CHAPTER 1

SYNOPSIS

In the present chapter we present an overview of the material in Chapters 2–10.

1.1 MULTISTAGE AND SEQUENTIAL ESTIMATION

Chapter 2 is devoted to the problem of determining the minimal sample size required to attain a prescribed precision, in the estimation of a parameter, or a function of parameters of the parent distribution. Consider, for example, the classical problem of estimating the mean of a normal distribution. Let $X_1, \ldots, X_n$ be independent, identically distributed (i.i.d.) random variables from a normal distribution $\mathcal{N}(\mu, \sigma)$. It is well known that, if the standard deviation σ is known, then a confidence interval for μ, with confidence level $1 - \alpha$, $0 < \alpha < 1$, is given by

$$\bar{X}_n \pm Z_{1-\alpha/2}\frac{\sigma}{\sqrt{n}}, \tag{1.1.1}$$

where $\bar{X}_n = \sum_{i=1}^{n} X_i/n$ is the sample mean and $Z_{1-\alpha/2} = \Phi^{-1}(1-\alpha/2)$ is the $(1-\alpha/2)$-quantile of the standard normal distribution $\Phi(\cdot)$. Thus, if one

Stage-Wise Adaptive Designs. By Shelemyahu Zacks

wishes to have a $(1-\alpha)$ level confidence for the mean, μ, with bounded length 2δ, the minimal required sample size is

$$n^0(\delta,\sigma) = \left\lfloor \frac{Z^2_{1-\alpha/2}\sigma^2}{\delta^2} \right\rfloor + 1. \tag{1.1.2}$$

Here $\lfloor x \rfloor$ denotes the largest integer *smaller* than x. We express the precision of the estimation by the bound 2δ on the length of the confidence interval and its confidence level $1-\alpha$. One can express the precision in terms of an estimation risk, like

$$R(\hat{\mu}_n,\mu) = AE_\sigma\{(\hat{\mu}_n - \mu)^2\}, \tag{1.1.3}$$

where $0 < A < \infty$ is a constant and $\hat{\mu}_n$ is an estimator of μ. For $\hat{\mu}_n = \bar{X}_n$ we have a risk of $A\sigma^2/n$. This risk is bounded by a desired positive constant ω, uniformly in σ, if the sample size is at least

$$n^*(\omega,\sigma^2) = \left\lfloor A\frac{\sigma^2}{\omega} \right\rfloor + 1. \tag{1.1.4}$$

We see that, in order to control the precision of the estimation, one needs to know the value of the nuisance parameter σ. The question is whether a procedure based on a sample of fixed size n can guarantee a desired precision when σ is *unknown*. Dantzig (1940) has proven that if σ is unknown there exists no such fixed-sample-size procedure. That is, there exists no fixed-width confidence interval for μ, in the normal case, if σ is unknown and the sample size is fixed.

Stein (1945, 1949) was the first one to show that a fixed-width confidence interval for μ in the normal case can be attained by a *two-stage* sampling procedure when σ is unknown. As will be shown, Stein's two-stage procedure is an *adaptive* procedure. It utilizes the results of the first stage to estimate σ and determines the required sample size based on this estimate. We describe this method and prove the result in Section 2.1. This classical result of Stein opened the field for many papers which dealt with various properties of two-stage and multistage procedures. A comprehensive review of the results in the literature is presented in the book *Sequential Estimation* of Ghosh, Mukhopadhyay, and Sen (1997). In Section 2.2 we present generalizations of Stein's procedure and the notions of consistency and asymptotic efficiency of the procedure. The exact distribution of the total (random) sample size is compared to its asymptotic normal distribution. Section 2.3 presents two-stage procedures for estimating the parameters of exponential distributions. We present there the exact distribution of the total sample size, N, and interesting results of Mukhopadhyay and Pepe (2006) and Zacks and Mukhopadhyay (2007) concerning a uniformly bounded risk estimation of the mean, β, of the exponential distribution. In Section 2.4 we present the Chow and Robbins (1965) procedure for a fixed-width confidence interval of a distribution

mean, μ, when the variance σ^2 is finite. We also prove there Wald's lemma and present Anscomb theorem on asymptotic normality. Section 2.5 presents a method for the exact determination of the distribution of the sample size in the exponential case and certain other characteristics of the estimators. This is based on a recent paper of Zacks and Mukhopadhyay (2006a). In Section 2.6 we show recent results of Zacks and Mukhopadhyay (2007) for a sequential fixed-width interval estimation of the log-odds in Bernoulli trials. Finally, in Section 2.7 we present the Bayesian formulation of sequential estimation.

