prior with support excluding $\lambda$.

**Lemma 4.6** *Let* $\mu_n = \inf_x \{E(\rho|\bar{X}_n = x) \geq \lambda\}$ *then* $\mu_n \to \mu \in (a, b)$*, where* $\mu$ *is defined in (4.11),*

**Proof:** Using $f(\bar{x}_n|\rho) \propto e^{\rho n \bar{x}_n - n\psi(\rho)} \propto e^{-nD_1(\bar{x}_n||\rho)}$, we have that

$$E(\rho|\bar{X}_n = x) \geq \lambda \iff \left(\int_{-\infty}^{a} + \int_{b}^{\infty}\right)(\rho - \lambda)e^{-nD_1(x||\rho)}\pi(\rho)d\rho \geq 0.$$

Given $\epsilon > 0$, we first prove that if $x \leq \mu - \epsilon$ then $E(\rho|\bar{X}_n = x) < \lambda$ for sufficiently large $n$. Suppose $x \leq \mu - \epsilon$. If $x < a$, then by Theorem 3.5 $D_1(x||a) < D_1(x||b)$. If $x \geq a$, by the same theorem, $D_1(x||a) < D_1(\mu||a) = D_1(\mu||b) < D_1(x||b)$. Therefore we can find constants $\delta_0$, $\delta_1 > 0$ such that $D_1(x||\rho) < D_1(x||b) - \delta_0$ for $\rho \in [a - \delta_1, a]$. Also, by the definition of $a$, there exists a constant $c > 0$ such that

$$-\int_{a-\delta_1}^{a}(\rho - \lambda)\pi(\rho)d\rho > c.$$

Therefore, for sufficiently large $n$, we have that

$$\begin{aligned}\int_{-\infty}^{a} + \int_{b}^{\infty} &\leq \left(\int_{a-\delta}^{a} + \int_{b}^{\infty}\right)(\rho - \lambda)e^{-nD_1(x||\rho)}\pi(\rho)d\rho \\ &< -ce^{-nD_1(x||b) - n\delta_0} + e^{-nD_1(x||b)}\int_{b}^{\infty}(\rho - \lambda)\pi(\rho)d\rho < 0.\end{aligned}$$

Hence $x > \mu - \epsilon$ and $\mu_n > \mu - \epsilon$. By the same argument it can be proved that $\mu_n < \mu + \epsilon$. Since $\epsilon$ is arbitrary, $\mu_n \to \mu$.

If $a = b = \lambda$, then $\mu = \lambda$ and clearly $\mu_n \to \lambda$. □

**Lemma 4.7** *If $\mu$ is the constant defined in (4.11), then for any $\epsilon > 0$,*

$$e^{-nD_1(\mu+\epsilon||a)} < E(\rho \vee \lambda) - g(n) < e^{-nD_1(\mu-\epsilon||a)}. \tag{4.12}$$

**Proof:** Referring to notations in Lemma 4.1, we have $A = \{\bar{x}_n \leq \mu_n\}$ and $B = \{\bar{x}_n > \mu_n\}$. By Lemma 4.6, for sufficiently large $n$, the following holds:

$$\int_{-\infty}^{a}\int_{\mu+\frac{\epsilon}{2}}^{\infty} \leq I_1 = \int_{-\infty}^{a}\int_{B}(\lambda-\rho)f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho \leq \int_{-\infty}^{a}\int_{\mu-\frac{\epsilon}{2}}^{\infty}.$$

A similar inequality can be obtained for $I_2 = \int_b^\infty \int_A (\lambda-\rho)f(\bar{x}_n|\rho)\pi(\rho)d\bar{x}_n d\rho$. By Theorem 3.10, (4.12) follows. □

**Theorem 4.8** *Let $n^*$ be the optimal sample size of the first stage, then*

$$n^* \sim \log N/D_1(\mu||a),$$

*where $\mu$ is defined as in (4.11).*

**Proof:** As in the proof of Lemma 2.12, $n^*(N) \to \infty$ as $N \to \infty$. Denote $\hat{n} = \log N/D_1(\mu||a)$. We now prove that $n^*(N)/\hat{n}(N) \to 1$. Let $c_1 = \underline{\lim}_{N\to\infty} n^*(N)/\hat{n}(N) \leq \overline{\lim}_{N\to\infty} n^*(N)/\hat{n}(N) = c_2$. If $c_1 < 1$ then there exists a number $\delta > 0$ and a subsequence $\{N_j\}$ such that $n^*(N_j) < (1-\delta)\hat{n}(N_j)$. For this $\delta$ we can find an $\epsilon > 0$ such that $1-\frac{\delta}{2} < D_1(\mu\pm\epsilon||a)/D_1(\mu||a) < 1+\frac{\delta}{2}$. By Lemma 4.7, for sufficiently large $n^*$,

$$\begin{aligned} W(n^*) &\leq n^*E(\rho) + (N-n^*)\left(E(\rho\vee\lambda) - e^{n^*D_1(\mu+\epsilon||a)}\right) \\ &\leq (1-\delta)\hat{n}E(\rho) + (N-(1-\delta)\hat{n})\left(E(\rho\vee\lambda - e^{-(1-\delta)\hat{n}D_1(\mu+\epsilon||a)}\right), \end{aligned}$$

and

$$-W(\hat{n}) \leq -\hat{n}E(\rho) - (N-\hat{n})\left(E(\rho \vee \lambda) - e^{\hat{n}D_1(\mu-\epsilon||a)}\right).$$

