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by

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TESTING FOR HOMOGENEITY IN FINITE MIXTURE MODELS IN GROUP SEQUENTIAL DESIGN

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Abstract

The problem of testing wether a sample is from a homogeneous population has been investigated in the recent years by many authors. It has been recognized that the limiting distribution of the likelihood ratio test for such homogeneity problems is very complex and difficult to implement. Therefore, recently, Chen et al (2001) proposed a modified likelihood ratio test for homogeneity in finite mixture models with general parametric kernel distribution families. In this thesis we provide a group sequential version of this modified likelihood ratio test. The group sequential tests are often used to reduce the sample size (number of observations) required for making decisions in statistical testing. In general, group sequential procedures require less sample than a fixed-sample (nonsequential) testing procedure with the same power and type I error. We used Monte Carlo simulations to illustrate the performance of the proposed group sequential procedures in the context of normal, binomial and Poisson mixtures. We apply the methods to a Poisson data set concerning the counts of number of accidents incurred by machinists.

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List of Acronyms

a.s. almost sure

ASN Average Sample Number

CDF Cumulative Distribution Function

LRT Likelihood Ratio Test

MLE Maximum Likelihood Estimate

MLRT Modified Likelihood Ratio Test

OBF O'Brien and Fleming

PDF Probability Density Function

PK Phase Known

PU Phase Unknown

1 Introduction

1.1 Finite Mixture Models

Suppose $X_1, ..., X_n$ are independent and identically distributed p-dimensional random vectors with probability density function $f(x_j)$ on $\mathbb{R}^p$. We say that X_j are from a finite mixture population if the density $f(x_j)$ can be written in the form

$$f(x_j) = \sum_{i=1}^{k} \gamma_i f_i(x_j), \tag{1.1}$$

where the $f_i(x_j)$ are the densities and the γ_i are nonnegative quantities that sum to one. That is:

$$0 \leq \gamma_i \leq 1 \ , i = 1, ..., k \text{ and } \sum_{i=1}^{k} \gamma_i = 1.$$

The quantities $\gamma_1, ..., \gamma_k$ are called the mixing proportions. The $f_i(x_j)$ are called the *component densities* or kernels of the mixture.

Finite mixture models have provided a mathematical-based approach to the statistical modeling of a wide variety of random phenomena. Fields in which mixture

models have been successfully applied include astronomy, biology, genetics, medicine, psychiatry, economics, engineering and marketing. In these applications, finite mixture models underpin a variety of techniques in major areas of statistics, including cluster and latent class analysis, discriminant analysis, image analysis, and survival analysis. Here we will briefly review some examples where finite mixture models are found to be useful models. For a detailed and complete coverage of finite mixture models, readers are referred to the books of Everitt and Hand (1981) and McLachlan and Peel (2000).

Linkage Analysis. Linkage analysis is a branch of human genetics that seeks the assignment of genetic loci to particular chromosome regions, or linkage groups, by the study of their cosegregation in families. Because of the wide availability of DNA polymorphism, linkage is now one of the principal methods used to investigate genetic diseases of unknown biochemical origin. When two genes (say, an unknown disease gene and a known marker gene) are close to each other on the same chromosome, they tend to stay in the same gamete after meiosis. The closer they are, the smaller the chance of being separated. A gamete with only one of the two alleles is called recombinant and the recombination fraction, denoted as θ, is a useful measure of distance. When θ is close to 0, the two genes are tightly linked and located close to each other on the same chromosome. When two genes are not linked, the recombination fraction takes the maximum possible value, $\theta = 0.5$. Sometimes, though, the underlying population is not homogeneous and the members of the population contain both linked and unlinked members. In such case, a binomial mixture model is often used to test the presence of linked fraction.

Cluster Analysis. Cluster analysis is an exploratory data analysis tool for solving classification problems. Its object is to sort cases into groups, or clusters, so that the degree of association is strong between members of the same cluster and weak between members of different clusters. Each cluster thus describes, in terms of the data collected, the class to which its members belong. Mixture models, usually Gaussian, provide a useful statistical model for such clustering in many areas among which is the recently expanding microarry data analysis.

Long-term survivor models. It happens sometimes that a cohort of individuals whose survival time is under study includes a group dying from a cause other than the cause of interest. In such cases, the analysis is handled by assuming that there is a fraction of cured subjects whose failure time is at infinity, when it comes to the cause of interest. That is, the cohort under study is thought of as they were made up of two sub-cohorts one following some sort of survival distribution with respect to the cause of interest and the other as a cured sub-subcohort. Therefore, a two-component mixture model would be appropriate for carrying out this type of analysis.

1.2 Homogeneity Testing Problems

Often in clinical applications, one could ask the question whether observed data are a sample from a single distribution or whether they have come from several separate distributions. For instance, a problem that frequently occurs in clinical trials is that some subjects are less susceptible to the treatment than others are. A mixture model has traditionally been proposed to describe the distribution of responses in treatment groups for such trials. As another example, consider the study of the genetic compo-

nents of complex human diseases. Researchers often rely heavily on the case control association designs to investigate such complex diseases. However, they are often in a dilemma as to whether they should recruit as many affected cases as they can in a study, which, in these cases, may constitute a heterogeneous group, or whether they should instead insist on a stricter case definition to achieve greater homogeneity. Testing for the homogeneity in this case will benefit both economics and design purposes.

The likelihood ratio test (LRT) is often used in parametric hypothesis testing. Under standard regularity conditions, the LRT statistic has the simple and elegant asymptotic χ^2-distribution under the null hypothesis (Lehmann 1999). Unfortunately with mixture models, regularity conditions do not hold for the LRT to have its usual asymptotic null distribution of χ^2 with degrees of freedom equal to the difference between the number of parameters under the null and alternative hypotheses. Ghosh and Sen (1985) considered the case of testing homogeneity against location-contaminated normal mixtures with known variance. They showed that, under a separation condition imposed on the parameter space, the likelihood ratio test statistic is asymptotically distributed as a supremum of a Gaussian process with mean zero and covariance kernel that depends on the true parameters under the null hypothesis. Titterington *et al.* (1985) consider the LRT of $H_0 : \gamma = 1$ versus $H_1 : 0 < \gamma < 1$, where γ is the mixing proportion of a two-component mixture. They derive that, asymptotically under H_0, the statistic follows a mixture of χ^2 distribution, $\frac{1}{2}\chi_0^2 + \frac{1}{2}\chi_1^2$, where χ_0^2 denotes the degenerate distribution that puts mass 1 at zero. A number of papers have been written on the LRT and modifications to it in special cases where

some of the parameters are known. Liang and Rathouz (1999) define a score function which is sensitive toward a given alternative. This method also has a nice mathematical and statistical properties through choice of the alternative, which is somewhat an arbitrary choice. Chen *et al.* (2001) propose a modified likelihood ratio test (MLRT) for homogeneity in the finite mixture models. The MLRT provides a nice solution to this situation by simply adding a penalty term to the log-likelihood function. The limiting distribution of the MLRT statistic is a mixture of chi-squared distribution for a large variety of mixture models. In addition, it is asymptotically most powerful under the local alternative models when there are no structural parameters (i.e., nuisance parameters).

1.3 Group Sequential Testing Procedures

Statistical sequential testing methods were originated by Abraham Wald in the 1940s during the second world war. They were invented in the context of industrial quality control and the main purpose was to reduce the sample size required for making decision in statistical testing procedures. The first version of sequential testing procedures was coined by Wald as Sequential Probability Ratio Test, SPRT. The name indicates that a likelihood ratio test is being used in a sequential fashion. The SPRT opened a century-long development in the field and quite many researchers worked in it. Sequential testing of hypotheses was introduced into the biomedical and clinical trials field during the 50s by Armitage (1960). As an alternative to the SPRTs, Armitage *et al.* (1969) suggested and studied the so-called "Repeated Significance Test" (RST). Its key idea is to perform conventional fixed-sample significance testing on the cumu-

lative data every time an observation arrives. That is, n_0 conventional fixed-sample tests will be performed if the total sample size attainable at the end of the study is n_0. The null hypothesis of interest is then rejected at the first inspection when the conventional fixed-sample test rejects it. The critical values, z_{α_i}, $i = 1, ..., n_0$, used for the intermediate testing, are obtained either by numerical integration as in Armitage *et al.* (1969) or from the approximating continuous time Wiener processes (Siegmund 1985).

Since, in double-blinded multi-centre clinical trials, frequent inspections may not be feasible, Pocock (1977) introduced a "group sequential" version of the RST. This approach performs a repeated significance testing only periodically as opposed to continuously testing after each observation. The conventional testing is performed at the pre-specified inspection times, $t_1, ..., t_K$, with a fixed number of patients (group of patients) recruited between each two inspection times; that is, the number of patients, $n_k - n_{k-1}$, recruited between the $t_{(k-1)}$th and t_kth inspection is same for all $k = 2, ..., K$. The critical values, c_{α_k}, $k = 1, ..., K$, used for the intermediate testing, are all same and equal to a constant, c. This constant is computed from the joint distribution (exact or approximate) of the K conventional test statistics by requiring that the overall significance level is a pre-specified Type I error α, i.e.,

$$P\{\text{Reject } H_0 \text{ at any } t_k \leq t_K\} = \alpha.$$

O'Brien and Fleming (1979) modified the constant boundary of Pocock's original group sequential method (i.e., c_{α_k} = constant for all $k \leq K$) to a square root boundary. In BHAT (1982), the O'Brien-Fleming method was used in the famous

Beta-Blocker Heart Attack Trial.

Lan and DeMets (1983) further extended this methodology to accommodate unequal group sizes. Their monitoring time scale was the cumulative fraction of information obtained up to the time of the current analysis out of the total information planned to be obtained at the end of the study. That is, if the maximum information planned for at the end of the study is I_K and I_k is the information obtained up to the kth analysis, then the kth analysis takes place at the time $t_k = I_k/I_K$. This formulation, with the help of Brownian motion approximation and an α-spending function, gives group sequential methods which require neither equal group sizes nor pre-fixed number of analysis K. For further details account of group sequential statistical inferences, we refer the reader to the monograph by Jennison and Turnbull (2000).

1.4 Thesis Objectives and Organization

The objective of the thesis is to devise group sequential procedures for testing the hypothesis that a population under study is homogeneous as opposed to being a two-component mixture. For this purpose, we use a sequential version of the modified likelihood ratio procedure of Chen *et al.* (2001). In chapter 2 of this thesis, we review the main results regarding the MLRT and the regularity conditions used to show its asymptotic properties. Chapter 3 reviews the various group sequential testing procedures that are commonly used in practice. Also, in chapter 3, we prove the main result of the thesis in the form of Brownian motion approximation to a continuous-time stochastic process obtained from the non-sequential MLRT. This Brownian mo-

tion approximation is then used to construct various types of group sequential testing procedures and their monitoring boundaries. In chapter 4 we report the results of extensive Monte Carlo simulations to assess the performance of the proposed group sequential tests in terms of type I errors, powers and average sample sizes needed to detect genuine heterogeneity of mixtures. Three different density functions: Normal, Poisson and Binomial, are considered for the simulation experiments. In Chapter 5, we apply some of the proposed procedures to accident data from Greenwood and Yule (1920), where the true model is suspected to be a mixture of Poisson distribution, and concluding remarks and directions for further research are also presented.

2 Likelihood Ratio Test

2.1 Ordinary Likelihood Ratio Test

Suppose we collected independent observations $X_1, ..., X_n$ from a common density $\{g(x, \theta) : \theta \in \Theta\}$, which is a probability density function (pdf) suspected to be a mixture of two densities. That is; we suspect that the pdf is of the form

$$g(x; \gamma, \theta) = (1 - \gamma) f(x, \theta_1) + \gamma f(x, \theta_2), \tag{2.1}$$

where $\theta_1 \leq \theta_2 \in \Theta$ and $0 \leq \gamma \leq 1$. To verify whether the density is of the form above as opposed to being of the form $f(x, \theta)$, one needs to statistically test the hypothesis of homogeneity

$$H_0 : \gamma = 0 \text{ or } \gamma = 1 \text{ or equivalently } \theta_1 = \theta_2$$

All of the above equivalent null hypotheses lead to the same conclusion that the observations are from a homogeneous population with one common density of the form $f(x; \theta)$.

The ordinary log-likelihood function is given by

$$l_n(\gamma, \theta_1, \theta_2) = \sum_{i=1}^{n} \log\{(1-\gamma)f(X_i, \theta_1) + \gamma f(X_i, \theta_2)\} \tag{2.2}$$

Let $\hat{\gamma}, \hat{\theta}_1, \hat{\theta}_2$ be the maximum likelihood estimators of the parameters under the whole parametric space $\Omega : \Omega_{H_0} \cup \Omega_{H_0}^C$, i.e., the maximizers of (2.2). Let also θ_0 be the maximizer of $l_n(1, \theta_0, \theta_0)$ over the parameter space $-\infty < \theta_0 < \infty$, i.e., maximum likelihood estimator of population parameter θ when the hypothesis of homogeneity is true. Then the LRT is to reject the null hypothesis H_0 if

$$R_n = 2\{l_n(\hat{\gamma}, \hat{\theta}_1, \hat{\theta}_2) - l_n(1, \hat{\theta}_0, \hat{\theta}_0)\} \tag{2.3}$$

is large enough. The asymptotic null distribution of R_n is used to determine a critical value for the test. However, due to the irregularity of the finite mixture models, the likelihood ratio statistic R_n does not have the usual χ^2 limiting distribution. The article by Ghosh and Sen (1985) provide a comprehensive account of the breakdown in regularity conditions for the classical asymptotic theory to hold for the likelihood ratio test statistic. Titterington *et al.* (1985) give a more intensive discussion regarding this problem.

2.2 Drawbacks of the Ordinary Likelihood Ratio Test

Chen and Chen (1998) show that when $f(x, \theta_0)$ is the true null distribution, the

asymptotic distribution of the LRT statistic for homogeneity H_0 is that of

$$\{\sup_{\theta\in\Theta} W^+(\theta)\}^2$$

where $W(\theta)$ is a Gaussian process with mean 0, variance 1 and autocorrelation function

$$\rho(\theta,\theta') = \frac{cov\{Z_i(\theta) - h(\theta)Y_i(\theta), Z_i(\theta') - h(\theta')Y_i(\theta_0)\}}{\sqrt{var\{Z_i(\theta) - h(\theta)Y_i(\theta_0)\}var\{Z_i(\theta') - h(\theta')Y_i(\theta_0)\}}}. \tag{2.4}$$

Here

$$Y_i(\theta) = Y_i(\theta,\theta_0) = \frac{f(X_i,\theta) - f(X_i,\theta_0)}{(\theta-\theta_0)f(X_i,\theta_0)}, \theta \neq \theta_0;\ Y_i(\theta_0) = Y_i(\theta_0,\theta_0) = \frac{f'(X_i,\theta_0)}{f(X_i,\theta_0)}. \tag{2.5}$$

$$Z_i(\theta) = Z_i(\theta,\theta_0) = \frac{Y_i(\theta) - Y_i(\theta_0)}{\theta-\theta_0}, \theta \neq \theta_0;\ Z_i(\theta_0) = Z_i(\theta_0,\theta_0) = \frac{dY_i(\theta,\theta_0)}{d\theta}|_{\theta=\theta_0}; \tag{2.6}$$

and

$$h(\theta) = \frac{E\{Y_i(\theta_0)Z_i(\theta)\}}{E\{Y_i^2(\theta_0)\}}. \tag{2.7}$$

This asymptotic result proves that the large sample behavior of the LRT is no longer a χ^2 distribution. Chen *et al.* (2001) summarize the main drawbacks of the LRT in these finite mixture problems. As we could see from the (2.4-2.7), the asymptotic distribution under the null hypothesis requires the true value of the unknown θ_0.

Chernoff and Lehmann (1954) also raise this issue in Pearson's χ^2-test with presence of nuisance parameters. Because of this complicated asymptotic distribution presented in the form of supremum of a Gaussian process, a simulation-based test is often used to obtain critical values for testing.