The numerical characteristics of two-stage and sequential procedures, like the expected total sample size, the expected value of the estimator, and the risk function, can generally be estimated by simulations. We emphasize and apply, as much as possible, exact numerical evaluation of these characteristics. Recursive numerical algorithms can be developed whenever the stopping variables depend on sums of independent random variables.

1.2 ADAPTIVE DESIGNS FOR GENERALIZED LINEAR MODELS

In Chapter 3 we discuss two types of adaptive design problems. The first is that of *quantal response* experiments in which the observed random variables are binary (Bernoulli trials) and the problem is that of determining the level x of an experimental factor. The second type of problem is that of determining the level x in a linear regression $Y = \alpha + \beta x + \epsilon$ so that Y satisfies certain tolerance requirements. We explain now the two problems in detail. For the quantal response problem, we consider m Bernoulli trials and denote by J_m the number of "successes," where J_m has binomial distribution $\mathcal{B}(m, F(\alpha + \beta x))$. The probability of success, $F(\alpha+\beta x)$, depends on an arbitrary location parameter, α, and a positive parameter, β (the inverse of a scale parameter), where x is a level of experimental factor (stress level, temperature, dosage of toxic material, etc). We will assume that $F(u)$ is a cumulative distribution function (c.d.f.). Thus, $F(\alpha + \beta x)$ is an increasing function of x.

In bioassays F is called a *tolerance distribution* (see Finney, 1964). In modern theory of generalized linear models, F is called a *link function*. The problem is to determine a value of x so that $F(\alpha+\beta x)$ has a certain required property. For example, in bioassays one is often seeking the value of a dose x which causes 50% mortality. This is called the median lethal dose (LD-50). For a given tolerance distribution

$$\text{LD-50} = \frac{F^{-1}(0.5) - \alpha}{\beta}.$$

This required dosage depends on the parameters α and β. Adaptive designs are called for when α and β are *unknown*. The objective is to perform a sequence of trials, estimate the unknown parameters after each stage, and determine the dosage for the next stage to maximize the information on the required LD-50.

In Sections 3.1–3.3 the objective is to determine the sequence of dosages $\{X_n\}$ which will come close to the one which maximizes the Fisher information. More specifically, suppose that $\alpha = 0$ and β is unknown. Given $J_m \sim \mathcal{B}(m, F(\beta x))$, the likelihood function of β is

$$L(\beta; J_m) = F(\beta x)^{J_m}(1 - F(\beta x))^{m - J_m}. \tag{1.2.1}$$

The corresponding score function is

$$\frac{\partial}{\partial \beta} \log L(\beta; J_m) = J_m \frac{x f(\beta x)}{F(\beta x)\bar{F}(\beta x)} - m \frac{x f(\beta x)}{F(\beta x)\bar{F}(\beta x)}, \tag{1.2.2}$$

where $f(u)$ is the density of $F(u)$ and $\bar{F}(u) = 1 - F(u)$. The Fisher information function is the variance of the score function, namely

$$I(\beta; x) = \frac{m x^2 f^2(\beta x)}{F(\beta x)\bar{F}(\beta x)}. \tag{1.2.3}$$

Let u^0 be a maximizer of

$$I(u) = \frac{u^2 f^2(u)}{F(u)\bar{F}(u)}. \tag{1.2.4}$$

If β is known, then the optimal x-value is

$$x^0 = \frac{u^0}{\beta}. \tag{1.2.5}$$

If both α and β are unknown, the Fisher information is the matrix

$$II(\alpha, \beta; x) = \frac{m f^2(\alpha + \beta x)}{F(\alpha + \beta x)\bar{F}(\alpha + \beta x)} \begin{pmatrix} 1 & x \\ x & x^2 \end{pmatrix}. \tag{1.2.6}$$