Replacing $\hat{n}$ with $\log N/D_1(\mu||a)$,

$$\begin{aligned} W(n^*) - W(\hat{n}) &\leq -N_j^{1-\frac{(1-\delta)D_1(\mu+\epsilon||a)}{D_1(\mu||a)}} + N_j^{-\frac{D_1(\mu-\epsilon||a)}{D_1(\mu||a)}} + O(\log N_j) \\ &\leq -N_j^{\delta/2+\delta^2/2} + N_j^{\delta/2} + O(\log N_j) \to -\infty. \end{aligned}$$

Thus, $c_1 \geq 1$. By the same token, $c_2 \leq 1$. □

**Example 6:** In this example, suppose the support of $\pi$, has a finite number of points, possibly including $\lambda$. Arrange them in order:

$$\text{supp}(\pi) = \{l_s, l_{s-1}, ..., l_1, \lambda, r_1, ..., r_{t-1}, r_t\}.$$

Let $\pi_1(\rho) = \pi(\rho)/(1-\pi(\lambda))$ for $\rho = l_s, ..., l_1, r_1, ..., r_t$. By Theorem 2.3, the worth function is

$$W(n;\pi) = (1-\pi(\lambda))W(n;\pi_1) + N\pi(\lambda).$$

From Theorem 4.8, $n^* \sim \log N/D_1(\mu||l_1)$, where $\mu = \frac{\psi(\theta_{l_1})-\psi(\theta_{r_1})}{\theta_{l_1}-\theta_{r_1}}$. □

# Chapter 5

# Two-armed bandit problems: both arms unknown

A more realistic situation in designing clinical trials is when both treatments are unknown. Colton (1963) and Canner (1970) have studied this case assuming that the numbers of patients assigned to both arms are the same. Cornfield, Halperin, & Greenhouse (1969) considered unbalanced designs, however they supposed that the sample sizes for both arms are linear in $N$.

In this chapter, I consider two-armed clinical trials with both arms unknown under a more general condition. Using limit theorems developed in Chapter 3, I obtain asymptotically optimal sample sizes for both arms, along with the coefficients of the approximations.

## 5.1 Decomposition and limit theorems

Let the response distribution be from a steep and minimal exponential family with cumulant generating function $\psi(\theta) = \psi_1(\theta_1) + \psi_2(\theta_2)$:

$$\left\{ f(x|\theta) = e^{\theta \cdot x - \psi(\theta)} \mu(dx) = e^{\theta_1 x_1 + \theta_2 x_2 - \psi_1(\theta_1) - \psi_2(\theta_2)} \mu(dx), \quad \theta \in \Theta \right\}$$

where $\mu$ is a $\sigma$-finite measure on the Borel subsets of $R^2$. As in previous chapters, let $\rho_1 = \psi_1'(\theta_1)$ and $\rho_2 = \psi_2'(\theta_2)$ (the respective means) denote a reparameterization of $(\theta_1, \theta_2)$. The prior of $(\rho_1, \rho_2)$ is denoted by $\pi(\rho_1, \rho_2)$.

## Assumptions

*A*. Assume that neither prior distribution is supported by one point. (Otherwise it can be reduced to the trivial case or the case with one arm known, as considered in last chapter).

*B*. Assume that $\Theta$ is a compact subset of $R^2$.

Let $n_1$ and $n_2$ be the numbers of patients assigned to each arm in the first stage, and let $X_{11}, ..., X_{1n_1}$ and $X_{21}, ..., X_{2n_2}$ be the responses. Denote $\bar{X}_{n_i} = (1/n_i)\sum_{j=1}^{n_i} X_{ij}$, $i = 1, 2$, and $\bar{X} = (\bar{X}_{n_1}, \bar{X}_{n_2})$. The worth function is

$$W(n_1,n_2;\pi) = n_1 E(\rho_1) + n_2 E(\rho_2) + (N - n_1 - n_2) E\{E(\rho_1|\bar{X}) \vee E(\rho_2|\bar{X})\}.$$

Let $g(n_1, n_2) = E\{E(\rho_1|\bar{X}) \vee E(\rho_2|\bar{X})\}$. The following lemma gives a decomposition of $g(n_1, n_2)$ to a sum of deviation probabilities.

**Lemma 5.1** *Let* $A = \{E(\rho_1|\bar{X}) \geq E(\rho_2|\bar{X})\}$, $B = \{E(\rho_1|\bar{X}) \leq E(\rho_2|\bar{X})\}$, *then*

$$g(n_1, n_2) = E(\rho_1 \vee \rho_2|\pi) - I_1 - I_2,$$

*where*

$$I_1 = \iint_{\rho_1 < \rho_2} \iint_A f(\bar{x}_1, \bar{x}_2|\rho)(\rho_2 - \rho_1)\pi(\rho) d\rho d\bar{x}_1 d\bar{x}_2,$$

$$I_2 = \iint_{\rho_1 > \rho_2} \iint_B f(\bar{x}_1, \bar{x}_2|\rho)(\rho_2 - \rho_1)\pi(\rho) d\rho d\bar{x}_1 d\bar{x}_2.$$