Finally, it is worth mentioning that the autocorrelation functions of the limiting Gaussian functionals, are different for different distributions. For example, Chen and Chen (1998) showed that, if $f(x,\theta)$ is a density of a $N(\theta,\sigma)$ with $\sigma = 1$ $\theta_0 = 0$, θ and $\theta' \neq 0$, we have the autocorrelation

$$\rho(\theta,\theta') = \frac{e^{\theta\theta'} - 1 - \theta\theta'}{\sqrt{(e^{\theta^2} - 1 - \theta^2)(e^{\theta'^2} - 1 - \theta'^2)}}.$$

However, for a Poisson distribution $e^{-\theta}\theta^x/x!$, $x = 1, 2, ...$, the autocorrelation is

$$\rho(\theta,\theta') = \frac{e^{\nu\nu'} - 1 - \nu\nu'}{\sqrt{(e^{\nu^2} - 1 - \nu^2)(e^{\nu'^2} - 1 - \nu'^2)}}$$

where

$$\nu = \frac{\theta - \theta_0}{\sqrt{\theta_0}} \qquad\qquad \nu' = \frac{\theta' - \theta}{\sqrt{\theta_0}}$$

2.3 Modified Likelihood Ratio Test

There are two complications in forming the asymptotic null distribution of the LRT. First one is that the null hypothesis $\gamma = 0$ or $\gamma = 1$ lies on the boundary of the parameter space. The second complication is that γ, θ_1 and θ_2 are not identifiable

under the null distribution. The main idea of the modified likelihood ratio test is to add an extra term in order to fix these two problems. The modified likelihood ratio test based on the following modified log-likelihood function $l'_n(\gamma, \theta_1, \theta_2)$ provides a satisfactory solution. For $0 < \gamma < 1, \theta_1, \theta_2 \in \Theta$ with $\theta_1 \leq \theta_2$, Chen *et al.* (2001) defined modified log-likelihood function as,

$$l'_n(\gamma, \theta_1, \theta_2) = \sum_{i=1}^{n} \log\{(1-\gamma)f(X_i, \theta_1) + \gamma f(X_i, \theta_2)\} + C\log\{4\gamma(1-\gamma)\}, \qquad (2.8)$$

where the constant $C > 0$ is used to control the level of modification to the log-likelihood function. Notice that in this formulation the values of $\gamma = 1$ and $\gamma = 0$ are excluded from the parameter space, however, the null hypothesis of homogeneity is now of the form $H_0 : \gamma = 1/2$.

Let $(\hat{\gamma}, \hat{\theta}_1, \hat{\theta}_2)$ maximize $l'_n(\gamma, \theta_1, \theta_2)$ over the full parameter space, $\Omega : \Omega_{H_0} \cup \Omega^C_{H_0}$ and let $\hat{\theta}_0$ maximize the null modified likelihood function $l'_n(\frac{1}{2}, \theta_0, \theta_0), \theta_0 \in \Theta$. The MLRT rejects the null hypothesis H_0 for large values of

$$M_n = 2\{l'_n(\hat{\gamma}, \hat{\theta}_1, \hat{\theta}_2) - l'_n(\frac{1}{2}, \hat{\theta}_0, \hat{\theta}_0)\} \qquad (2.9)$$

The additional term $C\log\{4\gamma(1-\gamma)\}$ in equation (2.8) is non-positive and is intended to discourage fits that result in values of γ that are close to either 0 or 1. In fact, we observe that the modification term explodes to negative infinity whenever γ is close to 0 or 1, thus solving the problem of the boundary during the estimation of the parameters and hopefully making the likelihood behave more tractably.

Chen *et al.* (2001) impose five regularity conditions on the kernel $f(x, \theta)$ which

must be met in order to establish the limiting distribution of the MLRT statistic. (Appendix A contains these conditions). Their main result is that, if conditions 1-5 in appendix A hold, the asymptotic null distribution of the MLRT statistic M_n is the mixture of χ_1^2 and χ_0^2 with equal weights, i.e.,

$$\frac{1}{2}\chi_0^2 + \frac{1}{2}\chi_1^2 \tag{2.10}$$

where χ_0^2 is a degenerate distribution with all its mass at 0.

Chen *et al.* (2001) suggested $C = \log(M)$ as an appropriate choice when the parameter θ is in the interval $[-M, M]$ for some large constant M. For instance, this could be the case when dealing with a practical problem in which the investigator can reasonably assume that the parameter will fall in a certain interval. However, based on the simulations done by Chen *et al.* (2001), the limiting distribution of the modified likelihood ratio test is not very sensitive to the choice of C. Also, to improve the limiting distribution for small samples, Chen *et al.* (2001) suggested the use of $p_n = P_{H_0}(M_n \leq 0)$ as the weight for the degenerate chi-square in the limiting distribution. The authors showed that the MLRT is asymptotically most powerful under the local alternatives (alternatives that are close to the null hypothesis). Through Monte Carlo simulations they also compared their MLRT to Neyman's $C(\alpha)$ test, the bootstrap test by McLachlan (1987) and the method of Davies (1987), and they found that the results of the MLRT are the most promising. Therefore, the MLRT is a reasonable choice to extensions to group sequential testing procedures.

3 Group Sequential MLRT

3.1 Introduction

Since last century, group sequential analysis has drawn great attention in clinical trials, epidemiological studies, quality control and safety studies. Group sequential experimentation is an area of statistics which is both of practical importance and also of great theoretical interest. Group sequential statistical analysis was originally developed to obtain economic benefits. Early stopping with positive results implies that the new product can be in market sooner whereas if a negative result is indicated, early stopping ensures that resources are not wasted. Group sequential methods typically lead to savings in sample size, time and cost in comparison to fix-sample (i.e., nonsequential) methods.

For ethical as well as practical reasons, investigators may wish to monitor a study and review it over time at interim looks to assess whether the research hypothesis is sufficiently supported to warrant early termination of the study. In a group sequential study, a test statistic is typically computed at each look and compared to a stopping boundary. Due to repeated looks at the data, this boundary is adjusted to maintain

some predetermined overall significance level. In order to design and monitor this type of study, the joint distribution of the sequentially computed statistics must be derived.

In section 3.2, we review the commonly used group sequential monitoring procedures with greater emphasis on the so called alpha-spending approach of Lan and DeMets (1983). Section 3.3 provides a simple group sequential study to help reader gain more understanding of the group sequential design. In section 3.4, we give the main result that the modified likelihood ratio test statistic behaves like a functional of a Brownian motion process and hence we illustrate how this result can be used to build monitoring boundaries, in particular, the Lan-Demets boundaries.

3.2 General Group Sequential Procedures

In general, a group sequential design with K planned interim analyses for testing the hypothesis $H_0 : \gamma = 0$ yields a sequence of test statistics $\{Z_1, ..., Z_k\}$. We say that this sequence of statistics has the *canonical joint distribution* with information levels $\{I_1, ..., I_k\}$ for the parameter γ if:

- $(Z_1, ..., Z_k)$ is multivariate normal,
- $E(Z_k) = \gamma\sqrt{I_k}$, $k = 1, ..., K$, and
- $Cov(Z_{k_1}, Z_{k_2}) = \sqrt{I_{k_1}/I_{k_2}}$, $1 \leq k_1 \leq k_2 \leq K$

This joint canonical distribution can often be shown to hold by approximating the sequence of statistics $Z_1, ..., Z_K$ by a Brownian motion process stopped at some time

points $t_1, ..., t_K$. These time points are usually given in the so called information time scale, $t_k = I_k/I_K$, where I_k is the information about the parameter of interest collected up to the analysis k and I_K is the information planned to be collected by the end of the study. The time points represent for each k, the fraction of information collected by the kth analysis. In many cases it can be shown that this fraction is approximately the same as the fraction of sample size collected up to the kth analysis, out of the total sample planned by the end of the study.

For example, suppose it is required to test a null hypothesis $H_0 : \gamma = 0$ versus $H_\alpha : \gamma \neq 0$. We consider group sequential tests in which up to K analysis are permitted and standardized statistics Z_k, $k = 1, ..., K$, are available at these analysis. If the sequence of statistics follows the canonical joint distribution, then we can easily compute monitoring boundaries $\pm c_1, ..., \pm c_K$ which satisfy a given type I error rate, α, by using numerical integrations that exploit the canonical joint distribution structure.

If, on the other hand, the canonical joint distribution does not hold, then computing the monitoring boundaries would require multivariate integrations that are highly computationally expensive even for number of analysis as large as $K = 7$.

There are many ways of choosing the boundaries $c_1, ..., c_K$, and in the next subsections we are going to review some boundaries that are commonly used in practice. We assume that the sequence of test statistics reject H_0 in favor of the alternative hypothesis only for large values of the test statistics.

Pocock's Procedure

Pocock (1977) adapted the idea of a "repeated significance test" at a constant nominal

significance level to analyze accumulating data at a relatively small number of times over the course of an experiment. This is the simplest group sequential procedure in the sense that it has constant monitoring boundaries (straight lines). This procedure assumed equal sample between analysis.

Formally, the test procedure is as follows:

- After group $k = 1, ..., K-1$ (with cumulative sample n_k)
  - if $|Z_k| \geq C_p(K, \alpha)$, stop and reject H_0
  - otherwise, continue to group $k+1$
- After group K
  - if $|Z_K| \geq C_p(K, \alpha)$, stop and reject H_0
  - otherwise, stop and accept H_0

The critical value $C_p(K, \alpha)$ is chosen to give a pre-fixed overall Type I error α, i.e.,

$$P_{\gamma=0}\{\text{Reject } H_0 \text{ at stage } k = 1, k = 2, ..., \text{ or } k = K\} = \alpha.$$

The Pocock's procedure results in a constant boundary, independent of the analysis, K. This constant boundary value is tabulated for various α and K (see Jennison and Turnbull (2000)). The Pocock's method is not based on any formal optimal properties such as minimizing sample size under some particular hypothesis. However, it is rational and easy-to-use form of stopping rule which gives the test an important position from a practical practical aspect. (Jennison and Turnbull 2000).

O'Brien & Fleming's Procedure

O'Brien and Fleming (1979) proposed a test in which the nominal significance levels needed to reject H_0 at each analysis increase as the study progresses. Thus, it is more difficult to reject H_0 at the earliest analyses but easier later on as the information available increases.

Consider the same experiment setup as in Pocock's Procedure, and assume that the sample sizes between analysis are equal. The O'Brien-Fleming test has the following algorithm

- After group $k = 1, ..., K-1$ (with cumulative
  - if $|Z_k| \geq C_B(K, \alpha)\sqrt{K/k}$, stop and reject H_0
  - otherwise, continue to group $k+1$
- After group K
  - if $|Z_K| \geq C_B(K, \alpha)$, stop and reject H_0
  - otherwise, stop and accept H_0

Since $C_B(K, \alpha)\sqrt{K/k}$ decreases with increasing k, the O'Brien-Fleming test has narrower boundaries at later analysis and hence, it is easier to reject H_0 at later analysis than at early analysis.

Error Spending Procedure

As both the Pocock and O'Brien & Fleming methods require equally spaced sample sizes between analyses, the boundaries cannot be computed in the course of the

monitoring process. In other words, modifying the times of analysis (say in the time scale of information fraction) or even reducing or increasing the frequency of interim analysis after the design stage, is not allowed. A violation of these assumptions leads to lower power and some times inflated type I error. To overcome such difficulties, Lan and DeMets (1983) proposed a flexible monitoring procedure known as the α-spending (or error-spending) function approach. The procedure requires only the specification, in advance, of an increasing function $\alpha(t)$, which characterizes the rate at which type I error, α, is spent.

Suppose the maximum number of analysis, K, is fixed before the study, and the Type I error is partitioned into probabilities $\alpha_1, ..., \alpha_K$, which sum to α. As information time $t_1 = I_1/I_K, ..., t_K = I_K/I_K = 1$ progresses, the two-sided critical values c_k for the standardized statistics $Z_{t_k}, k = 1, ..., K$, are calculated such that,

$$P_{\gamma=0}\{|Z_{t_1}| < c_1, ..., |Z_{t_{k-1}}| < c_{k-1}, |Z_{t_k}| \geq c_k\} = \alpha_k$$

Here, the Type I error is partitioned according to an error spending function $\alpha(t)$, which is non-decreasing and satisfies $\alpha(0) = 0$ and $\alpha(t) = \alpha$, for $t \geq 1$. The value of $\alpha(t)$ indicates the cumulative Type I error that is to be spent when a fraction t of the maximum anticipated information has been obtained. The error spending function and the target information level must be decided before the design stage before the experiment and data collection start.

The Type I errors allocated to each analysis are

$$\alpha_1 = \alpha(t_1) \tag{3.1}$$

$$\alpha_k = \alpha(t_k) - \alpha(t_{k-1}), k = 2, 3, ...K \tag{3.2}$$

Critical values c_k are computed successively to satisfy (3.2) by using numerical integration that exploit the canonical joint distribution of the test statistics. Equivalently, the cumulative error can be used to compute the boundaries

$$\alpha_k = \alpha(t_k) = \sum_{i=1}^{k} P\{|Z_{t_1}| < c_1, \ldots, |Z_{t_{i-1}}| < c_{i-1}, |Z_{t_i}| \geq c_i | H_0\}.$$

There are several α-spending functions proposed in the literature which result in various boundary shapes. There is no one best function, and often investigators use α-spending functions that approximate well the two well-known procedures of Pocock and O'Brien-Fleming. For instance, the function

$$\alpha(t) = \alpha t^{\rho}, \tag{3.3}$$

where $\rho > 0$ is a tuning parameter which controls the shape of the boundary, is studied in Lan and DeMets (1983). For $\rho = 1$ we get a boundary that mimics Pocock's boundary, whereas, $\rho = 2$ results in a boundary similar to that of O'Brien-Fleming.

The algorithm for monitoring a group sequential testing procedure is, thus, not different than the ones we have seen for Pocock's and O'Brien-Fleming's procedures.

3.3 An Illustrative Example

In a typical two-arm randomized clinical trial, subjects are recruited and divided into two groups, a control group A and an experimental group B. Suppose that, on the basis of a normally distributed response and a known common variance σ^2, we are interested in testing the null hypothesis of the equality of the means of the two populations, $H_0 : \mu_A - \mu_B = 0$, with overall significant level $\alpha = 0.05$ versus the alternative hypothesis $H_\alpha : |\mu_A - \mu_B| = \delta$ with power $1 - \beta$. Suppose the maximum projected sample size is 60 on each arm with 4 interim looks, the testing procedure will be carried out based on a two-sided O'Brien-Fleming boundary computed through the α-spending function $\alpha t^2 = .05t^2$. If we adopt a monitoring schedule with equal sample size increments at each analysis, then we should perform our analysis at the times when $n_1 = 30, n_2 = 60, n_3 = 90$ and $n_4 = 120$ cumulative sample sizes are available or equivalently, on the information fraction time scale, at times $t_1 = 30/120 = .25, t_2 = .5, t_3 = .75, t_4 = 1$. The test uses the following standardized statistic after each group of observations,

$$Z_k = \frac{1}{\sqrt{4\sigma^2/n_k}} \left(\bar{X}_{Ak} - \bar{X}_{Bk}\right) \tag{3.4}$$

where $k = 1, ..., 4$ and $\bar{X}_{Ak}$ and $\bar{X}_{Bk}$ are, respectively, sample mean for group A and B based on the cumulative data collected on each group up to the analysis k. The corresponding boundary values are $\{\pm 4.408, \pm 2.862, \pm 2.337, \pm 2.204\}$. The upper and lower arms of Figure 3.1 illustrate these boundaries at the four analysis times. Suppose that after the first analysis, our data gives a standardized test statistic with

the value 0.711 for the first 15 subjects. The test statistic Z_1 falls in the continuation region so, we continue data collection and we prepare for the second analysis. Suppose that the test statistic Z_2 at the second analysis has a value of 2.201 and is still within the continuation region. Thus, 45 subjects are collected in order to do the third analysis. At the third stage, we have a statistic Z_3 with a value of 2.685 and the procedure rejects the null hypothesis. Therefore, we stop the whole study and conclude our result that there is a significant difference between Group A and Group B in their mean responses. The design boundaries and testing statistics at each analysis are displayed in Figure 3.1.