This matrix is singular. One needs to perform trials at two different x-values in order to estimate both α and β. If one is interested in estimating a given linear combination of α and β, $\omega = \xi\alpha + \eta\beta$, the optimal values of x can be determined by the method of Elfing (see Chernoff, 1972, p. 13). In Section 3.1 we present a special case of this problem. We consider a problem of designing a reliability experiment in which m units (systems) are put on test, and the number of failures in a period of x time units is recorded. The question is how large should x be in order to maximize the Fisher information when the life distribution is exponential. Section 3.2 is devoted to adaptive designs to maximize the Fisher information when at each stage the estimation of unknown parameters is by the method of maximum-likelihood estimation (MLE). Section 3.3 discusses the Bayesian approach for adaptive estimation. The last section is devoted to an inverse regression problem. It is assumed that the observed random variable (r.v.) $Y_x \sim N(\alpha + \beta x, \sigma^2 x^2)$. The γ-quantile of this normal distribution is $Y_\gamma = \alpha + \beta x + \Phi^{-1}(\gamma)\sigma x$, where $\Phi^{-1}(\gamma)$ is the

γ-quantile of the standard normal distribution. If we aim that $Y_\gamma = \eta$, where η is a specified threshold, then the x-value should be

$$x_\gamma = \frac{\eta - \alpha}{\beta + \Phi^{-1}(\gamma)\sigma}. \tag{1.2.7}$$

This x-value depends on the parameters α, β, and σ. Adaptive procedures are discussed for cases where some or all of these parameters are unknown.

Design problems connected with generalized linear models attracted the attention of many researchers. The reader is referred to a recent review paper by Khuri, Mukherjee, Sinha, and Ghosh (2006). Dozens of relevant papers are listed in this review paper.

The Newton–Raphson method for iteratively solving nonlinear equations is introduced in this chapter. Stochastic approximation is discussed in Section 3.5.

1.3 ADAPTIVE METHODS FOR SAMPLING FROM FINITE POPULATIONS

Sampling from finite populations, also called sampling surveys, is an important branch of statistics. Sampling surveys are applied in many branches of science and technology which deal with finite populations. Polling the political or economic attitudes of people, estimating the total corn crop in a given county, estimating the total number of bears in a given region of Alaska, estimating the number of fish in a pond, and testing whether the proportion of non conforming items in a lot is acceptable, for example, are but a small number of applications of the theory and methodology of sampling from finite populations. Chapter 4 is devoted to adaptive methods in sampling from finite populations. Accordingly, we typically draw first an initial sample to estimate certain characteristics of the population, and then on the basis of the results obtained in the initial sample we design a two-stage sampling or a sequential one. In the spirit of the terminology of the first two chapters we use the term two-stage or multistage sampling for what is called in many books "double" or "multiphase" sampling. The term single- or two-stage sampling is used in the literature on sampling surveys in connection with cluster sampling. We hope that this will not cause confusion. There are two main streams in the theory of sampling from finite population. One is that of the design of random procedures for selecting the samples (see Cochran, 1977; Hedayat and Sinha, 1991; Thompson, 1992) and the other is that of modeling (superpopulation) the joint distributions of the variables in the population (see Basu, 1969; Bolfarine and Zacks, 1992; Cassel, Särndal, and Wretman, 1977). The two approaches, design and modeling, are different entirely and the associated adaptive methods are different. For this reason we present in the first section the two theoretical approaches and some basic results. Section 4.2 is devoted to two-stage and sequential estimation of the population mean for

attaining a fixed-width confidence interval with coverage probabilities close to the nominal. This section is complimentary to the material of the first two chapters. Section 4.3 deals with the adaptive allocation of the sample in stratified sampling and utilizing these results for a two-stage estimation of the population mean with a prescribed precision. Section 4.4 is devoted to an adaptive procedure for search of special elements of the population. This section presents an interesting procedure developed by Thompson (1992) and discussed also in Thompson and Seber (1996). Their method is called by them "adaptive cluster sampling," but the procedure is only similar to the classical single-stage cluster sampling. Thompson and Seber's methods are suitable for search of a rare species or a rare mineral or elements which tend to congregate in clusters whose location has to be found. Section 4.5 presents a Bayesian sequential procedure for estimating the size of a finite population. How many elements are there? Section 4.6 presents adaptive techniques for testing and rectifying software. There are two approaches in modeling the distribution of the length of time until a fault is found. One approach is called time domain modeling and the other is data domain modeling. Sequential stopping rules are discussed for the length of a test in these two domains. Section 4.7 is devoted to adaptive procedures in sampling acceptance schemes for quality assurance. Finally, Section 4.8 presents dynamic Bayesian prediction of the total value of (a) finite population(s) in a sequence of survey times. This type of dynamic prediction (forecasting) will be discussed in more detail in Chapter 5.