**Proof:** Let $f(\bar{x}) = f(\bar{x}_{n_1}, \bar{x}_{n_2})$ be the marginal density of $\bar{X}$. Note that

$$\begin{aligned}
E(\rho_1 \vee \rho_2) &= \int_\Theta (\rho_1 \vee \rho_2)\pi(\rho_1, \rho_2) d\rho_1 d\rho_2 \\
&= \int_{\rho_1 > \rho_2} \rho_1 \int_{A\cup B} f(\bar{x}|\rho)\pi(\rho) + \int_{\rho_1 < \rho_2} \rho_2 \int_{A\cup B} f(\bar{x}|\rho)\pi(\rho) \\
g(n_1, n_2) &= \left(\iint_A + \iint_B\right) \{E(\rho_1|\bar{X} = \bar{x}) \vee E(\rho_2|\bar{X} = \bar{x})\} f(\bar{x}) d\bar{x} \\
&= \iint_A E(\rho_1|\bar{x}) f(\bar{x}) d\bar{x} + \iint_B E(\rho_2|\bar{x}) f(\bar{x}) d\bar{x} \\
&= \iint_A \iint_\Theta \rho_1 f(\bar{x}|\rho)\pi(\rho) d\rho d\bar{x} + \iint_B \iint_\Theta \rho_2 f(\bar{x}|\rho)\pi(\rho) d\rho d\bar{x} \\
&= \left(\iint_A \iint_{\rho_1 > \rho_2} \rho_1 + \iint_A \iint_{\rho_1 < \rho_2} \rho_1 + \right. \\
&\qquad \left. \iint_B \iint_{\rho_1 > \rho_2} \rho_2 + \iint_B \iint_{\rho_1 < \rho_2} \rho_2 \right) f(\bar{x}|\rho)\pi(\rho) d\rho d\bar{x}.
\end{aligned}$$

Therefore, $g(n_1, n_2) - E(\rho_1 \vee \rho_2|\pi) = I_1 + I_2$. □

**Lemma 5.2** *Let* $n = \min\{n_1, n_2\}$. *Assume that prior* $\pi(\rho_1, \rho_2)$ *is continuous and positive on the region* $T_d = \{(\rho_1, \rho_2) : |\rho_1 - \rho_2| \le d\} \cap \Theta$, *then for* $\lambda = (\lambda_1, \lambda_2)' \in T_d$, *uniformly,*

$$E(\rho_i|\bar{X} = \lambda) = \lambda_i + o(n_i^{-1/2}), \qquad i = 1, 2.$$

*Therefore, if* $(\bar{x}_{n_1}, \bar{x}_{n_2}) \in T_d$, *the following holds uniformly;*

$$E(\rho_1 - \rho_2|\bar{x}_{n_1}, \bar{x}_{n_2}) = \bar{x}_{n_1} - \bar{x}_{n_2} + o(n^{-1/2}).$$

**Proof:** For $\lambda = (\lambda_1, \lambda_2)' \in T_d$ and a positive number $\delta$, denote

$$A_\delta(\lambda) = \{(\rho_1, \rho_2) : \lambda_i - \delta < \rho_i < \lambda_i + \delta, i = 1, 2\}.$$

For economy of notation, let $\varphi_i(\lambda_i, \rho_i) = e^{-n_i D_1(\lambda_i \| \rho_i)}$, $i = 1, 2$, and $\varphi(\lambda, \rho) = \varphi_1 \varphi_2$. Since $T_d$ is compact and $D_1(\cdot\|\cdot)$ is continuous, $\varphi(\lambda, \rho)$ approaches 0 exponentially outside the region $A_\delta$, and this holds uniformly for $\lambda \in T_d$. Therefore,

$$E(\rho_1|\bar{X}{=}\lambda) - \lambda_1 = \frac{\iint (\rho_1 - \lambda_1) e^{-n_1 D_1(\lambda_1||\rho_1) - n_2 D_1(\lambda_2||\rho_2)} \pi(\rho_1, \rho_2) d\rho_1 d\rho_2}{\iint e^{-n_1 D_1(\lambda_1||\rho_1) - n_2 D_1(\lambda_2||\rho_2)} \pi(\rho_1, \rho_2) d\rho_1 d\rho_2}$$

$$\sim \frac{\iint_{A_\delta} (\rho_1 - \lambda_1) \varphi(\lambda, \rho) \pi(\rho_1, \rho_2) d\rho_1 d\rho_2}{\iint_{A_\delta} \varphi(\lambda, \rho) \pi(\rho_1, \rho_2) d\rho_1 d\rho_2} = \frac{H_1}{H_2}.$$

Since $\pi(\rho_1, \rho_2)$ is positive on $T_d$, there exists a number $m > 0$ such that $\pi(\rho_1, \rho_2) > m$ on $T_d$ and, by Lemma 2.5,

$$H_2 \geq m \iint_{A_\delta} e^{-n_1 D_1(\lambda_1||\rho_1) - n_2 D_1(\lambda_2||\rho_2)} d\rho_1 d\rho_2 = O(n_1^{-1/2}) \left( \int_{\rho_2} \varphi_2 d\rho_2 \right).$$

By the compactness of $T_d$ and the continuity of $\pi(\rho_1, \rho_2)$ on $T_d$, for any given $\epsilon > 0$ and $\lambda \in T_d$, letting $c = \pi(\lambda_1, \lambda_2)$, there exists a $\delta > 0$ such that $c - \epsilon < \pi(\rho_1, \rho_2) < c + \epsilon$ on $A_\delta$ uniformly. And,

$$\begin{aligned} H_1 &\leq \left| (c+\epsilon) \iint_{\rho_1 < \lambda_1} (\rho_1 - \lambda_1) \varphi d\rho_1 d\rho_2 + (c - \epsilon) \iint_{\rho_1 > \lambda_1} (\rho_1 - \lambda_1) \varphi d\rho_1 d\rho_2 \right| \\ &= \left| (c+\epsilon) \int_{\lambda_1 - \delta}^{\lambda_1 - \delta} (\lambda_1 - \rho_1) \varphi_1 d\rho_1 + 2\epsilon \int_{\rho > \lambda_1} (\rho_1 - \lambda_1) \varphi_1 d\rho_1 \right| \left( \int_{\rho_2} \varphi_2 d\rho_2 \right). \end{aligned}$$