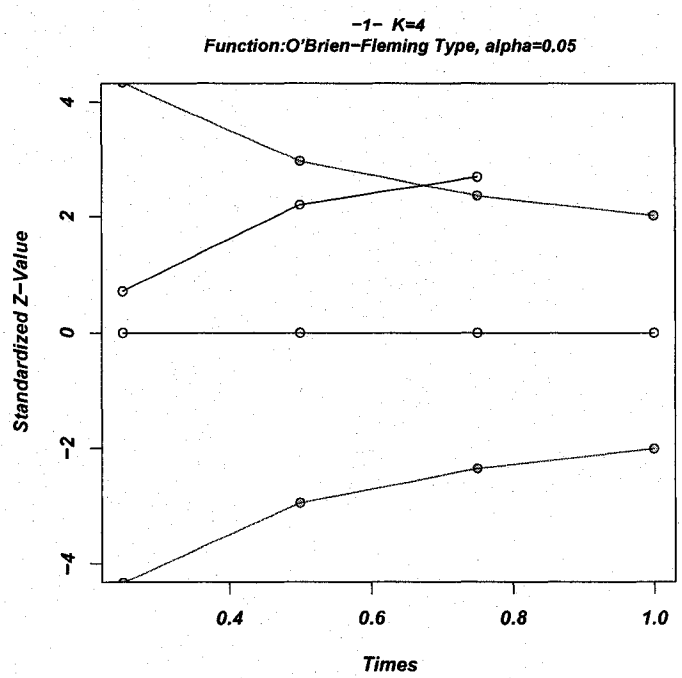

Figure 3.1: Group Sequential Design Example

3.4 Group Sequential MLRT

For the purpose of group sequential monitoring, it is sufficient to show that the finite dimensional distribution of a continuous processes, converge to those of a standard Brownian motion and that the MLRT is a some tractable function of such a process. The Brownian motion process has independent increment structure and joint multivariate normal distribution at any given set of K time points $t_1, t_2, ..., t_K$, as required by the general setup of group sequential methods described in the previous section. Therefore, the MLRT will also benefit from such canonical structure and the monitoring boundaries can then be computed by using the usual numerical integrations. We define a weighted and continuous version of the MLRT statistic as $[nt]/nM_{[nt]}$ for $n = 1, 2, 3, \ldots$ where $t \in [0, 1]$, $[nt]$ is the integer part of nt and n is the final sample size planned at the end of the study. This is simply a weighted interpolation of the modified likelihood ratio test M_n. It has been shown by Chen *et al.* (2001) that

$$M_n = \frac{((\sum_{i=1}^{n} W_i)^+)^2}{nE[W_1^2]} + o_p(1)$$

where $W_i = Z_i - hY_i$ and $h = E[YZ]/E[Y^2]$. The quantities $Y_i = Y_i(\theta_0)$ and $Z_i = Z_i(\theta_0)$ are defined in Section 2.2. The random variables W_i have mean zero and variance $E[W_i^2]$. Under the null hypothesis, H_0, and in virtue of condition 4 in the appendix, it is easy to see that

$$Var(W_i) = E\left[W_i^2\right] = E\left[(Z_i - hY_i)^2\right] \leq E\left[Z_i^2\right] + h^2 E\left[Y_i^2\right] + 2|h|E|Y_i Z_i| < \infty,$$

i.e., the random variables W_i have finite variance. By noticing that $[nt]/n \to t$ as $n \to \infty$, we can write the above approximation in terms of the interpolated MLRT process as follows,

$$\frac{[nt]}{n} M_{[nt]} = \left[\left(\frac{1}{\sqrt{n}} \sum_{i=1}^{[nt]} \frac{W_i}{\sqrt{EW_1^2}} \right)^+ \right]^2 + o_p(1)$$

For simplicity of notations, put $\xi_i = \frac{W_i}{\sqrt{EW_1^2}}$, which are i.i.d random variables with mean 0 and variance 1, and write the interpolated and normalized partial sum process

$$S_t^n = \frac{1}{\sqrt{n}} \sum_{i=1}^{[nt]} \xi_i, \quad t \in [0,1].$$

Now, classical results on convergence in distribution for random measurable functions on $[0,1]$ apply. In particular, Donsker's theorem (Billingsley 1968), states that, as $n \to \infty$, $S_t^n \xrightarrow{\mathcal{D}} B(t)$, where $B(t)$ is a standard Brownian motion on the interval $[0,1]$. Furthermore, since the function $h(x) = (x^+)^2$ is continuous, it follows that such convergence still holds under the the transformation $h(.)$ so that

$$h(S_t^n) = [(S_t^n)^+]^2 \xrightarrow{\mathcal{D}} [B(t)^+]^2.$$

As a consequence, the finite dimensional distributions of $[(S_t^n)^+]^2$ converge to those of the squared positive part of the Brownian motion process. That is; if $t_1, t_2, \ldots, t_K$

are fixed time points, then

$$\left(\left[(S^n_{t_1})^+\right]^2,\ldots,\left[(S^n_{t_K})^+\right]^2\right)\xrightarrow{\mathcal{D}}\left(\left[(B(t_1))^+\right]^2,\ldots,\left[(B(t_K))^+\right]^2\right).$$

Now, since $n/[nt]\to 1/t$ as $n\to\infty$, by using the multivariate version of Slutsky's theorem (Theorem 5.1.6 in Lehmann (1999, p.283)) and the Cramer-Wald device (see Lehmann (1999)), one can show that

$$\left(\left[\left(\sqrt{\frac{n}{[nt_1]}}S^n_{t_1}\right)^+\right]^2,\ldots,\left[\left(\sqrt{\frac{n}{[nt_K]}}S^n_{t_K}\right)^+\right]^2\right)\xrightarrow{\mathcal{D}}$$
$$\left(\left[\left(\frac{B(t_1)}{\sqrt{t_1}}\right)^+\right]^2,\ldots,\left[\left(\frac{B(t_K)}{\sqrt{t_K}}\right)^+\right]^2\right)$$

as $n\to\infty$. In summary, by setting $n_k/n=t_k$ where n_k is the sample size up to the analysis k and n is the sample size at the end of the study, we can state the following result:

Theorem 1 *Assume that conditions 1-5 in the appendix and H_0 hold, and let $0\le t_1\le t_2\le\ldots,\le t_K$ be some fixed time points in the interval $[0,1]$ for $k=1,...,K$ (fixed as $n\to\infty$). Then the modified likelihood ratio test process, $M_t=M_{[nt]}$ defined above has its finite dimensional distributions converging to those of the squared positive part of standardized Brownian motion. That is,*

$$(M_{t_1},\ldots,M_{t_K})\xrightarrow{\mathcal{D}}\left(\left[\left(\frac{B(t_1)}{\sqrt{t_1}}\right)^+\right]^2,\ldots,\left[\left(\frac{B(t_K)}{\sqrt{t_K}}\right)^+\right]^2\right)\ \text{as } n\to\infty$$

3.4.1 Information-based Design

As mentioned above, in a group sequential study designed according to an α-spending function approach, has three steps to follow. First, one has to specify an overall probability of type I error,α, and the total sample size needed for attaining certain desired power. Secondly, one has to decide the boundary type, which depends on the α-spending function, and the times of analysis, which are usually equally spaced in the sense that the analysis are performed at equal sample size increments. The third step is to compute the monitoring boundaries and start collecting the data. If the analysis times are modified along the way one has to modify the current and the future boundaries to adjust for the changes. These steps can also be formulated in the context of testing homogeneity of a mixture using the MLRT and with the help of the above theorem.

Suppose that we plan a group sequential study for testing the homogeneity in finite mixture models based on K interim analysis. Suppose that these interim analysis are planned at time points $0 = t_0 \leq t_1, \ldots, \leq t_K = 1$ when $n_1, ..., n_K$ cumulative samples are collected. Suppose also that we intend using a boundary based on $\alpha(t)$, an α-spending function. As we mentioned earlier, $\alpha(t)$ gives the cumulative portion of the Type I error that has been spent on or prior to the kth interim analysis. The boundaries, $c_1, c_2, \ldots, c_K$ for monitoring the MLRT statistic at the interim analysis $t_1, \ldots, t_K$ can be computed from the equations

$$\alpha_1 + ... + \alpha_k = \alpha(t_k) = \sum_{i=1}^{k} P\{M_{t_1} < c_1, \ldots, M_{t_{i-1}} < c_{i-1}, M_{t_i} \geq c_i | H_0\} \qquad (3.5)$$

for $k = 1, 2, \ldots, K$ and M_{t_i} is the MLRT value computed at time t_i, i.e., when there is n_i cumulative sample collected of the total n planned for. By using the approximating positive-part Brownian motion process defined in the theorem, this is almost the same as monitoring the process $\left[B^+(t_k)/\sqrt{t_k}\right]^2$ and therefore,

$$\begin{aligned}
\alpha(t_k) &\approx \sum_{i=1}^{k-1} P\left\{\left[\frac{B^+(t_1)}{\sqrt{t_1}}\right]^2 < c_1, \ldots, \left[\frac{B^+(t_{i-1})}{\sqrt{t_{i-1}}}\right]^2 < c_{i-1}, \left[\frac{B^+(t_i)}{\sqrt{t_i}}\right]^2 \geq c_i | H_0\right\} \\
&= \sum_{i=1}^{k-1} P\left\{\frac{B^+(t_1)}{\sqrt{t_1}} < \sqrt{c_1}, \ldots, \frac{B^+(t_{i-1})}{\sqrt{t_{i-1}}} < \sqrt{c_{i-1}}, \frac{B^+(t_i)}{\sqrt{t_i}} \geq \sqrt{c_i} | H_0\right\} \quad (3.6) \\
&= \sum_{i=1}^{k-1} P\left\{\frac{B(t_1)}{\sqrt{t_1}} < \sqrt{c_1}, \ldots, \frac{B(t_{i-1})}{\sqrt{t_{i-1}}} < \sqrt{c_{i-1}}, \frac{B(t_i)}{\sqrt{t_i}} \geq \sqrt{c_i} \mid H_0\right\} \quad (3.7)
\end{aligned}$$

The second equality, (3.6), is obvious and the third one, (3.7), follows by arguing that, since the numbers c_i are all strictly positive, the origin of the K-dimensional Euclidean space is always excluded from the volume of interest by the restriction $\frac{B(t_i)}{\sqrt{t_i}} \geq \sqrt{c_i}$. Therefore, the parts of the area of interest where some coordinates are negative and which, under the positive-part function, are collapsed to the hyperplanes defining the positive orthant can be thought of as being expanded back and hence, as giving, along with the volume in the positive orthant, the original volume under a multivariate normal density of the type given above. Thus, monitoring the process $\left[B^+(t_k)/\sqrt{t_k}\right]^2$ is same as monitoring $B(t_k)/\sqrt{t_k}$. The importance of (3.7) is that we can simply use the tabulated critical values for the known group sequential procedures such as Pocock and OBF procedures or any software that produces monitoring boundaries based on α-spending functions. For instance, if we were to conduct a group sequential monitoring using Pocock's boundary (which is a constant) with overall significance

level of $\alpha = 0.05$, then the desired constant boundary would be $c = C_P^2(0.1)$, where $C_P(0.1)$ is the Pocock boundary corresponding to the monitoring of a Z-score at level $\alpha = 0.1$.

In summary, the steps followed in designing the usual group sequential designs can also be followed in testing homogeneity of mixture via a group sequential MLRT.

4 Simulations

In order to assess the performance of the group sequential modified likelihood ratio test proposed in the previous chapter, we conduct several Monte Carlo simulations. The first two of these Monte Carlo simulations follow the same setups as in Chen *et al.* (2001) and they use Normal and Poisson mixture models. Apart from the null models (where homogeneity is assumed) four normal and four Poisson mixtures with different parameters are considered under the alternative hypothesis of non-homogeneity. The third simulation considers the binomial mixture models arising from genetic linkage analysis. We briefly introduce the background of the linkage analysis and relate our problem as testing the homogeneity in the binomial mixtures. The discussed *phase known* and *phase unknown* situations are both considered with various parameter settings.

4.1 Normal and Poisson Mixtures

The most important class of finite mixture densities is the class of normal mixtures. The reasons for the importance and widespread use of normal mixtures are not inci-

dental. One of the reasons is that a univariate normal distribution has a simple and concise representation requiring only two parameters, the mean μ and the variance σ^2. The normal density is symmetric, unimodal, and assumes the least prior knowledge in estimating an unknown probability density with a given mean and variance. These characteristics along with its well-studied status give normal mixture density models the power and effectiveness that other mixtures can hardly surpass. Fields in which normal mixture models are used are various ranging from genetics (Schork *et al.* 1996) to the study of sensitivity of medical screening tests (McDonnell *et al.* 1998), in the absence of gold standard, to machine learning applications. Within the statistical methodology, normal mixture models have been used in the investigation of the performances of certain estimators to departures from normality and in the development of robust estimators. Examples of many other areas where normal mixtures are applied can be found in McLachlan and Peel (2000).

The Poisson mixtures are used in many practical situations. Two important areas of applications for the Poisson mixtures are the modeling of over- or under-dispersion and zero-inflation in count data. Often, count data (mostly in toxicological, biological and medical data) are modeled as if they were coming from a Poisson distribution with certain mean (or rate). An important assumption of the Poisson distribution is that the mean and the variance are equal. Data sets in which evidence against mean-variance equality is present are called *over- or under-dispersed.* One way of dealing with such data is to fit a mixture of Poisson distributions with continuous mixing variable distributed as Gamma. The second problem referred to as zero-inflated Poisson distribution problem. It arises when there are more zeros in the data than

expected by a Poisson distribution. A common technique to handle such situations is to assume that the extra zeros are due to the presence of unobservable subpopulation whose counts are zero. Therefore, the model used in such cases is a two-component mixture, one from a Poisson distribution and the other taking only the value zero with some probability. However, the use of Poisson mixtures to account for over-under-dispersion has received considerable attention in the literature.

In the simulation setups, we draw random variables x_i from a mixture of two univariate normal components with common variance σ^2 and means μ_1 and μ_2 in proportions γ and $1-\gamma$ so that

$$f(x_i) = \gamma\phi(x_i;\mu_1,\sigma^2) + (1-\gamma)\phi(x_i;\mu_2,\sigma^2) \tag{4.1}$$

where

$$\phi(x_i;\mu,\sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} exp\{-\frac{1}{2}\frac{(x_i-\mu)^2}{\sigma^2}\}.$$

Similarly, we draw y_i from Poisson mixtures with only two components,

$$(1-\gamma)\theta_1^{y_i}\frac{exp(-\theta_1)}{y_i!} + \gamma\theta_2^{y_i}\frac{exp(-\theta_2)}{y_i!}. \tag{4.2}$$

The four alternative normal mixture models were chosen so that each model has mean $(1-\gamma)\theta_1 + \gamma\theta_2 = 0$ and variance $(1-\gamma)\theta_1^2 + \gamma\theta_2^2 = \frac{1}{4}$. The four Poisson mixture alternative models are chosen so that each of them has mean $(1-\gamma)\theta_1 + \gamma\theta_2 = 5$ and variance $(1-\gamma)(\theta_1-5)^2 + \gamma(\theta_2-5)^2 = 1$.

Although Chen *et al.* (2001) suggested the use of $C = \log(10) = 2.303$ for Normal mixtures with means falling in $[-10, 10]$, we have found, in the process of our simulations, that $C = 1$ gives better results. The values of the alternative being considered are summarized in Table 4.1. Two most commonly used test procedures, Pocock's procedure and O'Brien & Fleming's procedure, are considered in this simulation study.

Normal Mixtures			Poisson Mixtures		
γ	θ_1	θ_2	γ	θ_1	θ_2
0.50	-0.500	0.500	0.50	4.000	6.000
0.75	-0.866	0.289	0.75	3.268	5.577
0.90	-1.500	0.167	0.90	2.000	5.333
0.95	-2.179	0.115	0.95	0.641	5.229

Table 4.1: Parameters of the normal and Poisson models considered in the simulation study

Sample sizes were varied over the set $n = 50, 100, 150, 200, 500$, the nominal significance levels were varied over $\alpha = 0.01, 0.05, 0.10$ and at each combination of the above parameters and these sample sizes, 5000 Monte Carlo experiments were performed. Both the rejection rates and average sample sizes are recorded. For comparison purposes, results for the nonsequential designs are also reported. This, of course, corresponds to $K = 1$ (i.e., only one interim analysis).

Tables (4.2-4.7) report the simulation results for normal Mixtures and Tables (4.8-4.13) report the results for Poisson Mixtures. In general, the proposed procedures have similar behaviors with respect to both models, normal and Poisson. The simulated Type I errors at actual $\alpha = 0.01$ are mostly inflated as compared to $\alpha = 0.1, 0.05$. This is more so for the Poisson model as compared to the normal and Pocock's

procedure as compared to the OBF (see the blocks headed by H_0 in Tables 4.2-4.13). The OBF procedure's simulated type I error is within the expected limits in majority of the cases. This is quite reasonable as the Pocock procedure rejects more often at early stages given its straight line boundaries. When $\alpha = 0.05, 0.1$, both procedures maintain their type errors within the expected limits although the OBF is much better even for these type I error rates. The type I errors deviate more from the actual as the number of analyses, K, increase (as expected).

In terms of power, the OBF has slightly higher power than Pocock's procedure and both are lower but comparable to the power of the fixed-sample tests that have the same maximum sample size (see the columns headed by number of analysis=1). However, the sequential MLRT procedures (Pocock and OBF) both offer an average sample saving of $30-50\%$ over what a fixed-sample MLRT would require to make the same decision. For instance, an OBF procedure for testing homogeneity of normal mixtures (see the last row in the block $\gamma = 0.75$ of Table 4.6) with $K = 10$ analyses has power 97.69 and average sample size (ASN=227) whereas a similar fixed-sample test has 98.50 power and $n = 500$ sample size to detect heterogeneity of the mixture. The power of the sequential procedures decrease as K increases, as expected, and this decrease ranges from $0-5\%$ for K ranging from 1 to 10.