1.4 ADAPTIVE PREDICTION AND FORECASTING IN TIME SERIES ANALYSIS

Let $X_1, X_2, \ldots, X_t$ be the observed values of a time series at time t. We wish to *predict* the future value of X_{t+s}, $s \geq 1$. The future value of X_{t+s} is predicted rather than estimated, since X_{t+s} is a random variable. Denote by $\hat{X}_{t+s}(t)$ the predictor of X_{t+s} at time t, $s \geq 1$. The predictor $\hat{X}_{t+s}(t)$ is a statistic which depends on the observations up to time t. We will denote by $\hat{X}^{(n)}_{t+s}(t)$ a predictor of X_{t+s} based on the last n observations $(X_t, X_{t-1}, \ldots, X_{t-n+1})$, $n \leq t$. The *prediction mean-squared error* (PMSE) of a predictor $\hat{X}^{(n)}_{t+s}(t)$ is

$$\text{PMSE}\{\hat{X}^{(n)}_{t+s}(t)\} = E\{[\hat{X}^{(n)}_{t+s}(t) - X_{t+s}]^2\}. \tag{1.4.1}$$

Notice the difference between the PMSE of a predictor and the MSE of an estimator of a parameter of a distribution.

Generally, we choose a predictor which minimizes the PMSE. Such a predictor will be called *best*, or *minimal, PMSE*. If the structure of the time series is very simple, the best predictor might be a very simple one. In Chapter 5 we derive the best predictors for some time series (T.S.) models. We then present the theory of prediction based on *moving average smoothing*, *exponential smoothing*, and *dynamic linear models*. More specifically, we start

with the basic tools of T.S. analysis. We then discuss linear predictors for covariance stationary T.S. We then develop quadratic least squares predictors for nonstationary T.S. These follow by moving average predictors, predictors with exponential discounting and smoothing models for seasonal data. The chapter concludes with dynamic linear models (DLMs) and linear control.

There are many books on T.S. analysis, for example, Box, Jenkins, and Reinsel (1994), Fuller (1996), Anderson (1971), Brillinger (1975), Brockwell and Davis (1991), Chatfield (1975, 1984), Harrison and West (1989), Nelson (1973), Davis and Vinter (1985), and many more. We present here the forecasting algorithms in a unified manner. The emphasis is again on computing algorithms. In the Appendix one can find the SPLUS programs developed for this chapter. Certain formal derivations were done with MAPLE. We illustrate the adaptive algorithms on real-life data collected from various sources. For illustration purposes we use simulated data sets, the Dow Jones daily index for the year 1941, and some data sets which are frequently used in the literature.

1.5 ADAPTIVE SEARCH OF AN MTD IN CANCER PHASE I CLINICAL TRIALS

Clinical trials are designed to test a new drug or a new therapy on human subjects. Clinical trials proceed in phases which have different objectives and are conducted differently. Phase I trials are designed to explore the toxicity and the side effects of a new drug. Typically, the sample consists of 20–80 cancer patients in progressive stages of the disease. The aim is to find the *maximal tolerated dose* (MTD) of the new drug to avoid life-threatening toxicity and other unacceptable side effects. Phase II of clinical trials are generally pilot studies of moderate size concerned with evaluating efficacy and safety of the new drug. The MTD established in Phase I is usually the applied dose in Phase II. Phase III trials are of longer duration. The objective is to compare the new therapeutic treatment to an established standard or to several other treatments, and the presence of long-term side effects is monitored. In this phase, patients are allocated to different treatments by adaptive randomization procedures. Phase IV is that of additional testing of a treatment that has been approved for general use.

In Chapter 6 we discuss various methods of finding the MTD in cancer Phase I clinical trials. The human subjects participating in these trials are generally cancer patients who are in advanced stages of the disease and for whom alternative treatments have failed. For such patients toxicity might be severe. It is therefore desired that no more than one-third of the population of such patients will be induced to life-threatening toxicity. A dose which induces such a toxic reaction is called DLT. Thus, the MTD is often defined as the highest dose utilized in the trial for which 33% of the subjects manifest life-threatening toxicity. In the search for the MTD we will discuss methods which

avoid, with high probability, overdosing. This is, however, not a concern in many studies, since the patients participating in cancer Phase I clinical trials are already in life-threatening situations due to the advanced stages of their disease.