Referring to (4.6) in the proof of Lemma 4.2, the first integral inside the vertical bars has order of $o(n_1^{-1})$ uniformly. Therefore,

$$\frac{H_1}{H_2} \leq \epsilon O(n_1^{-1/2}), \qquad \text{or} \qquad \frac{H_1}{H_2} = o(n_1^{1/2}). \quad \square$$

**Lemma 5.3** *For $a \in R^1$, assume that the prior is positive on the region $|\rho_2 - \rho_1 - a| \leq \delta$ for some $\delta > 0$, then*

$$\begin{aligned} I &= \iint_{\rho_2 - \rho_1 > a} \iint_{\bar{x}_2 - \bar{x}_1 < a} f(\bar{x}_1, \bar{x}_2 | \rho_1, \rho_2)(\rho_2 - \rho_1) \pi(\rho) d\bar{x} d\rho \\ &\sim \iint_{\rho_2 - \rho_1 > a} \int_d^\infty \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}x^2} (\rho_2 - \rho_1) \pi(\rho) dx d\rho. \end{aligned}$$

*where* $d = (\rho_2 - \rho_1 - a)/\sqrt{\frac{\sigma_1^2(\rho_1)}{n_1} + \frac{\sigma_2^2(\rho_2)}{n_2}}$, *and* $\sigma_i^2(\rho_i) = \psi_i''(\theta_{\rho_1})$, $i = 1, 2$.

**Proof:** Let $\Lambda = \{(x_1, x_2) : x_2 - x_1 < a\}$. There exists a point $\nu \in \bar{\Lambda}$ such that $D_1(\Lambda||\rho) = D_1(\nu||\rho) = D(\theta_\nu||\theta)$. By the convexity of $D$, $\nu$ must be in the set $\partial\Lambda = \{(x_1, x_2) : x_2 - x_1 = a\}$, the boundary of $\Lambda$. Under this constraint, $\nu = (\nu_1, \nu_2)'$ satisfies:

$$\begin{cases} \nu_2 - \nu_1 = a, \\ \theta_{\nu_1} + \theta_{\nu_2} = \theta_1 + \theta_2. \end{cases} \tag{5.1}$$

Since $\rho_2 - \rho_1 > a$, it implies that $\theta_{\nu_1} - \theta_1 > 0$ and $\theta_{\nu_2} - \theta_2 < 0$. Otherwise, $\rho_1 = \psi_1'(\theta_1) > \nu_1 = \nu_2 - b > \psi_2'(\theta_2) - a = \rho_2 - a$, which is contradictory to that $\rho_2 - \rho_1 > a$.

Let $y_{ij} = x_{ij} - \nu_i$, and $G_i$ be the distributions obtained from $X_{i1}$ by exponential centering at $\nu_i$, and $H_{n_i}(x) = P(\sqrt{n_i}\bar{X}_{n_1} \leq x)$, $j = 1, ..., n_i$, $i = 1, 2$. The distribution $G_i$ depends only on $\nu_i$, and the mean and variance are 0 and $\psi_i''(\theta_{\nu_i})$. Denoting $\varphi(\nu, \rho) = e^{-n_1 D_1(\nu_1||\rho_1) - n_2 D_1(\nu_2||\rho_2)}$, by exponential centering, it follows that

$$\begin{aligned}
\iint_{\bar{x}_2 - \bar{x}_1 < b} f(\bar{x}_1, \bar{x}_2|\rho) d\bar{x} &= \int \cdots \int_{\bar{x}_2 - \bar{x}_1 < b} f(x_{11}, ..., x_{1n_1}, x_{21}, ..., x_{2n_2}|\rho) dx \\
&= \int \cdots \int_{\bar{y}_2 - \bar{y}_1 < 0} f(y_{11}, ..., y_{1n_1}, y_{21}, ..., y_{2n_2}|\rho) dy \\
&= \varphi(\nu, \rho) \int \cdots \int_{\bar{z}_2 - \bar{z}_1 < 0} e^{-n_1(\theta_{\nu_1} - \theta_1)\bar{z}_1 - n_2(\theta_{\nu_2} - \theta_2)\bar{z}_2} G_{n_1}(dz_1) G_{n_2}(dz_2) \\
&= \varphi(\nu, \rho) \iint_{\frac{z_1}{\sqrt{n_1}} > \frac{z_2}{\sqrt{n_2}}} e^{-\sqrt{n_1}(\theta_{\nu_1} - \theta_1) z_1 - \sqrt{n_2}(\theta_{\nu_2} - \theta_2) z_2} H_{n_1}(dz_1) H_{n_2}(dz_2) \\
&= \varphi \sqrt{n_1 n_2}(\theta_{\nu_1} - \theta_1)(\theta_{\nu_2} - \theta_2) \iint_{\frac{z_1}{\sqrt{n_1}} > \frac{z_2}{\sqrt{n_2}}} e^{-\sqrt{n_1}(\theta_{\nu_1} - \theta_1) z_1 - \sqrt{n_2}(\theta_{\nu_2} - \theta_2) z_2} \times \\
&\quad \times (H_{n_1}(z_1) - H_{n_1}(\tfrac{z_2\sqrt{n_1}}{\sqrt{n_2}}))(H_{n_2}(z_2) - H_{n_2}(\tfrac{z_1\sqrt{n_2}}{\sqrt{n_1}})) dz_1 dz_2.
\end{aligned}$$