Our simulation results for the fixed-sample MLRT design are consistent with those of Chen *et al.* (2001). It is evident that the group sequential MLRT, derived in this thesis, are well suited for both normal mixtures with known variances and Poisson mixtures. Even with a sample as small as 50 and mixtures with very high mixing proportions ($\gamma = 0.95$), the powers of the group sequential MLRTs are still very

reasonable. For practical use, however, we would recommend the OBF procedure over that of Pocock for it maintains better the type I error rates.

4.2 Binomial Mixtures: Application to Linkage Analysis

Genetic linkage is due to the phenomenon that alleles at different loci on a single chromosome are often transmitted together from parent to offspring. On the other hand, even when the loci are physically close, alleles on different homologous chromosomes are sometimes transmitted to one offspring. When the latter occurs, a recombination event is said to have separated the two loci. The recombination fraction θ, between two loci is the relative frequency of recombination. If the loci are on different chromosomes (i.e. $\theta = 0.5$), which implies no linkage, and if they are on the same chromosome, we suppose $0 \leq \theta < 0.5$.

There are two situations that commonly occur in human genetics, phase-known where the density function is a Binomial distribution function, and phase-unknown where the density function is the weighted sum of two symmetric binomial distributions (Ott 1999).

Phase-Known: Suppose we consider the case of autosomal linkage. Autosomal chromosomes occur as pairs, and if two loci are syntenic, then alleles inherited from a single parent must be on the same chromosome in the offspring. Autosomal loci are said to have known phase if the distribution of alleles on chromosome pairs can be determined without ambiguity.

Phase-Unknown: The phase-unknown occurs in many practical applications. For example, consider the case of a rare recessive disease, for which two alleles carrying a mutation must be present if the trait is expressed. Usually, the grandparents that have transmitted the disease alleles can not be determined and therefore, the parental phase is unknown even if the marker locus is fully informative.

Our main concern here is the detection of genetic linkage when linkage heterogeneity exists. Following Morton (1956), by linkage heterogeneity we mean variation in the recombination fraction between two loci studied in different families. Smith (1963) outlined several reasons for heterogeneity of human linkage data. It was postulated that the use of a statistical test that assumes homogeneity when heterogeneity is present will result in a considerable reduction in power to detect linkage. Testing the genetic linkage under heterogeneity is closely related to the problem of statistical inference from mixture models. Heterogeneity in linkage entails that, both in phase-known and phase unknown cases, the binomial models become two-component mixtures of binomials. The two components represent linked and unlinked subgroups of the population of families in a study. The density of the binomial mixture models representing the phase-known and phase-unknown are;

- PK case: $f(x_i;\theta)=\gamma B(m,\theta)+(1-\gamma)B(m,1/2)$
- PU case: $f(x_i;\theta)=\gamma[(1/2)B(m,\theta)+(1/2)B(m,1-\theta)]+(1-\gamma)B(m,1/2)$,

where γ is the fraction with linkage, m is the family size (which need not be the same for all families), θ is the recombination fraction in the linked families.

Here, we perform extensive Monte Carlo simulations to study the performance of the Pocock and OBF group sequential MLRTs for the type of binomial mixtures

explained above. As before, we take $n = 50, 100, 150, 200$ and 500 and family sizes of $m = 2, 4, 8$. The binomial variables x_i, which represent the number of recombinants in the family, are generated from the distribution $\gamma f(x_i;\theta)+(1-\gamma)f(x_i;0.5)$, $0 \leq \gamma \leq 1$ and $0 \leq \theta \leq 0.5$, where $f(x_i;\theta)$ represents either the single binomial or the symmetric weighted binomial described above. The log likelihood function is

$$l_n(\gamma,\theta) = \sum_{i=1}^{n} log\{\gamma f(x_i;\theta) + (1-\gamma)f(x_i;0.5)\} + Clog(4\gamma(1-\gamma))$$

for the chosen constant $C = 1$. Under the null hypothesis of $\theta = \theta_0 = 1/2$, both mixtures reduce to $B(m, 1/2)$. To generate the data under the alternatives when a portion of the families is linked, we have chosen $\gamma = 0.1, 0.2$ and $\theta = 0.1, 0.01$. For instance, the combination $(\gamma, \theta) = (0.1, 0.1)$ means that only 10% of the families are linked with recombination fraction $\theta = 0.1$. For each set of sample size $n = 50, 100, 150, 200, 500$ and family sizes $m = 2, 4, 8$ under both the null and alternative parameter configurations, 5000 Monte Carlo replicates are generated to estimate the power, the type I error and average sample sizes (ASN) for the various testing procedures.

In this simulation, we have used actual $\alpha = 0.01, 0.05, 0.1$, however, to save the space, we only report the results for $\alpha = 0.05$. From Tables (4.14-4.25), we can make the following remarks:

- Overall, in the PK case and specially for large family sizes $m = 4, 8$, both Pocock and OBF procedures maintain the actual type I error, although again, the OBF procedure seems to be doing better. The type I errors are inflated a bit in the PU cases for $m = 2$ and sometimes for $m = 4$.

- Both Pocock's procedure and OBF procedure are comparable in terms of power for detecting linkage heterogeneity and both are comparable, although bit lower, to that of the fixed-sample MLTRs. Both procedures save up to 50% of the sample sizes required by the fixed-sample MLRT, but they are about $0-5\%$ less powerful. For instance, the row headed by $n = 150$ in the last block of Table 4.20 reveals that an OBF procedure with $K = 10$ analysis would detect heterogeneity in populations, where $\gamma = 20\%$ of the families are linked with recombination fraction of $\theta = 1\%$, with power the 95.15% and average sample size of ASN=77. This is contrasted with the fixed-sample MLRT which would require $n = 150$ sample size and would detect the same heterogeneity with power 95.76%. This means that the OBF group sequential version of the MLRT procedure offered an average sample saving of 50% over the fixed-sample (nonsequential) design with virtually no loss of power.

- The statistical power for all the procedures is considerably smaller in the PU case than in the PK. This discrepancy in statistical power between the PK and PU cases depends heavily on the percentage of families linked, the recombination fraction among those linked and the family size. The power is, in general, higher when the fraction of linked families is higher and/or the fraction of recombinants within the linked families is higher. Of course, larger family size m also entails better power as does larger sample size, n. However, one could choose to lose some sample sizes by using the OBF procedure in order to have a larger statistical power.

In summary, we can again safely recommend the OBF group sequential MLRT

procedure for testing homogeneity in binomial mixtures that arise from genetic linkage analysis. A caution should be exercised if the family sizes are small ($m = 2$), as the type I errors could be inflated, especially in the PU cases.

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	1.26	(50.00)	1.24	(49.83)	1.08	(49.73)	0.84	(49.73)
	100	1.00	(100.00)	1.18	(99.67)	1.38	(99.304)	1.08	(99.36)
	150	1.54	(150.00)	1.36	(149.42)	1.30	(148.98)	1.18	(148.96)
	200	1.46	(200.00)	1.32	(199.22)	1.40	(198.54)	1.24	(198.70)
	500	1.22	(500.00)	1.20	(498.25)	1.22	(497.20)	1.48	(495.58)
$\gamma = 0.50$									
	50	14.32	(50.00)	11.94	(48.74)	11.16	(47.98)	8.80	(48.12)
	100	27.18	(100.00)	24.72	(94.64)	21.88	(92.34)	18.66	(92.62)
	150	36.68	(150.00)	35.50	(138.62)	32.12	(133.03)	30.06	(131.69)
	200	50.58	(200.00)	46.14	(179.36)	41.86	(169.98)	40.46	(167.57)
	500	89.60	(500.00)	87.50	(366.45)	84.70	(314.22)	83.04	(298.71)
$\gamma = 0.75$									
	50	15.80	(50.00)	15.94	(49.18)	12.86	(47.70)	11.64	(47.51)
	100	31.62	(100.00)	27.52	(94.01)	25.00	(90.09)	24.04	(90.28)
	150	46.60	(150.00)	42.16	(136.13)	38.06	(129.08)	34.72	(129.09)
	200	58.52	(200.00)	53.60	(175.64)	48.92	(163.64)	47.50	(160.41)
	500	94.02	(500.00)	92.42	(346.15)	90.32	(285.22)	89.34	(269.51)
$\gamma = 0.90$									
	50	18.46	(50.00)	17.24	(47.94)	15.24	(47.01)	14.42	(47.03)
	100	33.24	(100.00)	30.52	(93.08)	27.72	(89.57)	26.80	(89.13)
	150	46.38	(150.00)	43.90	(134.43)	41.70	(126.13)	38.14	(125.58)
	200	60.52	(200.00)	55.32	(172.96)	53.04	(159.19)	49.96	(156.54)
	500	94.36	(500.00)	93.28	(341.65)	91.22	(278.54)	89.90	(261.89)
$\gamma = 0.95$									
	50	15.26	(50.00)	15.02	(48.13)	13.30	(47.26)	11.98	(47.18)
	100	25.26	(100.00)	25.08	(94.23)	24.28	(90.24)	22.08	(89.97)
	150	38.00	(150.00)	36.12	(136.92)	32.88	(130.87)	31.92	(128.43)
	200	48.98	(200.00)	46.46	(177.56)	42.88	(166.54)	41.60	(163.00)
	500	85.94	(500.00)	85.20	(367.35)	82.24	(311.18)	80.42	(299.27)

Table 4.2: Pocock's Procedure: Normal Mixtures at $\alpha = 0.01$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.96	(50.00)	5.12	(49.24)	4.87	(48.77)	5.14	(48.62)
	100	5.32	(100.00)	5.70	(98.40)	5.12	(97.20)	5.37	(96.86)
	150	5.32	(150.00)	5.52	(147.43)	5.48	(145.66)	5.84	(145.09)
	200	4.88	(200.00)	5.21	(196.78)	5.95	(194.64)	5.32	(193.71)
	500	5.52	(500.00)	5.43	(491.48)	5.14	(485.41)	5.50	(481.00)
$\gamma = 0.5$									
	50	32.41	(50.00)	28.91	(46.17)	26.34	(44.46)	24.93	(44.05)
	100	49.31	(100.00)	46.27	(87.67)	42.74	(82.61)	40.53	(80.96)
	150	63.23	(150.00)	59.10	(124.89)	55.27	(113.98)	53.26	(111.63)
	200	73.94	(200.00)	70.09	(159.04)	66.11	(140.64)	64.20	(136.25)
	500	96.89	(500.00)	96.43	(312.95)	94.69	(237.24)	93.26	(217.84)
$\gamma = 0.75$									
	50	35.14	(50.00)	31.72	(45.82)	29.08	(43.61)	27.41	(43.36)
	100	53.33	(100.00)	50.59	(86.30)	47.33	(79.78)	45.02	(78.21)
	150	68.99	(150.00)	64.91	(121.82)	58.68	(106.21)	61.90	(109.36)
	200	79.74	(200.00)	75.36	(154.07)	71.86	(134.15)	69.93	(128.66)
	500	98.66	(500.00)	97.96	(297.80)	97.22	(214.88)	96.41	(197.23)
$\gamma = 0.9$									
	50	34.94	(50.00)	32.82	(45.55)	31.02	(43.21)	29.69	(42.67)
	100	53.37	(100.00)	50.98	(85.96)	48.61	(78.39)	46.39	(77.17)
	150	67.32	(150.00)	97.68	(131.80)	61.07	(108.99)	60.32	(104.78)
	200	76.90	(200.00)	74.48	(153.05)	72.20	(126.63)	64.28	(121.77)
	500	97.98	(500.00)	97.68	(297.35)	96.58	(215.76)	96.14	(194.32)
$\gamma = 0.95$									
	50	34.78	(50.00)	34.10	(45.26)	33.62	(42.36)	32.56	(41.61)
	100	53.22	(100.00)	51.70	(84.72)	49.66	(77.05)	48.50	(75.40)
	150	66.40	(150.00)	65.50	(119.63)	63.76	(104.69)	63.14	(99.95)
	200	76.16	(200.00)	76.52	(152.62)	73.72	(127.57)	73.34	(121.01)
	500	97.80	(500.00)	97.68	(297.35)	96.96	(212.02)	96.86	(185.76)

Table 4.3: Pocock's Procedure: Normal Mixtures at $\alpha = 0.05$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	9.06	(50.00)	9.50	(48.49)	9.56	(47.44)	9.12	(47.24)
	100	10.26	(100.00)	10.06	(96.80)	10.42	(94.82)	9.24	(94.29)
	150	9.70	(150.00)	9.32	(145.73)	10.44	(141.67)	10.52	(140.60)
	200	10.56	(200.00)	10.98	(192.70)	10.06	(189.14)	9.96	(187.72)
	500	10.44	(500.00)	10.52	(484.10)	10.40	(472.58)	10.68	(467.61)
$\gamma = 0.50$									
	50	41.86	(50.00)	41.14	(44.13)	38.28	(41.08)	34.90	(40.93)
	100	61.54	(100.00)	57.80	(82.87)	55.18	(74.24)	52.88	(72.19)
	150	74.34	(150.00)	69.92	(117.18)	67.56	(101.16)	65.06	(96.66)
	200	83.56	(200.00)	79.84	(146.58)	76.86	(122.64)	75.16	(116.79)
	500	98.96	(500.00)	98.14	(290.50)	97.08	(203.14)	96.56	(182.88)
$\gamma = 0.75$									
	50	45.82	(50.00)	44.34	(43.65)	41.86	(40.51)	39.58	(39.49)
	100	65.42	(100.00)	63.94	(80.76)	60.26	(71.62)	56.30	(70.23)
	150	78.16	(150.00)	75.74	(113.06)	72.72	(96.50)	71.08	(91.94)
	200	86.64	(200.00)	84.66	(141.64)	82.00	(114.82)	80.06	(109.80)
	500	99.26	(500.00)	99.14	(280.20)	98.44	(185.40)	98.28	(163.94)
$\gamma = 0.90$									
	50	46.12	(50.00)	44.50	(43.27)	42.46	(40.11)	39.42	(39.57)
	100	64.16	(100.00)	63.14	(80.75)	60.12	(70.98)	58.66	(68.40)
	150	76.56	(150.00)	73.72	(113.97)	72.46	(95.93)	71.58	(90.66)
	200	85.12	(200.00)	83.20	(143.40)	79.74	(117.82)	80.42	(107.45)
	500	99.06	(500.00)	98.56	(283.60)	98.32	(185.48)	98.26	(161.22)
$\gamma = 0.95$									
	50	39.44	(50.00)	37.44	(44.38)	35.76	(41.47)	35.48	(40.47)
	100	54.04	(100.00)	52.70	(84.27)	52.14	(74.52)	48.84	(73.57)
	150	66.48	(150.00)	64.08	(119.94)	62.62	(104.04)	61.42	(99.41)
	200	74.24	(200.00)	72.08	(153.12)	71.44	(128.18)	69.88	(121.53)
	500	95.20	(500.00)	95.38	(308.90)	94.78	(222.10)	84.40	(193.21)

Table 4.4: Pocock's Procedure: Normal Mixtures at $\alpha = 0.10$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	1.34	(50.00)	1.18	(49.92)	1.24	(49.85)	1.16	(49.82)
	100	1.42	(100.00)	1.14	(99.85)	1.54	(99.73)	1.06	(99.74)
	150	1.42	(150.00)	1.02	(149.78)	1.10	(146.67)	1.18	(149.67)
	200	1.30	(200.00)	1.26	(199.60)	1.20	(199.42)	1.34	(199.42)
	500	1.10	(500.00)	1.40	(499.10)	1.26	(498.54)	1.32	(498.54)
$\gamma = 0.50$									
	50	13.80	(50.00)	13.04	(49.30)	13.30	(48.56)	12.68	(48.81)
	100	27.56	(100.00)	26.48	(96.58)	24.62	(94.51)	24.10	(93.61)
	150	38.08	(150.00)	38.58	(142.22)	36.40	(137.39)	36.32	(135.35)
	200	49.56	(200.00)	49.10	(185.88)	49.12	(175.16)	48.38	(171.27)
	500	90.62	(500.00)	89.40	(393.90)	88.94	(341.40)	87.90	(324.88)
$\gamma = 0.75$									
	50	16.06	(50.00)	15.88	(48.97)	15.42	(48.16)	15.04	(48.03)
	100	31.92	(100.00)	30.84	(96.00)	29.62	(92.84)	29.32	(91.91)
	150	46.56	(150.00)	45.10	(140.87)	42.62	(134.62)	42.38	(132.16)
	200	58.30	(200.00)	55.48	(183.40)	56.60	(169.60)	54.90	(166.49)
	500	94.36	(500.00)	93.96	(369.95)	93.30	(316.86)	93.40	(296.92)
$\gamma = 0.90$									
	50	18.48	(50.00)	17.86	(48.69)	17.02	(47.92)	16.82	(47.67)
	100	31.90	(100.00)	31.40	(95.73)	30.66	(92.42)	32.14	(90.71)
	150	44.96	(150.00)	47.78	(138.30)	45.90	(131.83)	45.02	(129.58)
	200	58.54	(200.00)	58.22	(179.94)	57.98	(166.06)	58.36	(161.98)
	500	94.54	(500.00)	93.32	(365.60)	93.74	(306.36)	92.12	(291.09)
$\gamma = 0.95$									
	50	15.18	(50.00)	14.74	(48.95)	14.68	(48.19)	14.52	(47.90)
	100	26.76	(100.00)	25.48	(96.18)	27.40	(92.74)	26.14	(91.81)
	150	37.98	(150.00)	37.44	(141.26)	35.82	(135.09)	36.50	(132.86)
	200	45.86	(200.00)	48.38	(183.20)	45.66	(174.24)	46.70	(169.76)
	500	86.16	(500.00)	86.06	(391.25)	86.38	(334.80)	85.96	(320.68)