There are two approaches to dose escalation in cancer Phase I clinical trials. One is a nonparametric approach, like the up-and-down procedure and isotonic regression estimates. The other one is the modeling approach. The modeling approach connects the dosage to the probability of DLT via a tolerance distribution. Examples will be given later. A dose escalation scheme determines the dose for the nth patient as a function of the previous $(n-1)$ dosages and the observed level of toxicity manifested by the first $(n-1)$ subjects. Generally the trials start at a low dose which is considered "safe." It is desired that the doses assigned to the following patients will be as close as possible to the MTD but below it. This is a challenging problem. Babb, Rogatko, and Zacks (1998) developed a Bayesian procedure, called escalation with overdose control (EWOC), which is designed to fulfill these objectives. For a review of Bayesian methods in cancer Phase I clinical trials, see the article of Babb and Rogatko (2003). We start with a discussion of the up-and-down procedure, since it is the oldest one, and proceed to isotonic regression procedures. We then discuss Bayesian escalation schemes. The Bayesian approach is called for since the number of patients participating in Phase I studies is small, and procedures based on asymptotic results may not be appropriate. The literature on Phase I clinical trials contains dozens if not hundreds of papers. We list a few of these at the end of the chapter.

Six up-and-down procedures were evaluated with respect to the logistic tolerance distribution,

$$F(x;\alpha,\beta) = \frac{\exp(\alpha+\beta x)}{1+\exp(\alpha+\beta x)}.$$

Exact formulas for the expected value of the estimator of the MTD, as well as its MSE and probability of overdosing, were developed. The up-and-down procedures were compared numerically according to these characteristics. The EWOC method was compared by simulations to the continuous-reassessment method (CRM) of O'Quigley, Pepe, and Fisher (1990). We conclude the chapter with discussion of three-stage designs for Phase II clinical trials and discuss also some studies which combine toxicity and efficacy.

1.6 ADAPTIVE AND SEQUENTIAL PROCEDURES IN PHASE III CLINICAL TRIALS

In Chapter 7 we discuss adaptive and sequential procedures which are designed to be implemented in Phase III clinical trials, where the main objective is to test the efficacy of one or more new treatment(s) relative to one or more standard treatments. For this purpose we have to assign patients into two or more groups: the test group(s) and the control group(s). Since clinical trials are performed on human beings by doctors or medical technicians, one of the important problems is that of guarding against creeping bias. To avoid uncontrollable bias, patients are assigned to the various treatments at random, and if at all possible, neither the patients nor the persons who administer the treatments know exactly which treatment they give or receive. This obviously is sometimes impossible. Section 7.1 is devoted to randomizations in clinical trials. In Section 7.2 we discuss several randomization procedures designed to minimize imbalance due to random assignment of patients. Some of these procedures are adaptive. In particular, we discuss the random allocation rule, which is similar to sampling at random without replacement from a finite population. If N patients are assigned sequentially to treatments A or B, according to this rule, it is interesting to notice when one of the two treatments is assigned $N/2$ patients. We develop the distribution of the first time that one of the two treatments gets $N/2$ patients. We show that with high probability this event happens close to the last assignments. After that we discuss the truncated binomial design of Blackwell and Hodges (1957). This is followed by Efron's (1971) biased coin design (1971). Wei's (1977) urn designs are discussed next, and finally we discuss randomization procedures which are response adaptive. Excellent sources of material on randomization procedures in clinical trials are the books by Rosenberger and Lachin (2002) and Hu and Rosenberger (2006).

Section 7.3 is devoted to the sequential estimation of the success probability in Bernoulli trials, having fixed-width confidence intervals. We study analytically the characteristics of the stopping rule and in particular its distribution function. In Section 7.4 we develop a sequential procedure for estimating the success probability of Bernoulli trials with the criterion of *prescribed proportional closeness* of level $1-\alpha$, namely $P\{|\hat{p}_n - p| < \lambda p\} \geq 1-\alpha$, where $0 < \alpha, \lambda < 1$. This procedure requires large samples when $p < 1/2$ but gives more meaningful results for small p. In Section 7.5 we present sequential procedures for estimating the difference of the success probabilities of two treatments. Finally, Section 7.6 is devoted to the topic of group sequential testing. These methods are especially important when it is difficult or impractical to apply purely sequential procedures, in which analysis of the results must be done after each patient is treated. An important source of information on group sequential methods is in the book of Jennison and Turnbull (2000). We do not discuss in the present chapter bioequivalence testsbioequivalence tests. These are tests which are designed to establish the equivalence of two differ-

ent drugs or treatments in terms of patient response. Bioequivalence tests often require different types of designs than the ones discussed in the present chapter. The reader can find a good chapter on this subject in Jennison and Turnbull (2000).