We have used integration by parts in the last equality. On a compact set $\Theta$, the third derivative of cumulant generating function is bounded, and $\sigma_i^2 = \psi_i''(\theta_{\nu_i}) \geq \sigma_0^2$ for some $\sigma_0^2 > 0$. The bound for the Berry-Esseen theorem holds uniformly on $\Theta$. Applying the Berry-Esseen theorem gives that

$$\begin{aligned}
I &\sim \iint_{\rho_2-\rho_1>a} \iint_{\frac{z_1}{\sqrt{n_1}}>\frac{z_2}{\sqrt{n_2}}} \varphi e^{-\sqrt{n_1}(\theta_{\nu_1}-\theta_1)z_1-\sqrt{n_2}(\theta_{\nu_2}-\theta_2)z_2}\phi_1\phi_2(\rho_2-\rho_1)\pi(\rho)dzd\rho \\
&\sim \iint_{\rho_2-\rho_1>a} \iint_{z_2-z_1<a} \phi(z_1;\rho_1,\tfrac{\sigma_1^2(\rho_1)}{n_1})\phi(z_2;\rho_2,\tfrac{\sigma_2^2(\rho_2)}{n_2})(\rho_2-\rho_1)\pi(\rho)dzd\rho \\
&\sim \iint_{\rho_2-\rho_1>a} \int_d^\infty \frac{1}{\sqrt{2\pi}}e^{-\frac{1}{2}x^2}(\rho_2-\rho_1)\pi(\rho)dxd\rho_1d\rho_2,
\end{aligned}$$

where $\phi_i$ is normal density function with mean 0 and variance $\psi_i''(\theta_{\nu_i})$, $i = 1,2$. □

**Lemma 5.4** *Let* $n = \min\{n_1, n_2\}$ *and* $\epsilon_n = o(n^{-1/2})$*, then*

$$\iint_{\rho_1<\rho_2} \iint_{\{|\bar{x}_1-\bar{x}_2|<\epsilon_n\}} f(\bar{x}_1,\bar{x}_2|\rho_1,\rho_2)(\rho_2-\rho_1)\pi(\rho)d\bar{x}d\rho = o(n^{-1/2}).$$

**Proof:** The proof is similar to Theorem 3.11. First, we partition the integral as

$$\iint_{\rho_2-\rho_1>\epsilon_n} \iint_{|\bar{x}_1-\bar{x}_2|<\epsilon_n} + \iint_{0<\rho_2-\rho_1<\epsilon_n} \iint_{|\bar{x}_1-\bar{x}_2|<\epsilon_n} = I_1 + I_2.$$

Then $I_2$ is of order $o(n^{-1/2})$. Following the same procedure as in the proof of Lemma 5.3, we have that

$$\begin{aligned}
I_1 &\sim \iint_{\rho_1<\rho_2} \left(\Phi(\tfrac{\rho_2-\rho_1+2\epsilon_n}{\sigma(\rho_1,\rho_2)}) - \Phi(\tfrac{\rho_2-\rho_1}{\sigma(\rho_1,\ rho_2)})\right)(\rho_2-\rho_1)\pi(\rho)d\rho_1d\rho_2 \\
&= \int_{-\infty}^\infty d\rho_1 \int_0^\infty \left(\Phi(\tfrac{y+2\epsilon_n}{\sigma(\rho_1,y+\rho_1)}) - \Phi(\tfrac{y}{\sigma(\rho_1,y+\rho_1)})\right) y\pi(\rho_1,y+\rho_1)dy.
\end{aligned}$$

By (2.11) and Lemma 2.5, $I_1 = o(n^{-1/2})$. □

**Theorem 5.5** *Assume that prior $\pi(\rho_1, \rho_2)$ is continuous and positive on the region $|\rho_1 - \rho_2| \le \delta$, then*

$$I_1 = \iint_{\rho_1<\rho_2} \iint_A f(\bar{x}_1, \bar{x}_2|\rho)(\rho_2 - \rho_1)\pi(\rho)d\rho d\bar{x}_1 d\bar{x}_2 \sim \frac{1}{2}\left(\frac{c_1}{n_1} + \frac{c_2}{n_2}\right),$$

*where the constants $c_i$, $i = 1, 2$, are given by*

$$c_i = \int \pi(x, x)\sigma_i^2(x)dx. \tag{5.2}$$

**Proof:** Let $\sigma(\rho_1, \rho_2) = \sqrt{\frac{\sigma_1^2(\rho_1)}{n_1} + \frac{\sigma_2^2(\rho_2)}{n_2}}$, and $\Phi(x) = \int_{-\infty}^{x} \phi(x)dx$. By Lemmas 5.3 and 5.4,

$$\begin{aligned} I_1 &\sim \iint_{\rho_1<\rho_2} \left(1 - \Phi(\tfrac{\rho_2-\rho_1}{\sigma(\rho_1,\rho_2)})\right)(\rho_2 - \rho_1)\pi(\rho)d\rho_1 d\rho_2 \\ &= \int_{-\infty}^{\infty} d\rho_1 \int_{\rho_1}^{\infty} \left(1 - \Phi(\tfrac{\rho_2-\rho_1}{\sigma(\rho_1,\rho_2)})\right)(\rho_2 - \rho_1)\pi(\rho)d\rho_2 \\ &\overset{y=\rho_2-\rho_1}{=\!=} \int_{-\infty}^{\infty} d\rho_1 \int_0^{\infty} \left(1 - \Phi(\tfrac{y}{\sigma(\rho_1,y+\rho_1)})\right) y\pi(\rho_1, y + \rho_1)dy. \end{aligned}$$