Table 4.5: OBF's Procedure: Normal Mixtures at $\alpha = 0.01$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.58	(50.00)	5.20	(49.50)	5.04	(49.26)	5.44	(49.13)
	100	5.82	(100.00)	6.00	(98.82)	5.56	(98.13)	5.40	(98.16)
	150	5.32	(150.00)	5.14	(148.46)	5.34	(147.67)	5.60	(147.14)
	200	5.70	(200.00)	5.62	(197.80)	5.14	(196.65)	5.70	(196.04)
	500	5.12	(500.00)	5.24	(494.80)	4.96	(492.54)	5.30	(490.42)
$\gamma = 0.50$									
	50	30.98	(50.00)	30.12	(47.24)	30.12	(45.43)	28.76	(45.10)
	100	49.42	(100.00)	47.58	(90.27)	47.06	(85.87)	46.56	(83.07)
	150	62.02	(150.00)	61.68	(128.49)	60.04	(119.09)	60.76	(114.88)
	200	73.80	(200.00)	72.88	(165.04)	70.32	(150.33)	69.46	(144.50)
	500	97.06	(500.00)	96.90	(329.30)	96.56	(266.14)	96.40	(246.91)
$\gamma = 0.75$									
	50	35.32	(50.00)	33.90	(46.67)	33.32	(44.87)	31.12	(44.53)
	100	54.10	(100.00)	53.28	(89.02)	52.88	(82.71)	50.40	(81.88)
	150	68.92	(150.00)	67.26	(127.52)	65.04	(116.22)	66.08	(111.83)
	200	78.70	(200.00)	78.66	(159.74)	76.62	(141.92)	75.24	(138.13)
	500	98.50	(500.00)	98.34	(309.55)	98.18	(243.56)	97.69	(227.12)
$\gamma = 0.90$									
	50	34.60	(50.00)	34.98	(46.37)	33.14	(44.72)	33.52	(44.03)
	100	53.12	(100.00)	53.32	(88.26)	52.16	(81.70)	50.96	(80.83)
	150	67.64	(150.00)	67.14	(126.08)	66.36	(113.81)	65.18	(109.81)
	200	76.94	(200.00)	75.80	(160.32)	75.24	(141.50)	75.72	(141.50)
	500	97.76	(500.00)	97.76	(309.50)	97.82	(242.70)	97.98	(220.27)
$\gamma = 0.95$									
	50	29.88	(50.00)	29.74	(46.69)	28.92	(45.27)	28.04	(44.80)
	100	44.02	(100.00)	42.56	(90.59)	44.22	(84.70)	44.16	(82.81)
	150	56.48	(150.00)	56.10	(130.11)	56.72	(119.26)	53.94	(117.74)
	200	67.82	(200.00)	65.08	(167.36)	66.10	(149.34)	65.64	(144.93)
	500	93.88	(500.00)	93.18	(340.75)	93.18	(275.16)	92.80	(254.37)

Table 4.6: OBF's Procedure: Normal Mixtures at $\alpha = 0.05$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	9.48	(50.00)	8.94	(48.91)	9.70	(48.28)	9.14	(48.23)
	100	9.38	(100.00)	10.34	(97.48)	10.22	(96.43)	9.30	(96.23)
	150	10.32	(150.00)	10.34	(146.13)	10.36	(144.27)	9.78	(144.29)
	200	10.46	(200.00)	9.86	(194.96)	9.98	(192.22)	10.86	(191.82)
	500	10.00	(500.00)	10.04	(488.70)	10.78	(480.52)	11.24	(476.63)
$\gamma = 0.50$									
	50	43.13	(50.00)	42.36	(45.18)	41.08	(42.72)	40.32	(42.04)
	100	62.06	(100.00)	60.32	(84.71)	59.32	(77.89)	58.48	(75.46)
	150	74.08	(150.00)	72.68	(119.84)	72.22	(107.03)	71.94	(102.58)
	200	82.16	(200.00)	81.92	(151.38)	80.82	(129.86)	80.32	(125.61)
	500	98.98	(500.00)	98.62	(298.30)	98.38	(225.14)	98.02	(206.82)
$\gamma = 0.75$									
	50	46.42	(50.00)	45.44	(44.58)	42.94	(42.49)	44.08	(41.22)
	100	66.50	(100.00)	65.02	(82.70)	62.88	(75.28)	62.92	(72.81)
	150	77.88	(150.00)	77.02	(117.18)	77.20	(102.23)	75.26	(98.58)
	200	86.72	(200.00)	85.04	(147.64)	83.46	(126.75)	84.56	(117.60)
	500	99.54	(500.00)	99.10	(289.00)	98.90	(208.34)	98.96	(188.33)
$\gamma = 0.90$									
	50	45.10	(50.00)	45.36	(44.50)	44.18	(41.66)	44.28	(40.74)
	100	63.50	(100.00)	63.54	(83.13)	63.26	(74.76)	61.46	(73.49)
	150	75.22	(150.00)	76.30	(116.55)	74.52	(101.42)	75.32	(97.97)
	200	83.92	(200.00)	83.76	(147.18)	82.86	(124.88)	83.88	(116.82)
	500	99.10	(500.00)	98.96	(289.40)	98.54	(212.24)	98.68	(186.61)
$\gamma = 0.95$									
	50	37.00	(50.00)	38.44	(44.88)	39.00	(42.66)	37.82	(41.90)
	100	54.68	(100.00)	53.74	(85.66)	54.04	(78.17)	53.04	(76.83)
	150	66.04	(150.00)	64.52	(122.34)	65.34	(108.34)	65.34	(104.56)
	200	74.20	(200.00)	74.14	(156.32)	75.12	(133.89)	73.02	(129.74)
	500	96.32	(500.00)	95.74	(317.60)	96.08	(242.46)	95.28	(224.49)

Table 4.7: OBF's Procedure: Normal Mixtures at $\alpha = 0.10$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	1.32	(50.00)	1.34	(49.93)	1.32	(49.86)	1.02	(49.88)
	100	1.10	(100.00)	1.22	(99.73)	1.26	(99.72)	1.50	(99.65)
	150	1.40	(150.00)	1.36	(149.73)	1.54	(149.53)	1.30	(149.55)
	200	1.60	(200.00)	1.18	(199.60)	1.76	(199.24)	1.14	(199.34)
	500	1.18	(500.00)	1.12	(499.40)	1.84	(497.92)	1.04	(498.91)
$\gamma = 0.50$									
	50	9.26	(50.00)	8.80	(48.97)	7.78	(48.52)	7.54	(48.33)
	100	18.20	(100.00)	16.52	(96.41)	14.46	(94.84)	12.64	(94.78)
	150	26.18	(150.00)	23.98	(142.56)	19.94	(139.39)	19.86	(137.45)
	200	34.50	(200.00)	32.02	(185.82)	27.40	(180.58)	25.98	(179.02)
	500	74.56	(500.00)	68.84	(411.55)	64.78	(374.32)	63.88	(359.67)
$\gamma = 0.75$									
	50	13.80	(50.00)	12.24	(48.66)	11.22	(48.02)	9.68	(47.82)
	100	26.66	(100.00)	24.62	(94.53)	22.26	(92.14)	19.90	(91.76)
	150	39.14	(150.00)	36.36	(137.94)	33.66	(132.21)	30.26	(130.70)
	200	50.80	(200.00)	46.04	(178.38)	43.64	(168.78)	40.58	(166.34)
	500	89.66	(500.00)	87.86	(364.00)	85.10	(310.60)	83.36	(296.88)
$\gamma = 0.90$									
	50	29.14	(50.00)	28.14	(46.64)	25.76	(45.18)	23.70	(44.83)
	100	54.02	(100.00)	50.66	(87.57)	48.16	(81.40)	44.08	(80.30)
	150	69.72	(150.00)	67.86	(123.00)	63.74	(109.62)	62.44	(107.36)
	200	81.42	(200.00)	78.42	(153.62)	77.58	(131.76)	76.76	(124.74)
	500	99.56	(500.00)	99.28	(281.90)	99.24	(195.16)	98.88	(175.77)
$\gamma = 0.95$									
	50	62.16	(50.00)	60.46	(41.12)	59.32	(36.67)	57.30	(35.65)
	100	86.28	(100.00)	84.86	(70.96)	84.38	(57.80)	83.64	(52.85)
	150	95.00	(150.00)	94.20	(95.31)	94.28	(69.76)	94.12	(61.81)
	200	98.46	(200.00)	97.96	(116.66)	98.04	(77.64)	97.50	(68.74)
	500	99.98	(500.00)	100.0	(251.40)	100.0	(121.48)	100.0	(88.17)

Table 4.8: Pocock's Procedure: Poisson Mixtures at $\alpha = 0.01$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.42	(50.00)	5.76	(49.11)	5.88	(48.46)	5.54	(48.32)
	100	5.38	(100.00)	5.40	(98.37)	5.90	(97.02)	6.46	(96.10)
	150	5.32	(150.00)	5.36	(147.42)	5.40	(145.85)	5.62	(145.23)
	200	4.84	(200.00)	5.00	(197.00)	6.26	(193.54)	6.08	(192.77)
	500	5.2	(500.00)	5.28	(492.40)	6.06	(484.70)	5.38	(481.75)
$\gamma = 0.50$									
	50	23.82	(50.00)	22.30	(47.02)	21.06	(45.47)	20.54	(44.92)
	100	38.94	(100.00)	35.52	(90.67)	32.80	(85.54)	31.58	(84.64)
	150	49.76	(150.00)	46.14	(131.79)	42.18	(123.40)	39.50	(121.07)
	200	59.08	(200.00)	54.90	(170.34)	51.02	(155.31)	48.90	(151.86)
	500	89.90	(500.00)	87.40	(353.45)	83.16	(294.86)	82.94	(275.53)
$\gamma = 0.75$									
	50	32.02	(50.00)	28.94	(46.22)	26.88	(44.07)	24.98	(43.89)
	100	49.72	(100.00)	46.06	(87.77)	41.72	(82.25)	41.42	(79.81)
	150	63.82	(150.00)	59.06	(125.24)	55.38	(113.11)	53.28	(110.00)
	200	72.56	(200.00)	68.46	(159.60)	66.26	(139.88)	63.82	(136.43)
	500	96.94	(500.00)	95.90	(308.80)	94.46	(235.52)	93.66	(216.92)
$\gamma = 0.90$									
	50	49.20	(50.00)	44.96	(43.62)	42.86	(40.67)	41.98	(39.51)
	100	70.86	(100.00)	68.78	(79.44)	66.50	(68.74)	65.16	(65.95)
	150	85.56	(150.00)	83.50	(108.30)	80.20	(88.85)	80.30	(84.15)
	200	92.32	(200.00)	90.32	(134.64)	88.62	(106.68)	88.54	(96.74)
	500	99.88	(500.00)	99.82	(263.50)	99.78	(157.16)	99.82	(131.72)
$\gamma = 0.95$									
	50	72.08	(50.00)	71.42	(38.62)	71.30	(32.52)	69.22	(31.02)
	100	91.14	(100.00)	91.48	(65.39)	90.04	(49.17)	89.92	(44.57)
	150	96.92	(150.00)	97.42	(88.23)	96.94	(59.24)	97.22	(51.32)
	200	99.16	(200.00)	99.20	(110.48)	98.88	(67.12)	98.88	(55.97)
	500	99.98	(500.00)	100.0	(250.70)	100.0	(113.40)	100.0	(78.01)

Table 4.9: Pocock's Procedure: Poisson Mixtures at $\alpha = 0.05$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	9.72	(50.00)	9.74	(48.55)	10.96	(47.11)	10.98	(46.63)
	100	10.36	(100.00)	9.80	(96.90)	10.56	(94.36)	10.58	(93.66)
	150	10.00	(150.00)	10.10	(145.25)	9.66	(141.96)	11.32	(139.54)
	200	9.64	(200.00)	10.22	(193.14)	10.54	(188.81)	10.94	(186.23)
	500	11.16	(500.00)	10.48	(483.15)	11.52	(468.82)	10.92	(465.33)
$\gamma = 0.50$									
	50	34.88	(50.00)	33.00	(45.18)	30.50	(43.00)	30.74	(41.85)
	100	50.84	(100.00)	47.64	(85.40)	45.90	(78.62)	43.78	(76.77)
	150	61.78	(150.00)	58.78	(123.45)	54.48	(111.84)	52.64	(107.27)
	200	71.24	(200.00)	67.62	(157.54)	63.76	(138.52)	62.42	(132.03)
	500	94.22	(500.00)	92.42	(323.50)	90.48	(251.02)	89.22	(229.49)
$\gamma = 0.75$									
	50	41.94	(50.00)	41.22	(44.03)	38.74	(40.82)	36.36	(40.24)
	100	60.76	(100.00)	59.66	(82.19)	54.92	(74.00)	53.32	(71.79)
	150	74.78	(150.00)	71.12	(116.45)	68.18	(99.93)	65.80	(96.20)
	200	82.72	(200.00)	79.88	(146.60)	76.82	(122.07)	75.32	(115.88)
	500	98.70	(500.00)	97.66	(291.50)	97.46	(201.52)	96.82	(179.46)
$\gamma = 0.90$									
	50	58.58	(50.00)	55.70	(41.42)	53.94	(36.98)	52.94	(36.08)
	100	79.96	(100.00)	76.66	(74.18)	76.66	(61.28)	74.20	(57.45)
	150	90.16	(150.00)	88.14	(102.02)	86.16	(79.87)	85.48	(73.14)
	200	95.34	(200.00)	94.46	(125.74)	92.96	(92.94)	91.58	(83.63)
	500	99.96	(500.00)	99.86	(258.25)	99.84	(143.24)	99.88	(114.13)
$\gamma = 0.95$									
	50	76.76	(50.00)	75.72	(37.22)	76.08	(30.57)	74.40	(28.94)
	100	93.64	(100.00)	93.22	(63.19)	92.92	(44.83)	91.96	(40.48)
	150	98.36	(150.00)	98.36	(85.65)	98.36	(53.84)	97.80	(45.87)
	200	99.18	(200.00)	99.46	(107.44)	99.36	(61.67)	99.38	(49.44)
	500	100.0	(500.00)	100.0	(250.45)	100.0	(110.24)	100.0	(72.72)