There are hundreds of papers and several dozen books on the design and analysis of clinical trials in particular on multistage or sequential ones. We provide in the bibliography a sample of relevant references.

1.7 SEQUENTIAL ALLOCATION OF RESOURCES: THE ONE-ARMED AND MULTIARMED BANDITS APPLIED TO CLINICAL TRIALS

Consider a "two-armed bandit" slot machine. A gambler has a finite number, N, of coins (dollars) which he or she is ready to spend for fun. At each trial the gambler has to insert a coin either on the left-hand side or on the right. This is the cost, c, of a trial. To simplify, assume that each successful trial yields 10 coins. The left and right arms act independently, with probabilities p_1 or p_2 of success. These probabilities are, however, unknown. How should the gambler play in order to maximize the expected number of successes? This is the classical two-armed bandit problem. We can state the problem in more general terms. Suppose that there are K possible experiments to choose from in each trial. If experiment $\mathcal{E}_j$ $(j = 1, \ldots, K)$ is chosen, the reward is a random variable, X_j, having a distribution function F_j. If the same experiment is repeated, the resulting rewards $X_{j_1}, X_{j_2}, \ldots$ are i.i.d. We further assume, for simplicity, that $X_1, X_2, \ldots, X_K$ are mutually independent. A strategy $\boldsymbol{\tau} = (\tau_1, \tau_2, \ldots)$ is a sequence of random variables which assume values in $\{1, 2, \ldots, K\}$. If $\tau_n = j$, $j = 1, \ldots, K$, then the nth trial is on $\mathcal{E}_j$. For a given strategy $\boldsymbol{\tau}$, the *expected total discounted* reward is

$$W(\boldsymbol{\tau}, \boldsymbol{\alpha}) = \sum_{n=1}^{\infty} \alpha_n \sum_{j=1}^{K} E\{I\{\tau_n = j\} \cdot X_{jm_j(n)}\} \tag{1.7.1}$$

where $m_j(n) = \sum_{i=1}^{n} I(\tau_i = j)$ is the number of times $\mathcal{E}_j$ has been chosen during the first n trials. Furthermore, $\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \ldots)$ is called a *discounting sequence*. Generally $\alpha_n \geq 0$ for all $n = 1, 2, \ldots$, and to assure convergence of (1.7.1), when $\max_{1 \leq j \leq K} E\{|X_j|\} < \infty$, we have to require that $\sum_{n=1}^{\infty} \alpha_n < \infty$. In the classical Bernoulli bandits, which will be discussed in Section 8.1, one could use the sequence $\boldsymbol{\alpha}_{n^*} = (1, 1, \ldots, 1, 0, 0, \ldots)$ where the number of 1's at the head of the sequence is the number of possible trials, n^*, and all $\alpha_n = 0$ for $n > n^*$. The geometric sequence $\boldsymbol{\alpha} = (1, \alpha, \alpha^2, \alpha^3, \ldots)$ is especially important, as will be shown later.

For a given $\boldsymbol{\alpha}$ the problem is to find an optimal strategy $\boldsymbol{\tau}^0$ under which $W(\boldsymbol{\tau}, \boldsymbol{\alpha})$ is maximized, that is, $W(\boldsymbol{\tau}^0, \boldsymbol{\alpha}) = \sup_{\boldsymbol{\tau}} W(\boldsymbol{\tau}, \boldsymbol{\alpha})$. The problem is trivial if $F_1, F_2, \ldots, F_K$ are completely known, since in this case the optimal