Using (2.11) and Lemma 2.5,

$$I_1 = \frac{1}{2}\int_{-\infty}^{\infty} \pi(x, x) \cdot \left(\frac{\sigma_1^2(x)}{n_1} + \frac{\sigma_2^2(x)}{n_2}\right) dx.$$

The result follows using the definition of $c_i$ in (5.2). □

## 5.2 Approximations to optimal sample sizes

From Theorem 5.5, we have that

$$\begin{aligned} I_1 + I_2 &= E(\rho_1 \vee \rho_2) - g(n_1, n_2) \\ &\sim \int_{-\infty}^{\infty} \pi(x, x)\left(\frac{\sigma_1^2(x)}{n_1} + \frac{\sigma_2^2(x)}{n_2}\right) dx = \frac{c_1}{n_1} + \frac{c_2}{n_2}. \end{aligned} \tag{5.3}$$

The worth function can be approximated as

$$\hat{W}(n_1,n_2)=n_1E(\rho_1)+n_2E(\rho_2)+(N-n_1-n_2)\left(E(\rho_1\vee\rho_2)-\frac{c_1}{n_1}-\frac{c_2}{n_2}\right),$$

as $\min(n_1,n_2)\to\infty$. Then we have the following result.

**Theorem 5.6** *Define the asymptotic sample size as*

$$\hat{n}_i=\left(\frac{\sqrt{c_i}}{\sqrt{E(\rho_1\vee\rho_2)-E(\rho_i)}}\right)N^{1/2},\qquad i=1,2.$$

*Let* $(n_1^*,n_2^*)$ *be the optimal sample sizes on two arms, then*

$$\lim_{N\to\infty}n_i^*(N)/\hat{n}_i(N)=1,\qquad i=1,2.$$

**Proof:** First we prove that $\lim_{N\to\infty}n_i^*=\infty$, for $i=1,2$. Suppose that $\lim_{N\to\infty}n_1^*\neq\infty$, then there exists a series $\{N_j\}$ such that $n_1^*(N_j)\le n_0$. Using Jensen's inequality and the monotonicity of $g(n_1,n_2)$ (Theorem 2.1),

$$\begin{aligned}\frac{W(n_1^*,n_2^*)}{N} &\le E\{E(\rho_1|\bar{X}_{n_1^*})\vee E(\rho_2|\bar{X}_{n_2^*})\}\\ &\le E\{E(\rho_1|\bar{X}_{n_0})\vee\rho_2\}\\ &\le E\{E(\rho_1\vee\rho_2|\bar{X}_{n_0})\}=E(\rho_1\vee\rho_2).\end{aligned}$$

The last inequality is strict unless $E(\rho_1|\bar{X}_{n_0})=\rho_1$ almost everywhere, which happens only if $\rho_1$ has a one-point distribution. That is the one-arm-known case discussed in Chapter 4.

Clearly, $W(\hat{n}_1,\hat{n}_2)/N\to E(\rho_1\vee\rho_2)$, and therefore, for sufficiently large $N_j$, $W(n_1^*,n_2^*)/N_j<W(\hat{n}_1,\hat{n}_2)/N_j$, which contradicts with the optimality of $(n_1^*,n_2^*)$.

We prove that $n_1^*/\hat{n}_1 \to 1$. Let $c_1 = \underline{\lim}_{N\to\infty} n^*/\hat{n} \le \overline{\lim}_{N\to\infty} n^*/\hat{n} = c_2$. If $c_1 < 1$, then there exists a number $\delta > 0$ such that $n_1^* < (1-\delta)\hat{n}_1$. By (5.3), for sufficiently large $N$, hence large $n_1$ and $n_2$,

$$E(\rho_1 \vee \rho_2) - (1+\epsilon)\left(\frac{c_1}{n_1} + \frac{c_2}{n_2}\right) < g(n_1, n_2) < E(\rho_1 \vee \rho_2) - (1-\epsilon)\left(\frac{c_1}{n_1} + \frac{c_2}{n_2}\right).$$

For $t_1, t_2 > 0$, let

$$F(n_1, n_2; t_1, t_2) = n_1 E(\rho_1) + n_2 E(\rho_2) + (N - n_1 - n_2)\left(E(\rho_1 \vee \rho_2) - \frac{t_1}{n_1} - \frac{t_2}{n_2}\right).$$

Since $\partial^2 F/\partial n_i^2 < 0$, $F$ is concave and has unique maximum tending to:

$$NE(\rho_1 \vee \rho_2) - 2\sqrt{N}(\sqrt{t_1 C_1} + \sqrt{t_2 C_2}),$$

where $C_i = E(\rho_1 \vee \rho_2) - E(\rho_i)$, $i = 1, 2$.