Table 4.10: Pocock's Procedure: Poisson Mixtures at $\alpha = 0.10$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	1.32	(50.00)	1.34	(49.93)	1.32	(49.86)	1.02	(49.88)
	100	1.10	(100.00)	1.22	(99.73)	1.26	(99.72)	1.50	(99.65)
	150	1.40	(150.00)	1.36	(149.73)	1.54	(149.53)	1.30	(149.55)
	200	1.60	(200.00)	1.18	(199.60)	1.76	(199.24)	1.14	(199.34)
	500	1.18	(500.00)	1.12	(499.40)	1.84	(497.92)	1.04	(498.91)
$\gamma = 0.50$									
	50	10.66	(50.00)	9.26	(49.53)	7.96	(49.20)	9.08	(49.20)
	100	17.16	(100.00)	17.48	(97.84)	16.22	(96.53)	16.18	(96.53)
	150	26.70	(150.00)	24.84	(145.58)	24.88	(141.72)	23.62	(141.72)
	200	33.84	(200.00)	33.88	(191.46)	32.84	(184.97)	32.20	(182.41)
	500	73.90	(500.00)	73.46	(436.16)	71.40	(397.34)	71.22	(382.35)
$\gamma = 0.75$									
	50	15.18	(50.00)	14.66	(49.10)	13.54	(48.60)	13.90	(48.22)
	100	27.18	(100.00)	26.04	(96.67)	26.50	(93.88)	25.16	(93.19)
	150	40.44	(150.00)	38.60	(142.26)	39.10	(135.30)	37.12	(134.24)
	200	50.82	(200.00)	50.58	(184.84)	49.88	(175.47)	48.44	(171.64)
	500	90.02	(500.00)	89.80	(389.10)	88.60	(339.74)	88.30	(319.11)
$\gamma = 0.90$									
	50	30.76	(50.00)	28.50	(47.69)	28.48	(46.28)	28.82	(45.75)
	100	53.08	(100.00)	52.56	(90.36)	51.76	(85.17)	49.72	(83.55)
	150	70.74	(150.00)	70.52	(128.22)	68.90	(115.55)	67.88	(113.41)
	200	83.26	(200.00)	81.10	(161.38)	81.24	(141.54)	81.34	(134.20)
	500	99.38	(500.00)	99.54	(296.85)	99.36	(232.36)	99.20	(210.92)
$\gamma = 0.95$									
	50	62.90	(50.00)	60.78	(42.41)	62.40	(38.27)	61.72	(37.29)
	100	85.76	(100.00)	86.64	(73.15)	86.14	(61.53)	84.76	(58.74)
	150	95.36	(150.00)	95.50	(98.28)	94.88	(77.24)	94.56	(71.26)
	200	98.76	(200.00)	98.58	(118.60)	98.34	(87.89)	98.40	(78.94)
	500	100.0	(500.00)	100.0	(252.10)	100.0	(136.48)	100.0	(112.94)

Table 4.11: OBF's Procedure: Poisson Mixtures at $\alpha = 0.01$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.70	(50.00)	5.84	(49.46)	5.62	(49.03)	5.64	(49.03)
	100	5.40	(100.00)	5.24	(98.84)	5.66	(98.28)	5.12	(98.11)
	150	5.58	(150.00)	5.14	(148.52)	6.08	(148.52)	6.20	(146.98)
	200	5.38	(200.00)	5.12	(197.89)	5.34	(197.88)	5.80	(195.82)
	500	5.28	(500.00)	5.10	(494.35)	5.94	(494.35)	5.54	(490.46)
$\gamma = 0.50$									
	50	25.58	(50.00)	22.82	(47.85)	22.76	(46.72)	23.90	(45.95)
	100	38.08	(100.00)	36.42	(92.70)	35.94	(89.62)	35.82	(87.62)
	150	48.26	(150.00)	48.46	(135.18)	46.28	(128.48)	46.40	(124.91)
	200	58.32	(200.00)	57.66	(176.38)	57.44	(163.39)	57.28	(157.71)
	500	90.10	(500.00)	89.52	(368.85)	89.14	(315.66)	88.06	(299.95)
$\gamma = 0.75$									
	50	31.68	(50.00)	31.98	(46.99)	30.64	(45.30)	28.50	(45.04)
	100	48.16	(100.00)	48.04	(89.98)	46.52	(85.01)	46.94	(82.89)
	150	62.30	(150.00)	62.12	(129.66)	59.82	(119.84)	60.54	(115.07)
	200	73.32	(200.00)	71.52	(165.00)	71.80	(148.19)	71.74	(142.44)
	500	97.18	(500.00)	96.66	(326.45)	96.04	(264.90)	96.18	(243.20)
$\gamma = 0.90$									
	50	48.34	(50.00)	47.66	(44.58)	46.40	(40.71)	48.22	(40.71)
	100	70.80	(100.00)	70.48	(81.41)	70.74	(71.27)	68.16	(71.27)
	150	85.64	(150.00)	83.98	(113.16)	83.06	(97.31)	83.38	(91.52)
	200	91.30	(200.00)	91.20	(140.92)	90.84	(115.86)	91.08	(107.52)
	500	99.90	(500.00)	99.90	(268.10)	99.88	(182.36)	99.90	(162.48)
$\gamma = 0.95$									
	50	72.12	(50.00)	71.00	(39.67)	71.66	(34.33)	70.94	(32.85)
	100	91.00	(100.00)	91.12	(67.33)	91.60	(52.82)	90.94	(49.05)
	150	97.36	(150.00)	97.32	(90.11)	97.58	(64.33)	97.44	(57.84)
	200	98.96	(200.00)	99.12	(112.94)	99.18	(74.20)	99.06	(64.92)
	500	99.98	(500.00)	100.0	(251.30)	100.0	(120.72)	100.0	(91.96)

Table 4.12: OBF's Procedure: Poisson Mixtures at $\alpha = 0.05$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	10.58	(50.00)	10.14	(48.75)	9.90	(48.26)	10.62	(47.94)
	100	9.68	(100.00)	10.76	(97.21)	11.50	(95.80)	10.48	(95.62)
	150	9.72	(150.00)	10.34	(146.52)	10.64	(144.05)	11.18	(143.10)
	200	10.02	(200.00)	9.76	(195.64)	10.42	(192.44)	10.66	(191.08)
	500	10.16	(500.00)	10.12	(488.05)	10.74	(479.34)	10.94	(477.77)
$\gamma = 0.50$									
	50	35.72	(50.00)	33.86	(46.27)	35.20	(43.82)	34.74	(43.13)
	100	51.22	(100.00)	48.52	(88.33)	47.74	(82.57)	46.66	(81.00)
	150	62.06	(150.00)	60.52	(126.77)	60.54	(114.80)	57.80	(113.93)
	200	70.64	(200.00)	69.84	(162.52)	67.58	(147.12)	68.44	(140.52)
	500	93.76	(500.00)	93.24	(334.15)	92.66	(272.20)	93.26	(252.32)
$\gamma = 0.75$									
	50	45.22	(50.00)	41.70	(45.05)	41.10	(42.41)	40.44	(41.73)
	100	61.70	(100.00)	60.46	(84.49)	58.74	(77.62)	57.82	(75.76)
	150	74.36	(150.00)	71.44	(121.16)	71.66	(106.68)	70.18	(102.95)
	200	82.84	(200.00)	80.60	(152.76)	80.40	(130.53)	79.92	(125.31)
	500	98.44	(500.00)	98.22	(301.15)	97.70	(227.72)	98.20	(206.16)
$\gamma = 0.90$									
	50	58.78	(50.00)	57.66	(44.58)	57.40	(40.71)	55.74	(40.71)
	100	79.80	(100.00)	78.58	(81.41)	77.16	(71.27)	78.24	(71.27)
	150	89.90	(150.00)	88.92	(113.16)	88.42	(97.31)	87.76	(91.52)
	200	95.62	(200.00)	94.74	(140.92)	94.32	(115.86)	93.96	(107.52)
	500	99.96	(500.00)	99.98	(268.10)	99.98	(182.36)	99.88	(162.48)
$\gamma = 0.95$									
	50	76.72	(50.00)	77.74	(37.34)	76.52	(31.81)	76.28	(30.20)
	100	93.70	(100.00)	92.86	(64.51)	93.48	(47.98)	94.06	(43.35)
	150	98.16	(150.00)	97.46	(86.73)	98.38	(58.42)	97.82	(52.19)
	200	99.18	(200.00)	99.58	(109.02)	99.42	(68.40)	99.44	(57.78)
	500	100.0	(500.00)	100.0	(250.40)	100.0	(115.28)	100.0	(82.92)

Table 4.13: OBF's Procedure: Poisson Mixtures at $\alpha = 0.10$

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.72	(50.00)	4.90	(49.13)	5.28	(48.56)	5.94	(48.18)
	100	5.50	(100.00)	4.48	(98.60)	5.32	(97.30)	5.56	(96.41)
	150	4.78	(150.00)	4.58	(147.92)	5.15	(146.17)	4.98	(145.52)
	200	4.94	(200.00)	5.24	(196.92)	5.18	(194.73)	4.58	(194.73)
	500	4.84	(500.00)	5.06	(491.95)	4.96	(487.28)	4.40	(486.16)
$\gamma = 0.1$									
$\theta = 0.1$	50	18.92	(50.00)	19.58	(47.24)	17.94	(45.86)	18.18	(44.97)
	100	30.52	(100.00)	27.40	(92.56)	28.32	(88.34)	24.04	(87.83)
	150	39.62	(150.00)	36.68	(135.30)	34.02	(129.02)	33.28	(125.19)
	200	48.48	(200.00)	45.04	(177.58)	41.44	(163.71)	39.76	(162.66)
	500	78.96	(500.00)	76.44	(381.85)	74.70	(324.64)	71.30	(321.96)
$\gamma = 0.1$									
$\theta = 0.01$	50	24.82	(50.00)	25.30	(46.19)	23.40	(44.81)	23.32	(42.27)
	100	41.54	(100.00)	37.84	(90.08)	37.04	(84.26)	32.84	(80.46)
	150	53.90	(150.00)	50.12	(129.03)	46.12	(121.58)	45.58	(116.48)
	200	62.04	(200.00)	59.46	(168.04)	54.94	(152.38)	54.40	(135.67)
	500	91.48	(500.00)	91.40	(337.30)	89.02	(271.54)	87.26	(260.92)
$\gamma = 0.2$									
$\theta = 0.1$	50	48.24	(50.00)	46.50	(43.22)	42.82	(40.81)	42.78	(38.78)
	100	73.08	(100.00)	69.60	(79.26)	68.32	(69.59)	61.98	(67.81)
	150	85.74	(150.00)	83.76	(108.26)	80.84	(93.38)	79.42	(87.73)
	200	93.52	(200.00)	92.30	(134.84)	90.70	(107.36)	87.98	(103.02)
	500	99.96	(500.00)	99.92	(261.50)	99.80	(156.28)	99.80	(133.46)
$\gamma = 0.2$									
$\theta = 0.01$	50	62.30	(50.00)	61.66	(40.90)	57.54	(37.20)	57.50	(35.20)
	100	87.04	(100.00)	84.62	(71.89)	83.62	(59.46)	80.66	(55.19)
	150	96.00	(150.00)	94.50	(96.17)	94.50	(75.01)	92.32	(68.21)
	200	98.98	(200.00)	98.28	(117.42)	98.28	(84.66)	97.46	(76.36)
	500	100.0	(500.00)	100.0	(251.45)	100.0	(124.36)	100.0	(98.38)

Table 4.14: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=2 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.82	(50.00)	5.10	(49.22)	5.14	(48.68)	5.48	(48.16)
	100	4.92	(100.00)	5.18	(98.42)	5.28	(97.28)	4.64	(97.34)
	150	5.02	(150.00)	5.12	(147.62)	5.44	(145.74)	4.98	(145.48)
	200	4.34	(200.00)	4.92	(196.76)	5.20	(194.99)	5.70	(193.08)
	500	5.22	(500.00)	5.20	(492.65)	5.24	(486.78)	5.04	(484.88)
$\gamma = 0.1$									
$\theta = 0.1$	50	36.70	(50.00)	35.00	(45.36)	34.14	(42.45)	31.48	(41.50)
	100	55.62	(100.00)	51.96	(85.69)	49.18	(78.65)	48.28	(76.53)
	150	67.80	(150.00)	66.40	(121.35)	64.64	(107.26)	62.70	(101.78)
	200	77.54	(200.00)	77.78	(153.04)	74.48	(129.78)	73.48	(124.20)
	500	98.70	(500.00)	98.56	(293.85)	97.94	(210.44)	98.06	(186.36)
$\gamma = 0.1$									
$\theta = 0.01$	50	50.88	(50.00)	49.84	(43.07)	47.00	(39.49)	46.00	(37.86)
	100	77.86	(100.00)	72.50	(77.26)	72.42	(66.48)	70.56	(63.17)
	150	89.00	(150.00)	86.92	(106.25)	86.74	(85.58)	85.46	(77.45)
	200	95.14	(200.00)	94.82	(131.04)	93.48	(97.22)	93.72	(90.49)
	500	99.96	(500.00)	99.98	(257.30)	100.0	(144.58)	99.98	(120.17)
$\gamma = 0.2$									
$\theta = 0.1$	50	77.82	(50.00)	75.12	(38.24)	75.02	(32.14)	72.50	(30.32)
	100	95.96	(100.00)	94.58	(63.78)	94.72	(47.62)	93.10	(44.12)
	150	99.16	(150.00)	99.08	(84.86)	98.96	(56.83)	98.28	(49.55)
	200	99.82	(200.00)	99.86	(106.38)	99.86	(63.40)	99.86	(54.86)
	500	100.0	(500.00)	100.0	(250.05)	100.0	(108.92)	100.0	(75.93)
$\gamma = 0.2$									
$\theta = 0.01$	50	92.44	(50.00)	92.64	(33.19)	91.34	(25.58)	90.36	(22.94)
	100	99.74	(100.00)	99.60	(54.18)	99.62	(35.05)	99.40	(29.23)
	150	100.0	(150.00)	100.0	(76.64)	99.89	(41.56)	100.0	(33.15)
	200	100.0	(200.00)	100.0	(100.54)	100.0	(47.52)	100.0	(37.42)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.70)	100.0	(57.94)

Table 4.15: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=4 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.94	(50.00)	5.68	(49.13)	5.30	(48.60)	4.84	(49.60)
	100	5.08	(100.00)	5.18	(98.40)	5.78	(96.97)	5.22	(96.95)
	150	5.28	(150.00)	5.76	(147.41)	5.60	(145.82)	5.64	(144.94)
	200	4.14	(200.00)	5.60	(196.50)	5.66	(194.09)	5.64	(192.97)
	500	4.74	(500.00)	5.18	(491.00)	5.74	(484.68)	5.10	(485.69)
$\gamma = 0.1$									
$\theta = 0.1$	50	67.06	(50.00)	67.72	(38.78)	68.16	(33.77)	67.26	(32.10)
	100	90.12	(100.00)	89.56	(67.85)	89.30	(51.09)	88.68	(47.80)
	150	97.14	(150.00)	97.14	(92.01)	97.00	(63.98)	96.36	(56.15)
	200	99.16	(200.00)	99.14	(111.78)	99.10	(72.49)	99.02	(61.42)
	500	100.0	(500.00)	100.0	(250.65)	100.0	(115.42)	100.0	(82.36)
$\gamma = 0.1$									
$\theta = 0.01$	50	90.44	(50.00)	91.14	(31.69)	90.28	(25.25)	89.94	(23.68)
	100	99.00	(100.00)	99.22	(55.40)	99.32	(33.86)	99.24	(29.61)
	150	99.92	(150.00)	99.92	(78.26)	99.92	(44.61)	99.88	(32.12)
	200	99.98	(200.00)	100.0	(100.84)	100.0	(50.06)	99.98	(37.42)
	500	100.0	(500.00)	100.0	(250.05)	100.0	(100.96)	100.0	(56.12)
$\gamma = 0.2$									
$\theta = 0.1$	50	96.96	(50.00)	96.78	(29.43)	96.38	(20.87)	96.66	(18.21)
	100	99.94	(100.00)	99.92	(51.82)	99.92	(28.25)	99.96	(22.86)
	150	100.0	(150.00)	100.0	(78.40)	100.0	(36.15)	100.0	(25.90)
	200	100.0	(200.00)	100.0	(100.06)	100.0	(43.81)	100.0	(29.40)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.14)	100.0	(52.62)
$\gamma = 0.2$									
$\theta = 0.01$	50	99.94	(50.00)	99.89	(28.53)	99.94	(14.73)	99.82	(12.02)
	100	100.0	(100.00)	100.0	(50.14)	100.0	(21.67)	100.0	(15.28)
	150	100.0	(150.00)	100.0	(75.00)	100.0	(31.30)	100.0	(18.52)
	200	100.0	(200.00)	100.0	(100.50)	100.0	(40.43)	100.0	(23.07)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.00)	100.0	(50.09)