strategy is to choose for each trial the experiment for which $\int x\, dF_j(x)$ is maximal. The general problem, however, is difficult when some or all the distributions $F_1, \ldots, F_K$ are unknown or specified up to some unknown parameters. For example, suppose $F_1, \ldots, F_K$ are exponential distributions, that is, $F_j(x; \lambda_j) = 1 - \exp\{-\lambda_j x\}$, $j = 1, \ldots, K$, and the parameters $\lambda_1, \ldots, \lambda_K$ are unknown. A common approach to attack the problem is a Bayesian one. One has to assume a prior distribution $H(\lambda_1, \ldots, \lambda_K)$ over the parameter space $\Theta = \{\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_K) : 0 < \lambda_i < \infty,\ i = 1, \ldots, K\}$. After each trial, the prior distribution is converted to the posterior distribution given the observed data. More specifically, for the present example, the sufficient statistic after n trials is $\mathcal{D}_n = (S^{(1)}_{m_1(n)}, S^{(2)}_{m_2(n)}, \ldots, S^{(K)}_{m_K(n)}; \mathbf{m}(n))$, where $S^{(j)}_{m_j(n)} = \sum_{i=1}^{m_j(n)} X_{ji}$ and $\mathbf{m}(n) = (m_1(n), \ldots, m_K(n))$, where $m_j(n) \geq 0$ is the number of trials on $\mathcal{E}_j$ and $\sum_{j=1}^{K} m_j(n) = n$. Let $\mathcal{F}_n$ denote the σ-field generated by $\mathcal{D}_n$. The class of strategies under consideration is that for which $\tau_n \in \mathcal{F}_{n-1}$ for all $n \geq 1$, and τ_1 is a function of the prior distribution H, while τ_n is a function of the posterior distribution $H_{n-1}(\boldsymbol{\lambda} \mid \mathcal{F}_{n-1})$. Notice that if for some i, $i = 1, \ldots, K$, $m_i(n) = 0$, then $S^{(i)}_0 \equiv 0$. The Bayesian total discounted reward is

$$W(\boldsymbol{\tau}, \boldsymbol{\alpha}, H) = \sum_{n=1}^{\infty} \alpha_n \sum_{j=1}^{K} E_H\{I\{\tau_n(\mathcal{F}_{n-1}, H) = j\} \cdot X_j\}. \tag{1.7.2}$$

The problem is to find an optimal Bayesian strategy $\tau_n(\mathcal{F}_{n-1}, H)$ under which $W(\tau, \boldsymbol{\alpha}, H)$ is maximized, if such a strategy exists.

If the number of trials m^* is finite, an optimal strategy τ^0_H exists and can be found in principle by dynamic programming (see Berry and Friestedt, 1985, p. 24). Generally it is very difficult to obtain, even numerically, the optimal solution. Various approximations are available (see Ross, 1983; Hardwick and Stout, 1995, p. 223). If only F_1 is unknown, while $F_2, \ldots, F_K$ are known, the problem is reduced to the so-called *one-armed bandit* (OAB) problem. Indeed, if $\lambda = \max_{2 \leq j \leq K} E\{X_j\}$ we can consider only two arms: arm 1, A_1, (or experiment $\mathcal{E}_1$) whose distribution F_1 is not completely known; and arm 2, A_2, whose expected reward in each trial is λ. As proven in Berry and Friestedt (1985), if the discount sequence is *regular*, that is,

$$\frac{\alpha_{n+2}}{\alpha_{n+1}} \leq \frac{\alpha_{n+1}}{\alpha_n} \quad \text{for all} \quad n \geq 1, \tag{1.7.3}$$

then the optimal strategy in the OAB is to apply A_1 as long as it is optimal and then switch to A_2 and continue using it as long as the trials continue. Accordingly, the optimal strategy in the OAB problem is reduced to that of an optimal stopping time for the trials on A_1.

In the Bernoulli case of the OAB, the probability θ_1 of success in A_1 is unknown. Let $X_1 = 1, 0$, where $\theta_1 = P(X_1 = 1)$. Then let H be a prior

distribution of θ_1. Berry and Friestedt (1985) developed an index $\Lambda(\alpha, H)$ such that, as long as $\Lambda(\alpha, H) > \lambda$, it is optimal to apply A_1. Notice that after n trials on A_1, $n \geq 0$, the posterior distribution of θ_1, given $\mathcal{F}_n$, is substituted for H in $\Lambda(\alpha, H)$.

In Section 8.1 we discuss in some detail the one-armed Bernoulli bandits and give formulas for $\Lambda(\alpha, H)$ and some approximations. In Section 8.2 we discuss the optimal solution of Gittins and Jones (1974), who treated the case of infinite trials and a geometric discount sequence $(1, \alpha, \alpha^2, \ldots)$, $0 < \alpha < 1$. They developed a *dynamic allocation index*, called the *Gittins index*. The values of this index are adapted after each trial for each arm separately. The arm with the maximal index value is the optimal one for the next trial. Section 8.3 is devoted to some approximations proposed for medical trials. In Section 8.4 we present the paper of Lamprecht and Zacks (1998) on Bernoulli OAB with change point in A_1. That is, at some unknown time θ_1 changes to a value $\phi > \lambda$. Finally, in Section 8.5 we present the paper of Zacks (1973) on the optimal design of sequential estimation of the common mean of two normal distributions when one variance is unknown. If we knew which population has a smaller variance, then the optimal design is to sample all observations from this population. When one variance is unknown, the question is how long to sample from the population with unknown variance before switching to take all the remaining observations to the other population. This is a version of the OAB problem.