Having $n_1$ fixed, the maximal mode of $F$ is at $n_2 \le c_3\sqrt{N}$ for some $c_3 > 0$, so $n_2^*/N \to 0$. For $n_1^* < (1-\delta)\hat{n}_1$, $\partial F/\partial n_1 > 0$ when $t_1 > (1-\delta)c_1$; therefore, taking $\epsilon = \frac{\delta}{2}$,

$$\begin{aligned}
W(n_1^*, n_2^*) &< F(n_1^*, n_2^*; (1-\epsilon)c_1, (1-\epsilon)c_2) \\
&\le F((1-\delta)\hat{n}_1, n_2^*; (1-\epsilon)c_1, (1-\epsilon)c_2) \\
&\sim NE(\rho_1 \vee \rho_2) - 2\left((1-\delta)\sqrt{c_1 C_1} + \sqrt{(1-\epsilon)c_2 C_2}\right)\sqrt{N}, \\
W(\hat{n}_1, \hat{n}_2) &\sim NE(\rho_1 \vee \rho_2) - 2\left(\sqrt{c_1 C_1} + \sqrt{c_2 C_2}\right)\sqrt{N}.
\end{aligned}$$

Therefore, $W(n_1^*, n_2^*) - W(\hat{n}_1, \hat{n}_2) < 0$, when $\epsilon$ is sufficiently small. This shows that $c_1 \ge 1$. The argument for $c_2 \le 1$ is similar. Thus, $n_1^* \sim \hat{n}_1$. □

This result tells us to put more patients to the arm with higher expected rewards and higher uncertainty (because more information is needed for uncertain treatment).

## 5.3 Numerical comparisons

In this section, I compare the following three different procedures: (1) the optimal procedure; (2) asymptotically optimal procedure; and (3) a balanced procedure in which $N/4$ patients are assigned to each treatment in the first stage, and the remaining half of patients to the apparently better treatment. We use $W^*_{avg}$, $\hat{W}_{avg}$ and $\tilde{W}_{avg}$ to denote the average worths of the three procedures respectively.

Consider a two-armed clinical trial with dichotomous responses on both arms. Let $\rho_1$ and $\rho_2$ be the unknown success rates. Assume $\rho_1$ and $\rho_2$ are independent and have beta priors: $\rho_1 \sim \text{beta}(a_1, b_1)$ and $\rho_2 \sim \text{beta}(a_2, b_2)$.

Theorem 5.6 applies only when the support of prior is a closed subset of $(0, 1)$, which corresponds to a compact subset of canonical parameter space $R$. However, Theorem 5.6 still provides a good approximation to the optimal sample sizes, as will be seen in this example.

Table 5.1 shows the optimal sample sizes and the asymptotically optimal sizes, and the average worths for the three procedures. For each setting of priors, the sample sizes and the average worths are calculated for $N = 100$, 200, 500 and 1000. The worth of balanced procedure is calculated by the following formula:

$$\tilde{W}_{avg} = \frac{1}{4}E(\rho_1) + \frac{1}{4}E(\rho_2) + \frac{1}{2}E\{E(\rho_1|S_n) \vee E(\rho_2|S_n)\}.$$

By looking at the differences of worth functions from the optimal procedure, the asymptotic results are much better than the results of balanced procedure in maximizing the total number of successes over all patients.