Table 4.16: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=8 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	6.34	(50.00)	4.88	(49.43)	4.44	(48.84)	6.64	(47.75)
	100	4.52	(100.00)	4.98	(98.44)	5.06	(97.13)	5.02	(96.79)
	150	3.96	(150.00)	5.50	(147.30)	5.16	(146.35)	4.68	(145.90)
	200	5.22	(200.00)	4.66	(196.94)	5.06	(194.86)	4.80	(193.93)
	500	4.42	(500.00)	5.80	(491.40)	5.20	(486.66)	5.18	(483.53)
$\gamma = 0.1$									
$\theta = 0.1$	50	13.36	(50.00)	9.82	(48.98)	10.06	(47.71)	12.12	(46.30)
	100	14.44	(100.00)	14.52	(95.76)	13.70	(93.86)	13.28	(92.58)
	150	17.30	(150.00)	18.10	(142.31)	16.32	(139.72)	15.16	(138.40)
	200	24.54	(200.00)	18.82	(189.66)	19.40	(183.73)	17.48	(181.17)
	500	39.80	(500.00)	38.76	(450.90)	34.80	(426.54)	32.16	(422.21)
$\gamma = 0.1$									
$\theta = 0.01$	50	19.48	(50.00)	15.46	(48.34)	14.10	(46.99)	15.64	(45.46)
	100	22.58	(100.00)	22.24	(93.88)	19.76	(91.10)	19.00	(90.15)
	150	29.52	(150.00)	28.14	(139.40)	26.84	(133.87)	25.64	(131.93)
	200	39.36	(200.00)	33.52	(183.22)	31.56	(173.84)	28.96	(171.30)
	500	67.96	(500.00)	67.18	(405.10)	60.26	(370.14)	56.66	(361.64)
$\gamma = 0.2$									
$\theta = 0.1$	50	27.42	(50.00)	19.68	(47.93)	19.08	(46.10)	20.68	(44.17)
	100	33.82	(100.00)	32.24	(81.11)	28.72	(87.67)	27.52	(86.15)
	150	45.08	(150.00)	42.64	(132.92)	40.88	(125.84)	36.18	(125.09)
	200	57.68	(200.00)	49.94	(172.68)	47.82	(162.09)	43.58	(157.32)
	500	88.82	(500.00)	87.40	(358.55)	82.50	(303.68)	78.74	(294.83)
$\gamma = 0.2$									
$\theta = 0.01$	50	42.40	(50.00)	35.20	(46.25)	30.30	(43.68)	33.82	(41.27)
	100	58.62	(100.00)	55.62	(83.87)	52.20	(78.10)	48.00	(76.23)
	150	74.98	(150.00)	72.74	(118.73)	67.28	(107.45)	64.46	(105.26)
	200	86.74	(200.00)	81.44	(149.08)	80.06	(127.40)	74.76	(122.22)
	500	99.72	(500.00)	99.54	(276.05)	98.10	(192.34)	98.72	(172.54)

Table 4.17: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=2 (PU)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	3.50	(50.00)	3.84	(49.60)	4.36	(49.39)	4.20	(49.07)
	100	4.82	(100.00)	4.56	(99.13)	4.08	(98.83)	4.42	(98.59)
	150	4.74	(150.00)	4.98	(148.49)	4.50	(148.11)	4.54	(147.63)
	200	5.00	(200.00)	4.48	(198.48)	4.88	(196.94)	4.74	(197.00)
	500	4.94	(500.00)	5.56	(494.65)	4.28	(493.90)	4.82	(491.77)
$\gamma = 0.1$									
$\theta = 0.1$	50	24.48	(50.00)	23.48	(46.83)	23.12	(44.97)	21.82	(44.32)
	100	42.48	(100.00)	38.00	(90.93)	35.26	(85.57)	32.66	(84.05)
	150	56.38	(150.00)	52.00	(129.05)	47.78	(118.86)	45.08	(116.80)
	200	65.90	(200.00)	61.96	(165.28)	55.70	(152.75)	53.96	(145.84)
	500	94.86	(500.00)	93.36	(331.15)	90.30	(266.32)	89.22	(250.75)
$\gamma = 0.1$									
$\theta = 0.01$	50	42.36	(50.00)	38.22	(44.90)	35.84	(42.64)	36.92	(40.72)
	100	67.14	(100.00)	64.42	(82.37)	58.58	(75.40)	57.80	(70.84)
	150	82.26	(150.00)	77.42	(113.57)	74.58	(97.94)	73.26	(93.76)
	200	90.66	(200.00)	87.76	(140.86)	85.70	(117.19)	83.96	(109.58)
	500	99.88	(500.00)	99.88	(267.45)	99.72	(172.76)	99.56	(150.84)
$\gamma = 0.2$									
$\theta = 0.1$	50	61.08	(50.00)	57.54	(42.14)	53.80	(38.61)	51.88	(36.88)
	100	87.08	(100.00)	83.88	(73.55)	80.94	(61.88)	78.94	(57.89)
	150	95.54	(150.00)	94.96	(96.83)	92.96	(75.37)	91.72	(70.38)
	200	98.84	(200.00)	97.80	(118.68)	97.24	(87.28)	97.02	(77.46)
	500	100.0	(500.00)	100.0	(251.95)	100.0	(129.02)	100.0	(100.64)
$\gamma = 0.2$									
$\theta = 0.01$	50	86.74	(50.00)	82.70	(36.29)	81.76	(30.02)	79.14	(28.42)
	100	98.38	(100.00)	97.98	(59.47)	97.22	(42.20)	97.16	(37.04)
	150	99.90	(150.00)	97.22	(79.68)	99.80	(49.06)	99.74	(42.89)
	200	100.0	(200.00)	97.16	(102.26)	99.98	(56.44)	100.0	(45.07)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(103.44)	100.0	(66.49)

Table 4.18: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=4 (PU)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.14	(50.00)	5.92	(49.20)	5.62	(48.58)	5.02	(48.52)
	100	5.40	(100.00)	5.16	(98.33)	5.04	(97.49)	5.06	(96.97)
	150	4.54	(150.00)	5.10	(147.51)	5.46	(145.79)	5.60	(144.81)
	200	5.32	(200.00)	4.68	(197.20)	6.22	(193.50)	5.88	(192.46)
	500	4.74	(500.00)	6.00	(491.25)	5.16	(486.92)	4.96	(484.84)
$\gamma = 0.1$									
$\theta = 0.1$	50	68.10	(50.00)	69.34	(38.41)	67.02	(34.06)	66.54	(32.23)
	100	89.08	(100.00)	89.12	(67.85)	89.06	(51.22)	87.40	(48.69)
	150	97.26	(150.00)	96.92	(91.82)	97.10	(64.67)	96.42	(55.96)
	200	98.96	(200.00)	99.14	(113.24)	99.22	(72.64)	99.00	(60.07)
	500	100.0	(500.00)	100.0	(250.55)	100.0	(116.16)	100.0	(82.82)
$\gamma = 0.1$									
$\theta = 0.01$	50	89.50	(50.00)	90.70	(31.89)	90.16	(25.34)	90.64	(90.64)
	100	99.44	(100.00)	99.06	(55.64)	99.10	(33.80)	99.18	(99.18)
	150	99.88	(150.00)	99.90	(77.84)	100.0	(44.33)	99.94	(100.0)
	200	100.0	(200.00)	99.98	(100.96)	100.0	(50.54)	100.0	(100.0)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.72)	100.0	(100.0)
$\gamma = 0.2$									
$\theta = 0.1$	50	96.98	(50.00)	97.00	(31.89)	96.86	(25.34)	96.54	(23.46)
	100	99.98	(100.00)	100.0	(55.64)	99.94	(33.80)	99.94	(29.48)
	150	100.0	(150.00)	100.0	(77.84)	100.0	(44.33)	100.0	(32.67)
	200	100.0	(200.00)	100.0	(100.96)	100.0	(50.54)	100.0	(37.19)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.72)	100.0	(56.77)
$\gamma = 0.2$									
$\theta = 0.01$	50	99.92	(50.00)	99.88	(25.84)	99.84	(14.67)	99.92	(12.17)
	100	100.0	(100.00)	100.0	(50.12)	100.0	(21.74)	100.0	(15.61)
	150	100.0	(150.00)	100.0	(75.00)	100.0	(31.40)	100.0	(18.34)
	200	100.0	(200.00)	100.0	(100.00)	100.0	(40.44)	100.0	(23.16)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.0)	100.0	(50.09)

Table 4.19: Pocock's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=8 (PU)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.56	(50.00)	4.72	(49.57)	4.94	(49.19)	4.62	(49.20)
	100	5.56	(100.00)	4.78	(99.05)	5.08	(98.46)	5.10	(98.03)
	150	5.00	(150.00)	4.86	(148.38)	4.82	(147.67)	4.88	(147.56)
	200	5.00	(200.00)	5.30	(197.84)	4.58	(197.29)	4.72	(196.54)
	500	4.72	(500.00)	4.92	(495.95)	5.20	(482.36)	5.08	(490.92)
$\gamma = 0.1$									
$\theta = 0.1$	50	18.92	(50.00)	21.46	(47.13)	19.58	(47.13)	20.58	(46.49)
	100	31.22	(100.00)	28.82	(94.77)	29.78	(91.05)	29.92	(89.30)
	150	40.22	(150.00)	38.08	(138.54)	37.92	(132.43)	37.58	(130.78)
	200	50.00	(200.00)	46.50	(180.52)	46.10	(171.81)	46.08	(167.64)
	500	80.08	(500.00)	79.48	(402.00)	78.22	(353.90)	77.16	(339.52)
$\gamma = 0.1$									
$\theta = 0.01$	50	24.90	(50.00)	27.22	(47.87)	25.36	(46.20)	26.18	(45.29)
	100	41.16	(100.00)	38.98	(92.32)	37.90	(88.17)	39.80	(85.64)
	150	52.58	(150.00)	48.88	(133.65)	49.28	(125.67)	48.98	(124.53)
	200	62.04	(200.00)	60.96	(172.76)	61.78	(158.97)	59.76	(155.07)
	500	91.52	(500.00)	91.36	(361.35)	90.90	(303.84)	90.08	(284.87)
$\gamma = 0.2$									
$\theta = 0.1$	50	47.44	(50.00)	49.78	(45.47)	46.96	(42.62)	47.18	(41.23)
	100	73.46	(100.00)	71.62	(83.84)	71.62	(74.60)	71.04	(70.82)
	150	68.72	(150.00)	85.92	(112.44)	84.08	(98.56)	84.92	(94.10)
	200	93.38	(200.00)	92.64	(139.92)	92.28	(118.00)	92.90	(110.98)
	500	99.96	(500.00)	99.82	(268.55)	99.94	(186.80)	99.86	(167.47)
$\gamma = 0.2$									
$\theta = 0.01$	50	62.36	(50.00)	63.28	(43.25)	61.48	(39.30)	62.76	(38.04)
	100	86.64	(100.00)	85.90	(76.56)	86.10	(64.01)	84.72	(60.05)
	150	95.76	(150.00)	95.16	(99.45)	94.54	(82.45)	95.16	(77.00)
	200	98.82	(200.00)	98.76	(121.22)	98.68	(94.50)	98.46	(87.68)
	500	100.0	(500.00)	100.0	(252.00)	99.98	(146.88)	100.0	(128.79)

Table 4.20: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=2 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	5.42	(50.00)	5.46	(49.48)	5.76	(49.13)	5.34	(49.03)
	100	4.84	(100.00)	5.04	(98.97)	5.28	(98.42)	5.14	(98.29)
	150	4.96	(150.00)	5.22	(148.38)	5.34	(147.42)	6.34	(146.65)
	200	4.52	(200.00)	5.36	(198.10)	5.20	(196.71)	4.88	(196.62)
	500	5.28	(500.00)	4.92	(494.20)	4.54	(492.80)	5.26	(490.72)
$\gamma = 0.1$									
$\theta = 0.1$	50	35.80	(50.00)	35.74	(46.28)	34.80	(44.30)	38.02	(43.15)
	100	55.96	(100.00)	53.30	(88.33)	53.66	(81.68)	54.02	(78.86)
	150	68.72	(150.00)	67.78	(124.85)	68.86	(112.03)	67.00	(108.71)
	200	77.86	(200.00)	78.50	(160.12)	78.56	(138.96)	76.38	(133.60)
	500	98.60	(500.00)	98.68	(305.85)	98.66	(236.24)	98.82	(213.94)
$\gamma = 0.1$									
$\theta = 0.01$	50	50.20	(50.00)	51.80	(43.72)	51.04	(41.20)	54.04	(39.53)
	100	75.66	(100.00)	73.04	(81.07)	74.00	(70.93)	72.90	(68.89)
	150	88.18	(150.00)	89.06	(107.45)	87.88	(92.58)	88.12	(85.90)
	200	95.54	(200.00)	95.10	(136.36)	95.02	(107.41)	94.88	(99.88)
	500	99.94	(500.00)	100.0	(259.30)	99.98	(169.82)	99.98	(144.95)
$\gamma = 0.2$									
$\theta = 0.1$	50	78.50	(50.00)	77.02	(39.26)	76.82	(34.59)	78.84	(32.39)
	100	95.78	(100.00)	95.40	(66.60)	94.70	(52.42)	95.10	(49.20)
	150	99.38	(150.00)	99.38	(87.14)	99.24	(65.45)	98.92	(58.80)
	200	99.90	(200.00)	99.88	(108.14)	99.92	(73.90)	99.82	(67.12)
	500	100.0	(500.00)	100.0	(250.10)	100.0	(119.74)	100.0	(98.79)
$\gamma = 0.2$									
$\theta = 0.01$	50	92.60	(50.00)	92.24	(34.00)	92.66	(28.15)	92.76	(25.87)
	100	99.76	(100.00)	99.60	(56.13)	99.58	(38.89)	99.46	(35.29)
	150	100.0	(150.00)	100.0	(76.88)	99.98	(47.44)	100.0	(41.27)
	200	100.0	(200.00)	100.0	(100.60)	100.0	(53.50)	100.0	(46.57)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(102.02)	100.0	(70.64)

Table 4.21: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=4 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.92	(50.00)	4.92	(49.52)	5.34	(49.19)	5.24	(49.13)
	100	5.04	(100.00)	5.58	(98.73)	5.64	(98.32)	4.88	(98.32)
	150	4.54	(150.00)	4.96	(148.46)	4.84	(147.74)	5.22	(147.18)
	200	5.18	(200.00)	4.72	(198.22)	4.80	(197.13)	5.08	(196.62)
	500	4.96	(500.00)	5.12	(495.10)	4.36	(493.26)	5.38	(491.00)
$\gamma = 0.1$									
$\theta = 0.1$	50	67.88	(50.00)	68.50	(41.37)	67.90	(36.24)	68.04	(33.92)
	100	89.76	(100.00)	89.38	(70.66)	89.84	(58.18)	89.36	(53.82)
	150	97.26	(150.00)	97.16	(94.43)	97.06	(70.70)	97.30	(64.46)
	200	98.90	(200.00)	99.24	(115.38)	99.24	(81.68)	99.28	(72.39)
	500	100.0	(500.00)	100.0	(250.65)	100.0	(128.92)	100.0	(103.44)
$\gamma = 0.1$									
$\theta = 0.01$	50	90.18	(50.00)	89.80	(36.21)	90.32	(27.56)	90.56	(24.91)
	100	99.26	(100.00)	99.30	(55.89)	99.38	(39.48)	99.26	(34.81)
	150	99.98	(150.00)	99.98	(78.23)	99.94	(46.43)	99.97	(39.78)
	200	100.0	(200.00)	99.98	(100.84)	99.98	(56.01)	100.0	(44.49)
	500	100.0	(500.00)	100.0	(250.05)	100.0	(102.38)	100.0	(65.01)
$\gamma = 0.2$									
$\theta = 0.1$	50	97.10	(50.00)	96.98	(31.14)	97.02	(22.77)	97.38	(20.07)
	100	100.0	(100.00)	99.96	(52.37)	99.96	(32.34)	99.94	(28.13)
	150	100.0	(150.00)	100.0	(74.41)	100.0	(39.77)	100.0	(33.14)
	200	100.0	(200.00)	100.0	(100.08)	100.0	(47.29)	100.0	(37.16)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.26)	100.0	(58.87)
$\gamma = 0.2$									
$\theta = 0.01$	50	99.74	(50.00)	99.82	(27.04)	99.88	(15.54)	99.86	(13.06)
	100	100.0	(100.00)	100.0	(50.05)	100.0	(24.20)	100.0	(19.47)
	150	100.0	(150.00)	100.0	(75.00)	100.0	(31.83)	100.0	(22.40)
	200	100.0	(200.00)	100.0	(100.00)	100.0	(40.98)	100.0	(25.34)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.0)	100.0	(50.48)