An important book on the subject is the one mentioned earlier, by Berry and Friestedt (1985), entitled *Bandit Problems*. Another important book is that of Gittins (1989), entitled *Multi-Armed Bandit Allocation Indices*. These books contain dozens of relevant references.

1.8 SEQUENTIAL DETECTION OF CHANGE POINTS

Change-point problems have occupied a central position in statistical research during the last half century and are still a subject for interesting papers. A change point is an epoch at which the distribution of a specified random variable (vector) changes. The interesting problems are those where the epochs of the change points are unknown. Given a sequence of independent random variables $X_1, \ldots, X_n$, it is of interest to test whether they have the same distribution or whether there is a point after which the distributions change their law. More specifically, if $F_1, \ldots, F_n$ are the distributions of $X_1, \ldots, X_n$, is there an index τ such that $F_1 = \cdots = F_\tau$, $F_{\tau+1} = \cdots = F_n$, while $F_\tau \neq F_{\tau+1}$? In this case τ is a change point. Such problems of retrospective testing have been studied in a large number of papers. See Zacks (1983) for a survey of such papers. Chapter 9 is devoted to sequential detection procedures, with the objective of finding such change points as soon as they occur. Such procedures are of special importance for *statistical process control* (SPC). We discuss in this chapter three categories of sequential detection procedure: Bayesian sequen-

tial procedures (Sections 9.1 and 9.2), cumulative sums procedures (CUSUM, Section 9.3), and tracking procedures (Section 9.4). The rest of the chapter is devoted to related problems of a sequential nature.

Bayesian sequential stopping rules were studied in the early 1960s by Shiryaev (1963a,b), Bather (1963, 1967), Smith (1975), Zacks and Barzily (1981), Pollak (1985), and others. Recently, there are studies on Bayesian detection of change points in the intensity of a Poisson process by Peskir and Shiryaev (2002), Herbert and Jensen (2004), and Brown and Zacks (2006). CUSUM procedures were introduced in the 1950s by Page (1954, 1955, 1957). There are many papers on this subject. We discuss the asymptotic optimality of CUSUM procedures, as in Lorden (1971) and Pollak (1985). It is more difficult to derive the exact distribution of the stopping times of CUSUM. On this problem we present the results of Zacks (1981, 2004a). See also Woodall (1983, 1984) and Yashchin (1985).

Tracking methods provide current estimates of some parameters of interest of the stochastic process and flag whenever there is evidence of change points. Chernoff and Zacks (1964) have studied the problem of estimating the current mean of a simple normal (Gaussian) process which is subjected to changes in the mean at unknown time points. We provide a development of a Bayesian tracking algorithm, which estimates parameters of the posterior distributions of the means, μ_n $(n = 1, 2, \ldots)$, under the at-most-one-change-point (AMOC) model. Other tracking procedures which are based on adaptive Kalman filtering are cited. In particular see the study of Gordon and Smith (1988). Tracking procedures are discussed in Section 9.3. In Section 9.4 we present some results on recursive methods and change points. Finally, in Section 9.5 we study the problem of detecting faults in software. Each time of such detection is a change point in which the reliability of the software is increasing.

1.9 SEQUENTIAL METHODS IN INDUSTRIAL TESTING, RELIABILITY, AND DESIGN OF EXPERIMENTS

Statistical methods for quality control consist of three categories: sampling acceptance schemes, process control, and robust designs. All three areas of statistical procedures include adaptive methods. In Section 4.7 we present two-stage sampling inspection schemes. In Chapter 10, Section 10.1, we present the important *Wald sequential probability ratio test* (SPRT), for testing whether the quality level of a lot of items or of a process is up to a specified standard. These methods of statistical quality control were developed during World War II and were in common practice since then.

In Section 10.1 we develop the theory and operating characteristics of the Wald SPRT. The exact distribution of the stopping variable is derived for the exponential case. In Section 10.2 we present a few sequential methods to evaluate the operating characteristic function of reliability testing of equipment. In Section 10.3 we discuss additional sequential procedures for design

of experiments. Finally, in Section 10.4 we discuss another model of adaptive software reliability testing.

For the various schemes and practices of sampling acceptance by attributes or by variables, including the famous Skip-Lot and other procedures,Skip-Lot procedure see Chapter 9 of Kenett and Zacks (1998).