| Priors | $n_1^*$ | $n_2^*$ | $\hat{n}_1$ | $\hat{n}_2$ | $W_{avg}^*$ | $\hat{W}_{avg}$ | $\tilde{W}_{avg}$ | $W_{avg}^* - \hat{W}_{avg}$ | $W_{avg}^* - \tilde{W}_{avg}$ |
|---|---|---|---|---|---|---|---|---|---|
| | 5 | 6 | 7 | 7 | .6271 | .6254 | .5801 | .0017 | .0470 |
| $\rho_1 \sim \mathcal{B}(1,1)$ | 8 | 9 | 10 | 10 | .6373 | .6364 | .5817 | .0009 | .0556 |
| $\rho_2 \sim \mathcal{B}(1,1)$ | 14 | 15 | 15 | 15 | .6472 | .6469 | .5827 | .0003 | .0645 |
| | 20 | 21 | 22 | 22 | .6526 | .6524 | .5830 | .0002 | .0696 |
| | 6 | 7 | 8 | 8 | .4292 | .4279 | .3962 | .0013 | .0329 |
| $\rho_1 \sim \mathcal{B}(1,2)$ | 10 | 11 | 12 | 12 | .4385 | .4378 | .3981 | .0007 | .0405 |
| $\rho_2 \sim \mathcal{B}(1,2)$ | 16 | 18 | 19 | 19 | .4479 | .4476 | .3992 | .0003 | .0487 |
| | 24 | 26 | 27 | 27 | .4530 | .4529 | .3996 | .0001 | .0534 |
| | 1 | 18 | 4 | 14 | .6747 | .6697 | .5976 | .0050 | .0771 |
| $\rho_1 \sim \mathcal{B}(1,2)$ | 3 | 22 | 6 | 19 | .6789 | .6767 | .5987 | .0022 | .0802 |
| $\rho_2 \sim \mathcal{B}(2,1)$ | 6 | 34 | 9 | 31 | .6849 | .6832 | .5995 | .0017 | .0855 |
| | 10 | 48 | 13 | 44 | .6887 | .6885 | .5997 | .0002 | .0890 |
| | 8 | 7 | 9 | 9 | .5886 | .5872 | .5596 | .0014 | .0290 |
| $\rho_1 \sim \mathcal{B}(2,2)$ | 11 | 12 | 14 | 14 | .5982 | .5973 | .5618 | .0009 | .0364 |
| $\rho_2 \sim \mathcal{B}(2,2)$ | 19 | 20 | 22 | 22 | .6081 | .6077 | .5633 | .0003 | .0448 |
| | 28 | 29 | 31 | 31 | .6136 | .6134 | .5638 | .0001 | .0498 |
| | 2 | 17 | 6 | 16 | .6125 | .6086 | .5675 | .0038 | .0450 |
| $\rho_1 \sim \mathcal{B}(2,3)$ | 5 | 24 | 9 | 22 | .6181 | .6164 | .5693 | .0016 | .0487 |
| $\rho_2 \sim \mathcal{B}(3,2)$ | 10 | 39 | 15 | 36 | .6252 | .6247 | .5705 | .0005 | .0547 |
| | 17 | 52 | 21 | 51 | .6297 | .6295 | .5710 | .0002 | .0587 |
| | 8 | 7 | 11 | 11 | .4756 | .4735 | .4521 | .0020 | .0235 |
| $\rho_1 \sim \mathcal{B}(2,3)$ | 12 | 13 | 15 | 15 | .4847 | .4839 | .4545 | .0008 | .0302 |
| $\rho_2 \sim \mathcal{B}(2,3)$ | 21 | 22 | 24 | 24 | .4942 | .4939 | .4560 | .0003 | .0381 |
| | 31 | 32 | 35 | 35 | .4995 | .4994 | .4566 | .0002 | .0429 |
| | 7 | 9 | 10 | 10 | .3233 | .3216 | .2996 | .0017 | .0237 |
| $\rho_1 \sim \mathcal{B}(1,3)$ | 13 | 11 | 14 | 14 | .3316 | .3308 | .3015 | .0008 | .0300 |
| $\rho_2 \sim \mathcal{B}(1,3)$ | 19 | 21 | 22 | 22 | .3399 | .3396 | .3027 | .0003 | .0372 |
| | 30 | 28 | 31 | 31 | .3446 | .3444 | .3031 | .0001 | .0414 |
| | 6 | 5 | 8 | 8 | .6113 | .6097 | .5713 | .0016 | .0399 |
| $\rho_1 \sim \mathcal{B}(1,1)$ | 11 | 8 | 11 | 11 | .6207 | .6202 | .5731 | .0005 | .0476 |
| $\rho_2 \sim \mathcal{B}(2,2)$ | 16 | 15 | 18 | 18 | .6303 | .6301 | .5742 | .0002 | .0561 |
| | 24 | 23 | 25 | 25 | .6356 | .6356 | .5746 | .0001 | .0610 |

Table 5.1: Numerical comparison of different schemes. $W_{avg}^*$ is the worth calculated at optimal sample size $(n_1^*, n_2^*)$. $\hat{W}_{avg}$ is the worth calculated at the asymptotic sample size $(\hat{n}_1, \hat{n}_2)$. $\tilde{W}_{avg}$ is the worth of the strategy in which one assigns $N/4$ patients to each of the two treatments in the first stage and the remaining $N/2$ patients to the apparently better treatment in the second stage. For each case, the worth is calculated for $N = 100, 200, 500$ and $1000$.

# Chapter 6

# Further works

Some extensions may be done in the following directions:

(1) In Chapter 3, limit theorems are only developed when sets $A$ and $B$ are intervals in $R^1$, quadrants in $R^2$, and so on. More work can be done for general convex sets $A$ and $B$.

(2) In Bayesian applications, another commonly seen form of deviation probabilities is

$$\int_A \int_B f(\bar{x}_n|\rho)h(\bar{x}_n, \rho)\pi(\rho)d\bar{x}_n d\rho,$$

where $h(\bar{x}_n, \rho)$ is a function of $\bar{x}_n$ and $\rho$. One example is in estimating the expected quadratic loss where $h(\bar{x}_n, \rho) = (\bar{x}_n - \rho)^2$.

(3) In this dissertation, all approximations are derived only to the first order. Higher order approximation might be obtained using the following well-known normal expansions:

$$H_n(x) = \sum_{j=0}^{k} n^{-\frac{1}{2}j} P_j(-\Phi),$$

where $P_j$ are polynomials. Taking $k = 1$ gives the Berry-Esseen theorem. For details, see Bhattacharya and Rao (1976).

Based on those results, a higher order approximation to sample sizes in two-armed clinical trial designs may be obtained.

(4) Multi-armed clinical trials: an analogue that $n_i \sim (\frac{c_i}{E(\rho_1 \vee \cdots \rho_k)} N)^{1/2}$ might hold for $k$-armed bandit problems, where $c_i$, $i = 1, \cdots, k$ are constants to be specified. These results may require the development of limit theorems on high dimensional space.

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# Biography

Fusheng Su was born in Henan Province, China, on August 12, 1962. He received his BS in Mathematics from Nankai University, China, in July 1984. From 1985 to 1986, he entered a graduate program in Statistics at Wuhan University. During the years of 1984 to 1985 and 1987 to 1989, he held an assistant lecturer position in Xian Jiaotong University. He entered the graduate program in ISDS at Duke University at the end of 1989, and received his MS in Statistics in 1992. From 1993 to 1995, he had worked as Statistical Consultant and Statistician with Boots Pharmaceuticals, ClinTrials Research and A.R. Kamm Associates. While at Duke, he received one year research assistantship and a four-year teaching assistantship.