Table 4.22: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=8 (PK)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	6.04	(50.00)	4.10	(49.54)	5.14	(49.33)	4.96	(49.24)
	100	4.32	(100.00)	5.52	(99.27)	5.02	(98.64)	5.14	(98.41)
	150	4.50	(150.00)	5.00	(148.70)	5.24	(147.48)	5.26	(147.62)
	200	5.48	(200.00)	4.78	(198.42)	5.00	(196.90)	5.86	(195.82)
	500	5.04	(500.00)	4.96	(495.20)	4.54	(493.84)	5.10	(491.41)
$\gamma = 0.1$									
$\theta = 0.1$	50	13.34	(50.00)	10.66	(48.92)	10.64	(48.61)	11.72	(48.30)
	100	13.26	(100.00)	15.60	(97.85)	14.12	(96.37)	14.72	(95.13)
	150	17.20	(150.00)	19.66	(144.88)	18.78	(141.03)	18.36	(142.09)
	200	24.72	(200.00)	22.62	(192.30)	19.44	(188.66)	21.46	(185.23)
	500	42.20	(500.00)	39.74	(463.55)	39.12	(444.24)	36.72	(437.69)
$\gamma = 0.1$									
$\theta = 0.01$	50	17.94	(50.00)	15.34	(48.45)	14.84	(48.22)	15.46	(47.78)
	100	22.92	(100.00)	25.52	(96.35)	22.50	(94.04)	22.50	(92.77)
	150	29.24	(150.00)	31.58	(142.20)	30.46	(135.79)	30.38	(135.99)
	200	39.86	(200.00)	37.34	(186.96)	34.48	(179.77)	35.48	(175.29)
	500	68.06	(500.00)	67.50	(428.90)	66.62	(390.80)	64.56	(383.01)
$\gamma = 0.2$									
$\theta = 0.1$	50	25.84	(50.00)	20.06	(47.75)	21.22	(47.22)	22.54	(46.69)
	100	33.82	(100.00)	35.70	(94.41)	33.34	(91.02)	32.18	(89.61)
	150	44.36	(150.00)	46.12	(136.95)	45.48	(127.63)	45.06	(128.59)
	200	58.06	(200.00)	54.36	(179.92)	51.66	(167.63)	53.32	(161.58)
	500	88.86	(500.00)	87.94	(379.50)	87.46	(329.84)	85.42	(316.92)
$\gamma = 0.2$									
$\theta = 0.01$	50	41.88	(50.00)	34.64	(46.39)	35.30	(45.44)	37.12	(44.36)
	100	60.06	(100.00)	61.08	(89.14)	56.62	(83.16)	56.52	(79.94)
	150	74.28	(150.00)	75.18	(124.30)	74.08	(108.74)	73.60	(109.46)
	200	86.66	(200.00)	83.78	(156.46)	81.16	(138.02)	83.12	(128.90)
	500	99.52	(500.00)	99.52	(293.65)	99.38	(225.20)	99.32	(206.55)

Table 4.23: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=2 (PU)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	3.60	(50.00)	3.64	(49.60)	4.36	(49.34)	4.60	(49.17)
	100	4.52	(100.00)	4.80	(99.18)	4.22	(98.85)	4.78	(98.53)
	150	4.72	(150.00)	4.42	(148.85)	4.44	(147.72)	4.30	(148.07)
	200	5.04	(200.00)	4.78	(198.32)	5.34	(196.98)	5.08	(196.75)
	500	5.26	(500.00)	4.90	(495.55)	4.88	(492.78)	4.88	(491.33)
$\gamma = 0.1$									
$\theta = 0.1$	50	25.32	(50.00)	24.82	(47.85)	24.74	(46.34)	26.04	(45.57)
	100	42.72	(100.00)	41.44	(92.32)	39.90	(88.22)	39.54	(86.50)
	150	55.88	(150.00)	54.06	(134.06)	53.30	(125.22)	52.28	(121.30)
	200	67.00	(200.00)	65.40	(172.84)	61.44	(158.25)	62.52	(153.71)
	500	94.92	(500.00)	93.48	(352.10)	93.34	(294.70)	92.52	(276.08)
$\gamma = 0.1$									
$\theta = 0.01$	50	42.28	(50.00)	41.70	(45.98)	41.14	(43.70)	40.92	(42.83)
	100	67.24	(100.00)	66.26	(84.77)	65.34	(77.38)	65.84	(75.36)
	150	82.84	(150.00)	81.18	(118.55)	79.60	(105.56)	79.60	(99.09)
	200	90.38	(200.00)	89.14	(149.20)	88.44	(124.66)	88.76	(119.33)
	500	99.90	(500.00)	99.88	(276.90)	99.86	(203.70)	99.86	(182.45)
$\gamma = 0.2$									
$\theta = 0.1$	50	58.76	(50.00)	60.48	(43.41)	59.64	(39.95)	58.06	(39.17)
	100	86.62	(100.00)	85.66	(76.18)	84.50	(66.74)	85.14	(62.99)
	150	95.90	(150.00)	95.52	(102.06)	94.58	(85.19)	94.44	(79.00)
	200	98.86	(200.00)	98.38	(123.78)	98.28	(96.44)	98.08	(89.86)
	500	100.0	(500.00)	100.0	(252.90)	100.0	(150.92)	100.0	(132.19)
$\gamma = 0.2$									
$\theta = 0.01$	50	87.62	(50.00)	86.02	(38.70)	85.00	(33.00)	84.92	(30.72)
	100	98.42	(100.00)	98.60	(60.79)	98.02	(48.74)	98.38	(44.25)
	150	99.96	(150.00)	99.80	(81.81)	99.88	(58.88)	99.82	(52.47)
	200	100.0	(200.00)	99.98	(103.74)	99.98	(66.12)	100.0	(59.52)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(109.60)	100.0	(89.32)

Table 4.24: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=4 (PU)

		Number of Analysis							
		1		2		5		10	
	Size	α	ASN	α	ASN	α	ASN	α	ASN
H_0									
	50	4.64	(50.00)	4.52	(49.63)	3.64	(49.44)	4.90	(49.20)
	100	4.56	(100.00)	4.42	(99.08)	4.92	(98.54)	4.76	(98.46)
	150	4.88	(150.00)	4.64	(148.71)	4.06	(148.06)	4.94	(147.36)
	200	4.04	(200.00)	4.60	(198.26)	4.50	(197.54)	3.86	(197.41)
	500	5.20	(500.00)	5.22	(495.45)	4.90	(492.98)	4.68	(492.29)
$\gamma = 0.1$									
$\theta = 0.1$	50	61.30	(50.00)	61.26	(42.82)	58.98	(39.44)	60.92	(37.77)
	100	85.38	(100.00)	85.22	(75.44)	84.96	(63.33)	84.04	(60.20)
	150	94.56	(150.00)	94.18	(102.45)	94.08	(82.43)	94.08	(76.19)
	200	97.80	(200.00)	97.96	(124.12)	98.04	(94.75)	98.08	(86.37)
	500	99.94	(500.00)	100.0	(254.25)	100.0	(147.34)	100.0	(126.05)
$\gamma = 0.1$									
$\theta = 0.01$	50	83.18	(50.00)	84.70	(36.63)	85.22	(30.59)	83.80	(29.27)
	100	98.58	(100.00)	98.42	(59.87)	98.46	(42.95)	98.62	(38.71)
	150	99.86	(150.00)	99.82	(81.50)	99.82	(54.47)	99.80	(47.35)
	200	100.0	(200.00)	99.96	(102.86)	99.98	(59.18)	100.0	(51.47)
	500	100.0	(500.00)	100.0	(250.10)	100.0	(104.94)	100.0	(73.23)
$\gamma = 0.2$									
$\theta = 0.1$	50	94.24	(50.00)	95.04	(33.13)	94.10	(26.63)	94.54	(24.24)
	100	99.74	(100.00)	99.74	(54.35)	99.80	(36.69)	99.84	(32.33)
	150	100.0	(150.00)	100.0	(77.00)	99.96	(46.11)	99.98	(39.32)
	200	100.0	(200.00)	100.0	(100.36)	100.0	(52.51)	100.0	(44.15)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(101.56)	100.0	(67.41)
$\gamma = 0.2$									
$\theta = 0.01$	50	99.54	(50.00)	99.54	(27.25)	99.54	(18.99)	99.36	(16.25)
	100	100.0	(100.00)	100.0	(50.35)	100.0	(25.12)	100.0	(20.19)
	150	100.0	(150.00)	100.0	(75.00)	100.0	(33.58)	100.0	(26.18)
	200	100.0	(200.00)	100.0	(100.00)	100.0	(41.40)	100.0	(28.95)
	500	100.0	(500.00)	100.0	(250.00)	100.0	(100.0)	100.0	(51.26)

Table 4.25: OBF's Procedure: Binomial Mixtures at $\alpha = 0.05$ m=8 (PU)

5 Application and Concluding Remarks

5.1 Application to Accident Data

There has been considerable research conducted on the development of statistical models for predicting accidents. Despite numerous advancements made for improving the estimation tools of statistical models, the most common probabilistic structure used for modelling accidents remains the traditional Poisson distribution. Accidents data have been shown to exhibit over-dispersion, meaning that the variance is greater than the mean. The over-dispersion can be caused by various factors, such as data clustering, unaccounted temporal correlation, model misidentification. Lord *et al.* (2005) shows that as the number of trials increases and becomes very large, the distribution may be approximated by a Poisson process, where the magnitude of the over-dispersion is dependent on the characteristics of the Poisson trials. As stated in Chapter 4, finite Poisson mixtures are useful for describing situations where randomness and over dispersion are present. Since we do not have any control over when or where an accident would happen, it is very difficult to conduct an experiment in accident data. However, by allowing interim looks, one could access the data several

times before the complete collection of observations. In this chapter, we will apply the proposed procedure for testing the homogeneity in the case of a finite Poisson mixture which is illustrated by a real data set example.

We first briefly review the data set. It refers to the number of accidents incurred by 414 machinists over a period of three months. It was first analyzed by Greenwood and Yule (1920). They tried to fit a simple poisson model to the data and noticed that the result was very poor($\chi^2 = 57.81$ with $d.f = 2$) for the null hypothesis that there is only one component in the model). Karlis and Xekalaki (1999) suggest that a notable improvement could be achieved by using the Poisson mixture models. Their procedure leads to the selection of the model with a 3-component Poisson mixture. Table (5.1) reports the detail of the data.

Number of Accidents	0	1	2	3	4	5	6	7	8
Frequency	296	74	26	8	4	4	1	0	1

Table 5.1: Number of accidents incurred by 414 machinists over a period of 3 months

The test procedure we raised here addresses the homogeneity of population of accidents. We focus on the null hypothesis $k = 1$ versus $k = 2$ as the alternative hypothesis, where k is the number of components in the model. Our main concern is to check the validity of the modified likelihood ratio test. At the beginning stage of the test, we use the whole data set to check whether we get the same conclusion as Karlis and Xekalaki (1999) that the data comes from a finite Poisson mixture. The result of the MLRT test gives us a clear answer that the hypothesis of one Poisson component is rejected in favor of the alternative that the data comes from a two-component Poisson mixture ($\chi^2_1 = 86.33$ with p-value=0).

After the preliminary analysis, the proposed group sequential test procedure is conducted with combinations of a different number of analysis ($K = 2, 5$ and 10) and Type I errors ($\alpha = 0.01, 0.05$ and 0.10). The original data is in the order as shown in Table (5.1). We randomly shuffled the 414 observations in the data, to make sure that the order in which the data arrives is not systematic. After each shuffling, we perform a group sequential MLRT and record the analysis at which the null hypothesis is rejected and the MLRT statistic value at that stopping time. The results are reported in the Table (5.2).

	K	Stop Time		K	Stop Time
Pocock's Procedure			OBF's Procedure		
$\alpha = 0.01$			$\alpha = 0.01$		
	2	1		2	1
	5	2		5	1
	10	3		10	3
$\alpha = 0.05$			$\alpha = 0.05$		
	2	1		2	1
	5	1		5	1
	10	1		10	3
$\alpha = 0.10$			$\alpha = 0.10$		
	2	1		2	1
	5	1		5	2
	10	1		10	3

Table 5.2: Group Sequential MLRT for the Machinists accident Data

As we see from Table 5.2, the group sequential modified likelihood ratio test gives an excellent result. Most of the tests stop at the first look and largely save the sample size. Especially for tests with $K = 5$ and 10, only about 1/4 of the total sample size is used to conclude the result. This example once again supports the practical benefits of the MLRT in group sequential analysis.

5.2 Conclusions and Discussions

The problem of testing homogeneity in finite mixture model has been investigated by many authors. It has been shown in the statistical literature that the classical asymptotic theory for likelihood ratio test is not applicable because the null hypothesis is on the boundary of the parameter space rather than in its interior, as assumed in the classical theory. In this thesis we have considered a modified likelihood ratio test (MLRT) for such homogeneity hypotheses. The MLRT has nice asymptotic properties and quite good power in detecting heterogeneity. We provided some group sequential versions of the MLRT and studies their power, type I error rates and average sample sizes they require for detecting a genuine heterogeneity. We applied the methods to simulated data sets using Normal, Poisson and Binomial mixtures. We also applied the methods to data set concerned with the number of accidents incurred by 414 machinists over a period of three months.

We conclude from our simulation study that the O'Brien-Fleming (OBF) group sequential MLRT gives very promising results. It can reduce the sample needed for detecting heterogeneity in finite mixture models to almost half of what a nonsequential, with the same type I error and the same power, would require. The good performance of the OBF procedure holds in all the three models considered, namely Poisson, Normal and Binomial, but in particular it is strongly displayed in the case of the binomial mixtures that arise from genetic linkage analysis. As human genetic linkage studies are usually run over a long period of time in order to collect familial data, the proposed sequential methods would greatly reduce the cost and time needed for such studies.

The group sequential procedures presented can be extended to other similar tests of homogeneity of mixtures such as the score statistic proposed by Liang and Rathouz (1999), which enjoys a very good power.

Also, one could extend these methods to testing two-component mixtures against an alternative of three or more component mixtures and mixtures where the kernel density function has also nuisance parameters. For instance, Chen *et al.* (2004) extend the MLRT to finite mixture models with high dimensions (i.e. $k > 2$ components distribution):

$$f(x, \theta_i) = \gamma_1 f(x, \theta_1) + ... + \gamma_k f(x, \theta_k)$$

with the penalty term $C \sum_{i=1}^{k} \log(2\gamma_i)$, where $\theta_1 \leq ... \leq \theta_k$ and $\sum \gamma_i = 1$, as before. The asymptotic null distribution of this higher dimensional MLRT would also be a mixture of χ^2 distributions with mixing proportions depending on the model parameters. However, in these cases, the nice Brownian motion approximations that we have used to obtain the group sequential version, may not be as easy.

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Appendix A: Five Regularity Conditions on Kernel Distribution

Condition 1. *Wald's integrability conditions.* The kernel function $f(x,\theta)$ satisfies Wald's integrability conditions for consistency of the maximum likelihood estimate. It is sufficient to assume, for each $\theta \in \Theta$

1. $E|logf(x,\theta)| < \infty$

2. There exists ρ such that $E[logf(x,\theta,\rho)] < \infty$,where

$$f(x,\theta,\rho) = 1 + \sup_{|\theta'-\theta|\leq\rho} \{f(x,\theta')\}$$

Since the mixture distribution is identifiable and the space of densities is compact under the weak topology of distribution functions, the MLE of these densities as a distribution function is consistent.

Condition 2. *Smoothness.* The kernel function $f(x,\theta)$ has common support and is twice continuously differentiable with respect to θ. The first two derivatives are denoted by $f'(x,\theta)$ and $f''(x,\theta)$.

Condition 3. *Strong identifiability.* The kernel function $f(x,\theta)$ is strongly identifiable. We say $f(x,\theta)$ is strongly identifiability in the sense that, for any G_1 and G_2 such that

$$\int f(x,\theta)dG_1(\theta) = \int f(x,\theta)dG_2(\theta), \text{ for all } x,$$

we must have $G_1 = G_2$. The kernel function $f(x,\theta)$, together with its first two derivatives $f'(x,\theta)$ and $f''(x,\theta)$ are also identifiable in the following sense: for any

$\theta_1 \neq \theta_2$ in Θ,

$$\sum_{j=1}^{2} a_j f(x,\theta_j) + b_j f'(x,\theta_j) + c_j f''(x,\theta_j) = 0, \text{ for all } x,$$

implies that $a_j = b_j = c_j = 0$, $j = 1, 2$.

The identifiability required here is stronger than ordinary in the sense that, besides $f(x,\theta)$ itself, the first two derivatives are also identifiable. Chen (1995) proves that location and scale kernels are strongly identifiable if $f(\pm\infty,\theta) = f'(\pm\infty,\theta) = 0$. Using this argument, we can show that all regular exponential families are strongly identifiable.

Condition 4. *Uniform strong law condition of large numbers.* There exits integrable g with some $\delta > 0$ such that $|Y_i(\theta)|^{4+\delta} \leq g(X_i)$ and $|Y_i'(\theta)|^3 \leq g(X_i)$ for all $\theta \in \Theta$, where $Y_i(\theta)$ is as defined in (2.6).

Condition 5. *Tightness.* The processes $n^{\frac{1}{2}} \sum Y_i(\theta)$,$n^{\frac{1}{2}} \sum Y_i'(\theta)$ and $n^{\frac{1}{2}} \sum Y_i''(\theta)$ are tight, where $Y_i(\theta)$ and $Z_i(\theta)$ are defined as in (2.9) and (2.10).

The tightness condition ensures the weak convergence of the processes. It is noted that the tightness of $n^{-1/2} \sum Y_i(\theta)$ is in fact implied by Condition 4.

VITA AUCTORIS

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